ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 2792

Received 8th December 2023,
Accepted 9th February 2024

DOI: 10.1039/d3cc05994d

rsc.li/chemcomm

Pd-catalysed C–H alkynylation of benzophospholes†

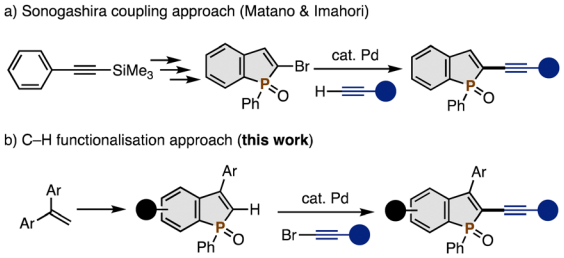
Yu Tokura,[a] Shibo Xu,[b] Kosuke Yasui,[a] Yuji Nishii[a] and Koji Hirano *[ab]

A palladium-catalysed C2–H alkynylation of benzophospholes with alkynyl bromides has been developed to afford the corresponding phosphole-alkyne conjugations in good to high yields. The C–C triple bond as well as terminal alkyne C–H bond in the obtained products is a good synthetic handle for further manipulations, thus giving the versatile π-conjugated benzophosphole derivatives. The optoelectronic properties of the newly synthesized conjugated benzophospholes are also described.

Because of its unique optoelectronic and physical properties, the phosphole nucleus has received significant attention as an important heteroaromatic core in the design of phosphorus-containing organic functional materials.[1] In particular, highly π-conjugated benzophospholes are frequently occurring in organic light-emitting diodes, solar cells, imaging dyes, and memory devices. Among them, the C2-alkynylated (benzo)-phospholes are attractive owing to their effective phosphole-alkyne π-conjugation as well as the versatile reactivity of the C–C triple bond and terminal alkyne C–H bond, which are additional synthetic handles for further functionalisations.[2] In 2013, Matano and Imahori reported the synthesis of C2-alkynylated benzophospholes by the palladium-catalysed Sonogashira coupling of C2-brominated benzophosphole, which was prepared from trimethylsilyl-protected phenylacetylene in a three-step manner (Scheme 1a).[3] However, there are few examples in the literature probably because of the somewhat tedious synthetic procedure for the preparation of the starting substrate. Thus, the development of a more concise and versatile synthetic methodology for C2-alkynylated benzophospholes is greatly appealing.

On the other hand, our research group recently focused on the synthetic potential of benzophosphole C–H activation[4] and developed the palladium-catalysed C2–H arylation and alkenylation reactions.[5] During continuing interest in this chemistry, we here report a palladium-catalysed C2–H alkynylation with alkynyl bromides to directly deliver the corresponding C2-alkynylated benzophospholes in good yields (Scheme 1b). Different from the related benzoheteroles including indoles and benzothiophenes,[6] to the best of our knowledge, the C–H alkynylation of the phosphole nucleus has not been reported yet. The starting C2–H benzophospholes are readily prepared from 1,1-diarylethenes in one synthetic operation.[7] Thus, the present C–H activation protocol can offer a convergent approach to the C2-alkynylated benzophospholes with high structural diversity. In addition, based on the established alkyne chemistry, the obtained products can be rapidly manipulated into more versatile π-conjugated benzophosphole derivatives. Their optoelectronic properties are also described.

We selected the C2–H benzophosphole oxide **1a** and triisopropylsilyl (TIPS)-substituted alkynyl bromide **2a** as model substrates and started optimisation studies (Table 1). In an early experiment, treatment of **1a** (0.10 mmol) with **2a** (2.0 equiv.) in the presence of 10 mol% $Pd(OAc)_2$ catalyst and CsOPiv base (2.0 equiv.) in heated 1,4-dioxane (1.0 mL at 110 °C) for 20 h afforded the desired **3aa** in 7% NMR yield (entry 1). Notably, the reaction occurred selectively at the C2–H

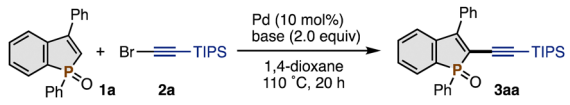


Scheme 1 Approaches to C2-alkynylated benzophospholes. (a) Sonogashira coupling approach and (b) C–H functionalisation approach.

