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Synthesis of Fluoroalkene Dipeptide Isosteres by an Intramolecular Redox Reaction Utilizing *N*-Heteorocyclic Carbenes (NHCs)

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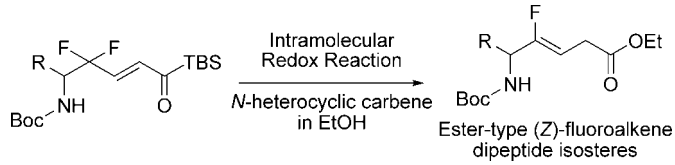

(*Z*)-Fluoroalkene dipeptide isosteres (FADIs **16**) have served as potential dipeptide mimetics possessing the substitution of fluoroalkenes for parent peptide bonds. Previously, we synthesized FADIs by reduction of γ,γ-difluoro-α,β-enoates with organocoppers or SmI_2, which prompted us to use an intramolecular redox reaction mediated by *N*-heterocyclic carbenes (NHCs) for the preparation of FADIs. Instead of the enoates, γ,γ-difluoro-α,β-enal **20** and γ,γ-difluoro-α,β-enoylsilane **34** were converted to FADIs by an NHC-mediated intramolecular redox reaction, whereby aldehyde components reduced the allylic difluoride component in an S_N2' manner with accompanying monodefluorination.

Introduction

Use of *N*-heterocyclic carbenes (NHCs, **2**) derived from thiazolium salts **1** as environmentally friendly reagents or catalysts has been increasing in a wide variety of organic transformations,[1] where benzoin-type condensation,[2] a Stetter-type reaction,[3] and an intra/intermolecular redox reaction[4,5] are involved (Scheme 1).[6] These types of reactions feature the *umpolung*[7] of carbonyl carbons, that is, nucleophilic attack of NHCs to carbonyl compounds such as aldehydes followed by a 1,2-proton shift allowing the aldehyde carbons to possess a negative charge (**4** or **5** in Scheme 1). The resulting nucleophilic carbons attack other carbonyls[2,8] or the β-carbon of α,β-unsaturated carbonyl compounds[3] (**6** or **7**) to afford benzoin-type **8** or Stetter-type **9**, respectively. Additionally, the formed negative charge can participate intramolecularly in the reduction of α,β-epoxy **10**,[4a] aziridinyl **11**,[4a] or unsaturated aldehydes **12**,[4c,d] followed by nucleophilic attack of the alcohols on the formed acylated NHCs to give β-hydroxy **13**, amino **14**, or

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(1) For recent reviews about NHC-mediated reactions, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000.

(2) Benzoin-type condensation, see: (a) Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 269–300. (b) Breslow, R. *Chem. Ind. (London, U.K.)* **1957**, 893–894. (c) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726. (d) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *37*, 3611–3614. (e) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893. (f) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124–5131. (g) Enders, D.; Kalfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745. (h) Enders, D.; Breuer, K.; Balensiefer, T. *Synthesis* **2003**, *8*, 1292–1295. (i) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, *9*, 2025–2035. (j) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728. (k) Enders, D.; Niemmeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463–1467. (l) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492–3494. (m) Zhao, H.; Foss, F. W., Jr.; Breslow, R. *J. Am. Chem. Soc.* **2008**, *130*, 12590–12591. (n) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367–1371. (o) Wong, F. T.; Patra, P. K.; Seayad, J.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 2333–2336.

(3) Stetter-type reaction: (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–712. (b) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899–1902. (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877. (d) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284–6289.

(4) Intramolecular redox reaction, oxidation to esters, see: (a) Chow, Y.-K. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127. (b) Reynolds, T. N.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. (d) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876. (e) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640. (f) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107–3110. Oxidation to amides, see: (g) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (h) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.

(5) Intermolecular redox reaction: (a) Inoue, H.; Tamura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 858–859. (b) Kageyama, Y.; Murata, S. *J. Org. Chem.* **2005**, *70*, 3140–3147. (c) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371–374. (d) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727–8730. (e) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331–4334.

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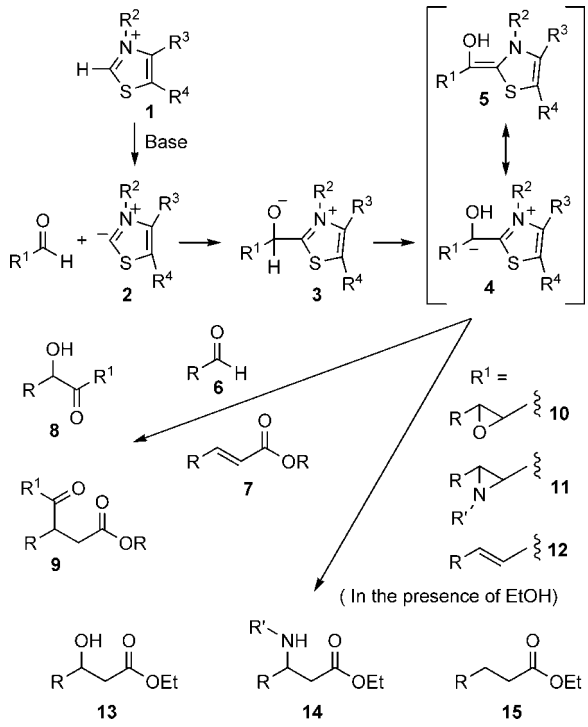
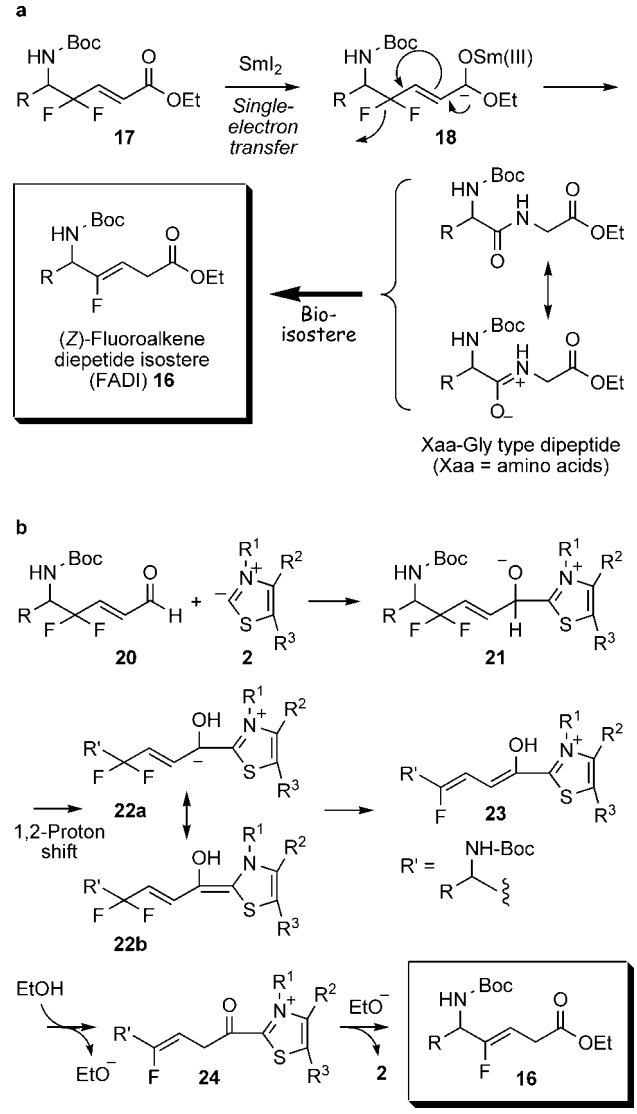
SCHEME 1



