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Tandem Oxidative C-H Amination and Iodization to Synthesize Difunctional Atropoisomeric P-Stereogenic Phosphinamides

Yan-Na Ma,[a] Xi Zhang,[a] and Shang-dong Yang*[a][b]

Abstract: **An efficient metal-free tandem intramolecular oxidative C-H amination and iodization of phosphinamide has been performed and a series of novel phosphorus heterocyclic compounds was obtained. This method provides a concise and highly valuable pathway for the synthesis of difunctional atropoisomeric P-stereogenic phosphinamides.**

Selective C-H bond amination has emerged as a powerful tool for the synthesis of complex nitrogen-containing molecules.[1] This methodology allows one to bypass the installation and subsequent removal of classical leaving groups and to reduce wastes and synthetic steps. Therefore, C-H bond amination has attracted a growing amount of attention in the past decades. In general, C-H amination has been propelled by transition metals to activate C-H bonds.[2] Additionally, metal free catalyzed direct oxidative C-H amination by different oxidants has also provide a concise and efficient pathway.[3] Because chiral amine compounds are powerful pharmacophore for defining new pharmaceutical and pivotal synthon for synthesis of chiral alkaloids and *N*-hybridize ligands.[4] Thus, the exploration and establishment of the novel and high effective methods of the asymmetric C-H amination become a challenging task.

Chiral aminophosphines are versatile building blocks that have been employed in modular syntheses of chiral ligands and organocatalysts.[5] Especially these ligands possessing both axial chirality and a P-stereogenic were proven very efficient and stereochemically stable.[6] However, catalytic asymmetric methods for highly enantioselective synthesis of P-stereogenic phosphines, especially the methods for P-stereogenic phosphorus heterocycles, remain very rare.[7] As an alternative strategy, selective asymmetric C-H activation using an atom-efficient phosphamide precurso has become an increasingly common topic for research. Recently Duan and Liu groups almost simultaneously report a Pd-catalyze enantioselective intramolecular C-H arylation to synthesize chira phosphinic amide (A, Scheme 1).[8] Moreover, subsequent studie by Han and coworkers demonstrated the enantioselectiv synthesis of P-stereogenic phosphinamides through Pd-catalyze desymmetric ortho C-H arylation of diarylphosphinamides wit boronic acids (B, Scheme 1).[9] Chang and coworkers hav developed the direct C-H amidation of arylphosphoryl compound by using an Ir^{III} catalyst system under mild conditions.[10] Ver recently, Cramer group discloses an enantioselective synthesis c cyclic phosphinamides with a P-stereogenic phosphorus (V) ator catalyzed by a $CpxRh^{III}$ complex (C, Scheme 1).[11] Thes significant advances towards chiral phosphinamides have bee driven by the transition metals to activate C-H bonds. To the bes of our knowledge, no example involves in preparation of chira phosphinamides via the metal free oxidative asymmetric C-I amination, which avoids the employment of expensive transitio metal and chiral ligand, and promises a potential for large-scal preparations. If the key challenge of overcoming the conflic between enantioselectivity with metal free C-H functionalizatio could be addressed, such sequence would offer great advantages In the last year, by using the chiral phosphrous oxide as directin group, we have succeeded to achieve the Pd(II)-catalyze asymmetric C-H activation via dynamic kinetic resolution.[12] W have questioned whether chiral phosphinamide and metal fre direct oxidative C-H amination might be successfully combined t create a new pattern for the synthesis of compounds containin both axial chirality and a P-stereogenic in large-scale throug dynamic kinetic resolution or desymmetrisation proccess (D Scheme 1).

