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# $BF_3 \cdot Et_2O$-Induced Decomposition of Ethyl 2-Diazo-3-hydroxy-3,3-diarylpropanoates in Acetonitrile: A Novel Approach to 2,3-Diaryl $\beta$-Enamino Ester Derivatives

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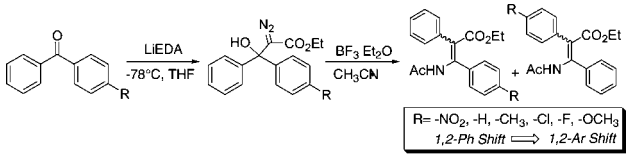


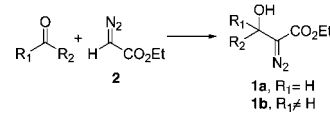

The $BF_3 \cdot Et_2O$-induced decomposition of ethyl 2-diazo-3-hydroxy-3,3-diarylpropanoates, prepared by the addition of a series of benzophenones to ethyl diazo(lithio)acetate, is reported and studied. By using acetonitrile as a solvent, the corresponding *N*-acyl $\beta$-enamino ester derivatives are obtained in good yields and with a diverse regioselectivity as the result of 1,2-aryl migration in the vinyl cation intermediates. The factors that govern the migratory aptitude as well as the mechanistic aspects of the reaction are discussed.

$\alpha$-Diazo-$\beta$-hydroxy esters of type **1a** and **1b** (Scheme 1) easily prepared by aldol-type condensation of ethyl diazoacetate (EDA, **2**) with an aldehyde or a ketone,[1] respectively, are versatile compounds endowed with a wealth of potential synthetic applications.[2]

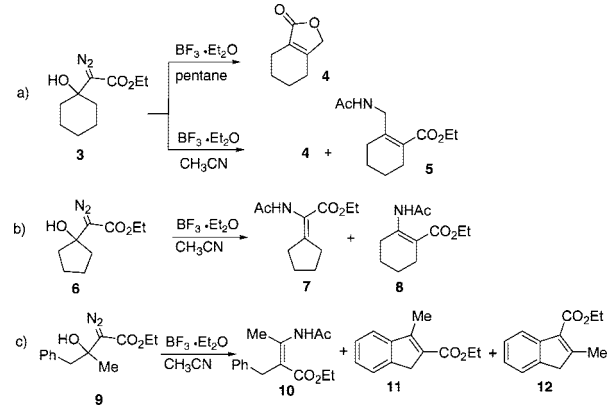
It has previously been reported,[1c,d,3] in particular, that when derivatives **1b** obtained from ketonic substrates, and therefore missing of the hydrogen atom $\alpha$ to the diazo moiety, are decomposed in the presence of stoichiometric amounts of boron trifluoride etherate ($BF_3 \cdot Et_2O$), they are transiently transformed by nitrogen loss into the corresponding vinyl cation intermediate which exhibits different transformation profiles according, mainly, to the solvent employed. Thus, exposure of **3**, prepared by reaction of cyclohexanone with ethyl diazo(lithio)acetate (LiEDA), to $BF_3 \cdot Et_2O$ (1.5 equiv) in pentane afforded lactone **4** in 75% yield, while ethyl 2-(acetamidomethyl)-1-cyclohexenecarboxylate (**5**) was the major product (38%), besides minor amounts of **4** (23%) when the same reaction was carried out in acetonitrile (Scheme 2a).[1d] Interestingly, the $BF_3 \cdot Et_2O$-catalyzed decomposition in acetonitrile of ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate (**6**) gave a different transformation profile. In this case, indeed, $\alpha$- and $\beta$-enamino ester derivatives **7** and **8** were found to be the only reaction products, in 55% and 6% yield, respectively (Scheme 2b).[1d] As a last example, when the acyclic $\beta$-diazo ester **9** was exposed to $BF_3 \cdot Et_2O$ in acetonitrile, the enamine **10** was obtained as the major product (53%), while indenes **11** and **12** were isolated in minor amounts (Scheme 2c).[1d]

The "$\alpha$-diazoesters/$BF_3 \cdot Et_2O$/acetonitrile route" to $\beta$-enamino ester derivatives, illustrated by the previous examples, is of great synthetic value because of the possibility to give access to biological active compounds[4] such as $\alpha$-[5] and $\beta$-amino acids,[6] alkaloids,[7] and peptides.[8] Although several approaches for the

