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Phosphorus(V)-catalyzed deoxydichlorination reactions of aldehydes

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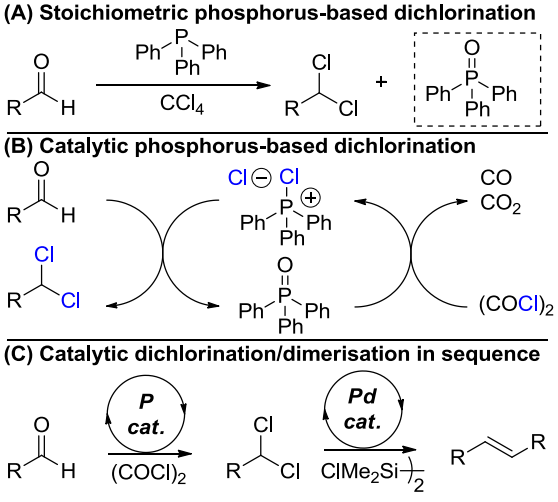
ABSTRACT

A phosphine oxide-catalyzed conversion of aldehydes into 1,1-dichlorides is reported. The reaction proceeds via a phosphorus(V)-catalysis manifold in which phosphine oxide turnover is achieved using oxalyl chloride as a consumable reagent. The new method is applicable to a range of aldehydes and, in combination with palladium-catalyzed reductive dimerization, gives rise to a new catalytic approach to the synthesis of stilbenes and a short formal synthesis of resveratrol.

1. Introduction

Geminal dihalides, particularly the dichlorides, are important intermediates in chemical synthesis. They participate in a wide range of useful carbon–carbon bond-forming processes including olefination reactions with carbonyl compounds,[1] alcohol and amine syntheses,[2] cyclopropanation[3] and aziridination reactions[4] as well as dimerization reactions to afford alkenes.[5] Moreover, they are present as functional groups in their own right in bioactive natural products.[6] The synthesis of geminal dihalides is usually achieved via deoxydichlorination of aldehydes—a transformation that can be achieved in a stoichiometric sense using BCl_3,[7] transition metal halides,[8] $SOCl_2$ in the presence of DMF/HMPA[9] or, most commonly, with PCl_5.[10] An alternative stoichiometric phosphorus(V)-based approach involves the use of the 'Appel conditions', i.e., triphenylphosphine in combination with carbon tetrachloride (Scheme 1A).[11]

At present many phosphorus-based reactions are compromised by the generation of triphenylphosphine oxide as a stoichiometric by-product, which impacts upon their atom efficiency[12] and complicates the purification process.[13] While some creative strategies have been developed to alleviate purification problems, e.g., polymeric phosphine reagents,[14] bipyridyl tagged phosphine reagents,[15] monolithic phosphines,[16] anthracene tagged reagents,[17] fluorous phosphines,[18] tetraaryl supported phosphines,[19] PEG-based polymers,[20] Rasta Resins,[21] and post reaction polymerization,[22] the fundamental problem of phosphine oxide generation in phosphorus(V)-based reactions is only just beginning to be addressed. To this end we have developed a system for halogenation under Appel conditions that is catalytic with respect to the phosphorus component by exploiting oxalyl chloride to induce phosphine oxide turnover.[23] In parallel to our catalysis work other groups have also been active in pursuing catalytic



Scheme 1. Deoxydichlorination under Appel conditions.

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deoxychlorination reactions[24] and variants of other phosphorus-based reactions,[25] which have included Aza-Wittig[26] and Wittig reactions,[27] Appel reactions,[28] Staudinger reactions,[29] reductions of silyl peroxides[30] as well as catalytic transfer hydrogenation reactions.[31] In this article, we describe the first examples of catalytic phosphorus(V)-based deoxydichlorination reactions of aldehydes (Scheme 1B) as well as the application of phosphorus catalysis in sequence with palladium catalysis to afford a new approach to bioactive stilbenes (Scheme 1C).

2. Results and discussion

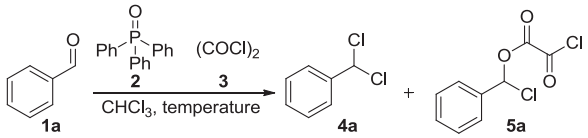
Given our catalytic reaction was predicated on the oxalyl chloride induced conversion of phosphine oxides into phosphonium salts[32,33] we began by establishing that a chlorophosphonium salt generated in this manner was effective for the deoxydichlorination of benzaldehyde in a stoichiometric sense (entry 1, Table 1). This room temperature reaction was not as fast as expected—only 14% of *gem*-dichloride **4a** was obtained after 10 min. The temperature was raised to 50 °C (entry 2), which afforded an acceptable 82% yield of the same product. The initial catalytic reaction (entry 3) conducted with 15 mol % of triphenylphosphine oxide afforded a 73% yield with **5a** accounting for the remainder of the mass-balance. To suppress the formation of **5a** a slow addition protocol was employed (entry 4) and, under this regime, the yield of **4a** was improved to 90%, with the remainder of the mass-balance in this case being the unreacted aldehyde. In further experiments the catalyst loading was decreased to 7.5 mol % and then 5 mol % affording yields of 85% and 70%, respectively, and a modified addition protocol was used (entries 5 and 6).

was catalyzed by the phosphine oxide. First a series of control reactions with representative substrates **1a**, **1d** and **1k** were carried out in the absence of triphenylphosphine oxide (entries 1–3, Table 3). Small amounts (maximum 12%—determined via ^{1}H NMR using $Cl_2CHCHCl_2$ as an internal standard) of products were observed for substrates **1a** and **1d** while no product was with **1k**. These results show that the phosphine oxide is necessary for acceleration of the deoxydichlorination reaction since the yields obtained in the presence of the catalyst were 85% (**4a** from **1a**), 98% (**4d** from **1d**) and 92% (**4k** from **1k**).

