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Ligand-free copper-catalyzed denitrogenative arylation of phosphorylamides with arylhydrazines

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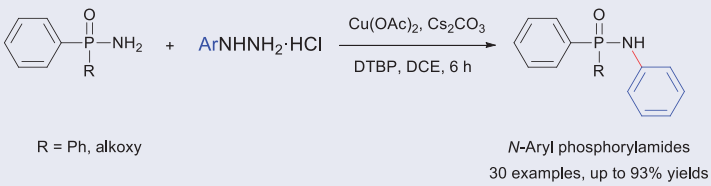
ABSTRACT

A straightforward arylation of phosphorylamides with arylhydrazines hydrochloride was herein demonstrated. The protocol proceeded in the presence of a catalytic loading of $Cu(OAc)_2$ as the catalyst, DTBP as the external oxidant and Cs_2CO_3 as the base, but without any ligands. And a series of *N*-aryl phosphorylamides were successfully obtained in high efficiency (up to 93% yields) with good substituents compatibility (up to 30 examples). Free radical mechanism was proposed for the facile methodology based on the results of control reactions and literature explorations.

GRAPHICAL ABSTRACT



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KEYWORDS
Arylhydrazines; copper catalysis; denitrogenative arylation; ligand-free; phosphorylamides

Introduction

Extraordinary biological properties,[1] broad applications in synthetic chemistry and material science[2] ensured the popularity of the organophosphorus compounds in the field and long-standing attention has been paid on the derivation of the versatile molecules. Among phosphorylamides which possessed a P–N bond within the molecules, have gained more and more research interests for the special architecture, as well for the versatile roles in medicinal chemistry[3] and catalysts design.[4] Thus, sacrifice have been paid for the readily transformations of the expedient molecules with excellent biological and clinical properties.[5,6] For example, synthesis of benzazaphosphole-1-oxides and phosphaisoquinolin-1-oxides has been successfully realized by inter/intra-molecular annulation reactions in the presence of different transition metal catalysts.[6] However, the topic remained underdeveloped and novel methods for the enrichment of the diversity of the –P(=O)–N– backboned molecules are still

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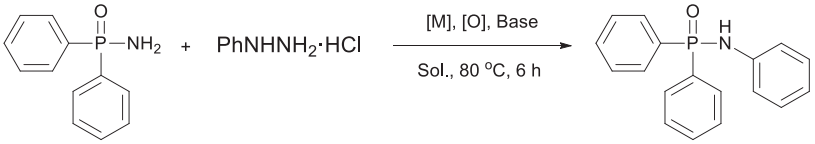
Supplemental data for this article can be accessed on the publisher's website.

highly desired for the further development of the topic. For instance, firstly reported by Guo,[7] arylation method of phosphinamides was demonstrated and different aryl groups were successfully installed on the amino groups, which was provided by aryl iodides, in the presence of CuI as catalyst and (±)-*trans*-cyclohexane-1,2-diamine as ligand. Successively, An and coworkers disclosed a general arylation protocol of phosphorylamides with the assistance of catalytic loading of $Cu(OAc)_2$ and TBAF (tetrabutylammonium fluoride), in which aryl siloxanes was applied as the aryl donators, forming a plenty of *N*-aryl phosphorylamides in high efficiency and functional group tolerance.[8] Then, the same products were successfully synthesized with aryl boronic acids in the presence of $Cu(OAc)_2$ from the same group.[9] Arylhydrazines, which was normally utilized as synthetic modules and identification reagents for the advantages including low-cost, high reactivity and easy availability,[10] came to our awareness as an efficient arylation reagent, which were able to supply different aryl groups through the C-N bonds cleavage with emission of N_2 and H_2O via the aryldiazene intermediate under oxidative conditions, leading to the formations of kinds of chemical bonds. For example, carbon-carbon bond construction, which was pioneered by Loh,[11] was successfully realized by transition metallic catalyzed systems, or even under metal-free conditions. Other carbon-hetero bonds, such as C-P[12] and C-S[13] bonds were readily formed through the denitrogenative mechanism, giving an access to arylphosphonates and diarylsulfides successfully. For example, recently, reactions between arylhydrazines and trialkylphosphites were described in the presence of CuO, providing arylphosphonates without any external reductants or ligands,[14] which shed light on that it was reasonable to exploit novel methods for the formation of C-N bond. Within this context, Co/Cu-cocatalyzed system was created for the arylation of anilines through the denitrogenative pathway.[15] Successively, An's groups also disclosed a new arylation protocol on *NH*-sulfoximines and sulfonamides under mild conditions (room temperature or 60 °C) in a similar manner.[16] Within this background, we wished to reported a general arylation method for the preparation of *N*-aryl phosphorylamides, which was also catalyzed by simple $Cu(OAc)_2$ salt without any organic ligands.

Discussion

Firstly, reactions between model substrates *P,P*-diphenyl phosphinamide (**1a**) and phenylhydrazine hydrochloride (**2a**) were carried out to investigate the optimal conditions of the arylation protocol, as summarized in Table 1. In the presence of di-*tert*-butyl peroxide (DTBP) and Na_2CO_3, activities of different palladium catalysts were tested in 1,2-dichloroethane at 80 °C for 6 hours. To our satisfactory, $PdCl_2$ was capable to make the reaction happen smoothly, and 32% of *N,P,P*-triphenyl phosphinamide (**3aa**) was successfully isolated after column chromatography (entry 1). Other palladium catalysts, such as $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$, ensured the occurrence of the transformation in 36 and 30% yields, respectively (entries 2 and 3). However, silver salts, like $AgNO_3$, AgOTf, AgOAc failed to make the protocol take place and no reaction was detected (entries 4–6). Then, various Cu(I)- and Cu(II) catalysts were logically examined in the system and it was found that Cu(I) salts offered general inferior performance to that Cu(II) catalysts did in the system (entries 7–14). Among all the Cu(II) salts tested, $Cu(OAc)_2$ (entry 12) gave the desired *N*-aryl phosphinamide **3aa** in 82% yield, which was distinguished from the others, like $CuCl_2$, $CuBr_2$, $Cu(OTf)_2$ and $CuSO_4$ (entries 10,

Table 1. Conditions optimization[a].



