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Preparation and Addition−Elimination Reactions of Benzyl α,*β*,*β*-Trifluoroacrylate. A New Stereoselective Approach to (*Z*)-*β*-Substituted α,*β*-Difluoroacrylates

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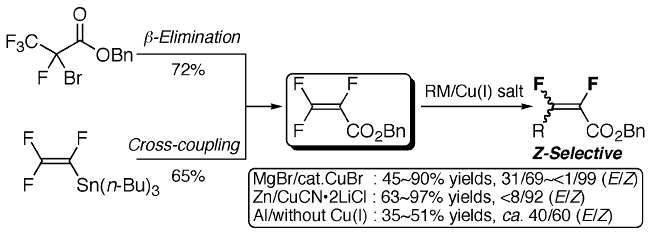

Benzyl α,*β*,*β*-trifluoroacrylate (**1**) was prepared in good yield via the reductive Br−F elimination of benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate or the palladium-catalyzed cross-coupling reaction of 1,2,2-trifluorovinylstannane with benzyl chloroformate. On treating **1** with various Grignard reagents or dialkylzinc reagents in the presence of copper(I) salt, the corresponding *β*-substituted α,*β*-difluoroacrylates were obtained in high yields with high *Z*-selectivity. Additionally, trialkylaluminum reagents were also found to be good nucleophiles, the corresponding addition−elimination products being afforded in good yields but with low stereoselectivity.

Introduction

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 such as α,*β*,*β*-trifluoroacrylates **1** and *β*-substituted α,*β*-difluoroacrylates **2** (Figure 1) 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]

1 **2**

FIGURE 1. Fluorinated acrylates.

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(1) For selected reviews on 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 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 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) For selected reports on transformation using fluorinated α,*β*-unsaturated carbonyl compounds as building blocks, see. (a) Wang, Y.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 3859−3862. (b) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 1109−1111. (c) Wang, Y.; Lu, L.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 10743−10746. (d) Crowley, P. J.; Fawcett, J.; Kariuki, B. M.; Moralee, A. C.; Percy, J. M.; Salafia, V. *Org. Lett.* **2002**, *4*, 4125−4128. (e) Essers, M.; Mück-Lichtenfeld, C.; Haufe, G. *J. Org. Chem.* **2002**, *67*, 4715−4721. (f) Ichikawa, J.; Wada, Y.; Fujiwara, M. Sakoda, K. *Synthesis* **2002**, 1917−1936. (g) Chanteau, F.; Essers, M.; Plantler-Royon, R.; Haufe, G.; Portella, R. *Tetrahedron Lett.* **2002**, *43*, 1677−1680. (h) Colmenares, L. U.; Zou, X.; Liu, J.; Asato, A. E.; Liu, R. S. H. *J. Am. Chem. Soc.* **1999**, *121*, 5803−5804. (i) Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J. Org. Chem.* **1996**, *61*, 2763−2769.

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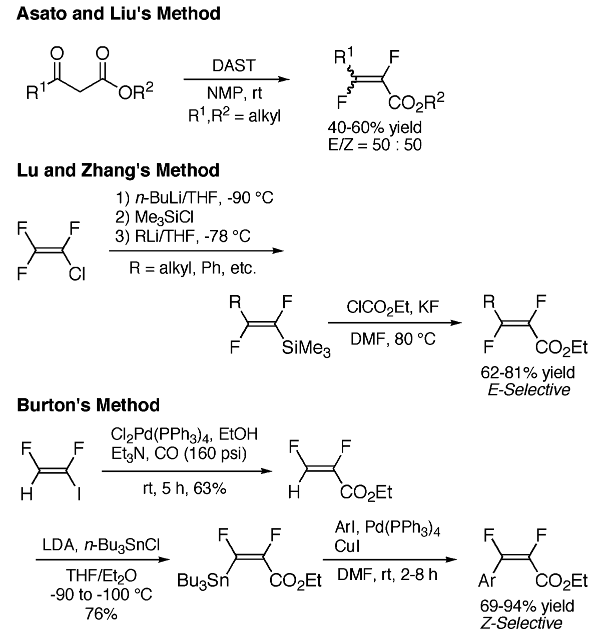
Although the preparation of α,*β*,*β*-trifluoroacrylates **1** has already been achieved by several groups, most of the methods for the preparation suffer from the defects that multiple steps are required and/or the chemical yield of **1** is poor.[8] For instance, Wakselman et al. reported the preparation of **1** in five steps from 2,2,3,3-tetrafluoropropanol,[8c] which involved the bromination of 2,3,3-trifluoroallyl alcohol, prepared from 2,2,3,3-tetrafluoropropanol and methyllithium, followed by oxidation, esterification with MeOH, and reductive elimination, leading to methyl α,*β*,*β*-trifluoroacrylate (**1**) in 15% overall yield. Paleta et al. prepared 1-adamantyl α,*β*,*β*-trifluoroacrylate (**1**) from 1,2-dichlorodifluoroethene in four steps (29% overall yield).[8a]

