Concise Synthesis of 2-Arylpropanoic Acids and Study of Unprecedented Reduction of 3-Hydroxy-2-arylpropenoic Acid Ethyl Ester to 2-Arylpropenoic Acid Ethyl Ester by $BH_3 \cdot THF$

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We have developed a concise method of synthesizing racemic arylpropanoic acids, which have been widely used as nonsteroidal anti-inflammatory drugs (NSAIDs). The synthesis involves only four steps from commercially available benzaldehyde. The synthesis incorporates an unprecedented reduction reaction, conversion of 3-hydroxy-2-arylpropenoic acid ethyl ester to 2-arylpropenoic acid ethyl ester by $BH_3 \cdot THF$. The reduction reaction has been investigated and optimized.

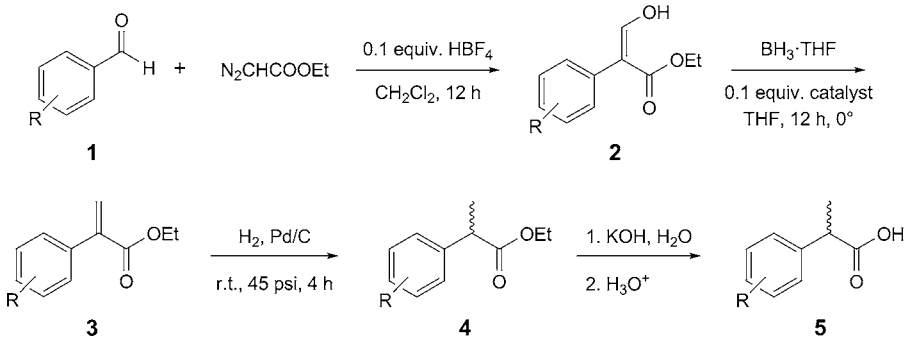
Introduction. – 2-Arylpropanoic acids (profens) are very important compounds and have been widely used as nonsteroidal anti-inflammatory drugs (NSAIDs) for the relief of acute and chronic rheumatoid arthritis and osteoarthritis, as well as for other connective tissue disorders and pains [1]. NSAIDs primarily inhibit the binding of arachidonic acid to the cyclo-oxygenase subunit of prostaglandin synthetase, and prevent the formation of various prostaglandins and thus control the inflammatory response [2]. Examples of some of the profens are fenoprofen, ibuprofen, ketoprofen, flurbiprofen, and naproxen. All of the profens are chiral and, except (*S*)-naproxen and (*S*)-flunoxaprofen, they are marketed in racemic form [3]. Although profen is a successful and widely used drug, it can cause some serious side effects, such as gastric intestinal (GI) disturbances, gastric or duodenal ulceration, dizziness, skin rash, and tinnitus, *etc*. [4]. The side effects related to gastroenteropathies are generally believed to be resulted from the direct contact effect, which can be attributed to the combination of local irritation produced by the free carboxylic group in the molecular structure and by local blockage of prostaglandin biosynthesis in the GI tract [5]. Thus, it is very important to synthesize a variety of profen analogues so that the side effects could be minimized. For example, recently, it has been reported that the methyl-monofluorinated ibuprofen was found to have an almost equal pharmacokinetic profile with an increased analgesic activity and diminished gastric damage in animal models comparing to the parent drug ibuprofen [6].

A number of synthesis routes are available for the preparation of both racemic [7] and optically active profens [8]. Most of these methods are applicable for a particular type of profen and some of them are not cost effective. In this article, we will present a general procedure to produce racemic arylpropanoic acids and their prochiral precursors in a few steps and also a study to understand the mechanism of an unprecedented reduction reaction, conversion of 3-hydroxy-2-arylpropenoic acid ethyl

ester **2** to 2-arylpropenoic acid ethyl ester **3** by $BH_3 \cdot THF$. Our method can be used to synthesize the optically pure profens by enantioselective hydrogenation of the prochiral precursors [9a–9e] or by enantiomeric resolution of the racemic profens [9f–9j].

The synthesis involves a three-step transformation to prepare 2-arylpropanoic acid **5** from 3-hydroxy-2-arylpropenoic acid ethyl ester **2** (*Scheme 1*). The starting material, 3-hydroxy-2-arylpropenoic acid ethyl ester **2**, was synthesized from the corresponding benzaldehyde **1** according to the method developed in our lab [10][11]. Reduction of the hydroxypropenoic acid ethyl ester **2** to propenoic acid ethyl ester **3** was achieved by using $BH_3 \cdot THF$. The olefin was then hydrogenated to give 2-arylpropanoic acid ester **4**, which was then hydrolyzed to give the desired 2-arylpropanoic acid **5**.

Scheme 1. *Preparation of 2-Arylpropanoic Acids from Aromatic Aldehyde*

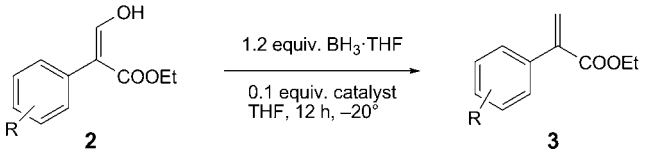


Results and Discussion. – To improve the overall yields for the final product **5**, we studied and optimized the synthetic procedure. The reaction described in *step 1* is reported elsewhere [10] and will not be discussed here.

Optimization of the Step 2. Previously, our lab reported the reduction of 3-hydroxy-2-(6-methoxy-2-naphthyl)propenoic acid ethyl ester to 2-(6-methoxy-2-naphthyl)propenoic acid ethyl ester by using $BH_3 \cdot THF$, as a method to synthesize a naproxen precursor [11]. This time, we wanted to establish this methodology as a general method for preparing 2-arylpropenoic acid ethyl esters **3**. To our delight, we were able to apply this methodology to convert a number of hydroxypropenoic acid ethyl esters **2** to their corresponding olefins **3** using $BH_3 \cdot THF$ in the presence of an amine catalyst. Initially, we carried out the reaction using piperidine as the catalyst. The reaction was carried out at $-20°$ for 12 h using 1.2 equiv. of $BH_3 \cdot THF$. After the aqueous workup and column chromatography, 2-arylpropeonic acid ethyl esters **3** were isolated in 20–61% yield (*Table 1*). As per our observation, the electron-withdrawing or electron-releasing groups have no effect on the yield of the product. To improve the yield, we investigated the nature and amount of catalysts and also temperature on this $BH_3 \cdot THF$ reduction reaction.