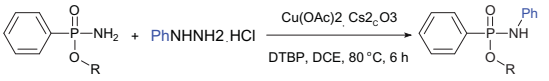
1a **2a** **3aa**

Entry	[M]	[O]	Base	Sol.	Yield[b]
1	$PdCl_2$	DTBP	Na_2CO_3	DCE	32%
2	$Pd(OAc)_2$	DTBP	Na_2CO_3	DCE	36%
3	$Pd(PPh_3)_2Cl_2$	DTBP	Na_2CO_3	DCE	30%
4	$AgNO_3$	DTBP	Na_2CO_3	DCE	n.d.
5	AgOTf	DTBP	Na_2CO_3	DCE	n.d.
6	AgOAc	DTBP	Na_2CO_3	DCE	n.d.
7	CuCl	DTBP	Na_2CO_3	DCE	25%
8	CuBr	DTBP	Na_2CO_3	DCE	32%
9	CuI	DTBP	Na_2CO_3	DCE	40%
10	$CuCl_2$	DTBP	Na_2CO_3	DCE	48%
11	$CuBr_2$	DTBP	Na_2CO_3	DCE	trace
12	$Cu(OAc)_2$	DTBP	Na_2CO_3	DCE	82%
13	$Cu(OTf)_2$	DTBP	Na_2CO_3	DCE	78%
14	$CuSO_4$	DTBP	Na_2CO_3	DCE	70%
15	$FeCl_2$	DTBP	Na_2CO_3	DCE	60%
16	$FeBr_2$	DTBP	Na_2CO_3	DCE	58%
17	$FeCl_3$	DTBP	Na_2CO_3	DCE	64%
18	$FeBr_3$	DTBP	Na_2CO_3	DCE	62%
19	$Cu(OAc)_2$	TBHP	Na_2CO_3	DCE	trace
20	$Cu(OAc)_2$	DCP	Na_2CO_3	DCE	80%
21	$Cu(OAc)_2$	*m*-CPBA	Na_2CO_3	DCE	n.d.
22	$Cu(OAc)_2$	$K_2S_2O_8$	Na_2CO_3	DCE	n.d.
23	$Cu(OAc)_2$	TBHP	K_2CO_3	DCE	70%
24	$Cu(OAc)_2$	TBHP	KOAc	DCE	58%
25[c]	**$Cu(OAc)_2$**	**DTBP**	**Cs_2CO_3**	**DCE**	**91%**
26	$Cu(OAc)_2$	DTBP	Et_3N	DCE	n.d.
27	$Cu(OAc)_2$	DTBP	DBU	DCE	n.d.
28	$Cu(OAc)_2$	DTBP	Cs_2CO_3	MeCN	84%
29	$Cu(OAc)_2$	DTBP	Cs_2CO_3	DMF	trace
30	$Cu(OAc)_2$	DTBP	Cs_2CO_3	DMSO	trace
31	$Cu(OAc)_2$	DTBP	Cs_2CO_3	Toluene	n.d.

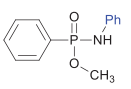
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol, 3 portions at 2 hours intervals), Cat. (10 mol%), [O] (0.6 mmol), Base (0.6 mmol) under air in Sol. (1.5 mL) at 80°C for 6 h.
[b]Isolated yields.
[c]The optimal conditions represented in bold.
[d]For not detected.

11, 13, and 14). Iron catalysts, for example, $FeCl_2$, $FeBr_2$, $FeCl_3$ and $FeBr_3$ made the reaction happen readily; however, lower efficiency were observed for up to 64% yield of **3aa** was isolated after the completion of the reaction (entries 15–18). Next, different oxidants were also subjected to the reactions for screening. *Tert*-Butyl hydroperoxide failed to make the reaction happen while dicumyl peroxide rendered the formation of **3aa** in 80% yield (entries 19 and 20). No reaction was detected in the presence of *m*-chloroperbenzoic acid (*m*-CPBA) and $K_2S_2O_8$ (entries 21 and 22). Amongst all the bases tested, inorganic bases, such K_2CO_3, KOAc, Cs_2CO_3, and organic bases, like Et_3N and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), Cs_2CO_3 showed superior performance in the system to the others and the highest 91% yield was observed (entries 23–27). For organic

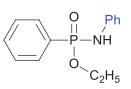
Table 2. Scope of phosphoryl amides[a].



