A method of mild deoxydichlorination of aldehydes catalyzed by Triphenylphosphine oxide

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This paper belongs to the Regular Issue.

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Abstract
The catalytic system of triphenylphosphine oxide and phthaloyl dichloride catalysing conversion of aldehydes to 1,1-dichlorides is reported. The reaction proceeds via a P (V) catalysis manifold in which triphenylphosphine oxide turnover is achieved using phthaloyl dichloride as a consumable reagent. The application of the developed method on substrates of different structures was demonstrated. We showed the use of unsaturated compounds, including aromatics with and without electron donating / withdrawing groups, as well as saturated aliphatic compounds. The possibility of using the developed method on a gram scale was also demonstrated with the deoxydichlorination reaction of 0.03 mol of benzaldehyde catalyzed by triphenylphosphine oxide as an example. The proposed method may be of interest for the production of different herbicides, insecticides and fungicides for the agricultural industry.

Keywords
aldehydes
Lewis base catalysis
organocatalysis
triphenylphosphine oxide
nucleophilic substitution
agricultural chemistry

1. Introduction
The development of methods for nucleophilic substitution (S_N) in sp³-hybridized carbon centers is the most significant and widespread problem of chemical transformations in organic synthesis [1–5]. Nucleophilic substitutions are general chemical transformations, as they allow, for example, strategic building of C–Cl, C–O, C–N and C–C bonds [6–15]. At the same time, compounds such as geminal dichlorides are important intermediates in the chemical synthesis of useful natural substances, including active biological compounds. Geminal dichlorides, especially dichlorides, are an important class of intermediates in organic synthesis. They were used for alkenylation of carbonyl compounds [16, 17], cyclopropanation and epoxidation [18–20], dimerization [21, 22] and other purposes [23–26].

In addition, geminal dichlorides are also encountered as structural motifs in polyhalogenated natural products [27, 28]. At the same time, one of the main areas of application of such compounds is agriculture. Herbicides, insecticides and fungicides are widely used for plant protection in the modern industry (Fig. 1) [29–31]. Most of the waste from such chemical industries contains various halogen-containing compounds, which are extremely toxic to both humans and the environment.

Also, the Dichlorides are an important class of intermediates in organic synthesis. They were used for alkenylation of carbonyl compounds [32, 33], cyclopropanation and epoxidation [34–36], dimerization [37, 38], etc. [39–42]. In addition, geminal dichlorides are also encountered as structural motifs in polyhalogenated natural products such as Caldariomycin, Danicalipin A and undecachlorosulfolipids A [43–48].

However, traditional synthetic methods often have low selectivity and low atom economy, resulting in the different products of chemical reactions [49–51]. Research in this area is at an early stage in the study of such catalytic reactions, but several efficient protocols for the production of dichlorides from aldehydes catalyzed by a Lewis base have been disclosed to date (Scheme 1). Dr. Denton with colleagues previously reported a method for the catalytic deoxydichlorination of aldehydes [52]. In this method, authors used a catalytic system of triphenylphosphine oxide (7.5–15 mol.%) and Oxalyl chloride. The proposed method works well with different unsaturated compounds, but gives a lower yield of 32% with aliphatic compounds.
In 2019, Dr. P. Huy showed new catalytic method transformation of aldehydes into geminal dichlorides using a catalytic system of $N$-formylpyrrolidine (5-10 mol\%) with phthaloyl dichloride (1.2-1.4 equiv). The proposed method exhibits the same catalytic activity as triphenylphosphine oxide [53]. Later Dr. Shipilovskikh with colleges proposed an alternative method for deoxydichlorination of aldehydes catalyzed by diphenyl sulfoxide, using a catalytic system of diphenyl sulfoxide (10 mol\%) and oxalyl chloride (1.5 equiv). The developed method showed excellent yields with unsaturated aldehydes [54].

In this work, we use the combination of the previously reported catalytic system and optimization of the reaction condition. We found that the catalytic activity of triphenylphosphine oxide can be increased by a factor of 10 compared to previously described methods. In addition, in the proposed method, reducing the catalyst load did not affect the catalytic activity in case of unsaturated aldehydes and in case of aliphatic aldehydes, the reaction yield increased to 10%.