Effect of Catalysts. Originally, piperidine was used as the catalyst for the conversion of hydroxypropenoic acid ethyl ester **2** to propenoic acid ethyl ester **3**. The amine is very important for this reduction reaction [11]. In order to improve the yield of the olefin,

Table 1. *Piperidine-Catalyzed Reduction of Hydroxyarylpropenoic Acid Ester*

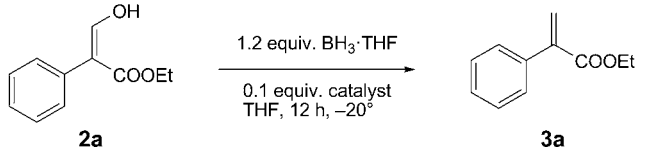


2 **3**

Entry	R	Product	Yield of isolated product [%]
1	2-NO_2 (**2b**)	**3b**	61
2	3,4-OCH_2O-6-NO_2 (**2c**)	**3c**	40
3	2-Cl-5-NO_2 (**2d**)	**3d**	20
4	4-MeO (**2e**)	**3e**	30

we performed the reduction reaction with several amines such as piperidine, CBS catalyst, 2-aminophenol, and Et_3N. The reaction was carried out at $-20°$ for 12 h with 1.2 equiv. of $BH_3 \cdot THF$ in presence of 10% amine. Among these bases, the racemic CBS catalyst afforded the best yield of 70% (*Table 2*). The CBS catalyst was prepared in the lab following procedures by *Corey* [12] and was used without further purification. 2-Aminophenol and Et_3N (*Entries 3* and *4*, *Table 2*) gave low yields, and a considerable amount of starting material was left in the reaction mixture after 12 h. Increasing amine loading to 20% lowered the yield even more. We believe that this happened due to the fact that the amine binds to BH_3, thus reducing the activity of the reagent and as a result, lowered the yield of the reaction.

Table 2. *Catalyst Screening*

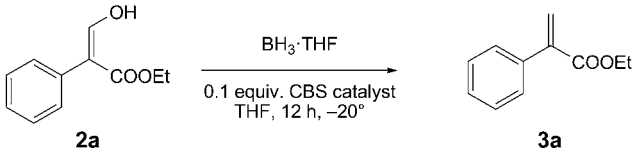


2a **3a**

Entry	Catalyst	Yield of isolated product [%]
1	Piperidine	50
2	CBS catalyst	70
3	2-Aminophenol	10
4	Et_3N	20

Amount of $BH_3 \cdot THF$. In order to determine the optimum $BH_3 \cdot THF$ concentration, we studied the reduction with various amounts of $BH_3 \cdot THF$. The reduction was carried out using the standard reaction condition as described previously, and the results are depicted in *Table 3*. From this study, we concluded that 1.2 equiv. of $BH_3 \cdot THF$ per equiv. of hydroxypropenoic acid ester are required to obtain the best yield of the product. However, excess $BH_3 \cdot THF$ lowers the yield of the olefin product, as it further reacts with $BH_3 \cdot THF$ to give an unidentified complex.

Table 3. *Optimization of the Amount of $BH_3 \cdot THF$*

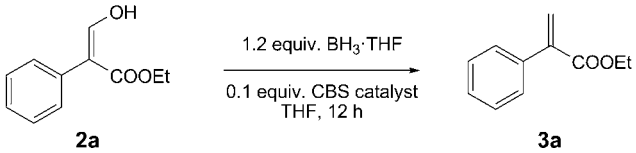


2a **3a**

Entry	$BH_3 \cdot THF$ [equiv.]	Yield of isolated product [%]
1	0.5	0
2	1	50
3	1.2	70
4	2	40
5	3	0

Effect of Temperature. In our next effort, we studied the temperature effect on the yield of the product of the reduction. The results are summarized in *Table 4*. From this study, $BH_3 \cdot THF$ was found to be inactive at $-78°$ and did not produce any olefin **3a**. At $-20°$, the reaction gave the best result and the aryl propenoic acid ethyl ester was obtained in 65% yield. At 0°, the reaction was almost comparable to the yield at $-20°$, whereas no olefin was obtained, when the reduction was performed at 40°, but some unidentified products were formed.

Table 4. *Temperature Screening*

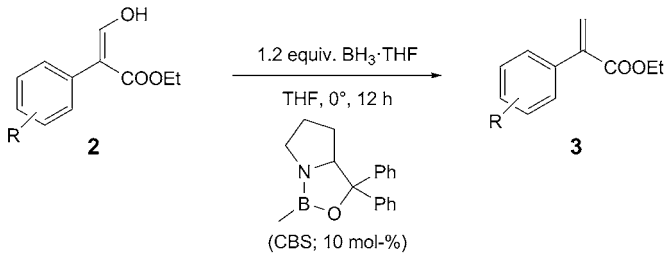


2a **3a**

Entry	Temperature [°]	Yield of isolated product [%]
1	–78	0
2	–20	65
3	0	60
4	40	0

Step 2 *with Optimized Reaction Condition*. The outcome of our experiments for the optimization of the yield for the reduction step suggest that *1*) the optimal amount of $BH_3 \cdot THF$ should be 1.2 equiv; *2*) the choice of catalyst should be 10% CBS; and *3*) the preferred temperature should be 0°. Although reactions both at $-20°$ and 0° gave the similar results, we choose to run the reaction at 0° rather than at $-20°$, mainly due to the ease of operation. With these optimal reaction conditions, we tried the reduction for a number of hydroxypropenoic acid ethyl esters using the CBS catalyst. The results are presented in *Table 5*. The yields of the corresponding olefins were good, around *ca.* 70%. The electron-donating or -withdrawing substituents on the hydroxyacrylate have no effect on the yield of the olefin product.

Table 5. *Optimized Reduction of Hydroxyarylpropenoic Acid Ethyl Ester*

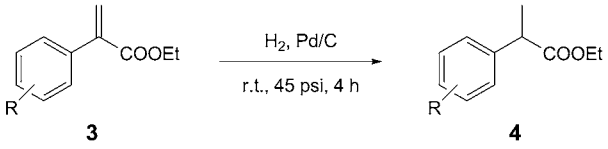


Entry	R	Product	Yield of isolated product [%]
1	H (**2a**)	**3a**	60
2	2-MeO (**2f**)	**3f**	70
3	4-Me (**2g**)	**3g**	66
4	2-Br (**2h**)	**3h**	69
5	2-Me (**2i**)	**3i**	65
6	2,4-Cl_2 (**2j**)	**3j**	70

Hydrogenation of Arylpropenoic Acid Ethyl Ester to Arylpropanoic Acid Ethyl Ester (*Step 3*). The third step was the hydrogenation on the propenoic acid ester **3** to the propanoic acid ester **4**. This procedure employs the typical hydrogenation reaction using palladium on carbon as the catalyst at 45 psi for four hours in MeOH. The yields were very high (*ca.* 90%), and purification was also simple. The catalyst was removed using *Celite*, and pentane was added to elute the product. Rotary evaporation of the solvent gave pure 2-arylpropanoic acid ethyl esters in high yields (*Table 6*).

