

Acid-Catalyzed Reactions of Aromatic Aldehydes with Ethyl Diazoacetate: An Investigation on the Synthesis of 3-Hydroxy-2-arylacrylic Acid Ethyl Esters

Matthew E. Dudley, Md. Monzur Morshed, Courtney L. Brennan, M. Shahidul Islam, M. Syarhabil Ahmad, Mary-Rose Atuu, Bryan Branstetter, and M. Mahmum Hossain*

Department of Chemistry, University of Wisconsin–Milwaukee, Milwaukee, Wisconsin 53211

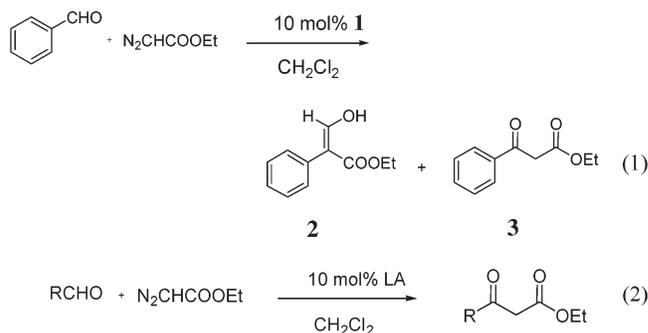
mahmun@uwm.edu

Received June 22, 2004

Several commercial Lewis acids, including those of the Brønsted type, specifically $\text{HBF}_4 \cdot \text{OEt}_2$, are able to catalyze the reaction between aromatic aldehydes and ethyl diazoacetate to produce 3-hydroxy-2-arylacrylic acid ethyl esters and 3-oxo-3-arylpropanoic acid ethyl esters. Reactions catalyzed by the iron Lewis acid $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}^+(\text{CO})_2(\text{THF})]\text{BF}_4^-$ (i.e., **1**) have the best yields and greatest ratio of 3-hydroxy-2-arylacrylic acid ethyl ester. The product distribution of **1** is not affected in the presence of Proton Sponge, but is dependent on temperature and the nature of the substrate aldehyde, whereas the activity of $\text{HBF}_4 \cdot \text{OEt}_2$ is affected by the presence of Proton Sponge and is reactive at temperatures as low as -78°C . Consequently, both **1** and $\text{HBF}_4 \cdot \text{OEt}_2$ are valuable catalysts in producing important 3-hydroxy-2-arylacrylic acid ethyl esters as precursors to biologically active compounds.

Introduction

Our group has found that the cyclopentadienyl dicarbonyl iron Lewis acid, $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}^+(\text{CO})_2(\text{THF})]\text{BF}_4^-$, **1**, catalyzes a variety of reactions including cyclopropanation,¹ aziridination,² and Diels–Alder reactions.³ Recently we reported the synthesis of 3-hydroxy-2-arylacrylic acid ethyl esters (3-hydroxyacrylates) along with 3-oxo-3-arylpropanoic acid ethyl esters (β -keto esters) from aromatic aldehydes and ethyl diazoacetate (EDA) catalyzed by **1** (eq 1).⁴ This method has been used in a three-step synthesis of the naproxen precursor 2-(6-methoxy-2-naphthyl)propanoic acid and other related compounds.⁵ Very recently, Kanemasa and co-workers also reported the synthesis of 3-hydroxyacrylates and β -keto esters from aromatic aldehydes and EDA using ZnCl_2 in the presence of chlorotrimethylsilane.⁶ Research by Roskamp focused on the reaction of aryl aldehydes and EDA catalyzed by commercial Lewis acids (LA) such as SnCl_2 , BF_3 , GeCl_2 , ZnCl_2 , ZnBr_2 , AlCl_3 , and SnCl_4 .⁷ The only product reported was β -keto ester produced in moderate to good yields (eq 2). When aromatic aldehydes were used, yields were considerably lower.



To determine if our iron Lewis acid (**1**) is unique, we decided to revisit those commercial Lewis acid catalysts to see if 3-hydroxyacrylates were indeed produced but overlooked. As part of our ongoing research, commercial Lewis acid, Brønsted acid, and substituent effect studies were utilized in the determination of what affects and controls the formation of 3-hydroxyacrylates and are reported herein. Our group is currently interested in 3-hydroxyacrylates because they have potential for further downstream synthesis of important biologically active compounds.

Results and Discussion

Lewis Acid Catalysis. The Lewis acids chosen for study were some of those reported by Roskamp.⁷ In each reaction the aldehyde was added to a flask charged with 15–25 mL of CH_2Cl_2 . The appropriate amount of catalyst (0.1 equiv) was added to the aldehyde (1.0 equiv) and the mixture was stirred. The EDA was diluted in approxi-

- (1) (a) Seitz W. J.; Hossain, M. M. *Tetrahedron Lett.* **1994**, 35, 7561.
 (b) Seitz, W. J.; Saha, A. K.; Hossain, M. M. *Organometallics* **1993**, 12, 2604. (c) Seitz, W. J.; Saha, A. K.; Casper, D.; Hossain, M. M. *Tetrahedron Lett.* **1992**, 33, 7755.
 (2) Mayer, M. F.; Hossain, M. M. *J. Org. Chem.* **1998**, 63, 6839.
 (3) Saha, A. K.; Hossain, M. M. *Tetrahedron Lett.* **1993**, 34, 3833.
 (4) Mahmood, S. J.; Hossain, M. M. *J. Org. Chem.* **1998**, 63, 3333.
 (5) Hossain, M. M. Synthesis of 2-Aryl Propanoic Acid Esters for the Production of Nonsteroidal Antiinflammatory Drugs, U.S. Patent 6,683,205 B2, January 27, 2004.
 (6) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, 40, 5055.
 (7) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, 54, 3258.

TABLE 1. Isolated Yields of 3-Hydroxyacrylate and β -Keto Ester from Reactions of EDA with Benzaldehyde Catalyzed by Lewis Acids^a

entry	Lewis acid	3-hydroxyacrylate (2), ^b %	β -keto ester (3), ^b %
1	SnCl ₂	1	62
2	SnCl ₂ ·2H ₂ O	15	59
3	ZnCl ₂	8	7
4	AlCl ₃	3	9
5	BF ₃ ·OEt ₂	21	18
6	SnCl ₄	18	24
7	HBF ₄ ·OEt ₂	42	21
8	1	58	25

^a 1 equiv of benzaldehyde was reacted with 1.2 equiv of EDA (which was added dropwise over 7 h) in the presence of 0.1 equiv of catalyst. The reaction was then stirred for an additional 14 h at room temperature. ^b Isolated yield.

TABLE 2. Percent Conversion to 3-Hydroxyacrylate from the Reaction of Benzaldehyde and EDA Catalyzed by **1, HBF₄·OEt₂, or NaBF₄ in the Presence/Absence of Proton Sponge^a**

entry	catalyst (0.1 equiv)	equiv of Proton Sponge	3-hydroxyacrylate (2), ^b %
1	1	0.01	60
2	1	0.1	50
3	HBF ₄ ·OEt ₂	0.1	5
4	NaBF ₄	0	0

^a The catalyst was dissolved in the appropriate solvent and then benzaldehyde and Proton Sponge were added. Equivalents are relative to benzaldehyde. The EDA was added dropwise and stirred as before. The reactions were performed at room temperature. ^b Analyzed by ¹H NMR, % conversion based on benzaldehyde to **2**.

mately 4 mL of CH₂Cl₂ and added dropwise over 6–7 h by using a syringe pump. All reactions were run at the temperatures indicated (Tables 1–5).

All of the catalysts investigated gave a mixture of 3-hydroxyacrylate and β -keto ester in different ratios. Some catalysts gave good overall yields and others gave low yields (Table 1). The most interesting results with respect to yield and ratio of products were those reactions catalyzed by SnCl₂, HBF₄·OEt₂, and **1**. For example, the main product observed from SnCl₂ and SnCl₂·2H₂O is the β -keto ester (entries 1 and 2, Table 1). In comparison, **1** gave mainly 3-hydroxyacrylate.⁴ Surprisingly, it was observed that HBF₄·OEt₂ also catalyzes the reaction between aromatic aldehydes and EDA to provide 3-hydroxyacrylates in good yields versus the corresponding β -keto esters.

The idea of using the HBF₄·OEt₂ acid as a catalyst came from the fact that HBF₄·OEt₂ is used in the synthesis of **1**.⁴ Acid impurities from HBF₄·OEt₂ could be a possible source of catalytic activity. To establish that **1**, and not HBF₄·OEt₂ impurities, was truly the catalyst in the reaction of aromatic aldehydes with EDA, the reaction was performed in the presence of Proton Sponge, 1,8-bis(dimethylamino)naphthalene. The activity of **1** was not inhibited by the addition of Proton Sponge (Table 2). In the case with HBF₄·OEt₂, the reaction was almost completely inhibited by the addition of Proton Sponge and only the aldehyde starting material was recovered.

