# A novel one-pot reaction involving organocopper-mediated reduction/transmetalation/asymmetric alkylation, leading to the diastereoselective synthesis of functionalized (*Z*)-fluoroalkene dipeptide isosteres†

**Tetsuo Narumi,[a] Ayumu Niida,[a] Kenji Tomita,[a] Shinya Oishi,[a] Akira Otaka,[ab] Hiroaki Ohno[a] and Nobutaka Fujii*[a]**

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**By a novel one-pot reaction sequence involving consecutive organocopper-mediated reduction, transmetalation and asymmetric alkylation, a highly diastereoselective synthesis of functionalized (*Z*)-fluoroalkene dipeptide isosteres was achieved in good to excellent yields.**

Alkene-based dipeptide isosteres containing (*E*)-alkene or (*Z*)-fluoroalkene units are thought to be potential dipeptide mimetics.[1,2] (*Z*)-Fluoroalkene dipeptide isosteres are structurally similar to (*E*)-alkene dipeptide isosteres (EADIs), but differ in their electrostatic nature, which plays a significant role in their intra- and intermolecular interactions. Of note, due to the presence of the highly electronegative fluorine substituent, (*Z*)-fluoroalkene dipeptide isosteres more faithfully resemble native peptides than do EADIs. In this regard, there is increasing interest in the development of efficient methodologies for the stereoselective and divergent synthesis of (*Z*)-fluoroalkene isosteres.

The organocopper- or samarium diiodide ($SmI_2$)-mediated reduction of α,β-enoates, possessing leaving group(s) at the γ-position, is an effective methodology for the stereoselective synthesis of (*E*)-olefins and (*Z*)-fluoroolefins.[3,4] The dienolate intermediates resulting from the reduction can be efficiently trapped *in situ* by an appropriate electrophile, such as alkyl halides, aldehydes and ketones. Recently, we have applied this reduction/direct alkylation methodology to the synthesis of α-alkylated (*E*)-alkene and (*Z*)-fluoroalkene dipeptide isosteres (Fig. 1).[5,6] Although this reduction/direct alkylation of the difluoroenoate **1** is extremely useful for the regio- and stereoselective formation of the required (*Z*)-fluoroalkene unit, this synthetic route has not addressed the stereoselective construction of α-side chains. Since amino acids have a center of chirality, the equivalent side chains must be introduced with high stereoselectivity into the peptide isosteres. Herein, we report the diastereoselective synthesis of highly functionalized (*Z*)-fluoroalkene dipeptide isosteres by a novel one-pot reaction sequence, involving organocopper-mediated reduction, transmetalation and asymmetric alkylation as the key steps.

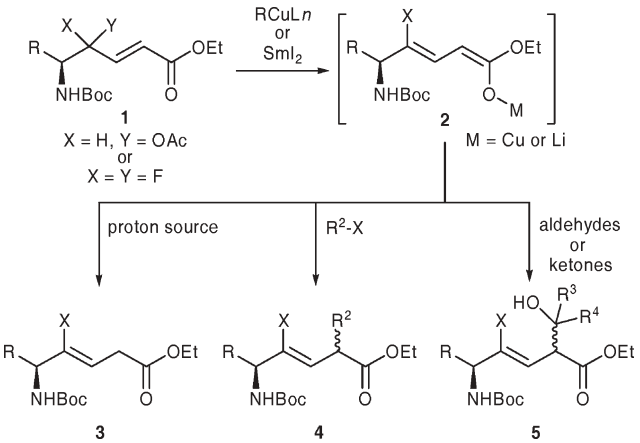
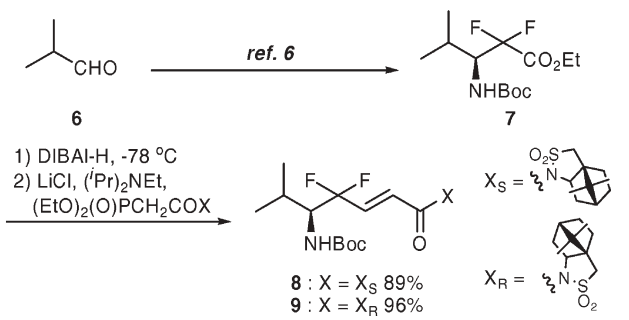



**Fig. 1** Synthesis of (*E*)-alkene or (*Z*)-fluoroalkene dipeptide isosteres by a reduction/direct alkylation methodology.