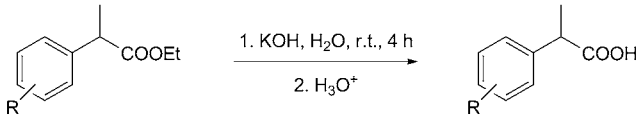
Hydrolysis of Arylpropanoic Acid Ethyl Esters **4** *to Arylpropanoic Acids* **5** (*Step 4*). The final step in the synthesis was to hydrolyze the ester group to an acid group. Aqueous KOH was added in acetone and the mixture was allowed to stir overnight at room temperature. After reaction was completed, the mixture was washed with Et_2O. The aqueous layer was acidified with aqueous HCl and extracted with Et_2O (three

Table 6. *Hydrogenation Reaction of Propenoic Acid Ethyl Ester*



Entry	R	Product	Yield of isolated product [%]
1	H (**3a**)	**4a**	95
2	2-MeO (**3f**)	**4f**	95
3	4-Me (**3g**)	**4g**	90
4	2-Br (**3h**)	**4h**	95
5	2-Me (**3i**)	**4i**	93
6	2,4-Cl_2 (**3j**)	**4j**	84

Table 7. *Hydrolysis of Arylpropanoic Acid Ethyl Ester*



4 **5**

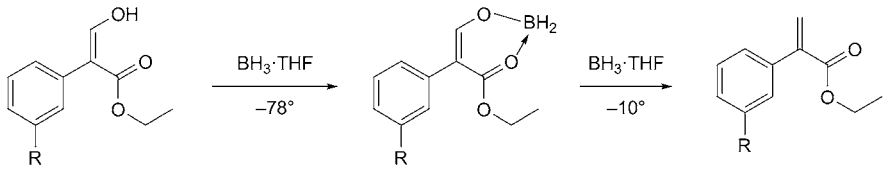
Entry	R	Product	Yield of isolated product [%]
1	H (**4a**)	**5a**	92
2	2-MeO (**4f**)	**5f**	90
3	4-Me (**4g**)	**5g**	93
4	2-Br (**4h**)	**5h**	90
5	2-Me (**4i**)	**5i**	95
6	2,4-Cl_2 (**4j**)	**5j**	90

times). The Et_2O layer was dried using anhydrous $MgSO_4$, and the solvent was removed by rotary evaporation to produce the product **5** as white solid. The yield for this hydrolysis was almost quantitative (*Table 7*).

Study of the Mechanism of BH_3·THF Reduction of Hydroxyarylpropenoic Acid Ethyl Ester. In our initial study towards the mechanism of *Step 2*, *i.e.*, reduction of hydroxypropenoic acid ethyl ester **2** to propenoic acid ethyl ester **3**, we identified and characterized a novel dihydroborane intermediate **6** (*Scheme 2*) [13]. Here, we would like to report the further development of our study to understand this unprecedented transformation.

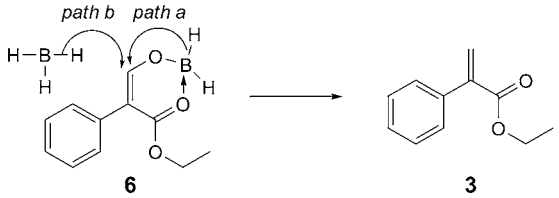
Hydride Migration. After the formation of the dihydroborane intermediate **6**, a hydride shift from BH_3 is needed to obtain the final product, propenoic acid ethyl ester **3**. This hydride migration could happen in an (*a*) intra- or (*b*) inter-molecular process, as shown in *Scheme 3*.

Scheme 2. *Formation of Dihydroborane Intermediate* **6**



2a R = H
2k R = NO_2 **6** **3**

Scheme 3. *Plausible Hydride Migration in the Reduction Reaction*



6 **3**

In our previous article [13], we proposed that hydride migration occurs through intermolecular fashion (*path b*). The evidences for this argument were: *1*) when 0.5 equiv. of BH_3 was used, no olefin was formed, once all BH_3 was used up. This assumption was verified by repeating the reaction using only 0.5 equiv. of BH_3, which showed very clearly that olefin formation ceased once all BH_3 had been consumed; and *2*) when BD_3 was used as reactant, NMR spectra of the olefin **3a** formed under those conditions showed that the deuterium was incorporated in the *cis* and *trans* positions in equal amounts, which is more likely to occur in an intermolecular rather than intramolecular hydrogen transfer step. Here, we performed more experiments to further prove that the hydride migration more likely occurs *via* the intermolecular process.

Since the intermediate **6** is very unstable, air- and temperature-sensitive, we aimed to synthesize more stable boron intermediates similar to the intermediate **6**, and we used catechoboron or 9-boronbicyclo[3,3,1]nonane (BBN). In addition, catechoboron or BBN have only one β-H hydrogen, and no intramolecular hydride shift is possible in such case.

Reaction of the Acrylate with Catechol Borane. A reaction was carried out using 2 equiv. of catechol borane and 1 equiv. of **2a** at 0°. As usual, H_2 gas evolved vigorously. In the NMR spectrum, the OH peak of **2** had disappeared instantly. We observed a new peak around 8.1 ppm (*Fig. 1*), which was characterized to belong to intermediate **7**. This intermediate was stable, and no formation of compound **3** was observed. After few hours, we added 1 equiv. of $BH_3 \cdot THF$, and we observed new peaks corresponding to the olefin **3**. Initially, the olefin peak was rising, as the intermediate peak was decreasing, and after several hours, we found the olefin peak decreasing along with the intermediate peak. This is due the further reaction of the olefin.

Reaction of the Acrylate with 9-BBN. A similar NMR study was carried out using 2 equiv. of 9-BBN and 1 equiv. of **2a** at 0°. As usual, H_2 evolved, and the signal of the OH group of ester **2** disappeared. We observed a new peak around 7.9 ppm (*Fig. 2*) which was attributed to the complex **8**. This intermediate **8** seemed to be stable, however no olefin **3** were observed. After few hours, we added 1 equiv. of $BH_3 \cdot THF$, and new peaks corresponding to the olefin was observed. Initially, the olefin peak was rising as the intermediate peak was decreasing, and after several hours, we found that the olefin peak was decreasing along with the intermediate peak. This is due to the further reaction of the olefin. These two experiments present further evidence that the hydride shift occurs in intermolecular fashion.