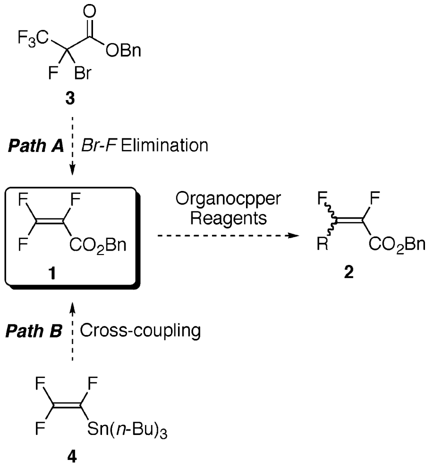
On the other hand, there have been found only a few examples for the preparation of *β*-substituted α,*β*-difluoroacrylates **2** in the literature.[9] Asato and Liu prepared **2** from *β*-keto esters using diethylaminosulfur trifluoride (DAST), the isomer ratios (*E*/*Z*) of **2** being almost 50:50.[9i] Lu and Zhang also reported that (*E*)-**2** was prepared by the coupling reaction of (*E*)-2-alkyl-1,2-difluorovinylsilane with ethyl chloroformate in the presence of KF.[9e] Recently, Burton et al. achieved the preparation of (*Z*)-*β*-stannyl-α,*β*-difluoroacrylates and subsequent palladium-catalyzed cross-coupling reaction with aryl iodides, which led to (*Z*)-*β*-aryl-α,*β*-difluoroacrylates **2**.[9a−c] This method, to our knowledge, is only one example for the *Z*-selective preparation of *β*-substituted α,*β*-difluoroacrylates (Scheme 1).

Herein are described convenient synthetic approaches to **1** via the reductive Br−F elimination of 2-bromo-2,3,3,3-tetrafluoropropanoate (**3**) (path A) or via the palladium-catalyzed cross-coupling reaction of 1,2,2-trifluorovinylstannane (**4**) with chloroformate (path B). In addition, are disclosed the stereoselective addition−elimination reactions of **1** with organocopper reagents derived from Grignard,[10] dialkylzinc, or trialkylaluminum reagents, leading to (*Z*)-*β*-substituted α,*β*-difluoroacrylates **2** (Scheme 2).

SCHEME 1. Reported Preparations of α,*β*-Difluoroacrylates 2



SCHEME 2. Synthetic Apparoaches to 1 and Addition−Elimination Reaction with Organocopper Reagents



Results and Discussion

Preparation of 1 via Path A. As a route to the desired trifluoroacrylate **1**, the reductive Br−F elimination of benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate (**3**) was initially studied, which could easily be prepared from the corresponding commercially available acid chloride. The results are summarized in Table 1. Thus, treatment of **3** with 1.1 equiv of zinc dust in Et_2O at room temperature for 0.5 h did not provide the desired *β*-elimination product **1** at all (entry 1). However, the addition of Et_2AlCl (1.3 equiv) as Lewis acid allowed the expected *β*-elimination reaction to proceed efficiently, producing the desired product **1** in 72% yield (entry 2). Various solvents, such as DME (1,2-dimethoxyethane), THF, C_6H_6, and DMF, were examined. The reaction in DME proceeded effectively to give **1** in 72% yield together with the α-reduction product **3-*H*** in

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(6) For selected reports on applications of organofluorine compounds, see: (a) Bégué, J. -P.; Bonnet-Delpon, D. *J. Fluorine Chem*. **2006**, *127*, 992−1012. (b) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem*. **2006**, *127*, 303−319. (c) Morimoto, K.; Irie, M. *Chem. Commun*. **2005**, 3895−3905. (d) Miethchen, R. *J. Fluorine Chem*. **2004**, *125*, 895−901. (e) Poss, A.; Nalowajok, D.; Demmin, T. R.; Nair, H. K. PCT Int. Appl. WO 2003073169, 2003. (f) Hatakeyama, J.; Watanabe, J.; Harada, Y. U.S. Patent Appl. Publ. 2001010890, 2001. (g) Hatakeyama, J.; Watanabe, A.; Harada, Y. Japanese Patent JP2001-226432A, 2001.

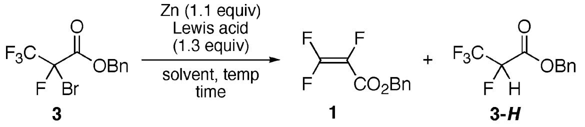
(7) (a) Essers, M.; Muck-Lichtenfeld, C.; Haufe, G. *J. Org. Chem*. **2002**, *67*, 4715−4721. (b) Jiang, B.; Zhang, X.; Shi, G. *Tetrahedron Lett.* **2002**, *43*, 6819−6821. (c) Huang, X. H.; He, P. Y.; Shi, G. Q. *J. Org. Chem*. **2000**, *65*, 627−629. (d) Wakselman, C.; Molines, H.; Tordeux, M. *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) Paleta, O.; Stepan, L *J. Fluorine Chem*. **1990**, *47*, 435−440. (b) Peter, B.; Klaus, H.; Werner, S.; Dieter, U. US Patent US 4835305, 1989. (c) Wakselman, C.; Nguyen, T.; Molines, H. PCT Int. Appl. WO 8911470, 1989. (d) Molines, H.; Wakselman, C. *J. Fluorine Chem*. **1984**, *25*, 447−451.

