Synthesis of Phosphate Stabilised Iodanes and their Application in Intramolecular Aryl Migrations

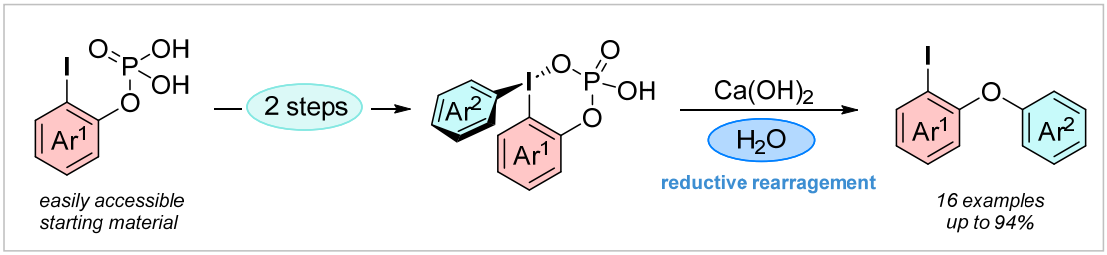
Jan Rick Koch[1], Mattis Damrath[1], Pim Puylaert[2], Boris J. Nachtsheim[1*]

Address: [1]Institute for Organic and Analytical Chemistry, University of Bremen, Leobener Straße 7, 28359 Bremen, Germany and [2]Institute for Inorganic Chemistry and Crystallography, University of Bremen, Leobener Straße 7, 28359 Bremen, Germany

Email: nachtsheim@uni-bremen.de

Abstract

A diverse set of these hydroxy-benzo[*e*]iodadioxaphosphinine oxides and derived diaryl iodonium salts are prepared and characterized by X-ray crystallography, featuring an out-of-plane geometry of the hypervalent bond for both compound classes. Treatment of the phosphate-stabilized diaryliodonium salts with $Ca(OH)_2$ results in an efficient base-induced intramolecular aryl migration under aqueous conditions, yielding iodo-substituted diaryl ethers with yields up to 94%. Our findings highlight the synthetic potential of this previously underexplored compound class in organic transformations.



Keywords

Hypervalent Iodine, Iodanes, Oxidation, Aryl Migration

Introduction

Hypervalent iodine compounds are versatile reagents for oxidative transformations in organic synthesis.[1–5] Substrates like Phenyliodine(III)diacetate (PIDA), 2-iodoxybenzoic acid (IBX) and Dess-Martin-Periodinan (**1**, DMP) can be used in alcohol oxidations[6–8], alkene functionalization[9, 10] or heterocycle syntheses[11, 12]. Most *O*-stabilized iodanes like IBX or DMP are characterized by a cyclic benziodoxolone structure, leading to higher thermal stability and more controlled reactivity.[13, 14] Such beneficial cyclic structures can also be accomplished with alcohol functionalities (**2**)[15] or through pseudo-cyclic interactions with tethered *N*-heterocycles (**3**)[16, 17] or sulfonyl-groups (**4**)[18]. (Figure 1, A).[19] So far, only a limited amount of phosphorus oxoacid substituted iodanes were described. Examples include [Hydroxy(phosphoryloxy)iodo]arenes **5** and its cyclic derivative **6**. While most phosphorus-containing iodanes like **5** and **6** are based on external P-O-ligands at the I(III) center[20, 21], only a few examples of intramolecular P-O-stabilization are known. *Balthazor et al.* reported the synthesis of the five-membered iodane **7** (Figure 1, A), whereas *Protasiewicz et al.* published the synthesis of a phosphorus-containing iodane with a pseudo cyclic structure. [22, 19] The first intramolecular phosphate stabilized iodane (**8a**) was synthesized by *J. E. Leffler* and *H. Jaffe* in 1973 by treating the corresponding phosphoric acid with peracetic acid.[23] However, these initial explorations are focused on the structure of these compounds without investigating their further reactivity. Herein, we want to present the synthesis of various phosphate-

substituted iodanes, their transformation into the stabilized-diaryl derivatives **9** and their reactivity in a base induced aryl migration (**10**, Figure 1, B).