[a] *Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*
[b] *Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan. E-mail: k_hirano@chem.eng.osaka-u.ac.jp*

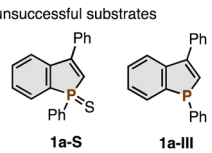
† Electronic supplementary information (ESI) available. CCDC 2279968, 2283132, 2283133, and 2285491. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc05994d

Table 1 Optimisation studies for Pd-catalysed C–H alkynylation of benzophosphole **1a** with TIPS-substituted alkynyl bromide **2a**[a]



Entry	Pd	Base	Yield (%)[b]
1	$Pd(OAc)_2$	CsOPiv	7
2	$Pd(OAc)_2$	KOPiv	8
3	$Pd(OAc)_2$	NaOPiv	38
4	$Pd(OAc)_2$	NaOAc	20
5	$Pd(OAc)_2$	Na_2CO_3	11
6	$Pd(OAc)_2$	$NaHCO_3$	0
7[c]	$Pd(OAc)_2$	NaOPiv	60
8[c]	$Pd(OPiv)_2$	NaOPiv	73
9[c]	$Pd(TFA)_2$	NaOPiv	65
10[c]	$PdCl_2$	NaOPiv	64
11[c]	$Pd_2(dba)_3$	NaOPiv	64
12[cd]	$Pd(OPiv)_2$	NaOPiv	84 (72, 68[e])

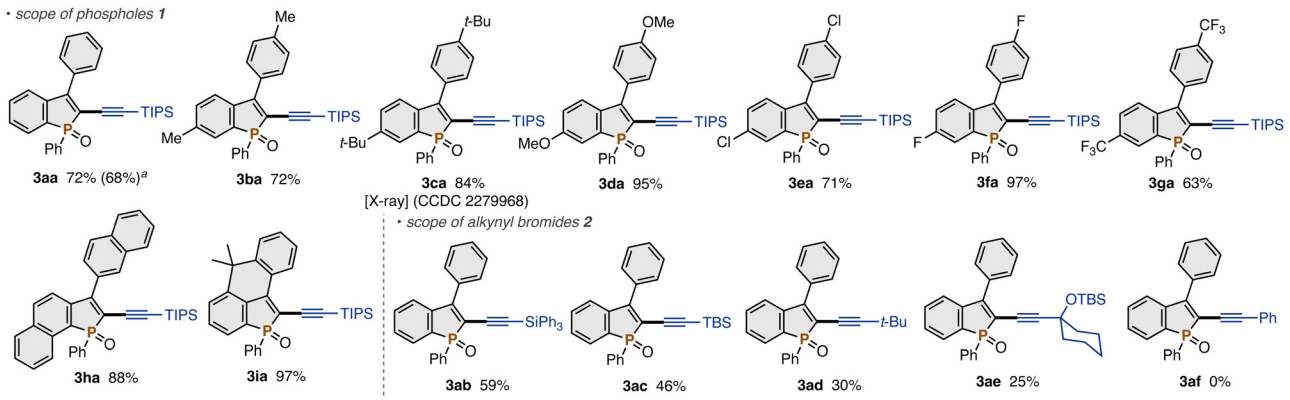
[a] Conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), Pd (0.010 mmol on Pd), base (0.20 mmol), 1,4-dioxane (1.0 mL), 110 °C, 20 h, N_2. [b] Estimated by $^{31}P\{^1H\}$ NMR with $P(O)(OEt)_3$ as the internal standard. Isolated yield of **3aa** is in parentheses. [c] At 60 °C. [d] In 1,4-dioxane (1.5 mL) for 48 h. [e] On a 1.0 mmol scale.



