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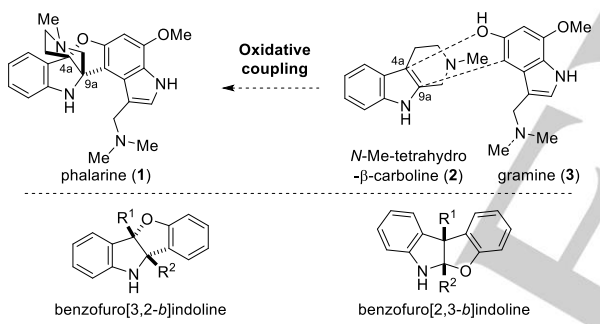
COMMUNICATION

Eight-Step Total Synthesis of Phalarine via Bioinspired Oxidative Coupling of Indole and Phenol

Lei Li, Kuo Yuan, Qianlan Jia, and Yanxing Jia*

Abstract: We report for the first time that the benzofuro[3,2-*b*]indoline framework could be obtained via PIDA-mediated direct oxidative coupling of 2,3-disubstituted-indoles with phenols. Application of this chemistry allows for an eight-step total synthesis of phalarine from commercially available tryptamine.

During the course of an agronomic investigation of the suitability of introducing *Phalaris coerulescens* (blue canary grass) into Australia, Colegate and co-workers isolated and identified a novel furanobisindole alkaloid, named phalarine (**1**) (Scheme 1).[1] Structurally, **1** possesses an unprecedented benzofuro[3,2-*b*]indoline moiety, which has not been found in any other natural product. However, its regioisomeric benzofuro[2,3-*b*]indoline moiety is found in natural products such as diazonamide A[2] and azonazine.[3] Biogenetically, **1** is postulated to arise from the direct oxidative coupling of *N*-Me-tetrahydro-β-carboline (**2**) with 5-hydroxy-7-methoxygramine (**3**) since **2** has been previously isolated from *Phalaris coerulescens*.[1]



Scheme 1. Structure and biogenetic synthesis of phalarine.

The intricate molecular architecture of **1** makes it an attractive target for synthetic chemists.[4-7] In 2007, the group of Danishefsky achieved the first total synthesis of racemic phalarine by using a novel 1,2-rearrangement of azaspiroindolenine to construct the benzofuro[3,2-*b*]indoline architecture.[4b,c] In 2010, they further accomplished the asymmetric synthesis of (-)-phalarine from L-tryptophan and assigned its absolute configuration.[4d] In 2011, Chen's group achieved the formal asymmetric synthesis of phalarine by employing a hypervalent iodine mediated oxidative double cyclization to form benzofuro[3,2-*b*]indoline core.[5]

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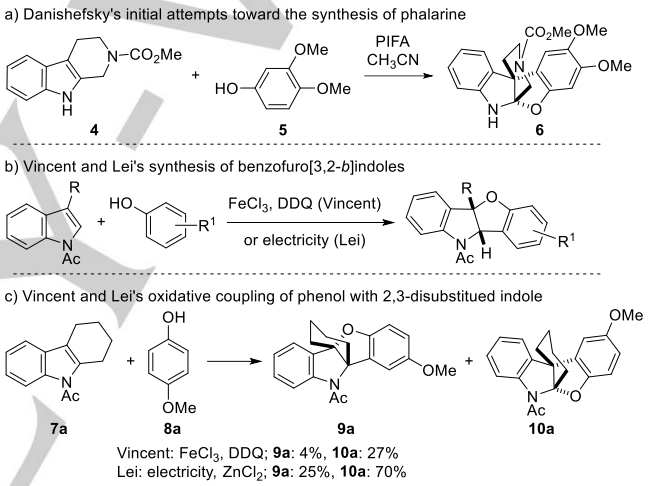
[b] Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Compared with these reported strategies, the direct oxidative coupling of **2** and **3** in a biomimetic manner would be a more straightforward approach to access phalarine. However, it proved to be highly challenging because the 3-position of indole is the most reactive site for electrophilic substitution, direct oxidative coupling of indoles and phenols produced predominantly the unwanted benzofuro[2,3-*b*]indolines.[4a,8-14] In 2006, the group of Danishefsky initially explored oxidative coupling of **4** and phenol **5** as the relevant models to simulate such biogenesis. However, only the undesired benzofuro[2,3-*b*]indoline **6** was obtained (Scheme 2a). [4a]



Scheme 2. a) Danishefsky's initial attempts toward the synthesis of phalarine; b) Vincent and Lei's synthesis of benzofuro[3,2-*b*]indoles by directly oxidative coupling of indoles and phenols; c) Vincent and Lei's oxidative coupling of phenol with 2,3-disubstitued indole.