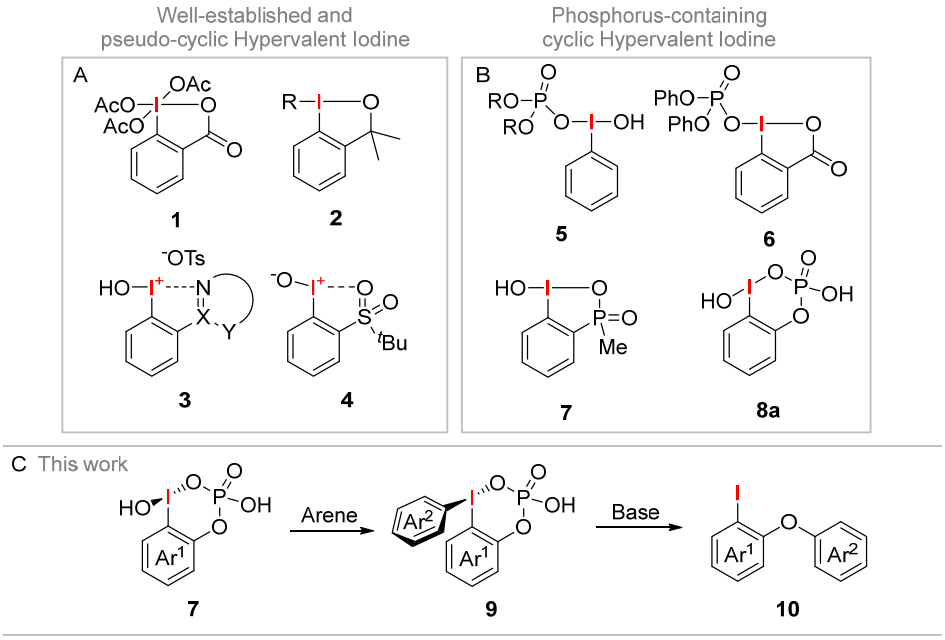
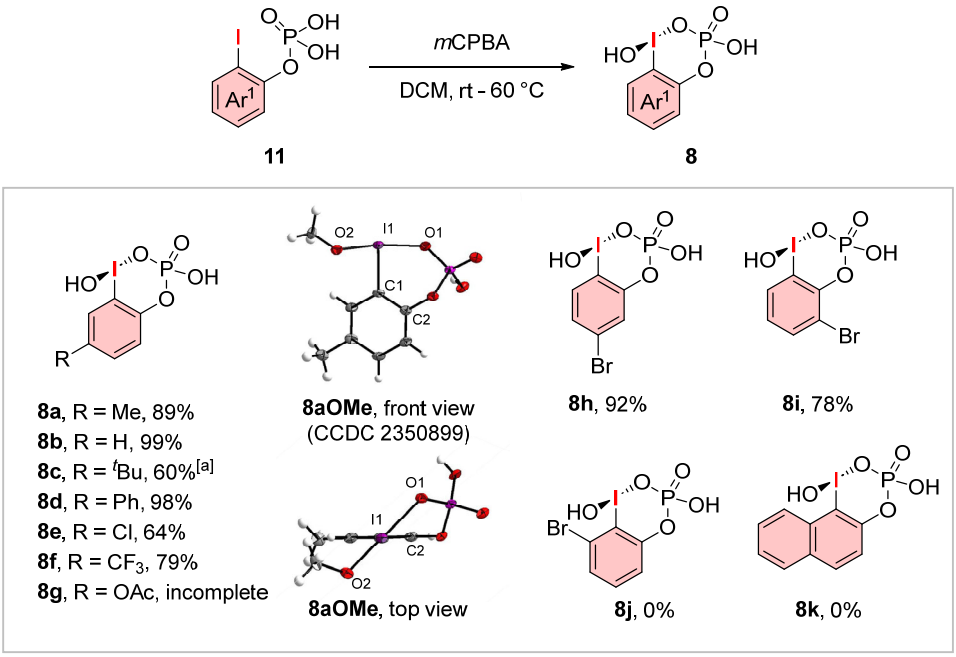


