Chimica Techno Acta
published by Ural Federal University
eISSN 2411-1414; chimicatechnoacta.ru

ARTICLE
2022, vol. 9(2), No. 20229202
DOI: 10.15826/chimtech.2022.9.2.02

A method of mild deoxydichlorination of aldehydes catalyzed by Triphenylphosphine oxide

D.A. Shipilovskikh [ab], M.F. Konkova [a], I.P. Nikonov [a], M.M. Gladysheva [a], S.A. Shipilovskikh [ac*]

a: Perm State University, 614990 Perm, Russia
b: Perm National Research Polytechnic University, 614990 Perm, Russia
c: ITMO University, 197101 St. Petersburg, Russia
* Corresponding authors: s.shipilovskikh@metalab.ifmo.ru

This paper belongs to the Regular Issue.

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

Received: 15.02.2022
Revised: 23.03.2022
Accepted: 23.03.2022
Available online: 25.03.2022

1. Introduction

The development of methods for nucleophilic substitution (S_N) in sp^3-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 dihalides are important intermediates in the chemical synthesis of useful natural substances, including active biological compounds. Geminal dihalides, 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.

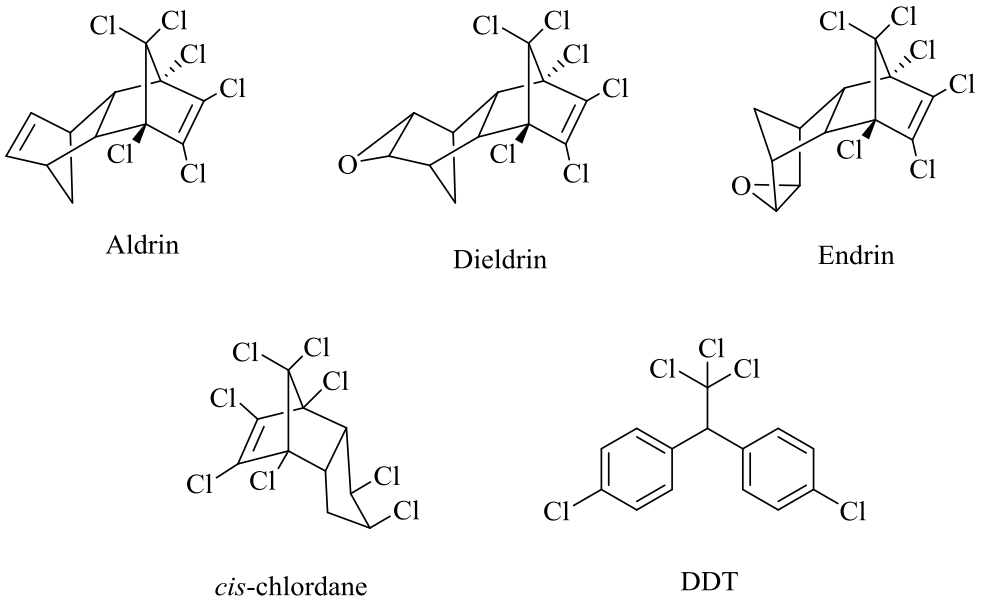


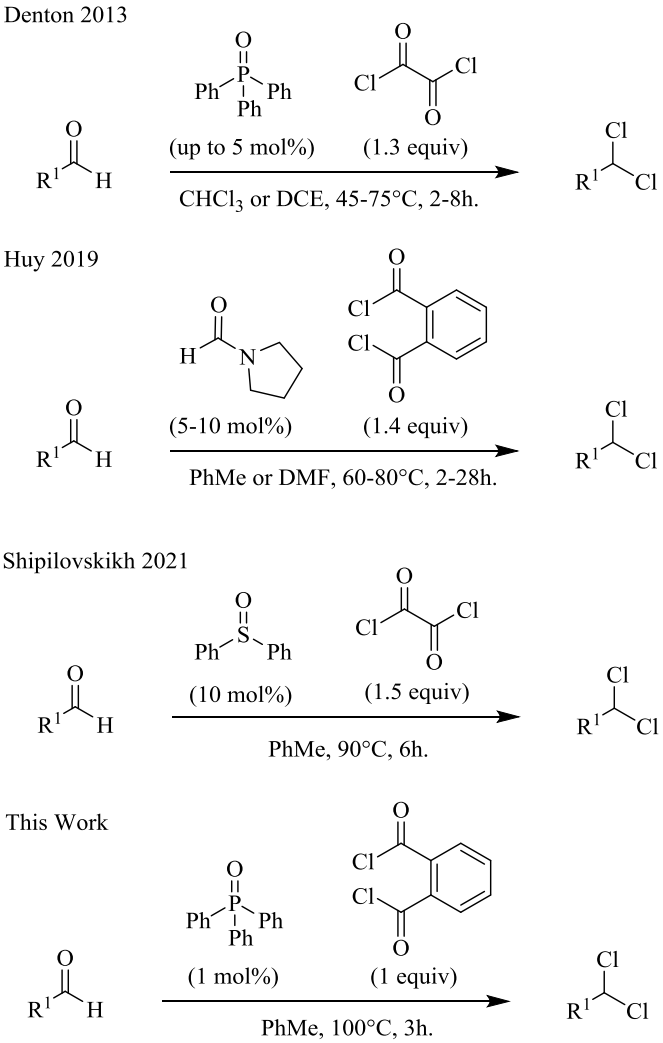
Fig. 1 The most used herbicides, insecticides and fungicides