saturated esters **15**, respectively. In these reactions, the aldehyde portion reduces the epoxide, aziridine, or alkene component with the aid of NHCs. Similar intermolecular reduction of a disulfide compound (lipoate) is involved in the sequence of reactions required for the formation of the acetyl coenzyme A (acetyl-CoA).[5a,9]

These attractive features of NHCs typified by *umpolung* prompted us to utilize NHCs for the preparation of fluoroalkene dipeptide isosteres (FADIs, **16**).[10−13] Recently, we have engaged in the synthesis of FADIs as a potential peptidomimetic by the reduction of γ,γ-difluoro-α,β-enoates **17** with samarium diiodide (SmI_2) or organocoppers (Scheme 2a).[14,15] In our proposed reaction mechanism including Sm or Cu, successive single-electron transfers (SETs)[14c,d,16] occur from metallic reagents, and the subsequent transfer of the two electrons into the π-electron system adjacent to the difluoromethylene group induces the pushing out of one of the fluorine atoms to give

SCHEME 2. (a) Synthesis of FADIs Using a SET Reaction; (b) Envisioned Synthesis of FADIs Using NHCs



the fluoroalkene moiety. On the basis of these issues, it is tempting to envision that the addition of NHCs to the carbonyl group in γ,γ-difluoro-α,β-enals **20** triggers the intramolecular redox reaction between the aldehyde and the allyl difluoro units to afford γ-fluoro-β,γ-enoates **16** in the presence of an appropriate alcohol (Scheme 2b). Along these lines, we herein report the attempt to synthesize FADIs and the synthetic feasibility of the NHC-mediated preparation of FADIs.

(6) For some recent examples (transesterification and amidation, a−d; homoenolate formation, e−g; others, h−j) without involving the above categories (refs 2−5), see: (a) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583–3586. (b) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587–3590. (c) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347–1349. (d) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453–2456. (e) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208. (f) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371. (g) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737. (h) Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 397–398. (i) Kano, T.; Sasaki, K.; Konishi, T.; Mii, H.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 4615–4618. (j) Suzuki, Y.; Ota, S.; Ueda, Y.; Sato, M. *J. Org. Chem.* **2008**, *73*, 2420–2423.

(7) For some representative reviews about *umpolung*, see: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258. (b) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, *14*, 2418–2439. (c) Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, 5629–5660. (d) Dickstein, J. S.; Kozlowski, M. C. *Chem. Soc. Rev.* **2008**, *37*, 1166–1173.

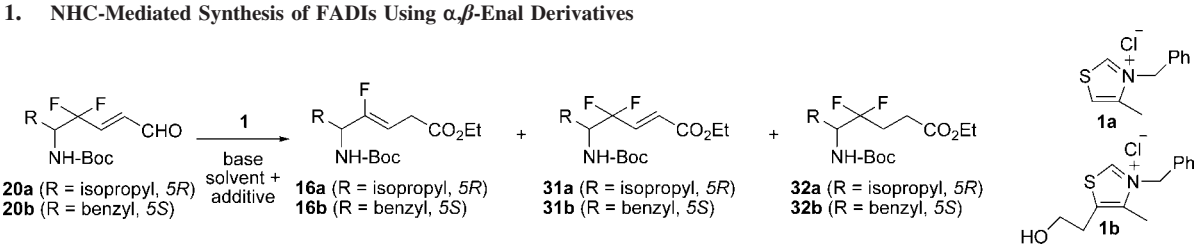
(8) For some examples of reactions to imine, see: (a) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696–9697. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654–1655. (c) Chan, A.; Scheidt, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 5334–5335. (d) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277–280.

(9) Rastetter, W. H.; Adams, J. *J. Org. Chem.* **1981**, *46*, 1882–1887.

(10) For some recent reviews for FADIs, see: (a) Welch, J. T.; Allmendinger, T. In *Peptidomimetics Protocols*; Kazmierski, W. M., Ed.; Humana Press: Totowa, NJ, 1999; pp 357−384. (b) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157.

(11) For physical chemistry study on FADIs, see: (a) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, *42*, 2101–2110. (b) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297–7300. (c) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *38*, 12613–12622. (d) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645–652. (e) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363–3384. (f) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. In *Organofluorine Compounds, Chemistry and Application*; Yamamoto, H., Ed.; Springer-Verlag: Berlin, Germany, 2000. (g) Urban, J. J.; Tillman, B. G.; Cronin, W. A. *J. Phys. Chem. A* **2006**, *110*, 11120–11129.