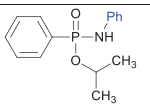
1b - 1q 2a 3ba - 3qa



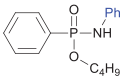
3ba, 85%



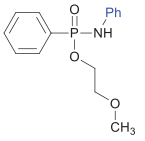
3ca, 88%



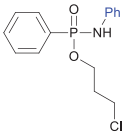
3da, 85%



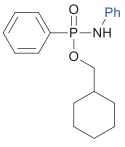
3ea, 80%



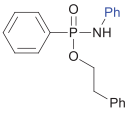
3fa, 82%



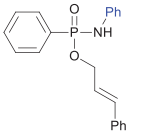
3ga, 78%



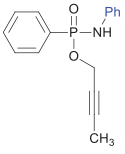
3ha, 82%



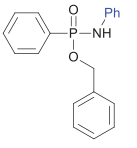
3ia, 83%



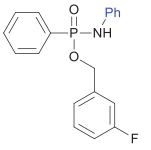
3ja, 87%



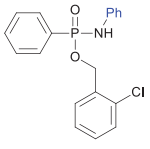
3ka, 88%



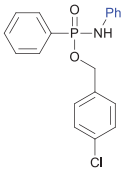
3la, 89%



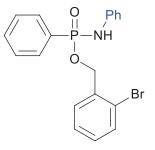
3ma, 75%



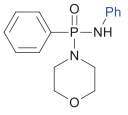
3na, 79%



3oa, 80%



3pa, 81%



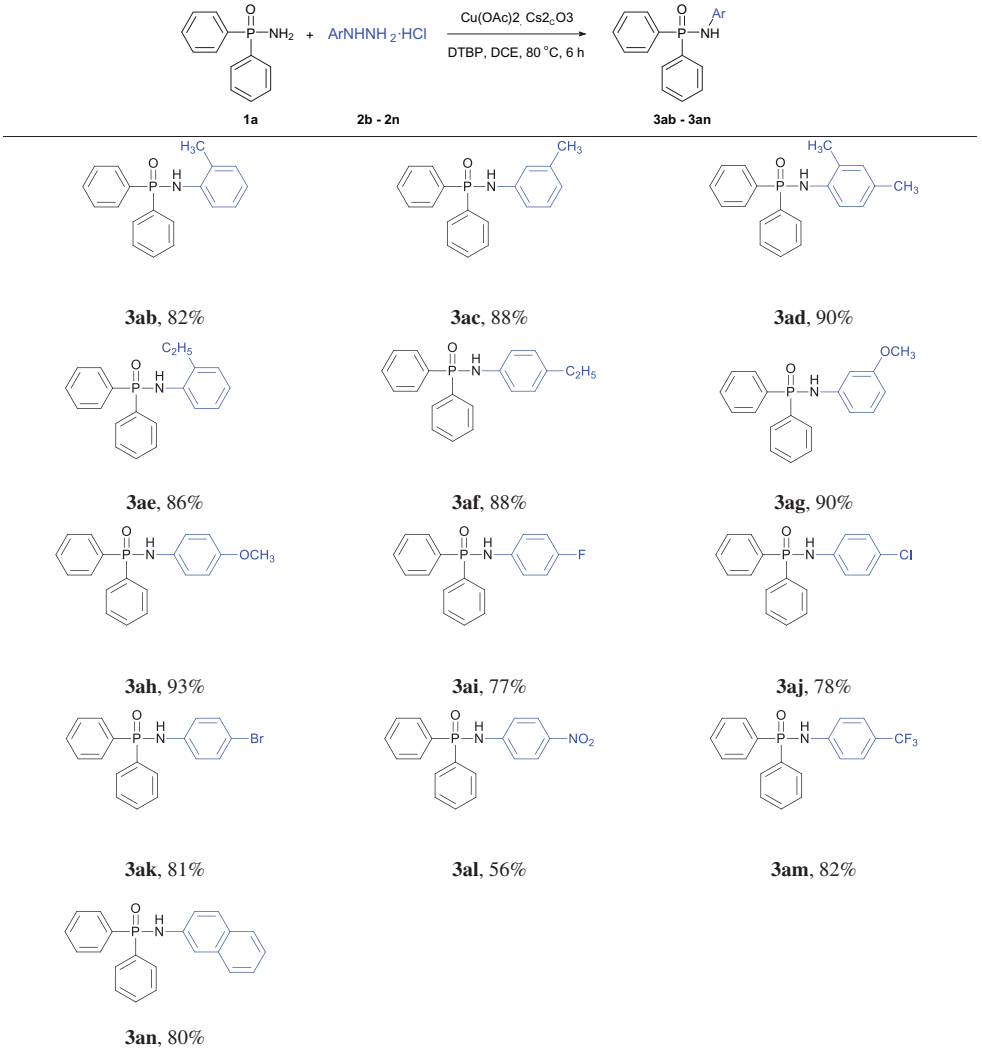
3qa, 48%

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol, 3 portions at 2 hours intervals), $Cu(OAc)_2$ (10 mol%), DTBP (0.6 mmol), Cs_2CO_3 (0.6 mmol) under air in DCE (1.5 mL) at 80 °C for 6 h.

solvents, similar efficiency was observed in acetonitrile (84% yield for entry 28), better than other solvents examined, like DMF, DMSO and toluene (entries 29–31).

Now that with the optimal reaction conditions in hands, examination of the substrate scope was successively carried out, which was shown in Table 2. *P*-Phenyl-*P*-methyl phosphonamide (**1b**) and *P*-Phenyl-*P*-ethyl phosphonamide (**1c**) reacted with phenylhydrazine hydrochloride in the catalytic system, offering the arylated product **3ba** and **3ca** in good yields, up to 88%. Other long chained alkyl substituted substrates were also

Table 3. Scope of arylhydrazine hydrochlorides[a].