(9) (a) Wang, Y.; Burton, D. J. *J. Org. Chem*. **2006**, *71*, 3859−3862. (b) Wang, Y.; Burton, D. J. *Org. Lett.* **2006**, *8*, 1109−1111. (c) Wang, Y.; Lu, L.; Burton, D. J. *J. Org. Chem*. **2005**, *70*, 10743−10746. (d) Zhang, X.; Lu, L.; Burton, D. J. *Collect. Czech. Chem. Commun*. **2002**, *67*, 1247−1261. (e) Zhang, Q.; Lu, L. *Tetrahedron Lett.* **2000**, *41*, 8545−8548. (f) McElroy, K. T.; Purrington, S. T.; Bumgerdner, C. L.; Burgess, J. P. *J. Fluorine Chem*. **1999**, *95*, 117−120. (g) Shi, G.; Cao, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 1969−1972. (h) Archibald, T. G.; Baum, K. *J. Org. Chem*. **1990**, *55*, 3562−3565. (i) Asato, A. E.; Liu, R. S. H. *Tetrahedron Lett.* **1986**, *27*, 3337−3340.

(10) Yamada, S.; Noma, M.; Konno, T.; Ishihara, T.; Yamanaka, H. *Org. Lett.* **2006**, *8*, 843−845.

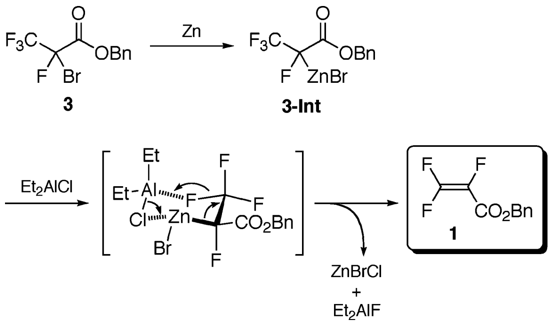
TABLE 1. Br−F Elimination of Benzyl Ester 3 with Zinc Dust



entry	solvent	Lewis acid	T (°C)	time (h)	yield[a] (%) of **1**	yield[a] (%) of **3-*H***	recovery[a] (%) of **3**
1	Et_2O	none	rt	0.5	0	31	57
2	Et_2O	Et_2AlCl	rt	0.5	72	8	0
3	DME	Et_2AlCl	rt	0.5	72	17	trace
4	THF	Et_2AlCl	rt	0.5	47	42	0
5	C_6H_6	Et_2AlCl	rt	0.5	0	46	19
6	DMF	Et_2AlCl	rt	0.5	0	97	0
7	Et_2O	Et_3Al	rt	0.5	70	28	0
8	Et_2O	Et_2Zn	rt	0.5	63	3	0
9	Et_2O	$BF_3{\cdot}OEt_2$	rt	0.5	0	35	59
10	Et_2O	Et_2AlCl	−20	0.5	48	16	0
11	Et_2O	Et_2AlCl	0	0.5	56	15	0
12	Et_2O	Et_2AlCl	reflux	0.5	72	18	0
13	Et_2O	Et_2AlCl	rt	1.0	70	16	0
14[b]	Et_2O	Et_2AlCl	rt	0.5	72	4	0

[a] Determined by ^{19}F NMR. [b] The amount of Et_2AlCl was 0.1 equiv.

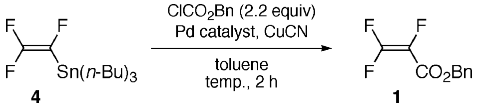
SCHEME 3. Possible Reaction Mechanism for the Et_2AlCl-Catalyzed Br−F Elimination of 3



17% yield, while the use of THF did not give a satisfactory result (entries 3 and 4). In the case of C_6H_6 or DMF, the β-elimination reaction did not take place at all, the α-reduction product **3-*H*** being afforded in 46% or 97% yields, respectively (entries 5 and 6). It was found, moreover, that triethylaluminum and diethylzinc were effective as Lewis acid but $BF_3{\cdot}OEt_2$ was not at all (entries 7−9). The reaction at room temperature or at reflux temperature gave a higher yield of **1** than did the reaction at 0 or −20 °C (entries 10 and 11). Eventually, treatment of **3** with 1.1 equiv of zinc dust in the presence of 0.1 equiv of Et_2AlCl as Lewis acid in Et_2O at room temperature for 0.5 h led to the best result, the acrylate **1** being obtained in 72% yield (entry 14).

A possible reaction mechanism for the Et_2AlCl-catalyzed Br−F elimination of the benzyl ester **3** is outlined in Scheme 3. Thus, 2-bromo-2,3,3,3-tetrafluoropropanoate **3** reacts with zinc dust to form an intermediary **3-Int**. This intermediate may undergo the Br−F elimination assisted with Et_2AlCl through a six-membered transition state, which would be facilitated by an interaction between Al and F.[11] Then, the elimination of ZnBrCl and Et_2AlF takes place simultaneously to lead to the desired product, benzyl α,β,β-trifluoroacrylate (**1**). The resulting Et_2AlF may act as Lewis acid catalyst.