TABLE 1. NHC-Mediated Synthesis of FADIs Using α,β-Enal Derivatives



entry	substrate	precatalyst (30 mol %)	base (30 mol %)	solvent + (additive, equiv)	conditions	product(s) (yield %, NMR)
1	**20a**	**1a**	*N*,*N*-diisopropylethylamine (DIPEA)	THF + (EtOH, 3 equiv)	rt, 15 h	**16a** (36), **31a** + **32a** (12), **20a** (51)[a]
2	**20a**	**1a**	DIPEA	toluene + (EtOH, 3 equiv)	rt, 15 h	**16a** (26), **31a** + **32a** (18), **20a** (55)[a]
3	**20a**	**1a**	DIPEA	toluene + (EtOH, 5 equiv)	70 °C, 18 h	**16a** (12), **31a** + **32a** (23)[b], **20a** (−)[c]
4	**20b**	**1a**	DBU	THF + (EtOH, 10 equiv)	70 °C, 3 h	**16b** (6), **31b** + **32b** (8)[b], **20b** (21)[c]
5	**20a**	**1a**	DIPEA	EtOH	70 °C, 7 h	**16a** (66)[c]
6	**20b**	**1b**	DIPEA	EtOH	70 °C, 20 h	**16b** (70)[c]

[a] Yields (product ratio) were determined by NMR measurements. [b] Obtained as mixtures. [c] Isolated yield.

Results and Discussion

As requisite substrates for reaction evaluation, we first selected δ-amino-γ,γ-difluoro-α,β-enal derivatives **20** (Scheme 3). In the course of previous studies on FADIs, we have already established the synthetic routes for chiral α,α-difluoro-β-amino acid derivatives (**28** or **29**) utilizing the Honda-Reformatsky reaction.[14d,17] In situ formed chiral imines **27** resulting from the reaction of an appropriate aldehyde, **25a** or **25b**, with chiral phenyl glycinol derivative **26** in the presence of molecular sieves was subjected to one-pot Honda-Reformatsky conditions ($BrCF_2CO_2Et$ + Et_2Zn in the presence of catalytic amount of $RhCl(PPh_3)_3$) to yield the chiral fluorinated β-amino esters **28**.[18] Hydrogenolitic removal of the chiral auxiliary with $Pd(OH)_2$/C−H_2 followed by *N*-Boc protection gave the *N*-Boc-chiral β-amino acid derivatives **29**. DIBAL-H reduction of the resulting ester (**29a** or **29b**) followed by the Wittig reaction with Ph_3P=CHCHO (in benzene, 60 °C) yielded requisite substrate **20a** (65%) or **20b** (60%) with accompanying dienes **30**, respectively. Having the substrates, we next examined the feasibility of the NHC-initiated synthesis of FADIs, and the results are summarized in Table 1.

Reaction of **20a** with NHC, derived from precatalyst **1a** and *N*,*N*-diisopropylethylamine (DIPEA) (30 mol % each), in THF or toluene in the presence of EtOH at room temperature afforded desired FADI **16a**, albeit in low chemical yields (Table 1, entries 1 and 2).[19] In addition to the starting material, these reactions accompanied the formation of nonnegligible quantities of side products including difluoro-α,β-enoate **31a** and saturated ester **32a**. Reactions at elevated temperature (70 °C) did not lead to an increase in the yield of **16** so much as to the formation of unidentified side products (Table 1, entries 3 and 4). Yields of desired FADIs were dramatically improved by a reaction in the presence of **1a** or **1b**[20] in EtOH at 70 °C (Table 1, entries 5 and 6), even though the conversion remained at a moderate level along with the formation

(12) For some literature about the synthesis of FADIs or fluoroalkene units, see: (a) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301–7304. (b) Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett.* **1994**, *35*, 6033–6036. (c) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107–3111. (d) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291–304. (e) Van der Veken, P.; Senten, K.; Kertèsz, I.; Meester, I. D.; Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768–1780. (f) Dutheuil, G.; Lei, X.; Pannecoucke, X.; Quirion, J.-C. *J. Org. Chem.* **2005**, *70*, 1911–1914. (g) Sano, S.; Kuroda, Y.; Saito, K.; Ose, Y.; Nagao, Y. *Tetrahedron* **2006**, *62*, 11881–11890. (h) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 1290–1292. (i) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Org. Lett.* **2007**, *9*, 3465–3468. (j) Lamy, C.; Hofmann, J.; Parrot-Lopez, H.; Goekjian, P. *Tetrahedron Lett.* **2007**, *48*, 6177–6180. (k) Wnuk, S. F.; Lalama, J.; Garmendia, C. A.; Robert, J.; Zhu, J.; Pei, D. *Bioorg. Med. Chem.* **2008**, *16*, 5090–5102.

(13) Some recent examples of (*E*)-alkene-type dipeptide isosteres, see: (a) Oishi, S.; Miyamoto, K.; Niida, A.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Kuroda, Y.; Asai, A.; Fujii, N. *Tetrahedron* **2006**, *62*, 1416–1424. (b) Sasaki, Y.; Niida, A.; Tsuji, T.; Shigenaga, A.; Fujii, N.; Otaka, A. *J. Org. Chem.* **2006**, *71*, 4969–4979, and references cited therein.

(14) Synthesis of FADIs using copper- or SmI_2-mediated reductive defluorination: (a) Otaka, A.; Mitsuyama, E.; Watanabe, H.; Oishi, S.; Tamamura, H.; Fujii, N. *Chem. Commun.* **2000**, 1081–1082. (b) Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 285–287. (c) Otaka, A.; Watanabe, H.; Yukimasa, A.; Oishi, S.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 5443–5446. (d) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634–1645. (e) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.; Fujii, N. *Org. Lett.* **2006**, *8*, 613–616. (f) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720–4722. (g) Tomita, K.; Narumi, T.; Niida, A.; Oishi, S.; Ohno, H.; Fujii, N. *Biopolymers* **2007**, *88*, 272–278. (h) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Tetrahedron* **2008**, *64*, 4332–4346.