Notably, the group of Vincent reported the first access to the benzofuro[3,2-*b*]indolines in 2014, by the direct oxidative coupling of 3-substituted *N*-Ac-indoles and phenols in the presence of DDQ and $FeCl_3$, in which the Ac protecting group played a crucial role in reversing the regioselectivity (Scheme 2b).[15] In 2017, Lei and co-workers achieved the same transformation by using electricity.[16] Unfortunately, the regioselectivity was reversed with the use of 2,3-disubstituted *N*-Ac-indoles (Scheme 2c).[15,16] The desired benzofuro[3,2-*b*]indoline was obtained in 25% yield when 2 equiv. of $ZnCl_2$ was added under electrolytic conditions.[16]

As discussed above, the key step to streamline the total synthesis of phalarine is to prepare the desired benzofuro[3,2-*b*]indoline framework via direct oxidative coupling of 2,3-disubstituted indole and phenol. Inspired by the roles of Directed Metalation Groups (DMG) in controlling C2 and C7 regioselectivity during indole functionalization, changing the size of DMGs may lead to the control of C=O bond orientation, due to the different steric demand.[17] Taking PIDA-mediated oxidative coupling of *N*-protected tetrahydrocarbazole with phenol as an

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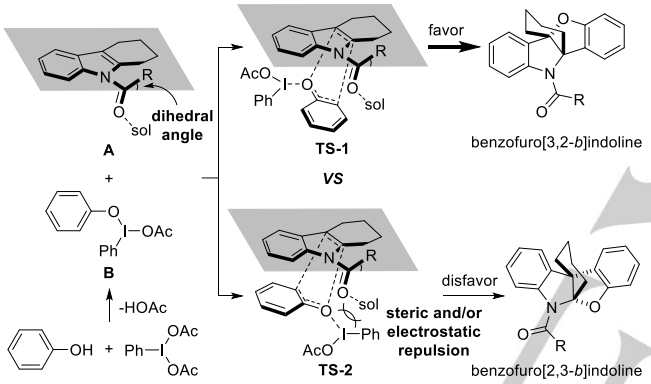
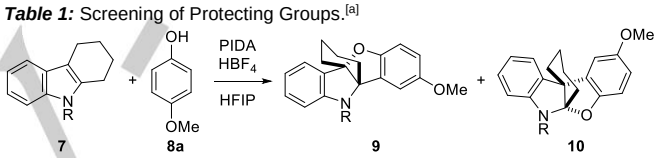
example, we envisioned that the high steric demand of indole *N*-protecting groups may lead to larger dihedral angle between the plane of tetrahydrocarbazole and R-C=O in intermediate **A**, which would result in steric and/or electrostatic repulsion for other attacking groups (Scheme 3).[18] Since the size of the carbonyl group is evidently smaller than the R group, the electrophilic intermediate **B**, formed by ligand exchange between phenol and PIDA, has to approach **A** in the direction of the carbonyl group. Two possible transition states (TS), **TS-1** and **TS-2**, could be considered to lead to two regioisomeric adducts benzofuro[3,2-*b*]indoline and benzofuro[2,3-*b*]indoline, respectively. As the bulkiness of R group is increased, the dihedral angle would be enlarged. Thus, the repulsion between carbonyl group and iodanyl group would be enhanced in **TS-2**, the less hindered **TS-1** should be favored, allowing the formation of predominantly the desired benzofuro[3,2-*b*]indoline. Herein, we have achieved the reversal of regioselectivity in the oxidative coupling of indoles with phenols to access the benzofuro[3,2-*b*]indolines. By utilizing this method, the concise synthesis of phalarine was realized.



