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Highly Regioselective Friedel–Crafts Reactions of Electron-Rich Aromatic Compounds with Pyruvate Catalyzed by Lewis Acid-Base: Efficient Synthesis of Pesticide Cycloprothrin

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Abstract: An efficient synthesis of aromatic lactate esters is reported *via* highly regioselective Friedel–Crafts reactions of electron-rich aromatic compounds with pyruvate ester promoted by $TiCl_4$ in the presence of basic Al_2O_3. The utility of the reaction is shown by the efficient synthesis of the pesticide cycloprothrin in high yield.

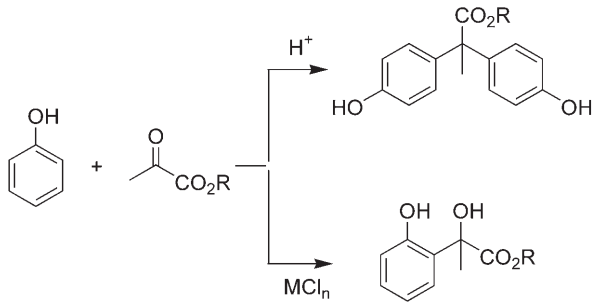
Keywords: alumina; aromatic lactate esters; Friedel–Crafts reactions; pyruvate ester; titanium(IV) chloride

Introduction

2-Arylpropanoic acids signify a medicinally important class of non-steroidal, anti-inflammatory agents.[1] Especially, the 2-arylpropenoic acid possessing an ethoxy group in the *para* position of the aromatic ring is an important intermediate for the preparation of the pesticide cycloprothrin, which is used in controlling insects and acaroids of crops. Each year these pests destroy an estimated 15% of agricultural crops in the United States and even more than that in developing countries.[2] The classical procedure that is frequently used in the preparation of the compound cycloprothrin, involves the reaction of an appropriate phenylacetic acid ester with ethyl oxalate under basic conditions, followed by treating the resultant oxalo ester with aqueous formaldehyde in the presence of K_2CO_3.[3] Contrarily, 2-arylpropenoic acids can be generated from 2-aryllactate esters, reported to be produced by the reaction of aromatic Grignard reagent with pyruvate esters,[4] benzoyl formate ester with methyl Grignard reagent[5] or alkylation of α-hydroxyphenylacetic acid ester with iodomethane;[6] however, all these methods are not straightforward.

The most atom-economic and efficient method for the formation of 2-arylpropenoic acid esters is through the Friedel–Crafts reaction of an aromatic compound with pyruvate esters and dehydration of 2-aryllactate esters. It has been reported that the addition of a phenol to pyruvic acid under acidic conditions generated a polymeric material or bis-adducts in the *para* position of phenol.[7] When the reaction was carried out in the presence of Lewis acidic conditions, such as with chlorides of a metal in a high oxidation state, e.g., tetravalent titanium, zirconium or trivalent boron and aluminum, the aromatic substitution resulted in an aldol-type coupling product in the *ortho* position of the phenolic oxygen atom (Scheme 1).[8]

The mechanism of acid-catalyzed diphenylation of pyruvate ester has been proposed by Ohwada through



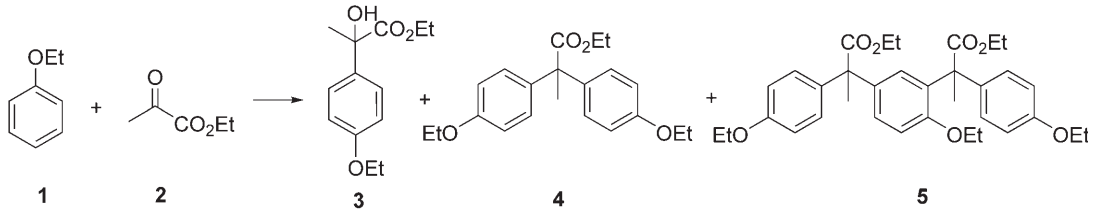
Scheme 1. Reaction of phenol with pyruvate esters catalyzed by a Brønsted acid or a Lewis acid.

