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Citation	Organic Letters. 2019, 21(5), p. 1467-1470
Version Type	AM
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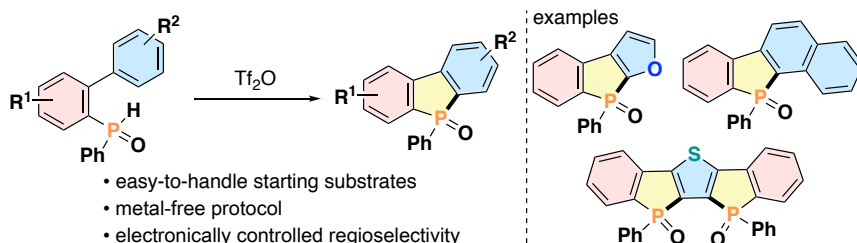
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Synthesis of Dibenzophospholes by Tf₂O-Mediated Intramolecular Phospha-Friedel–Crafts-Type Reaction

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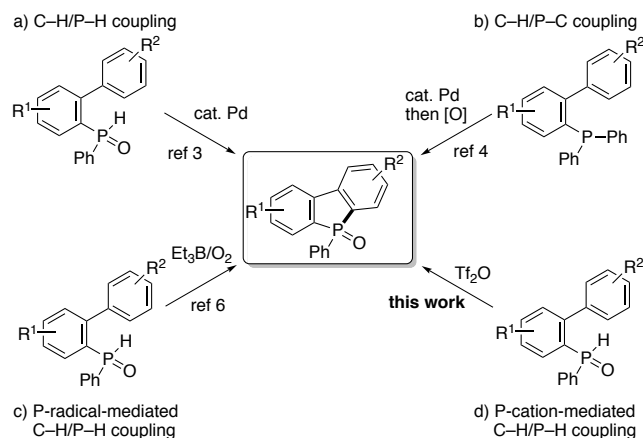
Supporting Information Placeholder



ABSTRACT: A Tf₂O-mediated intramolecular phospha-Friedel–Crafts-type reaction of secondary biarylphosphine oxides has been developed. The reaction is promoted simply by Tf₂O to form the corresponding dibenzophospholes under metal-free conditions. The starting substrates are readily available and easy-to-handle phosphine oxides, and the regioselectivity is controlled by the innate electronic nature. Thus, this newly developed protocol can provide concise and complementary approach to the highly π -conjugated dibenzophospholes of potent interest in material chemistry.

A dibenzophosphole is a key motif in the design of phosphorus-containing functional organic materials.¹ Accordingly, considerable attention has been focusing on the rapid and concise synthesis of the dibenzophosphole framework. Although the conventional synthetic procedures required tedious and multistep sequences with complicated and unstable starting substrates and/or reagents,² recent advances in the transition-metal-catalyzed C–H functionalization provide a potentially more efficient approach to the above target structure, as exemplified by the palladium-catalyzed intramolecular C–H/P–H³ and C–H/P–C⁴ couplings of biarylphosphine derivatives (Scheme 1a and b).⁵ Although somewhat specific, the Et₃B/O₂-initiated radical phosphination of biarylphosphine oxide also provides the corresponding dibenzophosphole efficiently (Scheme 1c).⁶ On the other hand, the intramolecular phospha-Friedel–Crafts reaction (PFC)⁷ is traditional but can be a good alternative to the aforementioned direct couplings. However, its synthetic potential has not been studied well: only a few examples were reported by using biarylphosphinic acid substrates and excess PCl₅ under harsh conditions (refluxed PhNO₂ solvent), and the regioselectivity in the reaction was also not mentioned.⁸ Thus, there still remains a large demand for development of the dibenzophosphole synthesis via intramolecular PFC reaction.

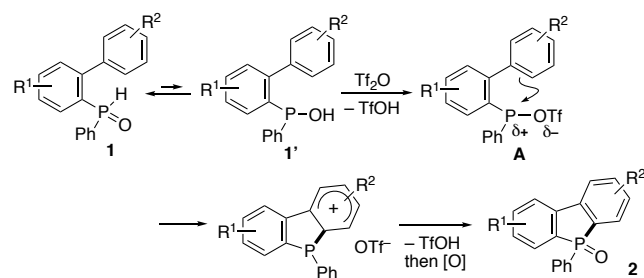
Scheme 1. Direct C–H Phosphination Approaches to Dibenzophospholes