**SCHEME 1. Synthesis of $\alpha$-Diazo-$\beta$-hydroxy Esters**




**SCHEME 2. $BF_3 \cdot Et_2O$-Induced Decomposition of Cyclic and Acyclic $\alpha$-Diazo-$\beta$-hydroxy Esters**

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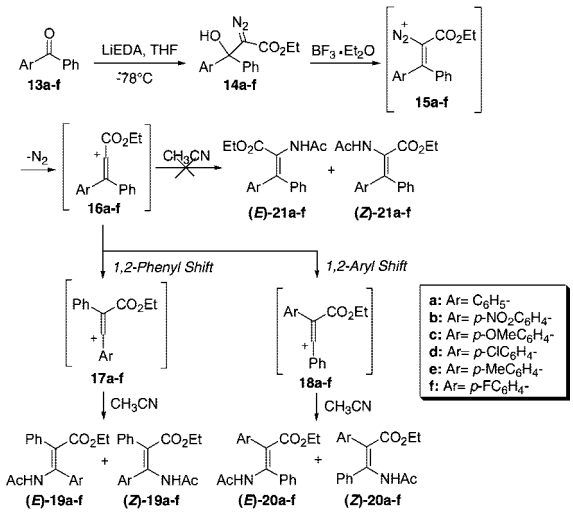
**SCHEME 3. Mechanism of the Formation of 3,3-Diaryl α-Enamino and 2,3-Diaryl β-Enamino Esters from Benzophenones**

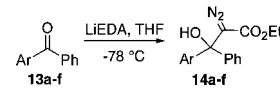



synthesis of these derivatives have been reported,[9] most of them suffer from limitations, and new, facile, and efficient methods for their preparation are therefore still required.

With this aim in mind and as a further extension of our study in the field, we have prepared a series of ethyl 2-diazo-3-hydroxy-3-aryl-3-phenylpropanoates (**14a**[10]**−f**), starting from the corresponding 4-substituted benzophenones (**13a−f**), and explored their $BF_3 \cdot Et_2O$-induced decomposition (Scheme 3). By using acetonitrile as a solvent, the corresponding β-enamino ester derivatives are the only products formed during the reaction as the result of 1,2-aryl or 1,2-phenyl migration in the corresponding vinyl cations **16a−f**. The factors that affect the vinyl rearrangement as well as the mechanistic aspects of the reaction are herein reported and discussed.

Ethyl 2-diazo-3-hydroxy-3-aryl-3-phenylpropanoates **14a−f** were prepared by adding the corresponding benzophenones **13a−f** to a THF solution of LiEDA salt at −78 °C (Table 1). After the addition completion, the reaction mixture was quenched at the same temperature with a THF solution of acetic acid followed by workup to furnish the desired compounds **14a−e** in good yields, except for the **14f** obtained in 37% yield (Table 1, educt f).

**TABLE 1. Synthesis of Ethyl 2-Diazo-3-hydroxy-3-aryl-3-phenylpropanoates 14a−f**




| educt | Ar | products | isolated yield[a] |
|---|---|---|---|
| **a** | $C_6H_5-$ | **14a**[10] | 82% |
| **b** | $p$-$NO_2C_6H_4-$ | **14b** | 60% |
| **c** | $p$-$OMeC_6H_4-$ | **14c** | 64% |
| **d** | $p$-$ClC_6H_4-$ | **14d** | 98% |
| **e** | $p$-$MeC_6H_4-$ | **14e** | 73% |
| **f** | $p$-$FC_6H_4-$ | **14f** | 37% |

[a] Calculated after purification by flash chromatography on silica gel.

**TABLE 2. $BF_3 \cdot Et_2O$-Induced Decomposition of Ethyl 2-Diazo-3-hydroxy-3-aryl-3-phenylpropanoates 14a−f**

| | | products ratio[a] | |
|---|---|---|---|
| educt | isolated yield | 1,2-Ph shift *E*-19:*Z*-19 | 1,2-Ar shift *E*-20:*Z*-20 |
| **13a** | 90% | 51:49 | |
| **13b** | 87% | 36:21 | 0:43 |
| **13c** | 90% | 6[b]:18 | 18[b]:58 |
| **13d** | 92% | 7:35 | 11:47 |
| **13e** | 97% | 19[b]:27[b] | 19[b]:35[b] |
| **13f** | 88% | 19:21 | 36:24 |

[a] Calculated after purification by flash chromatography on silica gel. [b] Obtained as an inseparable isomeric *E*- or *Z*-mixture (the relative ratios were calculated by $^1H$ NMR).