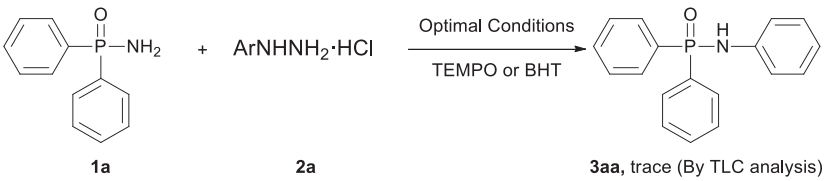
[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol, 3 portions at 2 hours intervals), $Cu(OAc)_2$ (10 mol%), DTBP (0.6 mmol), Cs_2CO_3 (0.6 mmol) under air in DCE (1.5 mL) at 80 °C for 6 h.

compatible in the system, and in a similar manner, *P*-isopropyl- and *P*-*n*-butyl-phosphonamides **3da** and **3ea** were successfully isolated in 85% and 80% yields, respectively. *P*-(1-methoxyethyl)- and *P*-(1-chloropropyl)- phosphonamide **3fa** and **3ga** were also obtained in 82 and 78% yields, separately. Surprisingly, cyclo-alkyl groups, which was exemplified by the employment of *P*-phenyl-*P*-cyclohexylmethyl phosphonamide (**1h**) in the transformation, forming the desired phenylated product **3ha** in 82% yield. Then, the activities of arylated alkyl groups, for example, phenylethyl group was well tolerated in the protocol and the corresponding phosphonamide **3ia** was readily arylated by the $Cu(OAc)_2$-mediated system, in 83% yield. Other unsaturated substituents were also compatible in the transformation and *N*,*P*-diphenyl phosphonamidic-(*E*)-cinnamyl ester

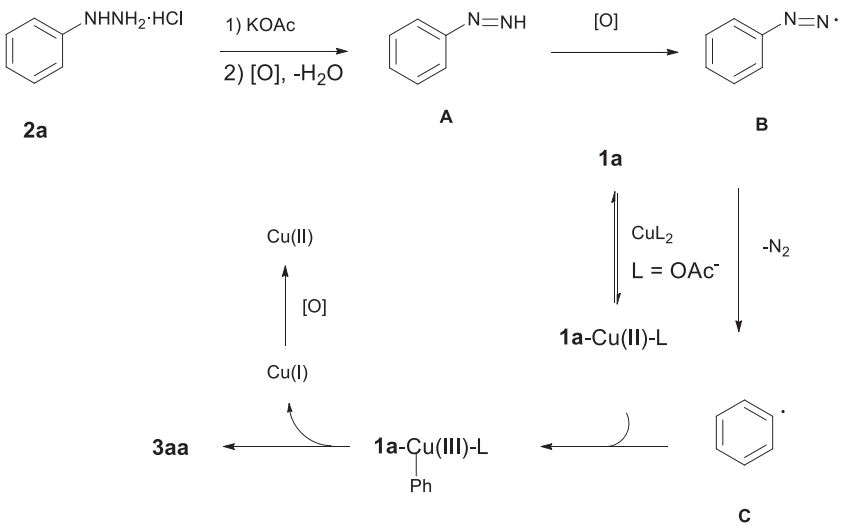
(**3ja**) and phosphonamidic-2-butynyl ester (**3ka**) were isolated with good efficiency, in up to 88% yields. Benzyl groups decorated phosphonamides, such as *P*-benzyl- (**1l**), *P*-3-fluorobenzyl- (**1m**), *P*-2-chlorobenzyl- (**1n**), *P*-4-chlorobenzyl- (**1o**) and *P*-2-bromobenzyl- (**1p**) were furnished smoothly in yields from 75 to 89%. Worthy of note that the positions of the halo atoms on the benzyl groups did not affect the efficiency of the transformation significantly, and comparison of the formation of **3na** and **3pa**, in 79 and 81% yields, respectively. Beyond our expectations, *N*-(*p*-tolyl)-*P*-(4-morpholinyl)-*P*-phenyl phosphinamide (**3qa**) was gained in moderate yield, up to 48%.

Successively, the examination of the substrate scope was logically extended to the arylhydrazines hydrochlorides, as shown in Table 3. Different tolylhydrazine hydrochloride salts were firstly tested in the system. Worthy of note, the positions of the methyl groups did not affect the efficiency of the transformation significantly, and the corresponding products **3ab**–**3ad** were isolated in yields from 82 to 90%. Similarly, ethyl group substituted arylhydrazine hydrochlorides, were also subjected to the optimal reaction conditions and the desired arylated products were furnished in 86 and 88% yields, respectively. Electron sufficient phenyl groups, which possessed a methoxy group on the either the *meta*- or the *para*- positions, offering the best performance in the arylation protocol and methoxyphenyl decorated phosphoryl amides were successfully produced in excellent yields, up to 93%. Halo atoms on the *para*-positions of the arylhydrazine hydrochlorides, such as 4-fluorophenylhydrazine hydrochloride (**2i**), 4-chlorophenylhydrazine hydrochloride (**2j**), 4-bromophenylhydrazine hydrochloride (**2k**) gave the arylated phosphoryl amides in a range of 77–81% yields, lower than that alkyl and alkoxyl groups offered in the system. Logically, electron-deficient phenylhydrazine hydrochlorides gave inferior effects to the catalytic transformation and *para*-nitrophenylhydrazine hydrochloride (**2l**) and *para*-trifluoromethylphenylhydrazine hydrochloride (**2m**) arylated the phosphinamide successfully in the Cu(II)-mediated transformation, allowing the formation of the corresponding *N*-aryl phosphinamides in 56 and 82% yields, respectively. Finally, polyarylhydrazine hydrochloride, which was exemplified by 2-naphthylhydrazine hydrochloride (**2n**), showed good compatibility in the system and *N*-(2-naphthyl) phosphinamide (**3an**) was isolated successfully in 80% yield.

