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Novel Synthesis of (*Z*)-Difluoroacrylates via a Highly Stereoselective Addition–Elimination Reaction

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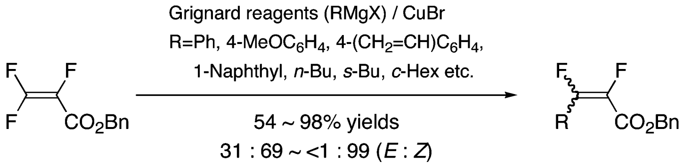
ABSTRACT



On treating readily prepared benzyl 2,3,3-trifluoroacrylate with various Grignard reagents, e.g., aryl-, alkyl-, or alkenylmagnesium halide, in the presence of a catalytic amount of copper(I) salt in THF at −78 °C for 1 h, the corresponding α,*β*-difluoroacrylates were obtained in 54–98% yields with high *Z*-selectivity.

α,*β*-Unsaturated carbonyl compounds occupy a central position in organic synthesis owing to their wide utility as potent synthetic blocks, particularly as Michael acceptors for conjugate addition reactions[1] or dienophiles and dipolarophiles for cycloaddition reactions.[2−4] Fluorinated acrylates and their derivatives are likewise of great synthetic value as building blocks for constructing various sorts of fluorine-containing compounds,[5] which attract much attention in biological and materials chemistry.[6]

Therefore, it is a very significant subject to develop a convenient and effective route to such fluorinated acrylates and related compounds.[7] Out of such compounds, α,*β*-difluoro-α,*β*-unsaturated esters[8] have been recognized to be very useful synthetic intermediates. Several examples of the *E*-selective synthesis[9] of such *vic*-difluorinated carbonyl compounds has appeared in the literature, while the *Z*-selective synthesis of them has not been realized at all. We wish to disclose the highly *Z*-selective synthesis of α,*β*-difluoroacrylates **2** based on the addition−elimination reaction of 2,3,3-trifluoroacrylate (**1**) with organocopper reagents.

The starting ester, benzyl 2,3,3-trifluoroacrylate (**1**), was readily prepared in two steps as shown in Scheme 1.[10]

On treating 2-bromo-2,3,3,3-tetrafluoropropanoyl chloride with benzyl alcohol in the presence of Et_3N in Et_2O at room temperature for 20 h, the corresponding benzyl ester was obtained in 94% yield. Subsequent reductive dehalogena-

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[1] For selected reviews on the conjugate addition reactions, see: (a) Hayashi, T. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 13-21. (b) Jagnou, K.; Lautens, M. *Chem. Rev*. **2003**, *103*, 169−196. (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem*. **2002**, 3221−3236. (d) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3751−3771. (e) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061.

[2] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990.

[3] For selected reviews on the Diels−Alder reactions, see: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667. (b) Francesco, F.; Priana, P.; Ferdinando, P.; Luigi, V. *Eur. J. Org. Chem.* **2001**, 439−455.

[4] For reviews on the 1,3-dipolar cycloaddition reactions, see: (a) Kanemasa, S. *Synlett* **2002**, 1371−1387. (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Commun.* **2000**, 1449−1458. (c) Kanemasa, S. *Nippon Kagaku Kaishi* **2000**, 155−165.

[5] (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231. (b) Qiu, X.; Meng, W.; Qing, F. *Tetrahedron* **2004**, *60*, 6711−6745. (c) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16. (d) Ichikawa, J.; Wada, Y.; Fujiwara, M. Sakoda, K. *Synthesis* **2002**, 1917−1936. (e) Soloshonok, V. A. *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Wiley: New York, 1999. (f) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Kodansha: Tokyo, 1998.

[6] (a) O'Hagen, D.; Rzepa, H. S. *Chem. Commun*. **1997**, 645−652. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; Vol. 639. (c) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1993. (d) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley-Interscience: New York, 1991.

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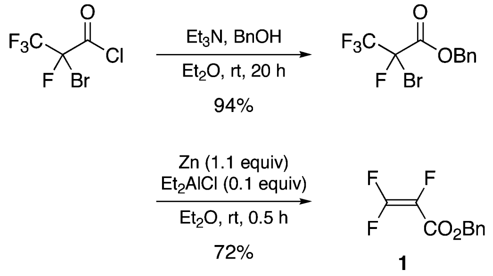
Scheme 1. Preparation of Starting Material **1**



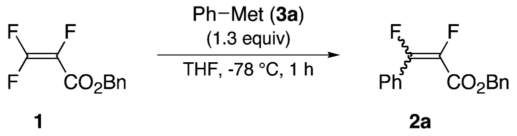
tion by zinc dust in the presence of a catalytic amount of Et$_2$AlCl provided benzyl 2,3,3-trifluoroacrylate (**1**) in 72% yield.

