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One-Pot, Fluoride-Promoted Wittig Reaction

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One-Pot, Fluoride-Promoted Wittig Reaction

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Abstract: A one-pot, fluoride-promoted Wittig reaction was developed. The reactions of ethyl α-bromoacetate with aliphatic, aromatic, and heteroaromatic aldehydes in the presence of tri-n-butylphosphine and tetrabutylammonium fluoride produced α,β-unsaturated esters in good to excellent yields and *E*-stereoselectivity. Under the same conditions, reactions of ethyl α-bromopropionate, α-bromo acetonitrile, and α-bromoacetophenone with aliphatic and aromatic aldehydes in the presence of tri-n-butylphosphine and tetrabutylammonium fluoride produced the expected α,β-unsaturated derivatives in good *E*-stereoselectivity. The protocol was extended to semistabilized ylides and applied to the synthesis of some combretastatin analogs.

Keywords: Tetra-*n*-butylammonium fluoride, α,β-unsaturated compounds, Wittig reaction

INTRODUCTION

The Wittig reaction is one of the most important methods for the carbon–carbon double bond synthesis starting from carbonyl compounds.[1] It is traditionally carried out in a homogeneous medium using a base [BuLi, PhLi, $NaNH_2$, sodium bis(trimethylsilyl)amide (NaHMDS), or lithium bis (trimethylsilyl)amide (LiHMDS)] to generate a stabilized or a semistabilized phosphonium ylide, in anhydrous aprotic solvents [tetrahydrafuran (THF), dimethylformamide (DMF), C_6H_6, $CHCl_3$]. Heterogeneous Wittig

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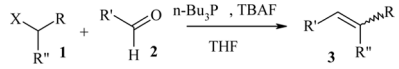


Scheme 1. $\mathbf{X} = \text{Br, CI;}$ $\mathbf{R} =$ -COOEt, -COPh, -CN, 3,4,5-trimethoxyphenyl-; $\mathbf{R}' =$ Ph-,$PhCH_2CH_2$-, 4-MeO-Ph-, 4-Br-Ph-, 4-NO_2-Ph-, 3-4-dimethoxyphenyl-,2-(2-formyl)-phenyl-,2-furanyl-, 2-thiophenyl-2, 2-(5-hydroxymethyl)-furanyl-, (2,2-dimethyldioxolanyl)-; and $\mathbf{R}'' =$ H,Me.

reactions, in liquid–liquid[2] or solid–liquid phase,[3] are less common. Since the discovery of the Wittig reaction in the 1950s, several variations of the experimental conditions have been reported to improve the efficiency of this fundamental reaction. Higher temperatures[4] or pressures,[5] additives,[6] microwaves,[7] sonication,[8] ionic solvents,[9] and water[10] have been considered to improve yields, experimental conditions, and environmental impact.

In this article, we report a one-pot Wittig reaction performed using the fluoride anion as the base[11](Scheme 1).

RESULTS AND DISCUSSION

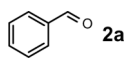
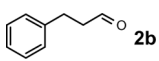
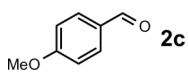
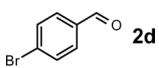
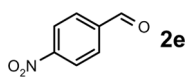
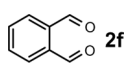
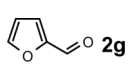
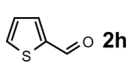
Our attention was focused first on stabilized ylides to obtain α,β-unsaturated compounds (esters, ketones, nitriles), useful precursors of hydroxy and amino acids (or ketones) and their derivatives.

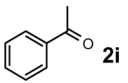
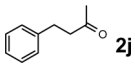
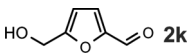
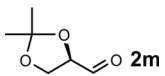
Two series of experiments were carried out. In the first series, a variety of electrophiles (aldehydes and ketones) was reacted with the same halogen derivative, ethyl α-bromoacetate, in the presence of n-Bu_3P[12] (Table 1); in the second series, the investigation was extended to a variety of haloderivatives, precursors of either stabilized or semistabilized ylides (Tables 2 and 3). For one model system (ethyl α-bromo acetate and benzaldehyde), the reaction was also carried out by replacing n-Bu_3P with the less nucleophilic but more convenient (crystalline, air-stable, and odorless) Ph_3P, with no significant influence on product formation and stereochemistry (Table 1, footnote *f*).