While these results were encouraging we were conscious of the fact that the concentration of chloride ions in the foregoing control reactions was lower than in the catalytic reactions, as no chlorotriphenylphosphonium chloride was formed. Thus, in a second experiment, a chloroform solution of oxalyl chloride was added to a solution of benzaldehyde and tetra-*n*-butylammonium chloride (7.5 mol %) (entry 4, Table 3). The result showed that more of the unwanted by-products **5a** and **5′a** were formed in this case; however, none of the dichloride product **4a** was detected.

In a final study we sought to establish the reactivity of by-product **5a** with respect to potential phosphine oxide-mediated conversion into product **4a**. To this end a solution of **5a** was prepared according to Scheme 2—this was necessary since attempts to isolate and purify **5a** had proven unsuccessful. The solution containing **5a** was treated, in a second step (Eq. 1), with triphenylphosphine oxide under reaction conditions identical to those employed for the catalytic reactions. This resulted in the formation of 1% (determined via ^{1}H NMR using $Cl_2CHCHCl_2$ as an internal standard) of product **4a**. This is in contrast with the 85% yield of **4a** obtained using the optimized conditions (entry 1, Table 2) and in-

Table 1
Optimization of catalytic dichlorination reactions



Entry	Ph_3PO mol %	$(COCl)_2$ mol %	T (°C)	Addition protocol/time	Yield **4a**%
1	120	120	rt	One portion, 10 min	14[a]
2	120	120	50	One portion, 10 min	82[a]
3	15	120	55	One portion, 2 h	73[b]
4	15	120	55	**1a** and $(COCl)_2$ added to $(COCl)_2$ and Ph_3PO, 2 h	90[a]
5	7.5	130	55	$(COCl)_2$ added to **1a** and Ph_3PO, 2 h	85[a]
6	5.0	130	55	$(COCl)_2$ added to **1a** and Ph_3PO, 2 h	70[b]

[a] Isolated yield after flash chromatography.
[b] Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

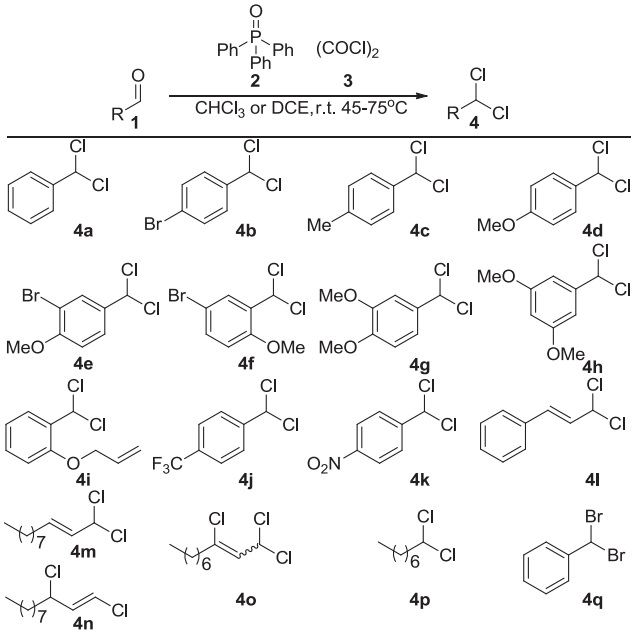
We next examined the substrate scope of the catalytic reaction (Table 2) using the catalyst loading and addition protocol described in entry 5 of Table 1. The results depicted in Table 2 demonstrate that the new protocol is effective for unfunctionalized and halo-substituted aryl aldehydes (entries 1 and 2) as well as electron rich (entries 4–9) and electron poor substrates (entries 10 and 11). With regard to aliphatic aldehydes activated aldehydes cinnamaldehyde and *trans*-2-undecanal (entries 12 and 13) were dichlorinated in good yield. In the later example a mixture of 1,1- and 1,3-dichlorides was obtained.[34] The chlorination of undec-2-ynal (entry 14) proceeded in moderate yield and afforded the trichlorinated product **4o** instead of the expected dichlorinated alkene. Unactivated aliphatic aldehydes were poor substrates as exemplified by entry 15. Finally, deoxybromination of benzaldehyde was possible in moderate yield (entry 16) using oxalyl bromide.

With a catalytic protocol in hand we next conducted several experiments in order to establish that the dichlorination process dicates that **5a** is stable under the catalytic reaction conditions and does not intervene in the major catalytic pathway to the geminal dichloride product.

At this juncture we sought to combine the newly developed dichlorination procedure with an interesting and underutilized palladium-catalyzed reductive dimerization process developed by Matsumoto[5a] in order to develop a new catalytic approach to the synthesis of stilbenes[35] from aldehydes[36] (Scheme 1C). We began our studies by establishing a one-pot conversion of benzaldehyde **1a** into *trans*-stilbene **6a** (Scheme 3).

We next explored the one-pot conversion of aldehyde **1g** into stilbene **6b**, which was accomplished in a 64% overall yield (Scheme 4A). The structure and stereochemistry of the olefin within **6b** was secured via X-ray crystallography.[36b,37,38] In a final study we investigated a reductive cross-coupling reaction of two geminal dichlorides in a formal synthesis of the bioactive stilbene resveratrol (Scheme 4B).[39,40] Gratifyingly, the cross-coupling of previously prepared 1,1-dichlorides **4h** and **4d** took place in

Table 2
Scope of catalytic dichlorination reaction[a]



Entry	Product	T (°C)	Solvent	Yield **4**%
1	**4a**	55	$CHCl_3$	85[b]
2	**4b**	55	$CHCl_3$	86[b]
3	**4c**	55	$CHCl_3$	93,[c] 91[b]
4	**4d**	45	$CHCl_3$	98[c]
5	**4e**	45	$CHCl_3$	90,[c] 90[b]
6	**4f**	45	$CHCl_3$	94,[c] 86[b]
7	**4g**	45	$CHCl_3$	99[c]
8	**4h**	45	$CHCl_3$	88[b]
9	**4i**	55	$CHCl_3$	85[b]
10	**4j**	75	DCE	89[b]
11	**4k**	75	DCE	92[b]
12	**4l**	75	DCE	86[b]
13	**4m**+**4n**	75	DCE	48,[b] 41[b]
14	**4o**	75	DCE	52[b]
15	**4p**	75	DCE	32[b]
16	**4q**	55	$CHCl_3$	49[b,d]

