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Communication

Synthesis of polycyclic spiro-fused indolines *via* IBX-mediated cascade cyclization

Zhiguo Zhang[a,*], Xiaoqing Song[a], Guofeng Li[a], Xiang Li[a], Dan Zheng[b], Xuna Zhao[a], Huanran Miao[a], Guisheng Zhang[a,*], Lantao Liu[c]

[a] *Henan Key Laboratory of Organic Functional Molecule and Drug Innovation, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China*

[b] *Quality and Technique Supervision, Inspection and Testing Center of Xuchang City, Xuchang 461000, China*

[c] *The College of Chemistry and Chemical Engineering, Shangqiu Normal University, Shangqiu 476000, China*

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ABSTRACT

We report a 2-iodoxybenzoic acid (IBX)-mediated intarmolecular oxidative spiro-fused tandem cyclization reaction of tryptophan analogs bearing an *N*-arylamides side-chain to rapidly afford polycyclic spiroindolines featuring multiple stereocenters including a quaternary stereocenters under mild reaction conditions. Among them, a novelty azaphosphol idine-containing spiroindoline compound is synthesized for the first time. It may open the door to azaphos pholidine-containing spiroindoline compound of potential interest in synthetic and medicinal chemistry. A plausible mechanism is proposed.

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A large number of complex indole- and indoline-containing alkaloids have been isolated from the natural products [1–4] and have become an area of intensive interest in synthetic organic chemistry [5–9]. Currently, C3-spirocyclization toward polycyclic indoles and indolines has been well studied [10,11]. And C2-spirocyclization of indolines is also occasionally reported although low reactivity at this position [12–15]. In addition, the construction of complex polycyclicindolines involving the C2- and C3-positions completed by a multistep reaction have also been well investigated (Scheme 1a) [16–23]. Cycloaddition reaction is the most commonly used domino process to synthesize complex polycyclic indolines with the C2- and C3-positions participating in the transformation simultaneously (Scheme 1b) [24–31]. Synthesis of polycyclic spiroindolines with oxa- and/or aza-tandem C2- and C3-cyclizations is relatively rare (Scheme 1c) [32–34]. In 1999, Ciufolini *et al.* [34] reported a total synthesis that produced oxa- and aza-polycyclic spiro-fused indolines in the presence of BOP-Cl, Burgess reagent, and $PhI(OAc)_2$ starting from tryptophan analogs and (*S*)-phenylalaninol (Scheme 1d). They achieved five kinds of desired oxazine-containing spiro-fused cyclic structures *via* four steps reactions, but no more than 50% yields were obtained in the final transformation even for adjust the substituents of the tryptophan analogs, lowering the overall yields. However, the highlight of the reaction is the nucleophilic N and O atom on the side chain expressing electrophilicity, and reacted simultaneously with both C2- and C3-position of indoles core in the final oxidative cyclization step. Another worthy-of-noting similar case is Dess – Martin periodinane-mediated cyclization reaction of unsaturated anilides by Nicolaou in 2002 [35]. A plethora of phenoxazine-containing heterocycles are accessible in 0–57% yields by employing γ,δ-unsaturated amides, urethanes, or ureas as substrates *via* an *o*-imidoquinones species oxidized in site from the arylamide moiety. Despite these significant advances, important issues such as high yield, broad applicability, functional group tolerance, and process economy remain to be improved for the existing protocols [24,36,37]. Thus, it remains challenging to efficiently synthesize oxazine-containing polycyclicindolines relevant to biological systems through cascade sequence with the C2- and C3-positions of the indole analogues participate in the transformation simultaneously.

The importance of hypervalent iodine reagents in organic synthesis has been amply demonstrated in recent years [38–44]. Recently, we reported a series of efficient and chemoselective methods to convert various secondary *N*-arylamides to primary amides in high yields with the treatment of organoiodines in mixed solvents of H_2O and HFIP (Scheme 1e, path a) [45,46]. These regiospecific C(aryl)-N bond cleavage reaction without touching

* Corresponding authors.
E-mail addresses: zhangzg@htu.edu.cn (Z. Zhang), zgs6668@yahoo.com (G. Zhang).

