Iron Lewis Acid Catalyzed Reactions of Aromatic Aldehydes with Ethyl Diazoacetate: Unprecedented Formation of 3-Hydroxy-2-arylacrylic Acid Ethyl Esters by a Unique 1,2-Aryl Shift

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The iron Lewis acid $[\eta^5\text{-}(C_5H_5)Fe(CO)_2(THF)]BF_4$ (**1**) was found to catalyze reactions of ethyl diazoacetate (EDA) and aromatic aldehydes, yielding 3-hydroxy-2-arylacrylic acid ethyl esters and the corresponding β-keto esters. According to the literature, this is the first report of the formation of enol esters from EDA and aromatic aldehydes. The yield of the enol esters increased with electron-rich aldehydes. With 2,4-dimethoxybenzaldehyde the only product isolated was the corresponding enol ester in 80% yield. However, in the presence of electron-deficient aldehydes such as *p*-nitrobenzaldehyde, formation of enol ester decreased to 32%. The most unique feature of these reactions is that enol esters are formed by an unusual 1,2-aryl shift, from a possible intermediate **8**, which in turn is formed from the reaction of the iron aldehyde complex **7** and EDA.

Introduction

With or without a catalyst, diazo alkanes are known to react with aldehydes to form homologated ketones along with epoxides.[1] Anselme and co-workers investigated several aspects of lithium bromide promoted homologation of aldehydes with aryldiazomethanes.[2] They reported that, in the presence of 10-fold excess of LiBr, aldehydes reacted with aryldiazomethanes but gave only the homologated product, β-diketones in excellent yields. Later, Roskamp reported that aldehydes also react with ethyl diazoacetate to form, mainly, β-keto esters with moderate to good yields.[3] This reaction was catalyzed by a variety of Lewis acids (e.g., BF_3, $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $SnCl_2$, $GeCl_2$, $SnCl_4$). Recently, Espenson et al. reported the synthesis of trans epoxides from aldehydes and ethyl diazoacetate using methylrhenium trioxide as a catalyst.[4] Later, Aggarwal and co-workers reported the direct synthesis of asymmetric epoxides from aldehydes and phenyldiazomethane using catalytic amounts of enantiomerically pure sulfides and $Rh_2(OAc)_2$.[5] We recently reported the synthesis of cis epoxides and ketones from aromatic aldehydes and phenyldiazomethane using cyclopentadienyl dicarbonyl iron Lewis acid as a catalyst.[6] Although a precedent exists for the formation of ketones or epoxides from the reactions of aromatic aldehydes with ethyl diazoacetate, the formation of 3-hydroxy-2-arylacrylic acid ethyl ester from these reactions has never been reported. Herein, we will describe the unprecedented formation of 3-hydroxy-2-arylacrylic acid ethyl esters from the reactions of aromatic aldehydes with ethyl diazoacetate in the presence of 10 mol % of iron Lewis acid $[\eta^5\text{-}(C_5H_5)Fe^+(CO)_2(THF)]BF_4^-$ (**1**).

Results and Discussion

The iron Lewis acid **1** was synthesized in high yield by protonation of the known methyl complex (η^5-$C_5H_5)Fe(CO)_2CH_3$.[7] The iron Lewis acid **1** in catalytic concentration was observed to induce the reaction between EDA and different aromatic aldehydes, e.g., benzaldehyde, *p*-tolualdehyde, and *p*-nitrobenzaldehyde, forming enol esters **4** along with β-keto esters **5** (Scheme 1). The formation of epoxide was not observed in any of these reactions. In the presence of 10 mol % of **1**, 1.2 equiv of benzaldehyde was found to consume all of the EDA to provide 58% of enol ester **4a** and 25% of β-keto ester **5a** at room temperature. The yields of enol esters increased at lower temperatures; for example, at 0 °C the reaction of EDA and benzaldehyde gave a 70% yield of **4a** and 19% of **5a**. Even when the reaction was run at lower temperature, i.e., at −78 °C, the yield of enol ester remained the same. When EDA and *p*-anisaldehyde were treated without catalyst **1** under reaction conditions, neither of the products was formed; only starting materials were isolated from the reaction mixture.[8]