Substituent Effects. We had reported⁴ earlier that substituents on the aromatic aldehyde play an important role in product distribution when reactions are catalyzed by **1**. Electron-donating groups favor the formation of

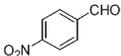
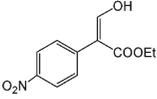
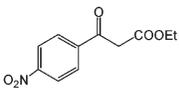
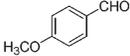
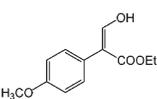
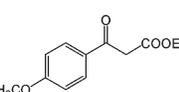
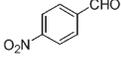
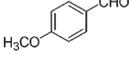
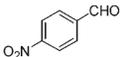
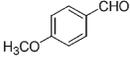
3-hydroxyacrylates, whereas electron-withdrawing groups favor the β -keto ester. To ascertain if this is true with other catalysts, several reactions were performed with electron-rich and electron-poor aldehydes catalyzed by commercial Lewis acids (SnCl₂, **1**, and HBF₄·OEt₂, Table 3). To compare the results, all reactions were carried out at room temperature under the same conditions.

In the case of SnCl₂, the nature of the substituent has no effect on product distribution, the main product was β -keto ester. No formation of 3-hydroxyacrylate was observed with electron-rich or electron-poor aldehyde. The yields of β -keto esters were low with electron-rich groups (entry 3, Table 3) and high with electron-poor substituents such as the *p*-nitro group (entry 2, Table 3). However, with HBF₄·OEt₂ product distribution depends on the nature of the substituents and is similar to that of **1**,⁴ i.e., more 3-hydroxyacrylate with electron-rich aldehyde (entry 6, Table 3) and less 3-hydroxyacrylate with electron-poor aldehyde (entry 5, Table 3). After evaluating the results thus far, it was determined that the highest yields and ratios of 3-hydroxyacrylates were obtained in reactions catalyzed by **1** and also by HBF₄·OEt₂.

Role of Substrate. Following this preliminary study, a comparison of the catalytic activity of **1** and HBF₄·OEt₂ was performed with a variety of carbonyl substrates. The results of these reactions are summarized in Table 4. Evaluation of acid-sensitive aromatic aldehydes such as furfuraldehyde (entries 1 and 2, Table 4) produced interesting results. At 0 °C, **1** gave only 3-hydroxyacrylate in 70% yield, whereas HBF₄·OEt₂ at 0 °C (entry 1, Table 4) gave a mixture of decomposed side products that appeared polymeric in nature by ¹H NMR. Due to the mild nature of **1**, it is useful for substrates that are sensitive to protic acids such as furfuraldehyde. Analysis of aromatic ketones such as acetophenone and trifluoroacetophenone (entries 5–8, Table 4) showed that only acetophenone reacted with HBF₄·OEt₂, while no reaction was observed in the presence of **1**, whereas trifluoroacetophenone was unreactive regardless of the catalyst used (entries 7 and 8, Table 4). Trifluoroacetophenone's inability to react may be explained by the powerful electron-withdrawing effect of the trifluoromethyl group on the neighboring carbonyl carbon, thus preventing activation of the ketone. The reaction of salicylaldehyde (entries 10 and 11, Table 4) and *o*-aminobenzaldehyde (entries 12 and 13, Table 4) produced only small amounts (10–20%) of product, namely benzofuran-3-carboxylic acid ethyl ester and 3-ethoxycarbonyl indole in the presence of HBF₄·OEt₂. These products are formed from 3-hydroxyacrylates by acid-catalyzed cyclization (Scheme 1). These aldehydes were deemed essentially unreactive in the presence of **1**. A potential explanation for this result is due to deactivation of the catalyst since both aldehydes contain an electron donor (e.g., –OH or –NH₂) in the ortho position, which can compete at the reactive site for the aldehyde's carbonyl oxygen and consequently inhibit the Lewis acidity of **1**.

Entries 14–29 (Table 4) show various substituted benzaldehyde derivatives at different temperatures. Actually, in terms of EWG/EDG substituent effects, the product distributions of 3-hydroxyacrylates and β -keto esters catalyzed by either HBF₄·OEt₂ or **1** are similar at 0 °C.

TABLE 3 Yields of 3-Hydroxyacrylates and β -Keto Esters from the Reactions of *p*-Methoxy- and *p*-Nitrobenzaldehyde with EDA Catalyzed by SnCl_2 , $\text{HBF}_4 \cdot \text{OEt}_2$, and **1**^a

entry	aldehyde	Lewis acid	3-hydroxyacrylate	% ^c	β -keto ester	% ^c
1 ^b		SnCl_2		1		62
2		SnCl_2		0		80
3		SnCl_2		0		30
4 ^b		$\text{HBF}_4 \cdot \text{OEt}_2$		42		21
5		$\text{HBF}_4 \cdot \text{OEt}_2$		27		54
6		$\text{HBF}_4 \cdot \text{OEt}_2$		44		21
7 ^b		1		58		25
8		1		35		44
9		1		45		35

^a 1 equiv of aldehyde was reacted with 1.2 equiv of EDA (which was added dropwise over 7 h) in the presence of 0.1 equiv of the catalyst. The reaction was then stirred for an additional 14 h at room temperature. ^b Results from Table 1. ^c Isolated yield.

Interestingly, it is possible to perform the reaction at $-78\text{ }^\circ\text{C}$ in the presence of $\text{HBF}_4 \cdot \text{OEt}_2$. At this temperature the yield of the 3-hydroxyacrylate is significantly improved (entries 9, 15, 20, and 30, Table 4). In some cases, the only product isolated from the reaction was the desired 3-hydroxyacrylate, whereas **1** is ineffective as a catalyst at this temperature (entries 4 and 17, Table 4) due to slow dissociation of the THF ligand from **1**.⁴

Brønsted Acid Catalysis. Following the observation that H^+ (Brønsted acidity of $\text{HBF}_4 \cdot \text{OEt}_2$) may specifically catalyze the formation of 3-hydroxyacrylates from aromatic aldehydes and EDA, an investigation into the activity of several commercial Brønsted acids was performed to verify the potential source of catalytic activity of $\text{HBF}_4 \cdot \text{OEt}_2$. A number of Brønsted acids with varying acid strengths were investigated. Results are summarized in Table 5.

It became apparent that yield was dependent on the following order: $\text{BF}_4^- > \text{HSO}_4^- > \text{NO}_3^- > \text{ClO}_4^- > \text{Cl}^-$ and CH_3COO^- . Those Brønsted acids with nonnucleophilic anions gave the best results, for example, sulfuric acid (entry 9, Table 4) and $\text{HBF}_4 \cdot \text{OEt}_2$ (Table 3), whereas acids with nucleophilic anions such as Cl^- , AcO^- , and NO_3^- gave only a trace or small amount of product since they readily quench EDA according to Scheme 2.^{8,9,10,11}

To investigate why acids such as sulfuric acid and $\text{HBF}_4 \cdot \text{OEt}_2$ are reactive, EDA degradation experiments were performed in the NMR tube. In a 1.0-equiv sample of EDA in the presence of 0.5 equiv of sulfuric acid at temperatures below $0\text{ }^\circ\text{C}$, the methine 1H proton of EDA (broad singlet, 4.74 ppm) is still present, in addition to an intermediate having 2H singlet protons as observed by ¹H NMR (4.78 ppm) and ¹³C NMR (67.2 ppm). The ¹³C DEPT, edited HSQC, and HMBC spectra of this mixture confirmed that both of these proton singlets are bound on the methine carbon of the intermediate, suggesting a diazonium salt similar to the protonated intermediate **25** as represented in Scheme 2. Interestingly, at temperatures above $0\text{ }^\circ\text{C}$, rapid loss of nitrogen and subsequent coordination of the dianion of sulfuric acid is observed producing the final compound, 2,2'-[sulfonylbis(oxy)]bisacetic acid diethyl ester, $(\text{CH}_3\text{CH}_2\text{OCOC}_2\text{H}_2\text{O})_2\text{SO}_2$ (**27**). This NMR study revealed that rapid decomposition of EDA by sulfuric acid occurs at room temperature and consequently neutralizes the acidity of sulfuric acid. This neutralization of the acid catalyst explains why limited formation of 3-hydroxy-

(8) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(9) Holmberg, B. *Chem. Ber.* **1908**, *41*, 1343.

(10) Curtius, T. J. *Prakt. Chem.* **1889**, *39*, 128.