(15) Taguchi's group independently developed the reductive defluorination protocols for the synthesis of FADIs, see: (a) Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Chem. Lett.* **2002**, 28–29. (b) Nakamura, Y.; Okada, M.; Horikawa, H.; Taguchi, T. *J. Fluorine Chem.* **2002**, *117*, 143–148. (c) Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Tetrahedron Lett.* **2002**, *43*, 5845–5847. (d) Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 5741–5753. (e) Nakamura, Y.; Okada, M.; Koura, M.; Tojo, M.; Saito, A.; Sato, A.; Taguchi, T. *J. Fluorine Chem.* **2006**, *127*, 627–636.

(16) (a) Chounan, Y.; Ibuka, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2003–2004. (b) Chounan, Y.; Horino, H.; Ibuka, T.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1953–1959.

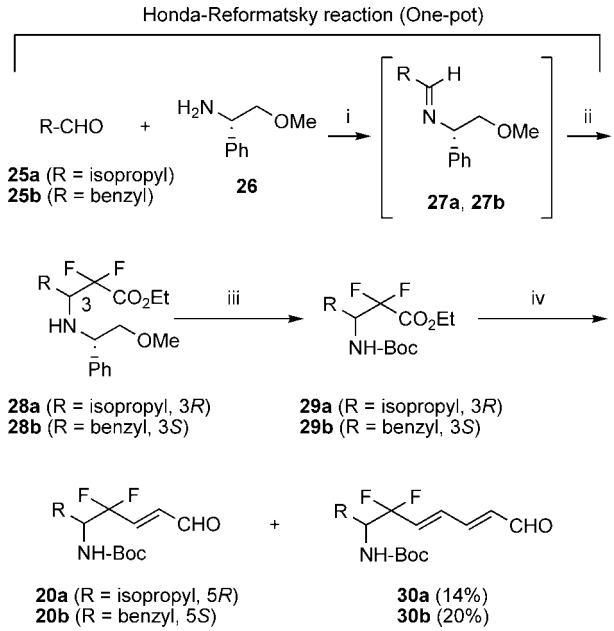
(17) Honda-Reformatsky reaction: (a) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307–308. (b) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549–2551. (c) Kanai, K.; Wakabayashi, H.; Honda, T. *Heterocycles* **2002**, *58*, 47–51. (d) Boyer, N.; Gloanec, P.; De Nanteuil, G.; Jubault, P.; Quirion, J.-C. *Tetrahedron* **2007**, *63*, 12352–12366.

(18) The use of isolated imine in Honda-Reformatsky type reaction affords difluoro-β-lactam derivatives, see: (a) Sato, K.; Tarui, A.; Matsuda, S.; Omote, M.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **2005**, *46*, 7679–7681. (b) Tarui, A.; Kondo, K.; Taira, H.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Heterocycles* **2007**, *73*, 203–208. (c) Tarui, A.; Ozaki, D.; Nakajima, N.; Yokota, Y.; Sokeirik, Y. S.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron Lett.* **2008**, *49*, 3839–3843.

(19) Fluoroalkene compounds obtained in this study as major isomers have coupling constants ($^3J_{HF}$ = 35.3−37.0). Those values are very consistent with those of compounds possessing (*Z*)-fluoroalkene units. See: Waschüsch, R.; Carran, J.; Savignac, P. *Tetrahedron* **1996**, *52*, 14199–14216. (*E*)-Fluoroalkenes have smaller coupling constants ($^3J_{HF}$ = 20.0−21.2).[12a]

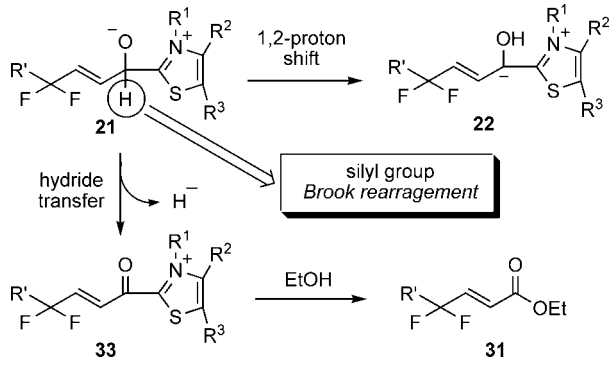
(20) Although precatalysts (**1a** and **1b**) were equally effective for the conversion, column chromatographical purification of the crude obtained by the reaction with **1b** was more easily conducted than that with **1a**. Therefore, we preferentially used NHC precursor **1b** at the experiments described later.

SCHEME 3[a]



[a] Reagents and conditions: (i) molecular sieves 3 Å, THF; (ii) $BrCF_2CO_2Et$, Et_2Zn, $RhCl(PPh_3)_3$, THF−hexane; (iii) $Pd(OH)_2/C$, H_2, EtOH, then $(Boc)_2O$, THF; (iv) DIBAL-H, CH_2Cl_2-toluene, then $Ph_3P{=}CHCHO$, benzene.

SCHEME 4

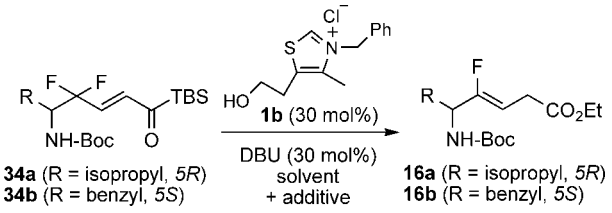


of unidentified side products. One possible explanation for generating the α,β-enoate derivatives **31** is that the hydrogen atom present in aldehyde−NHC adduct **21** formally does not shift on the oxyanion as a proton (1,2-proton shift, **21** to **22**) but moves away as a hydride anion,[21] thereby leading to the formation of α,β-enoates (**21** to **31** via **33**, Scheme 4). We speculated that the preferential conversion of oxyanion **21** to the corresponding carboanion species **22** could cause the enoates **31** not to be generated. On the basis of this assumption, utilization of a 1,2-Brook rearrangement[22] involving the 1,2-migration of a silyl group alternate to the proton seemed to suppress the formation of side product **31** by the efficient conversion of oxyanions to carboanions. Recently, reactions of acylsilanes with NHCs followed by the 1,2-Brook rearrangement with a wide variety of synthetic applications

(21) Chan, A.; Scheidt, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 4558–4559.