Meanwhile, our research group recently developed a metal-free, Tf₂O-promoted protocol for the generation of highly electrophilic and reactive phosphonium cation equivalents from readily available and stable secondary phosphine oxides and successfully applied it to phosphinative cyclization⁹ and formal [3+2] cycloaddition¹⁰ with alkynes. During our continuing interest in this chemistry,¹¹ we envisioned our blueprint for the synthesis of dibenzophospholes via the phosphonium cation intermediate. Herein, we report a Tf₂O-mediated intramolecular PFC reaction of biarylphosphine oxides (Scheme 1d). The reaction proceeds under metal-free conditions, and the regioselectivity is controlled by the innate electronic nature of substrates. Additionally, several heteroarene-fused dibenzophospholes are also readily prepared. Thus, the

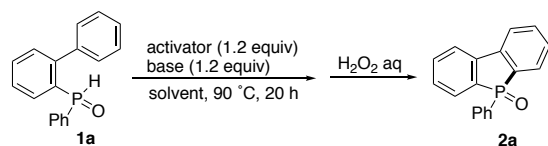
present protocol can provide useful and complementary access to various dibenzophosphole derivatives.

Scheme 2. Working Hypothesis



Our initial working scenario is shown in Scheme 2. The secondary biarylphosphine oxide **1** undergoes the tautomerization to the corresponding hydroxylphosphine **1'**. If its OH group is activated with $\text{ Tf}_2\text{O}$, a highly electrophilic phosphonium cation equivalent **A** could be formed.¹² The highly reactive and electrophilic phosphorus center can be readily trapped with the proximal aromatic ring, and subsequent rearomatization with the concomitant removal of proton delivers the desired dibenzophosphole **2** (intramolecular PFC reaction).¹³ On the basis of the above hypothesis, we started optimization studies with bi-phenylphosphine oxide **1a** as the model substrate (Table 1). In an initial experiment, treatment of **1a** (0.10 mmol) with $\text{ Tf}_2\text{O}$ (1.2 equiv) in the presence of DMAP (1.2 equiv) in DCE at 90 °C (almost same conditions as those in our previous work)¹⁰ was followed by quenching with $\text{ H}_2\text{O}_2$ aq to afford the desired dibenzophosphole oxide **2a** in 81% GC yield (entry 1). Subsequently, we screened several organic and inorganic bases (entries 2–6), but surprisingly the reaction proceeded smoothly even in the absence of any bases (entry 6), which prompted us to reconsider our initial working hypothesis (vide infra). The solvent evaluation (entries 7–10) revealed that less polar toluene gave a better result, leading to **2a** in 90% isolated yield (entry 7). Notably, under conditions in entry 7 the initially formed P(III) dibenzophosphole can be spontaneously oxidized with residual $\text{ Tf}_2\text{O}$ and/or its derivatives in situ, and thus the corresponding dibenzophosphole oxide **2a** was observed as the sole product even without any additional oxidative workup with $\text{ H}_2\text{O}_2$ aq.¹⁴ Although we also tested other activating reagents including $(\text{ CF}_3\text{ CO})_2\text{ O}$, $\text{ Ts}_2\text{ O}$, and TfOH , $\text{ Tf}_2\text{ O}$ still proved to be optimal (entries 11–13). The reaction could also be conducted on a 10-fold larger scale (1.0 mmol) with good reaction efficiency, thus indicating reproducibility and reliability of the present protocol (entry 7).

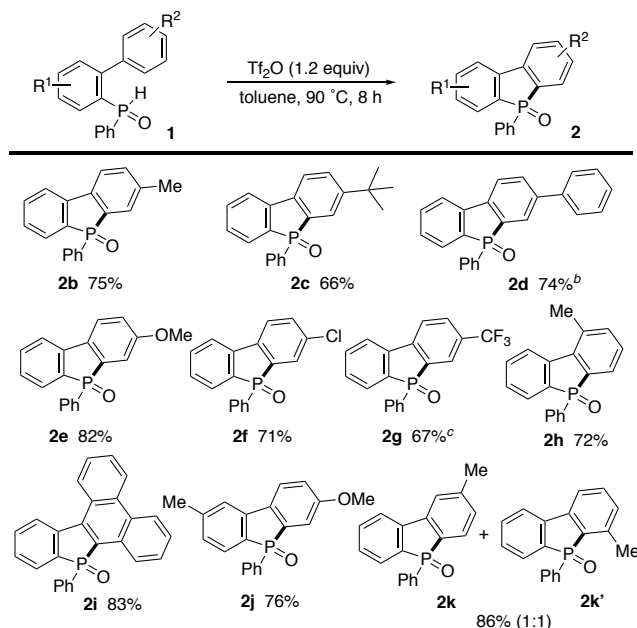
Table 1. Optimization for Metal-Free Intramolecular PFC Reaction of Biphenylphosphine Oxide **1a for Synthesis of Dibenzophosphole Oxide **2a**^a**