the observation of the dication formed from 1,2-diones in Friedel–Crafts reactions of benzene. The reactive pyruvate esters in the Friedel–Crafts reactions of aromatic substrates under acid conditions are considered to be *O,O*-diprotonated 1,2-dicarbonyl species to give *gem*-diphenyl propionates.[9] Taking into account the subsequent steps of the mechanism, we conceived that removal of the proton acid released from the Friedel–Crafts reaction and masking the hydroxy group of phenol, would allow discrimination of bisadduct on the one hand, whereas it would disallow the aldol-type addition on the other hand, affording a regioselective monophenylation product in the *para* position. Thus, we undertook a reinvestigation of the Friedel–Crafts reaction of the electron-rich alkoxybenzenes with pyruvate esters, thereby observing that when this reaction was carried out in a Lewis acid-base system it afforded the monoadduct in the *para* position. The mechanism of this reaction is different from the previously reported Friedel–Crafts reactions of aromatic compound with pyruvate ester, which was considered as a Lewis acid-catalyzed aldol reaction mechanism.[8]

Results and Discussion

Initially, the reaction of ethoxybenzene and ethyl pyruvate was carried out under normal Friedel–Crafts reaction conditions using a Brønsted acid or a Lewis acid as catalyst (Table 1). When the mixture of ethoxybenzene and ethyl pyruvate in CH_2Cl_2 was treated with concentrated H_2SO_4 at 0 °C for 4 h, a bisadduct **4** was isolated in 12% yield (entry 1). The efficacy of various Lewis acids was tested for the reaction. All reactions gave the bisadducts as the major component. Among these catalysts, $BF_3 \cdot OEt_2$, $FeCl_3$ and $AlCl_3$ were found to give the bisadduct **4** in high yield along with monophenylation product **3** (entries 2 to 4). When the reaction was performed using $TiCl_4$ at 0 °C or at lower temperature (−15 °C), the bisadduct was not only produced as a major product, but also a triadduct **5** was found (entries 5 and 6). A stepwise Friedel–Crafts reaction was the preferred reaction based on these observations. The first Friedel–Crafts reaction of ethoxybenzene with ethyl pyruvate was promoted by a Lewis acid to give 2-aryllactate **3**, which underwent a second Friedel–Crafts reaction with pyruvate ester catalyzed by the proton acid released from the first step. Thus, we supposed that with the proton acid being trapped with a base, the formation of the bisadduct **4** would be suppressed. Additionally, the base was applied as an additive in the reaction. When an organic base was employed as an additive, such as triethylamine and pyridine, the Friedel–Crafts reaction failed (entries 7 and 8). However, to our delight, when the base was changed to a solid inorganic base, the reaction gave the expected monoadduct 2-(*p*-

Table 1. Friedel-Crafts reaction of ethoxybenzene with ethyl pyruvate under various reaction conditions.[a]



1 2 3 4 5

Entry	Lewis Acid	Base	Temp.	Reaction Time [h]	Yield [%][b]		
					3	**4**	**5**
1	H_2SO_4	–	0 °C	4	0	12	0
2	$BF_3 \cdot OEt_2$	–	−5 °C	4	5	68	0
3	$FeCl_3$	–	−15 °C	4	5	65	0
4	$AlCl_3$	–	0 °C	4	15	41	0
5	$TiCl_4$	–	0 °C	4	15	60	11
6	$TiCl_4$	–	−15 °C	8	5	34	3
7	$TiCl_4$	NEt_3	−15 °C	4	0	0	0
8	$TiCl_4$	Py	−15 °C	4	0	0	0
9	$TiCl_4$	Al_2O_3	−15 °C	7	78	3	0
10	$TiCl_4$	Na_2CO_3	−10 °C	5	55	9	0
11	$TiCl_4$	BaO	−5 °C	5	47	7	0
12	$AlCl_3$	Al_2O_3	−15 °C	2	40	39	0
13	$FeCl_3$	Al_2O_3	−15 °C	2	20	41	0