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 (δ) were measured in ppm with respect to the solvent ($CDCl_3$, ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm; [D6] DMSO, ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 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).

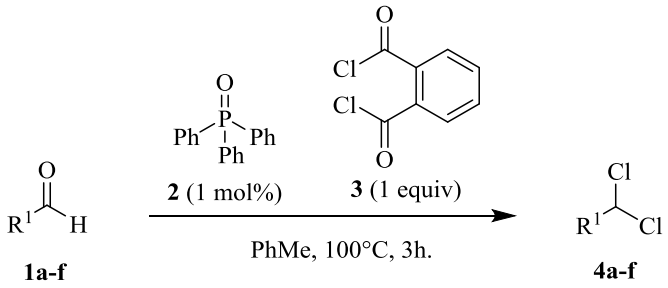


Scheme 1 Catalytic deoxydichlorination of aldehydes to 1,1-dichlorides

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 (Ph_3PO) (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/Et_2O – 19/1). For gram-scale example , the mixture was purified by distillation. The general method for synthesis is shown in Scheme 2.



R^1 = Ph(a), 4-MeC_6H_4(b), 4-BrC_6H_4(c), 2-$MeOC_6H_4$(d), styryl(e), C_7H_{16}(f).

Scheme 2 General method for synthesis

2.1.1. (Dichloromethyl)benzene 4a

Obtained from **1a** (106 mg, 1 mmol), triphenylphosphine oxide (Ph_3PO) (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 (142 mg, 88%, for gram-scale 4.05 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.73 (*s*, 1H, CH), 7.44–7.46 (*m*, 3H, H_{Ar}), 7.64–7.66 (*m*, 2H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 72.2, 126.0, 128.9, 123.0, 140.3 [55].

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

Obtained from **1b** (120 mg, 1 mmol), triphenylphosphine oxide (Ph_3PO) (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%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.42 (*s*, 3H, CH_3), 6.69 (*s*, 1H, CH), 7.16–7.24 (*m*, 2H, H_{Ar}), 7.44–7.51 (*m*, 2H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 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 (Ph_3PO) (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%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.70 (s, 1H, CH), 7.43–7.49 (*m*, 2H, H_{Ar}), 7.49–7.56 (*m*, 2H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 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.

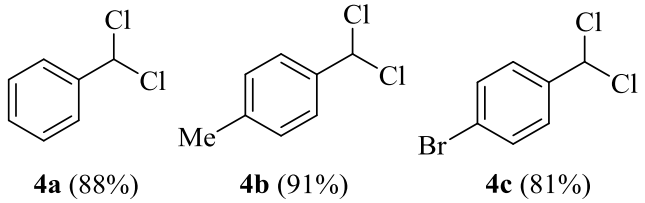


Fig. 2 1-(Dichloromethyl)benzene **4a**, (Dichloromethyl)-4-methylbenzene **4b** and 1-Bromo-4-(dichloromethyl)benzene **4c**

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

Obtained from **1d** (136 mg, 1 mmol), triphenylphosphine oxide (Ph_3PO) (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%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.87 (*s*, 3H, CH_3), 6.93–7.17 (*m*, 1H, CH, 2H, H_{Ar}), 7.29–7.32 (*o*, 1H, H_{Ar}), 7.71–7.83 (*m*, 2H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 54.1, 64.5, 109.3, 120.1, 127.1, 128.3, 130.0, 152.4 [53].