The data are summarized in Tables 1–3 and illustrate some general features of this new protocol. In Table 1, the results previously obtained[10a] in water and SDS (sodium dodecyl sulfate)–water solution have been reported for comparison.

In each case, with only the exception of aldehyde **2m** (Table 1, entry 12), the main, if not only, product was the *E*-isomer. Diastereoisomeric ratios and yields depended on both the electrophile and the halogen derivative and were generally good to very good for aldehydes (alkyl, aryl, heteroaryl). Phthalyldialdehyde (**2f**) yielded the *E,E* product exclusively: no *E,Z* or *Z,Z* isomers were observed.

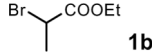
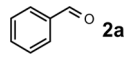
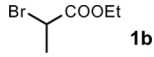
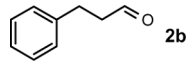
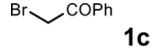
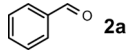
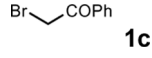
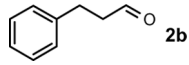
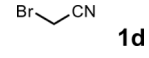
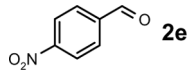
Table 1. Wittig reaction of aromatic, heteroaromatic, aliphatic aldehydes, and ketones with ethyl α-bromo acetate in the presence of tri-*n*-butyl phosphine

					Reactions performed in (water) and in [SDS-water solution][j]	
Entry	Electrophile	Reaction time[a]	Product, isolated yield (%)	*E*/*Z* Ratio (%)[e]	Product, yield (%)	*E*/*Z* ratio (%)
1	 **2a**	2.5 h	**3aa**, 92	94:6[f]		
2	 **2b**	2.5 h	**3ab**, 91	>99:1	(79) [88]	(81:19) [75:25]
3	 **2c**	2.5 h	**3ac**, 83	92:8	(68) [76]	(96:4) [98:2]
4	 **2d**	2.5 h	**3ad**, 89	93:7		
5	 **2e**	2.5 h	**3ae**, 98	>99:1	(88) [87]	(87:13) [90:10]
6	 **2f**	2.5 h[b]	**3af**, 73	>99:1		
7	 **2g**	2.5 h	**3ag**, 87	95:5	(82) [85]	(80:20) [89:11]
8	 **2h**	2.5 h	**3ah**, 91	93:7		

9	 **2i**	16 h	**3ai**, 21[c]	—[g]
10	 **2j**	16 h	**3aj**, 18[c,d]	—[g]
11	 **2k**	2.5 h	**3ak**, 81	85:15[h,i]
12	 **2m**	3 h	**3am**, 60	28:72

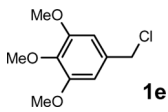
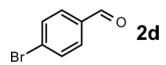
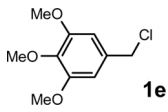
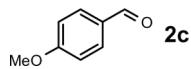
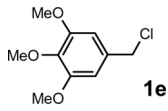
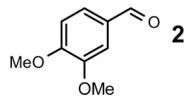
[a]Conditions: **1a**/*n*-Bu_3P/**2**/*n*-Bu_4NF = 1:1:1.1:1.2 molar ratio; THF at room temperature.
[b]**1a**/*n*-Bu_3P/**2**/*n*-Bu_4NF = 1:1:0.5:1.2 molar ratio.
[c]^1H NMR yields of the crude reaction mixture.
[d]Reaction also carried out at 70°C; after 16 h, 32% yield by ^1H NMR of the crude reaction mixture.
[e]E/Z determined by ^1H NMR.
[f]Reaction carried out also with PPh_3 in 86% yield and unchanged diastereoisomeric ratio.
[g]Mixture of *E* and *Z* isomers.
[h]Both *E* and *Z* isomers were isolated and characterized.
[i]When TBDMS protects the hydroxylic functionality, the reaction yield is 87%.
[j]SDS: sodium dodecyl sulphate; Ref. 10a.