Role of H_2O in the Reduction. In our previously proposed mechanism [11], we assumed that H_2O is required for the formation of product, and to verify this speculation, we added D_2O to find out whether the H in the olefin comes from H_2O or not. After analysis of the product, we did not find any incorporation of deuterium in the product. We also observed that, when we were monitoring the reaction in the NMR tube, we found the formation of product without the addition of H_2O. We assumed that H_2O is not required for the reaction, and it is only useful to quench the reaction that removes the excess of boron compounds.

Effect of Hydride Source. In order to check if the reaction occurs with an other hydride source, we tried the reaction under standard conditions with various hydrides such as $LiAlH_4$ and DIBAL-H at different temperatures. But none of these reducing agents gave the desired olefin. These experiments suggest that the reduction is specific to $BH_3 \cdot THF$.

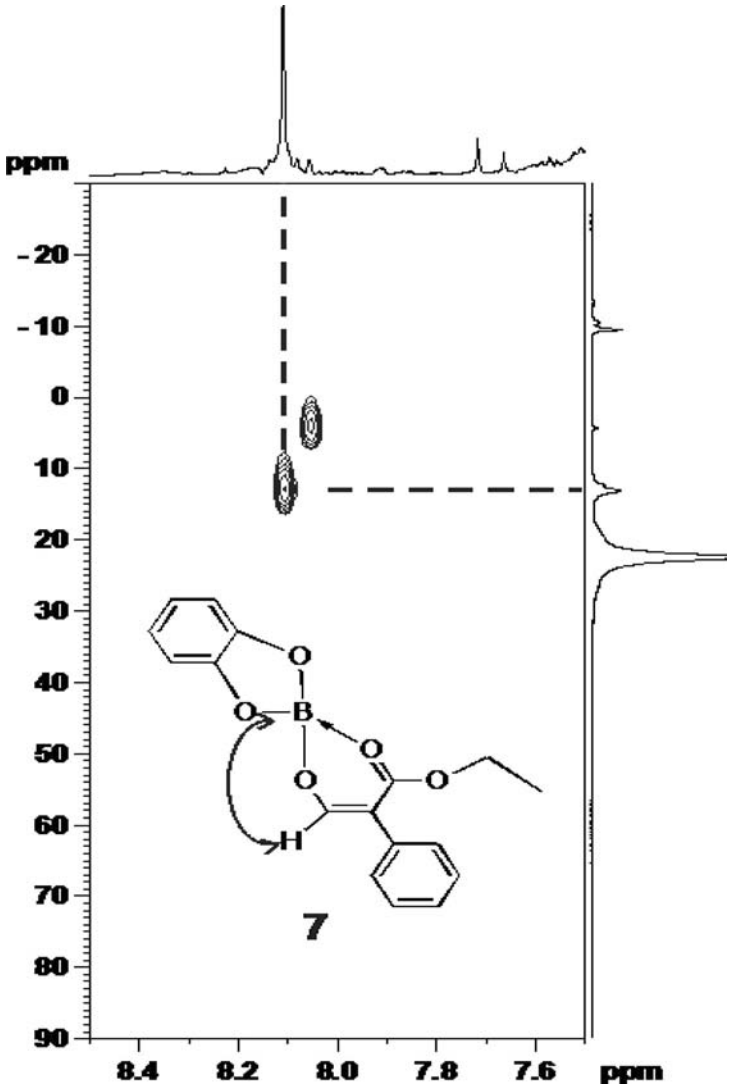


Fig. 1. *Long-range optimized* $^{1}H\{^{11}B\}$ *HSQC experiment* (mixing time 12.5 ms) *of a 2:1 mixture of catechol-borane and hydroxypropenoic acid ethyl ester* **2** *after one hour at 268 K.* The correlation arising from intermediate **7** is highlighted.

Conclusions. – In conclusion, a general method for the synthesis of prochiral arylpropenoic acid ethyl ester has been developed. These prochiral precursors of profens were synthesized in two steps with good yields, and these compounds can be converted to the respective optically active profens by asymmetric hydrogenation. A method to achieve the racemic profens is also provided. These racemic profens can be converted to optically active profens by chiral resolution.