[a] All reactions were carried out with ethoxybenzene (2 mmol), ethyl pyruvate (2.2 mmol) and Lewis acid (2 mmol) in 6 mL of CH_2Cl_2 under argon. The concentration of the additive base was 5 mmol when required.
[b] Yield of isolated product.

ethoxyphenyl)lactate ester **3** as the major product. The best result was obtained when Al_2O_3 was used as base together with $TiCl_4$ as Lewis acid; monoadduct **3** was isolated in 78% yield along with 3% of bisadduct **4** (entry 9). Consequently, the ratio of monoadduct to bisadduct was greatly improved to give the major monoadduct by using $TiCl_4/Na_2CO_3$, Al_2O_3 and BaO, $FeCl_3$-Al_2O_3 or $AlCl_3$-Al_2O_3 as promoter (entries 10 to13).

Next, we carried out the $TiCl_4$-Al_2O_3 catalyzed electrophilic addition reaction of methyl pyruvate with a variety of electron-rich aromatic compounds to better understand both the scope and the generality of this method (Table 2). As shown in Table 2, the reaction of ethoxybenzene with methyl pyruvate gave the 2-(*p*-ethoxyphenyl)lactate ester **6a** in 85% yield (entry 1). Treatment of anisole afforded the monophenylation product **6b** in 91% yield (entry 2). Furthermore, 1,2- and 1,4-dimethyoxybenzenes yielded the respective monophenylation product in high yields without isolation of any diphenylation product (entries 3 and 4). Thioanisole was subject to the reaction conditions to give monoadduct **6e** in 87% yield (entry 5). Aiming at developing an asymmetrical versions of this reaction, the L-(−)-menthyl pyruvate was synthesized and used to probe the asymmetric induction. The asymmetric induction obtained was reflected in a ratio of 1:3 of the diastereoisomers (entry 6). It was reported that the reaction of indole with carbonyl compounds in the presence of a Lewis acid or a proton acid afforded the bis-indolealkane derivatives.[10] Extending this Lewis acid-base reaction system to the addition reaction of indole derivatives with methyl pyruvate ester, the reaction gave only the monoadducts **6g**–**i** in good yield (entries 7–9).

In order to understand the mechanism of the $TiCl_4$-base-catalyzed Friedel–Crafts reaction of electron-rich aromatic compounds with pyruvate esters, the reaction was carried out with NMR monitoring. Initially, a 1:1 mixture of anisole and $TiCl_4$ in $CDCl_3$ was stirred for 3 hours at 0 °C and monitored by ^1H NMR. As illustrated in Figure 1, comparison of the ^1H NMR spectrum of the mixture of anisole-$TiCl_4$ with the standard ^1H NMR spectrum of anisole showed that both ^1H NMR signals of anisole were the same. This indicated that $TiCl_4$ did not directly bind to and react with anisole. A similar ^1H NMR experiment was carried out for methyl pyruvate-$TiCl_4$ in $CDCl_3$ (Figure 2). A great chemical shift change was observed in Figure 2. The signals at

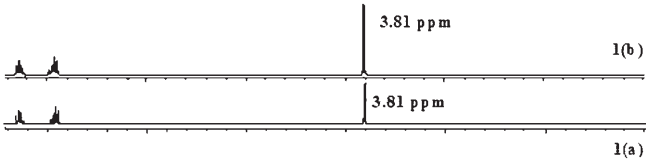


Figure 1. (a) Anisole in $CDCl_3$; (b) 3 hours after $TiCl_4$ was added to the solution of anisole in $CDCl_3$.

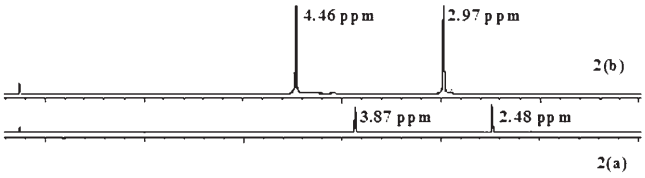


Figure 2. (a) Methyl pyruvate in $CDCl_3$; (b) 3 hours after $TiCl_4$ was added to the solution of methyl pyruvate in $CDCl_3$.