Table 2. Wittig reaction of aromatic and aliphatic aldehydes with α-bromo derivatives in the presence of tri-*n*-butyl phosphine

Entry	Bromo derivative	Electrophile	Reaction time[a]	Product, isolated yield (%)	*E*/*Z* ratio (%)[b]
1	 **1b**	 **2a**	16 h	**3ba**, 42	95:5
2	 **1b**	 **2b**	16 h	**3bb**, 49	89:11
3	 **1c**	 **2a**	2.5 h	**3ca**, 88	>99:1
4	 **1c**	 **2b**	2.5 h	**3cb**, 78	>99:1
5	 **1d**	 **2e**	0.5 h	**3de**, 68[c]	>99:1[c]

[a]Conditions: **1**/*n*-Bu_3P/**2**/*n*-Bu_4NF = 1:1:1.1:1.2; THF at room temperature.
[b]*E*/*Z* determined by ^1H NMR.
[c]The reported yield concerns the *E* isomer only. By ^1H NMR, the crude mixture contains 95% yield of *E*/*Z* (72:28) isomers: the *E* isomer only was purified.

Table 3. Wittig reaction of aromatic aldehydes with 3,4,5-trimethoxybenzyl chlorides in the presence of tri-butyl phosphine: synthesis of functionalized stilbenes

Entry	Chloro derivative	Electrophile	Reaction time[a]	Product, isolated yield (%)	*E*/*Z* ratio (%)[b]
1	 **1e**	 **2d**	16 h	**3ed**, 81	71:29
2	 **1e**	 **2c**	16 h	**3ec**, 50	68:32
3	 **1e**	 **2l**	16 h	**3el**, 36	65:35

[a]Conditions:**1**/*n*-Bu_3P/**2**/*n*-Bu_4NF = 1:1.1:1.1:1.
[b]Both *E* and *Z* isomers were isolated and characterized.

In contrast, longer reaction times, poor yields, and very poor diastereoselection were observed when ketones were used as electrophiles (Table 1, entries 9 and 10), although no by-products were observed and the unreacted ketones were easily recovered.

Longer reaction times were also observed when a branched α-bromo ester was used (Table 2, entries 1 and 2) to create a trisubstituted double bond: in this case, the reaction with aldehydes proceeded in reasonable yields and high stereoselection to give α-methyl-α,β-unsaturated esters, useful intermediates in the synthesis of insect pheromones and other natural products.[13]

To enlarge the scope of the method, an α-bromoketone and an α-bromonitrile were tested: the former gave the *E*-isomer in excellent stereoselectivity and good yields (Table 2, entries 3 and 4), whereas the latter gave a mixture of *E*/*Z* isomers of the α,β-unsaturated nitrile (Table 2, entry 5).

Some other points are worth mentioning: no aldol self-condensation occurred with carbonyl substrates containing α-hydrogen atoms (Table 1, entries 2 and 12; Table 2, entries 2 and 4) and no racemization, even partial, were observed in the presence of an α-stereogenic carbon (Table 1, entry 12). Furthermore, a free hydroxyl function is tolerated: for example the compound **3ak**, an important building block in the preparation of a polymer employed in photography and microlithography[14] was obtained from **2k** in 81% yield and with good stereoselectivity (Table 1, entry 11). A slightly better yield (87%) was obtained by protecting the hydroxylic function as its tert-butyldimethylsilyl derivative (TBDMS) derivative.

The investigation was then extended to semistabilized ylides from benzyl chlorides and applied to the synthesis of multifunctionalized stilbenes[15a] with the final aim of optimizing a new and convenient synthetic approach to biologically active molecules, analogs to combretastatins and resveratrol (Table 3).[15b–f] A trimethoxybenzyl phosphonium halide was required for this; it is a highly deactivated substrate toward deprotonation as compared to an ethoxycarbonylmethyl-phosphonium halide.