To take a deeper insight into the mechanism of the arylation protocol, control reaction was conducted in the presence of different radical scavengers, as shown in Scheme 1. For example, addition of TEMPO or BHT was conducted to the reaction mixture under the standard conditions. However, no free radical-TEMPO or BHT adducts were detected or isolated, and the yield of the denitrogenative transformation was dramatically depressed and only trace of the desired product was observed by TLC analysis. The results indicated the reaction might take place in the free radical pathway.



Scheme 1. Control reactions with additions of TEMPO or BHT.



Scheme 2. Proposed mechanism of the denitrogenative arylation protocol.

Successively, analysis on EPR (Electron Paramagnetic Resonance)[17] was carried out to obtain more information on the possible free-radical transformation, as exemplified by the reaction between **1a** and **2a**. To our satisfactory, **2a** gave expected signal in the presence of $Cu(OAc)_2$ (0.1 equiv.), Cs_2CO_3 (2.0 equiv.) and DTBP (2.0 equiv.) in DCE at 80 °C, giving a g_e factor as 2.0024 (in a range of 2.0020–2.0025 for aryl radicals), while **1a** offered no any signal under the same conditions.

Thus, based on the EPR analysis and literature explorations, the illation would easily come into our mind that the denitrogenative arylation protocol likely took place via an aryl radical intermediate, which was generated *in situ* from arylhydrazine hydrochloride under the oxidative surroundings. As shown in Scheme 2, the possible mechanism of the transformation was proposed based on the literature explorations and results of above-mentioned experiments. Starting with the treatment of phenylhydrazine hydrochloride with the base (Cs_2CO_3), corresponding phenylhydrazine was formed, which could offer another key intermediate phenyldiazene (**A**) upon the interaction with oxidant DTBP, along with the formation of a molecular of H_2O. With the assistance of the oxidant, the key intermediate **A** was transformed quickly into phenyldiazene radical **B**. Along the emission of a dinitrogen molecule, formation of phenyl radical particle **C** was realized and successive coupling with the Cu(II)-phosphorylamide complex took place easily to afford the desired product **3aa** and Cu(I) species. Then, the Cu(I) species was reoxidized in the presence of DTBP for the next catalytic circle.

Conclusions

In conclusion, we have demonstrated an easy-operated *N*-arylation of phosphorylamides with arylhydrazine hydrochlorides in the presence of $Cu(OAc)_2$ under oxidative conditions. The protocol feathered for generality in the synthesis of *N*-aryl phosphorylamides with high efficiency. And further explorations for the synthetical and clinical applications of the products were still on-going in our laboratory.

Experimental

Typical synthetic procedure of N-aryl phosphoryl amides 3

Under the air atmosphere, a Schlenk tube (35 mL) equipped with a magnetic bar, arylhydrazine hydrochloride **2** (0.6 mol in three portions at the interval of 2 hours) was added to the mixture of phosphoryl amide **1** (0.3 mmol), $Cu(OAc)_2$ (10 mol%), DTBP (0.6 mmol), Cs_2CO_3 (0.6 mmol) in dry DCE (3.0 mL). Then, the reaction mixture was allowed to stir at 80 °C for 6 hours. After the consumption of **1**, as monitored by TLC analysis, the mixture was filtered through a short celite pad and washed with methane (15 mL × 3). The filtrate was concentrated, and the oily crude product was purified by column chromatography using silica gel (200–300 mesh) as stationary phase and a mixture of *n*-hexane and ethyl acetate (ca. 5:1) as eluent to give the corresponding arylated products **3** (R_f=ca.0.3 otherwise noted).

Spectra data of P,P,N-triphenyl phosphorylamide (3aa)

White solid (111.4 mg, 76% yield). m.p. 230–232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (dd, $J = 12.3$, 7.5 Hz, 4H), 7.53 (t, $J = 7.0$ Hz, 2H), 7.49–7.43 (*m*, 4H), 7.14 (*t*, $J = 7.5$ Hz, 2H), 6.98 (d, $J = 7.8$ Hz, 2H), 6.89 (*t*, $J = 7.3$ Hz, 1H), 5.35 (d, $J = 9.2$ Hz, 1H) (ppm). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 140.5$, 132.4 (J_{C-P}=3.0 Hz), 132.1 (J_{C-P}=10.0 Hz), 132.1 (J_{C-P}=129.0 Hz), 129.0 (J_{C-P}=13.0 Hz), 129.4, 122.0, 118.7 (J_{C-P}=7.0 Hz) (ppm). ^{31}P NMR ($CDCl_3$, 160 MHz): $\delta = 18.4$ ppm. IR (in KBr): ν = 3111, 3070, 2960, 2930, 2890, 1600, 1494, 1434, 1408, 1270, 1184, 1100, 1031, 930, 803, 748 (cm^{-1}). MS (ESI): *m/z* (%)=218.1, 294.1 (100). HRMS (ESI): *m/z* calcd for $[M + H]^+$: 294.1042; found: 294.1051.

Full experimental details, ^{1}H and ^{13}C NMR spectra are accessible via the "Supplementary Content" section of this article's webpage.