*Figure 1: A: Common intramolecular stabilized iodanes **1-4.** B: P-O-stabilized iodanes **5-8**, C: Aim of this work.*

Results and Discussion

Starting with the oxidation of various *o*-iodo phenyl phosphates (**11**), the corresponding cyclic iodosophenylphosphoric acids **8a-f** and **8h-i** were obtained by using *m*CPBA as the oxidant (Scheme 1). The established oxidation reagents like Oxone® and Selectfluor® were incompatible due to the formation of various side products like multiple fluorinations. Electron-rich and poor substituted iodanes (**8a-f**, **8h-i**) in *ortho*-, *meta*- and *para*-position regarding the iodine centre were obtained in high yields of up to 99%. The acetylated derivate **8g** was not accessible due to incomplete oxidation. Substrates with a second *ortho*-substituent next to the iodine (**8j-k**) could not be isolated due to the *ortho*-effect in stabilised-iodanes.[24] Instead of the desired oxidation instant deiodination was observed. We obtained the X-Ray structure of the methoxy ligand-exchanged derivate **8aOMe** and gained further insights into the solid-

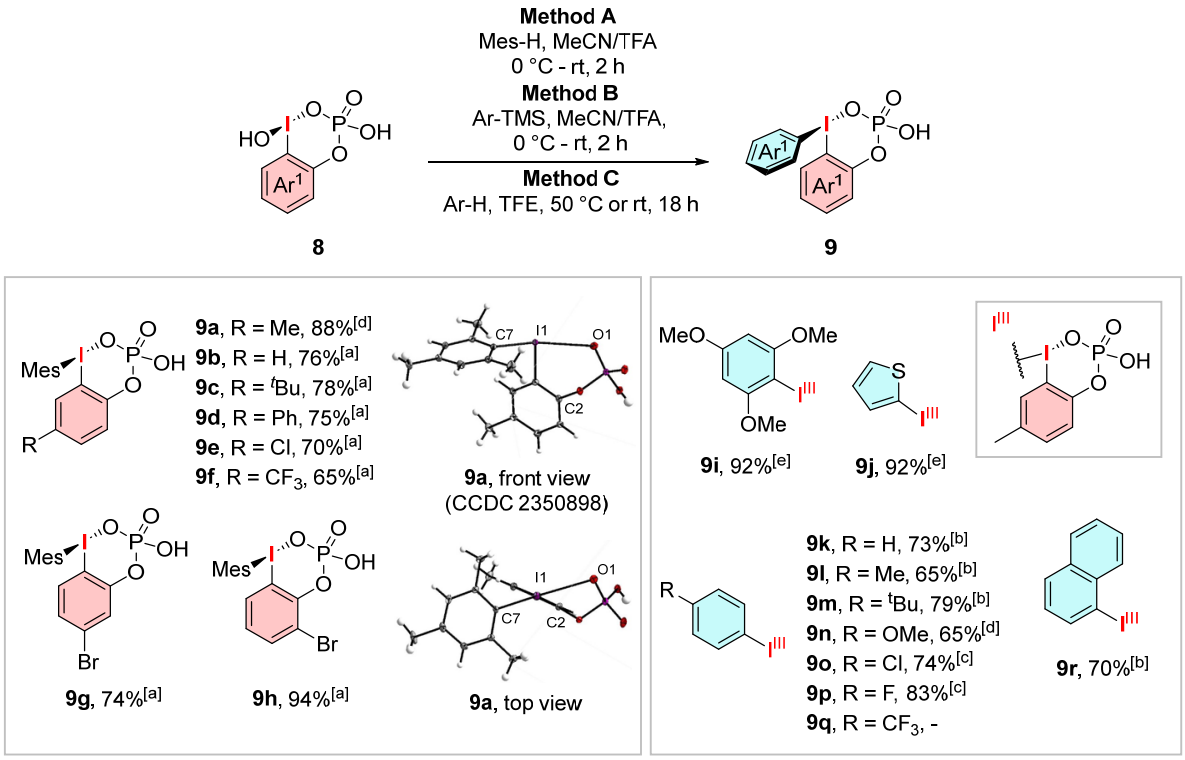
state structure. Therein, the cyclic structure was confirmed with an I1-O1 distance of 2.27 Å and an O1-I1-C1-C2 angle of 43.8° which generates an out-of-plane geometry.