To determine the effects of substituents on benzaldehyde upon formation of enol esters vs keto esters, other aromatic aldehydes were investigated. The results of these reactions are summarized in Table 1. The yields of enol esters were observed to be dependent on the nature of the substituent on benzaldehyde. With electron-

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(8) A control reaction between benzaldehyde and EDA resulted in the recovery of the starting reagents, but due to difficulties in separating the mixture by column chromatography, the control reaction was run between *p*-anisaldehyde and EDA instead.

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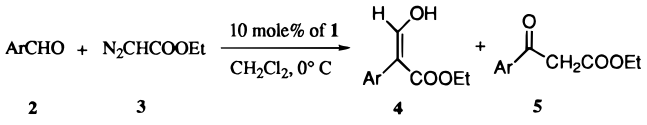
Scheme 1



2 3 4 5

2a, Ar=Ph
2b, Ar= *p*-CH_3Ph
2c, Ar= *p*-OCH_3Ph
2d, Ar= 2,4-$(OCH_3)_2$Ph
2e, Ar= *p*-ClPh
2f, Ar= *p*-NO_2Ph

Table 1. Isolated Yields of Enol Esters and *β*-Keto Esters from Reactions of EDA[a] with Aromatic Aldehydes Catalyzed by 10 mol % of 1

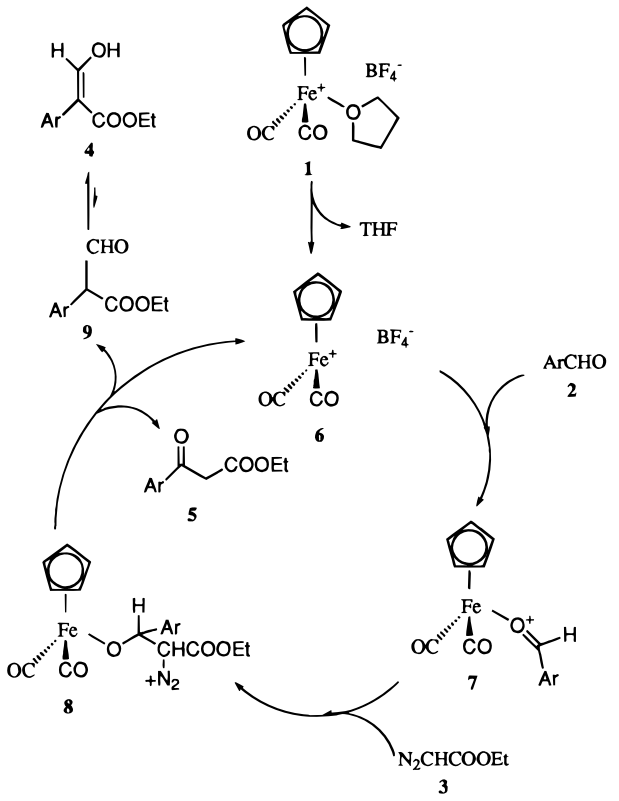
			time (h)		% yield[b,c]	
entry	aldehyde (1.2 equiv)	temp (°C)	of addn	after addn	**4**	**5**
1	benzaldehyde	rt	6	8	58	25
2	benzaldehyde	0	6	8	70	19
3	benzaldehyde	−78	6	8	68	19
4	*p*-tolualdehyde	0	6	8	67	19
5	*p*-methoxybenzaldehyde	0	6	8	60	20
6	2,4-dimethoxybenzaldehyde	0	6	8	80	
7	*p*-chlorobenzaldehyde	0	6	8	50	41
8	*p*-nitrobenzaldehyde	0	6	8	32	56

[a] One equivalent of EDA was used unless otherwise stated. [b] Yields based upon EDA. [c] Isolated yield.

rich aldehydes such as 2,4-dimethoxybenzaldehyde, the only product isolated was enol ester in 80% yield; no formation of *β*-keto ester was observed. From *p*-anisaldehyde 60% of enol ester and 20% of keto ester were obtained and from *p*-tolualdehyde 67% of enol ester was isolated. However, in the presence of electron-withdrawing groups in the aldehyde the yield of enol esters were low. For example, 50% and 32% of enol esters were isolated from *p*-chloro- and *p*-nitrobenzaldehyde, respectively.