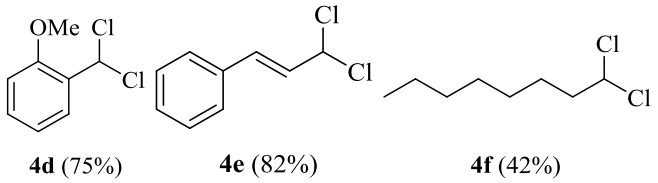
2.1.5. (3,3-Dichloroprop-1-en-1-yl)benzene 4e

Obtained from **1e** (132 mg, 1 mmol), triphenylphosphine oxide (Ph_3PO) (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%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.33 (*d*, J = 7.6 Hz, 1H, CH), 6.40 (*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, H_{Ar}). ^{13}C NMR ($CDCl_3$, 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 (Ph_3PO) (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%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.92 (*t*, J = 7.2 Hz, 3H, CH_3), 1.31 (*m*, 8H, CH_2), 1.55 (*m*, 2H, CH_2), 2.20 (*m*, 2H, CH_2), 5.74 (*t*, J = 6.2 Hz, 1H, $CHCl_2$). ^{13}C NMR ($CDCl_3$, 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.



4d (75%) **4e** (82%) **4f** (42%)

Fig. 3 1-(dichloromethyl)-2-methoxybenzene **4d**, (3,3-Dichloroprop-1-en-1-yl)benzene **4e** and 1,1-dichlorooctane **4f**

3. Results and Discussion

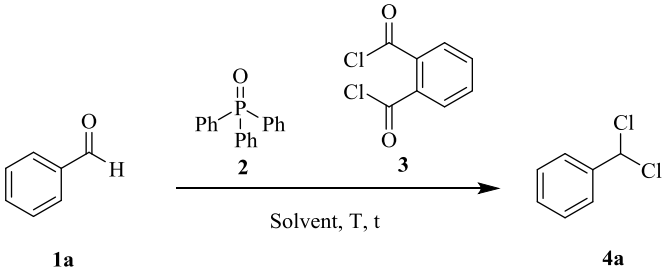
The investigation commenced with establishing the best conditions for the deoxydichlorination of aldehydes, employing benzaldehyde **1a** as a model substrate (Table 1). First, the catalytic triphenylphosphine oxide was investigated. Then, the effects of the solvent, temperature, and equivalents of phthaloyl 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 Ph_3PO 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.% Ph_3PO 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.% Ph_3PO 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 Ph_3PO at 100 °C for 3 hours and found that using 1 mol.% Ph_3PO 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[a]

entry	equiv of phthaloyl dichloride	mol.% Ph_3PO	solvent	*T* (°C)	*t* (h)	conv. (%)[b]
1	2	–	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	Et_2O	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

[a]General conditions: **1a** (0.01 mmol, 1 mol.%) Ph_3PO, 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.

[b]Conversion to **4a** was calculated from GC.

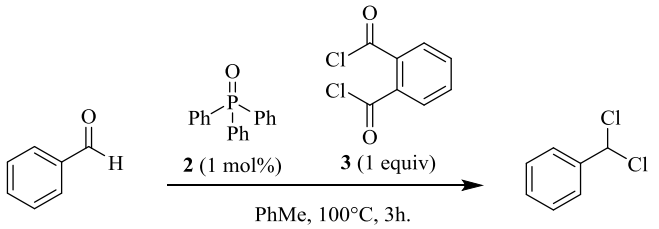


1a **2** **3** **4a**

Scheme 3 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.



1a (0.03 mol) **2** (1 mol%) **3** (1 equiv) **4a** (4.05g 84%)