Nevertheless, the reaction of trimethoxybenzyl chloride (**1e**) proceeded equally well (81% yield) with respect to α-bromoacetate **1a** when 4-bromobenzaldehyde (**2d**) was used, although with a longer reaction time (16 h) and little stereoselectivity. Even the less electrophilic aldehydes **2c** and **2l** reacted to give compounds **3ec** (50%) and **3el** (36%), albeit in lower yields.

CONCLUSIONS

α,β-Unsaturated compounds (such as esters, nitriles, ketones) are generally prepared by Wittig, HWE,[16] Heck,[17] Stille,[18] Peterson,[19] and

Reformatsky/β-elimination reactions.[20] These compounds can be also prepared via Cope rearrangement,[21] olefin methatesis,[22] or from acetylenic derivatives.[23] Despite their general usefulness, all these methodologies have some limitations such as lack of stereochemistry control (in particular, when the trisubstituted double bond is concerned), expensive reagents, requirement of anhydrous solvents and/or inert atmosphere, high temperature, multistep processes, or metal activation.

In this article, we have presented a convenient access to α,β-unsaturated esters and α,β-unsaturated ketones, in good yields and with good/total *E* stereoselectivity via a one-pot Wittig reaction promoted by tetrabutyl ammonium fluoride. In contrast to other methods reported in the literature, readily enolizable aldehydes can be used: fluoride is sufficiently basic to deprotonate the phosphonium salt but it does not catalyze side reactions such as aldol condensation. For the same reason, other functionalities such as hydroxyl groups are compatible with the transformation. In addition, this transformation takes place even in an open atmosphere, with no requirement of anhydrous solvents, through a one-pot sequential process where consecutive reactions (three or four depending on the substrate) are performed without workup and/or intermediate isolation [phosphonium salt formation, phosphonium salt deprotonation, Wittig condensation, deprotection of a silyl group when present].

In addition, this method can be also utilized to stereoselectively prepare trisubstituted β-alkyl-α,β-unsaturated esters, although in lower yields.

EXPERIMENTAL

General

^{1}H NMR spectra were measured on spectrometers at 400 MHz, and ^{13}C NMR were measured on spectrometers at 50 and 100 MHz. Thin-layer chromatography (TLC) was carried out on plates with 250 μm of silica gel. THF, hexane, and AcOEt were commercial products, as were *n*-Bu_3P, Ph_3P, tetra-*n*-butylammonium fluoride (TBAF) solution (1M in THF), halo derivatives **1a**–**e**, aldehydes, and ketones **2a**–**m**.

General Procedure for One-Pot, Fluoride-Promoted Wittig Reaction

Ethyl (*E*)-3-phenyl-prop-2-Enoate (**3aa**)

Ethyl α-bromo acetate (0.50 mmol, 87.0 mg) was weighed in a test tube (equipped with magnetic bar). The solvent (technical grade THF,

0.5 mL) was added, and the test tube was cooled in an ice bath at 0°C. *n*-Bu_3P (0.50 mmol, 127 μL) was then added dropwise. When the addition was completed, the ice bath was removed. After 5 min, benzaldehyde was added (0.55 mmol, 56 μL), followed by the *n*-Bu_4NF solution (1 M in THF, 0.6 mL). The reaction was monitored by TLC (silica gel; AcOEt/petroleum ether 1/99). After 2.5 h, the solvent was removed under reduced pressure, and the crude material was purified by column chromatography (SiO_2, AcOEt/hexane 1/99) to remove salts, phosphine oxide, and unreacted benzaldehyde, yielding **3aa** (80.9 mg, 92%).

Colorless oil (lit.[24]: mp = 12°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 16.0 Hz, 1H), 7.53 (m, 2H), 7.39 (m, 3H), 6.44 (d, J = 16.0 Hz, 1H), (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.2, 44.8, 134.6, 130.4, 130.4, 129.1, 128.2, 60.7, 14.5. HRMS calcd. for $C_{11}H_{12}O_2$ (M^+): 176.083730; found: 176.083300.