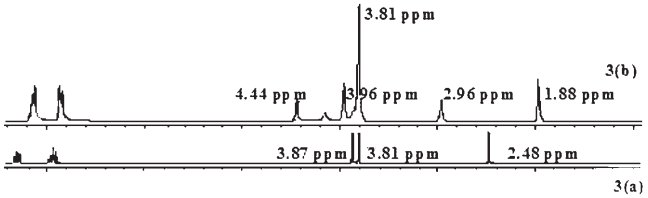
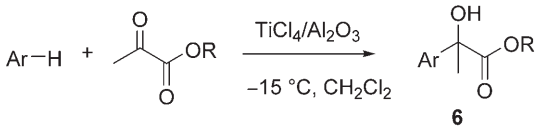


Figure 3. (a) Mixture of anisole with methyl pyruvate in $CDCl_3$; (b) 3 hours after $TiCl_4$ was added to the mixture of anisole and methyl pyruvate in $CDCl_3$.

2.48 ppm ($CH_3COCO_2CH_3$) and 3.87 ppm ($CH_3COCO_2CH_3$) were downshifted to 2.97 ppm and 4.46 ppm, respectively. This observation indicated that there was a certain action between $TiCl_4$ and the pyruvate ester to generate a complex compound. Finally, the mixture of anisole with methyl pyruvate in the presence of $TiCl_4/Al_2O_3$ in $CDCl_3$ was tracked by ^1H NMR (Figure 3). The complex of $TiCl_4$ with methyl pyruvate ester was first observed at 2.96 ppm and 4.44 ppm. After three hours, the signal of the monophenylation product appeared at 1.88 ppm [$CH_3C(Ar)OHCO_2CH_3$] and 3.96 ppm [$CH_3C(Ar)OHCO_2CH_3$]. The above observation indicated that primarily a complex of $TiCl_4$ with methyl pyruvate was produced, followed by the attachment of the complex to the electron-rich site of the aromatic compounds to give the monoadduct.

Based on the above observations, a tentative mechanism for this Friedel–Crafts reaction was proposed as shown in Scheme 2. At first, $TiCl_4$ was bound to the carbonyl of methyl pyruvate to give an active Ti(IV)-pyruvate complex cation **A**. This coordination was followed by the addition to the electron-rich site of the aromatic compounds to generate an aromatic cation intermediate **B**. The aromatic cation intermediate **B** underwent aromatization by elimination of hydrogen chloride to give the titanium trichloride-monoadduct compound **C**. If the reaction was carried out without a base, the released HCl from the reaction would decompose **C** to give the monoadduct, which would undergo dehydration immediately catalyzed by the acid to afford the cation **D**. The cation **D** further attacked a second aromatic molecule to give a bisadduct. Thus, when a base was added to remove HCl, the second step of the Friedel–Crafts was suppressed, terminating the reaction in intermediate **C** to give a monoadduct after reaction.

Table 2. Friedel–Crafts reactions of electron-rich aromatic compounds with methyl pyruvate.[a]