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References

[1] (a) McCarthy, M.; Guiry, P. J.; Axially Chiral Bidentate Ligands in Asymmetric Catalysis. *Tetrahedron.* **2001**, *57*, 3809–3844. DOI: 10.1016/S0040-4020(01)00087-4.(b) Tang, W.; Zhang, X.; New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029–3070. DOI: 10.1021/cr020049i.(c) Methot, J. L.; Roush, W. R.; Nucleophilic Phosphine Organocatalysis. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. DOI: 10.1002/adsc.200404087.(d) Köhn, M.; Breinbauer, R.; The Staudinger Ligation—a Gift to Chemical Biology. *Angew. Chem. Int. Ed.* **2004**, *43*, 3106–3116. DOI: 10.1002/anie.200401744.(e) Grushin, V. V.; Mixed Phosphine – Phosphine Oxide Ligands. *Chem. Rev.* **2004**, *104*, 1629–1662. DOI: 10.1021/cr030026j.(f) Grabulosa, A.; Granell, J.; Muller, G.; Preparation of Optically Pure P-Stereogenic Trivalent Phosphorus Compounds. *Coord. Chem. Rev.* **2007**, *251*, 25–90. DOI: 10.1016/j.ccr.2006.05.009.(g) Lühr, S.; Holz, J.; Börner,

A.; The Synthesis of Chiral Phosphorus Ligands for Use in Homogeneous Metal Catalysis. *ChemCatChem.* **2011**, *3*, 1708–1730. DOI: 10.1002/cctc.201100164.

[2] (a) K. B. Dillon, F. Mathey, J. F. Nixon. Phosphorus-Carbon Heterocyclic Chemistry. In *Phosphorus: The Carbon Copy*; John Wiley & Sons: Chichester, 1998.(b) Seto, H.; Kuzuyama, T.; Seto, H.; Kuzuyama, T.; Bioactive Natural Products with Carbon–Phosphorus Bonds and Their Biosynthesis. *Nat. Prod. Rep.* **1999**, *16*, 589–596. DOI: 10.1039/a809398i.(c) Peng, A. Y.; Ding, Y. X.; Synthesis of 2H-1,2-Oxaphosphorin 2-Oxides via Ag2CO3-Catalyzed Cyclization of (Z)-2-Alken-4-Ynylphosphonic Monoesters. *Org. Lett.* **2005**, *7*, 3299–3301. DOI: 10.1021/ol051126+.(d) Li, X.; Zhang, D.; Pang, H.; Shen, F.; Fu, H.; Jiang, Y.; Zhao, Y.; Synthesis of a Diverse Series of Phosphacoumarins with Biological Activity. *Org. Lett.* **2005**, *7*, 4919–4922. DOI: 10.1021/ol051871m.(e) Li, B.; Zhou, B.; Lu, H.; Ma, L.; Peng, A.-Y.; Phosphaisocoumarins as a New Class of Potent Inhibitors for Pancreatic Cholesterol Esterase. *Eur. J. Med. Chem.* **2010**, *45*, 1955–1963. DOI: 10.1016/j.ejmech.2010.01.038.(f) Ruda, G. F.; Wong, P. E.; Alibu, V. P.; Norval, S.; Read, K. D.; Barrett, M. P.; Gilbert, I. H.; Aryl Phosphoramidates of 5-Phospho Erythronohydroxamic Acid, a New Class of Potent Trypanocidal Compounds. *J. Med. Chem.* **2010**, *53*, 6071–6078. DOI: 10.1021/jm1004754.

[3] (a) Rewcastle, G. W.; Baguley, B. C.; Cain, B. F.; Potential Antitumor Agents. 37. Organophosphorus Derivatives of 9-Anilinoacridine. *J. Med. Chem.* **1982**, *25*, 1231–1235. DOI: 10.1021/jm00352a027.(b) Hrubiec, R. T.; Shyam, K.; Cosby, L. A.; Furubayashi, R.; Sartorelli, A. C.; Synthesis and Evaluation of 2-Substituted 1-Methyl-1-(4-Tolylsulfonyl)Hydrazines as Antineoplastic Agents. *J. Med. Chem.* **1986**, *29*, 1299–1301. DOI: 10.1021/jm00157a033.(c) Sørensen, M. D.; Blaehr, L. K. A.; Christensen, M. K.; Høyer, T.; Latini, S.; Hjarnaa, P.-J. V.; Björkling, F.; Cyclic Phosphinamides and Phosphonamides, Novel Series of Potent Matrix Metalloproteinase Inhibitors with Antitumour Activity. *Bioorg. Med. Chem.* **2003**, *11*, 5461–5484. DOI: 10.1016/j.bmc.2003.09.015.(d) Mucha, A.; Kunert, A.; Grembecka, J.; Pawełczak, M.; Kafarski, P.; A Phosphonamidate Containing Aromatic N-Terminal Amino Group as Inhibitor of Leucine Aminopeptidase—Design, Synthesis and Stability. *Eur. J. Med. Chem.* **2006**, *41*, 768–772. and the citations therein. DOI: 10.1016/j.ejmech.2006.03.023.

[4] (a) Liu, L.; Zhang, A.-A.; Wang, Y.; Zhang, F.; Zuo, Z.; Zhao, W.-X.; Feng, C.-L.; Ma, W.; Asymmetric Synthesis of P-Stereogenic Phosphinic Amides via Pd(0)-Catalyzed Enantioselective Intramolecular C–H Arylation. *Org. Lett.* **2015**, *17*, 2046–2049. DOI: 10.1021/acs.orglett.5b00122.(b) Han, Z. S.; Zhang, L.; Xu, Y.; Sieber, J. D.; Marsini, M. A.; Li, Z.; Reeves, J. T.; Fandrick, K. R.; Patel, N. D.; Desrosiers, J.-N.; et al. Efficient Asymmetric Synthesis of Structurally Diverse P-Stereogenic Phosphinamides for Catalyst Design. *Angew. Chem. Int. Ed.* **2015**, *54*, 5474–5477. DOI: 10.1002/anie.201500350.(c)Wang, L.; Du, Z.; Wu, Q.; Jin, R.; Bian, Z.; Kang, C.; Guo, H.; Ma, X.; Gao, L.; Organocatalytic Enantioselective Synthesis of P -Stereogenic Chiral Oxazaphospholidines. *Eur. J. Org. Chem.* **2016**, *2016*, 2024–2028. DOI: 10.1002/ejoc.201600100.