TABLE 2. Cross-Coupling Reaction of 4 with Benzyl Chloroformate



entry	catalyst	mol % of Pd	equiv of CuCN	T (°C)	yield[a] (%) of **1**	recovery[a] (%) of **4**
1	$Cl_2Pd(PPh_3)_2$	5	1.1	rt	0	83
2	$Cl_2Pd(PPh_3)_2$	5	1.1	50	19	36
3	$Cl_2Pd(PPh_3)_2$	5	1.1	80	43	0
4	$Cl_2Pd(PPh_3)_2$	5	0.5	80	52	0
5	$Cl_2Pd(PPh_3)_2$	5	0.1	80	65 (51)	0
6	$Cl_2Pd(PPh_3)_2$	10	0.1	80	42	0
7	$Cl_2Pd(PPh_3)_2$	1	0.1	80	20	30
8[b]	$Cl_2Pd(PPh_3)_2$	5	0.1	reflux	17	0
9[c]	$Cl_2Pd(PPh_3)_2$	5	0.1	80	0	0
10[d]	$Cl_2Pd(PPh_3)_2$	5	0.1	80	22	0
11[e]	$Cl_2Pd(PPh_3)_2$	5	0.1	80	14	21
12	$Pd(OAc)_2$	5	0.1	80	0	42
13	$Cl_2Pd(PhCN)_2$	5	0.1	80	0	40
14	$Pd(PPh_3)_4$	5	0.1	80	16	0

[a] Determined by ^{19}F NMR. Value in parentheses is of the isolated yield. [b] THF was employed as the solvent. [c] DMF was employed as the solvent. [d] CuBr was used instead of CuCN. [e] CuI was used instead of CuCN.

Preparation of 1 via Path B. We next examined the palladium-catalyzed cross-coupling reaction of 1,2,2-trifluorovinylstannane (**4**)[12] with benzyl chloroformate for the preparation of **1**.[13] The results are collected in Table 2. Thus, the reaction of **4** with 2.2 equiv of benzyl chloroformate in the presence of 5 mol % of $Cl_2Pd(PPh_3)_2$ and 1.1 equiv of CuCN in toluene at room temperature for 2 h did not occur at all, the vinylstannane **4** being recovered in 83% yield (entry 1). As shown in entries 2−7, it was observed that the reaction temperature, the amount of copper(I) salt, and the palladium catalyst significantly affected the chemical yield of **1**. The best yield (51% isolated) was given when the reaction was performed in the presence of 5 mol % of $Cl_2Pd(PPh_3)_2$ and 0.1 equiv of CuCN in toluene at 80 °C for 2 h (entry 5). The reaction in THF at reflux temperature or in DMF at 80 °C was reluctant, the acrylate **1** being obtained in very low yield or not obtained at all (entries 8 and 9). Other copper(I) salts (CuBr and CuI) or palladium catalysts ($Pd(OAc)_2$, $Cl_2Pd(PhCN)_2$, and $Pd(PPh_3)_4$) were found to be ineffective for the coupling reaction (entries 10−14).

Reaction of 1 with Organocopper Reagents: Reaction of 1 with Organocopper Reagents Derived from Organolithium or Grignard Reagents.[10] We investigated the reaction of **1** with various organometallic reagents, particularly organocopper

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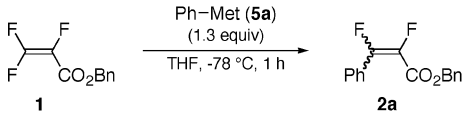
(11) For related reports on the interaction between metal and fluorine atom, see: (a) Yamazaki, T. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 911−918. (b) Ishihara, T. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 313−322. (c) Ooi, T.; Furuta, K.; Maruoka, K. *Chem. Lett.* **1998**, 817−818. (d) Ooi, 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.

(12) (a) Banger, K. K.; Brisdon, A. K.; Gupta, A. *Chem. Commun.* **1997**, 139−140. (b) Burdon, J.; Coe, P. L.; Haslock, I. B.; Powell, R. L. *J. Fluorine Chem.* **1999**, *99*, 127−131.

(13) For related reports on the cross-coupling reaction of fluorinated vinylstannane with chloroformates, see: (a) Arany, A.; Crowley, P. J.; Fawcett, J.; Hursthouse, M. B.; Kariuki, B. M.; Light, M. E.; Moralee, A. C.; Percy, J. M.; Salafia, V. *Org. Biomol. Chem.* **2004**, *2*, 455−465. (b) Jeong, I. H.; Park, Y. S.; Kim, M. S.; Song, Y. S. *J. Fluorine Chem.* **2003**, *120*, 195−209.

TABLE 3. Reaction of 1 with PhLi or PhMgBr in the Absence or Presence of CuBr



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

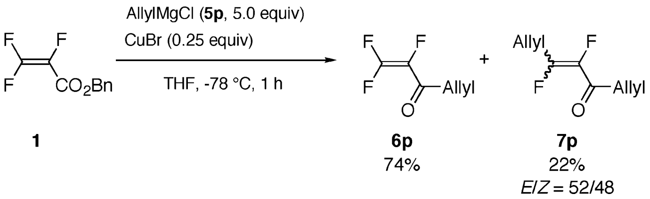
[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield. [b] The starting acrylate **1** was recovered in 55% yield. [c] The starting acrylate **1** was recovered in 42% yield.