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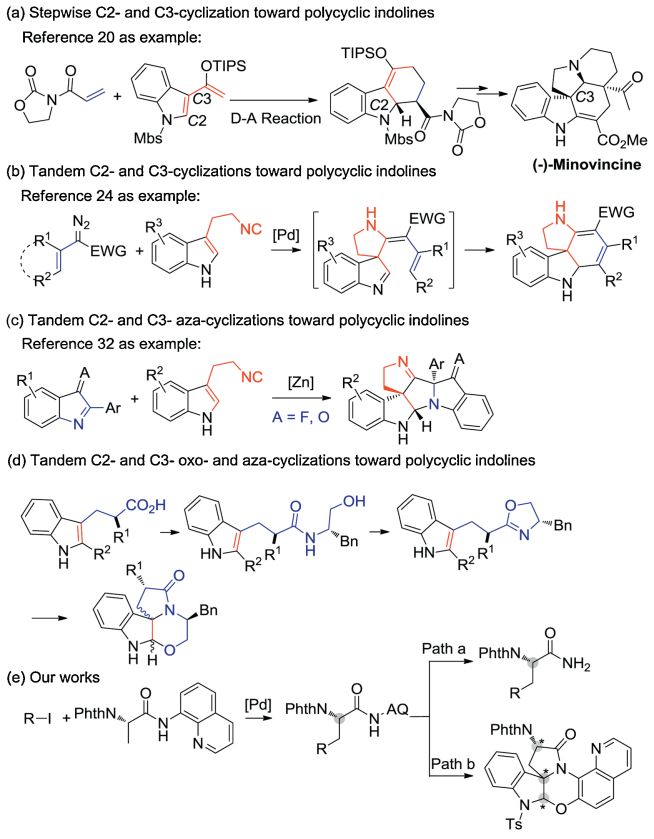
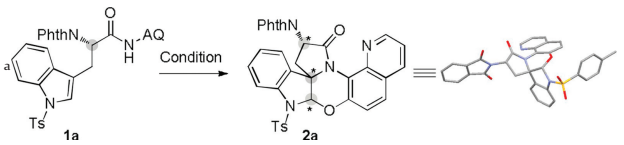


Scheme 1. C2- and C3-cyclization toward polycyclic indolines.

the C(carbonyl)-N bond in the amides, not only further enriches the amino group protecting chemistry, but also provides a way for the facile removal of the aminoquinolines (AQ) directing group under mild conditions. During these research, we found a tryptophan analogs, which was derived from Pd-catalyzed AQ-directed β-C (sp^3)-H indolization of aminoacid derivatives, produced the oxazine-containing polycyclic spiro-fused indolines *via* domino C2- and C3-oxidative cross-coupling reaction, rather than the primary amide *via* C(aryl)-N bond cleavage reaction (Scheme 1e, path b). This competitive observation motivated us to optimize the efficient tandem strategies for construction of structure diverse oxazine-containing complex polycyclicindolines due to their importance for biomolecular and application for pharmaceutical lead discovery [47–49].

As shown in Table 1, tryptophan derivative **1a** was selected as the model substrate [50]. We were pleased to see that the tandem cyclization took place to afford the polycyclic indoline **2a** in 96% yield with good diastereoisomer (dr: *ca.* 10:1) in the presence of 2 equiv. of IBX in mixed solvents of HFIP and H_2O (3:1) at 60 °C for 0.5 h (entry 1). The structure of **2a** was confirmed by X-ray crystallography studies (CCDC: 1890504). Compared with the results performed in the mixed solvents of HFIP and H_2O in the ratio of 1:1, obviously, increasing solubility is helpful in improving the yield of target molecule (entry 2). As expected, the reaction did not occur in H_2O due to the poor solubility of IBX (entry 3). No product was obtained in HFIP either, and a large amount of substrate was recovered (83%) (entry 4). This observation indicated that H_2O is involved in the transformation [35]. Moreover, increasing the ratio of HFIP and H_2O to 5:1 gave a slightly lower yield than that of 3:1 (entry 5). Other organic solvents including 2,2,2-trifluoroethanol (TFE), 2,2,3,3-tetrafluoro-1-propanol (TFP), 2,2,3,3,4,4,5,5-octafluoro-1-pentanol (OFP) mixed with H_2O in the ratio of 3:1 not gave a higher yield (entries 6–8). Reactions