Initially, the reaction of **1** with organolithium reagent was investigated as shown in Table 1. Thus, treatment of **1** with 1.3 equiv of phenyllithium in THF at −78 °C for 1 h gave a complex mixture (entry 1). Even in the presence of CuBr (1.3−0.13 equiv), any trace of the desired product was not detected at all (entries 2−4). In sharp contrast, Grignard reagent was found to be a good nucleophile in the present reaction as described in entries 5−8.

Although the reaction without copper(I) salt did not lead to a satisfactory result (entry 5), the reaction in the presence of 1.3 equiv of CuBr proceeded smoothly to give the desired **2a** in 60% yield (entry 6). In this case, high Z selectivity was observed. Eventually, we found that the optimum yield and stereoselectivity[11] (94%, E/Z = 14/86) were achieved when 0.13 equiv of CuBr was employed (entry 8). No improvement of the yield and the stereoselectivity was observed in the reaction using 0.65 equiv of CuBr (entry 7).

Subsequently, we examined the reactions of **1** with various Grignard reagents (**3a**−**o**) in the presence of CuBr under the optimized conditions. The results are tabulated in Table 2. As shown in entry 2,4-methoxyphenylmagnesium bromide (**3b**) could also participate nicely in the reaction to afford the corresponding β-arylated product **2b** in a highly stereoselective manner. The position of a methoxy group on the aromatic ring exerted much effect on the efficiency of reaction. 2-Methoxyphenyl Grignard reagents (**3d**) gave no

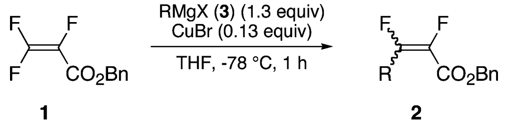
Table 1. Reaction of **1** with Organometallic Reagent **3a**



entry	Met	CuBr (equiv)	yield[a] (%) of **2a**	E/Z[a]
1	Li	none	complex mixture	
2[b]	Li	1.30	0	
3[c]	Li	0.65	0	
4	Li	0.13	complex mixture	
5	MgBr	none	5	43:57
6	MgBr	1.30	60	9:91
7	MgBr	0.65	62	12:88
8	MgBr	0.13	94 (90)	14:86

[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [b] The starting material **1** was recovered in 55% yield. [c] The starting material **1**was recovered in 42% yield.

Table 2. Reaction of **1** with Various Grignard Reagents in the Presence of a Catalytic Amount of CuBr



entry	R	yield[a] (%) of **2**	E/Z[a]	recovery[a] (%) of **1**
1	Ph (**a**)	94 (90)	14:86	0
2	4-MeOC$_6$H$_4$ (**b**)	93 (84)	16:84	0
3	3-MeOC$_6$H$_4$ (**c**)	38	11:89	36
4[b]	3-MeOC$_6$H$_4$ (**c**)	56 (55)	12:88	20
5	2-MeOC$_6$H$_4$ (**d**)	0		59
6	4-MeC$_6$H$_4$ (**e**)	70 (64)	11:89	0
7[b]	4-MeC$_6$H$_4$ (**e**)	97 (87)	14:86	0
8	4-(CH$_2$=CH)C$_6$H$_4$ (**f**)	51	9:91	47
9[b]	4-(CH$_2$=CH)C$_6$H$_4$ (**f**)	97 (89)	12:88	0
10	α-Naphthyl (**g**)	36	8:92	60
11[b]	β-Naphthyl (**g**)	74 (70)	5:95	16
12	β-Naphthyl (**h**)	46	12:88	53
13[b]	β-Naphthyl (**h**)	98 (90)	8:92	0
14	4-CF$_3$C$_6$H$_4$ (**i**)	6	16:84	91
15	n-Bu (**j**)	92 (77)	14:86	0
16[c]	Bn (**k**)	70	28:72	0
17[b,c]	Bn (**k**)	84 (80)	31:69	0
18	4-Pentenyl (**l**)	43	14:86	37
19[b]	4-Pentenyl (**l**)	82 (81)	6:94	0
20	*s*-Bu (**m**)	94 (87)	14:86	0
21	*c*-Hex (**n**)	91 (83)	9:91	0
22	β-Styryl (**o**)	22	<1:99	41
23[b]	β-Styryl (**o**)	85 (45)	4:96	0

[a] Determined by ^{19}F NMR. Values in parentheses are the isolated yield. [b] A large excess amount of organocopper reagent (RMgBr, 5.0 equiv; CuBr, 0.25 equiv) was used. [c] Benzylmagnesium chloride (**3k**) was employed as the Grignard reagent.