With this design principles in mind, we have firstl synthesized the chiral phosphinic amide **1a** through our previou Pd-catalyzed cascade asymmetric cross-coupling reaction an further reacted with lithium methylamide in high yield wit excellent enantioselectivity,[13] and wished to achieve th asymmetric synthesis of atropoisomeric azaphosphaannulation compounds under metal free reaction conditions. We initially studied the asymmetric metal free C-H amination reaction of **1a** with different oxidants in CH_3CN (Table 1, entries 1-5). To our delighted, when NIS was used, the desired azaphosphaannulated product **2a** with iodization at 5' position was obtained in 31% yield with good diastereoselectivity through desymmetrisation process. In many metal free oxidative C-H amination reactions, hypervalent iodine(III) species possessing an iodine-nitrogen bond are efficient reagents in oxidative C-H amination of nonprefunctionalized arenes and heteroarenes.[14] Encouraged by

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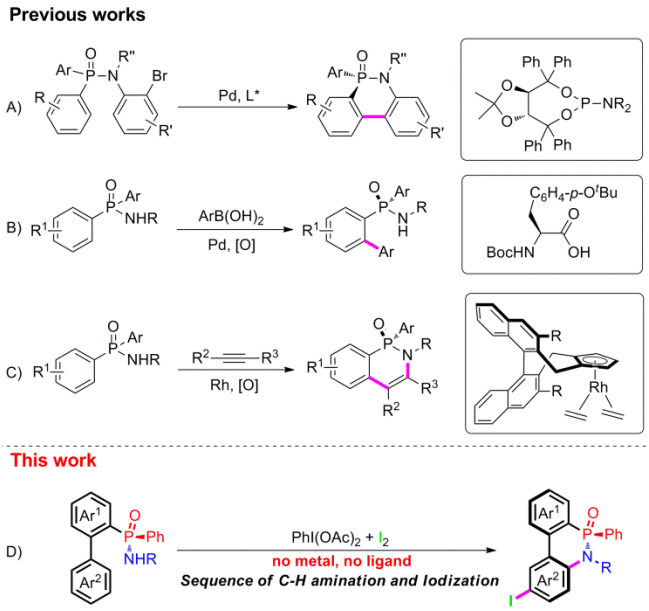
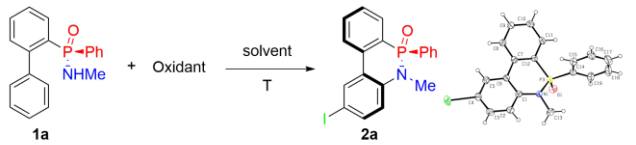


Scheme 1. Various Strategies for Synthesis of Chiral Phosphinamides

this result, we further optimized the reaction conditions and screened other hypervalent iodine catalytic system. When we used $PhI(OAc)_2$+I_2 to prompt this reaction, the desired product was improved to 75% yield with good diastereoselectivity (entry 6). Based on this result, the influence of other oxidants was also examined, BPO, *m*CPBA, $K_2S_2O_8$, $(NH_4)_2S_2O_8$ could also propelled the reaction and the desired product was obtained in different yields with good dr value with I_2 as the iodine sources (entries 7-11). Next, we have evaluated other iodine sources,

Table 1. Reaction Conditions Screening.[a]