Table 1
Reaction optimization.



Entry	Solvent	Time (h)	Yield of **2a** (%)	Recovered of **1a** (%)
1	HFIP/H_2O (3/1)	0.5	96	0
2	HFIP/H_2O (1/1)	0.5	74	0
3	H_2O	2	NR	91
4	HFIP	2	NR	83
5	HFIP/H_2O (5/1)	1.5	79	0
6	TFE/H_2O (3/1)	16	79	18
7	TFP/H_2O (3/1)	7	71	20
8	OFP/H_2O (3/1)	7	57	28
9	HFIP/H_2O (3/1)	24	77[b]	0
10	HFIP/H_2O (3/1)	4	79[c]	0

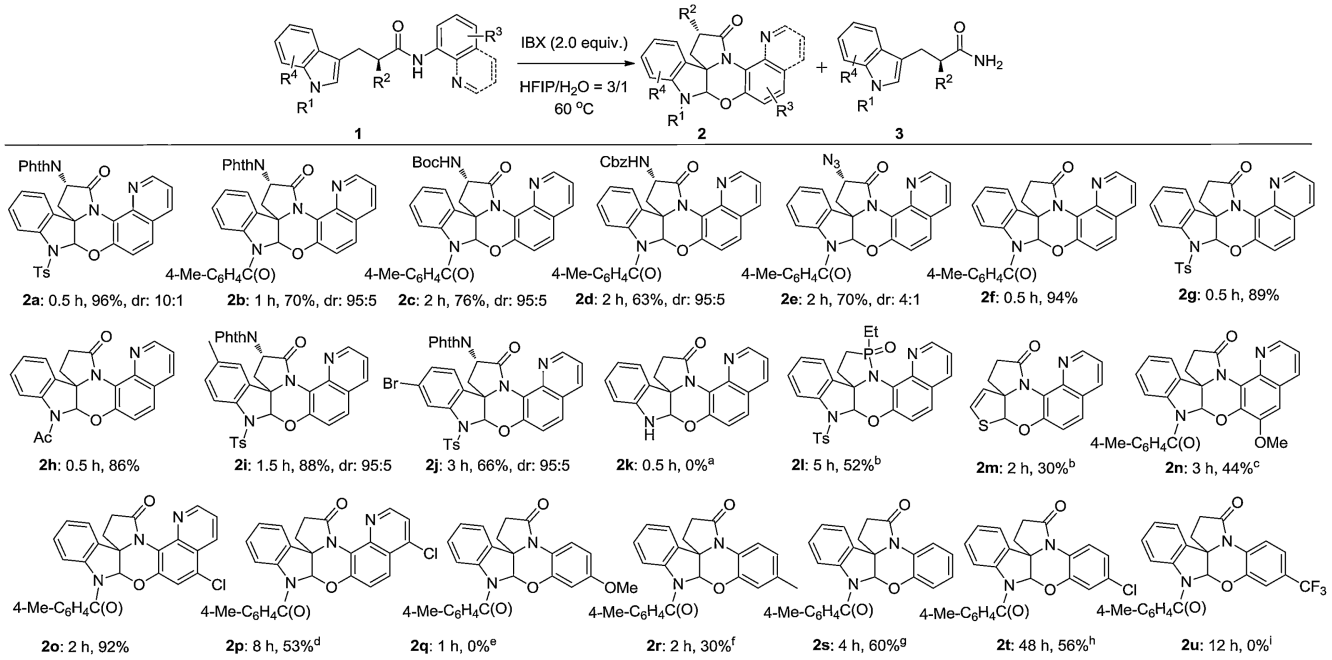
[a] Unless otherwise indicated, reactions were conducted with 0.2 mmol of **1a** and 2.0 equiv. of IBX in 2 mL of solvent at 60 °C, isolated yield.
[b] The reaction was performed at 25 °C.
[c] The reaction was performed at 45 °C.