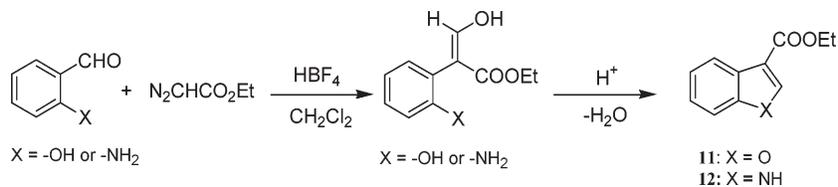
(11) Curtius, T.; Schwan. *J. Prakt. Chem.* **1895**, *51*, 358.

TABLE 4. Results from the Reactions of Various Aromatic Carbonyl Compounds with EDA Catalyzed by Iron Lewis Acid **1 or $\text{HBF}_4 \cdot \text{OEt}_2^a$**

entry	substrate	Lewis acid	temp. (°C)	3-hydroxyacrylate	% ^b	β -keto ester	% ^b
1		$\text{HBF}_4 \cdot \text{OEt}_2$	0		0		0
2		$\text{HBF}_4 \cdot \text{OEt}_2$	-78		50		50
3		1	0		70		0
4		1	-78		0		0
5		$\text{HBF}_4 \cdot \text{OEt}_2$	RT ^{c,d}		74	----	0
6		1	RT ^c		Trace	----	0
7		$\text{HBF}_4 \cdot \text{OEt}_2$	RT ^{c,d}	----	0	----	0
8		1	RT ^d	----	0	----	0
9		$\text{HBF}_4 \cdot \text{OEt}_2$	-78		74		0
10		$\text{HBF}_4 \cdot \text{OEt}_2$	0		20 ^c	----	0
11		1	0		0	----	0
12		$\text{HBF}_4 \cdot \text{OEt}_2$	0		23 ^f	----	0
13		1	0		0	----	0
14		$\text{HBF}_4 \cdot \text{OEt}_2$	0		75		15
15		$\text{HBF}_4 \cdot \text{OEt}_2$	-78		90		0
16		1	0		60		20
17		1	-78		4		0
18		$\text{HBF}_4 \cdot \text{OEt}_2$	0		60		35
19		1	0		74		15
20		$\text{HBF}_4 \cdot \text{OEt}_2$	-78		51		15
21		1	0		67		19
22		$\text{HBF}_4 \cdot \text{OEt}_2$	0		45		35
23		1	0		72		20
24		$\text{HBF}_4 \cdot \text{OEt}_2$	0		55		34
25		1	0		62		17
26		$\text{HBF}_4 \cdot \text{OEt}_2$	0		35		53
27		1	0		32		56
28		$\text{HBF}_4 \cdot \text{OEt}_2$	0		45		33
29		1	0		35		20
30		$\text{HBF}_4 \cdot \text{OEt}_2$	-78		76	----	0

^a 1 equiv of substrate was reacted with 1.2 equiv of EDA (which was added dropwise over 6 to 7 h) in the presence of 0.1 equiv of catalyst and stirred for an additional 14 h at that temperature unless otherwise stated. ^b Yields based upon starting aldehyde or ketone. ^c 3 equiv of EDA were used. ^d The reaction was allowed to stir for an additional 2–4 days. ^e Only product isolated was benzofuran-3-carboxylic acid ethyl ester (**11**). ^f The only product isolated was 3-ethoxycarbonyl indole (**12**).

SCHEME 1



SCHEME 2

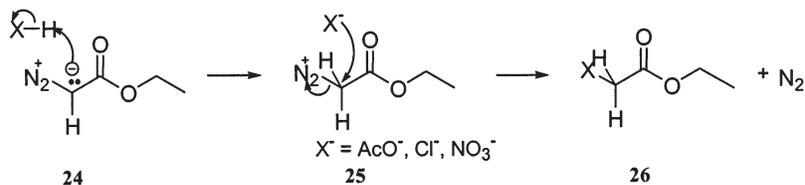


TABLE 5. Results from the Reactions of Benzaldehyde with EDA Catalyzed by 0.1 equiv of Brønsted Acids

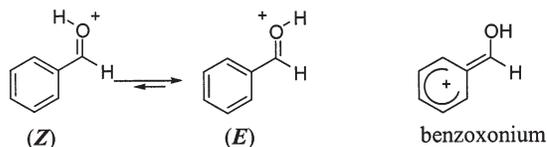
entry	Brønsted acid	temp. °C	3-hydroxy-acrylate (2), ^a %	β -keto ester (3), ^a %
1	CH ₃ COOH	rt	0 ^b	0 ^b
2	HCl (dry)	rt	trace ^{b,c}	trace ^b
3	HCl (12 M)	0	trace ^b	0 ^b
4	HNO ₃ (15.8 M)	rt	trace ^b	0 ^b
5	HNO ₃ (15.8 M)	0	18	0
6	HClO ₄ (9.2 M)	0	10	0
8	H ₂ SO ₄	rt	6 ^b	0 ^b
9	H ₂ SO ₄	0	26	0
10	H ₂ SO ₄	-78	33	7

^a Isolated yield unless otherwise stated. ^b From the analysis of reaction mixture by proton NMR. ^c Ethylchloroacetate was isolated from this reaction.

acrylate (entry 8, Table 5) occurs in reactions at room temperature, whereas at 0 °C or below, the slow neutralization of sulfuric acid during dropwise addition of EDA permits activation of benzaldehyde by the sulfuric acid to form 3-hydroxyacrylates (entries 9 and 10, Table 5). This phenomenon observed with sulfuric acid is even more true for HBF₄·OEt₂.

In the presence of 0.1 equiv of HBF₄·OEt₂ with 1 equiv of EDA at or below 0 °C, the 1H methine proton of EDA (4.74 ppm) shows practically no decomposition and consequently neutralization of HBF₄·OEt₂ is prevented. This result is borne out by ¹H NMR because HBF₄·OEt₂ exhibits a broad acid peak at 10.3 ppm even in the presence of EDA. This NMR study confirms that 0.1 equiv of HBF₄·OEt₂ is almost completely available to activate the benzaldehyde in the presence of EDA and is not as susceptible to neutralization as sulfuric acid. This is a unique characteristic of HBF₄·OEt₂ in comparison to the other Brønsted acids investigated and is the reason for its effectiveness as a catalyst in 3-hydroxyacrylate synthesis (Table 3, entry 4 and Table 4, entry 9). Interestingly, a small amount of ethyl fluoracetate forms with higher concentrations of acid (1 equiv).

After our investigation of commercially available Brønsted and Lewis acids (Tables 1 and 5), it became apparent that catalysts containing the BF₄⁻ anion (i.e., **1** and HBF₄·OEt₂) gave the best results. Investigation of the BF₄⁻ anion and its derivatives provided a rational approach in finding the potential source of catalytic activity. No reaction was observed with NaBF₄ thus eliminating the BF₄⁻ anion as a potential catalyst (Table 2). Simi-

FIGURE 1. (*Z*)-, (*E*)-*O*-protonated and benzoxonium carbocations of benzaldehyde.

larly, if BF₃ was the catalyst (from the decomposition of HBF₄·OEt₂), then results for HBF₄·OEt₂ and BF₃·OEt₂ should be the same, but they are not (Table 1). Ultimately, H⁺ was identified as the catalyst, after a reaction with a 1:1 ratio of HBF₄·OEt₂ and Proton Sponge showed no activity and only starting materials were observed by ¹H NMR (Table 2). This result is plausible because H⁺ can easily coordinate to the aldehyde carbonyl forming an oxonium ion with BF₄⁻ as the counterion. This may further be explained by the idea that BF₄⁻ is not as nucleophilic as Cl⁻ or CH₃COO⁻ and thus the resultant *O*-protonated benzaldehyde carbocation would be stabilized and not destroyed by the BF₄⁻ anion (Figure 1).

To investigate the presence of the carbocation of *O*-protonated benzaldehyde, an acid titration study was performed at -100 °C (Figure 2), using NMR. ¹³C NMR studies were carried out with various concentrations of HBF₄·OEt₂ (1, 2.5, and 6.5 equiv) in the presence of substrate benzaldehyde and CD₂Cl₂. Upon increasing concentration of HBF₄·OEt₂ in the ¹³C coupled spectrum, the coupling constants for both the (*E*)- and (*Z*)-conformations of *O*-protonated benzaldehyde carbocations increase with increasing acid concentration. Proton exchange is rapid between (*E*)- and (*Z*)-conformations. Assignment of the (*E*)-conformation at 202.7 ppm (*J*_{CH} = 196.18 Hz) and the (*Z*)-conformation at 204.1 ppm (*J*_{CH} = 185.86 Hz) with use of 6.5 equiv of HBF₄·OEt₂ is in agreement with previous work by Olah et al. with superacid media.¹² Furthermore, another carbocation species is present in the mixture at 206.2 ppm (*J*_{CH} = 189.3 Hz) that does not undergo rapid exchange; we believe this absorption belongs to the benzoxonium carbocation. In summary, the presence of these cationic species of benzaldehyde provides an essential require-

(12) Olah, G. A.; Reddy, V. P.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1999**, *121*, 9994.