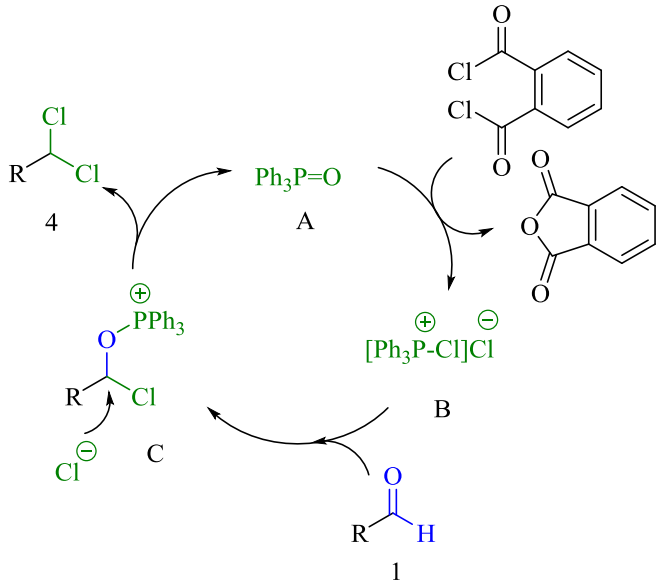
Scheme 4 Gram-scale application of deoxydichlorination of benzaldehyde catalyzed by triphenylphosphine oxide

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.



Scheme 5 The proposed mechanism related to cyclic transformation of substances

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.

Author contributions

Conceptualization: S.A.S.
Data curation: M.F.K., I.P.N.
Formal Analysis: M.F.K., I.P.N., M.M.G.
Funding acquisition: D.A.S., S.A.S.
Investigation: D.A.S., M.F.K., I.P.N., M.M.G.
Methodology: I.P.N., M.M.G.
Project administration: S.A.S.
Resources: D.A.S., S.A.S.
Software: D.A.S., S.A.S.
Supervision: S.A.S.
Validation: D.A.S., M.F.K., S.A.S.
Visualization: D.A.S., I.P.N., S.A.S.
Writing – original draft: D.A.S., S.A.S.
Writing – review & editing: D.A.S., S.A.S.

Conflict of interest

The authors declare no conflict of interest.

Additional information

Authors' IDs:
Shipilovskikh, Daria A., Scopus ID 57193555475;
Shipilovskikh, Sergei A., Scopus ID 34168423100.

Website of
Perm State University, http://en.psu.ru;
Perm National Research Polytechnic University, https://pstu.ru/en;
ITMO University, https://en.itmo.ru.

References

1. Li J, Huang ChYu, Li ChJ. Deoxygenative functionalizations of aldehydes, ketones and carboxylic acids. Angew Chem Int Ed Engl. 2021:202112770. doi:10.1002/anie.202112770
2. Beddoe RH, Sneddon HF, Denton RM. The catalytic Mitsunobu reaction: a critical analysis of the current state-of-the-art. Org Biomol Chem. 2018;(42):7774-7781. doi:10.1039/C8OB01929K
3. Roya R, Saha S. Scope and advances in the catalytic propargylic substitution reaction. RSC Adv. 2018;(8):31129-31193. doi:10.1039/C8RA04481C
4. Hakim Siddiki SMA, Rashed N, Ali A, Toyao T, Hirunsit P, Ehara M, Shimizu K. Lewis acid catalysis of Nb_2O_5 for reactions of carboxylic acid derivatives in the presence of basic inhibitors. Chem Cat Chem. 2019;(11):383-396. doi:10.1002/cctc.201801239
5. Jovanovic MD, Petkovic MR, Savic VM. Polycyclic Compounds from Allenes via Palladium-Mediated intramolecular carbopalladation/nucleophilic substitution cascade processes. Synthesis 2021;(53):1035-1045. doi:10.1055/s-0040-1705994
6. Huy PH. Lewis Base catalysis promoted nucleophilic substitutions – recent advances and future directions. Eur J Org Chem. 2020;(1):10-27. doi:10.1002/ejoc.201901495
7. Beddoe RH, Andrews KG, Magné V, Cuthbertson JD, Saska J, Shannon-Little AL, Shanahan SE, Sneddon HF, Denton RM. Redox-neutral organocatalytic Mitsunobu reactions. Sci. 2019;365(6556)910-914. doi:10.1126/science.aax3353
8. Shipilovskikh SA, Rubtsov AE. Dehydration of oxime to nitriles. AIP Conf Proc. 2019;2063:030019. doi:10.1063/1.5087327
9. Huy PH, Hauch T, Filbrich I. Lewis Base catalyzed nucleophilic substitutions of alcohols. Synlett. 2016;27(19):2631-2636. doi:10.1055/s-0036-1588633
10. Kohlmeyer C, Schäfer A, Huy PH., Hilt G. Formamide-catalyzed nucleophilic substitutions: mechanistic insight and rationalization of catalytic. ACS Catal. 2020;10(19):11567-11577. doi:10.1021/acscatal.0c03348
11. Shipilovskikh SA, Vaganov VY, Denisova EI, Rubtsov AE, Malkov AV. Dehydration of amides to nitriles under conditions of a catalytic appel reaction. Org Lett. 2018;20(3):728-731. doi:10.1021/acs.orglett.7b03862
12. Huy PH, Mbouhom C. Formamide catalyzed activation of carboxylic acids – versatile and cost-efficient amidation and esterification. Chem Sci. 2019;10:7399-7406. doi:10.1039/C9SC02126D
13. Motsch S, Schütz C, Huy PH. Systematic evaluation of sulfoxides as catalysts in nucleophilic substitutions of alcohols. Eur J Org Chem. 2018:4541-4547. doi:10.1002/ejoc.201800907