entry	activator	base	solvent	yield (%) ^b
1	$\text{ Tf}_2\text{ O}$	DMAP	DCE	81
2	$\text{ Tf}_2\text{ O}$	pyridine	DCE	84
3	$\text{ Tf}_2\text{ O}$	2,6-lutidine	DCE	67
4	$\text{ Tf}_2\text{ O}$	$\text{ Et}_3\text{ N}$	DCE	84
5	$\text{ Tf}_2\text{ O}$	$\text{ K}_2\text{ CO}_3$	DCE	73
6	$\text{ Tf}_2\text{ O}$	none	DCE	84
7 ^c	$\text{ Tf}_2\text{ O}$	none	toluene	(90), (66) ^d
8	$\text{ Tf}_2\text{ O}$	none	 PhCF_3	64
9	$\text{ Tf}_2\text{ O}$	none	1,4-dioxane	41
10	$\text{ Tf}_2\text{ O}$	none	DMF	22
11	$(\text{ CF}_3\text{ CO})_2\text{ O}$	pyridine	toluene	9
12	$\text{ Ts}_2\text{ O}$	pyridine	toluene	13
13	 TfOH	none	toluene	20

^a Reaction conditions: **1a** (0.10 mmol), activator (0.12 mmol), base (0.12 mmol), solvent (1.5 mL), 90 °C, 20 h, N_2 then $\text{ H}_2\text{O}_2$ aq (30%, ca. 5 drops). ^b GC yield. Isolated yield in parentheses. ^c Reaction time was 8 h. Without $\text{ H}_2\text{O}_2$ aq workup. ^d 1.0 mmol scale.

Scheme 3. $\text{ Tf}_2\text{ O}$ -Promoted Intramolecular PFC Reaction of Various Biarylphosphine Oxides **1a**



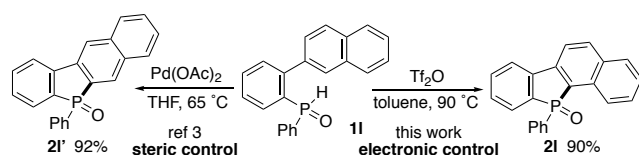
^a Reaction conditions: **1** (0.10 mmol), $\text{ Tf}_2\text{ O}$ (0.12 mmol), toluene (1.5 mL), 90 °C, 8 h, N_2 . Isolated yields are shown. The formed P–C bonds are indicated with bold lines. ^b 20 h. ^c 120 °C.

With conditions in entry 7 in Table 1, the intramolecular PFC reaction of several biarylphosphine oxides **2** was performed (Scheme 3). The standard reaction conditions were equally compatible with electron-neutral (Me, *t*-Bu, Ph), -donating (OMe), and -withdrawing (Cl and CF_3) groups, and the corresponding dibenzophospholes **2b–g** were obtained in good yields (66–82%). The Me substituent at the *ortho* position was also tolerated (**2h**). Additionally, the higher π -conjugated system **2i** and dibenzophosphole **2j** bearing functional groups on both benzene

rings were readily prepared from the corresponding biarylphosphine oxides without any difficulties. On the other hand, the *meta*-substituted substrate gave an almost 1:1 regiomixture of **2k** and **2k'**, which is reflected by the electronically controlled ring closing process as shown in Scheme 2: in contrast, under the reported palladium-catalyzed conditions, the more sterically accessible **2k** was preferably formed (ca. 9:1–10:1).^{3,4}

The more salient unique and positive regioselectivity was observed in the reaction with the 2-naphthyl-substituted substrate **1l** (Scheme 4). Under the palladium catalysis, **1l** was known to be cyclized exclusively at the less sterically congested position to form **2l'** (left).¹⁵ On the other hand, in the Tf₂O-mediated protocol, the regioselectivity was mainly dominated by the electronic factors to deliver the opposite regioisomer **2l** selectively (right). Such a complementary regioselectivity can provide divergent access to the dibenzophosphole from the same starting substrate.