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(7) (a) Essers, M.; Muck-Lichtenfeld, C.; Haufe, G. *J. Org. Chem.* **2002**, *67*, 4715−4721. (b) Jiang, B.; Zhang, X.; Shi, G. *Tetrahedron Lett.* **2002**, *43*, 6819−6821. (c) Huang, X. H.; He, P. Y.; Shi, G. Q. *J. Org. Chem.* **2000**, *65*, 627−629. (d) Wakselman, C.; Molines, H.; Tordeux, M. *J. Fluorine Chem.* **2000**, *102*, 211−213. (e) Ito, H.; Saito, A.; Kakuuchi, A.; Taguchi, T. *Tetrahedron* **1999**, *55*, 12741−12750. (f) Ichikawa, J.; Yokota, N.; Kobayashi, M.; Minami, T. *Synlett* **1993**, 186−188. (g) Bumgardner, C. L.; Burgess, J. P.; Everett, T. S.; Purrington, S. T. *J. Fluorine Chem.* **1992**, *56*, 189−193. (h) Thenappan, A.; Burton, D. J. *J. Org. Chem.* **1990**, *55*, 4639−4642. (i) Krishnan, G.; Sampson, P. *Tetrahedron Lett.* **1990**, *31*, 5609−5612. (j) Archibald, T. G.; Baum, K. *J. Org. Chem.* **1990**, *55*, 3562−3565.

(8) (a) Zhang, Q.; Lu, L. *Tetrahedron Lett.* **2000**, *41*, 8545−8548. (b) McElroy, K. T.; Purrington, S. T.; Bumgerdner, C. L.; Burgess, J. P. *J. Fluorine Chem.* **1999**, *95*, 117−120. (c) Shi, G.; Cao, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 1969−1972. (d) Archibald, T. G.; Baum, K. *J. Org. Chem.* **1990**, *55*, 3562−3565.

(9) (a) Zhang, X.; Lu, L.; Burton, D. J. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1247−1261. (b) Zhang, Q.; Lu, L. *Tetrahedron Lett.* **2000**, *41*, 8545−8548. (c) Asato, A. E.; Liu, R. S. H. *Tetrahedron Lett.* **1986**, *27*, 3337−3340.

(10) Ishihara, T.; Noma, M.; Sato, K.; Konno, T.; Yamanaka, H. A new convenient and efficient entry to the preparation of α,β,β-trifluoroacrylates and their reaction with Grignard reagents in the presence of copper(I) salt. Presented at the 13th European Symposium on Fluorine Chemistry, Bordeaux, France, July 15−20, 2001, 1-P6.

(11) The stereochemistry of products was determined on the basis of a coupling constant $J_{\text{F-F}}$ (= 6.5 Hz).

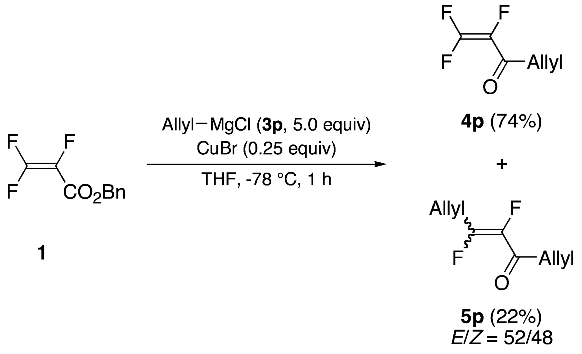
product **2d**, and 3-methoxyphenylmagnesium bromide (**3c**) provided the product **2c** in only 38% yield (entries 5 and 3, respectively). Tolyl- (**3e**), 4-vinylphenyl- (**3f**), and α- and *β*-naphthyl Grignard reagents (**3g** and **3h**) were found to be somewhat less reactive, the desired products being produced in 70%, 51%, 36%, and 46% yields, respectively (entries 6, 8, 10, and 12). The reaction with Grignard reagent bearing an electron-withdrawing group on the benzene ring, such as 4-(trifluoromethyl)phenylmagnesium bromide (**3i**), did not give a satisfactory result (entry 14). In the case of alkyl Grignard reagents such as *n*-Bu- (**3j**), *s*-Bu- (**3m**), and *c*-C_6H_{11}MgBr (**3n**), the corresponding *β*-alkylated difluoroacrylates **2j**, **2m**, and **2n** were obtained in 91−94% yields with high *Z*-selectivity (entries 15, 20, and 21). However, the reaction with benzyl (**3k**) or 4-pentenyl Grignard reagent (**3l**) led to a significant decrease of *Z*-selectivity or chemical yield (entries 16 and 18).