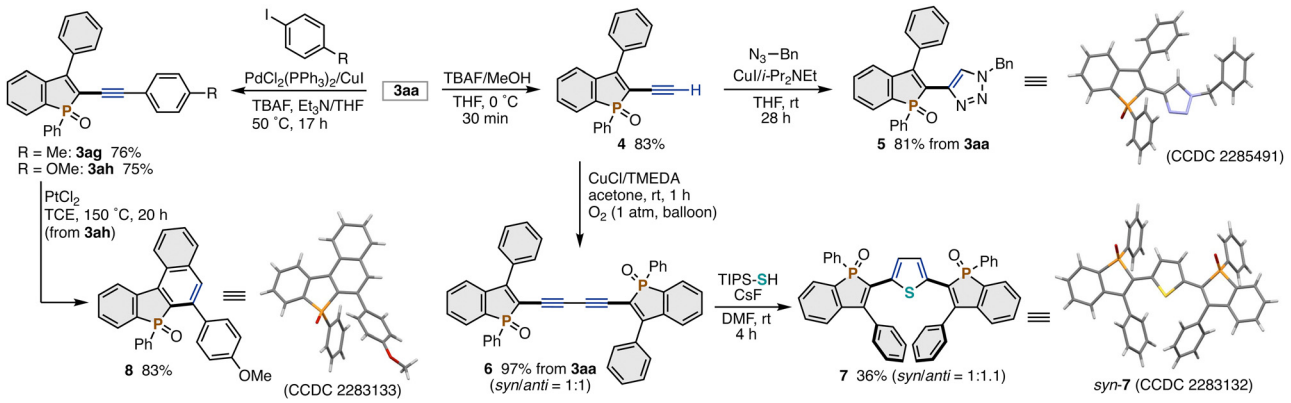
position over the *ortho* C–Hs on the phenyl ring despite the potential directing ability of the phosphole P═O moiety.[8] This preliminary but promising result prompted us to investigate basic additives in detail. While KOPiv showed a similar performance (entry 2), NaOPiv increased the yield to 38% (entry 3). Other sodium bases such as NaOAc, Na_2CO_3, and $NaHCO_3$ were less effective (entries 4–6). Thus, with NaOPiv as the optimal base, we then screened other reaction parameters. The lower reaction temperature (60 °C) further improved the reaction efficiency (entry 7). The Pd source also affected the yield of **3aa** to some extent (entries 8–11): as far as we tested, $Pd(OPiv)_2$ was found to be the best precursor (entry 8). After additional fine-tuning, the C2-alkynylated **3aa** was finally obtained in 84% NMR yield (72% isolated yield) under slightly diluted conditions for prolonged reaction periods (1.5 mL 1,4-dioxane, 48 h; entry 12). The reaction could also be conducted on a 1.0 mmol scale with a comparable product yield. We also tested other bases, solvents, and alkynyl coupling partners, but better yields of **3aa** were not observed. The use of the corresponding phosphole sulfide **1a-S** and P(III) phosphole **1a-III** instead of phosphole oxide **1a** furnished no C–H alkynylated products (see the ESI† for more details).

With the optimal conditions (Table 1, entry 12), we examined the scope of the C–H alkynylation reaction (Scheme 2). Several substituted benzophosphole oxides **1** participated in the reaction: both electron-donating (methyl, *tert*-butyl, and methoxy) and -withdrawing substituents (chloro, fluoro, and trifluoromethyl) were equally compatible under the standard reaction conditions to produce the corresponding C2-alkynylated benzophospholes **3ca–ga** in 63–97% yields. The reaction of the more π-conjugated naphthalene-fused phosphole derivative also occurred with a comparable efficiency (**3ha**). Moreover, the carbon-bridged tricyclic system **3ia** was formed in 97% yield. On the other hand, the C2,3-free benzophosphole provided an inseparable mixture of C2-, C3-, and C2,C3-alkynylated products in *ca.* 2 : 1 : 1 ratio, which was assigned by ^1H and $^{31}P\{^1H\}$ NMR analysis as well as HRMS (see the ESI† for more details). The structure of **3ca** was unambiguously confirmed by X-ray analysis (CCDC 2279968†). More detailed functional group compatibility was investigated by the robustness screen[9] (see the ESI†). In addition to **2a**, some sterically congested silyl-substituted alkynyl bromides underwent the C–H coupling reaction: triphenylsilyl- and *tert*-butyldimethylsilyl (TBS)-protected C2-alkynylphospholes **3ab** and **3ac** were obtained in acceptable yields. The bulky *tert*-butyl- and *tert*-propargylic alcohol derivatives could also be employed albeit with moderate efficiency (**3ad** and **3ae**). On the other hand, the less sterically demanding phenyl acetylene derivative did not form the coupling product **3af** probably because of self-dimerisation reactions under the optimal conditions.