[a] Chloroform or DCE solution of $(COCl)_2$ (1.3 equiv) was added to a solution of Ph_3PO and appropriate aldehyde (1.0 equiv) in chloroform or DCE over 2–8 h at 45–75 °C.
[b] Isolated yield after flash chromatography.
[c] Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.
[d] $(COBr)_2$ was used instead of $(COCl)_2$.

moderate yield to afford trimethyl resveratrol **6c**. This constitutes the first example of a reductive cross-coupling process using the Matsumoto system and represents a highly step-economic formal synthesis of resveratrol.[40]

3. Conclusions

In conclusion, the phosphorus(V)-catalyzed conversion of aldehydes into geminal dichlorides has been accomplished using oxalyl chloride to induce phosphine oxide turnover. The combination of this dichlorination protocol with palladium-catalyzed reductive coupling provides a new approach to stilbenes and a formal synthesis of resveratrol.

4. Experimental

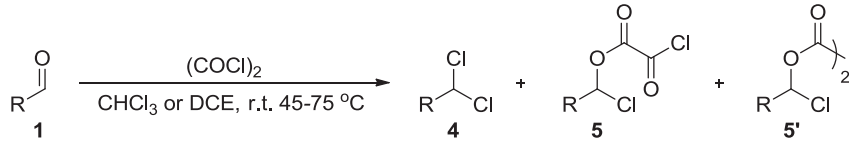
4.1. General information

Glassware was dried in an oven overnight before use. All solvents and reagents were used as supplied unless otherwise stated. Thin layer chromatography was carried out on Polgram SIL G/UV254 silica-aluminium plates and plates were visualized using ultra-violet light (254 nm) or $KMnO_4$ solution. For flash column chromatography, fluorochem silica gel 60, 35–70 mesh was used. NMR data was collected at either 270 MHz, or 400 MHz. Data was manipulated directly from the spectrometer or via a networked PC with appropriate software. Reference values for residual solvent were taken as δ=7.27 ($CDCl_3$) for ^{1}H NMR; δ=77.1 ($CDCl_3$) for ^{13}C NMR. Multiplicities for coupled signals are designated using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sex=sextet, br=broad signal and ap=apparent. The coupling constants are reported in Hertz. ^{13}C multiplicities were assigned using a DEPT sequence. Where appropriate, COSY, HMQC and HMBC experiments were performed to aid assignment. High-resolution mass spectrometry data were quoted to four decimal places (0.1 mDa) with error limits for acceptance of ±5.0 ppm (defined as calcd/found mass 10^{-6}). Mass spectra were acquired on a VG micromass 70E, VG autospec or micromass LCTOF. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR instrument as dilute chloroform solutions or as neat solids using an ATR device. Melting points were recorded on a Stuart manual melting point apparatus, with 0.1 °C resolution. Single crystal X-ray diffraction was carried out by the X-ray crystallography department at the University of Nottingham using a Bruker SMART 1000 CCD area detector diffractometer. Microanalyses were carried out on a model CE-440 Elemental Analyzer.

4.2. General procedure to determine the yield via ^{1}H NMR using an internal standard

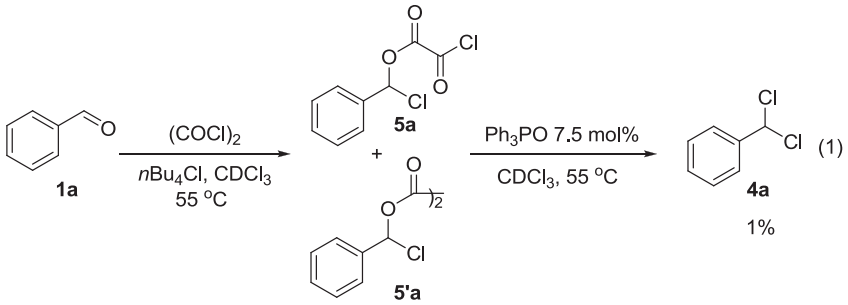
The crude reaction mixture was dissolved in $CDCl_3$ and transferred to a volumetric flask (two washings of the original flask were done after transfer) that was subsequently made up to the correct volume with further $CDCl_3$. To a 1 mL aliquot of this solution was added 1,1,2,2-tetrachlorethane (accurately approximately

Table 3
Control reactions

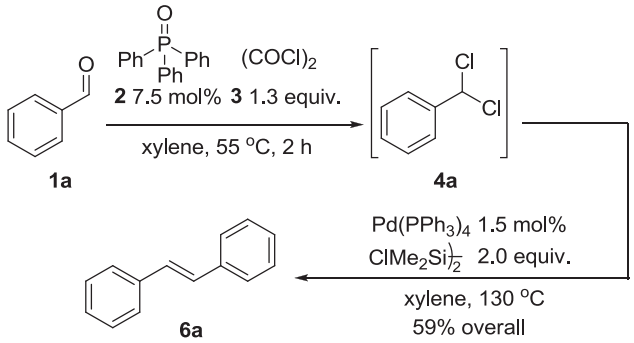


Entry	Substrate	Cl^- source	T (°C)	t/h	Solvent	Yield **4a**[a]/%	**1** recovered[a]
1	**1a**	n/a	55	2	$CHCl_3$	**4a** (7%), **5a**+**5′a** (trace)	83
2	**1d**	n/a	45	2	$CHCl_3$	**4d** (12%), **5d**+**5′d** (major)	n/a
3	**1k**	n/a	75	8	DCE	**4c** (0%)	>95%
4	**1a**	^{n}Bu$_4$NCl, 7.5 mol %	55	2	$CHCl_3$	**4a** (0%), **5a**+**5′a** (major)	38