conducted at 25 °C and 45 °C gave slightly lower yields of **2a**, besides requiring dramatically more reaction time (entries 9 and 10).

With the optimal reaction conditions in hand (Table 1, entry 1), we then evaluated the scope of tryptophan analogs [51–53]. As shown in Scheme 2, Ts-group protected tryptophan derivative **1a** gave **2a** in 96% yield with *ca.* 10:1 dr value. Preliminary exploration on the protecting group on the N atom of indole moiety suggested that the 4-methylbenzoyl protect group also fit for the aminoacid substrates. Compound **2b** worked well to give the primary amide products in good yield. Variants of various amino groups such as BocNH- (**1c**), CbzNH- (**1d**), and N_3- (**1e**) on the side chain were well tolerated and generated corresponding products **2c**, **2d** and **2e** in 76%, 63% and 70% yields, respectively. The experiments of non-tryptophan analogs with a 4-methylbenzoyl protect group for the cyclization were also performed. Compound **1f** gave a slightly higher yield (**2f**: 94%) than that of Ts- and Ac-protected substrates **1g** (**2g**: 89%) and **1h** (**2h**: 86%). To our delight, starting materials **1i** and **1j** with Me- and Br-substitution on the indole moiety also worked well, and gave products **2i** and **2j** in 88% and 66% yields, respectively. However, *N*-unprotected starting material **1k** failed to give desired compound **2k**.

Pleasingly, phosphinamide derivative possessing an amino-quinoline unit (**1l**) [54] also worked, and polycyclicindolines **2l** was synthesized in 52% yield, along with small amounts of unidentified byproducts. To the best of our knowledge, this novelty azaphos-pholidine-contaning spiroindoline compound is synthesized for the first time. This unusual spiroheterocycles open the door to a series of new azaphospholidine-containing spiroindoline com-pound of potential application in synthetic and medicinal chemistry. In addition, this strategy was also amenable to the building of thieno[1,4]oxazino[2,3-*h*]quinolinone structure (**2m**) although a slightly lower yield was obtained.

In addition, we found that the substitution on the quinoline significantly affects the reaction. The reactant (**1n**) with an alkoxyl (MeO-) at the 6-position afforded the desired fused cyclic product **2n** in 44% yield, along with 25% primary amide byproduct **3n**. The reactant bearing a Cl- group located at the 5-position gave the target product **2o** in a yield of 92%. Even the materials with the Cl-group at the 4-position of the AQ moiety can also deliver the product **2p** in moderate yield, along with a small number of



Scheme 2. Extended scope of tryptophan analogs. Isolated yield on 0.2 mmol scale under the standard conditions and the dr value was determined by ^{1}H NMR. [a] Complex mixture. [b] Alone with some unidentified byproduct. [c] 25% of **3n** was obtained. [d] 8% of **3n** was obtained. [e]43% of **3n** was obtained. [f] 36% of **3n** was obtained. [g] 27% of **3n** was obtained. [h] 34% of **1t** was recovered. [i] 93% of **1u** was recovered.

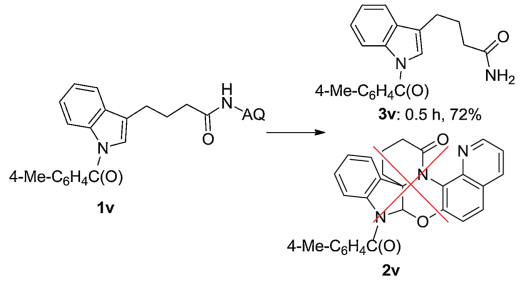
primary amides byproducts **3p**, which was generated by cleavage of the amide.