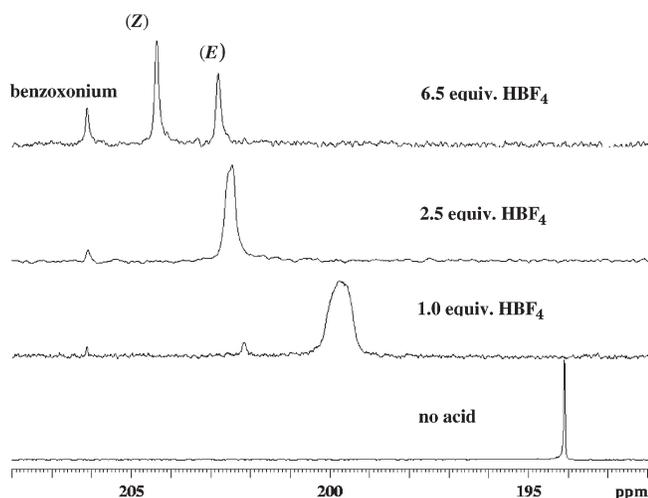


FIGURE 2 ^{13}C NMR decoupled spectra of benzaldehyde at various concentrations of $\text{HBF}_4\cdot\text{OEt}_2$ at $-100\text{ }^\circ\text{C}$.

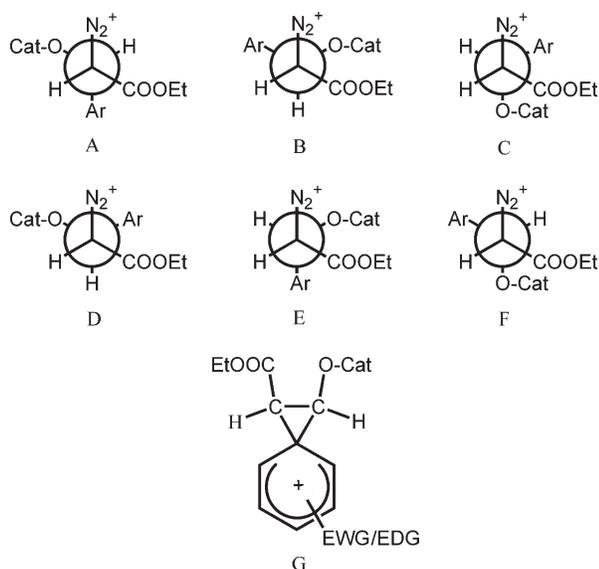


FIGURE 3 Newman projections (i.e., rotamers A through F) of possible transition states and a phenonium ion transition state (G) resulting from aryl migration.

ment for activation of benzaldehyde prior to attack by EDA to form product in the reaction mixture.

Rotamers and Regioselectivity. In each case where a metal–halogen type catalyst was used (SnCl_2 , AlCl_3) significantly more β -keto ester than 3-hydroxyacrylate forms. Work by Kanemasa using the metal–halogen type catalyst SnCl_4 provides an explanation. Kanemasa's suggested chelation transition state orients the migrating hydride (from the aldehyde) and leaving nitrogen (from EDA) anti to one another.⁶ This transition state reduces the steric interactions and facilitates β -keto ester formation.

The catalysts, other than those of the metal–halogen type, bind to the aldehyde first and then the nucleophilic methine carbanion of EDA can attack either the *re*- or *si*-face of the aldehyde. Thus six Newman projections can be drawn (Figure 3). The effectiveness of **1**, which is a bulky catalyst, must originate from its ability to direct the activated aldehyde and EDA to form the lowest

energy rotamer, which favors aryl migration. Rotamer A, the lowest energy rotamer, contains the least number of bulky interactions. Thus the groups that come into eclipse with each other upon migration and subsequently form 3-hydroxyacrylate are minimized with rotamer A, where the aryl group is anti to the leaving N_2 group. β -Keto ester formation can be explained by hydride migration from the next higher energy rotamer D. The four remaining rotamers are not reasonable at low temperature because there is a large steric interaction when the bulky catalyst and ester group are next to one another.

In the case of a less bulky catalyst such as $\text{HBF}_4\cdot\text{OEt}_2$, rotamer A is still the lower energy rotamer thus favoring the formation of 3-hydroxyacrylate. At lower temperature with $\text{HBF}_4\cdot\text{OEt}_2$, a significant increase in yield of 3-hydroxyacrylate is observed. In some cases, no formation of β -keto ester (entries 9, 15, 20, and 30, Table 4) is observed, suggesting rotamer A predominates over other rotamers at this temperature. This result implies that thermodynamic control can influence the selectivity (3-hydroxyacrylate vs β -keto ester) of $\text{HBF}_4\cdot\text{OEt}_2$.

Moreover, it is also possible with **1** or $\text{HBF}_4\cdot\text{OEt}_2$ that aryl migration is favorable over hydride (Figure 3, rotamers B and D) or oxo migration (rotamers C and F) due to its ability to stabilize an intermediate carbocation by the formation of phenonium ion (Figure 3, G). The stabilized phenonium ion is a result of rotamers A and E. Rotamer A being the most stable of the rotamer configurations provides an explanation for 3-hydroxyacrylate formation at low temperatures. Furthermore, this stabilized phenonium ion provides a reason why more 3-hydroxyacrylate formation is observed with electron-donating groups (EDG), since electron-donating groups can enhance the stability of the resultant phenonium ion thus favoring selective formation of 3-hydroxyacrylate. Likewise, electron-withdrawing groups (EWG) destabilize the phenonium ion resulting in decreased formation of 3-hydroxyacrylate.

Conclusion

In summary, our results from these studies indicate that both $\text{HBF}_4\cdot\text{OEt}_2$ and **1** are efficient catalysts for the formation of 3-hydroxyacrylates from aromatic aldehydes and EDA. In the case of acids such as $\text{HBF}_4\cdot\text{OEt}_2$, the catalyst appears to be H^+ , whereas **1** exhibits Lewis acidity at the iron center and is not dependent on H^+ . In both cases, the reaction requires activation of the aromatic aldehyde followed ultimately by loss of N_2 and subsequent rearrangement (either phenyl or hydride migration) to the products 3-hydroxyacrylate or β -keto ester, respectively. The nonnucleophilic behavior of the catalyst anion (BF_4^-) plays two roles: (1) in preventing deactivation of the aldehyde toward the addition of the relatively weak nucleophilic methine carbanion of EDA and (2) in preventing degradation (i.e., loss of N_2) of EDA prior to nucleophilic addition to aldehyde. Furthermore, selective phenyl migration is enhanced in the presence of electron-rich aldehydes, i.e., those with EDG substituents. The outcome of the reaction yield (3-hydroxyacrylate or β -keto ester) is dependent on temperature, which is readily explained by the stability of various rotamer configurations resulting from nucleophilic addition of EDA to the aromatic aldehyde.

In conclusion, we feel the selectivity of both **1** and $\text{HBF}_4 \cdot \text{OEt}_2$ have potential as selective catalysts for future work on downstream synthesis of biologically important compounds from 3-hydroxyacrylates.

Experimental Section

General Considerations. 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 with standard Schlenk techniques. All of the glass flasks were flamed under vacuum and filled with nitrogen prior to use. Column chromatography was performed with silica gel (40–140 mesh). HPLC grade CH_2Cl_2 was distilled under N_2 from P_2O_5 . HPLC grade pentane was distilled from sodium under an inert atmosphere immediately prior to use. Reagent grade Et_2O and tetrahydrofuran were freshly distilled under a N_2 atmosphere from sodium benzophenone ketyl. Benzaldehyde, *p*-tolualdehyde, and *p*-anisaldehyde were purified by extraction with NaHCO_3 solution, washed with water, dried over Na_2SO_4 , and distilled under vacuum. *p*-Nitrobenzaldehyde and *p*-chlorobenzaldehyde were purified by recrystallization from ethanol and dried under vacuum for several days. Ethyl diazoacetate (EDA) was obtained from Aldrich Chemical Co.