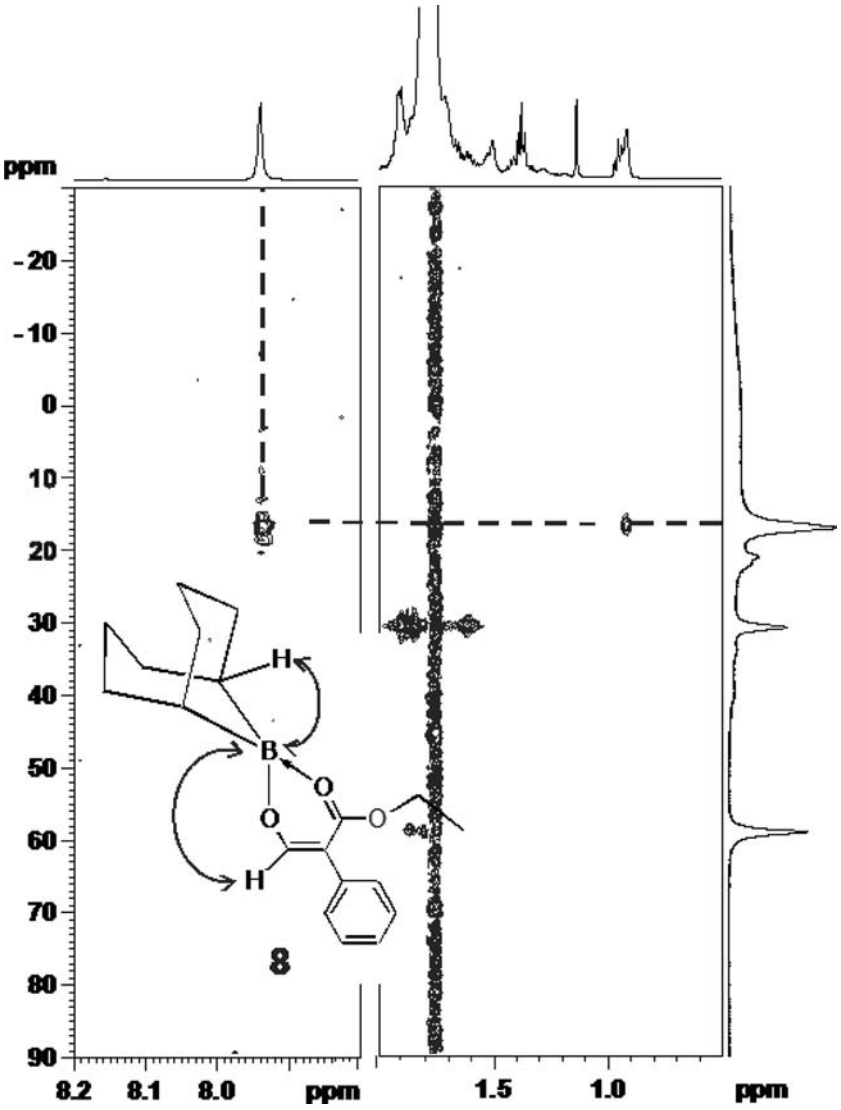


Fig. 2. *Long-range $^{1}H\{^{11}B\}$ HMBC spectrum* (mixing time 50 ms) *of a 2:1 mixture of 9-BBN and the hydroxypropenoic acid ethyl ester* **2** *after 24 h at room temperature* (298 K). Correlations from the intermediate **8** are highlighted.

Experimental Part

General Considerations. All operations were performed under a dry N_2 atmosphere with standard *Schlenk* techniques. Column chromatography (CC): silica gel (SiO_2; 40–140 mesh). HPLC grade CH_2Cl_2 was distilled under N_2 from P_2O_5. HPLC grade pentane was distilled from Na under an inert atmosphere immediately prior to use. Reagent grade Et_2O and THF were freshly distilled under a N_2 atmosphere from sodium benzophenone ketyl. Compounds **2a**, **2b**, **2c**, **2d**, **2e**, **2g**, and **2j** were synthesized by the

known published procedure [10][11]. NMR Data: *Bruker 300* MHz instrument: the chemical shifts (δ) are expressed in ppm relative to tetramethylsilane, and $CDCl_3$ was used as the solvent. Elemental analyses: *Perkin-Elmer 240C* elemental analyzer was employed.

General Procedure for the Preparation of 3-Hydroxy-2-aryl Propenoic Acid Ethyl Esters (**2**). In a typical experiment, 1 equiv. of aromatic aldehyde (3–6 mmol) was dissolved in 20–30 ml of freshly dist. CH_2Cl_2 under N_2. Then, 0.3–0.6 mmol (0.1 equiv) of catalyst $HBF_4 \cdot OEt_2$ was added and stirred for several minutes and cooled down to the temp. required from $-78°$ to $0°$. Then, 1.2 equiv. of ethyl diazoacetate (EDA) was diluted with 5–15 ml of CH_2Cl_2 and dripped slowly from a gas-tight syringe using a syringe pump over a period of 7–18 h. After the addition was complete, NMR and TLC were taken to check if the reaction was complete. If not, the mixture was stirred for more hours, until no more starting material was observed. The reaction was stopped by passing through a SiO_2 plug and the solvent removed using rotary evaporation. The products were isolated by CC (2–20% Et_2O in pentane). ^{1}H-NMR was recorded and compared to literature values.

3-Hydroxy-2-(2-methoxyphenyl)propenoic Acid Ethyl Ester (= *Ethyl 3-Hydroxy-2-(2-methoxyphenyl)prop-2-enoate*; **2f**) [14]. From 2.00 g (14 mmol) of *o*-anisaldehyde, 2.01 g (17.63 mmol) of EDA, and 0.2 ml (1.4 mmol) of $HBF_4 \cdot OEt_2$ at $-78°$. Yield: 95%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 12.10 (*d*, $J = 13$, 1 H, OH); 7.50 (*d*, $J = 13$, 1 H, =CH); 7.00–7.70 (*m*, 4 H, Ph); 4.26 (*q*, $J = 7$, 2 H, OCH_2); 3.80 (*s*, 3 H, MeO); 1.29 (*t*, $J = 7$, 3 H, Me).

3-Hydroxy-2-(2-bromophenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(2-Bromophenyl)-3-hydroxyprop-2-enoate*; **2h**) [15]. From 1.5 g (8.1 mmol) of 2-bromobenzaldehyde, 1.11 g (9.7 mmol) of EDA, and 0.11 ml (0.81 mmol) $HBF_4 \cdot OEt_2$ at $-78°$. Yield: 89%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 11.99 (*d*, $J = 13$, 1 H, OH); 7.70 (*d*, $J = 13$, 1 H, =CH); 7.20–7.40 (*m*, 4 H, Ph); 4.25 (*q*, $J = 7$, 2 H, OCH_2); 1.32 (*t*, $J = 7$, 3 H, Me).

3-Hydroxy-2-(2,5-dichlorophenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(2,5-Dichlorophenyl)-3-hydroxyprop-2-enoate*; **2i**) [14]. From 2.0 g (11.4 mmol) of 2,5-dichlorobenzaldehyde, 1.56 g (13.7 mmol) of EDA, and 0.15 ml (1.14 mmol) of $HBF_4 \cdot OEt_2$ at $-78°$. Yield: 60%. ^{1}H-NMR ($CDCl_3$) 300 MHz): 12.06 (*d*, $J = 13$, 1 H, OH); 7.20–7.60 (*m*, 4 H, =CH and Ph); 4.22 (*q*, $J = 7$, 2 H, OCH_2); 1.25 (*t*, $J = 7$, 3 H, Me).

General Procedure for Reduction of 3-Hydroxy-2-arylpropenoic Acid Ethyl Esters **2** *to 2-Arylpropenoic Acid Ethyl Esters* **3**. In a typical experiment, 1 equiv. of 3-hydroxy-2-arylpropenoic ethyl ester **2** was dissolved in 20–30 ml of freshly dist. THF under N_2. Then, 0.1 equiv. of CBS catalyst or piperidine was added. Then, the soln. was cooled to $0°$ and 1.2 equiv. of $BH_3 \cdot THF$ were added and the progress of the reaction was monitored using TLC and NMR. The mixture was kept at $0°$ for 5–6 h, until the enol peak had disappeared. Then, the reaction was quenched with 10 ml of H_2O, and the mixture was stirred for several min. THF was removed by rotary evaporation, and the residue was extracted with Et_2O. Removal of the Et_2O yielded a liquid product. CC was performed using 1–2% Et_2O in pentane to obtain the product in 50–70% yield.