(22) For literature for 1,2-Brook rearrangement, see: (a) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065–2084. (b) Takeda, K.; Yamawaki, K.; Hatakeyama, N. *J. Org. Chem.* **2002**, *67*, 1786–1794. (c) Takeda, K.; Sawada, Y.; Sumi, K. *Org. Lett.* **2002**, *4*, 1031–1033. (d) Takeda, K.; Onishi, Y. *Tetrahedron Lett.* **2000**, *41*, 4169–4172. (e) Tanaka, K.; Takeda, K. *Tetrahedron Lett.* **2004**, *45*, 7859–7861. (f) Koudai, T.; Masu, H.; Yamaguchi, K.; Takeda, K. *Tetrahedron Lett.* **2005**, *46*, 6429–6432.

TABLE 2. NHC-Mediated Synthesis of FADIs Using α,β-Enoylsilanes



entry	substrate	solvent + (additive, equiv)	conditions	product(s) (isolated yield %)
1	**34a**	THF + (EtOH, 10 equiv)	rt, 24 h	**16a** (37)[a]
2	**34a**	THF + (EtOH, 10 equiv)	70 °C, 3 h	**16a** (53)[b]
3	**34b**	THF + (EtOH, 10 equiv)	70 °C, 3 h	**16b** (41)[b]
4	**34a**	EtOH	rt, 24 h	**16a** (39), **34a** (45)
5	**34a**	EtOH	70 °C, 3 h	**16a** (81)
6	**34b**	EtOH	70 °C, 2 h	**16b** (91)

[a] Starting materials were recovered. [b] Unidentified materials were formed, whereas starting materials disappeared.

have been addressed by the Scheidt group.[23] Next, we turned our attention to the use of γ,γ-difluoro-α,β-enoylsilanes for the NHC-mediated preparation of FADIs.

Requisite enoylsilanes **34** was prepared by the DIBAL-H reduction of the *N*-Boc-protected difluoro-β-amino acid ester **29**, followed by carbon chain elongation via Horner-Emmons olefination using dimethyl phosphonoacylsilanes.[24] We next examined the synthesis of FADIs using obtained α,β-enoylsilanes **34** and summarized the results in Table 2.

In these examinations, the thiazolium salt **1b** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were used for generation of the corresponding NHC catalyst.[20,25] First, reactions in THF containing EtOH (10 equiv) were attempted. Treatment of enoylsilane **34a** with NHC in THF in the presence of EtOH at room temperature gave the desired FADI **16a** in 37% yield with recovery of the starting material (Table 2, entry 1). Increasing the temperature (70 °C) for the reaction of enoylsilanes **34** caused the starting materials to be consumed; however, isolated yields held at a moderate level as a result of the formation of unidentified compounds (Table 2, entries 2 and 3).[26] Next, EtOH was used as the reaction solvent. Although the reaction at room temperature was not completed, the efficient conversions to FADI **16** were achieved by treatments at 70 °C for 2−3 h where the reactions proceeded in high diastereoselectivity [(*Z*):(*E*) = 96:4; Table 2, entries 5 and 6]. Compared with the reaction of the aldehydes **20**, that of the acylsilanes **34** proceeded efficiently to yield desired FADIs **16** in high yield,[27] which could be attributed to factors shown in Scheme 5 as well as the facile transformation to the carboanion intermediate **36** as mentioned in the previous section.

(23) For literature about the use of acylsilanes in the presence of NHCs, see: (a) Mattoson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315. (b) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465–2468. (c) Mattoson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363–4366. (d) Mattoson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715–5724.

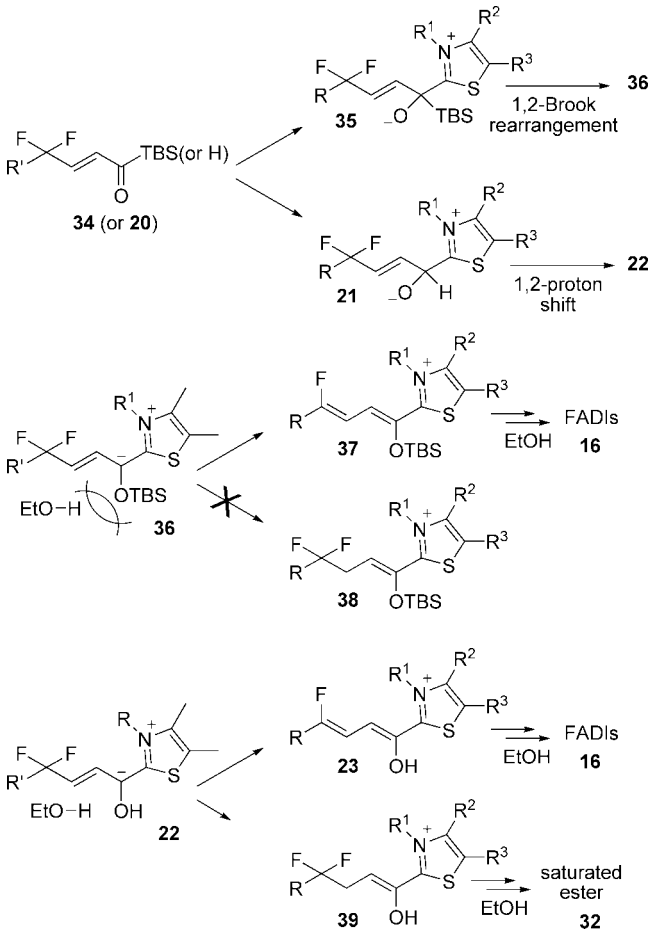
(24) Diethylphosphonoacylsilane: (a) Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113–4134. (b) Nowick, J. S.; Danheiser, R. L. *J. Org. Chem.* **1989**, *54*, 2798–2802.