Catalytic Reaction: General Procedure. For each experiment, 1.5–5.0 mmol of the aldehyde was dissolved in 15–25 mL of freshly distilled dichloromethane under nitrogen. A 0.1-equiv sample of the appropriate catalyst was added and then the reaction mixture was stirred. Ethyl diazoacetate (1.2 equiv; EDA) was diluted in 4 mL of freshly distilled dichloromethane and drawn into a gas-tight syringe. The diluted EDA was then added to the aldehyde over a period of 6–7 h with the help of a syringe pump. The reaction mixture was allowed to stir for an additional 16–24 h. Each reaction was quenched by adding THF, to remove any products that might be bound to catalyst. The reaction mixture was filtered through a silica plug and the solvent removed by rotary evaporation. Products were isolated by column chromatography (2–10% ether in pentane/hexane or 2–10% ethyl acetate in pentane/hexane) and identified by comparing spectra to known ^1H NMR. ^1H and ^{13}C NMR and elemental analysis were applied to characterize the new compounds.

SnCl_2 -catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 1% yield from 0.029 g (0.149 mmol) of SnCl_2 , 0.15 mL (1.49 mmol) of benzaldehyde, and 0.2 mL (1.78 mmol) of EDA at room temperature. ^1H NMR (CDCl_3): δ 12.2 (d, 1H, J = 13 Hz), 7.3 (m, 5H). In addition, 62% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated. ^1H NMR (CDCl_3 , 300 MHz): δ 7.4–8.0 (m, 5H), 4.20 (q, 2H), 3.98 (s, 2H), 1.24 (t, 3H).

$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ -catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 15% yield from 0.034 g (0.149 mmol) of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, 0.15 mL (1.49 mmol) of benzaldehyde, and 0.2 mL (1.78 mmol) of EDA at room temperature. In addition, 59% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated.

ZnCl_2 -catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 8% yield from 0.021 g (0.149 mmol) of ZnCl_2 , 0.15 mL (1.49 mmol) of benzaldehyde, and 0.2 mL (1.78 mmol) of EDA at room temperature. In addition, 7% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated.

AlCl_3 -catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 3% yield from 0.020 g (0.149 mmol) of AlCl_3 , 0.15

mL (1.49 mmol) of benzaldehyde, and 0.2 mL (1.78 mmol) of EDA at room temperature. In addition, 9% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated.

$\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 21% yield from 0.014 g (0.099 mmol) of $\text{BF}_3 \cdot \text{OEt}_2$, 0.10 mL (0.99 mmol) of benzaldehyde, and 0.18 mL (1.49 mmol) of EDA at room temperature. In addition, 18% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated.

SnCl_4 -catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 18% yield from 0.018 g (0.149 mmol) of SnCl_4 , 0.15 mL (1.49 mmol) of benzaldehyde, and 0.2 mL (1.78 mmol) of EDA at room temperature. In addition, 24% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 42% yield from 0.068 mL (0.497 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.50 mL (4.97 mmol) of benzaldehyde, and 0.66 mL (5.96 mmol) of EDA at room temperature. In addition, 21% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated.

At -78°C , 74% of 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated from 0.068 mL (0.497 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.50 mL (4.97 mmol) of benzaldehyde, and 0.66 mL (5.96 mmol) of EDA.

Iron Lewis acid-catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 58% yield from 0.206 g (0.58 mmol) of the iron Lewis acid, 0.7 g (5.8266 mmol) of benzaldehyde, and 0.735 g (6.99 mmol) of EDA at room temperature. In addition, 25% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was isolated.

SnCl_2 -catalyzed reaction between *p*-nitrobenzaldehyde and EDA: 3-Oxo-3-(4-nitrophenyl)propanoic acid ethyl ester (**5**)⁴ was isolated in 80% yield from 0.024 g (0.124 mmol) of SnCl_2 , 0.185 g (1.24 mmol) of *p*-nitrobenzaldehyde, and 0.17 mL (1.24 mmol) of EDA at room temperature. ^1H NMR (CDCl_3 , 300 MHz): δ 8.3 (m, 4H), 4.3 (q, 2H), 4.0 (s, 2H), 1.3 (t, 3H).

SnCl_2 -catalyzed reaction between *p*-methoxybenzaldehyde and EDA: 3-Oxo-3-(4-methoxyphenyl)propanoic acid ethyl ester (**6**)⁴ was isolated in 30% yield from 0.024 g (0.125 mmol) of SnCl_2 , 0.15 mL (1.25 mmol) of *p*-methoxybenzaldehyde, and 0.17 mL (1.25 mmol) of EDA at room temperature. ^1H NMR (CDCl_3 , 300 MHz): δ 7.2 (m, 4H), 4.3 (q, 2H), 3.8 (s, 2H), 3.6 (s, 3H), 1.3 (t, 3H).

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between *p*-nitrobenzaldehyde and EDA: 3-Hydroxy-2-(4-nitrophenyl)acrylic acid ethyl ester (**4**)⁴ was isolated in 27% yield from 0.017 mL (0.124 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.0185 g (1.24 mmol) of *p*-nitrobenzaldehyde, and 0.17 mL (1.24 mmol) of EDA at room temperature. ^1H NMR (CDCl_3 , 300 MHz): δ 12.4 (d, 1H), 8.2 (d, 2H), 7.5 (d, 2H), 7.4 (d, 1H). In addition, 54% of 3-oxo-3-(4-nitrophenyl)propanoic acid ethyl ester (**5**)⁴ was isolated.

At 0°C , 35% of 3-hydroxy-2-(4-nitrophenyl)acrylic acid ethyl ester (**4**)⁴ and 53% of 3-oxo-3-(4-nitrophenyl)propanoic acid ethyl ester (**5**)⁴ were isolated from 0.017 mL (0.124 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.0185 g (1.24 mmol) of *p*-nitrobenzaldehyde, and 0.17 mL (1.24 mmol) of EDA.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between *p*-methoxybenzaldehyde and EDA: 3-Hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester (**6**)⁴ was isolated in 44% yield from 0.071 mL (0.125 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.70 mL (5.14 mmol) of *p*-methoxybenzaldehyde, and 1.47 mL (6.17 mmol) of EDA at room temperature. ^1H NMR (CDCl_3 , 300 MHz): δ 12.03 (d, 1H, J = 12.6), 7.27 (d, 1H), 7.19 (d, 2H), 6.9 (d, 2H), 3.83 (s, 3H). In addition, 21% of 3-oxo-3-(4-methoxyphenyl)propanoic acid ethyl ester (**7**)⁴ was isolated. ^1H NMR (CDCl_3 , 300 MHz): δ 7.3–6.9 (m, 4H), 4.27 (q, 2H), 3.80 (s, 2H), 3.46 (s, 3H), 1.26 (t, 3H).

At 0°C , 75% of 3-hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester (**6**)⁴ and 15% of 3-oxo-3-(4-methoxyphenyl)propanoic acid ethyl ester (**7**)⁴ were isolated from the reaction of 1.00

(13) Beccalli, E. M.; La Rosa, C.; Marchesini, A. *J. Org. Chem.* **1984**, *49*, 4287.

(14) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290.

mL (8.073 mmol) of *p*-methoxybenzaldehyde, 0.11 mL (0.0807 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, and 0.94 mL (8.00 mmol) of EDA for 24 h.

At -78°C , 90% of 3-hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester (**6**)⁴ was isolated from the reaction of 1.00 mL (8.073 mmol) of *p*-methoxybenzaldehyde, 0.11 mL (0.0807 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, and 0.94 mL (8.00 mmol) of EDA for 24 h. No 3-oxo-3-(4-methoxyphenyl)propanoic acid ethyl ester (**7**)⁴ was isolated.

Iron Lewis acid-catalyzed reaction between *p*-nitrobenzaldehyde and EDA: 3-Hydroxy-2-(4-nitrophenyl)acrylic acid ethyl ester (**4**)⁴ was isolated in 35% yield from 0.0448 g (0.133 mmol) of **1**, 0.203 g (1.33 mmol) of *p*-nitrobenzaldehyde, and 0.18 mL (1.33 mmol) of EDA at room temperature. In addition, 44% of 3-oxo-3-(4-nitrophenyl)propanoic acid ethyl ester (**5**)⁴ was isolated.

At 0°C , 32% of 3-hydroxy-2-(4-nitrophenyl)acrylic acid ethyl ester (**4**)⁴ and 56% of 3-oxo-3-(4-nitrophenyl)propanoic acid ethyl ester (**5**)⁴ were isolated from the reaction of 0.0448 g (0.133 mmol) of **1**, 0.203 g (1.33 mmol) of *p*-nitrobenzaldehyde, and 0.18 mL (1.33 mmol) of EDA for 24 h.