Piperidine-Catalyzed Reduction of 3-Hydroxy-2-arylpropenoic Acid Ethyl Esters **2** *with* $BH_3 \cdot THF$. 2-(2-Nitrophenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(2-Nitrophenyl)prop-2-enoate*; **3b**). From 0.5 g (2.1 mmol) of *ethyl 3-hydroxy-2-(2-nitrophenyl)prop-2-enoate* (**2b**), 3.8 ml (3.8 mmol) of $BH_3 \cdot THF$, and 42 µl (0.42 mmol) of piperidine at $0°$. Yield: 61%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.04 (*d*, $J = 8$, 1 H, Ph); 7.57 (*t*, $J = 8$, 1 H, Ph); 7.44 (*t*, $J = 8$, 1 H, Ph); 7.28 (*m*, 1 H, Ph); 6.47 (*s*, 1 H, =CH); 5.80 (*s*, 1 H, =CH); 4.13 (*q*, $J = 7$, 2 H, OCH_2); 1.14 (*t*, $J = 7$, 3 H, Me).

2-(4,5-Methylenedioxy-2-nitrophenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(6-Nitro-1,3-benzodioxol-5-yl)prop-2-enoate*; **3c**). From 0.48 g (1.7 mmol) of *ethyl 3-hydroxy-2-(6-nitro-1,3-benzodioxol-5-yl)prop-2-enoate* (**2c**), 3 ml (3.07 mmol) of $BH_3 \cdot THF$, and 34 µl (0.34 mmol) of piperidine at $0°$. Yield: 40%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.65 (*s*, 1 H, Ph); 7.28 (*s*, 1 H, Ph); 6.77 (*s*, 1 H, =CH); 6.17 (*s*, 2 H, OCH_2O); 5.79 (*s*, 1 H, =CH); 4.22 (*q*, $J = 7$, 2 H, OCH_2); 1.24 (*t*, $J = 7$, 3 H, Me). Anal. calc. for $C_{12}H_{11}NO_6$ (265.22): C 54.34, H 4.18, N 5.28; found: C 53.79, H 4.15, N 5.03.

2-(5-Chloro-2-nitrophenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(5-Chloro-2-nitrophenyl)prop-2-enoate*; **3d**). From 0.463 g (1.7 mmol) of *ethyl 2-(2-chloro-5-nitrophenyl)-3-hydroxyprop-2-enoate* (**2d**), 3 ml (3.07 mmol) of $BH_3 \cdot THF$ 0.463 g (1.7 mmol), and 30 µl of piperidine (0.34 mmol) at $0°$. Yield: 20%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.19 (*m*, 2 H, Ph); 7.28 (*d*, $J = 2$, 1 H, Ph); 6.67 (*s*, 1 H, =CH); 5.91 (*s*,

1 H, =CH); 4.30 (*q*, *J* = 7, 2 H, OCH_2); 1.31 (*t*, *J* = 7, 3 H, Me). Anal. calc. for $C_{11}H_{10}ClNO_4$ (255.65): C 51.68, H 3.94, N 5.48; found: C 51.32, H 3.91, N 5.20.

2-(4-Methoxyphenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(4-Methoxyphenyl)prop-2-enoate*; **3e**) [16]. From 0.1 g (0.45 mmol) of *ethyl 3-hydroxy-2-(4-methoxyphenyl)prop-2-enoate* (**2e**), 1.4 ml (1.4 mmol) of $BH_3 \cdot THF$, and 5 µL of piperidine (0.045 mmol) at 0°. Yield: 30%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.37 (*d*, *J* = 9, 2 H, Ph); 6.88 (*d*, *J* = 9, 2 H, Ph); 6.25 (*d*, *J* = 1, 1 H, =CH); 5.82 (*d*, *J* = 1, 1 H, =CH); 4.28 (*q*, *J* = 7, 2 H, OCH_2); 3.81 (*s*, 3 H, MeO); 1.33 (*t*, *J* = 7, 3 H, Me).

CBS-Catalyzed Reduction of 3-Hydroxy-2-arylpropenoic Acid Ethyl Esters **2** *with* $BH_3 \cdot THF$. *2-Phenylpropenoic Acid Ethyl Ester* (= *Ethyl 2-Phenylprop-2-enoate*; **3a**) [17]. From 0.2 g (1.0 mmol) of *ethyl 3-hydroxy-2-phenylprop-2-enoate* (**2a**), 1.0 ml (1.0 mmol) of $BH_3 \cdot THF$, and 0.1 ml (0.10 mmol) of CBS catalyst at 0°. Yield: 70%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30–7.60 (*m*, 5 H, Ph); 6.35(*d*, *J* = 1, 1 H, =CH); 5.90 (*d*, *J* = 1, 1 H, =CH); 4.27 (*q*, *J* = 7, 2 H, OCH_2); 1.22 (*t*, *J* = 7, 3 H, Me).

2-(2-Methoxyphenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(2-Methoxyphenyl)prop-2-enoate*; **3f**) [18]. From 0.45 g (2.1 mmol) of **2f**, 2.52 ml (2.52 mmol) of $BH_3 \cdot THF$, and 0.2 ml (0.2 mmol) at 0°. Yield: 70%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30–7.70 (*m*, 4 H, Ph); 6.27 (*d*, *J* = 1, 1 H, =CH); 5.84 (*d*, *J* = 1, 1 H, =CH); 4.29 (*q*, *J* = 7, 2 H, OCH_2); 3.83 (*s*, 3 H, MeO); 1.20 (*t*, *J* = 7, 3 H, Me).

2-(4-Methylphenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(4-Methylphenyl)prop-2-enoate*; **3g**) [19]. From 0.55 g (2.69 mmol) of **2g**, 3.23 ml (3.23 mmol) of $BH_3 \cdot THF$, and 0.2 ml (0.2 mmol) at 0°. Yield: 65%. ^{1}H-NMR ($CDCI_3$, 300 MHz): 7.30–7.60 (*m*, 4 H, Ph); 6.31 (*d*, *J* = 1, 1 H, =CH); 5.87 (*d*, *J* = 1, 1 H, =CH); 4.29 (*q*, *J* = 7, 2 H, OCH_2); 2.34 (*s*, 3 H, Me); 1.29 (*t*, *J* = 7, 3 H, Me).

2-(2-Bromophenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(2-Bromophenyl)prop-2-enoate*; **3h**) [20]. From 0.66 g (2.43 mmol) of ethyl 2-(2-bromophenyl)-3-hydroxyprop-2-enoate (**2h**), 2.91 ml (2.91 mmol) of $BH_3 \cdot THF$, and 0.2 ml (0.2 mmol) at 0°. Yield: 69%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.00–7.50 (*m*, 4 H, Ph); 6.53 (*d*, *J* = 1, 1 H, =CH); 5.77(*d*, *J* = 1, 1 H, =CH); 4.28 (*q*, *J* = 7, 2 H, OCH_2); 1.23 (*t*, *J* = 7, 3 H, Me).