14. Huy PH, Filbrich I. A general catalytic method for highly cost- and atom-efficient nucleophilic substitutions. Chem Eur J. 2018;24:7410. doi:10.1002/chem.201800588
15. Fukazawa Y, Vaganov VY, Shipilovskikh SA, Rubtsov AE, Malkov AV. Stereoselective synthesis of atropisomeric bipyridine N,N′-dioxides by oxidative coupling. Org Lett. 2019;21(12):4798–4802. doi:10.1021/acs.orglett.9b01687
16. Concellón JM, Rodríguez-Solla H, Díaz P, Llavona R. The first sequential reaction promoted by manganese: complete stereoselective synthesis of (E)-α,β-unsaturated esters from 2,2-dichloroesters and aldehydes. J Org Chem. 2007;72:4396. doi:10.1021/jo070209w
17. Concellón JM, Rodríguez-Solla H, de Amo V, Díaz P. Stereoselective olefination reactions promoted by rieke manganese. Synth. 2009;15:2634–2645. doi:10.1055/s-0029-1216880
18. Oudeyer S, Leonel E, Paugam JP, Nédélec JY. Formation of epoxides and *N*-arylaziridines via a simple Mg-Barbier reaction in DMF. Tetrahedron. 2014;70:919–923. doi:10.1016/j.tet.2013.12.016
19. Zhou YY, Uyeda C. Reductive cyclopropanations catalyzed by dinuclear nickel complexes. Angew Chem Int Ed. 2016;55:3171–3175. doi:10.1002/anie.201511271
20. Durán-Peña MJ, Flores-Giubi ME, Botubol-Ares JM, Harwood LM, Collado IG, MacÍas-Sánchez AJ, Hernández-Galán R. Chemoselective and stereoselective lithium carbenoid mediated cyclopropanation of acyclic allylic alcohols. Org Biomol Chem. 2016;14(9):2731–2741. doi:10.1039/c5ob02617b
21. Barrero AF, Herrador MM, Del Moral JFQ, Arteaga P, Akssira M, El Hanbali F, Arteaga JF, Diéguez HR, Sánchez EM. Couplings of benzylic halides mediated by titanocene chloride: Synthesis of bibenzyl derivatives. J Org Chem. 2007;72(6):2251–2254. doi:10.1021/jo062492p
22. Eisch JJ, Qian Y, Rheingold AL. Nickel(II)-carbene intermediates in reactions of geminal dihaloalkanes with nickel(0) reagents and the corresponding carbene capture as the phosphonium ylide. Eur J Inorg Chem. 2007;(11):1576–1584. doi:10.1002/ejic.200601106
23. Giannerini M, Fañanas-Mastral M, Feringa BL. *Z*-selective copper-catalyzed asymmetric allylic alkylation with grignard reagents. J Am Chem Soc. 2012;134(9):4108–4111. doi:10.1021/ja300743t
24. Li H, Müller D, Guénée L, Alexakis A. Copper-catalyzed enantioselective synthesis of axially chiral allenes. Org Lett. 2012;14(23):5880–5883. doi:10.1021/ol302790e
25. Li H, Grassi D, Guénée L, Bürgi T, Alexakis A. Copper-catalyzed propargylic substitution of dichloro substrates: Enantioselective synthesis of trisubstituted allenes and formation of propargylic quaternary stereogenic centers. Chem Eur J. 2014;20(50):16694–706. doi:10.1002/chem.201404668
26. Brześkiewicz J, Loska R, Makosza M. α-Chlorobenzylation of nitroarenes via vicarious nucleophilic substitution with benzylidene dichloride: Umpolung of the friedel-crafts reaction. J Org Chem. 2018;83(15):8499–8508. doi:10.1021/acs.joc.8b01091
27. Nilewski C, Carreira EM. Recent advances in the total synthesis of chlorosulfolipids. Eur J Org Chem. 2012;(9):1685–1698. doi:10.1002/ejoc.201101525
28. Chung WJ, Vanderwal CD. Stereoselective halogenation in natural product synthesis. Angew Chem Int Ed. 2016;55:4396–4434. doi:10.1002/anie.201506388
29. Murawska A, Migdal P, Roman A. Effects of plant protection products on biochemical markers in honey bees. Agriculture. 2021;11(7):648. doi:10.3390/agriculture11070648
30. Syafrudin M, Kristanti RA, Yuniarto A, Hadibarata T, Rhee J, Alonazi WA, Algarni TS, Almarri AH, Al-Mohaimeed AM. Pesticides in drinking water - a review. Int J Environ Res Public Health. 2021;18(2):468. doi:10.3390/ijerph18020468
31. Tudi M, Ruan HD, Wang L, Lyu J, Sadler R, Connell D, Chu C, Phung DT. Agriculture development, pesticide application and its impact on the environment. Int J Environ Res Public Health. 2021;18(3):1112. doi:10.3390/ijerph18031112