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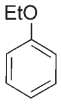
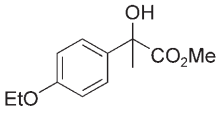
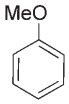
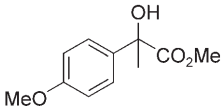
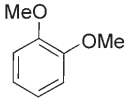
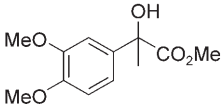
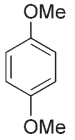
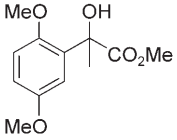
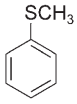
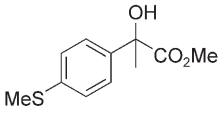
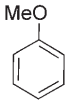
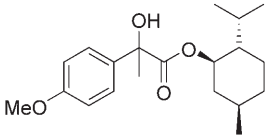
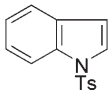
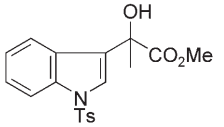
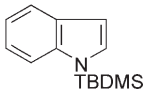
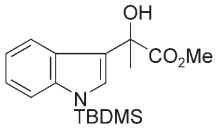
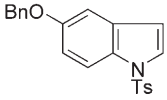
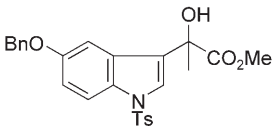
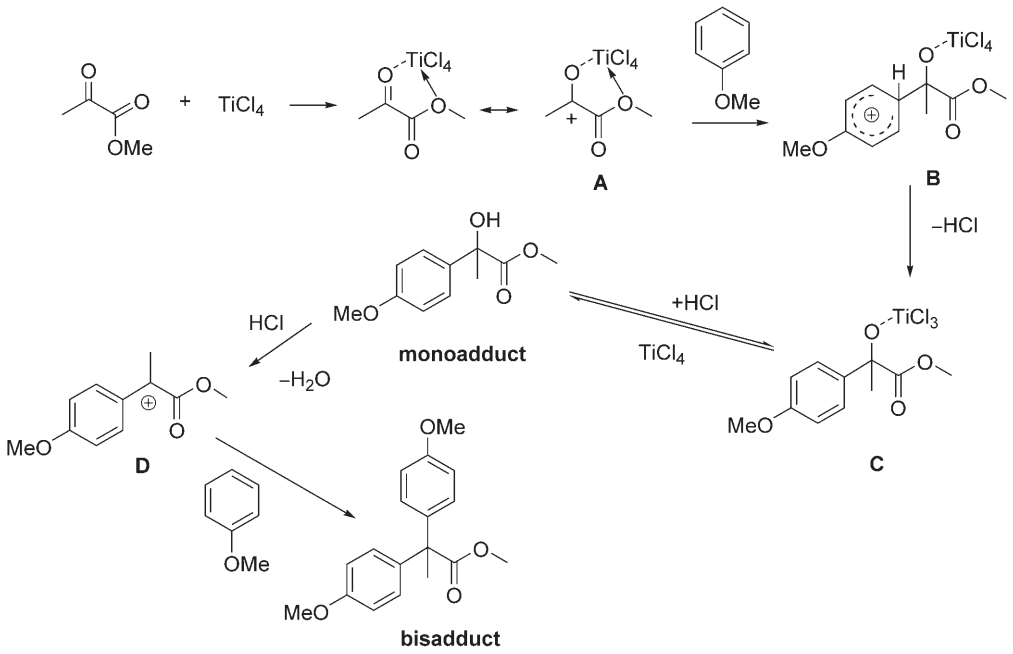
Entry	ArH	Reaction Time [h]	Product		Yield [%][b]
1		8		**6a**	85
2		6		**6b**	91
3		5		**6c**	82
4		5		**6d**	74
5		12		**6e**	87
6		3		**6f**	91[c]
7		7		**6g**	95[d]
8		5		**6h**	52[e]
9		5		**6i**	74[d]