Iron Lewis acid-catalyzed reaction between *p*-methoxybenzaldehyde and EDA: 3-Hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester (**6**)⁴ was isolated in 45% yield from the reaction of 0.139 g (0.414 mmol) of **1**, 0.563 g (4.14 mmol) of *p*-methoxybenzaldehyde, and 1.18 mL (4.96 mmol) of EDA at room temperature. In addition, 35% of 3-oxo-3-(4-methoxyphenyl)propanoic acid ethyl ester (**7**)⁴ was isolated.

At 0°C , 60% of 3-hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester (**6**)⁴ and 20% of 3-oxo-3-(4-methoxyphenyl)propanoic acid ethyl ester (**7**)⁴ were isolated from the reaction of 0.0487 g (0.145 mmol) of **1**, 0.178 mL (1.45 mmol) of *p*-methoxybenzaldehyde, and 0.19 mL (1.45 mmol) of EDA.

At -78°C , 4% of 3-hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester (**6**)⁴ was isolated from the reaction of 0.4 g (2.938 mmol) of *p*-methoxybenzaldehyde, 0.260 g (0.77 mmol) of **1**, and 0.1 mL (0.77 mmol) of EDA.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between furfuraldehyde and EDA: 50% of 3-hydroxy-2-(2-furyl)acrylic acid ethyl ester (**8**)⁶ was isolated from the reaction of 0.50 g (5.2 mmol) of furfuraldehyde, 0.0457 g (0.5 mmol) of HBF_4 , and 0.65 mL (6.24 mmol) of EDA at -78°C . ¹H NMR (CDCl_3 , 300 MHz): δ 12.3 (d, 1H), 7.8 (d, 1H), 7.3 (s, 1H), 6.4 (d, 2H), 4.4 (q, 2H), 1.3 (t, 3H). In addition, 50% of 3-oxo-3-(2-furyl)propanoic acid ethyl ester (**9**)¹⁵ was isolated. ¹H NMR (CDCl_3 , 300 MHz): δ 13.4 (s, 1H), 7.8 (s, 1H), 7.6 (s, 1H). At 0°C under similar conditions there were unidentified decomposition products.

Iron Lewis acid-catalyzed reaction between furfuraldehyde and EDA: 3-Hydroxy-2-(2-furyl)acrylic acid ethyl ester (**8**)⁶ was isolated in 70% yield from 0.50 g (5.2 mmol) of furfuraldehyde, 0.0457 g (0.52 mmol) of **1**, and 0.65 mL (6.24 mmol) of EDA at 0°C . ¹H NMR (CDCl_3 , 300 MHz): δ 12.3 (d, 1H), 7.8 (d, 1H), 7.3 (s, 1H), 6.4 (d, 2H), 4.4 (q, 2H), 1.3 (t, 3H). There was no 3-oxo-3-(2-furyl)propanoic acid ethyl ester (**9**).¹⁵ There was no reaction at -78°C under similar conditions, only furfuraldehyde was recovered.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between acetophenone and EDA: 2-Phenylacetoacetic acid ethyl ester (**10**)¹⁶ was isolated in 74% yield from the reaction of 2.0 g (0.0166 mol) of acetophenone, 0.5 mL (3.32 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, and 5.0 mL (0.05 mol) of EDA at room temperature. ¹H NMR (CDCl_3 , 300 MHz): δ 13.14 (s, 1H), 7.1–7.4 (m, 5H), 4.7 (s, 1H), 4.25 (q, $J = 7.1$ Hz), 2.20 (s, 3H), 1.87 (s, 3H), 1.29 (t, 3H, $J = 7.2$ Hz), 1.20 (t, 3H, $J = 7.2$). There was no reaction at 0°C under similar conditions, only acetophenone was recovered.

Iron Lewis acid-catalyzed reaction between acetophenone and EDA: 2-Phenylacetoacetic acid ethyl ester (**10**)¹⁶ was isolated in trace amount from 0.2 g (1.66 mmol) of

acetophenone, 0.11 g (0.332 mmol) of **1**, and 0.5 mL (5.0 mmol) of EDA at room temperature. There was no reaction at 0°C under similar conditions, only acetophenone was recovered.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between trifluoroacetophenone and EDA: No product was observed by ¹H NMR, when 0.2 g (1.15 mmol) of trifluoroacetophenone was in the presence of 0.032 mL (0.23 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$ and 0.56 mL (5.55 mmol) of EDA at 0°C or room temperature.

Iron Lewis acid-catalyzed reaction between trifluoroacetophenone and EDA: No product was observed by ¹H NMR when 0.2 g (1.15 mmol) of trifluoroacetophenone was in the presence of 0.04 g (0.115 mmol) of **1** and 0.155 mL (1.38 mmol) of EDA at 0°C or room temperature.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between salicylaldehyde and EDA: 3-Benzofurancarboxylic acid ethyl ester (**11**)¹⁷ was isolated in 20% yield from the reaction of 0.026 mL (0.19 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.170 mL (1.87 mmol) of salicylaldehyde, and 0.306 mL (2.25 mmol) of EDA at 0°C . ¹H NMR (CDCl_3 , 300 MHz): δ 8.22 (s, 1H), 8.06 (m, 1H), 7.55 (m, 1H), 7.37 (m, 2H), 3.95 (q, 4H), 1.3 (t, 3H). No 3-oxo-3-(2-hydroxyphenyl)propanoic acid ethyl ester¹⁸ formed in the reaction as observed by ¹H NMR.

Iron Lewis acid-catalyzed reaction between salicylaldehyde and EDA: There was no reaction at 0°C under similar conditions, only salicylaldehyde was recovered.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between 2-aminobenzaldehyde and EDA: Indole-3-carboxylic acid ethyl ester (**12**)¹⁹ was isolated in 23% yield from the reaction of 0.035 mL (0.25 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.225 mL (2.48 mmol) of 2-aminobenzaldehyde, and 0.0405 mL (2.98 mmol) of EDA at 0°C . ¹H NMR (CDCl_3 , 300 MHz): δ 8.66 (s, 1H, NH), 8.21 (m, 1H), 7.94 (d, 1H, $J = 3$ Hz), 7.43 (m, 1H), 7.32 (m, 1H), 4.44 (q, 2H, $J = 7$ Hz), 1.45 (t, 3H, $J = 7$ Hz).

Iron Lewis acid-catalyzed reaction between 2-aminobenzaldehyde and EDA: There was no reaction at 0°C under similar conditions, only 2-aminobenzaldehyde was recovered.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between *o*-tolualdehyde and EDA: 3-Hydroxy-2-(2-methylphenyl)acrylic acid ethyl ester (**13**)²⁰ was isolated in 60% yield from the reaction of 0.28 mL (2.04 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 2.5 g (20.39 mmol) of *o*-tolualdehyde, and 2.859 g (24.468 mmol) of EDA at 0°C . ¹H NMR (CDCl_3 , 300 MHz): δ 12.0 (d, 1H), 7.3 (m, 5H), 4.2 (q, 2H), 2.22 (s, 3), 1.24 (q, 3H). In addition, 35% of 3-oxo-3-(2-methylphenyl)propanoic acid ethyl ester (**14**)²¹ was isolated. ¹H NMR (CDCl_3 , 300 MHz): δ 6.9–7.5 (m, 4H), 5.70 (s, 1H), 2.40 (s, 3H), 2.04 (s, 3H).

Iron Lewis acid-catalyzed reaction between *o*-tolualdehyde and EDA: 3-Hydroxy-2-(2-methylphenyl)acrylic acid ethyl ester (**13**)²⁰ was isolated in 74% yield from the reaction of 0.206 g (0.58 mmol) of **1**, 0.70 g (5.83 mmol) of *o*-tolualdehyde, and 0.735 g (6.99 mmol) of EDA at 0°C for 24 h. In addition, 15% of 3-oxo-3-(2-methylphenyl)propanoic acid ethyl ester (**14**)²¹ was isolated.

$\text{HBF}_4 \cdot \text{OEt}_2$ -catalyzed reaction between *p*-tolualdehyde and EDA: 3-Hydroxy-2-(4-methylphenyl)acrylic acid ethyl ester (**15**)^{4,13} was isolated 51% yield from the reaction of 0.0046 mL (0.34 mmol) of $\text{HBF}_4 \cdot \text{OEt}_2$, 0.41 mL (3.4 mmol) of *p*-tolualdehyde, and 0.50 mL (4.2 mmol) of EDA at 0°C . ¹H

(17) Henke, B. R.; Aquino, C. J.; Birkema, L. S.; Croom, D. K.; Dougherty, R. W., Jr.; Ervin, G. N.; Grizzle, M. K.; Hirst, G. C.; James, M. K.; Johnson, M. F.; Queen, K. L.; Sherrill, R. G.; Sugg, E. E.; Suh, E. M.; Szweczyk, J. W.; Unwalla, R. J.; Yingling, J.; Willson, T. M. *J. Med. Chem.* **1997**, *40*, 2706.