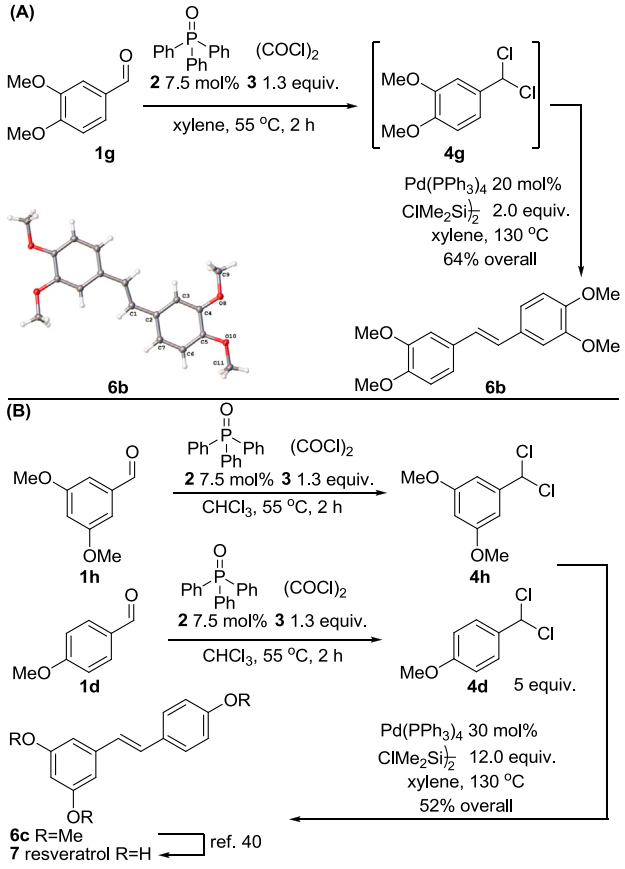
[a] Yield determined by ^{1}H NMR spectroscopy using $Cl_2CHCHCl_2$ as an internal standard.



Scheme 2. The reactivity of by-products **5a** and **5b′** in the presence of catalyst.



Scheme 3. Combining deoxydichlorination with reductive dimerization.



Scheme 4. Synthesis of bioactive stilbenes.

15–80 mg). The ^{1}H NMR spectrum was recorded and the mass of the product calculated according to the equation below:

$$\begin{aligned}\text{mass}_{\text{Product}} &= (\text{area}_{\text{Product}}/\text{area}_{\text{standard}}) \\ &\cdot(\text{MW}_{\text{Product}}/\text{MW}_{\text{standard}})\cdot\text{mass}_{\text{standard}} \\ &\cdot\text{purity factor}_{\text{standard}}\cdot n\cdot m/\text{purity factor}_{\text{aldehyde}}\end{aligned} \quad (1)$$

where n corrects for the amount of the crude reaction mixture used and m corrects for the number of protons associated with the resonance used.

4.3. Synthesis of 1,1-dichlorides

Method a: To a solution of triphenylphosphine oxide (21.0 mg, 75.5 μmol) in $CHCl_3$ (1.0 mL) was added the appropriate aldehyde (1.00 equiv, 1.00 mmol). Oxalyl chloride (110 μL, 1.30 mmol) as a solution in $CHCl_3$ (1.0 mL) was then added over 2 h via syringe pump at 55 °C after which time the solvent was removed in vacuo. Purification by flash chromatography (silica, 0–10% Et_2O/pet. ether) gave the pure 1,1-dichlorides.

Method b: As general method a, with the exception that the reaction was conducted at 45 °C.

Method c: To a solution of triphenylphosphine oxide (21.0 mg, 75.5 μmol) in DCE (1.0 mL) was added the appropriate aldehyde (1.00 equiv, 1.00 mmol). Oxalyl chloride (110 μL, 1.30 mmol) as a solution in DCE (1.0 mL) was then added over 8 h via syringe pump at 75 °C after which time solvent was removed in vacuo. Purification by flash chromatography (silica, 0–10% Et_2O/pet. ether) gave the pure 1,1-dichlorides.

Method d: Same as general method c, with the exception that a 2 h slow addition time was employed.

4.3.1. (Dichloromethyl)benzene ***4a***.[41] The following reagents were combined in the amounts indicated below in accordance with method a. Benzaldehyde (101 μL, 0.990 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol). Purification by flash column chromatography (silica, 10% Et_2O/pet. ether) afforded (dichloromethyl)benzene **4a** as a colourless oil (137 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.65 (m, 2H, Ar**H**), 7.48–7.39 (m, 3H, Ar**H**), 6.75 (s, 1H, C**H**Cl_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 123.0, 128.8, 126.2, 71.9.

4.3.2. 1-Bromo-4-(dichloromethyl)benzene ***4b***.[42] The following reagents were combined in the amounts indicated below in accordance with method a. 4-Bromobenzaldehyde (185 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave 1-bromo-4-(dichloromethyl)benzene **4b** (226 mg, 94%) by ^{1}H NMR. Purification by flash column chromatography (silica, 10% Et_2O/pet. ether) afforded 1-bromo-4-(dichloromethyl)benzene **4b** as a colourless oil (206 mg, 86%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.59–7.52 (m, 2H, Ar**H**), 7.49–7.43 (m, 2H,

ArH), 6.68 (s, 1H, CHCl$_2$); ^{13}C NMR (68 MHz, CDCl$_3$) δ 139.4, 132.1, 127.9, 124.1, 71.0.

4.3.3. 1-(Dichloromethyl)-4-methylbenzene ***4c***.[43] The following reagents were combined in the amounts indicated below in accordance with method a. 4-Methylbenzaldehyde (120 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave 1-(dichloromethyl)-4-methylbenzene **4c** (163 mg, 93%) by ^{1}H NMR. Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 1-(dichloromethyl)-4-methylbenzene **4c** as a colourless oil (159 mg, 91%). ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.51–7.44 (m, 2H, ArH), 7.27–7.19 (m, 2H, ArH), 6.71 (s, 1H, CHCl$_2$), 2.39 (s, 3H, CH$_3$); ^{13}C NMR (68 MHz, CDCl$_3$) δ 140.2, 137.7, 129.5, 126.1, 71.9, 21.4.