reagents, in detail. The results are summarized in Table 3. Thus, the reaction of **1** with 1.3 equiv of phenyllithium in THF at −78 °C for 1 h led to a complex mixture (entry 1). Even addition of CuBr (1.3−0.13 equiv) did not improve the reaction at all (entries 2−4). In entries 5−8, the reactions with phenylmagnesium bromide in the absence or presence of CuBr were conducted. Although the reaction without copper(I) salt did not give a satisfactory result (entry 5), the reaction in the presence of 1.3 equiv of CuBr proceeded smoothly to give the β-substituted α,β-difluoroacrylate **2a** in 60% yield (entry 6).[14] Of much significance is that high *Z*-selectivity was observed in the reaction. Changing the amount of CuBr from 1.3 to 0.65 equiv did not affect the yield as well as the stereoselectivity (entry 7). However, the use of 0.13 equiv of CuBr led to a dramatic improvement in the reaction, **2a** being afforded in 94% (90% isolated) as an isolated yield with good *Z*-selectivity (entry 8).

Subsequently, we carried out addition−elimination reactions of **1** with various Grignard reagents (**5a**−**o**) in the presence of 0.13 equiv of CuBr. The results are tabulated in Table 4.

4-Methoxyphenylmagnesium bromide (**5b**) could participate nicely in the reaction to afford the corresponding β-arylated α,β-difluoroacrylate **2b** in a highly stereoselective manner (entry 2). However, 3-methoxyphenylmagnesium bromide (**5c**) provided the product **2c** in only 38% yield, and 2-methoxyphenylmagnesium bromide (**5d**) gave no arylated product **2d** (entries 3 and 5). Tolyl- (**5e**), 4-vinylphenyl- (**5f**), and α- and β-naphthylmagnesium bromide (**5g** and **5h**) were somewhat less efficient, the corresponding products being produced in 70% (64% isolated), 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 (**5i**), did not give a satisfactory result (entry 14). In the case of alkyl Grignard reagents, like *n*-Bu- (**5j**), *s*-Bu- (**5m**), and *c*-C_6H_{11}MgBr (**5n**), the corresponding β-alkylated α,β-difluoroacrylates **2j**, **2m**, and **2n** were obtained in 91−94% (77−87% isolated) yields with high *Z*-selectivity (entries 15, 20, and 21). The reaction with benzyl- (**5k**) or 4-pentenylmagnesium bromide (**5l**) resulted in a significant decrease of the *Z*-selectivity or chemical yield (entries 16 and 18). Additionally, the reaction with an alkenyl Grignard reagent, such as β-styrylmagnesium bromide (**5o**), gave the corresponding β-vinylated product **2o** in only 22% yield, together with a large recovery of the starting acrylate **1** (entry 22).

SCHEME 4. Reaction of 1 with Allylmagnesium Chloride (5p) in the Presence of a Catalytic Amount of CuBr



Further attempts were made to improve the chemical yield for the less efficient Grignard reagents **5c**,**e**−**h**,**k**,**l**,**o**. On conducting these reactions by use of 5.0 equiv of Grignard reagent in the presence of 0.25 equiv of CuBr in THF at −78 °C for 1 h, the corresponding products were given in 56−98% (55−90% isolated) yields with high *Z*-selectivity (entries 4, 7, 9, 11, 13, 17, 19, and 23).

When allylmagnesium chloride (**5p**) was employed as Grignard reagent, the 1,2-adduct **6p** and the 1,2:1,4-bis-adduct **7p** were obtained in 74% and 22% yields, respectively (Scheme 4).

Reaction of 1 with Organocopper Reagents Derived from Organozinc Reagents. We also examined the reaction of **1** with organocopper reagents derived from organozinc reagents. The results are summarized in Table 5.

The reaction of **1** with diethylzinc (**8q**) in the absence of a copper(I) salt in THF at −78 °C for 1 h did not proceed at all, no β-ethylated difluoroacrylate **2q** being detected (entry 1). Although various sorts of copper(I) salts, such as CuCl, CuBr, CuI, and CuCN, were used together with TMSCl,[15] the desired β-ethylated product **2q** was not formed at all (entries 2−5). However, when **1** was treated with **8q** in the presence of CuCN·2LiCl, prepared from CuCN and 2.0 equiv of LiCl, and TMSCl in THF at −78 °C for 1 h, the addition−elimination reaction took place smoothly to afford the corresponding difluoroacrylate **2q** in 80% yield with high *Z*-selectivity (*E*/*Z* = 6/94) (entry 6).[16] A more extended reaction time resulted in a slight increase in the conversion to **2q** (entry 7). As shown in entries 8 and 9, the reaction at higher temperature (−20 °C) or in the absence of TMSCl also proceeded smoothly to give the corresponding product **2q** in high yields, though the stereoselectivity slightly decreased.

Subsequently, the reactions of **1** with other commercially available dialkyl- or diarylzinc reagents, such as diisopropylzinc

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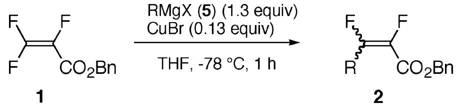
(14) For related reports on Michael addition reactions with organocopper reagents derived from Grignard reagents, see: (a) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Fluorine Chem.* **1999**, *97*, 91−96. (b) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025−4028. (c) Aguiar, A. M.; Irelan, J. R. S. *J. Org. Chem.* **1969**, *34*, 4030−4031. (d) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308−2316.