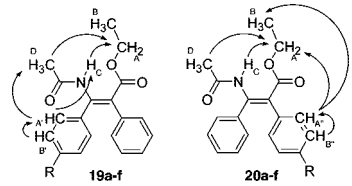
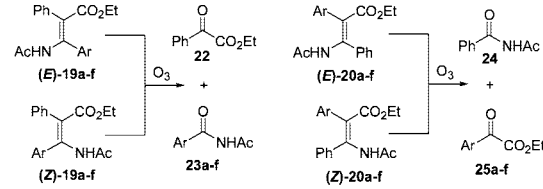



**FIGURE 1.** Diagnostic $^1H$ NMR NOE for **19a−f** and **20a−f**.

**SCHEME 4. Ozonolysis of the Products Resulting from 14a−f $BF_3 \cdot Et_2O$-Induced Decomposition Reaction**




The α-diazo-β-hydroxy esters **14a−f** thus obtained were dissolved in acetonitrile, and the resulting mixture was added dropwise at room temperature to a solution of freshly distilled $BF_3 \cdot Et_2O$ (1.5 equiv), affording the corresponding enamino esters arising from 1,2-phenyl- (**19a−f**) and 1,2-aryl-shifts (**20a−f**), respectively, in high yields (87−97%, Table 2).

The reaction products were identified by NMR and NOESY spectroscopy analysis: diagnostic $^1H$ NMR NOE enhancements were observed, indeed, between (i) $H_A-H_C$ and $H_B-H_D$ in *Z*-**19a−f** and *Z*-**20a−f**, (ii) $H_{A'}-H_D$ and $H_{A'}-H_C$ in *Z*-**19a−f**, and (iii) $H_{A'}-H_A$ and $H_{A''}-H_B$ in *Z*-**20a−f** (Figure 1).

To further confirm their structures, compounds **19a−f** and **20a−f** were submitted to ozonolysis affording the corresponding α-ketoesters **22** and **25a−f** as the sole products of reaction (Scheme 4), thus ruling out that the decomposition of ethyl 2-diazo-3-hydroxy-3-aryl-3-phenylpropanoates **14a−f** gives exclusively β-enamino acid derivatives.

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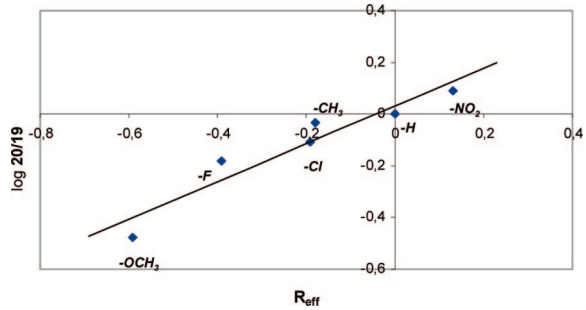
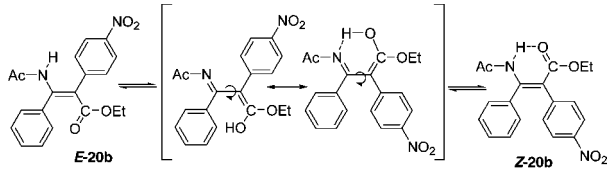



**FIGURE 2.** Plot of parametrized resonance effect ($R_{eff}$) versus log **20/19**.

**SCHEME 5. Isomerization of *E*-20b into *Z*-20b**




A deeper inspection of the results reported in Table 2 revealed that 1,2-phenyl and 1,2-aryl migration, which dominated over the solvent trapping, was influenced by the electronic effect imposed by the ring substituents. In particular, it is interesting to note that the presence of a *p*-$NO_2$ substituent (Table 2, educt **13b**) reduces the migratory aptitude of the aryl group, while a 1,2-aryl shift is favored with *p*-OMe, *p*-Cl, *p*-Me, and *p*-F substitution (Table 2, educt **13c**−**f**). To substantiate this electronic effect, the relative migratory aptitude of the aryl groups, indicated as the logarithm of the **20/19** ratio, was analyzed with their respective parametrized resonance effects ($R_{eff}$), inductive effects ($F$), and Hammett $\sigma$ values.[11] As shown in Figure 2, the data fit well to $R_{eff}$ ($r^2 = 0.91$), indicating that an aryl with electron-donating group (for mesomeric effect) is endowed with a higher tendency to migrate at the more electrophilic carbon, in agreement with the α-vinyl cation formation.[12] On the contrary, no correlation was observed either with the inductive effects ($F$) or with the Hammett $\sigma$ values (data not shown), thus ruling out that the resonance is the only electronic parameter which influences the aryl migration process.