Scheme 1: Oxidation of *o*-iodo phenyl phosphates into iodosophenylphosphoric acids **8a-k** and X-Ray structure of **8aOMe**. General reaction conditions: **8** (1.00 eq), *m*CPBA (2.00 eq), DCM (0.2 M), stirring 5 min at rt and 2 h at 60 °C. [a] reaction at rt with 1.20 eq *m*CPBA.

We then further examined their reactivity and tried to synthesize diarylated analogues (Scheme 2). By using an excess of mesitylene, as suitable electron-rich arene for the coupling, in an MeCN/TFA mixture, we were able to generate the *ortho*-phosphate stabilized species **9a-h** in high yields of up to 94%. The synthesis of other strong electron-rich derivatives **9i-j** and **9n** can be carried out in high yields of up to 92% but reaches its limits already for *tert*-butylbenzene. The regioselective coupling of arenes with more than one reactive side was achived using an excess of their trimethylsilyl-substituted derivatives in MeCN/TFA. Using this method, we were able to obtain the less electron rich compounds **9k-m**, **9o-p** and **9r** in yields from 65-83%. Utilization of one equivalent of the fluorinated and chlorinated trimethylsilyl arenes suppressed the formation of an undesired diaryliodonium species. Arenes with stronger electron-withdrawing trifluoromethyl groups could not be converted into the desired product **9q**.

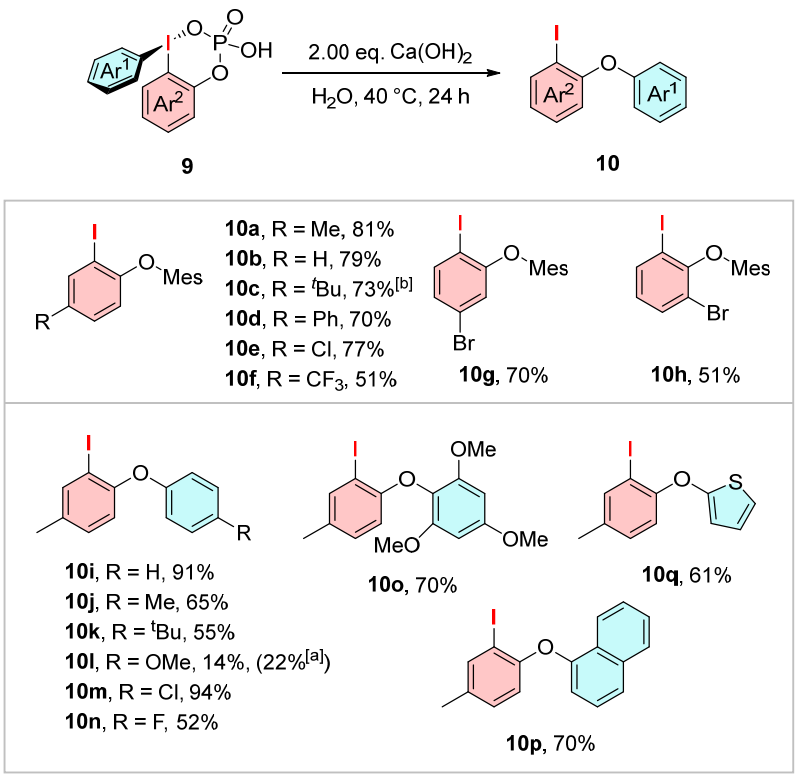
Again, we were able to obtain a crystal structure for the phosphate-stabilized iodane **9a**, which shows the same cyclic geometry, but with an elongated I1-O1 bond length of 2.99 Å whereas the O1-I1-C1-C2 angle of 40.3° creates a similar out-of-plane geometry as observed in **8a**.