The scope of other substrates was also evaluated. Reaction of **1q** gave the primary amide **3q** in 43% yield, rather than desired polycyclic product **2q**. Interestingly, compounds **1r**-**1t** afforded oxazine-containing polycyclicindolines **2r**-**2t** in 30%, 60% and 56% yields, along with 36%, 27% and 34% primary amide **3r**-**3t**, respectively. In contrast, functional groups such as CF_3- (**1u**) interfered with the IBX-mediated oxidation-cyclization tandem reaction with starting material largely recovered.

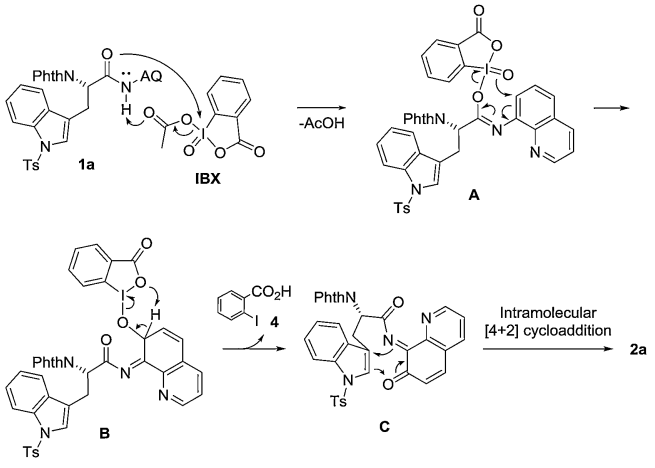
As a further test of the power of this strategy in building of complex molecular diversity, we enlisted the indole analogs with a longer side chain (**1v**) as a substrate [55,56] and tested the formation of the complex polycyclic **2v** (Scheme 3). As a result, no target molecule formed, and only primary amide **3v** was observed (72%) [45].

As outlined in Scheme 4, the IBX-mediated spiro-fused cyclization likely starts with the reaction of amide O atom of **1a** with iodo center of IBX to form iodoimidate **A** by releasing one molecular of AcOH [45,57]. Intramolecular nucleophilic attack of the oxo group on the iodine center of **A** onto the *ortho*-position of AQ group triggers dearomatization of the aniline moiety and the cleavage of the O—I bond to form **B** [35,57]. Deprotonation and cleavage of O—I bond of **B** gives *o*-iminoquinone species **C** and 2-iodobenzoic acid (**4**) [58]. The *o*-imidoquinone **C** then engages the proximate olefin in an inverse electron demand hetero Diels-Alder reaction to furnish the observed polycyclic **2a** [35]. It should be noted that **4** was observed in the transformation as a byproduct.

In summary, an IBX-mediated intarmolecular oxidation spiro-fused cyclization of tryptophan analogs bearing an *N*-arylamides side-chain was developed for rapidly access to polycyclic spiroindolines in moderate to excellent yields under mild conditions. This tandem reaction features high efficiency in the construction of two stereocenters in one step including one quaternary carbon stereocenter harboring 5–8 rings. Among them, a novel azaphosphol-idine-contaning spiroindoline compound is synthesized for the first time. It may open the door to a series of azaphos-pholidine-containing spiroindoline compound of potential interest in synthetic and medicinal chemistry. Mechanistic studies showed oxidation of the aryl group produced an *o*-iminoquinone intermediate which afforded terminal products *via* intramolecular hetero Diels-Alder reaction. Overall, this strategy nicely complements the construction of structure diverse oxazine-



Scheme 3. Attempt for complex molecular.



Scheme 4. Proposed mechanism.

containing complex polycyclicindolines for biomolecular purpose in future.

Declaration of competing interest

We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.11.001.

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