The synthesis of the key intermediates, *N*-enoyl sultams **8** and **9**, is illustrated in Scheme 1. The α,α-difluoro-β-amino ester **7**[6] was reduced to an aldehyde and then subjected to Horner–Wadsworth–Emmons-type coupling with (*S*)- or (*R*)-*N*-diethoxyphosphonoacetylcamphorsultam[7] to give *N*-enoyl sultam **8** or **9** in an *E*-selective manner.

Initially, we examined the organocopper- and $SmI_2$-mediated reduction of **8**. Both reactions, using the Gilman reagent ($Me_2CuLi{\cdot}LiI{\cdot}2LiBr$ at −78 °C for 30 min) and the cyano




**Scheme 1** Synthesis of the substrate for one-pot organocopper-mediated reduction/asymmetric alkylation.

[a]*Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: nfujii@pharm.kyoto-u.ac.jp*
[b]*Graduate School of Pharmaceutical Sciences, The University of Tokushima, Tokushima 770-8505, Japan*

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Gilman reagent ($Me_2CuLi{\cdot}LiCN{\cdot}2LiBr$ at −78 °C for 30 min), proceeded smoothly to yield the desired reduction product in 95 and 74% yields, respectively (Table 1, entries 1 and 2). Although the electron-donating ability of higher order cuprate ($Me_3CuLi_2{\cdot}LiI{\cdot}3LiBr$) is more effective than those of the Gilman and cyano Gilman reagents,[8] the reaction of **8** with higher order cuprate ($Me_3CuLi_2{\cdot}LiI{\cdot}3LiBr$ at −78 °C for 30 min) afforded the reduction product in only a moderate yield (Table 1, entry 3). On the other hand, reaction with $SmI_2$,[9] which is well-recognized as a powerful one-electron reducing reagent,[10] afforded only a mixture of unidentified compounds (Table 1, entry 4). Based on these results, we chose the Gilman reagent as our reducing reagent.

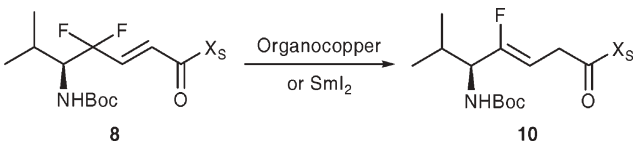
Next, we carefully examined trapping of the dienolate intermediate with alkyl halides to construct the stereogenic center at the α-position. Initial attempts to trap the Cu or Li dienolates of intermediate **11a**, derived from **8** by organocopper-mediated reduction, with methyl iodide only furnished complex mixtures (Scheme 2). This prompted us to use the more reactive tin dienolate, which could be generated by the organocopper-mediated reduction of **8**, followed by treatment with triphenyltin chloride and HMPA.[11] Sequential reaction of **8** with Gilman reagent, triphenyltin chloride/HMPA and methyl iodide selectively afforded the α-methyl fluoroalkene isostere derivative (L-Val–ψ[(*Z*)-CF=CH]–L-Ala) (**12a**) in 93% isolated yield with exclusive *Z*-selectivity.‡ The diastereoselectivity of this reaction proved to be 80%, which was confirmed by RP-HPLC analysis.

In a similar manner, the use of benzyl bromide, *tert*-butyl bromoacetate and allyl bromide stereoselectively gave the corresponding α-substituted fluoroalkene dipeptide isosteres **12b**, **12c** and **12d**, respectively, in excellent yields (Table 2, entries 2 to 4). The reaction with methyl 3-bromopropionate gave the reduction product **10** with no alkylated product (Table 2, entry 5). Next, we attempted to synthesize epimeric (L,D)-type isosteres in a similar manner using (*R*)-sultam derivatives **9**. The reaction with Gilman reagent, followed by asymmetric alkylation *via* transmetalation, proceeded smoothly to afford the corresponding (L,D)-type α-substituted fluoroalkene isosteres **13a–13d** in high yields and with good to excellent diastereoselectivities (Table 2, entries 6 to 9).

Finally, the chiral auxiliary of **12b** was removed by hydrolysis under basic conditions to give the Boc–L-Val–ψ[(*Z*)-CF=CH]–L-Phe–OH isostere (**14**) in 75% yield with 96% de (Scheme 3). We observed neither epimerization of the α-alkyl groups nor isomerization of the double bond during cleavage of the chiral auxiliary.§

In conclusion, we have developed a novel and highly diastereoselective one-pot synthesis of functionalized (*Z*)-fluoroalkene dipeptide isosteres. The utility of the newly developed methodology can be found in the high-to-excellent regio- and stereoselectivities upon construction of the (*Z*)-fluoroalkene unit and α-side chain. Further studies using the developed methodology on the synthesis and evaluation of bioactive peptides with fluoroalkene isosteres are now in progress.