(15) For related reports on Michael addition reactions with organocopper reagents derived from organozinc reagents in the presence of TMSCl, see: (a) Nakamura, M.; Nakamura, E. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 632−644. (b) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390−2392. (c) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056−8066. (d) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368−3370.

(16) For related reports on the preparation of organocopper reagents by the treatment of organozinc reagents with CuCN·2LiCl, see: (a) Rozema, M. J.; AchyuthaRao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956−1958. (b) AchyuthaRao, S.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735−5741. (c) Ref. 15b.

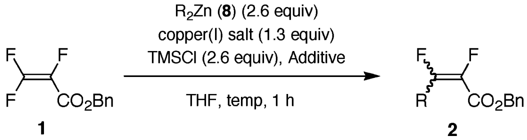
TABLE 4. Reaction of 1 with Various Grignard Reagents (5) in the Presence of a Catalytic Amount of CuBr



entry	R	yield[a] (%) of **2**	E/Z[a]	recovery[a] (%) of **1**	entry	R	yield[a] (%) of **2**	E/Z[a]	recovery[a] (%) of **1**
1	Ph (**a**)	94 (90)	14:86	0	12	β-naphthyl (**h**)	46	12:88	53
2	4-MeOC$_6$H$_4$ (**b**)	93 (84)	16:84	0	13[b]	β-naphthyl (**h**)	98 (90)	8:92	0
3	3-MeOC$_6$H$_4$ (**c**)	38	11:89	36	14	4-CF$_3$C$_6$H$_4$ (**i**)	6	16:84	91
4[b]	3-MeOC$_6$H$_4$ (**c**)	56 (55)	12:88	20	15	n-Bu (**j**)	92 (77)	14:86	0
5	2-MeOC$_6$H$_4$ (**d**)	0		59	16[c]	Bn (**k**)	70	28:72	0
6	4-MeC$_6$H$_4$ (**e**)	70 (64)	11:89	0	17[b,c]	Bn (**k**)	84 (80)	31:69	0
7[b]	4-MeC$_6$H$_4$ (**e**)	97 (87)	14:86	0	18	4-pentenyl (**l**)	43	14:86	37
8	4-(CH$_2$=CH)C$_6$H$_4$ (**f**)	51	9:91	47	19[b]	4-pentenyl (**l**)	82 (81)	6:94	0
9[b]	4-(CH$_2$=CH)C$_6$H$_4$ (**f**)	97 (89)	12:88	0	20	s-Bu (**m**)	94 (87)	14:86	0
10	α-Naphthyl (**g**)	36	8:92	60	21	c-Hex (**n**)	91 (83)	9:91	0
11[b]	α-Naphthyl (**g**)	74 (70)	5:95	16	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 of the isolated yield. [b] A large excess amount of organocopper reagent (RMgBr, 5.0 equiv; CuBr, 0.25 equiv) was used. [c] Benzylmagnesium chloride (**5k**) was employed as Grignard reagent.

TABLE 5. Reaction of 1 with Organocopper Reagents Derived from Dialkylzinc (8) and Copper(I) Salt



entry	R	copper(I) salt	additive	T (°C)	yield[a] (%) of **2**	E/Z[a]	recovery[a] (%) of **1**
1		none	none	−78	0		93
2		CuCl	none	−78	0		70
3		CuBr	none	−78	0		71
4		CuI	none	−78	0		78
5	Et (**q**)	CuCN	none	−78	0		quant
6[b]		CuCN	LiCl	−78	80	6:94	15
7[b,c]		CuCN	LiCl	−78	89 (63)	8:92	5
8[b]		CuCN	LiCl	−20	80	20:80	0
9[b,d]		CuCN	LiCl	−78	87	14:86	11
10[b,c]	i-Pr (**r**)	CuCN	LiCl	−78	98 (97)	2:98	0
11[b,c]	Me (**s**)	CuCN	LiCl	−78	0		89
12[b,c]	Ph (**a**)	CuCN	LiCl	−78	0		85

[a] Determined by ^{19}F NMR. Values in parentheses are of the isolated yield. [b] Two equiv of LiCl was employed based on CuCN. [c] Carried out for 2 h. [d] TMSCl was not employed.

(**8r**), dimethylzinc (**8s**), and diphenylzinc (**8a**), were conducted under the optimized reaction conditions (entry 7 in Table 5). Diisopropylzinc (**8r**) participated in the addition−elimination reaction to afford the corresponding β-isopropylated α,β-difluoroacrylate **2r** in excellent yield with high Z-selectivity (97% isolated; $E/Z = 2/98$) (entry 10). In the case of dimethylzinc (**8s**) or diphenylzinc (**8a**), the expected reaction did not occur at all, the starting acrylate **1** being recovered in 89% and 85% yields, respectively (entries 11 and 12). It was found that dialkylzinc reagents prepared in situ by literature methods[17] were not efficient for the reaction.

Reaction of 1 with Organoaluminum Reagents.[18] The reactions of **1** using organoaluminum reagents **9** were also examined, and the results are shown in Table 6.