The decomposition of the ethyl 2-diazo-3-hydroxy-3-phenyl-3-(4-nitro-phenyl)propanoate (**14b**) deserves an additional comment. Indeed, while the TLC and the $^1$H NMR of the crude reaction mixture showed the formation of four distinct products (two low polar and two more polar), unexpectedly, only derivatives *Z*-**19b**, *Z*-**20b**, and *E*-**19b** were recovered after purification. We supposed that 3-acetylamino-2-(4′-nitro-phenyl)-3-phenyl-acrylic acid ethyl ester (*E*-**20b**) underwent an acidic *trans*−*cis* isomerization, maybe induced by silica gel, as the result of a low inversion energy barrier and a strong push−pull system made more effective by the presence of an electron-withdrawing group (−$NO_2$) at the α-carbonyl position (Scheme 5).[13] A further energy contribution to the *trans*−*cis* inversion derives from the presence in the *Z*-form of a stabilizing intramolecular hydrogen bond between the carbonyl and the enamine group, absent in the corresponding *E*-isomers.

In conclusion, we reported the $BF_3 \cdot Et_2O$-induced decomposition reaction of a series of α-diazo-β-hydroxy esters prepared from the corresponding benzophenones. The reaction proceeds via 1,2-aryl or 1,2-phenyl migration of the α-aryl-α-phenylvinyl cation, a process which resulted in strong dependence on the electronic properties of the aryl substituents. We believe that this methodology may provide facile access to a variety of aryl substituted *N*-acyl β-enamino esters, useful building blocks for the synthesis of chiral β-amino acids as well as other biologically important compounds.

## Experimental Section

**General Procedure for the Synthesis of Ethyl 2-Diazo-3-hydroxy-3-aryl-3-phenylpropanoates 14a−f.** To a stirring solution of LDA [prepared from addition of *n*-BuLi (1.6 mmol) to a −78 °C solution of diisopropylamine (2 mmol) in THF (2.5 mL)] was added a cooled solution of EDA (**2**; 1.5 mmol) in dry THF (2.5 mL) at −78 °C in 15 min. After 10 min from the end of the addition, a THF (5 mL) solution of benzophenone (**13a**−**f**; 1 mmol) in THF (5 mL) was then added in 10 min at −78 °C. After 15 min a cooled (−78 °C) solution of AcOH (0.15 mL) in THF (10 mL) was added in 5 min. The reaction mixture was taken into $H_2O$ and extracted with EtOAc (3 × 25 mL). The combined organic fractions were dried over with $Na_2SO_4$ and evaporated in vacuum. The crude residue was purified with flash chromatography eluting with a solution of Hex/EtOAc (9:1, v:v).

**Ethyl 2-Diazo-3-hydroxy-3,3-diphenylpropanoate (14a)[10]:** yellow solid; 82% yield. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.27 (t, 3H, $J$ = 7.2 Hz), 4.25 (q, 2H, $J$ = 7.2 Hz), 4.98 (br, 1H), 7.31−7.43 (m, 10H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ: 14.3, 61.3, 78.9, 126.8, 128.1, 143.3, 167.3.

**Ethyl 2-Diazo-3-hydroxy-3-(4-chlorophenyl)-3-phenylpropanoate (14d):** yellow solid; 98% yield. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.29 (t, 3H, $J$ = 7.2 Hz), 4.27 (q, 2H, $J$ = 7.2 Hz), 5.00 (br, 1H), 7.27−7.44 (m, 9H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ: 14.3, 61.4, 78.5, 126.7, 128.3, 128.4, 128.5, 134.1, 142.2, 142.8, 167.2.

**General Procedure for Decomposition of Ethyl 2-Diazo-3-hydroxy-3-aryl-3-phenylpropanoates 14a−f.** To a magnetically stirred solution of freshly distilled $BF_3 \cdot Et_2O$ (1.66 mmol) in dry acetonitrile (5 mL) was added a solution of α-diazo-β-hydroxy ester **14a**−**f** (1.11 mmol) in dry acetonitrile (30 mL) with a syringe pump (0.02 mmol/min) at room temperature. After the end of the addition, the reaction mixture was stirred for additional 30 min at room temperature and then poured into a saturated solution of $NaHCO_3$ (75 mL), extracted with EtOAc (3 × 25 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuum. The crude residue was purified by flash chromatography eluting with a solution of petroleum ether/EtOAc (6:4, v:v).