Additionally, the reaction with an alkenyl Grignard reagent, such as *β*-styrylmagnesium bromide (**3o**), gave the corresponding *β*-vinylated product **2o** only in 22% yield, together with a large recovery of the starting ester **1** (entry 22).

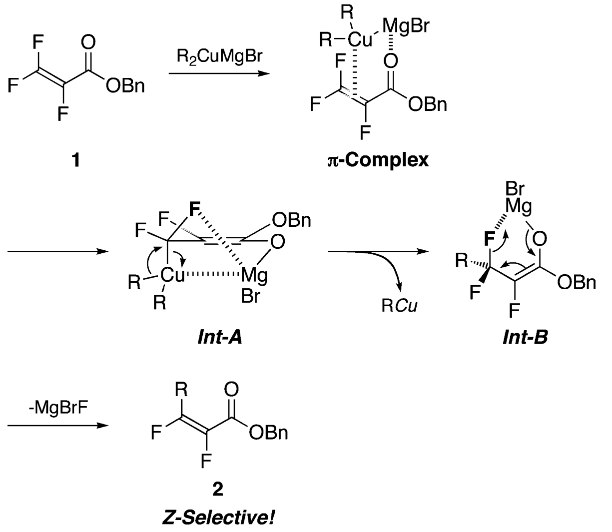
We further attempted to improve the chemical yield for the less effective Grignard reagents. Thus, the reaction of **1** was carried out by employing 5.0 equiv of Grignard reagent in the presence of 0.25 equiv of CuBr in THF at −78 °C for 1 h. Reactions with **3e−h**,**k**,**l**,**o** provided with good results, the corresponding products in 74−97% yields with high *Z*-selectivity.

Interestingly, when allylmagnesium chloride (**3p**) was employed as Grignard reagent, the 1,2-adduct **4p** and the 1,2- and 1,4-adduct **5p** were obtained in 74% and 22% yields, respectively (Scheme 2).

Scheme 2. Reaction of **1** with Allylmagnesium Chloride (**3p**) in the Presence of CuBr



Scheme 3. Plausible Reaction Mechanism



A plausible mechanism for the reaction of **1** with organocopper reagents is outlined in Scheme 3. The in situ generated copper reagent may make coordination with an olefinic double bond accompanying an interaction between the magnesium (Mg) and a carbonyl oxygen atom to form a *π*-complex. Subsequent oxidative addition of the copper species into **1** leads to an enolate-like intermediate (**Int-A**), which will be in a rigid conformation due to a double interaction of Mg with the copper and a fluorine atom.[12] Then, the reductive elimination of the copper species (R*Cu*) takes place to form **Int-B**, followed by simultaneous elimination of MgBrF, leading to the final product, (*Z*)-α,*β*-difluoroacrylate **2**.

In conclusion, we have demonstrated that the reaction of benzyl 2,3,3-trifluoroacrylate (**1**) with various Grignard reagents in the presence of a catalytic amount of CuBr proceeded effectively to provide the corresponding (*Z*)-α,*β*-difluoroacrylates **2** in good to excellent yields with high *Z*-selectivity. The present reaction will serve as the first efficient means for the *Z*-selective synthesis of α,*β*-difluoro-α,*β*-unsaturated esters.

Supporting Information Available: Characterization data and ^{1}H NMR and ^{13}C NMR spectra of **2a−2h**,**2j−2o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] For related reports on the interaction between metal and fluorine atom, see: (a) Yamazaki, T. *J. Synth. Org. Chem. Jpn*. **2004**, *62*, 911−918. (b) Ishihara, T. *J.* Synth. Org. Chem. Jpn. **1999**, *57*, 313−322. (c) Ooi, T.; Furuta, K.; Maruoka, K. *Chem. Lett.* **1998**, 817−818. (d) Ooi, T.; Kagoshima, N.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 7105−7108. (e) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754−5755. (f) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679−5682. (g) Yamazaki, T.; Kitazume, T. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 665−674. (h) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Org. Chem.* **1995**, *60*, 8140−8141. (i) Hanamoto, T.; Fuchikami, T. *J. Org. Chem.* **1990**, *55*, 4969−4971.