As shown in entries 1 and 2, the reaction in THF or Et$_2$O at −78 °C for 2 h did not provide any trace of the β-ethylated difluoroacrylate **2q**, while the use of dichloromethane, toluene, and hexane as the solvent resulted in the formation of the addition−elimination product **2q** in 40%, 12%, and 57% yields, respectively (entries 3−5). In these cases, **2q** was obtained as a mixture of E/Z isomers (ca. 35/65). Raising the reaction temperature (−20 °C, 0 °C, and rt) was found to be very effective, giving rise to the corresponding product **2q** in 69−75% yields as a mixture of E/Z isomers (E/Z = 36/64 to 45/55)

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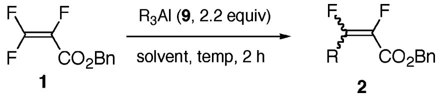
(17) For related reviews on the preparation of organozinc reagents, see: (a) Nakamura, E. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley & Sons: New York, 2002. (b) Knochel, P.; Millet, N.; Rodriguez, A. L. *Org. React.* **2001**, *58*, 417−731. (c) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8319. (d) Knochel, P.; Jones, P., Langer, F. In *A Practical Approach—Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1998. (e) Knochel, P. *Synlett* **1995**, 393−403. (g) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

(18) For related reports on Michael addition reactions with organoaluminum reagents without copper(I) salt, see: (a) Elzner, S.; Maas, S.; Engel, S.; Kunz, H. *Synthesis* **2004**, 2153−2164. (b) Carreño, M. C.; González, M. P.; Ribagorda, M.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 3687−3693. (c) Carreño, M. C.; González, M. P.; Ribagorda, M. *J. Org. Chem.* **1996**, *61*, 6758−6759. (d) Rück, K.; Kunz, H. *Synthesis* **1993**, 1018−1028. (e) Rück, K.; Kunz, H. *Synlett* **1992**, 343−344. (f) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4792−4797.

TABLE 6. Reaction of 1 with Trialkylaluminum Reagents



entry	R	Cu(I) salt	solvent	T (°C)	yield[a] (%) of **2**	E/Z[a]	recovery[a] (%) of **1**
1	Et (**q**)	none	THF	−78	0		82
2			Et_2O	−78	0		79
3			CH_2Cl_2	−78	40	35:65	56
4			toluene	−78	12	nd[b]	73
5			hexane	−78	57	35:65	39
6			hexane	−20	75 (51)	43:57	22
7			hexane	0	70	41:59	22
8			hexane	rt	69	36:64	18
9[c]			hexane	−20	75	40:60	19
10[d]		CuBr	hexane	−78	33	33:67	66
11[d]		CuI	hexane	−78	42	38:62	57
12[d]		CuCN	hexane	−78	55	44:56	45
13	Me (**s**)	none	hexane	−20	0		88
14	*i*-Bu (**t**)	none	hexane	−20	69 (35)	38:62	28
15	*n*-Oct (**u**)	none	hexane	−20	53 (43)	32:68	14

[a] Determined by ^{19}F NMR. Values in parentheses are of the isolated yields. [b] Not determined. [c] The amount of **9q** was 4.4 equiv. [d] The amount of Cu(I) salt was 1.1 equiv.

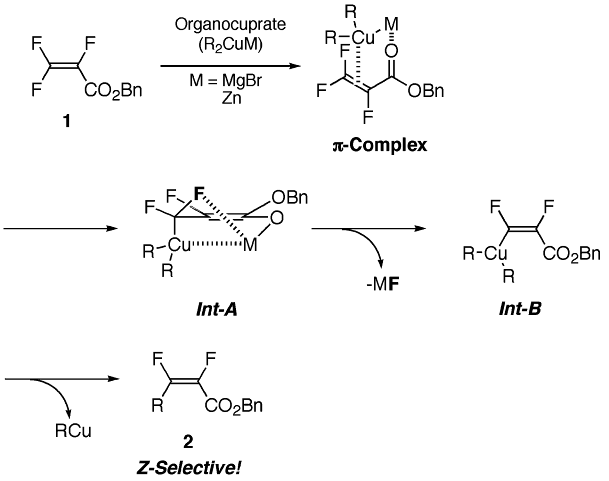
(entries 6−8). As shown in entry 9, the reaction with 4.4 equiv of **9q** in hexane at −20 °C for 2 h also proceeded smoothly to give the β-ethylated product **2q** in 75% yield (*E*/*Z* = 40/60). In entries 10−12, even when a copper(I) salt, like CuBr, CuI, and CuCN, was employed in the reaction, neither chemical yield nor *E*/*Z* isomer ratio was improved.[19]

The reactions of **1** with other commercially available trialkylaluminum reagents, such as trimethyl- (**9s**), triisobutyl- (**9t**), and tri-*n*-octylaluminum (**9u**), were carried out under the optimized reaction conditions (entry 6 in Table 6). The reaction with trimethylaluminum (**9s**) gave no β-methylated difluoroacrylate **2s** (entry 13). Triisobutyl (**9t**) or tri-*n*-octylaluminum reagents (**9u**) participated smoothly in the addition−elimination reaction, leading to the corresponding β-alkylated products **2t** and **2u** in 69% (35% isolated) and 53% (43% isolated) yields, respectively (entries 14 and 15).