(25) Mixing of **1b** and DBU in THF resulted in facile formation of the corresponding NHC catalyst compared with that of **1b** and DIPEA.

(26) Although the reaction of **34b** in the presence of MeOH afforded the corresponding FADI methyl ester in a slightly higher yield than that using EtOH as additive, the use of 2-propanol as an additive gave a complex mixture.

(27) Attempted reaction of aldehyde **20b** in the presence of **1b** and DBU in EtOH at 70 °C was not completed within 2 h to give FADI **16b** in 24% isolated yield.

SCHEME 5. Comparison of Reactions Using Enals with Those of Enoylsilanes



Addition of the NHC to the enoylsilanes **34** or enals **20** followed by 1,2-Brook rearrangement or 1,2-proton shift gave an allyl anion-like species **36** or **22**, respectively. Protonation on the γ-position adjacent to the CF_2 group by EtOH resulted in the formation of saturated ester **32**. Compared with the γ-position of intermediate **22**, that of **36** seems to be robustly shielded by the bulky TBS group. Therefore, protonation on the γ-position of **36** is kinetically unfavorable, leading to the preferential formation of defluorination products **37**.[14d,28]

A trap of silyl enol ether-type compounds **37** with electrophiles such as alkyl halides or aldehydes in the presence of a fluoride anion could be applicable to the synthesis of α-substituted FADIs; however, reaction of the enoylsilanes **34** with NHC most efficiently proceeded in EtOH, working both as an electrophilic proton source and as a nucleophilic ethoxide source for the regeneration of the catalyst. Therefore, various attempts to prepare α-substituted FADIs, including reactions using alkyl halides and alkoxides in aprotic solvents, resulted in failure to yield the desired products.

In conclusion, the NHC-mediated intramolecular redox reaction of γ,γ-difluoro-α,β-enals **20** or -enoylsilanes **34** was successfully applied to the synthesis of FADIs **16**. The use of enoylsilanes **34** as a starting material gave more favorable results than that of enals **20**, owing to the formation of allyl anion-like species **36** and efficient reductive defluorination because of the presence of the silyl group. This NHC-mediated redox reaction oxidizes aldehydes or aldehyde equivalents to carboxylic esters. Oxidative transformation to other carboxylic derivatives such as amides should be possible. This possibility will be discussed in the succeeding paper, where incorporation of α-substitutions also yet to be achieved in this study will also be mentioned.

(28) (a) Yoshida, A.; Mikami, K. *Synlett* **1997**, 1375–1376. (b) Yoshida, A.; Hanamoto, T.; Inanaga, J.; Mikami, K. *Tetrahedron Lett.* **1998**, *39*, 1777–1780.

Experimental Section

(5*R*,2*E*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4,4-difluoro-6-methylhept-2-enal (20a). To a solution of ester **29a**[14d] (1.0 g, 3.4 mmol) in CH_2Cl_2 (9.0 mL) was added dropwise a solution of DIBAL-H in toluene (0.99 M, 6.8 mL, 6.8 mmol) at −78 °C under argon, and the mixture was stirred for 15 min. The reaction was quenched with saturated citric acid and extracted with Et_2O. The extract was washed with saturated citric acid and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily aldehyde, which was used immediately in the next step without further purification. To a solution of $Ph_3P{=}CHCHO$ (1.0 g, 3.4 mmol) in benzene (8.0 mL) was added the above aldehyde in benzene at 40 °C under argon, and the mixture was stirred for 1.5 h at this temperature. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:10) gave the title compound **20a** (612 mg, 65% yield) and **30a** (144 mg, 14% yield). Compound **20a**: white powder, mp 33−35 °C. $[\alpha]_D^{26}$ + 25.2 (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.98 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 1.42 (s, 9H), 2.19−2.27 (m, 1H), 3.98 (dsept, J = 4.0 and 22.4 Hz, 1H), 4.68 (d, J = 10.4 Hz, 1H), 6.48 (dd, J = 7.6 and 15.6 Hz, 1H), 6.69 (ddd, J = 9.6, 13.6, and 15.6 Hz, 1H), 9.64 (d, J = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 17.0, 20.7, 26.9, 28.1, 57.8 (dd, J = 23.6 and 29.0 Hz), 80.3, 120.1 (t, J = 246.0 Hz), 133.9 (t, J = 7.4 Hz), 145.0 (t, J = 26.6 Hz), 155.6, 191.9. HRMS (ESI) *m*/*z*: (M + H^+) calcd for $C_{13}H_{22}F_2NO_3$, 278.1568; found, 278.1556. Anal. Calcd for $C_{13}H_{21}F_2NO_3$: C, 56.31; H, 7.63; N, 5.05. Found: C, 56.07; H, 7.63; N, 5.05.

Compound **30a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.96 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 7.2 Hz, 3H), 1.42 (s, 9H), 2.16−2.24 (m, 1H), 3.94 (dquint, J = 2.0 and 8.8 Hz, 1H), 4.78 (d, J = 10.4 Hz, 1H), 6.21 (dd, J = 11.0 and 13.6 Hz, 1H), 6.29 (dd, J = 7.6 and 15.6 Hz, 1H), 6.78 (t, J = 13.2 Hz, 1H), 7.11 (dd, J = 11.2 and 15.2 Hz, 1H), 9.62 (d, J = 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 16.8, 20.6, 27.0, 28.1, 58.0 (dd, J = 23.2 and 29.4 Hz), 79.9, 120.1 (t, J = 244.2 Hz), 131.5 (t, J = 9.3 Hz), 134.4 (t, J = 25.7 Hz), 134.8, 148.2, 155.7, 193.0. HRMS (ESI) *m*/*z*: (M + Na^+) calcd for $C_{15}H_{23}F_2NO_3Na$, 326.1544; found, 326.1536.