1a 2a

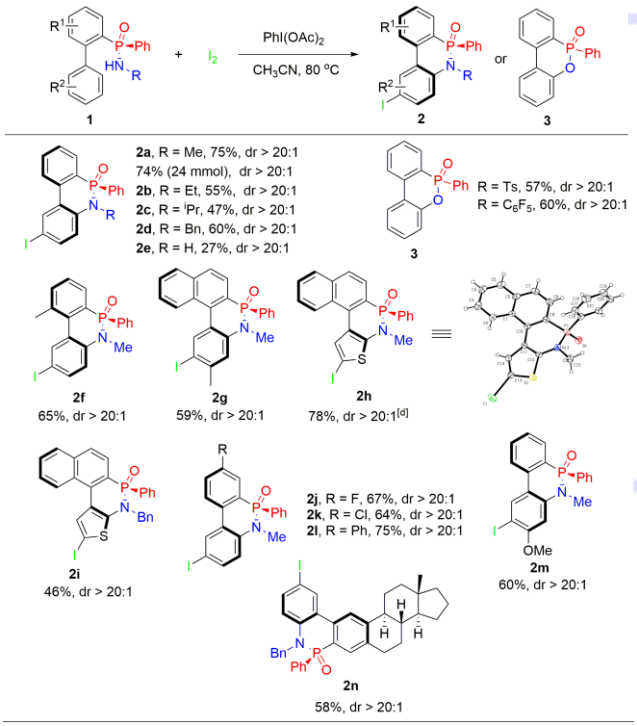
entry	oxidant (2 eq)	additive (2 eq)	solvent	result[b,c]
1	$PhI(OAc)_2$		CH_3CN	n.r.
2	$PhI(TFA)_2$		CH_3CN	n.r.
3	$K_2S_2O_8$		CH_3CN	n.r.
4	NIS		CH_3CN	31%, dr > 20:1
5	AgOAc		CH_3CN	n.r.
6	$PhI(OAc)_2$	I_2	CH_3CN	75%, dr > 20:1
7	$PhI(TFA)_2$	I_2	CH_3CN	trace
8[d]	BPO	I_2	CH_3CN	73%, dr > 20:1
9	*m*CPBA	I_2	CH_3CN	48%, dr > 20:1
10	$K_2S_2O_8$	I_2	CH_3CN	21%, dr > 20:1
11	$(NH_4)_2S_2O_8$	I_2	CH_3CN	19%, dr > 20:1
12	$PhI(OAc)_2$	KI	CH_3CN	n.r.
13	$PhI(OAc)_2$	NaI	CH_3CN	n.r.
14	$PhI(OAc)_2$	NH_4I	CH_3CN	n.r.
15	$PhI(OAc)_2$	Bu_4NI	CH_3CN	n.r.
16	$PhI(OAc)_2$	I_2	DMF	75%, dr > 20:1
17	$PhI(OAc)_2$	I_2	toluene	75%, dr > 20:1
18	$PhI(OAc)_2$	I_2	DME	75%, dr > 20:1
19	$PhI(OAc)_2$	I_2	dioxane	59%, dr > 20:1
20	$PhI(OAc)_2$	I_2	DCE	71%, dr > 20:1
21	$PhI(OAc)_2$	I_2	CH_3NO_2	71%, dr > 20:1

[a] Reaction conditions: 0.2 mmol of **1a**, 0.4 mmol of oxidants and 0.4 mmol iodine sources in different solvents (2.0 mL) under air atmosphere. [b] Isolated yields. [c] The values of *p*/*o* and dr were determined by ^{1}H NMR and ^{31}P NMR. [d] BPO = Benzoperoxide.

while no product was obtained when KI, NaI, NH_4NI, Bu_4NI were used (entries 12-15). Results of solvents screening indicated that the reaction could proceed smoothly in almost all of the solvents and showed good reactivity (entries 16-21). Finally, we selected CH_3CN as the solvent which exhibited the best reactivity when other substrates were used and the optimized reaction conditions are as follows: I_2 as the iodine source, $PhI(OAc)_2$ as the oxidant in CH_3CN at 80 °C under air atmosphere.

With the optimized reaction conditions in hand, we firstly examined the *N*-protecting group. When *N*-alkyl or *N*-benzyl phosphinic amides were used, the desired products were obtained in good yields with excellent diastereoselectivities (Table 2, **2a-2d**). Meanwhile the free phosphinic amide can also been used into this reaction and the desired product was obtained in 27% yiel with good selectivity (**2e**). While when the protecting group wa electronic-withdrawing tosyl or pentafluorobenzyl, we only gc the racemic substrates. When these two substrates were used, w obtained the intramolecular C-H hydroxylation product and th iodine atom didn't been introduced (**3**). Base on these result different substituted phosphinic amides were screened unde metal free reaction conditions to demonstrate the scope an limitations of this reaction. For the 2′-substituted biphenyl-2-y phosphinic amides, we want to achieve the synthesis of axiall chiral azaphosphaannulated product through dynamic kineti resolution process, while we didn't obtain the pure product whic illustrated that the steric effect impacted the reactivity. So w trained our attention to the asymmetric C-H amination throug desymmetrisation process. For our reaction, the dynamic kineti resolution mainly toward the 2′-substituted biphenyl-2-y phosphinic amides, which can easily take racemization under th reaction conditions. The desymmetrisation process mainly towar the substrates with no substituents at the 2‘ position and the