Possible Reaction Mechanism. Scheme 5 depicts a possible reaction mechanism for the addition−elimination reaction of **1** with organocopper reagents derived from Grignard reagents or dialkylzinc reagents and copper(I) salts.

The in situ generated organocuprate[14,16,17g] may coordinate with an olefinic double bond, followed by an interaction between magnesium or zinc metal (M) and the carbonyl oxygen atom, to form a π-complex.[20] Subsequent oxidative addition of the copper species leads to an enolate-like intermediate **Int-A**, which will be in a rigid conformation due to a dual interaction of metal (M) with copper and fluorine atom.[11] Then, the elimination of MF takes place to form **Int-B**, followed by simultaneous reductive elimination of RCu, leading to the final product, (*Z*)-benzyl α,β-difluoroacrylate **2**.

SCHEME 5. Possible Reaction Mechanism



Conclusions

In conclusion, we have achieved an efficient and facile preparation of benzyl α,β,β-trifluoroacrylate (**1**) via Et_2AlCl-catalyzed reductive Br−F elimination of benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate **(3)** or via the palladium-catalyzed cross-coupling reaction of 1,2,2-trifluorovinylstannane **(4)** with benzyl chloroformate. The reaction of benzyl α,β,β-trifluoroacrylate **1** with various Grignard reagents **5** in the presence of a catalytic amount of CuBr gave the corresponding β-substituted benzyl α,β-difluoroacrylates **2** in good to excellent yields with high *Z* selectivity. Similarly, the acrylate **1** also reacted with commercially available dialkylzinc reagents **8** in the presence of CuCN·2LiCl, leading to (*Z*)-β-alkylated acrylates **2** in excellent yields in a *Z*-selective manner. Trialkylaluminum reagents **9** could also participate in the addition−elimination reaction to afford the corresponding β-alkylated products **2** as a mixture of the *E* and *Z* isomers in good yields.

Experimental Section

Typical Procedure for Reaction of 1 with Phenylmagnesium Bromide (5a) in the Presence of a Catalytic Amount of CuBr. A 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a thermometer, a rubber septum, and an inlet tube for argon was charged with a suspension of CuBr (0.009 g, 0.065 mmol) in THF (0.5 mL). To this suspension was slowly dropwise added a 0.85 M solution of phenylmagnesium bromide (**5a**, 0.76 mL, 0.65 mmol) in THF at −78 °C. To the resulting solution was slowly added 0.108 g (0.50 mmol) of **1** in THF (1.5 mL) via a syringe at −78 °C. After being stirred for 1 h at −78 °C, the reaction mixture was poured into ice-cooled water (50 mL), followed by extraction with Et_2O (30 mL × 5). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography of the residue using hexane/benzene (2:1) yielded benzyl 2,3-difluoro-3-phenylacrylate (**2a**, 0.123 g, 90%).

Benzyl 2,3-difluoro-3-phenyl-2-propenoate (2a). (*Z*)-**2a**: mp 60−61 °C; ^1H NMR ($CDCl_3$) δ 5.17 (s, 2H), 7.17−7.32 (m, 5H), 7.36−7.53 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 67.2, 128.0, 128.5, 129.3 (dd, J = 3.3, 3.3 Hz), 131.4, 134.5, 135.1, 137.2 (dd, J = 254.5,

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[19] For related reports on Michael addition reactions of organocopper reagents derived from trialkylaluminum, see: (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376−1378. (b) Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843−2845. (c) Polet, D.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 1529−1532. (d) Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* **1995**, *51*, 743−754. (e) Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Synlett* **1994**, 679−680. (f) Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron Lett.* **1994**, *35*, 8591−8594. (g) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178−3186.

[20] For related reports on π-complex between transition metal and polyfluorinated alkene, see: (a) Braun, T.; Noveski, D.; Neumann, B.; Stammler, H.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 2745−2748. (b) Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261−7265. (c) Siedle, A. R.; Newmark, R. A. *Organometallics* **1989**, *8*, 1442−1450.

21.9 Hz), 156.3 (dd, $J = 267.1, 16.4$ Hz), 160.2 (dd, $J = 29.4, 8.0$ Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −99.88 (d, $J = 6.6$ Hz, 1F), −148.73 (d, $J = 6.6$ Hz, 1F). (*E*)-**2a**: ^{1}H NMR ($CDCl_3$) δ 5.15 (s, 2H), 7.15−7.32 (m, 5H), 7.34−7.51 (m, 5H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −133.85 (d, $J = 127.6$ Hz, 1F), −162.16 (d, $J = 127.6$ Hz, 1F); IR (KBr) 3040, 1736, 1666, 1447, 1277, 1084, 968 cm^{-1}; HRMS (EI) calcd for (M^+) $C_{16}H_{12}F_2O_2$ 274.0805, found 274.0801. Anal.Calcd for $C_{16}H_{12}F_2O_2$: C, 70.07; H, 4.41. Found: C, 69.67; H, 4.27.

Supporting Information Available: General experimental procedures for the preparation of **1** and the reaction with various organocopper reagents, characterization data for new compounds (**1**, **2a**−**c**,**e**−**h**,**j**−**o**,**q**,**r**,**t**,**u**, **3**, and **4**), and copies of ^{1}H and ^{13}C NMR spectra for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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