Scheme 4. Reaction of 2-Naphthyl Substrate **1l**



An additional feature of the present strategy is accommodation of heteroaromatic rings (Figure 1). The furan- and thiophene-fused bent-type dibenzophosphole derivatives **2m** and **2n** were successfully prepared in good yields under identical conditions. The structure of **2n** was also confirmed by X-ray crystallography (CCDC 1889358). In these cases, the reaction occurred exclusively at the more electron-rich α -position of heterocycles, which is consistent with the electronically controlled PFC reaction mechanism. The more π -conjugated benzothiophene-condensed **2o** was readily synthesized. Moreover, the ladder-type analogue **2p** was also accessible. In the reaction of indole-containing substrate, the regioselectivity was moderate (**2q**:**2q'** = 5:1), but a synthetically acceptable combined yield (51%) was observed.

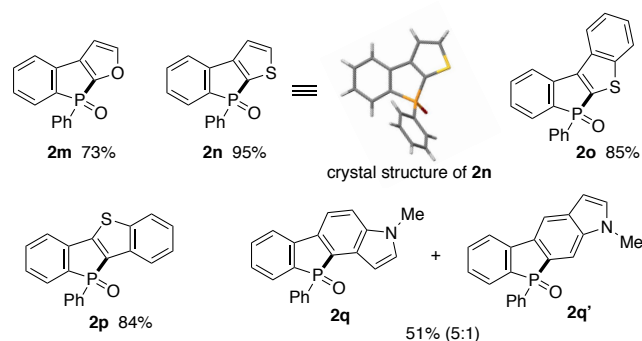
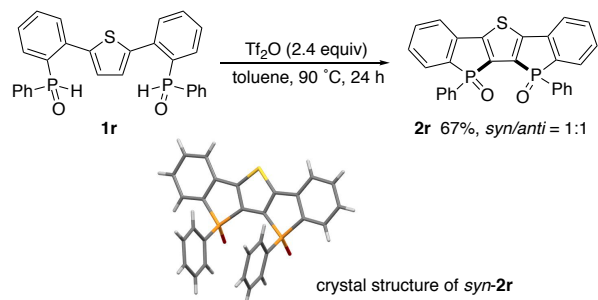


Figure 1. Structure and isolated yields of heteroarene-fused dibenzophosphole derivatives. The formed P–C bonds are indicated with bold lines. See Scheme 1 for reaction conditions.

Finally, we carried out the double cyclization reaction of **1r** (Scheme 5). Pleasingly, the reaction proceeded well under the standard conditions to form the structurally novel dibenzophospholothienophene **2r** in 67% yield with ca. 1:1 *syn/anti* ratio.¹⁶ The *syn*-isomer of **2r** was successfully crystallized and analyzed by single crystal X-ray diffraction (CCDC 1891190). The result demonstrates the high synthetic potential of Tf₂O-promoted, metal-free protocol for the synthesis of other highly condensed phosphole derivatives.

Scheme 5. Double Cyclization of **1r** to Form Dibenzophospholothienophene **2r**



Given the unexpected result that the reaction proceeded smoothly in the absence of any bases (entry 6 in Table 1), we monitored the reaction mixture of **1a** with Tf₂O in toluene-*d*₈ by NMR to reconsider the reaction mechanism. While preliminary, a five-coordinated, Tf₂O adduct is believed to be a more plausible intermediate than the initially proposed low coordinated phosphonium cation species. Thus, an alternative P(V)-mediated pathway may be operative in the C–P bond forming step. However, additional mechanistic studies are necessary for the conclusive statement (see the Supporting Information for details).

In conclusion, we have revisited the classical phosphafriedel–Crafts-type reaction of the biarylphosphine derivatives and developed metal-free, Tf₂O-mediated conditions for the synthesis of dibenzophospholes. The newly developed protocol is simple, practical, and compatible with several functional groups and heteroaromatic rings, and the observed regioselectivity is apparently controlled by the innate electronic nature, thus providing a good alternative to the reported transition-metal-catalyzed C–H phosphination strategies.^{3,4} Additional mechanistic investigation and further application of related electrophilic phosphination reaction to other phosphorus-containing organic molecule synthesis are ongoing in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx.

¹H, ¹³C{¹H}, and ³¹P{¹H} NMR spectra, ORTEP drawing, and NMR studies (PDF)

Accession Codes

CCDC 1889358 and 1891190 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Nos. JP 15H05485 (Grant-in-Aid for Young Scientists (A)) and 18K19078 (Grant-in-Aid for Challenging Research (Exploratory)) to K.H. and JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M. We thank Dr. Yuji Nishii (Osaka University) for his assistance in obtaining X-ray diffraction data.

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- (14) A similar phenomenon was observed in our previous work, see ref 10.
- (15) In the original paper, the structure of **21'** was wrong and revised by X-ray analysis later in the addition/correction. See ref 3b.
- (16) The *syn/anti* relative stereochemistry was tentatively assigned.