The TIPS-protected C2-alkynylated benzophosphole **3aa** can be readily and variously derivatised (Scheme 3). The simple



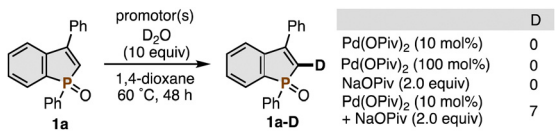
Scheme 2 Pd-catalysed C–H alkynylation of benzophospholes **1** with alkynyl bromides **2**. Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), $Pd(OPiv)_2$ (0.010 mmol), NaOPiv (0.20 mmol), 1,4-dioxane (1.5 mL), 60 °C, 48 h, N_2. Isolated yields are shown. [a] On a 1.0 mmol scale.



Scheme 3 Derivatisation of C2-alkynylated benzophosphole **3aa**.

protodesilylation proceeded upon treatment with TBAF and MeOH in THF to afford the terminal alkyne **4** in 83% yield. In addition, the crude **4** directly underwent the copper-catalysed azide–alkyne cycloaddition and Glaser coupling without any additional purification, delivering the benzophosphole-triazole hybrid **5**[2d] and two phosphole-containing 1,3-diynes **6**,[2c] respectively, in acceptable 2-step yields. The 1,3-diyne moiety in **6** was further transformed by the cyclisation with TIPS-SH/CsF to the phosphole-thiophene-phosphole ter(hetero)aryl **7**. On the other hand, the desilylative Sonogashira coupling reaction of **3aa** with aryl iodides was also possible to give the corresponding arylalkyne-substituted phospholes **3ag** and **3ah** in good yields, which can complement the unsuccessful reaction using the aryl-substituted alkynyl bromide (**3af** in Scheme 2). Subsequent $PtCl_2$-catalysed cycloisomerisation of **3ah** with concomitant aryl migration furnished the acene-type molecule **8** in a synthetically useful yield.[10] The structures of **5**, **7**, and **8** were determined by X-ray analysis (CCDC 2285491, 2283132, and 2283133†).

To get some mechanistic insight into the C–H cleavage step of **1a**, we performed the H/D exchange reaction of **1a** with D_2O (Scheme 4). In the presence of $Pd(OPiv)_2$ or NaOPiv alone, no deuterium incorporation was observed even after 48 h. In sharp contrast, the combination of $Pd(OPiv)_2$ and NaOPiv gave the deuterated benzophosphole **1a-D** albeit with a moderate deuterium content. These results suggest the cooperative effect of Pd and Na in the C–H metalation process, where the P=O moiety coordinates to the Lewis acidic Na cation to increase the acidity of the proximal C2–H bond[11] and it then can be cleaved by the $Pd(OPiv)_2$-involved concerted metalation-deprotonation (CMD).[12] In addition, the H/D exchange was observed selectively at the C2 position but not at the *ortho* position of the phenyl ring on P, which is consistent with the observed high regioselectivity in Table 1 and suggests that the regioselectivity



Scheme 4 Deuterium incorporation experiments.

in the alkynylation can be determined in the C–H cleavage step. On the basis of the aforementioned findings, the reaction of benzophosphole **1a** with alkynyl bromide **2a** is believed to proceed through (1) the $Pd(OPiv)_2$-promoted C2–H metalation of NaOPiv-coordinated **1a** to form a benzophosphole-Pd intermediate, (2) addition–elimination with **2a**, giving **3aa** along with Pd–Br species, and (3) ligand exchange with NaOPiv to regenerate the catalytically active starting $Pd(OPiv)_2$. We cannot completely exclude the possibility of the Pd(0)/(II) redox cycle including the oxidative addition of **2a** to Pd(0),[5a] but the control experiment with the independently prepared Pd(II)-alkynyl complex did not form the alkynylated product at all (Schemes S4 and S5, ESI†). The proposed C–H activation mechanism is also consistent with the reactivity trend dependent on the phosphorus moiety (Table 1 and Scheme S1, ESI†), in which only the most electron-withdrawing P=O successfully gave the product: the less electron-withdrawing P=S and P(III) groups cannot ensure the acidity enough for the successful C–H cleavage.[13] However, at present, the base-assisted internal electrophilic substitution (BIES) mechanism[14] is also plausible. Further studies remain to be elucidated.