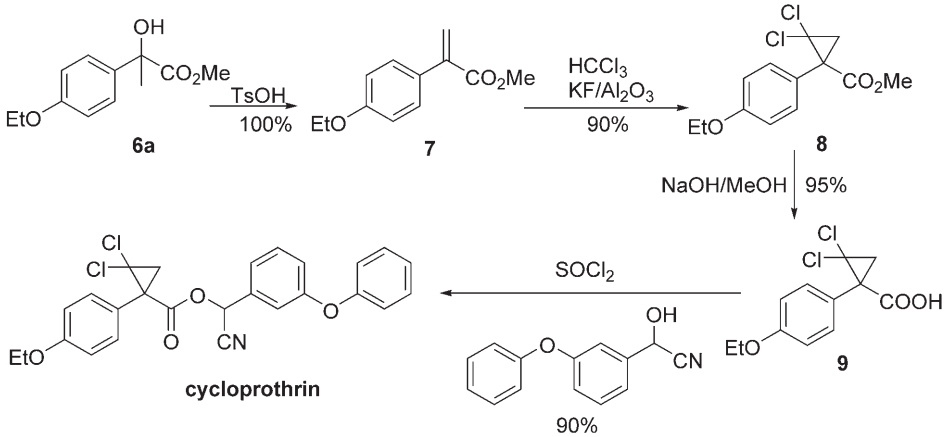
[a] All reactions were carried out with ArH (2 mmol), pyruvate (2.2 mmol), $TiCl_4$ (2 mmol) and Al_2O_3 (5 mmol) in 6 mL CH_2Cl_2 under argon.
[b] Yield of isolated product.
[c] A 1:3 mixture of diastereoisomers as determined by ^1H NMR analysis of the reaction crude product.
[d] Ts = *p*-toluenesulfonyl.
[e] TBDMS = *tert*-butyldimethylsilyl.

Since the synthesis of the 2-aryllactate ester constitutes an important target in organic synthesis and therefore better evaluates the usefulness of the present methodology, we focused our attention on the synthesis of the biologically important pesticide, cycloprothrin. Previous syntheses of this compound were carried out by several methods, however, these routes were either laborious, or comprised of steps of low yields, or required a



Scheme 2. Tentative mechanism for the Friedel–Crafts reaction of aromatic compounds with pyruvate esters.

harsh reagent and conditions.[4,5,6] Consequently, we were interested in the preparation of this compound, and we report hereafter an improved route to cycloprothrin by utilizing the relatively eco-friendly reaction conditions. The strategy proceeds through the 2-(*p*-ethoxylphenyl)lactate ester (**6a**) and provides the shortest routes and gives the highest yield of cycloprothrin achieved to date (Scheme 3). The phenyllactate **6a** was dehydrated simply by heating in toluene along with a catalytic amount of *p*-toluenesulfonic acid to yield the phenylpropenate **7** in nearly quantitative yield. The addition of **7** to dichlorocarbene generated from chloroform in the presence of 50% sodium hydroxide and the phase-transfer catalyst triethylbenzylammonium chloride gave *gem*-dichlorocyclopropanecarboxylate **8** in 65% yield.[11] The addition of dichlorocarbene was induced at 60 °C with extremely exothermic conditions that caused a vigorous reflux of the solvent to give a black tar product. Thus, the research for safe conditions for dichlorocyclopropanation is very important due to the exothermic reaction when the reaction is scaled up to the tons scale. It is known that KF/Al_2O_3 is a useful solid-supported reagent for base-induced organic reactions.[12] When phenylpropenate **7** was treated with chloroform in the presence of KF/Al_2O_3 in acetonitrile at room temperature, *gem*-dichlorocyclopropanecarboxylate **8** was obtained in 90% yield. The KF/Al_2O_3-promoted dichlorocyclopropanation was carried out with simple manipulations and proceeded very smoothly under mild conditions. These salient advantages led to



Scheme 3. Synthesis of the pesticide cycloprothrin.

a process for the preparation of cycloprothrin that is more easily to scale up in a very efficient way. Finally, cycloprothrin was synthesized in 62% total yield in 5 steps (starting from ethoxybenzene) compared with the existing procedure in 9 steps.[3]

Conclusion

In conclusion, we have shown the monophenylation of electron-rich aromatic compounds with pyruvate ester using a Lewis acid-base system. This efficient method provides a simple and practical procedure for the synthesis of 2-aryllactate esters in high regioselectivity. Preliminary mechanistic studies indicate the involvement of a Ti(IV)-pyruvate complex species as the reaction intermediate. The mildness of the reaction conditions and low cost of reagents should make the present methodology synthetically useful. This search for the construction of organic molecules allowed us to develop a new protocol for the efficient synthesis of the important pesticide cycloprothrin in high yield.