Scheme 2: Arylation of iodosophenylphosphoric acids into **9a-r** and X-Ray structure of **9a**. General reaction conditions: [a] Method A: **8** (1.00 eq.), mesitylene (2.00 eq.), MeCN/TFA (1:1, 0.1 M), stirring 5 min at 0 °C and 2 h at rt. [b] Method B: **8** (1.00 eq.), TMS-arene (1.50 eq.), MeCN/TFA (1:1, 0.1 M), stirring 5 min at 0 °C and 2 h at rt. [c] Method B with 1.00 eq. of TMS-arene. [d] Method C: **8** (1.00 eq.) arene (2.00 eq.), TFE (0.1 M), stirring at 50 °C for 18 h. [e] Method C with stirring at rt.

To demonstrate the reactivity of these phosphate-stabilized diaryliodonium salts the aryl migration into diaryl ethers was investigated. A reaction which was previously described for *ortho*-triflate-substituted iodonium salts by *Han et al.*[25] Starting with the literature conditions of Cs_2CO_3 in MeCN the diaryl ether **10a** was obtained in a high yield of 98%, whereas the reaction was carried out at 80 °C instead of room temperature. Due to their potential physiological relevance, we investigated this reaction under aqueous conditions (See ESI, Table 1) and obtained the diaryl ether **10a** in a yield of 81% with the use of $Ca(OH)_2$ as a base at 40 °C.

Under these optimized conditions, all previously synthesized arylated iodanes **9** were examined (Scheme 3). Different substitutions in *meta*- and *para*-position to the iodine center caused a minor variance in the reactivity, which yielded the ethers **10b-e** and **10g** in up to 79%. Strong electron withdrawing groups (**10f**) and another substitution in the second *meta*-position to the iodine (**10h**) resulted in the diminished yields. The phenyl-substituted derivative **10i** yielded the diarylether in 91%, whereas the toluyl-substituted compound **10j** was obtained in a lower yield of 65%. Even more electron-rich arenes, like *tert*-butyl- and methoxy-substituted derivates (**10k**+**10l**), resulted in moderate yields of 55%, respectively 14%.



Scheme 3: Substrate scope of diaryl ethers **10a-q** synthesized from **9**. General reaction conditions: **9** (100 µmol), $Ca(OH)_2$ (2.00 eq.), H_2O (2 mL), 40 °C, 24 h. [a] at room temperature, [b] 48 h reaction time.

For the latter the yield could be increased to 22% by conducting the reaction at room temperature. In contrast to the high yield of 94% for the chlorinated derivative **10m**, the fluorinated ether **10n** was obtained in a moderate yield of 52%, while the main side product was generally the iodinated arene as mentioned in the optimization (See ESI,

Table 1). Furthermore, the TMP-, naphthalene- and thiophene compounds **10o**, **10p**, and **10q** were obtained in good yields of up to 70%.

Conclusion

In summary, we synthesized a variety of different iodosophenylphosphoric acids, which could be converted into phosphate-stabilized diaryliodonium salts through ligand exchange with different arenes. The X-ray data of both compound classes confirmed a cyclic structure that leads to an out-of-plane distortion of the hypervalent bond. These novel iodanes were successfully applied in base-induced intramolecular aryl migrations in an aqueous medium to obtain various iodo-substituted diaryl ethers in yields of up to 94%. Since this interesting reactivity was observed in aqueous solution under ambient conditions, potential physiological relevance might be operational and is part of further investigations in our laboratory.

Supporting Information

Experimental procedures, analytical data (^{1}H-, ^{13}C- and ^{19}F-NMR-chemical shifts, IR-bands, melting points) including the corresponding NMR-spectra and X-Ray data can be found in the supporting information.