4.3.4. 1-(Dichloromethyl)-4-methoxybenzene ***4d***.[43] The following reagents were combined in the amounts indicated below in accordance with method b. 4-Methoxybenzaldehyde (136 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave 1-(dichloromethyl)-4-methoxybenzene **4d** (187 mg, 98%) by ^{1}H NMR. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54–7.49 (m, 2H, ArH), 7.94–7.89 (m, 2H, ArH), 6.71 (s, 1H, CHCl$_2$), 3.84 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.7, 132.8, 127.6, 114.0, 71.8, 55.5.

4.3.5. 2-Bromo-4-(dichloromethyl)-1-methoxybenzene ***4e***. The following reagents were combined in the amounts indicated below in accordance with method b. 3-Bromo-4-methoxybenzaldehyde (215 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave 2-bromo-4-(dichloromethyl)-1-methoxybenzene **4e** (243 mg, 90%) by ^{1}H NMR. Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 2-bromo-4-(dichloromethyl)-1-methoxybenzene **4e** as a colourless oil (243 mg, 90%). ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.79 (d, J=2.3 Hz, 1H, ArH), 7.49 (dd, J=8.7 and 2.3 Hz, 1H, ArH), 6.90 (d, J=8.7 Hz, 1H, ArH), 6.65 (s, 1H, CHCl$_2$), 3.93 (s, 1H, CH$_3$); ^{13}C NMR (68 MHz, CDCl$_3$) δ 157.0 (Cq), 134.0 (Cq), 131.4 (CH), 126.6 (CH), 111.8 (CH), 111.5 (CH), 70.6 (CH), 56.5 (CH$_3$); IR ν_{max} (CHCl$_3$) 3011, 2971, 2946, 2910, 2841, 1602, 1572, 1498, 1462, 1441, 1407, 1309, 1289, 1281, 1263, 1190, 1151, 1055, 1020, 908, 893, 660 cm^{-1}; HRMS (EI$^+$) [M$^+$] $C_8H_8OBrCl_2$ calcd 267.9057, found 267.9052.

4.3.6. 4-Bromo-2-(dichloromethyl)-1-methoxybenzene ***4f***. The following reagents were combined in the amounts indicated below in accordance with method b. 5-Bromo-2-methoxybenzaldehyde (215 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave 4-bromo-2-(dichloromethyl)-1-methoxybenzene **4f** (202 mg, 94%) by ^{1}H NMR. Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 4-bromo-2-(dichloromethyl)-1-methoxybenzene **4f** as a white solid (185 mg, 86%). Mp 47.8–48.8 °C; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.93 (d, 1H, J=2.5 Hz, ArH), 7.45 (dd, J=8.8 and 2.5 Hz, 1H, ArH), 7.11 (s, 1H, CHCl$_2$), 6.77 (d, J=8.8 Hz, 1H, ArH), 3.88 (s, 3H, CH$_3$); ^{13}C NMR (68 MHz, CDCl$_3$) δ 153.6 (Cq), 133.9 (Cq), 131.1 (CH), 130.5 (CH), 113.3 (CH), 112.7 (CH), 65.3 (CH), 56.1 (CH$_3$); IR ν_{max} (CHCl$_3$) 3011, 2969, 2943, 2908, 2842, 1596, 1577, 1486, 1462, 1440, 1409, 1308, 1276, 1257, 1186, 1169, 1121, 1029, 885, 820, 624 cm^{-1}; HRMS (ESI$^+$) [M+H$^+$] $C_8H_8OBrCl_2$ calcd 268.9130, found 268.9130.

4.3.7. 4-(Dichloromethyl)-1,2-dimethoxybenzene ***4g***.[44] The following reagents were combined in the amounts indicated below in accordance with method b. 3,4-Dimethoxybenzaldehyde (166 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave 4-(dichloromethyl)-1,2-dimethoxybenzene **4g** (219 mg, 99%) by ^{1}H NMR. ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.15 (d, J=2.1 Hz, 1H, ArH), 7.06 (dd, J=8.8 and 2.1 Hz, 1H, ArH), 6.82 (d, J=8.8 Hz, 1H, ArH), 6.69 (s, 1H, CHCl$_2$), 3.93 (s, 3H, OCH$_3$), 3.90 (s, 3H, OCH$_3$); ^{13}C NMR (68 MHz, CDCl$_3$) δ 150.3, 149.3, 133.0, 118.5, 110.3, 109.1, 72.0, 56.0, 56.0.

4.3.8. 1-(Dichloromethyl)-3,5-dimethoxybenzene ***4h***.[45] The following reagents were combined in the amounts indicated below in accordance with method b. 3,5-Dimethoxybenzaldehyde (166 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol). Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 1-(dichloromethyl)-3,5-dimethoxybenzene **4h** as a colourless oil (195 mg, 88%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.74 (d, J=2.3 Hz, 2H, ArH), 6.64 (s, 1H, CHCl$_2$), 6.48 (t, J=2.3 Hz, 1H, ArH), 3.83 (s, 6H, CH$_3$ ×2); ^{13}C NMR (68 MHz, CDCl$_3$) δ 160.9, 142.4, 104.3, 101.9, 71.7, 55.6.