The reaction mechanism at this point has not been fully investigated. Formation of the products through an iron carbene intermediate from the reaction of EDA with the Fp^+ moiety is a possibility. Previously, we have synthesized the iron carbene, Fp^+=CHPh by the method developed in our lab.[9] The carbene was then reacted with aromatic aldehydes, and no homologated ketones or epoxides were isolated. On the basis of this earlier result we can speculate that the reaction of EDA with aldehydes in the presence of iron Lewis acid will also not proceed via the carbene complex, Fp^+=CH(COOEt).[10] However, benzaldehyde does react with Lewis acid to form a stable *σ*-benzaldehyde complex which has been fully characterized by us[6] and by Protasiewicz.[11] Moreover, the benzaldehyde complex was found to react with EDA to provide the corresponding enol ester **4a** and *β*-keto ester **5a**, in 58% and 22% yields, in same ratio (2.5:1) as that of the original reaction (entry 1, Table 1). This strongly suggests the formation of the aldehyde complex **7** in this catalytic reaction (Scheme 2). Lack of any reaction between EDA and benzaldehyde when THF was used as a solvent suggests the initial dissociation of THF to form

Scheme 2



the highly reactive 16e complex **6**. Nucleophilic attack of EDA to the aldehyde complex **7** resulted in the formation of **8**. From complex **8**, the presence of an electron-donating group will enhance 1,2 migration of an aryl group over a hydride migration.[12] As a result, more aldehyde ester product **9** is likely to be formed than keto ester **5** and equilibrium of aldehyde ester was shown to favor the enol ester form (Scheme 2). The presence of an electron-withdrawing group should slow the 1,2 migration of the aryl group, and formation of less enol ester product would be expected.

The most important feature of this reaction is the migration of the 1,2-aryl group from intermediate **8** to provide the enol ester **4**. Although 1,2-aryl migration seems quite reasonable in the presence of a Lewis acid in the reaction of aromatic aldehydes with EDA, to the best of our knowledge this is the first report of such a migration. Previously, in the presence of a variety of Lewis acids, even with very electron-rich aldehydes such as 3,4-methylenedioxybezaldehyde, migration of aryl groups was not observed.[3]

Due to the fact that transition-metal catalysts are known to rearrange epoxides to ketones and aldehydes,[13] the mechanism involving an initial formation of the epoxide, ethyl-3-arylglycidate, from complex **8** and rearrangement to the corresponding enol ester and keto ester by **1** could also be a possibility (Scheme 3). This mechanism was discounted, since we observed no formation of **4a** and/or **5a** from ethyl-3-phenylglycidate in the presence of Lewis acid **1** under similar reaction conditions.

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(10) So far, there is no known procedure to synthesize this iron carbene complex. Attemps to detect it by low-temperature ^{1}H NMR from the reaction of **1** with EDA was also unsucessful, see: Seitz, W. J.; Saha, A. J; Hossain, M. M. *Organometalics* **1993**, *12*, 2604.