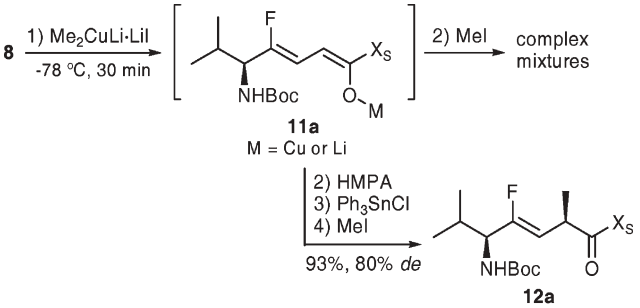
**Table 1** Organocopper- and $SmI_2$-mediated reduction of *N*-enoyl sultam **8**




**8** **10**

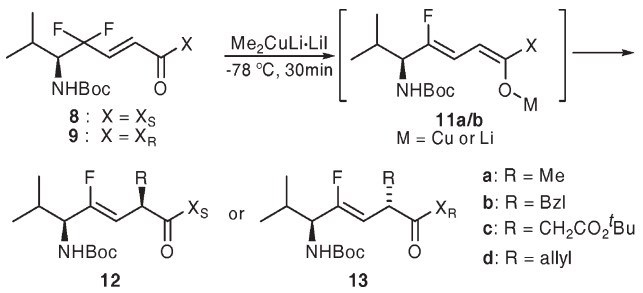
| Entry | Reagent (equivalents) | Conditions | Yield[b] (%) |
|---|---|---|---|
| 1 | $Me_2CuLi{\cdot}LiI$[a] (4) | −78 °C, 30 min | 95 |
| 2 | $Me_2CuLi{\cdot}LiCN$[a] (4) | −78 °C, 30 min | 74 |
| 3 | $Me_3CuLi_2{\cdot}LiI$[a] (4) | −78 °C, 30 min | 52 |
| 4 | $SmI_2$ (6) | 0 °C, 30 min | —[c] |

[a] In the presence of Li salts (LiCl and/or LiBr). [b] Isolated yield. [c] A mixture of unidentified compounds was obtained.



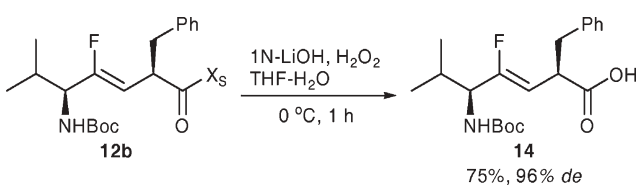

**Scheme 2** Diastereoselective synthesis of a L-Val-L-Ala-type (*Z*)-fluoroalkene isostere.

**Table 2** Diastereoselective synthesis of functionalized (*Z*)-fluoroalkene dipeptide isosteres by one-pot reduction/transmetalation/asymmetric alkylation




| Entry | Electrophiles | Substrate | Products[a] (%) | de[b] (%) |
|---|---|---|---|---|
| 1 | MeI | **8** | **12a** (93)[c] | 80 |
| 2 | Bn–Br | **8** | **12b** (93)[c] | 95 |
| 3 | $BrCH_2CO_2{}^tBu$ | **8** | **12c** (80)[c] | >95 |
| 4 | Allyl–Br | **8** | **12d** (99)[c] | >95 |
| 5 | $BrCH_2CH_2CO_2Me$ | **8** | **10** (91) | — |
| 6 | MeI | **10** | **13a** (69)[c] | 91 |
| 7 | Bn–Br | **10** | **13b** (77)[c] | 90 |
| 8 | $BrCH_2CO_2{}^tBu$ | **10** | **13c** (71)[c] | 94 |
| 9 | Allyl–Br | **10** | **13d** (79)[c] | 92 |

[a] Isolated yield. [b] Determined by RP-HPLC of the purified products. [c] A trace amount of γ-alkylated products was detected by RP-HPLC.