Scheme 3. Our strategy to reverse the regioselectivity.

To explore the planned synthetic strategy, the key oxidative coupling between indoles and phenols for the synthesis of benzofuro[3,2-*b*]indolines was investigated first. Since Vincent reported that oxidative coupling of **7a** and **8a** with $FeCl_3$ and DDQ provided **9a** and **10a** in only 4% and 27% yield, respectively (Scheme 2c),[15] we firstly optimized the oxidation conditions to increase the yields of **9a** and **10a** by using **7a** and **8a** as model substrates (for the detailed information see SI). We were delighted to find that the desired **9a** and **10a** could be obtained in 97% with a ratio of 1 to 6.5 under the optimal reaction conditions (PIDA in the presence of HBF_4 in HFIP at RT) (Table 1, entry 1). In fact, the formation of undesired benzofuro[2,3-*b*]indoline **10a** as the major product in 84% yield is very interesting because very few intermolecular oxidative couplings between indoles and phenol leading to benzofuro[2,3-*b*]indolines are known.[9,11,12] The steric and electronic effects of different nitrogen protecting groups (the carbonyl, sulfonyl, and alkoxycarbonyl) were subsequently examined.[19] Therefore, tetrahydrocarbazole with different nitrogen protecting groups were prepared and subjected to react with *p*-methoxyphenol (**8a**) under the optimized condition (Table 1). As anticipated, the nitrogen protecting groups had significant effect on both the regioselectivity and yield. The Cl_3CO-protected substrate **7b** did not give any coupling products (Table 1, entry 2). Gratifyingly, the other substrates with carbonyl groups (**7c**-**7e**) all provided the coupling products in good to excellent yields (Table 1, entries 3-5), in which **7c** and **7d** slightly favoured the formation of the desired benzofuro[3,2-*b*]indolines **9c** and **9d**, respectively, and Bz-protected **7c** provided the desired **9c** with the highest yield. The Ts-protected substrate **7f**, similar to **7a**, gave the undesired **10f** as the major product (Table 1, entry 6). Surprisingly, the Cbz-protected substrate **7g** gave the undesired **10g** as the sole product (Table 1, entry 7). Encouraged by these promising results, the tetrahydrocarbazoles protected by benzoyl groups with different electronic properties (**7h**-**k**) were further prepared and examined (Table 1, entries 8-11). However, all of them (**7h**-**k**) gave similar regioselectivity to that of **7c**. The 1-naphthoyl and 2-naphthoyl-protected **7l** and **7m** were also evaluated, which gave similar regioselectivity and yield with that of **7c** (Table 1, entries 12-13). Thus, we have accomplished a regioselective oxidative coupling between 2,3-substituted indoles and phenols favouring the formation of the benzofuro[3,2-*b*]indolines.

Table 1: Screening of Protecting Groups.[a]



Entry	Compound	R	Yield[b]	Ratio of **9**:**10**
1	**7a**	Ac	97%	1:6.5
2	**7b**	Cl_3CCO	0	-
3	**7c**	**Bz**	**98%**	**1:0.9**
4	**7d**	Piv	53%	1:0.8
5	**7e**	acryloyl	82%	1:1
6	**7f**	Ts	69%	1:3.1
7	**7g**	Cbz	45%	0:1
8	**7h**	*p*-Br-Bz	86%	1:0.9
9	**7i**	*p*-NO_2-Bz	87%	1:0.9
10	**7j**	*p*-MeO-Bz	95%	1:1
11	**7k**	*o*-Me-Bz	86%	1:1.1
12	**7l**	1-naphthoyl	97%	1:0.9
13	**7m**	2-naphthoyl	97%	1:0.9

[a] Reaction conditions: **7** (0.1 mmol), **8a** (0.15 mmol), PIDA (0.15 mmol), HBF_4 (0.02 mmol), HFIP (1 mL), RT, 1 min. [b] Isolated yield was given.