32. Hirayama T, Okaniwa M, Banno H, Kakei H, Ohashi A, Iwai K, Ohori M, Mori K, Gotou M, Kawamoto T, Yokota A, Ishikawa T. Synthetic studies on centromere-associated protein-e (cenp-e) inhibitors: 2. application of electrostatic potential map (EPM) and structure-based modeling to imidazo[1,2-a]pyridine derivatives as anti-tumor agents. J Med Chem. 2015;58:8036–8053. doi:10.1021/acs.jmedchem.5b00836
33. Barma DK, Kundu A, Bandyopadhyay A, Kundu A, Sangras B, Briot A, Mioskowski C, Falck J.R. A highly stereospecific synthesis of (E)-α,β-unsaturated esters. Tetrahedron Lett. 2004;45:59175920. doi:10.1016/j.tetlet.2004.05.113
34. Oudeyer S, Léonel E, Paugam J. P., Nédélec J.-Y. Epoxide formation by indirect electroreductive coupling between aldehydes or ketones and activated gem-dichloro compounds. Synthesis. 2004;3:389–400. doi:10.1055/s-2004-815915
35. Cahard E, Schoenebeck F, Garnier J, Cutulic SPY, Zhou S, Murphy JA. Electron transfer to benzenes by photoactivated neutral organic electron donor molecules. 2012;51:3673–3676. doi:10.1002/anie.201200084
36. Roth HD, Sauers RR, Theisen KJ, Neshchadin D, Gescheidt G. Radical cations of disubstituted cyclopropanes: stereoelectronic effects on hyperfine coupling. J Phys Org Chem. 2014;27:218–225. doi:10.1002/poc.3269
37. Cao H, Wang Q. E-Stilbene derivatives synthesized by stereoselective reductive coupling of benzylic gem-dibromide promoted by Cu/polyamine. Tetrahedron Letters. 2017;58:2703–2706. doi:10.1016/j.tetlet.2017.05.072
38. Povie G, Segawa Y, Nishihara T, Miyauchi Y, Itami K. Synthesis and size-dependent properties of [12], [16], and [24] carbon nanobelts. J Am Chem Soc. 2018;140:10054–10059. doi:10.1021/jacs.8b06842
39. Povie G, Segawa Y, Nishihara T, Miyauchi Y, Itami K. Synthesis of a carbon nanobelt. Sci. 2017;356:172-175. doi:10.1126/science.aam8158
40. Lin Z, Yu D, Zhang Y. Propargylic amines constructed via copper-catalyzed three-component coupling of terminal alkynes, benzal halides and amines. Tetrahedron Letters. 2011;52:4967–4970. doi:10.1016/j.tetlet.2011.07.099
41. Shioe K, Ishikura S, Horino Y, Abe H. Facile Preparation of Dehydrodigallic Acid and Its Derivative for the Synthesis of Ellagitannins. Chem Pharm Bull. 2013;61:1308–1314. doi:10.1248/cpb.c13-00458
42. Sturala J, Etherington MK, Bismillah AN, Higginbotham HF, Trewby W, Aguilar JA, Bromley EHC, Avestro A-J, Monkman AP, McGonigal PR. Excited-State Aromatic Interactions in the Aggregation-Induced Emission of Molecular Rotors. J Am Chem Soc. 2017;139:17882–17889. doi:10.1021/jacs.7b08570
43. Chana CY, Barnard PJ. Rhenium complexes of bidentate, bis-bidentate and tridentate N-heterocyclic carbene ligands. Dalton Transactions. 2015;44:19126–19140. doi:10.1039/C5DT03295D
44. Wang L, Moss RA, Krogh-Jespersen K. Hammett Analyses of Halocarbene–Halocarbanion Equilibria. Org Lett. 2013;15:2014–2017. doi:10.1021/ol400698y
45. Lee J, Yoon S, Chang R. Chlorosulfolipid (Danicalipin A) membrane structure: hybrid molecular dynamics simulation studies. J Phys Chem Lett. 2021;19:4537–4542. doi:10.1021/acs.jpclett.1c01026
46. Gropp C, Fischer S, Husch T, Trapp N, Carreira EM, Diederich F. Molecular recognition and cocrystallization of methylated and halogenated fragments of danicalipin a by enantiopure alleno-acetylenic cage receptors. J Am Chem Soc. 2020;142:4749–4755. doi:10.1021/jacs.9b13217
47. Moss FR, Cabrera GE, McKenna GM, Salerno GJ, Shuken SR, Landry ML, Weiss TM, Burns NZ, Boxer SG. Halogenation-dependent effects of the chlorosulfolipids of ochromonas danica on lipid bilayers. ACS Chem Biol. 2020;11:2986–2995. doi:10.1021/acschembio.0c00624
48. Boshkow J, Fischer S, Bailey AM, Wolfrum S, Carreira EM. Stereochemistry and biological activity of chlorinated lipids: a study of danicalipin A and selected diastereomers. Chem Sci. 2017;8:6904–6910. doi:10.1039/C7SC03124F