2. Experimental

Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR spectra.

The $^{1}$H and $^{13}$C NMR spectra were recorded at 400 MHz for $^{1}$H and 100 MHz for $^{13}$C NMR at the temperature of 303 K; the chemical shifts ($\delta$) were measured in ppm with respect to the solvent (CDCl$_3$, $^{1}$H: $\delta = 7.26$ ppm, $^{13}$C: $\delta = 77.16$ ppm; [D6] DMSO, $^{1}$H: $\delta = 2.50$ ppm, $^{13}$C: $\delta = 39.52$ ppm). The coupling constants ($J$) are given in Hertz. The splitting patterns of apparent multiplets associated with an averaged coupling constants were designated as $s$ (singlet), $d$ (doublet), $t$ (triplet), $q$ (quartet), $sept$ (septet), $m$ (multiplet), $dd$ (doublet of doublets) and $br$ (broadened). The melting points were determined with a «Stuart SMP 30», the values are uncorrected. Flash chromatography was performed on silica gel Macherey Nagel (40–63 µm).

Scheme 1 Catalytic deoxydichlorination of aldehydes to 1,1-dichlorides
The reaction progress was monitored by GC/MS analysis and thin layer chromatography (TLC) on aluminum backed plates with Merck Kiesel 60 F254 silica gel. The TLC plates were visualized either by UV radiation at a wavelength of 254 nm or stained by exposure to a Dragendorff’s reagent or potassium permanganate aqueous solution. All the reactions were carried out using dried and freshly distilled solvent.

2.1. General method for synthesis of dichlorides from aldehyde

Triphenylphosphine oxide (Ph₃PO) (3 mg, 0.01 mmol, 0.01 equiv, 1 mol%), and phthaloyl dichloride (203 mg, 1.00 mmol, 1 equiv) were dissolved in 8 mL of anhydrous toluene in a 25 mL round bottom flask equipped with a magnetic stirring bar. After wards, aldehydes 1a-e (1 mmol, 1 equiv) in 2 mL of anhydrous toluene were slowly added to this solution with vigorous stirring at 0 °C, followed by heating up to 100 °C and stirring the mixture for 3 h. The reaction progress was monitored by GC-MS. After the reaction was complete, the solution was filtered and concentrated in vacuum. The crude mixture thus obtained was purified by flash chromatography on silica (petroleum ether/Et₂O – 19/1). For gram-scale example , the mixture was purified by distillation. The general method for synthesis is shown in Scheme 2.

![Scheme 2 General method for synthesis](image)

Scheme 2 General method for synthesis

2.1.1. (Dichloromethyl)benzene 4a

Obtained from 1a (106 mg, 1 mmol), triphenylphosphine oxide (Ph₃PO) (3 mg, 0.01 mmol, 0.01 equiv, 1 mol%), and phthaloyl dichloride (203 mg, 1.00 mmol, 1 equiv) in anhydrous toluene (10 mL). Colorless oil (143 mg, 75%). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 6.33 (s, 1H, CH), 7.64–7.66 (m, 2H, H₉), 7.71–7.83 (m, 2H, H₈). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 54.0, 64.5, 109.3, 120.1, 127.1, 128.3, 130.0, 152.4 [53].

2.1.2. 1-(Dichloromethyl)-4-methylbenzene 4b

Obtained from 1b (120 mg, 1 mmol), triphenylphosphine oxide (Ph₃PO) (3 mg, 0.01 mmol, 0.01 equiv, 2 mol%), and phthaloyl dichloride (203 mg, 1.00 mmol, 1 equiv) in anhydrous toluene (10 mL). Colorless oil (159 mg, 91%). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 2.42 (s, 3H, CH₃), 6.69 (s, 1H, CH), 7.16–7.24 (m, 2H, H₉), 7.44–7.51 (m, 2H, H₈). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 21.8, 71.6, 126.0, 129.1, 137.2, 140.7 [56].

2.1.3. 1-Bromo-4-(dichloromethyl)benzene 4c

Obtained from 1c (185 mg, 1 mmol), triphenylphosphine oxide (Ph₃PO) (3 mg, 0.01 mmol, 0.01 equiv, 1 mol%), and phthaloyl dichloride (203 mg, 1.00 mmol, 1 equiv), in anhydrous toluene (10 mL). Colorless oil (194 mg, 81%). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 5.90 (s, 1H, CH), 7.49–7.50 (m, 2H, H₈). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 72.0, 124.2, 128.1, 131.7, 139.5 [53].