[5] Stankevič, M.; Bazan, J.; Two-Fold Modification of the Phenyl Substituent in Phenylphosphonic Acid Monoester Monoamides. *J. Org. Chem.* **2012**, *77*, 8244–8256. and citations therein. DOI: 10.1021/jo301526k.

[6] (a) Tang, W.; Ding, Y.-X.; Synthesis of Phosphaisoquinolin-1-Ones by Pd(II)-Catalyzed Cyclization of o -(1-Alkynyl)Phenylphosphonamide Monoesters. *J. Org. Chem.* **2006**, *71*, 8489–8492. DOI: 10.1021/jo0614644.(b) Park, S.; Seo, B.; Shin, S.; Son, J.-Y.; Lee, P. H.; Rhodium-Catalyzed Oxidative Coupling through C–H Activation and Annulation Directed by Phosphonamide and Phosphinamide Groups. *Chem. Commun.* **2013**, *49*, 8671. DOI: 10.1039/c3cc44995e.l.(c) Kim, Y. R.; Cho, S.; Lee, P. H.; Metal-Free Azaphosphaannulation of Phosphonamides through Intramolecular Oxidative C–N Bond Formation. *Org. Lett.* **2014**, *16*, 3098–3101. DOI: 10.1021/ol501207w.(d) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O.; Cobalt-Catalyzed, Aminoquinoline-Directed Functionalization of Phosphinic Amide sp 2 C–H Bonds. *ACS Catal.* **2016**, *6*, 551–554. DOI: 10.1021/acscatal.5b02391.

[7] Li, J.; Zhang, S. L.; Tao, C. Z.; Fu, Y.; Guo, Q. X.; Cu-Catalyzed Arylation of Phosphinic Amide Facilitated by (±)-Trans-Cyclohexane-1,2-Diamine. *Chin. Chem. Lett.* **2007**, *18*, 1033–1036. DOI: 10.1016/j.cclet.2007.07.028.

[8] Zhong, L.; Su, Q.; Xiao, J.; Peng, Z.; Dong, W.; Zhang, Y.; An, D.; Ligand-Free Copper-Catalyzed Arylation of Phosphonamides and Phosphinamides with Aryl Siloxanes. *Asian J. Org. Chem.* **2017**, *6*, 1072–1079. DOI: 10.1002/ajoc.201700110.

[9] Xu, Y.; Su, Q.; Dong, W.; Peng, Z.; An, D.; The Chan-Evans-Lam N-Arylation of Phosphonic/Phosphinic Amides. *Tetrahedron.* **2017**, *73*, 4602–4609. DOI: 10.1016/j.tet.2017.06.028.

[10] (a) Tomakinian, T.; Guillot, R.; Kouklovsky, C.; Vincent, G.; Synthesis of Benzofuro[3,2-b]Indoline Amines via Deamination-Interrupted Fischer Indolization and Their Unexpected Reactivity towards Nucleophiles. *Chem. Commun.* **2016**, *52*, 5443–5446. DOI: 10.1039/C6CC00365F.(b) Wei, W.; Wen, J.; Yang, D.; Guo, M.; Wang, Y.; You, J.; Wang, H.; Direct and Metal-Free Arylsulfonylation of Alkynes with Sulfonylhydrazides for the Construction of 3-Sulfonated Coumarins. *Chem. Commun.* **2015**, *51*, 768–771. DOI: 10.1039/C4CC08117J.(c) Senadi, G. C.; Hu, W. P.; Lu, T. Y.; Garkhedkar, A. M.; Vandavasi, J. K.; Wang, J. J.; I 2 –TBHP-Catalyzed Oxidative Cross-Coupling of N -Sulfonyl Hydrazones and Isocyanides to 5-Aminopyrazoles. *Org. Lett.* **2015**, *17*, 1521–1524. DOI: 10.1021/acs.orglett.5b00398.(d) Wu, Q.; Liu, P.; Pan, Y. M.; Xu, Y. L.; Wang, H. S.; Cu(OTf)2-Catalyzed Three-Component Annulation Reaction: one-Pot Synthesis of 4,5-Dihydropyrazole from Aldehydes, Hydrazines and Alkenes. *RSC Adv.* **2012**, *2*, 10167–10170. DOI: 10.1039/c2ra21106h.(e) Wang, X.; Pan, Y. M.; Huang, X. C.; Mao, Z. Y.; Wang, H. S.; A Novel Methodology for Synthesis of Dihydropyrazole Derivatives as Potential Anticancer Agents. *Org. Biomol. Chem.* **2014**, *12*, 2028–2032. DOI: 10.1039/C3OB42432D.(f) Yao, P.; Pd-Catalyzed Homocoupling of Arylhydrazines via C-N Cleavage under O 2. *Appl. Organometal. Chem.* **2014**, *28*, 194–197. DOI: 10.1002/aoc.3108.