We finally investigated the optoelectronic properties of some newly synthesized π-conjugated benzophosphole derivatives (Fig. S1–S13 and Tables S10 and 11 in the ESI†). Compared to the C3–H C2-alkynylated benzophosphole previously reported by Matano and Imahori,[3] both the absorption and emission maxima of the C3-phenylated **3ah** were red-shifted by *ca.* 20 nm. On the other hand, the differential pulse voltammetry (DPV) analysis of **3ah** showed the uniquely increased reduction potential (−1.86 V *vs.* −2.02 V[3]) even with the maintenance of the oxidation potential, thus suggesting that the Ph group at the C3 position mainly affects the LUMO level. The properties of benzophosphole-triazole hybrid **5** were generally similar to the corresponding non-benzofused phosphole-triazole conjugation analogue.[2d] The two phosphole-linked 1,3-diynes **6** showed a remarkably low LUMO level (−3.41 eV). The phosphole-thiophene-phosphole conjugations *syn*-**7** and *anti*-**7** exhibited large bathochromic shifts of the emission maxima (532–537 nm) and distinctly smaller Stokes shifts, which are reflected by their relatively rigid structures associated with the less steric

repulsion between the five-membered phosphole and thiophene heteroaromatic skeletons. Almost all values of *syn*-**7** and *anti*-**7** are identical, thus indicating that the optoelectronic properties are less dependent on the stereochemistry on phosphorus. Among them, the fluorescence quantum yields of MeO-substituted **3ah** and its annulated derivative **8** were relatively good (0.74 and 0.52, respectively).

In conclusion, we have developed a palladium-catalysed C–H alkynylation of benzophosphole with alkynyl bromides. The resulting alkyne moiety could be a good synthetic handle for further manipulations. Combined with the ready availability of the starting C2–H benzophospholes and the straightforwardness of the C–H activation protocols, the present strategy can provide a modular approach to various phosphole-based π-conjugated molecules of potent interest in materials chemistry.[15]

This work was supported by JSPS KAKENHI Grant No. JP 22H02077 (Grant-in-Aid for Scientific Research(B), to K. H.) as well as by JST FOREST Program, Grant Number JPMJFR211X to K. H.

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 Reviews and accounts: (*a*) T. Baumgartner and R. Réau, *Chem. Rev.*, 2006, **106**, 4681; (*b*) Y. Matano and H. Imahori, *Org. Biomol. Chem.*, 2009, **7**, 1258; (*c*) M. P. Duffy, W. Delaunay, P.-A. Bouit and M. Hissler, *Chem. Soc. Rev.*, 2016, **45**, 5296; (*d*) Y. Matano, *Chem. Rec.*, 2015, **15**, 636; (*e*) H. Tsuji, K. Sato, L. Ilies, Y. Itoh, Y. Sato and E. Nakamura, *Org. Lett.*, 2008, **10**, 2263; (*f*) C. Wang, M. Taki, Y. Sato, A. Fukazawa, T. Higashiyama and S. Yamaguchi, *J. Am. Chem. Soc.*, 2017, **139**, 10374; (*g*) P. Demay-Drouhard, J. R. Gaffen, C. B. Caputo and T. Baumgartner, *Can. J. Chem.*, 2023, **101**, 146.

2 (*a*) E. Y.-H. Hong, C.-T. Poon and V. W.-W. Yam, *J. Am. Chem. Soc.*, 2016, **138**, 6368; (*b*) A. F.-F. Cheung, E. Y.-H. Hong and V. W.-W. Yam, *Chem. – Eur. J.*, 2018, **24**, 1383; (*c*) Y. Matano, M. Nakashima and H. Imahori, *Chem. Lett.*, 2021, **50**, 1581; (*d*) Y. Matano, M. Nakashima, A. Saito and H. Imahori, *Org. Lett.*, 2009, **11**, 3338.