49. Takeda T, Endo Y, Reddy ACS, Sasaki R, Fujiwara T. Transformation of ketones into 1-chloro and 1,1-dichloro-1-alkenes by means of a polychloromethane-titanocene(II) system. Tetrahedron. 1999;55:2475. doi:10.1016/S0040-4020(99)00021-6
50. Takeda T, Sasaki R, Fujiwara T. Carbonyl Olefination by Means of a *gem*-Dichloride–$Cp_2Ti[P(OEt)_3]_2$ System. J Org Chem. 1998;63(21):7286–7288. doi:10.1021/jo980724h
51. Sindra HC, Santos CVP, Mattos MCS. Trihaloisocyanuric acids: useful reagents for conversion of benzaldehydes into benzylidene dihalides under appel conditions. Lett Org Chem. 2020;17(8):590–595. doi:10.2174/1570178617666200121110618
52. An J, Tang X, Moore J, Lewis W, Denton RM. Phosphorus(V)-catalyzed dichlorination reactions of aldehydes. Tetrahedron. 2013;69:8769–8776. doi:10.1016/j.tet.2013.07.100
53. Huy PH. Formamide catalysis facilitates the transformation of aldehydes into geminal dichlorides. Synthesis. 2019;51(12):2474–2483. doi:10.1055/s-0037-1611798
54. Gorbunova IA, Shipilovskikh DA, Shipilovskikh SA. Deoxydichlorination of aldehydes catalyzed by Diphenyl sulfoxide. Chim Techno Acta. 2021;8(4):20218408. doi:10.15826/chimtech.2021.8.4.08
55. Burton KI, Elser I, Waked AE, Wagener T, Andrews RJ, Glorius F, Stephan DW. Bipyridinium and phenanthrolinium dications for metal-free hydrodefluorination: distinctive carbon-based reactivity. Chem Eur J. 2021;27(45):11730–11737. doi:10.1002/chem.202101534
56. Moghaddam KR, Aghapour G. One-pot, oxidative and selective conversion of benzylic silyl and tetrahydropyranyl ethers to gem-dichlorides using trichloroisocyanuric acid and triphenylphosphine as an efficient and neutral system. Phosphorus Sulfur Silicon Relat Elem. 2020;196(4):398–406. doi:10.1080/10426507.2020.1845680