Table 2. Scope of the Metal Free C-H Amination.[a]



[a] Reaction conditions: 0.5 mmol of **1**, 1.0 mmol of $PhI(OAc)_2$ and 1.0 mmol I_2 in different CH_3CN (5.0 mL) under air atmosphere. [b] Isolated yields. [c] The values of *p*/*o* and dr were determined by ^{1}H NMR and ^{31}P NMR. [d] 0.5 mmol **1h** and 1.25 mmol NIS in DCM at 70 °C.

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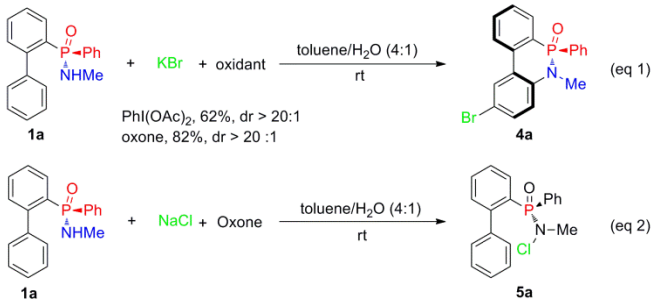
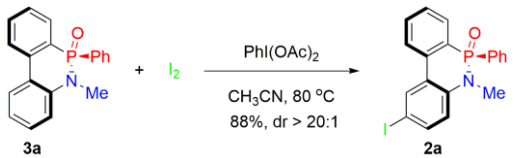
symmetry will be broken when the C-H amination occurred. To our delight, the 6′-substituented substrates showed good reactivity and diastereoselectivity through desymmetrisation process (**2f** and **2g**). When the phenyl group was replaced by thiophene, the corresponding poly heterocycle product **2h** and **2i** was obtained with good yield and excellent selectivity which was confirmed by single-crystal *X*-ray crystallography (**2h**). For the substrates with the substituted group lies on the *meta*-position of the phosphinic amide group, good results were obtained (**2j-2l**). Moreover, the 4'-substituted phosphinic amides also exhibited good activity accompanying with excellent selectivities (**2g** and **2m**). Finally, we also extended this method to modify estrone and afforded chiral atropoisomeric product **2n** in moderate yield with high diastereoselectivity, which is an important steroid.

In light of the above results, we next changed the iodine sources to other halogenation reagents and anticipated to achieve the bromination and chlorination. Firstly, KBr was used instead of I_2 to the bromination reaction with **1a** as the model substrate. As we expected, the desired bromination product **4a** was obtained in 62% yield with excellent selectivity when toluene/H_2O (4:1) was used as the solvent (eq 1, Scheme 2). A higher yield of 82% was gained if the $PhI(OAc)_2$ was changed to oxone. While when NaCl was used, we only obtained the *N*-chlorination compound **5a** as the *N*-Cl bond was relatively stable which indicated that the N-X compounds were the reaction intermediate (eq 2, Scheme 2).



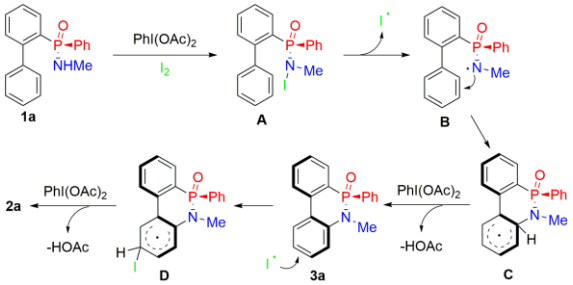
Scheme 2. Intramolecular Metal Free C-H Amination Bromination.