After obtaining the optimized reaction conditions and suitable protecting group of indole, the scope of this reaction was examined with respect to the phenols and indoles (Table 2). A diverse set of phenols are suitable reaction partners (**9n**-**9w**, Table 2). Unexpectedly, all of them gave better regioselectivity than that of *p*-methoxyphenol (**8a**), in which the *p*-phenoxyphenol,

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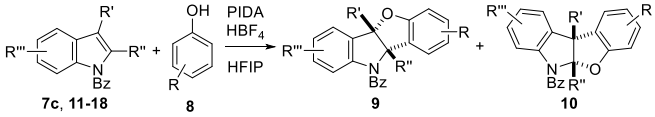
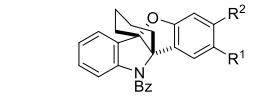
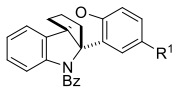
phenol and *p*-NHTFA-phenol gave the corresponding **9p**, **9q** and **9w** as the sole products, respectively. The indoles fused with five and seven-membered rings as well as with different substituents at C2/C3/C5 were then examined. Most of them favoured the formation of the desired benzofuro[3,2-*b*]indolines (**9x**-**9ab** and **9ae**, Table 2). However, 5-substituted tetrahydrocarbazole, 2,3-dimethylindole, and indole gave the undesired regioisomers as major products (**10ac**, **10ad**, **10af**, and **10ag**, Table 2). Most notably, tetrahydro-β-carboline could be used as the reaction partner, providing the desired **9ah** and **9ai** (confirmed by X-ray crystallography)[20] as major products. Overall, the substituents on both phenols and indoles also have the effects on the regioselectivity. Although we could not fully understand how other factors affect the regioselecivity, these results indicated the complexity of the mechanism of this unusual reaction.

Table 2: Substrate scope of the oxidative coupling.[a,b]

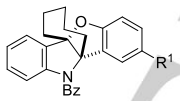




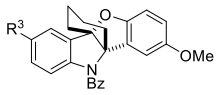
R^1 = OMe, R^2 = H, **9c**: 52%, **10c**: 46%
R^1 = OMe, R^2 = Br, **9n**: 40%, **10n**: 13%
R^1 = OMe, R^2 = F, **9o**: 36%, **10o**: 22%
R^1 = OPh, R^2 = H, **9p**: 47%, **10p**: n.d.[c]
R^1 = H, R^2 = H, **9q**: 25%, **10q**: n.d.
R^1 = NHTs, R^2 = H, **9r**: 87%, **10r**: 8%
R^1 = NHBoc, R^2 = H, **9s**: 65%, **10s**: 29%
R^1 = NHAc, R^2 = H, **9t**: 83%, **10t**: 13%
R^1 = NHAc, R^2 = Cl, **9u**: 64%, **10u**: 17%
R^1 = NHAc, R^2 = F, **9v**: 64%, **10v**: 17%
R^1 = $NHCOCF_3$, R^2 = H, **9w**: 50%, **10w**: n.d.



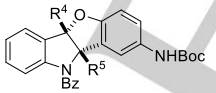
R^1 = NHTs, **9x**: 47%, **10x**: 8%
R^1 = NHBoc, **9y**: 54%, **10y**: 40%
R^1 = NHAc, **9z**: 50%, **10z**: 42%



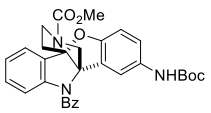
R^1 = NHAc, **9aa**: 59%, **10aa**: 36%
R^1 = NHTs, **9ab**: 49%, **10ab**: 24%



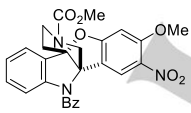
R^3 = Cl, **9ac**: 35%, **10ac**: 53%
R^3 = OMe, **9ad**: 12%, **10ad**: 58%



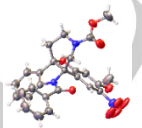
R^4 = Me, R^5 = H, **9ae**: 62%, **10ae**: 8%
R^4 = Me, R^5 = Me, **9af**: 28%, **10af**: 54%
R^4 = H, R^5 = H, **9ag**: n.d., **10ag**: 42%



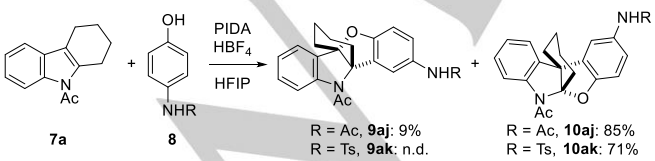
9ah: 25%, **10ah**: n.d.