2-(2-Methylphenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(2-Methylphenyl)prop-2-enoate*; **3i**) [19]. From 0.70 g (3.40 mmol) of **2i**, 4.1 ml (4.10 mmol) of $BH_3 \cdot THF$, and 0.34 ml (0.34 mmol) at 0°. Yield: 66%. ^{1}H-NMR ($CDCI_3$, 300 MHz): 7.3–7.6 (*m*, 4 H, Ph); 6.51 (*d*, *J* = 2, 1 H, =CH); 5.72 (*d*, *J* = 2, 1 H, =CH); 4.27 (*q*, *J* = 7, 2 H, OCH_2); 2.24 (*s*, 3 H, Me); 1.32 (*t*, *J* = 7, 3 H, Me).

2-(2,4-Dichlorophenyl)propenoic Acid Ethyl Ester (= *Ethyl 2-(2,4-Dichlorophenyl)prop-2-enoate*; **3j**) [21]. From 0.95 g (3.6 mmol) of *ethyl 2-(2,4-dichlorophenyl)-3-hydroxyprop-2-enoate* (**2j**), 4.32 ml (4.32 mmol) of $BH_3 \cdot THF$, and 0.36 ml (0.36 mmol) at 0°. Yield: 70%. ^{1}H-NMR ($CDCl_3$ 300 MHz): 7.20–7.40 (*m*, 4 H, Ph); 6.59 (*d*, *J* = 1, 1 H, =CH); 5.93 (*d*, *J* = 1, 1 H, =CH); 4.31 (*q*, *J* = 7, 2 H, OCH_2); 1.32 (*t*, *J* = 7, 3 H, Me).

General Procedure of the Hydrogenation of 2-Arylpropenoic Acid Ethyl Esters **3** *to 2-Arylpropanoic Acid Ethyl Esters* **4**. In a typical experiment, 1 equiv. of olefin was dissolved in 5–10 ml of freshly dist. MeOH in a high-pressured hydrogenation flask. Then, 0.1 equiv. of Pd/C was added in the reaction flask. Atmospheric air was removed and replaced by H_2 gas three times and the pressure of H_2 gas was increased to 45 psi. The reactions were performed for 4 h and then passed through a *Celite* pad, and all products formed were arylpropanoic acid ethyl ester.

2-Phenylpropanoic Acid Ethyl Ester (= *Ethyl 2-Phenylpropanoate*; **4a**) [22]. From 0.2 g (1.13 mmol) of **3a** and 0.1 equiv. of Pd/C at 45 psi H_2 pressure. Yield: 95%. ^{1}H-NMR ($CDCl_3$ 300 MHz): 7.30–7.60 (*m*, 5 H, Ph); 4.20 (*q*, *J* = 7, 2 H, OCH_2); 3.95 (*q*, *J* = 7, 1 H, CH); 1.52 (*d*, *J* = 7, 3 H, Me); 1.27 (*t*, *J* = 7, 3 H, Me).

2-(2-Methoxyphenyl)propanoic Acid Ethyl Ester (= *Ethyl 2-(2-Methoxyphenyl)propanoate*; **4f**) [23]. From 0.40 g (1.94 mmol) of **3f** and 0.1 equiv. of Pd/C at 45 psi H_2 pressure. Yield: 95%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30–7.60 (*m*, 5 H, Ph); 4.18 (*q*, *J* = 7, 2 H, OCH_2); 3.92 (*q*, *J* = 7, 1 H, CH); 3.87 (*s*, 3 H, MeO); 1.52 (*d*, *J* = 7, 3 H, Me); 1.27 (*t*, *J* = 7, 3 H, Me).

2-(4-Methylphenyl)propanoic Acid Ethyl Ester (= *Ethyl 2-(4-Methylphenyl)propanoate*; **4g**) [24]. From 0.20 g (1.0 mmol) of **3g** and 0.1 equiv. of Pd/C at 45 psi H_2 pressure. Yield: 90%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30–7.60 (*m*, 5 H, Ph); 4.11 (*q*, *J* = 7, 2 H, OCH_2); 3.95 (*q*, *J* = 7, 1 H, CH); 2.40 (*s*, 3 H, Me); 1.52 (*d*, *J* = 7, 3 H, Me); 1.27 (*t*, *J* = 7, 3 H, Me).

2-(2-Bromophenyl)propanoic Acid Ethyl Ester (= *Ethyl 2-(2-Bromophenyl)propanoate*; **4h**) [25]. From 0.40 g (1.56 mmol) of **3h** and 0.1 equiv. of Pd/C at 45 psi H_2 pressure. Yield: 95%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30–7.60 (*m*, 4 H, Ph); 4.15 (*q*, *J* = 7, 1 H, CH); 3.90 (*q*, *J* = 7, 2 H, OCH_2); 1.52 (*d*, *J* = 7, 3 H, Me); 1.27 (*t*, *J* = 7, 3 H, Me).

2-(2-Methylphenyl)propanoic Acid Ethyl Ester (= *Ethyl 2-(2-Methylphenyl)propanoate*; **4i**) [26]. From 0.30 g (1.57 mmol) of **3i** and 0.1 equiv. of Pd/C at 45 psi H_2 pressure. Yield: 93%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.03–7.60 (*m*, 4 H, Ph); 4.15 (*q*, *J* = 7, 1 H, OCH_2); 3.94 (*q*, *J* = 7, 1 H, CH); 2.36 (*s*, 3 H, Me); 1.49 (*d*, *J* = 7, 3 H, Me); 1.27 (*t*, *J* = 7, 3 H, Me).

2-(2,4-Dichlorophenyl)propanoic Acid Ethyl Ester (= *Ethyl 2-(2,4-Dichlorophenyl)propanoate*; **4j**). From 0.66 g (2.69 mmol) of **3j** and 0.1 equiv. of Pd/C at 45 psi H_2 pressure. Yield: 84%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.30–7.60 (*m*, 3 H, Ph); 4.11 (*q*, *J* = 7, 2 H, OCH_2); 3.90 (*q*, *J* = 7, 1 H, CH); 1.52 (*d*, *J* = 7, 3 H, Me); 1.27 (*t*, *J* = 7, 3 H, Me).