Next, the reaction mechanism was studied, when free radical scavengers TEMPO or BHT were added to the reaction mixture, no product was detected. So we proposed that the reaction went through a radical process. Meanwhile the intramolecular amination compound **3a** was subjected to the reaction conditions and the desired iodization product **2a** was obtained in 88% yield (Scheme 3). So we suggested that **3a** was initially formed as an intermediate.



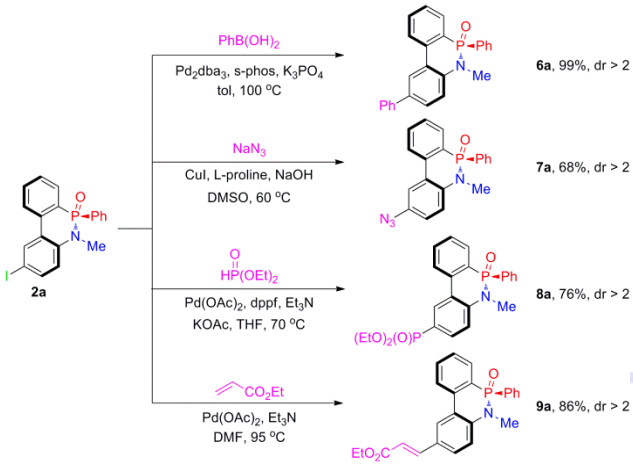
Scheme 3. Study of Mechanism.

On the basis of these results and previous reports,[15] a plausible mechanism is shown in Scheme 4. Firstly, the N-I bond is formed under the effect of $Ph(OAc)_2$ and I_2 which is very unstable, and easily undergoes thermal homolytic cleavage to generate the phosphonamidyl radical **B**. Then the radical is trapped by the arene to give intermediate **C**. Rearomatization of **C** under the $PhI(OAc)_2$ to provide intermediate **3a**. As the intermediate **3a** is an electron-rich arene which can immediately occur iodization under the reaction conditions to give the desired product **2a**.



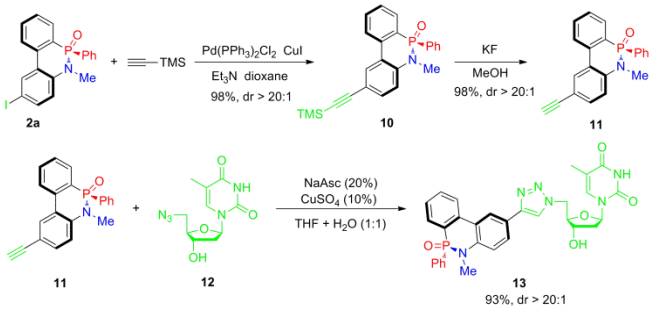
Scheme 4. A Plausible Mechanism.

To demonstrate the versatility of iodinated products in cross coupling reactions, we explored various coupling reactions wit **2a** (Scheme 5). Suzuki-Miyaura coupling with phenylboronic aci afforded triaryl derivative **6a** in quantitative yield. Reacting wit NaN_3 gave the azide compound **7a** in 68% yield.[16] Th phosphinated product **8a** was achieved in 76% yield wit $Pd(OAc)_2$ as the catalyst.[17] Heck coupling with ethyl acrylat gave the vinylation derivative **9a** in 86% yield.[18].



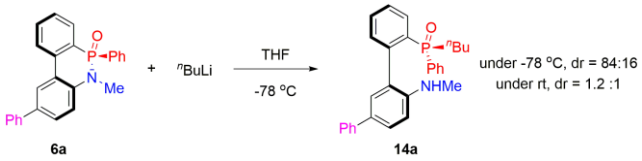
Scheme 5. The Coupling Reactions of **2a**.