**Scheme 3** Cleavage of the chiral auxiliary.

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## Notes and references

‡ Fluoroalkene compounds obtained in this study have coupling constants in the range $J_{HF}$ = 35.6–37.8 Hz. These values are consistent with those of compounds possessing (*Z*)-fluoroolefin units.[12]

§ The absolute configurations of the alkyl groups at the α-position were determined by circular dichroism measurements using an empirical rule after converting to the corresponding methyl esters.[13]

1 S. Oishi, T. Kamano, A. Niida, Y. Odagaki, N. Hamanaka, M. Yamamoto, K. Ajito, H. Tamamura, A. Otaka and N. Fujii, *J. Org. Chem.*, 2002, **67**, 6162; P. Wipf and J. Xiao, *Org. Lett.*, 2005, **7**, 103; J. Xiao, B. Weisblum and P. Wipf, *J. Am. Chem. Soc.*, 2005, **127**, 5742; H. Tamamura, K. Hiramatsu, S. Ueda, Z. Wang, S. Kusano, S. Terakubo, J. O. Trent, S. C. Peiper, N. Yamamoto, H. Nakashima, A. Otaka and N. Fujii, *J. Med. Chem.*, 2005, **48**, 380; C. L. Jenkins, M. M. Vasbinder, S. J. Miller and R. T. Raines, *Org. Lett.*, 2005, **7**, 2619.

2 R. J. Abraham, S. L. R. Ellison, P. Schonholzer and W. A. Thomas, *Tetrahedron*, 1986, **42**, 2101; T. Allmendinger, P. Furet and E. Hungerbühler, *Tetrahedron Lett.*, 1990, **31**, 7297; T. Allmendinger, E. Felder and E. Hungerbühler, *ACS Symp. Ser.*, 1991, **456**, 186; P. V. D. Veken, K. Senten, I. Kerèsz, I. D. Meester, A.-M. Lambeir, M.-B. Maes, S. Scharpè, A. Haemers and K. Augustyns, *J. Med. Chem.*, 2005, **48**, 1768; Y. Nakamura, M. Okada, A. Sato, H. Horikawa, M. Koura, A. Saito and T. Taguchi, *Tetrahedron*, 2005, **61**, 5741; A. Niida, K. Tomita, M. Mizumoto, H. Tanigaki, T. Terada, S. Oishi, A. Otaka, K. Inui and N. Fujii, *Org. Lett.*, 2006, **8**, 613.

3 A. Otaka, A. Yukimasa, J. Watanabe, Y. Sasaki, S. Oishi, H. Tamamura and N. Fujii, *Chem. Commun.*, 2003, 1834.

4 A. Otaka, E. Mitsuyama, H. Watanabe, H. Tamamura and N. Fujii, *Chem. Commun.*, 2000, 1081.

5 A. Otaka, H. Watanabe, E. Mitsuyama, A. Yukimasa, H. Tamamura and N. Fujii, *Tetrahedron Lett.*, 2001, **42**, 285; A. Otaka, H. Watanabe, A. Yukimasa, S. Oishi, H. Tamamura and N. Fujii, *Tetrahedron Lett.*, 2001, **42**, 5443.

6 A. Otaka, J. Watanabe, A. Yukimasa, Y. Sasaki, H. Watanabe, T. Kinoshita, S. Oishi, H. Tamamura and N. Fujii, *J. Org. Chem.*, 2004, **69**, 1634.

7 W. Oppolzer, D. Dupuis, G. Poli, T. M. Raynham and G. Bernardinelli, *Tetrahedron Lett.*, 1988, **29**, 5885.

8 T. Ibuka, T. Aoyagi, K. Kitada, F. Yoneda and Y. Yamamoto, *J. Organomet. Chem.*, 1985, **287**, C18; T. Ibuka, T. Aoyagi and Y. Yamamoto, *Chem. Pharm. Bull.*, 1986, **34**, 2417.

9 P. Girard, J. K. Namy and H. B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693.

10 For some recent reviews, see: G. A. Molander, *Chem. Rev.*, 1992, **92**, 29; G. A. Molander, *Tetrahedron*, 1998, **54**, 3321; A. Krief and A.-M. Laval, *Chem. Rev.*, 1999, **99**, 745; P. Steel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2727.

11 P. A. Tardella, *Tetrahedron Lett.*, 1969, **10**, 1117; H. Nishiyama, K. Sakuta and K. Itoh, *Tetrahedron Lett.*, 1984, **25**, 223; H. Nishiyama, K. Sakuta and K. Itoh, *Tetrahedron Lett.*, 1984, **25**, 2487; M. Suzuki, A. Yanagisawa and R. Noyori, *J. Am. Chem. Soc.*, 1985, **107**, 3348; M. Suzuki, A. Yanagisawa and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 4718.

12 R. Waschüsch, J. Carran and P. Savignac, *Tetrahedron*, 1969, **52**, 14199.

13 T. Ibuka, H. Habashita, S. Funakoshi, N. Fujii, K. Baba, M. Kozawa, Y. Oguchi, T. Uehara and Y. Yamamoto, *Tetrahedron: Asymmetry*, 1990, **1**, 389.

 