(5*S*,2*E*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4,4-difluoro-6-phenylhex-2-enal (20b). By the use of procedures similar to those employed for the preparation of enal **20a**, ester **29b** (500 mg, 1.45 mmol) was converted into the title compound **20b** (285 mg, 60% yield) and **30b** (48.5 mg, 19% yield). Compound **20b**: colorless crystal, mp 93−95 °C (recrystallized from EtOAc−*n*-hexane). $[\alpha]_D^{26}$ + 32.9 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.27 (s, 9H), 2.74 (dd, J = 11.2 and 14.4 Hz, 1H), 3.23 (d, J = 14.4 Hz, 1H), 4.37 (br s, 1H), 4.53 (d, J = 8.5 Hz, 1H), 6.51 (dd, J = 7.0 and 15.6 Hz, 1H), 6.71 (ddd, J = 9.6, 13.6, and 15.6 Hz, 1H), 7.20−7.33 (m, 5H), 9.62 (d, J = 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 28.0, 33.8, 55.2 (dd, J = 24.8 and 30.3 Hz), 80.3, 119.5 (t, J = 244.5 Hz), 126.8, 128.5, 129.1, 134.3 (t, J = 7.4 Hz), 136.0, 144.2 (t, J = 26.6 Hz), 156.3, 191.9. HRMS (ESI) *m*/*z*: (M + H^+) calcd for $C_{17}H_{22}F_2NO_3$, 326.1568; found, 326.1566. Anal. Calcd for $C_{17}H_{21}F_2NO_3$: C, 62.76; H, 6.51; N, 4.31. Found: C, 62.87; H, 6.56; N, 4.22.

Compound **30b** (mixture of diastereomers at diene position, 10:1): white powder. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.21 (s, 9H: major isomer), 1.34 (s, 9H: minor isomer), 2.70 (dd, J = 11.2 and 14.0 Hz, 1H), 3.17−3.32 (1H), 4.13 (br, 1H), 4.53 (d, J = 8.8 Hz, 1H), 5.98−6.33 (2H), 6.81 (t, J = 13.2 Hz, 1H: major isomer),

6.91 (t, J = 12.4 Hz, 1H: minor isomer), 7.08 (dd, J = 10.8 and 15.2 Hz, 1H: major isomer), 7.20−7.32 (m, 5H), 7.50−7.54 (m, 1H: minor isomer), 9.62 (d, J = 7.2 Hz, 1H: major isomer), 10.22 (d, J = 7.6 Hz, 1H: minor isomer). HRMS (ESI) m/z: ($M + Na^+$) calcd for $C_{19}H_{23}F_2NO_3Na$, 374.1544; found, 374.1558.

NHC-Mediated Synthesis of FADIs Using α,β-Enal at 70 °C in Toluene (Table 1, entry 3). To a suspension of NHC-precursor **1a** (12.2 mg, 0.054 mmol) in toluene (0.5 mL) was added DIPEA (9.4 μL, 0.054 mmol) at room temperature under argon. After 15 min of stirring, a mixture of **20a** (50 mg, 0.18 mmol) and EtOH (53 μL, 0.90 mmol) in toluene (0.5 mL) was added to the above mixture. The reaction mixture was stirred at 70 °C until the starting material was completely consumed. The reaction was quenched with NH_4Cl(aq) and extracted with Et_2O. The extract was washed with 1 M HCl, $NaHCO_3$(aq), and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:8) gave the FADI **16a** (12% yield) and a mixture of **31a** and **32a** (23% combined yield) with spectroscopic data identical to those reported in literature.[14d] Compound **16a** is an enantiomer of authentic sample ($[\alpha]_D^{21}$ − 31.0 (*c* 1.02, $CHCl_3$)). Compound **16a**: $[\alpha]_D^{25}$ 25.8 (*c* 1.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.94 (d, J = 3.2 Hz, 3H), 0.96 (d, J = 3.2 Hz, 3H), 1.45 (s, 9H), 1.26 (t, J = 6.8 Hz, 3H), 1.90 (sext, J = 6.8 Hz, 1H), 3.10 (dd, J = 7.4 and 17.4 Hz, 1H), 3.16 (dd, J = 7.4 and 17.4 Hz, 1H), 3.99 (dt, J = 8.2 and 19.2 Hz, 1H), 4.14 (t, J = 6.8 Hz, 2H), 4.72 (d, J = 8.2 Hz, 1H), 4.98 (dt, J = 7.2 and 36.8 Hz, 1H). HRMS (ESI) m/z: ($M + Na^+$) calcd for $C_{15}H_{26}FNNaO_4$, 326.1744; found, 326.1746.

Experimental procedures similar to those employed in entry 3 were used for entries 1 and 2 (reaction temperature: room temperature) and entry 4 (substrate, **20b**; base, DBU; reaction temperature, 70 °C). In entries 1 and 2, the ratio of compounds included in the crude materials was determined by NMR measurement in comparison with NMR data of authentic samples. In entry 4, **16b**, a mixture of **31b** and **32b**, and **20a** (starting material) were purified by column chromatography over silica gel with EtOAc−*n*-hexane. Obtained materials showed spectroscopic data identical to those of authentic samples.[14d]

NHC-Mediated Synthesis of FADIs Using α,β-Enal at 70 °C in EtOH (Table 1, entries 5 and 6). To a solution of the NHC precursor (**1a** or **1b**, 0.034 mmol) in EtOH (0.5 mL) was added DIPEA (5.9 μL, 0.034 mmol) at room temperature under argon with additional stirring at this temperature for 15 min. To the resulting mixture was added a solution of α,β-enal (**20a** or **20b** to the **1a** or **1b** mixture, respectively, 0.114 mmol) in EtOH (0.5 mL) at room temperature. The reaction mixture was stirred at 70 °C until the starting material (**20a** or **20b**) was completely consumed. The reaction was quenched with NH_4Cl(aq) and extracted with Et_2O. The extract was washed with 1 M HCl, $NaHCO_3$(aq), and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:8) gave the FADIs (**16a**, 66% yield; **16b**, 70% yield).