The "click chemistry" has recently emerged to become one c the most powerful tools in drug discovery, chemical biology, an proteomic applications. Herein, we also selected the product **2a** a starting material to undergo the click chemistry with 5′-azido-5 deoxythymidine **12** by the Cu(II)-catalyzed 1,3-dipolar azide alkyne cycloaddition (CuAAC) reactions (Scheme 6). Firstly, **2** was installed the terminal alkyne through the Sonogashir coupling reaction and removal of trimethylsilyl to obtain **11** i 96% yield.[19] Following a "click" reaction,[20] compound **11** wa reacted with 5′-azido-5′-deoxythymidine **12** to afford the desire cycloaddition product **13** in 93% yield with excellent dr value.



Scheme 6. Click chemistry with **2a**.

To demonstrate the existence of the axial chirality, the P-N bond cleavage of **6a** was examined using ^{n}BuLi as the nucleophilic reagent.[8a] The dr values of the ring-opening product were 84:16 under -78 ^{o}C and 1.2:1 when the temperature was increased to room temperature (Scheme 7). As the ring-opening compound **14a** only contain two substituents at the axis, so the axial chirality cannot be keeped at room temperature and took racemization. While for the cyclization products, the biaryl axis cannot rotate easily. This maybe attribute to the rigid structure of the 6-membered N,P-heterocycle. So we think our products exist axial chirality.



Scheme 7. The experiment to certify the existence of axial chirality.

In summary, we have described a metal-free radical tandem oxidative C-H amination and iodization reaction under mild reaction conditions. With this method, we achieved the synthesis of azaphosphaannulation compounds with iodization or bromination at 5' position in good yield and selectivity and the iodization product can be further used into various coupling reactions and the "click chemistry" to modify the pharmacologically relevant molecules.

Experimental Section

General procedure for the asymmetric C-H amination and iodization:

A solution of 154 mg (0.5 mmol, 1.0 equiv) **1a**, 322 mg (1.0 mmol, 2.0 equiv) $PhI(OAc)_2$ and 254 mg (1.0 mmol, 2.0 eq) I_2 in 5 mL CH_3CN was stirred at 80 ^{o}C until the substrate **1a** disappeared. Then the reaction mixture was cooled to room temperature and diluted with 15 mL dichloromethane. After 20 mL water was added and the aq. layer was was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography on silica gel to give the pure product **2a** (162 mg, 75%, dr > 20:1, ee = 99%).

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Keywords: Metal free • Oxidative C-H Amination • Iodization • P-Stereogenic Phosphinamides

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Entry for the Table of Contents (Please choose one layout only)

Layout 2:

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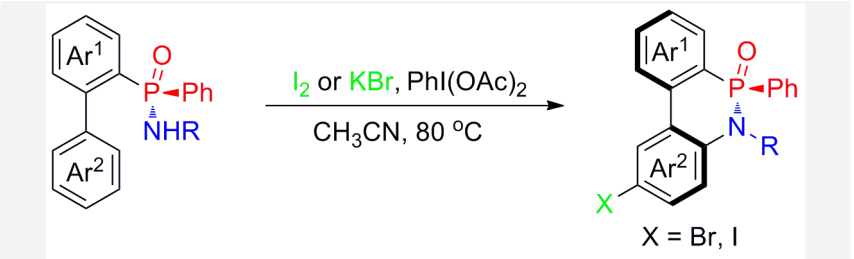
Yan-Na Ma,[a] Xi Zhang,[a] and Shang-dong Yang[a][b]*……..…
Page – Page

Tandem Oxidative C-H Amination and Iodization to Synthesize Difunctional Atropoisomeric P-Stereogenic Phosphinamides



An efficient metal-free tandem intramolecular oxidative C-H amination and iodization of phosphinamide has been performed and a series of novel phosphorus heterocyclic compounds was obtained. This method provides a concise and highly valuable pathway for the synthesis of difunctional atropoisomeric P-stereogenic phosphinamides.