[11] Zhu, M. K.; Zhao, J. F.; Loh, T. P.; Palladium-Catalyzed C–C Bond Formation of Arylhydrazines with Olefins via Carbon–Nitrogen Bond Cleavage. *Org. Lett.* **2011**, *13*, 6308–6311. DOI: 10.1021/ol202862t.

[12] (a) Chen, Y.; Guo, S.; Li, K.; Qu, J.; Yuan, H.; Hua, Q.; Chen, B.; Palladium-Catalyzed Direct Denitrogenative C-3-Arylation of 1 H -Indoles with Arylhydrazines Using Air as the Oxidant. *Adv. Synth. Catal.* **2013**, *355*, 711–715. DOI: 10.1002/adsc.201200997.(b) Peng, Z.; Hu, G.; Qiao, H.; Xu, P.; Gao, Y.; Zhao, Y.; Palladium-Catalyzed Suzuki Cross-Coupling of Arylhydrazines via C–N Bond Cleavage. *J. Org. Chem.* **2014**, *79*, 2733–2738. DOI: 10.1021/jo500026g.(c) Ravi, M.; Chauhan, P.; Kant, R.; Shukla, S. K.; Yadav, P. P.; Transition-Metal-Free C-3 Arylation of Quinoline-4-Ones with Arylhydrazines. *J. Org. Chem.* **2015**, *80*, 5369–5376. DOI: 10.1021/acs.joc.5b00739.(d) Zhang, H.; Wang, C.; Li, Z.; Wang, Z.; Palladium-Catalyzed Denitrogenative Hiyama Cross-Coupling with Arylhydrazines under Air. *Tetrahedron. Lett.* **2015**, *56*, 5371–5376. DOI: 10.1016/j.tetlet.2015.06.095.(e) Taniguchi, T.; Imoto, M.; Takeda, M.; Matsumoto, F.; Nakai, T.; Mihara, M.; Mizuno, T.; Nomoto, A.; Ogawa, A.; Metal-Free C–H Arylation of Aminoheterocycles with Arylhydrazines. *Tetrahedron.* **2016**, *72*, 4132–4140. DOI: 10.1016/j.tet.2016.05.056.(f) Zhang, J. Q.; Cao, J.; Li, W.; Li, S. M.; Li, Y. K.; Wang, J. T.; Tang, L.; Palladium/Copper-Catalyzed Arylation of Alkenes with N′-acyl arylhydrazines. *New J. Chem.* **2017**, *41*, 437–441. DOI: 10.1039/C6NJ03718F.(g) Kocaoğlu, E.; Karaman, M. A.; Tokgöz, H.; Talaz, O.; Transition-Metal Catalyst Free Oxidative Radical Arylation of N -Methylpyrrole. *ACS Omega.* **2017**, *2*, 5000–5004. DOI: 10.1021/acsomega.7b00988.(h) Wang, X.; Huang, Y.; Xu, Y.; Tang, X.; Wu, W.; Jiang, H.; Palladium-Catalyzed Denitrogenative Synthesis of Aryl Ketones from Arylhydrazines and Nitriles Using O2 as Sole Oxidant. *J. Org. Chem.* **2017**, *82*, 2211–2218. . DOI: 10.1021/acs.joc.6b02697.

[13] (a) Xu, W.; Hu, G.; Xu, P.; Gao, Y.; Yin, Y.; Zhao, Y.; Palladium-Catalyzed C–P Cross-Coupling of Arylhydrazines with H-Phosphonates via C–N Bond Cleavage. *Adv. Synth. Catal.* **2014**, *356*, 2948–2954. DOI: 10.1002/adsc.201400155.(b) Chen, S.-Y.; Zeng, R.-S.;

Zou, J.-P.; Asekun, O. T.; Copper-Catalyzed Coupling Reaction of Arylhydrazines and Trialkylphosphites. *J. Org. Chem.* **2014**, *79*, 1449–1453. DOI: 10.1021/jo4022474.

[14] (a) Wang, C.; Zhang, Z.; Tu, Y.; Li, Y.; Wu, J.; Zhao, J.; Palladium-Catalyzed Oxidative Cross-Coupling of Arylhydrazines and Arenethiols with Molecular Oxygen as the Sole Oxidant. *J. Org. Chem.* **2018**, *83*, 2389–2394. DOI: 10.1021/acs.joc.7b02926.(b) Zhao, Z.; Lian, Y.; Zhao, C.; Wang, B.; Palladium-Catalyzed Desulfitative Arylation of Sulfonamides with Sodium Arylsulfinates. *Syn. Commun.* **2018**, *48*, 1436–1442. DOI: 10.1080/00397911.2018.1452262.

[15] Sun, W. B.; Zhang, P. Z.; Jiang, T.; Li, C. K.; An, L. T.; Shoberu, A.; Zou, J. P.; CoPc/Cu(OAc)2-Catalyzed N-Arylation of Amines with Arylhydrazines Leading to N-Aryl Amines. *Tetrahedron.* **2016**, *72*, 6477–6483. DOI: 10.1016/j.tet.2016.08.058.

[16] Dong, W.; Liu, C.; Ma, X.; Zhang, Y.; Peng, Z.; Xie, D.; An, D.; Copper-Catalyzed Denitrogenative N-Arylation of Sulfoximines and Sulfonamides with Arylhydrazines. *Tetrahedron.* **2019**, *75*, 3886–3893. DOI: 10.1016/j.tet.2019.05.039.

[17] Gerson, F.; Huber, W., Eds. Organic Radicals Centered on One, Two, or Three Atoms. In *Electron Spin Resonance Spectroscopy of Organic Radicals*, Wiley-VCH: Weinheim, 2003, pp 185.