4.3.9. 1-(Allyloxy)-2-(dichloromethyl)benzene ***4i***. The following reagents were combined in the amounts indicated below in accordance with method a. 2-(Allyloxy)benzaldehyde (150 μL, 0.998 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol). Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 1-(allyloxy)-2-(dichloromethyl)benzene **4i** as a colourless oil (185 mg, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (dd, J=7.8 and 1.8 Hz, 1H, ArH), 7.37–7.31 (m, 1H, ArH), 7.25 (s, 1H, CHCl$_2$), 7.10–7.04 (m, 1H, ArH), 6.91–6.86 (m, 1H, ArH), 6.13–6.02 (m, 1H, OCH$_2$CH), 5.49–5.42 (m, 1H, CH=CH$_2$), 5.36–5.31 (m, 1H, CH=CH$_2$), 4.66–4.61 (m, 2H, OCH$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.6 (Cq), 132.7 (CH), 131.1 (CH), 129.0 (Cq), 128.2 (CH), 121.4 (CH), 117.9 (CH$_2$), 112.1 (CH), 69.3 (CH$_2$), 66.5 (CH); IR ν_{max} (CHCl$_3$) 3083, 2926, 1650, 1602, 1588, 1488, 1457, 1424, 1363, 1323, 1290, 1254, 1163, 1104, 1047, 1018, 996, 936, 850, 660, 594 cm^{-1}; HRMS (EI$^+$) [M$^+$] $C_{10}H_{10}OCl_2$ calcd 216.0109, found 216.0111.

4.3.10. 1-(Dichloromethyl)-4-(trifluoromethyl)benzene ***4j***.[46] The following reagents were combined in the amounts indicated below in accordance with method c. 4-(Trifluoromethyl)benzaldehyde (174 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave 1-(dichloromethyl)-4-(trifluoromethyl)benzene **4j** (215 mg, 94%) by ^{1}H NMR. Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 1-(dichloromethyl)-4-(trifluoromethyl)benzene **4j** as a colourless oil (204 mg, 89%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75–7.67 (m, 4H, ArH), 6.75 (s, 1H, CHCl$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.9, 132.1 (q, J=32.8 Hz), 126.8, 126.0 (q, J=3.8 Hz), 123.7 (q, J=270.1 Hz), 70.6.

4.3.11. 1-(Dichloromethyl)-4-nitrobenzene ***4k***.[42] The following reagents were combined in the amounts indicated below in accordance with method c. 4-Nitrobenzaldehyde (151 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol). Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 1-(dichloromethyl)-4-nitrobenzene **4k** as a colourless oil (190 mg, 92%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.31–8.26 (m, 2H, ArH), 7.81–7.75 (m, 2H, ArH), 6.78 (s, 1H, CHCl$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.6, 146.3, 127.5, 124.2, 69.9.

4.3.12. (E)-(3,3-Dichloroprop-1-en-1-yl)benzene ***4l***.[9a] The following reagents were combined in the amounts indicated below in accordance with method d. Cinnamaldehyde (132 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol) gave (*E*)-(3,3-dichloroprop-1-en-1-yl)benzene **4l** (178 mg, 95%) by ^{1}H NMR. Purification by flash column chromatography (silica, 5% Et$_2$O/pet. ether) afforded (*E*)-(3,3-dichloroprop-1-en-1-yl)benzene **4l** as a colourless oil (161 mg, 86%). ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.50–7.31 (m, 5H, ArH), 6.74 (d,

J=15.3 Hz, 1H, PhC**H**), 6.49 (dd, J=15.3 and 7.9 Hz, 1H, C**H**CHCl$_2$), 6.37 (d, J=7.9 Hz, 1H, C**H**Cl$_2$); ^{13}C NMR (68 MHz, CDCl$_3$) δ 134.4, 132.2, 129.2, 128.9, 127.9, 127.3, 71.4.

*4.3.13. (E)-1,1-Dichloroundec-2-ene (**4m**) and (E)-1,3-dichloroundec-1-ene **4n**.* The following reagents were combined in the amounts indicated below in accordance with method d. (*E*)-Undec-2-enal (168 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol). Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded (*E*)-1,1-dichloroundec-2-ene **4m** as a colourless oil (106 mg, 48%), and (*E*)-1,3-dichloroundec-1-ene **4n** as a colourless oil (92 mg, 41%). (*E*)-1,1-Dichloroundec-2-ene **4m**, ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.17–6.13 (m, 1H, C**H**Cl$_2$), 5.92–5.79 (m, 2H, C**H**=C**H**Cl$_2$), 2.13–2.06 (m, 2H, C**H**$_2$CH=CHCl$_2$), 1.51–1.21 (m, 12H, CH$_3$C**H**$_2$ ×6), 0.89 (t, J=7.0 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.6 (CH), 129.9 (CH), 71.5 (CH), 31.9 (CH$_2$), 31.4 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 28.5 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_2$). (*E*)-1,3-Dichloroundec-1-ene **4n**, ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.29 (dd, J=13.3 and 0.6 Hz, 1H, CH=C**H**Cl), 6.01 (dd, J=13.3 and 9.0 Hz, 1H, C**H**=CHCl), 4.40–4.33 (m, 1H, C**H**ClCH=CHCl), 1.90–1.74 (m, 2H, C**H**$_2$CHClCH=CHCl), 1.51–1.21 (m, 12H, CH$_3$C**H**$_2$ ×6), 0.89 (t, J=7.0 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.2 (CH), 121.2 (CH), 60.0 (CH), 38.5 (CH$_2$), 31.9 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.0 (CH$_2$), 26.4 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_3$).

*4.3.14. (E)-1,3-Dichloroundec-1-ene **4n**.* A mixture of (*E*)-1,1-dichloroundec-2-ene and (*E*)-1,3-dichloroundec-1-ene (321 mg, 1.44 mmol) was dissolved in DCE (2.0 mL). The solution was stirred under N$_2$ at 75 °C for 40 h. The solvent was removed in vacuo. Purification by flash chromatography (silica, 1% Et$_2$O/pet. ether) afforded (*E*)-1,3-dichloroundec-1-ene **4m′** as a colourless oil (273 mg, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.29 (dd, J=13.3 and 0.6 Hz, 1H, CH=C**H**Cl), 6.01 (dd, J=13.3 and 9.0 Hz, 1H, C**H**=CHCl), 4.40–4.33 (m, 1H, C**H**ClCH=CHCl), 1.90–1.74 (m, 2H, C**H**$_2$CHClCH=CHCl), 1.51–1.21 (m, 12H, CH$_3$C**H**$_2$ ×6), 0.89 (t, J=7.0 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 134.2 (CH), 121.2 (CH), 60.0 (CH), 38.5 (CH$_2$), 31.9 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.0 (CH$_2$), 26.4 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_3$); IR ν_{max} (CHCl$_3$) 3067, 2929, 2857, 1620, 1466, 1378, 1286, 934, 834, 637 cm^{-1}; HRMS (EI$^+$) [M$^+$–HCl] C$_{11}$H$_{19}$Cl calcd 186.1175, found 186.1172.