The structures of 1-(Dichloromethyl)benzene 4a, (Dichloromethyl)-4-methylbenzene 4b and 1-Bromo-4-(dichloromethyl)benzene 4c are shown in Fig. 2.

![Fig. 2 1-(Dichloromethyl)benzene 4a, (Dichloromethyl)-4-methylbenzene 4b and 1-Bromo-4-(dichloromethyl)benzene 4c](image)

2.1.4. 1-(dichloromethyl)-2-methoxybenzene 4d

Obtained from 1d (136 mg, 1 mmol), triphenylphosphine oxide (Ph₃PO) (3 mg, 0.01 mmol, 0.01 equiv, 1 mol%), and phthaloyl dichloride (203 mg, 1.00 mmol, 1 equiv), in anhydrous toluene (10 mL). Colorless oil (143 mg, 75%). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 6.93–7.17 (m, 1H, CH, 2H, H₈), 7.29–7.32 (m, 1H, H₇), 7.71–7.83 (m, 2H, H₆). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 54.1, 64.5, 109.3, 120.1, 127.1, 128.3, 130.0, 152.4 [53].

2.1.5. (3,3-Dichloroprop-1-en-1-yl)benzene 4e

Obtained from 1e (132 mg, 1 mmol), triphenylphosphine oxide (Ph₃PO) (3 mg, 0.01 mmol, 0.01 equiv, 1 mol%), and phthaloyl dichloride (203 mg, 1.00 mmol, 1 equiv), in anhydrous toluene (10 mL). Colorless oil (153 mg, 82%). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 6.33 (d, J = 7.6 Hz, 1H, CH), 6.49 (dd, J = 14.7 and 7.6 Hz, 1H, CH), 6.72 (d, J = 14.7 Hz, 1H, CH), 7.30–7.50 (m, 5H, H₆). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 73.5, 127.1, 128.1, 129.0, 129.2, 132.5, 134.7 [53].

2.1.6. 1,1-Dichlorooctane 4f

Obtained from 1f (128 mg, 1 mmol), triphenylphosphine oxide (Ph₃PO) (3 mg, 0.01 mmol, 0.01 equiv, 1 mol%), and phthaloyl dichloride (203 mg, 1.00 mmol, 1 equiv), in anhydrous toluene (10 mL). Colorless oil (77 mg, 42%). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 0.92 (t, J = 7.2 Hz, 3H, CH₃), 1.31 (m, 8H, CH₂), 1.55 (m, 2H, CH₂), 2.20 (m, 2H, CH₂), 5.74 (t, J = 6.2 Hz, 1H, CHCl). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 14.0, 22.9, 26.3, 28.7, 29.6, 32.0, 43.9, 73.7.

The structures of 1-(dichloromethyl)-2-methoxybenzene 4d, (3,3-Dichloroprop-1-en-1-yl)benzene 4e and 1,1-Dichlorooctane 4f are shown in Fig. 3.
3. Results and Discussion

The investigation commenced with establishing the best conditions for the deoxydichlorination of aldehydes, employing benzaldehyde 1a as a model substrate (Table 1). First, the catalytic triphenylphosphine oxide was investigated. Then, the effects of the solvent, temperature, and equivalents of phthaloyl dichloride on the conversion in the reaction were studied. Phthaloyl dichloride on its own did not produce (Dichloromethyl)benzene 4a (entry 1). The use of stoichiometric quantities of Ph3PO and 2 equiv of phthaloyl dichloride in DCM resulted in low conversion of 1a into 4a (Scheme 3, Table 1, entry 2). With 10 mol.% Ph3PO and 2 equiv of phthaloyl dichloride, 4a was formed in 16% conversion after 3 h (entry 3), which increased to 40% after changing the solvent to toluene (entry 4). Raising the temperature to 100 °C with 10 mol.% Ph3PO and using 2 equiv of phthaloyl dichloride led to the best results of conversion to 95% (entry 9). We then studied the catalytic activity of Ph3PO at 100 °C for 3 hours and found that using 1 mol.% Ph3PO gives a similar result (95% conversion, entry 11). Finally, we studied the effect of the equivalents of phthaloyl dichloride on the conversion of the reaction and found that the use of phthaloyl dichloride at an equivalent of 100 mol.% gives a similar conversion, 95% (entry 12). However, reducing the equivalents of phthaloyl dichloride to 50 mol.% yields the conversion of 43% (entry 13).