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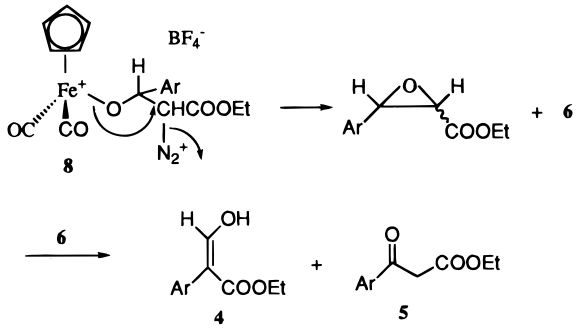
Scheme 3



In summary, a unique reaction was observed between aryl aldehydes and EDA in the presence of **1**, providing the 3-hydroxy-2-arylacrylic acid ethyl ester. Currently, work is underway to utilize this novel reaction in the preparation of important building blocks of some biologically active natural and unnatural compounds.

Experimental Section

General Considerations. Infrared spectra were recorded using a Nicolet MX-1 FT-IR spectrometer. Proton and carbon 13 spectra were obtained on a Bruker 250 MHz NMR spectrometer. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane, and $CDCl_3$ was used as the solvent. All organometallic operations were performed under a dry nitrogen atmosphere using standard Schlenk techniques. All of the glass flasks were flamed under vacuum and filled with nitrogen prior to use. Column chromatography was performed using silica gel (40−140 mesh). HPLC reagent grade CH_2Cl_2 was distilled under nitrogen from P_2O_5. HPLC reagent grade pentane was distilled from sodium under an inert atmosphere immediately prior to use. Reagent grade diethyl ether and tetrahydrofuran were freshly distilled under a nitrogen atmosphere from sodium benzophenone ketyl. Benzaldehyde, *p*-tolualdehyde, and *p*-anisaldehyde were purified by extraction with sodium bicarbonate solution, washed with water, dried over sodium sulfate, and distilled under vacuum. *p*-Nitrobenzaldehyde and *p*-chlorobenzaldehyde were purified by recrystallization from ethanol and then dried under vacuum for several days. Ethyl diazoacetate (EDA) was obtained from Aldrich Chemical Co.

Synthesis of Iron Lewis acid (1). A 6.0 g (0.017 mol) sample of cyclopentadienyl dicarbonyl iron dimer, $[CpFe(CO)_2]_2$ (Aldrich), was dissolved in 45 mL of degassed THF in a flame-dried side-armed flask. To this stirred solution was added 1.28 g (0.055 mol) of sodium metal (Aldrich) in a 1% Na−Hg amalgam, and the reaction mixture was stirred for 1.5 h at room temperature. After that time the reaction mixture was cooled to −78 °C and the resulting Fp anion was transferred to another flame-dried flask with the help of a filter stick. The solution was cooled to 0 °C, and 8.0 g (0.056 mol) of methyl iodide (Aldrich) was added dropwise. The color of the solution changed from wine red to yellow. The reaction mixture was allowed to stir for 1 h at 0 °C; then the solvent was removed under reduced pressure and the residue was purified by chromatography on a column containing silica gel using pentane as eluant. Removal of the solvent resulted in the formation of the iron methyl complex in 90% (5.85 g) yield.[7] ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.7 (s, 5H), 0.09 (s, 3H). A 4.5 g (0.023 mol) sample of methyl complex was dissolved in 15 mL of methylene chloride and was cooled to −78 °C. To this cooled solution was added 3.56 mL (0.9 equiv) of $HBF_4{\cdot}OEt_2$ dropwise. The color changed from yellow to red. The reaction mixture was stirred for 30 min at −78 °C; then 8 mL of THF was added and the mixture was stirred for another $^1/_2$ h. The temperature was maintained at 0 °C. The solvent was removed under reduced pressure. Repeated recrystallizaton from CH_2Cl_2/THF at −78 °C resulted in the formation of THF-bound iron Lewis acid[14] in 91% yield (7.65 g). ^{1}H NMR (CD_3COCD_3, 250 MHz): δ 5.71 (s, 5H), 3.63 (t, 4H), 1.82 (m, 4H).