3 Y. Matano, Y. Hayashi, K. Suda, Y. Kimura and H. Imahori, *Angew. Chem., Int. Ed.*, 2009, **48**, 4002.

4 Selected recent reviews on C–H activation: (*a*) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603; (*b*) P. Gandeepan, T. Muller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192; (*c*) S. Rej, Y. Ano and N. Chatani, *Chem. Rev.*, 2020, **120**, 1788; (*d*) N. Y. S. Lam, K. Wu and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2021, **60**, 15767.

5 (*a*) S. Xu, K. Nishimura, K. Saito, K. Hirano and M. Miura, *Chem. Sci.*, 2022, **13**, 10950; (*b*) Y. Tokura, S. Xu, Y. Kojima, M. Miura and K. Hirano, *Chem. Commun.*, 2022, **58**, 12208.

6 For examples of C–H alkynylation of indoles and benzothiophenes, see: (*a*) I. V. Seregin, V. Ryabova and V. Gevorgyan, *J. Am. Chem. Soc.*, 2007, **129**, 7742; (*b*) J. P. Brand, J. Charpentier and J. Waser, *Angew. Chem., Int. Ed.*, 2009, **48**, 9346; (*c*) J. P. Brand and J. Waser, *Angew. Chem., Int. Ed.*, 2010, **49**, 7304; (*d*) T. de Haro and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 1512; (*e*) L. Yang, L. Zhao and C.-J. Li, *Chem. Commun.*, 2010, **46**, 4184; (*f*) X. Jie, Y. Shang, P. Hu and W. Su, *Angew. Chem., Int. Ed.*, 2013, **52**, 3630. For a recent review on the C-H alkynylation of arenes, see: (*g*) J. A. S. Sarala, S. Bhowmick, R. L. de Carvalho, S. A. Al-Thabati, M. Mokhtar, E. N. da Silva Júnior and D. Maiti, *Adv. Synth. Catal.*, 2021, **363**, 4994.

7 K. Nishimura, K. Hirano and M. Miura, *Org. Lett.*, 2020, **22**, 3185.

8 Y. Unoh, T. Satoh, K. Hirano and M. Miura, *ACS Catal.*, 2015, **5**, 6634.

9 K. D. Collins and F. Glorius, *Nat. Chem.*, 2013, **5**, 597.

10 Attempts to apply the double cyclisation reaction of **6** under the same $PtCl_2$-mediated conditions remained unsuccessful.

11 The C2–H of phosphole is innately relatively acidic, but the coordination to the Na cation can further increase its acidity, thus accelerating the C–H metalation via CMD-type process. For pK_a values of phosphole derivatives and related heteroaromatics, see: (*a*) D. Delaere, N. Pham-Tran and M. T. Nguyen, *J. Phys. Chem. A*, 2003, **107**, 7514; (*b*) L. D. Quin, J. G. Bryson and C. G. Moreland, *J. Am. Chem. Soc.*, 1969, **91**, 3308; (*c*) K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568.

12 For selected reviews on CMD, see: (*a*) D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1118; (*b*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (*c*) D. L. Davies, S. A. Macgregor and C. L. McMullin, *Chem. Rev.*, 2017, **117**, 8649. The use of NaBr instead of NaOPiv did not promote any D incorporation reaction (*vs.* Scheme 4), thus suggesting an additional role of NaOPiv as the OPiv donor.

13 $Ph_2P{=}O$ shows a larger Hammett substituent constant than $Ph_2P{=}S$ and Ph_2P (σ_m = 0.38, 0.29, and 0.11, respectively), see: C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.

14 T. Rogge, J. C. A. Oliveira, R. Kuniyil, L. Hu and L. Ackermann, *ACS Catal.*, 2020, **10**, 10551.

15 We preliminarily tried the reaction with (D)-N-Ac-alanine as the chiral ligand. Successful conversion (76%) was observed, and the product **3aa** was obtained with 65 : 35 er, thus suggesting the possibility of asymmetric catalysis. See the ESI† for more details.