References

1. Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016,** *116* (5), 3328–3435. doi:10.1021/acs.chemrev.5b00547

2. Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009,** *48* (48), 9052–9070. doi:10.1002/anie.200904689
3. Rocq, C.; Denis, M.; Canesi, S. *Chem. Commun.* **2023,** *59* (43), 6495–6508. doi:10.1039/D3CC01603J
4. Singh, F. V.; Shetgaonkar, S. E.; Krishnan, M.; Wirth, T. *Chem. Soc. Rev.* **2022,** *51* (18), 8102–8139. doi:10.1039/d2cs00206j
5. Peng, X.; Rahim, A.; Peng, W.; Jiang, F.; Gu, Z.; Wen, S. *Chem. Rev.* **2023,** *123* (4), 1364–1416. doi:10.1021/acs.chemrev.2c00591
6. Yadav, J.; Reddy, B.; Basak, A.; Venkat Narsaiah, A. *Tetrahedron* **2004,** *60* (9), 2131–2135. doi:10.1016/j.tet.2003.12.056
7. Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009** (16), 2086–2099. doi:10.1039/b823399c
8. Bensberg, K.; Savvidis, A.; Ballaschk, F.; Gómez-Suárez, A.; Kirsch, S. F. *Chem. Eur. J.* **2024,** *30* (20), e202304011. doi:10.1002/chem.202304011
9. Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005,** *7* (22), 5071–5074. doi:10.1021/ol052080n
10. Kitamura, T.; Yoshida, K.; Mizuno, S.; Miyake, A.; Oyamada, J. *J. Org. Chem.* **2018,** *83* (24), 14853–14860. doi:10.1021/acs.joc.8b02473
11. Du, L.-H.; Wang, Y.-G. *Synthesis* **2007,** *2007* (5), 675–678. doi:10.1055/s-2007-965922
12. Kawai, H.; Okusu, S.; Tokunaga, E.; Shibata, N. *Eur. J. Org. Chem.* **2013,** *2013* (29), 6506–6509. doi:10.1002/ejoc.201301096
13. Yoshimura, A.; Saito, A.; Zhdankin, V. V. *Adv. Synth. Catal.* **2023,** *365* (16), 2653–2675. doi:10.1002/adsc.202300275
14. Boelke, A.; Vlasenko, Y. A.; Yusubov, M. S.; Nachtsheim, B. J.; Postnikov, P. S. *Beilstein J. Org. Chem.* **2019,** *15* (1), 2311–2318. doi:10.3762/bjoc.15.223

15. Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015,** *115* (2), 650–682. doi:10.1021/cr500223h

16. Boelke, A.; Lork, E.; Nachtsheim, B. J. *Chem. Eur. J.* **2018,** *24* (70), 18653–18657. doi:10.1002/chem.201804957

17. Boelke, A.; Sadat, S.; Lork, E.; Nachtsheim, B. J. *Chem. Commun.* **2021,** *57* (60), 7434–7437. doi:10.1039/D1CC03097C

18. Macikenas, D.; Skrzypczak-Jankun, E.; Protasiewicz, J. D. *Angew. Chem. Int. Ed.* **2000,** *39* (11), 2007–2010. doi:10.1002/1521-3773(20000602)39:11<2007:AID-ANIE2007>3.0.CO;2-Z

19. Meprathu, B. V.; Justik, M. W.; Protasiewicz, J. D. *Tetrahedron Lett.* **2005,** *46* (31), 5187–5190. doi:10.1016/j.tetlet.2005.05.111

20. Moss, R. A.; Zhang, H. *J. Am. Chem. Soc.* **1994,** *116* (10), 4471–4472. doi:10.1021/ja00089a044

21. Koser, G. F.; Lodaya, J. S.; Ray, D. G.; Kokil, P. B. *J. Am. Chem. Soc.* **1988,** *110* (9), 2987–2988. doi:10.1021/ja00217a058

22. Balthazor, T. M.; Miles, J. A.; Stults, B. R. *J. Org. Chem.* **1978,** *43* (23), 4538–4540. doi:10.1021/jo00417a037

23. Leffler, J. E.; Jeffe, H. *J. Org. Chem.* **1973,** *38* (15), 2719–2721. doi:10.1021/jo00955a033

24. Parida, K. N.; Moorthy, J. N. *Chem. Eur. J.* **2023,** *29* (34), e202203997. doi:10.1002/chem.202203997

25. Chen, H.; Han, J.; Wang, L. *Angew. Chem. Int. Ed.* **2018,** *57* (38), 12313–12317. doi:10.1002/anie.201806405