*4.3.15. (Z/E)-1,1,3-Trichlorodec-2-ene **4o**.* The following reagents were combined in the amounts indicated below in accordance with method d. Dec-2-ynal (152 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol). Purification by flash column chromatography (silica, pet. ether) afforded (*Z*/*E*)-1,1,3-trichlorodec-2-ene **4o** as colourless oil (63.5 mg, 52%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.58 (d, J=9.1 Hz, C**H**Cl$_2$), 6.35 (d, J=9.9 Hz, C**H**Cl$_2$), 6.09 (d, J=9.9 Hz, CHCl$_2$C**H**), 5.97 (d, J=9.1 Hz, CHCl$_2$C**H**), 2.45–2.25 (m, CClC**H**$_2$), 1.66–1.51 (m, CClCH$_2$C**H**$_2$), 1.45–1.23 (m, CH$_3$C**H**$_2$ ×4), 0.90 (t, J=6.8 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.2, 138.4, 127.9, 125.8, 66.9, 66.0, 39.0, 34.5, 31.7, 29.1, 29.0, 28.7, 28.5, 27.1, 26.9, 22.7, 14.1. IR ν_{max} (CHCl$_3$) 2930, 2858, 2237, 1644, 1466, 1380, 1254, 1111, 909, 857, 656, 588 cm^{-1}; HRMS (EI$^+$) [M$^+$] C$_{10}$H$_{17}$Cl$_3$ calcd 242.0396, found 242.0397.

*4.3.16. 1,1-Dichlorodecane **4p**.*[1b] The following reagents were combined in the amounts indicated below in accordance with method c. Decanal (312 mg, 2.00 mmol), oxalyl chloride (220 μL, 2.60 mmol) and triphenylphosphine oxide (42.0 mg, 0.151 mmol). Purification by flash column chromatography (silica, 1% Et$_2$O/pet. ether) afforded 1,1-dichlorodecane **4p** as a colourless oil (135 mg, 32%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.75 (t, J=6.1 Hz, 1H, C**H**Cl$_2$), 2.24–2.16 (m, 2H, CHCl$_2$C**H**$_2$), 1.60–1.50 (m, 2H, CHCl$_2$CH$_2$C**H**$_2$), 1.40–1.22 (m, 12H, CH$_3$C**H**$_2$ ×6), 0.90 (t, J=7.2 Hz, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 73.8, 43.8, 31.9, 29.5, 29.4, 29.3, 28.6, 26.1, 22.8, 14.2.

*4.3.17. (Dibromomethyl)benzene **4q**.*[43] To a solution of triphenylphosphine oxide (126 mg, 0.452 mmol) in CHCl$_3$ (3.0 mL) was added benzaldehyde (303 μL, 2.97 mmol) followed by oxalyl bromide (366 μL, 3.90 mmol) as a solution in CHCl$_3$ (3.0 mL) over 7 h via syringe pump at 55 °C. The solvent was removed in vacuo and purification by flash chromatography (silica, 5% Et$_2$O/pet. ether) gave (dibromomethyl)benzene **4q** as a colourless oil (367 mg, 49%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62–7.56 (m, 2H, Ar**H**), 7.42–7.31 (m, 3H, Ar**H**), 6.67 (s, 1H, C**H**Cl$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 142.0, 129.9, 128.7, 126.6, 41.1.

4.4. Synthesis of stilbenes

*4.4.1. (E)-1,2-Diphenylethene **6a**.*[47] To a solution of triphenylphosphine oxide (21.0 mg, 75.5 μmol) in xylene (0.5 mL) was added benzaldehyde (101 μL, 1.00 mmol) followed by oxalyl chloride (93.0 μL, 1.10 mmol) as a solution in xylene (0.5 mL) over 2 h via syringe pump at 55 °C. The (COCl)$_2$ and HCl were removed in vacuo and 1,2-dichloro-1,1,2,2-tetramethyldisilane (373 μL, 2.00 mmol) and Pd(PPh$_3$)$_4$ (16.0 mg, 13.9 μmol) were then added. The reaction mixture was heated to 130 °C and stirred under N$_2$ for 3 h. The reaction was diluted with pentane (3.0 mL) and filtered. The solvent was removed in vacuo. Purification by flash chromatography (silica, 5% Et$_2$O/pet. ether) afforded (*E*)-1,2-diphenylethene **6a** as a white solid (53.4 mg, 59%). Mp 124.2–125.8 °C (reported[48] 123–124 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58–7.53 (m, 4H, Ar**H**), 7.43–7.37 (m, 4H, Ar**H**), 7.33–7.27 (m, 2H, Ar**H**), 7.15 (s, 2H, C**H**=C**H**); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.4, 128.8, 128.8, 127.7, 126.6.