Table 1: Optimization of the reaction conditions

| entry | equiv of phthaloyl dichloride | mol.% Ph3PO | solvent | T (°C) | t (h) | conv. (%) |
|-------|-----------------------------|-------------|---------|--------|------|----------|
| 1     | 2                           | 0           | DCM     | 40     | 1    | 0        |
| 2     | 2                           | 100         | DCM     | 40     | 1    | 8        |
| 3     | 2                           | 10          | DCM     | 40     | 3    | 16       |
| 4     | 2                           | 10          | Tol     | 40     | 3    | 40       |
| 5     | 2                           | 10          | MeCN    | 40     | 3    | 10       |
| 6     | 2                           | 10          | DCE     | 40     | 3    | 18       |
| 7     | 2                           | 10          | THF     | 40     | 3    | 32       |
| 8     | 2                           | 10          | EtO     | 30     | 3    | 6        |
| 9     | 2                           | 10          | Tol     | 100    | 3    | 95       |
| 10    | 2                           | 5           | Tol     | 100    | 3    | 95       |
| 11    | 2                           | 1           | Tol     | 100    | 3    | 95       |
| 12    | 1                           | 1           | Tol     | 100    | 3    | 95       |
| 13    | 0.50                        | 1           | Tol     | 100    | 3    | 43       |

General conditions: 1a (0.01 mmol, 1 mol.% Ph3PO, dry solvent, slowly addition of aldehydes. The reactions were carried out for 1–3 h before an aliquot (50 μL) was taken, quenched with aqueous solvent (1 mL), and analyzed by GC.

Conversion to 4a was calculated from GC.

![Scheme 3](image-url) The reaction for optimization conditions

The substrate scope was investigated next. As shown, the reaction works well with different types of aromatic aldehydes, including donor and acceptor substituents at the fourth position of the ring. The use of cinnamaldehyde under the reaction conditions also showed good results. However, the use of aliphatic aldehydes led to the low catalytic activity, which is consistent with the research described previously.

In addition, we studied the possibility of transferring the developed method from the milligram-scale to the gram-scale of (dichloromethyl)benzene, which shows the possibility of industrial application of the developed methods (Scheme 4). The possibility of using 1 mol.% catalyst based on triphenylphosphine oxide, as well as the complete transition of chlorine into the final product, significantly reduces the amount of waste that is toxic to the environment and humans. Also, the results obtained are superior to those described earlier, which indicates the prospects for further development of this catalytic system.

![Scheme 4](image-url) Gram-scale application of deoxydichlorination of benzaldehyde catalyzed by triphenylphosphine oxide

The proposed mechanism is depicted in Scheme 5. We believe that the catalytic cycle start with a quick formation of the intermediate dichlorotriphenylphosphane (B) upon treatment of triphenylphosphine oxide (A) with phthaloyl dichloride. Next, in catalytic cycle, the intermediate B reacts with aldehyde 1 via oxygen to form the intermediate C, which then undergoes elimination to furnish geminal dichloride 4 and to regenerate the catalyst A.

4. Conclusions

We developed a highly atom economy protocol for a catalytic deoxydichlorination of aldehydes under modified Appel conditions catalyzed by 1 mol.% of triphenylphosphine oxide. The salient features of the method are: (i) operationally simplicity, (ii) low catalyst loading (1 mol.%), (iii) medium reaction times and (iv) mild conditions and...
all transfer chlorine from phthaloyl dichloride. Also, we showed applications of the developed method on the gram-scale.

Supplementary materials

No supplementary data are available.

Funding

This study was funded by the Russian Science Foundation grant No. 20–73–00081, https://www.rscf.ru/en.

Acknowledgments

None.

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Conflict of interest

The authors declare no conflict of interest.

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