(5*R*,2*E*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4,4-difluoro-6-methylhept-2-enoylsilane (34a). To a solution of ester **29a** (1.0 g, 3.4 mmol) in CH_2Cl_2 (9.0 mL) was added dropwise a solution of DIBAL-H in toluene (0.99 M, 6.84 mL, 6.77 mmol) at −78 °C under argon, and the mixture was stirred for 15 min at this temperature. The reaction was quenched with saturated citric acid and extracted with Et_2O. The extract was washed with saturated citric acid and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily aldehyde, which was used immediately in the next step without further purification. To a mixture of LiCl (201 mg, 4.75 mmol), $(MeO)_2P(O)CH_2COTBS$[24] (1.26 g, 4.75 mmol), and DIPEA (827 μL, 4.75 mmol) in MeCN (5.0 mL) was added the resulting aldehyde in MeCN (4.0 mL) under argon at 0 °C. After being stirred at room temperature for 4 h, the reaction was quenched with NH_4Cl(aq) and extracted with Et_2O. The extract was washed with 0.5 M HCl and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:20) gave the title compound **34a** (1.10 g, 83% yield) as yellow crystals with a mp of 67−68 °C. $[\alpha]_D^{25}$ + 8.3 (*c* 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.24 (s, 3H), 0.26 (s, 3H), 0.92−0.94 (m, 12H), 0.99 (d, J = 6.8 Hz, 3H), 1.43 (s, 9H), 2.10−2.20 (m, 1H), 3.96 (dquint, J = 3.2 and 10.4 Hz, 1H), 4.68 (d, J = 10.4 Hz, 1H), 6.39 (dt, J = 11.6 and 15.6 Hz, 1H), 6.75 (d, J = 15.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): −6.6, 16.7, 20.7, 26.4, 27.4, 28.2, 58.2 (dd, J = 24.2 and 27.2 Hz), 80.1, 120.7 (t, J = 243.9 Hz), 132.8 (t, J = 28.0 Hz), 135.5 (t, J = 6.5 Hz), 155.7, 235.6. HRMS (ESI) m/z: ($M + H^+$) calcd for $C_{19}H_{36}F_2NO_3Si$, 392.2433; found, 392.2420.

(5*S*,2*E*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4,4-difluoro-6-phenylhex-2-enoylsilane (34b). By the use of procedures similar to those described for the preparation of enoylsilane **34a**, ester **29b** (500 mg, 1.45 mmol) was converted into the title compound **34b** (540 mg, 84% yield) as yellow powder with a mp of 41−44 °C. $[\alpha]_D^{26}$ + 20.3 (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.24 (s, 3H), 0.25 (s, 3H), 0.93 (s, 9H), 1.26 (s, 9H), 2.67 (dd, J = 11.2 and 14.0 Hz, 1H), 3.20 (d, J = 14.0 Hz, 1H), 4.35 (br s, 1H), 4.52 (d, J = 10.4 Hz, 1H), 6.44 (dt, J = 12.0 and 16.0 Hz, 1H), 6.71 (d, J = 16.0 Hz, 1H), 7.20−7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): −6.5, 16.7, 26.4, 28.1, 34.4, 55.4 (dd, J = 24.7 and 30.3 Hz), 80.1, 120.1 (t, J = 243.7 Hz), 126.7, 128.5, 129.2, 132.4 (t, J = 26.6 Hz), 136.2, 154.9, 235.7. HRMS (ESI) m/z: ($M + H^+$) calcd for $C_{23}H_{36}F_2NO_3Si$, 440.2433; found, 440.2432; Anal. Calcd for $C_{23}H_{35}F_2NO_3Si$: C, 62.84; H, 8.02; N, 3.19. Found: C, 62.73; H, 7.96; N, 3.22.

NHC-Mediated Synthesis of FADIs Using α,β-Enoylsilanes in THF (Table 2, entries 1−3). To a white suspension of the NHC precursor **1b** (9.2 mg, 0.034 mmol) in THF (0.5 mL) was added DBU (5.1 μL, 0.034 mmol) at room temperature under argon. A reddish orange suspension was immediately formed. After 15 min of stirring, a solution of α,β-enoylsilane **34a** or **34b** (0.11 mmol) in THF (0.5 mL) and EtOH (66 μL, 1.13 mmol) was added to the above mixture. After being stirred at room temperature for 24 h or at 70 °C for 3 h, the reaction was quenched with NH_4Cl(aq) and extracted with Et_2O. The extract was washed with 1 M HCl, $NaHCO_3$(aq), and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:8) gave the FADIs (entry 1, **16a**, 37%; entry 2, **16a**, 53%; entry 3, **16b**, 41%).

NHC-Mediated Synthesis of FADIs Using α,β-Enoylsilanes in EtOH (Table 2, entries 4−6). To a colorless solution of the NHC precursor **1b** (9.2 mg, 0.034 mmol) in EtOH (0.5 mL) was added DBU (5.1 μL, 0.034 mmol) at room temperature under argon. A yellow solution was immediately formed with additional stirring at this temperature for 15 min. To the resulting yellow solution was added a solution of α,β-enoylsilane **34a** or **34b** (0.11 mmol) in EtOH (0.5 mL). After being stirred at room temperature for 24 h or at 70 °C for 2−3 h, the reaction was quenched with NH_4Cl(aq) and extracted with Et_2O. The extract was washed with 1 M HCl, $NaHCO_3$(aq), and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:8) gave the FADIs (entry 3, **16a**, 37% and **34a**, 45%; entry 2, **16a**, 81%; entry 3, **16b**, 91%).

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **16a**, **20a**, **20b**, **30a**, **30b**, **34a**, and **34b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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