(18) Cushman, M.; Nagarathnam, D.; Burg, D. L.; Geahlen, R. L. *J. Med. Chem.* **1991**, *34*, 798.

(19) Kakehi, A.; Ito, S.; Funahashi, T.; Ota, Y. *J. Org. Chem.* **1976**, *41*, 1570.

(20) Hornback, J. M.; Poundstone, M. L.; Vadlamani, B.; Graham, S. M.; Gabay, J.; Patton, S. T. *J. Org. Chem.*, **1988**, *53*, 5597.

(21) (a) Sicker, D.; Mann, G. *Collect. Czech. Chem. Commun.* **1998**, *53*, 839. (b) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952.

(15) Balaji, B. S.; Chanda, B. M. *Tetrahedron* **1998**, *54*(43), 13237.

(16) Kagan, J.; Agdeppa, D. A., Jr.; Mayers, D. A.; Singh, S. P.; Walters, M. J.; Wintermute, R. D. *J. Org. Chem.* **1976**, *41*, 2355.

NMR (CDCl₃, 300 MHz): δ 12.2 (d, 1H), 7.3 (m, 5H), 2.4 (s, 3H). In addition, 15% of 3-oxo-3-(4-methylphenyl)propanoic acid ethyl ester (**16**)^{4,14} was isolated. ¹H NMR (CDCl₃, 300 MHz): δ 7.2–7.8 (m, 4H), 4.17 (q, 2H), 3.92 (s, 2H), 2.36 (s, 3H), 1.22 (t, 3H).

Iron Lewis acid-catalyzed reaction between *p*-tolualdehyde and EDA: 3-Hydroxy-2-(4-methylphenyl)acrylic acid ethyl ester (**15**)^{4,13} was isolated in 67% yield from the reaction of 0.1158 g (0.34 mmol) of **1**, 0.50 mL (4.1 mmol) of *p*-tolualdehyde, and 0.40 mL (3.4 mmol) of EDA at 0 °C. In addition, 19% of 3-oxo-3-(4-methylphenyl)propanoic acid ethyl ester (**16**)^{4,14} was isolated.

HBF₄·OEt₂-catalyzed reaction between 2,5-dimethylbenzaldehyde and EDA: 3-Hydroxy-2-(2,5-dimethylphenyl)acrylic acid ethyl ester (**17**)²² was isolated in 45% yield from the reaction of 0.168 g (0.122 mmol) of HBF₄·OEt₂, 1.5 g (12.26 mmol) of 2,5-dimethylbenzaldehyde, and 1.96 mL (16.78 mmol) of EDA at 0 °C for 24 h. ¹H NMR (CDCl₃, 300 MHz): δ 12.0 (d, 1H), 7.3 (m, 5H), 4.2 (q, 2H), 2.19 (s, 3H), 2.13 (s, 3H), 1.20 (t, 3H). In addition, 35% of 3-oxo-3-(2,5-dimethylphenyl)propanoic acid ethyl ester (**18**)²³ was isolated. ¹H NMR (CDCl₃, 300 MHz): δ 7–7.5 (m, 3H), 4.24 (q, 2H), 3.95 (s, 2H), 2.35 (s, 3H), 2.18 (s, 3H), 1.33 (t, 3H).

Iron Lewis acid-catalyzed reaction between 2,5-dimethylbenzaldehyde and EDA: 3-Hydroxy-2-(2,5-dimethylphenyl)acrylic acid ethyl ester (**17**)²² was isolated in 72% yield from the reaction of 0.175 g (0.5217 mmol) of **1**, 0.718 g (5.217 mmol) of 2,5-dimethylbenzaldehyde, and 0.658 g (6.26 mmol) of EDA at 0 °C for 24 h. In addition, 20% of 3-oxo-3-(2,5-dimethylphenyl)propanoic acid ethyl ester (**18**)²³ was isolated.

HBF₄·OEt₂-catalyzed reaction between *p*-bromobenzaldehyde and EDA: 3-Hydroxy-2-(4-bromophenyl)acrylic acid ethyl ester (**19**)¹³ was isolated in 55% yield from 0.15 mL (1.60 mmol, 300 mg) of *p*-bromobenzaldehyde, 0.022 mL (0.16 mmol) of HBF₄·OEt₂, and 0.261 mL (1.92 mmol) of EDA at 0 °C for 24 h. ¹H NMR (CDCl₃, 300 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), 1.26 (t, 3H). In addition, 34% of 3-oxo-3-(4-bromophenyl)propanoic acid ethyl ester (**20**) was isolated. ¹H NMR (CDCl₃, 300 MHz): δ 7.3–6.9 (m, 4H), 4.27 (q, 2H), 1.26 (t, 3H).

Iron Lewis acid-catalyzed reaction between *p*-bromobenzaldehyde and EDA: 3-Hydroxy-2-(4-bromophenyl)acrylic acid ethyl ester (**19**)¹³ was isolated in 62% yield from the reaction of 0.33 g (1.78 mmol) of *p*-bromobenzaldehyde, 0.0334 mL (0.101 mmol) of **1**, and 0.291 mL (2.14 mmol) of EDA at 0 °C for 24 h. In addition, 17% of 3-oxo-3-(4-bromophenyl)propanoic acid ethyl ester (**20**)²⁴ was isolated.

HBF₄·OEt₂-catalyzed reaction between 2-nitro-5-chlorobenzaldehyde and EDA: 3-Hydroxy-2-(2-nitro-5-chlorophenyl)acrylic acid ethyl ester (**21**) was isolated in 45% yield from the reaction of 0.015 mL (0.11 mmol) of HBF₄·OEt₂, 0.2 g (1.1 mmol) of 2-nitro-5-chlorobenzaldehyde, and 0.154 g (1.32 mmol) of EDA at 0 °C. ¹H NMR (CDCl₃, 300 MHz): δ 12.04 (d, 1H, *J* = 13 Hz), 8.00 (d, 1H, *J* = 7 Hz), 7.46 (d, 1H, *J* = 5 Hz), 7.34 (d, 1H, *J* = 2 Hz), 7.30 (s, 1H), 4.19 (br q, 2H, *J* = 3 Hz), 1.90 (t, 3H, *J* = 7 Hz). ¹³C NMR (CDCl₃, 75.5 MHz): δ 169.4, 162.4, 147.2, 139.3, 132.0, 130.9, 129.2, 126.4, 105.8, 61.4, 14.0. High-resolution mass (*m/z*): obsd 271.023881 amu, calcd 271.024750 amu. In addition, 33% of 3-oxo-3-(2-nitro-5-chlorophenyl)propanoic acid ethyl ester (**22**) was isolated. ¹H NMR (CDCl₃, 300 MHz): δ 8.15 (d, 1H, *J* = 8.6 Hz), 7.61 (d, 1H, *J* = 8.8 Hz), 7.51 (d, 1H, *J* = 2.2 Hz), 4.19 (q, 2H, *J* = 7.3 Hz), 3.89 (s, 2H), 1.27 (t, 3H, *J* = 7.2 Hz). ¹³C NMR (CDCl₃, 75.5 MHz): δ 193.2, 167.4, 130.7, 129.1, 126.1, 61.5, 48.8, 13.9.

Anal. Calcd for C₁₁H₁₀O₆: C, 48.63; H, 3.71; N, 5.16. Found: C, 48.97; H, 3.92; N, 4.71.

Iron Lewis acid-catalyzed reaction between 2-nitro-5-chlorobenzaldehyde and EDA: 3-Hydroxy-2-(2-nitro-5-chlorophenyl)acrylic acid ethyl ester (**21**) was isolated in 35% yield and 3-oxo-3-(2-nitro-5-chlorophenyl)propanoic acid ethyl ester (**22**) in 20% yield from the reaction of 0.037 g (0.11 mmol) of **1**, 0.2 g (1.1 mmol) of 2-nitro-5-chlorobenzaldehyde, and 0.154 g (1.32 mmol) of EDA at 0 °C for 24 h.