*4.4.2. (E)-1,2-Bis(3,4-dimethoxyphenyl)ethene **6b**.*[37f] To a solution of triphenylphosphine oxide (21.0 mg, 0.0755 mmol) in xylene (0.5 mL) was added 3,4-dimethoxybenzaldehyde (166 mg, 1.00 mmol) followed by oxalyl chloride (93.0 μL, 1.10 mmol) as a solution in xylene (0.5 mL) over 2 h via syringe pump at 55 °C, (COCl)$_2$. The (COCl)$_2$ and HCl were removed in vacuo and 1,2-dichloro-1,1,2,2-tetramethyldisilane (373 μL, 2.00 mmol) and Pd(PPh$_3$)$_4$ (231 mg, 0.200 mmol) were added. The reaction mixture was heated to 130 °C and stirred under N$_2$ for 3 h. The reaction was diluted with propane (3.0 mL) and filtered. The solvent was removed in vacuo. Purification by flash chromatography (silica, 50% Et$_2$O/pet. ether) afforded (*E*)-1,2-bis(3,4-dimethoxyphenyl)ethene **6b** as a white solid (96.0 mg, 64%). Mp 153.6–154.8 °C (reported[49] 154–155 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.08–7.02 (m, 4H, Ar**H**), 6.93 (s, 2H, C**H**=C**H**), 6.86 (d, J=8.2 Hz, 2H, Ar**H**), 3.96 (s, 3H, OC**H**$_3$), 3.91 (s, 3H, OC**H**$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.2, 148.8, 130.8, 126.7, 119.6, 111.4, 108.7, 56.0, 56.0.

*4.4.3. (E)-1,3-Dimethoxy-5-(4-methoxystyryl)benzene **6c**.*[50] The following reagents were combined in the amounts indicated below in accordance with method b. 3,5-Dimethoxybenzaldehyde (166 mg, 1.00 mmol), oxalyl chloride (110 μL, 1.30 mmol) and triphenylphosphine oxide (21.0 mg, 75.5 μmol). Purification by flash column chromatography (silica, 10% Et$_2$O/pet. ether) afforded 1-(dichloromethyl)-3,5-dimethoxybenzene as a colourless oil (195 mg, 88%). The following reagents were combined in the amounts indicated below in accordance with method b. 4-Methoxybenzaldehyde (680 mg, 5.00 mmol), oxalyl chloride (550 μL, 6.50 mmol) and triphenylphosphine oxide (105 mg, 37.7 μmol). The solvent was removed in vacuo. The crude mixture was re-dissolved in xylene (5.0 mL) and then 1-(dichloromethyl)-3,5-dimethoxybenzene (195 mg, 0.880 mol), 1,2-dichloro-1,1,2,2-tetramethyldisilane (2.23 μL, 12.0 mmol) and Pd(PPh$_3$)$_4$ (347 mg, 0.300 mmol) were added. The reaction mixture was heated to 130 °C and stirred under

N_2 for 3 h after which the cooled reaction was quenched with EtOAc (30.0 mL) and filtered and the solvent was removed in vacuo. Purification by flash chromatography (silica, 10% EtOAc/pet. ether) afforded (*E*)-1,3-dimethoxy-5-(4-methoxystyryl)benzene **6c** as a white solid (123 mg, 52%). Mp 52.6–54.5 °C (reported[39f] 52–54 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2H, Ar**H**), 7.06 (d, *J*=16.3 Hz, 1H, C**H**=CH), 6.95–6.89 (m, 3H, Ar**H** ×2 and CH=C**H**), 6.67 (d, *J*=2.3 Hz, 2H, Ar**H**), 6.40 (t, *J*=2.3 Hz, 1H, Ar**H**), 3.85 (s, 9H, OC**H**$_3$ ×3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.5, 139.8, 130.0, 128.8, 127.9, 126.7, 114.2, 104.4, 99.7, 55.4, 55.4; HRMS (ESI^+) [M+Na^+] $C_{17}H_{18}NaO_3$ calcd 293.1148, found 293.1135.

4.5. Control reactions

Table 3, entry 1: To a solution of benzaldehyde (101 μL, 0.991 mmol) in $CHCl_3$ (1.0 mL) was added oxalyl chloride (110 μL, 1.30 mmol) as a solution in $CHCl_3$ (1.0 mL) over 2 h via syringe pump at 55 °C. The solvent was removed in vacuo, gave **4a** (11 mg, 7%) and trace amount of **5a** and **5′a** by ^{1}H NMR. 83% of benzaldehyde was recovered by ^{1}H NMR.

Table 3, entry 2: To a solution of 4-methoxybenzaldehyde (136 mg, 1.00 mmol) in $CHCl_3$ (1.0 mL) was added oxalyl chloride (110 μL, 1.30 mmol) as a solution in $CHCl_3$ (1.0 mL) over 2 h via syringe pump at 45 °C. The solvent was removed in vacuo, gave **5f**, **8f** as the major product and **4f** (23 mg, 12%) by ^{1}H NMR.

Table 3, entry 3: To a solution of 4-nitrobenzaldehyde (151 mg, 1.00 mmol) in DCE (1.0 mL) was added oxalyl chloride (110 μL, 1.30 mmol) as a solution in DCE (1.0 mL) over 8 h via syringe pump at 75 °C. The solvent was removed in vacuo. No **4c** formed by ^{1}H NMR. >95% of 4-nitrobenzaldehyde was recovered by ^{1}H NMR.

Table 1, entry 4: To a solution of benzaldehyde (101 μL, 0.991 mmol) in $CHCl_3$ (1.0 mL) was added ^{n}Bu_4NCl (21.0 mg, 0.0760 mmol). Then oxalyl chloride (110 μL, 1.30 mmol) as a solution in $CHCl_3$ (1.0 mL) was added over 2 h via syringe pump at 55 °C. The solvent was removed in vacuo. No **4a** formed by ^{1}H NMR. 38% of benzaldehyde was recovered by ^{1}H NMR. Compounds **5a** and **8a** was formed as the major product by ^{1}H NMR.

Equation 1: To a solution of benzaldehyde (101 μL, 0.991 mmol) in $CHCl_3$ (1.0 mL) was added ^{n}Bu_4NCl (21.0 mg, 0.0760 mmol). Then oxalyl chloride (110 μL, 1.30 mmol) as a solution in $CDCl_3$ (1.0 mL) was added over 2 h via syringe pump at 55 °C affording a mixture of **1a** (37%), **5a** and **5′a** (**5a** and **5′a** 63% combined). The solvent was removed in vacuo. The mixture was re-dissolved in $CDCl_3$ and treated with triphenylphosphine oxide (21.0 mg, 75.5 μmol). The reaction mixture was stirred at 55 °C for 2 h affording **4a** (1%).

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