Experimental Section

General Experimental Procedures

Infrared (IR) spectra were determined with a FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz in $CDCl_3$ using TMS as an internal standard. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Mass spectra were obtained by the EI method. Microanalyses were carried out on a Heraeus Rapid-CHNO instrument. All moisture-sensitive reactions were done under an argon atmosphere in oven-dried (150 °C) glassware. Flash chromatography was performed using silica gel H (10–40 μm). Standard reagents and solvents were purified according to known procedures.

General Procedure for the Friedel–Crafts Reaction of Electron-Rich Aromatic Compounds to Pyruvate Esters

To a solution of pyruvate ester (2.2 mmol) and aromatic compound (2 mmol) in dried CH_2Cl_2 (5 mL) was added basic Al_2O_3 (510 mg, 5 mmol). The mixture was cooled to −15 °C. $TiCl_4$ (416 mg, 2.2 mmol) was added dropwise to the reaction mixture under an argon atmosphere. The mixture was stirred for 3–12 hours at −15 °C and poured into the ice-water (10 mL). The mixture was filtered and the filtrate was extracted with CH_2Cl_2 (15 mL × 2). The combined organic phase was washed with 1 N NaOH and brine solutions. The organic phase was dried with Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography on silica gel (hexane : EtOAc = 12 : 1) to afford the aromatic lactate ester.

Methyl 1-(4-Ethoxyphenyl)-2,2-dichlorocyclopropane-1-carboxylic Acid (8)

To a solution of methyl 2-(4-ethoxyphenyl)lactate (**6a**) (4.48 g, 20 mmol) in toluene (20 mL) were added *p*-toluenesulfonic acid (0.20 g, 1.45 mmol) and hydroquinone (20 mg). The mixture was heated at reflux for 3 hours under a Dean–Stark trap. The cooled reaction mixture was washed with 10% NaOH (10 mL × 2). The organic layer was evaporated under reduced pressure. The residue in CH_3CN (40 mL) was treated with H_2O (1.1 mL), $CHCl_3$ (2.4 mL) and KF/Al_2O_3 (20.0 g). The mixture was stirred at room temperature overnight. The KF/Al_2O_3 was removed by filtration and washed with CH_3CN. The combined filtrate was evaporated and purified by recrystallization from methanol and H_2O to give the product; yield: 4.95 g (85%).

1-(4-Ethoxyphenyl)-2, 2-dichlorocyclopropane-1-carboxylic Acid (9)

To a solution of methyl 1-(4-ethoxyphenyl)-2, 2-dichlorocyclopropane-1-carboxylic acid (**8**) (11.0 g, 38 mmol) in MeOH (4 mL) was added 10% NaOH (50 g). The mixture was refluxed for 3 hours. The cooled reaction mixture was extracted with toluene (10 mL × 2). The aqueous phase was acidified with 6 N HCl slowly at 0 °C. The precipitated acid **9** was filtered and crystallized in the pure state from the methanol and water; yield: 9.94 g (95%).

Cycloprothrin

The compound **9** (1.4 g, 5.1 mmol) was treated with thionyl chloride (3 mL) and refluxed for 1 hour. The excess thionyl chloride was then evaporated under vacuum to give the carbonyl chloride **10**, which was used for the next step of the reaction without further purification.

Sodium cyanide (0.25 g, 5.1 mmol) in water (5 mL) was added to a solution of *m*-phenoxybenzaldehyde and tetrabutylammonium bromide (50 mg) in toluene (5 mL) at 0 °C for 1 h. Then, the above prepared carbonyl chloride **10** was added and the mixture allowed to stand at room temperature for 2 hours. After extracting with toluene, the combined organic phase was washed consecutively with aqueous $NaHCO_3$ solution, water, brine and finally dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum to give the cycloprothrin as an oil; yield: 90%.

Characterization data for all products are given in the Supporting Information.

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