Catalytic Reaction. General Procedure. In a typical experiment, 0.30−0.60 mmol of the catalyst was dissolved in 5−6 mL of freshly distilled methylene chloride under nitrogen; then an appropriate amount of aldehyde was added and the solution was cooled to 0 °C. One equivalent of ethyl diazoacetate was diluted with 3−4 mL of freshly distilled dichloromethane and was drawn into a gastight syringe. It was then added to the reaction mixture dropwise over a period of 6−7 h with the help of a syringe pump. After the addition was complete, the reaction mixture was stirred for another 6−12 h at 0 °C. The reaction was stopped by adding 9−10 mL of diethyl ether, which caused the catalyst to precipitate from the solution. Any remaining metal moiety was removed by filtration through a plug of silica. The solvent was removed by rotary evaporation, and the products were isolated by column chromatography (2−10% ether in pentane). The products were finally identified by comparing the ^{1}H NMR spectra to those of known compounds. The new compounds were characterized by ^{1}H and ^{13}C NMR and elemental analysis.

3-Hydroxy-2-phenylacrylic acid ethyl ester (4a)[15] was isolated in 70% yield from the reaction of 0.1410 g (0.42 mmol) of the Lewis acid, 0.51 mL (5.0 mmol) of benzaldehyde, and 0.53 mL (4.2 mmol) of EDA at 0 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 12.2 (d, 1H, J = 13 Hz), 7.3 (m, 5H). In addition, 19% of **3-oxo-3-phenylpropionic acid ethyl ester (5a)**[16] was isolated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.4−8.0 (m, 5H), 4.20 (q, 2H), 3.98 (s, 2H), 1.24 (t, 3H).

3-Hydroxy-2-*p*-tolylacrylic acid ethyl ester (4b)[15] was isolated in 67% yield from the reaction of 0.1158 g (0.34 mmol) of the Lewis acid, 0.50 mL (4.1 mmol) of *p*-tolualdehyde, and 0.40 mL (3.4 mmol) of EDA at 0 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 12.2 (d, 1H, J = 13 Hz), 7.3 (m, 5H), 2.4 (s, 3H). In addition, 19% of **3-oxo-3-*p*-tolylpropionic acid ethyl ester (5b)**[16] was isolated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.2−7.8 (m, 4H), 4.17 (q, 2H), 3.92 (s, 2H), 2.36 (s, 3H), 1.22 (t, 3H).

3-Hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester (4c)[15] was isolated in 60% yield from the reaction of 0.1345 g (0.40 mmol) of the Lewis acid, 0.58 mL (4.8 mmol) of *p*-methoxybenzaldehyde, and 0.47 mL (4.0 mmol) of EDA at 0 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 12.08 (d, 1H, J = 13 Hz), 7.27 (d, 1H, J = 13 Hz), 7.18 (d, 2H, J = 9 Hz), 6.9 (d, 2H, J = 9 Hz), 3.82 (s, 3H). In addition, 20% of **3-(4-methoxyphenyl)-3-oxopropionic acid ethyl ester (5c)**[16] was isolated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.3−6.9 (m, 4H), 4.27 (q, 2H), 3.80 (s, 2H), 3.46 (s, 3H), 1.26 (t, 3H).

3-Hydroxy-2-(2,4-dimethoxyphenyl)acrylic acid ethyl ester (4d) was isolated in 80% yield from the reaction of 0.0981 g (0.29 mmol) of the Lewis acid, 0.5895 g (3.5 mmol) of 2,4-dimethoxybenzaldehyde, and 0.34 mL (2.9 mmol) of EDA at 0 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 11.89 (d, 1H, J = 13 Hz), 7.12 (d, 1H, J = 13 Hz), 7.00 (d, 1H, J = 9 Hz), 6.47 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 14.16, 55.28, 55.35, 60.30, 98.86, 104.21, 116.23, 131.13, 131.81, 159.11, 160.81, 162.52, 172.08. Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.30. Found: C, 61.73; H, 6.18. No β-keto ester was isolated from this reaction.