Data

Ethyl (*E*)-5-Phenyl-pent-2-enoate (**3ab**)[25]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (m, 2H), 7.23 (m, 3H), 7.04 (dt, J = 9.1 Hz, J = 15.8 Hz, 1H), 5.89 (d, J = 15.8 Hz, 1H), (q, J = 7.1 Hz, 2H), 2.81 (m, 2H), 2.56 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 147.9, 140.7, 128.4, 128.3, 126.1, 121.8, 60.1, 34.3, 33.8, 14.2. HRMS calcd. for $C_{13}H_{16}O_2$ (M^+): 204.115030; found: 204.115810.

Ethyl (*E*)-3-(4-Methoxyphenyl)-prop-2-enoate (**3ac**)[24c,26]

Colorless crystals; mp = 48–50°C (CH_2Cl_2, petroleum ether) (lit.[24c]: mp = 48–50°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, J = 15.9 Hz, 1H), 7.50 (d, J = 8.76 Hz, 2H), 6.93 (d, J = 8.76 Hz, 2H), 6.33 (d, J = 15.9 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 161.3, 144.2, 129.6, 127.2, 115.7, 114.3, 60.3, 55.3, 14.3. HRMS calcd. for $C_{12}H_{42}O_3$ (M^+): 206.094294; found: 206.094310.

(*E*)-3-(4-Bromophenyl)-prop-2-enoate (**3ad**)[24d,27]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, J = 16.0 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 6.43 (d, J = 16.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$,

100 MHz) δ 166.6, 143.1, 133.4, 132.1, 129.3, 124.4, 119.0, 60.5, 14.2. HRMS calcd. for $C_{11}BrH_{11}O_2$ (M^+): 253.994241; found: 253.994610.

Ethyl (*E*)-3-(4-Nitrophenyl)-prop-2-enoate (**3ae**)[24a,d,3b,1]

Colorless crystals; mp = 139–140°C (CH_2Cl_2, petroleum ether) (lit[24d]: 140–141°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 16.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 16.4 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 148.4, 141.5, 140.5, 128.5, 124.1, 122.5, 60.9, 14.2. HRMS calcd. for $C_{11}H_{11}NO_4$(M^+): 221.068808; found: 221.068510.

Diethyl 3,3′-(1,2-Phenylene)-bisacrylate (**3af**)[28]

Colorless crystals; mp = 77–78°C (CH_2Cl_2, petroleum ether) (lit.[28]: mp = 75–76°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, J = 15.8 Hz, 2H), 7.59 (m, 2H), 7.41 (m, 2H), 6.37 (d, J = 15.8 Hz, 2H), 4.32 (q, J = 7.1 Hz, 4H), 1.37 (t, J = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 141.2, 134.3, 129.9, 127.6, 121.9, 60.6, 14.2. HRMS calcd. for $C_{16}H_{18}O_4$ (M^+): 274.120509; found: 274.120670.

Ethyl (*E*)-3-Furan-2-yl-prop-2-enoate (**3ag**)[29,26b]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (m, 1H), 7.44 (d, J = 15.8 Hz, 1H), 6.62 (m, 1H), 6.48 (m, 1H), 6.33 (d, J = Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 151.5, 144.6, 130.9, 115.9, 114.5, 112.2, 60.4, 14.3. HRMS calcd. for $C_9H_{10}O_3$ (M^+): 166.062994; found: 166.063540.

Ethyl (*E*)-3-Thiophen-2-yl-prop-2-enoate (**3ah**)[30]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 15.7 Hz, 1H), 7.39 (m, 1H), 7.27 (m, 1H), 7.07 (m, 1H), 6.26 (d, J = 15.7 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 139.6, 137.0, 130.7, 128.3, 128.0, 117.1, 60.5, 14.3. HRMS calcd. for $C_9H_{10}O_2S$ (M^+): 182.040151; found: 182.039690.