HBF₄·OEt₂-catalyzed reaction between 2-nitroveratraldehyde and EDA: 3-Hydroxy-2-(2-nitro-4,5-dimethoxyphenyl)acrylic acid ethyl ester (**24**) was isolated in 76% yield from the reaction of 0.040 mL (0.25 mmol) of HBF₄·OEt₂, 0.410 g (2.0 mmol) of 2-nitroveratraldehyde, and 0.41 mL (3.72 mmol) of EDA at –78 °C for 24 h. ¹H NMR (CDCl₃, 300 MHz): δ 11.93 (d, 1H, *J* = 13 Hz), 8.11 (d, 1H, *J* = 9 Hz), 7.28 (d, 1H, *J* = 13 Hz), 6.92 (m, 1H), 6.73 (d, 1H, *J* = 3 Hz), 4.16 (br q, 2H), 3.93 (s, 3H), 1.19 (t, 3H, *J* = 7 Hz). ¹³C NMR (CDCl₃, 75.5 MHz): δ 169.9, 163.0, 161.4, 142.1, 131.8, 127.4, 117.4, 112.6, 107.2, 61.1, 55.8, 13.7. Anal. Calcd for C₁₂H₁₃NO₆: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.68; H, 4.92; N, 5.02. No β -keto ester was isolated from this reaction.

NMR study of EDA with 0.1 equiv of HBF₄·OEt₂ and benzaldehyde: A 1:0.1 ratio of EDA to HBF₄·OEt₂ was cautiously prepared by mixing in a 5-mm NMR tube 0.6 mL of CDCl₃, 0.0394 mL (0.312 mmol) of EDA, and 0.0043 mL (0.031 mmol) of HBF₄·OEt₂. A total of 0.0315 mL (0.0312 mmol) of benzaldehyde was titrated in thirds and product was observed by ¹H NMR. The resultant NMR sample was passed through 0.2 g of silica gel and the product completely isomerized to 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ as observed by NMR.

NMR titration of benzaldehyde with HBF₄·OEt₂: The NMR sample was prepared by mixing 0.0315 mL (0.0312 mmol) of benzaldehyde and 0.6 mL of CD₂Cl₂ in a 5-mm NMR tube. The tube was then cooled in a dry ice/acetone bath and ¹³C decoupled and coupled NMR spectra recorded at 173K. The sample was then titrated with 0.0428 mL (0.0312 mmol, 1.0 equiv), 0.0642 mL (0.0468 mmol, 2.5 equivs total), and 0.1284 mL (0.0936 mmol, 6.5 equiv total) of HBF₄·OEt₂, respectively. After each titration of acid, the ¹³C decoupled and coupled NMR spectra were recorded at 173 K.

Proton Sponge Study: General Procedure. The same general procedure was followed except that Proton Sponge was added to the reaction flask before the EDA was added.

Iron Lewis acid-catalyzed reaction between benzaldehyde and EDA with Proton Sponge: At 0.1 equiv of Proton Sponge, 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was observed in 50% conversion relative to benzaldehyde starting material by ¹H NMR from the reaction of 0.0633 g (0.188 mmol) of **1**, 0.200 g (1.88 mmol) of benzaldehyde, 0.0396 g (0.188 mmol) of Proton Sponge, and 0.263 mL (2.256 mmol) of EDA at room temperature.

At 0.01 equiv of Proton-Sponge, 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was observed in 60% conversion relative to benzaldehyde starting material by ¹H NMR from the reaction of 0.0633 g (0.188 mmol) of iron Lewis acid (**1**), 0.200 g (1.88 mmol) of benzaldehyde, 0.004 g (0.0188 mmol) of Proton Sponge, and 0.263 mL (2.256 mmol) of EDA at room temperature.

HBF₄·OEt₂-catalyzed reaction between benzaldehyde and EDA with Proton Sponge: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was observed in 5% conversion relative to benzaldehyde starting material by ¹H NMR from the reaction of 0.405 g (3.98 mmol) of benzaldehyde, 0.0566 mL (0.398 mmol) of HBF₄·OEt₂, 0.0853 g (0.398 mmol) of Proton Sponge, and 0.560 mL (4.80 mmol) of EDA at room temperature.

NaBF₄-catalyzed reaction between benzaldehyde and EDA: Only starting materials were observed by ¹H NMR from the reaction of 0.0437 g (0.40 mmol) of NaBF₄, 0.405 g (3.98

(22) Gustafsson, D.; Nystrom, J.-e. *PCT Int. Appl.* 136, 1997.

(23) Hofer, W.; Maurer, F.; Riebel, H. J.; Schroeder, R.; Uhrhan, P.; Homeyer, B.; Behrenz, W.; Hammann, I. *Ger. Offen.* 39, 1977.

(24) Emelina, E. E.; Semenova, N. A.; Ershov, B. A. *Zh. Organicheskoi Khim.* 1974, 1Q 1034.

mmol) of benzaldehyde, and 0.56 mL (4.80 mmol) of EDA at room temperature with stirring.

Bronsted Acid Study: General Procedure. About 0.1 equiv of acid catalyst was transferred to a flame-dried flask and dissolved in the appropriate solvent (if not soluble, then enough CH_2Cl_2 was added to completely dissolve the catalyst). The corresponding amount of 1.0 equiv of benzaldehyde was added and then 1.2 equiv of EDA dissolved in a small amount of CH_2Cl_2 was added over 1 h. The reaction was allowed to stir 12–18 h. Crude product was filtered through a small amount of silica with ether and the solvent was removed by rotary evaporation. The ratio of 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ to β -keto ester (**3**)¹⁴ was monitored by integrating OH doublet at ~12 ppm and the CH_2 β -keto ester singlet at ~3.8 ppm in the ¹H NMR spectra.

Acetic acid-catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was observed in 0.4% conversion relative to benzaldehyde starting material by ¹H NMR from the reaction of 0.405 g (3.98 mmol) of benzaldehyde, 0.023 mL (0.398 mmol) of acetic acid, and 0.56 mL (4.80 mmol) of EDA at room temperature. In addition, 0.1% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was observed.

HCl (dry)-catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was observed in 0.4% conversion relative to benzaldehyde starting material by ¹H NMR from the reaction of 0.405 mL (3.98 mmol) of benzaldehyde, 0.015 g (0.41 mmol) of HCl dry gas, and 0.56 mL (4.8 mmol) of EDA at room temperature. In addition, 0.1% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ and 10% of ethyl chloroacetate was observed.

HCl (concentrated)-catalyzed reaction between benzaldehyde and EDA: No 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ or β -keto ester were isolated from the reaction of 0.035 mL (12 M, 0.042 mmol) of HCl, 0.43 mL (4.2 mmol) of benzaldehyde, and 0.5 mL (5.0 mmol) of EDA at 0 °C.

HNO₃-catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was observed in 3.7% conversion relative to benzaldehyde starting material by ¹H NMR from the reaction of 0.405 mL (3.98 mmol) of benzaldehyde, 0.024 mL (15.8 M, 0.40 mmol) of HNO₃, and 0.56 mL (4.8 mmol) of EDA at room temperature. In addition, 0.2% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was observed.

At 0 °C, 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 18% yield from 0.027 mL (15.8 M, 0.42 mmol) of HNO₃, 0.43 mL (4.2 mmol) of benzaldehyde, and 0.5 mL (5.0 mmol) of EDA.

HClO₄-catalyzed reaction between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 10% yield from 0.046 mL (9.2 M, 0.042 mmol) of HClO₄, 0.43 mL (4.2 mmol) of benzaldehyde, and 0.5 mL (5.0 mmol) of EDA at 0 °C.

H₂SO₄-catalyzed reactions between benzaldehyde and EDA: 3-Hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was observed in 5.6% conversion relative to benzaldehyde starting material by ¹H NMR from the reaction of 0.405 mL (3.98 mmol) of benzaldehyde, 0.0213 mL (0.40 mmol) of H₂SO₄, and 0.56 mL (4.8 mmol) of EDA at room temperature. In addition, 0.2% of 3-oxo-3-phenylpropanoic acid ethyl ester (**3**)¹⁴ was observed and 20% of 2,2'-[sulfonylbis(oxy)]bisacetic acid diethyl ester (**27**) was observed and characterized. ¹H NMR (CDCl₃, 300 MHz): δ 4.82 (s, 4H), 4.22 (q, 4H), 1.27 (t, 6H). ¹³C NMR (CDCl₃, 75.5 MHz): δ 67.2, 62.2, 13.9. FAB MS [M + 1]: 271amu. Anal. Calcd for C₈H₁₄O₈S: C, 35.56; H, 5.223. Found: C, 35.44; H, 5.11.

At 0 °C, 3-hydroxy-2-phenylacrylic acid ethyl ester (**2**)¹³ was isolated in 26% yield from 0.024 mL (18.1 M, 0.042 mmol) of H₂SO₄, 0.43 mL (4.2 mmol) of benzaldehyde, and 0.5 mL (5.0 mmol) of EDA.

JO0489418