3-Hydroxy-2-(4-chlorophenyl)acrylic acid ethyl ester (4e)[15] was isolated in 50% yield from the reaction of 0.2013 g (0.60 mmol) of the Lewis acid, 1.0135 g (7.2 mmol) of *p*-chlorobenzaldehyde, and 0.70 mL (6.0 mmol) of EDA at 0 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 12.25 (d, 1H, 13), 7.25 (m, 5H). In addition, 41% of **3-(4-chlorophenyl)-3-oxopropionic acid ethyl ester (5e)**[17] was isolated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.8−7.3 (m, 4H), 4.14 (q, 2H), 3.90 (s, 2H), 1.21 (t, 3H).

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3-Hydroxy-2-(4-nitrophenyl)acrylic acid ethyl ester (4f) was isolated in 32% yield from the reaction of 0.1093 g (0.33 mmol) of the Lewis acid, 0.5980 g (4.0 mmol) of *p*-nitrobenzaldehyde, and 0.39 mL (3.3 mmol) of EDA at 0 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 12.37 (d, H, J = 13 Hz), 8.19 (d, 2H, J = 9 Hz), 7.44 (d, 2H, J = 9 Hz), 7.41 (d, 1H, J = 13 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 170.7, 164.7, 141.1, 129.7, 123.4, 107.4, 61.5, 14.1. Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.60; N, 5.90. Found: C, 55.86; H, 4.62; N, 5.77. In addition, 56% of **3-(4-nitrophenyl)-3-oxopropionic acid ethyl ester (5f)**[16] was isolated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 8.4−7.9 (m, 4H), 4.29 (q, 2H), 4.03 (s, 2H), 1.28 (t, 3H).

Control Reaction between *p*-Anisaldehyde and EDA at Room Temperature. A 0.50 mL (4.1 mmol) sample of benzaldehyde was dissolved in 12 mL of methylene chloride; then 0.48 mL (4.1 mmol) of EDA was added. The reaction mixture was stirred at room temperature for 12 h. Solvent was removed by rotary evaporation, producing a yellow oil. The residual oil was then chromatographed on a column of silica gel and eluted with 2−10% ether in pentane to recover 94% of *p*-anisaldehyde and 92% of EDA.

Synthesis and Reaction of Benzaldehyde Complex with Ethyl Diazoacetate. A 0.7892 g (2.345 mmol) sample of iron Lewis acid **1**, 4.98 g (46.90 mmol) of benzaldehyde, and 25 mL of CH_2Cl_2 were stirred for 3 h at room temperature. Subsequently, the solvent was removed under reduced pressure and the remaining residue was repeatedly washed with diethyl ether to obtain the σ-bonded complex.[6] ^{1}H NMR (CD_2Cl_2): δ 9.65 (1H, s), 7.61−7.96 (5 H, m), and 5.50 (5 H, s). Then 1 equiv of ethyl diazoacetate was added all at once to this σ-bonded complex, and the resultant mixture was stirred at room temperature for 12 h. Ether was added to precipitate out the catalyst, and the products were separated from the catalyst by passing the reaction mixture through a plug of silica. Solvent was removed by rotary evaporation, and the products were isolated by column chromatography (2−10% ether in pentane) yielding 58% of 3-hydroxy-2-phenylacrylic acid ethyl ester and 22% 3-oxo-3-phenylpropionic acid ethyl ester.

Reaction of Iron Lewis Acid with Ethyl 3-Phenylglycidate. A 0.1408 g (0.420 mmol) sample of iron Lewis acid **1** was dissolved in 8 mL of CH_2Cl_2; then 0.80 mL (4.200 mmol) of *cis*/*trans*-ethyl 3-phenylglycidate was added. The mixture was allowed to stir at O °C for 12 h followed by the addition of 10 mL of diethyl ether to precipitate out the catalyst. The mixture was passed through a plug of silica to filter out the catalyst. Solvent was removed by rotary evaporation only to recover the starting ethyl 3-phenylglycidate in 92% yield. No trace of either the enol or the β-keto ester was observed.

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