**Ethyl (2*Z*)-3-(Acetylamino)-2,3-diphenylacrylate (*Z*-19a):** yellow-brown oil; 44% yield. UV ($H_2O$, $CH_3CN$): 230.38, 301.48. $^1$H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, 3H, $J$ = 7.1 Hz), 2.13 (s, 3H), 4.20 (q, 2H, $J$ = 7.1 Hz), 6.94−6.95 (m, 2H), 7.01−7.06 (m, 2H), 7.06−7.13 (m, 6H), 11.34 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 14.1, 25.0, 60.9, 113.2, 126.3, 127.2, 127., 127.9, 128.7, 131.8, 135.2, 135.2, 151.5, 168.3, 169.3. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.64; H, 6.56; N, 4.32.

**Ethyl (2*E*)-3-(Acetylamino)-2,3-diphenylacrylate (*E*-19a):** white solid (mp: 156−157 °C); 46% yield. UV ($H_2O$, $CH_3CN$): 225.79, 292.26. $^1$H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, $J$ = 7.1 Hz), 1.81 (s, 3H), 3.95 (q, 2H, $J$ = 7.1 Hz), 6.81 (s, 1H), 7.33−7.44 (m, 10H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 13.6, 23.6, 61.0, 123.4, 128.1, 128.3, 128.4, 129.1, 129.1, 135.3, 136.6, 140.8, 168.7. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.54; H, 6.48; N, 4.51.

**Ethyl (2*Z*)-3-(Acetylamino)-3-(4-chlorophenyl)-2-phenylacrylate (*Z*-19d):** yellow oil; 32% yield. UV ($H_2O$, $CH_3CN$): 234.02, 303.65. $^1$H NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, 3H, $J$ = 7.1 Hz), 2.14 (s,

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3H), 3.69 (s, 3H), 4.19 (q, 2H, $J$ = 7.1 Hz), 6.92−6.94 (m, 4H), 7.05 (psd, 2H, $J$ = 8.6 Hz), 7.09−7.10 (m, 3H), 11.34 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 25.0, 61.1, 113.7, 126.6, 127.4, 127.7, 130.0, 131.7, 133.7, 133.8, 134.7, 150.3, 168.4, 169.2. Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.74; H, 5.58; N, 3.89.

**Ethyl (2*E*)-3-(Acetylamino)-3-(4-chlorophenyl)-2-phenylacrylate (*E*-19d):** white solid (mp: 157−158 °C); 6.5% yield. UV ($H_2O$, $CH_3CN$): 228.26, 295.23. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.97 (t, 3H, $J$ = 7.1 Hz), 1.84 (s, 3H), 3.98 (q, 2H, $J$ = 7.1 Hz), 6.82 (br, 1H), 7.32−7.38 (m, 6H), 7.41−7.45 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 13.7, 23.6, 61.1, 124.1, 128.5, 128.6, 129.1, 129.2, 129.3, 130.6, 135.0, 139.9, 168.3, 168.3. Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.49; H, 5.18; N, 3.95.

**Ethyl (2*Z*)-3-(Acetylamino)-2-(4-chlorophenyl)-3-phenylacrylate (*Z*-20d):** yellow oil; 43% yield. UV ($H_2O$, $CH_3CN$): 233.43, 303.62. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.20 (t, 3H, $J$ = 7.1 Hz), 2.12 (s, 3H), 4.19 (q, 2H, $J$ = 7.1 Hz), 6.87 (psd, 2H, $J$ = 8.6 Hz), 6.98−7.00 (m, 2H), 7.04 (psd, 2H, $J$ = 8.6 Hz), 7.10−7.14 (m, 3H), 11.36 (br, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 14.1, 25.0, 61.0, 111.8, 127.5, 127.6, 128.1, 128.6, 132.3, 133.1, 133.7, 134.9, 152.1, 168.3, 169.0. Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.51; H, 5.78; N, 3.83.

**Ethyl (2*E*)-3-(Acetylamino)-2-(4-chlorophenyl)-3-phenylacrylate (*E*-20d):** white solid (mp:153−155 °C); 10% yield. UV ($H_2O$, $CH_3CN$): 227.88, 296.56. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.90 (t, 3H, $J$ = 7.1 Hz), 1.83 (s, 3H), 3.95 (q, 2H, $J$ = 7.1 Hz), 6.79 (br, 1H), 7.27 (psd, 2H, $J$ = 8.6 Hz), 7.37−7.43 (m, 7H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 13.5, 23.6, 61.1, 123.0, 128.1, 128.3, 129.3, 130.6, 134.0, 134.3, 136.5, 141.4, 168.4, 168.4. Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.23; H, 5.31; N, 4.02.

**Supporting Information Available:** Detailed description of experimental procedures, a listing of all spectroscopic data, elemental analysis, as well as copies of NMR spectra ($^1$H and $^{13}$C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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