Ethyl (*E*)-3-(5-Hydroxymethylfuran-2-yl)-prop-2-enoate (**3ak**-*E*)[31]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 15.7 Hz, 1H), 6.56 (d, J = 3.3 Hz, 1H), 6.39 (d, J = 3.3 Hz, 1H), 6.31 (d, J = 15.7 Hz,

1H), 4.65 (s, 2H), 4.25 (q, $J = 7.1$ Hz, 2H), 2.30 (bs, 1H), 1.33 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 156.4, 150.6, 130.7, 115.7, 115.4, 110.0, 60.3, 57.4 14.1. HRMS calcd. for $C_{10}H_{12}O_4$ (M^+): 196.073559; found: 196.073590.

Ethyl (*z*)-3-(5-Hydroxymethylfuran-2-yl)-prop-2-enoate (**3ak**-*Z*)[31]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, $J = 3.4$ Hz, 1H), 7.77 (d, $J = 12.8$ Hz, 1H), 6.43 (d, $J = 3.4$ Hz, 1H), 5.76 (d, $J = 12.8$ Hz, 1H), 4.65 (s, 2H), 4.25 (q, $J = 7.1$ Hz, 2H), 2.30 (bs, 1H), 1.35 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 155.3, 150.5, 130.1, 117.8, 115.9, 110.4, 60.0, 57.5 14.1. HRMS calcd. for $C_{10}H_{12}O_4$ (M^+): 196.073559; found: 196.074280.

Ethyl (*Z*)-3-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-prop-2-enoate (**3am**-*Z*)[32]

Colorless oil. $[\alpha]^{25}_D = +129.35$ (c = 0.02, chloroform) (lit.[32d]: $[\alpha]^{17}_D = +124.3$; c = 0.534, chloroform). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.36 (dd, $J = 6.8$ Hz, $J = 11.6$ Hz, 1H), 5.85 (d, $J = 11.6$ Hz, 1H), 5.50 (m, 1H), 4.38 (m, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.63 (m, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 120.7, 109.6, 73.5, 69.3, 60.4, 26.5, 25.3, 14.1. HRMS calcd. for $C_{10}H_{16}O_4$ (M^+): 200.104859; found: 200.105109.

Ethyl (*E*)-2-Methyl-3-phenyl-prop-2-enoate (**3ba**)[33]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (s, 1H), 7.42 (m, 4H), 7.34 (m, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.15 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 138.5, 135.9, 129.5, 128.6, 128.3, 128.1, 60.8, 14.2, 13.9. HRMS calcd. for $C_{12}H_{14}O_2$ (M^+): 190.099380; found: 190.099520.

Ethyl (*E*)-2-Methyl-5-phenyl-pent-2-enoate (**3bb**)[34]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 2H), 7.24 (m, 3H), 6.84 (t, $J = 14.6$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.78 (m, 2H), 2.53 (m, 2H), 1.82 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 141.1, 140.8, 128.4, 128.3, 128.2, 126.0, 60.3, 34.6, 30.5, 14.2, 12.2. HRMS calcd. for $C_{14}H_{18}O_2$ (M^+): 218.130680; found: 218.130910.

(*E*)-1,3-Diphenyl-propenone (**3ca**)[35]

Colorless crystals; mp = 56–57°C (petroleum ether) (lit.[35d]: mp = 57–58°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, J = 7.3 Hz, 2H), 7.85 (d, J = 15.7 Hz, 1H), 7.55 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.3, 144.7, 138.1, 134.7, 132.6, 130.4, 128.8, 128.5, 128.4, 128.3, 121.1. HRMS calcd. for $C_{15}H_{12}O$ (M^+): 208.088815; found: 208.088680.

(*E*)-1,5-Diphenyl-pent-2-en-1-one (**3cb**)[36]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, J = 7.9 Hz, 2H), 7.39 (m, 8H), 7.14 (m, 1H), 6.92 (d, J = 15.4 Hz, 1H), 2.90 (m, 2H), 2.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.8, 148.4, 140.7, 137.7, 132.5, 128.6, 128.5, 128.4, 128.3, 126.4, 126.1, 34.5, 34.4. HRMS calcd. for $C_{17}H_{16}O$ (M^+): 236.120115; found: 236.120940.