General Procedure to Hydrolyze Arylpropanoic Acid Ethyl Esters **4** *to Aryl Propanoic Acids* **5**. In a typical experiment, arylpropanoic acid ethyl ester (2.20–0.56 mmol) was dissolved in 20 ml of acetone. An aq. soln. of KOH (4.40–1.12 mmol) was added to the reaction flask and stirred overnight. Then, the mixture was washed with Et_2O. The aq. layer was then acidified, and the product was extracted with Et_2O. The solvent was removed by rotary evaporation to yield almost pure solid product in almost quantitative yield.

2-Phenylpropanoic Acid (**5a**) [27]. From 0.10 g (0.56 mmol) of **4a** and 1.12 mmol of aq. KOH. Yield: 90%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 11.93 (*s*, 1 H, OH); 7.30–7.60 (*m*, 5 H, Ph); 3.9 (*q*, *J* = 7, 1 H, CH); 1.49 (*d*, *J* = 7, 3 H, Me).

2-(2-Methoxyphenyl)propanoic Acid (**5f**) [28]. From 0.23 g (1.40 mmol) of **4f** and 2.80 mmol of aq. KOH. Yield: 90%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 11.93 (*s*, 1 H, OH); 7.30–7.60 (*m*, 4 H, Ph); 4.16 (*q*, *J* = 7, 1 H, CH); 3.86 (*s*, 3 H, MeO); 1.52 (*d*, *J* = 7, 3 H, Me).

2-(4-Methylphenyl)propanoic Acid (**5g**) [29]. From 0.30 g (1.56 mmol) of **4g** and aq. KOH (3.12 mmol). Yield: 93%. ^{1}H- NMR ($CDCl_3$, 300 MHz): 12.63 (*s*, 1 H, OH); 7.30–7.60 (*m*, 4 H, Ph); 3.80 (*q*, *J* = 7, 1 H, CH); 2.40 (*s*, 3 H, Me); 1.50 (*d*, *J* = 7, 3 H, Me).

2-(2-Bromophenyl)propanoic Acid (**5h**) [30]. From 0.23 g (0.9 mmol) of **4h** and aq. KOH (1.8 mmol). Yield: 90%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 12.20 (*s*, 1 H, OH); 7.3–7.6 (*m*, 4 H, Ph); 3.77 (*q*, *J* = 7, 1 H, CH); 1.56 (*d*, *J* = 7, 3 H, Me).

2-(2-Methylphenyl)propanoic Acid (**5i**) [29]. From 0.10 g (0.50 mmol) of **4i** and aq. KOH (1.0 mmol). Yield: 95%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 12.13 (*s*, 1 H, OH); 7.20–7.50 (*m*, 4 H, Ph); 4.02 (*q*, *J* = 7, 1 H, CH); 2.36 (*s*, 3 H, Me); 1.52 (*d*, *J* = 7, 3 H, Me).

2-(2,4-Dichlorophenyl)propanoic Acid (**5j**) [31]. From 0.56 g (2.20 mmol) of **4j** and aq. KOH (4.40 mmol). Yield: 90%. ^{1}H-NMR ($CDCl_3$, 300 MHz): 12.55 (*s*, 1 H, OH); 7.30–7.60 (*m*, 3 H, Ph); 3.80 (*q*, *J* = 7, 1 H, CH); 1.64 (*d*, *J* = 7, 3 H, Me).

Reaction Mechanism Study. Reduction of Acrylate **2a** *with Various Reducing Agents. Attempted Reduction of Acrylate with DIBAL-H*. 0.098 g (0.51 mmol) of **2a** was added to a dried side arm-round bottom flask. The flask was kept under N_2 gas. THF (10 ml) was added, and the mixture was cooled to 0°. DIBAL-H (1M, 1.02 ml, 1.02 mmol) was added to the mixture and stirred for 20 h at 0°. After the aqueous workup, no propenoic acid ethyl ester **3a** was obtained. Some unidentified product was obtained. The reaction was repeated at −78°, and no product formation was observed.

Attempted Reduction of Acrylate **2a** *with LiAlH$_4$*. 0.11 g (0.55 mmol) of **2a** was added to a dried side arm-round bottom flask. The flask was kept under N_2 gas. THF (10 ml) was added, and the mixture was kept at 0°. $LiAlH_4$ (1M, 1.1 ml, 1.1 mmol) was added to the mixture which was kept at 0° for 20 h. After the aqueous workup, no propenoic acid **3a** was obtained. Some unidentified product was obtained. The reaction was repeated at different temps. (r.t., 60°, and at −78°), and no product formation was observed.

Attempted Reduction of Acrylate **2a** *with Catechol Borane*. 0.15 g (0.78 mmol) of **2a** was added to a dried side arm-round bottom flask. The flask was kept under N_2 gas. THF (15 ml) was added and the mixture was cooled to 0°. Catechol borane (0.096 g, 0.78 mmol) was added, and the mixture was stirred for 20 h at 0°. After the aqueous workup, no propenoic acid ethyl ester **3a** was obtained.

Attempted Reduction of Acrylate **2a** *with 9-BBN.* 0.054 g (0.28 mmol) of **2a** was added to a dried side arm-round bottom flask. The flask was kept under N_2 gas. THF (10 ml) was added, and the mixture was cooled to 0°. 9-BBN (1.13 ml, 0.56 mmol) was added, and the mixture was stirred for 20 h at 0°. After the aqueous workup, no propenoic acid ethyl ester **3a** was obtained.

NMR Study of the Reduction of **2a** *with Catechol Borane.* 0.058 g (0.30 mmol) of compound **2a** was added to an NMR tube under N_2. 0.3 ml of (D_8)THF was added, and the mixture was kept at −78°. Catechol borane (0.07 g, 0.76 mmol) was added, and the reaction was monitored by ^{1}H-NMR at 0°. Within 2 h, a monohydroborane intermediate was formed. But no 2-phenylpropenoic acid ester **3a** was observed. After 18 h, 1 equiv. of $BH_3 \cdot$THF was added at −5°, and formation of **3a** was observed.

NMR Study of the Reduction of **2a** *with 9-BBN.* 0.04 g (0.21 mmol) of **2a** was added to an NMR tube under N_2. 0.3 ml of (D_8)THF was added, and the mixture was kept at −78°. 9-BBN (0.86 ml, 0.43 mmol) was added, and the reaction was monitored by NMR at 0°. Within 3 h, a monohydroborane intermediate was formed. But no propenoic acid ester **3a** was observed. After 20 h, 1 equiv. of $BH_3 \cdot$THF (0.21 ml, 0.21 mmol) was added at −5°, and formation of propenoic acid ester **3a** was observed.

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