(*E*)-3-(4-Nitrophenyl)-acrylonitrile (**3de**-*E*)[37]

Colorless crystals; mp = 200–201°C (CH_2Cl_2, petroleum ether) (lit.[37b]: mp = 200–201°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 16.6 Hz, 1H), 6.08 (d, J = 16.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 147.7, 139.1, 128.1, 124.3, 116.9, 101.0. HRMS calcd. for $C_9H_6N_2O_2$ (M^+): 174.042928; found: 174.042950.

(*E*)-2-(4′-Bromophenyl)-1-(3,4,5-trimethoxyphenyl)ethene (**3ed**-*E*)[38]

Colorless crystals; mp = 157–158°C (CH_2Cl_2, petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 16.2 Hz, 1H), 6.95 (d, J = 16.2 Hz, 1H), 6.75 (s, 2H), 3.94 (s, 6H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.4, 138.2, 136.1, 132.6, 131.7, 129.3, 127.9, 126.8, 121.2, 103.7, 60.9, 56.1. HRMS calcd. for $C_{17}H_{17}BrO_3$ (M^+): 348.036106; found: 348,034760.

(*Z*)-2-(4′-Bromophenyl)-1-(3,4,5-trimethoxyphenyl)ethene (**3ed**-*Z*)[38]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 12.1 Hz, 1H), 6.53 (d, J = 12.1 Hz, 1H), 6.46 (s, 2H), 3.86 (s, 3H), 3.70 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 137.4, 136.2, 132.0, 131.3, 130.8, 130.6, 128.5, 120.9, 106.0, 60.8,

55.8. HRMS calcd. for $C_{17}H_{17}BrO_3$ (M^+): 348.036106; found: 348.036290.

(*E*)-2-(4′-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethene (**3ec**-*E*)[38b,c]

Colorless crystal; mp = 156–157°C (CH_2Cl_2, petroleum ether) (lit.[38c]: mp = 152–155°C).^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 2H), 6.94 (m, 4H), 6.74 (s, 2H), 3.95 (s, 6H), 3.90 (s, 3H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.3, 153.3, 137.7, 133.4, 130.0, 127.7, 127.5, 126.5, 114.1, 103.4, 60.9, 56.1, 55.2. HRMS calcd. for $C_{18}H_{20}rO_4$ (M^+): 300.136159; found. 300.136200.

(*Z*)-2-(4′-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethene (**3ec**-*Z*)[38b,c]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.52 (m, 3H), 6.45 (d, J = 12.1 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.71 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.7, 152.9, 132.8, 130.2, 129.6, 129.4, 128.6, 113.5, 106.0, 108.7, 60.8, 55.8, 55.2. HRMS calcd. for $C_{18}H_{20}rO_4$ (M^+): 300.136159; found: 300,135800.

(*E*)-2-(3′,4′-Dimethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethene (**3el**-*E*)[39]

Colorless crystals; mp = 141–142°C (CH_2Cl_2, petroleum ether) (lit.[39a]: mp = 139–140°C).^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (m, 2H), 6.91 (m, 3H), 6.74 (s, 2H), 3.95 (s, 3H), 3.92 (s, 6H), 3.90 (s, 3H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 149.0, 148.8, 137.7, 133.2, 130.2, 127.8, 126.6, 119.6, 111.2, 108.7, 103.3, 60.8, 56.0, 55.8, 55.7. HRMS calcd. for $C_{19}H_{22}O_5$ (M^+): 330.146724; found; 330.146360

(*Z*)-2-(3′,4′-Dimethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)ethene (**3el**-*Z*)[39]

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (m, 3H), 6.55 (s, 2H), 6.53 (d, J = 12.1 Hz, 1H), 6.48 (d, J = 12.1 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.73 (s, 6H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 148.4, 148.2, 137.1, 133.0, 129.8, 129.7, 128.8, 121.9, 111.8, 110.8, 105.9, 60.8, 55.9, 55.8, 55.6. HRMS calcd. for $C_{19}H_{22}O_5$ (M^+): 330.146724; found: 330.146580.

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