9ai: 27%, **10ai**: 4%

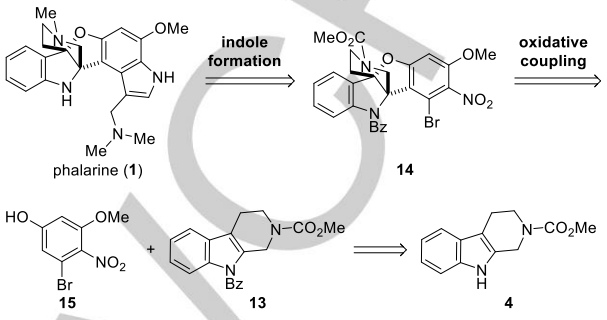


[a] Reaction conditions: **7a** or **11**-**18** (0.1 mmol), **8** (0.15 mmol), PIDA (0.15 mmol), HBF_4 (0.02 mmol), HFIP (1 mL), RT, 1 min. [b] Isolated yield was given. [c] n.d.: not detected.



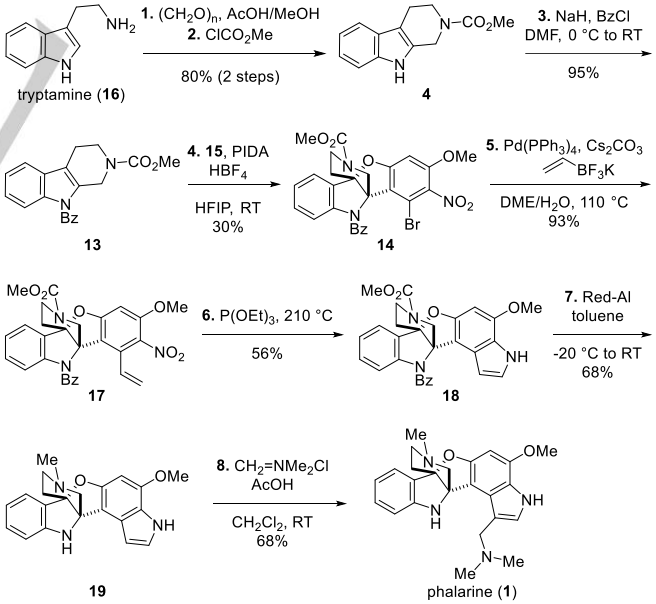
Scheme 4. Reaction of **7a** with *p*-NHAc-phenol and *p*-NHTs-phenol.

As observed above, oxidative coupling of **7c** and different phenols gave the corresponding **9** and **10** with different ratios (**9c** and **9n**-**9w**, Table 2). To further verify that either the *N*-protecting group or the electronic nature of phenols has a significant effect on the regioselectivity, the oxidative coupling of the Ac-protected substrate **7a** with *p*-NHAc-phenol and *p*-NHTs-phenol were performed (Scheme 4). They afforded the undesired **10aj** and **10ak** as the major products, respectively. All our results and the previous reports[15,16] clearly indicated that the *N*-protecting group significantly affected the regioselectivity.



Scheme 5. Retrosynthetic analysis of phalarine.

Having solved the regioselectivity of direct oxidative coupling of indoles and phenols, we turned our attention to the total synthesis of **1**. We envisaged that **1** could be generated from pentacycle **19** by a sequence of indole formation and Mannich-type nucleophilic reaction (Scheme 5). The pentacycle **19** could be rapidly accessed by oxidative coupling of Bz-protected carboline **18** with the known 3-bromo-5-methoxy-4-nitrophenol **20**.[21] Carboline **18** could be prepared by Bz-protection of the known **4**,[4] which was readily prepared from commercially available tryptamine in two steps.



Scheme 6. Total synthesis of phalarine.

We then commenced the total synthesis of phalarine (Scheme 6). The known carboline **4** was prepared in 80% overall yield from commercially available tryptamine (**21**) following a reported procedure.[4] Protection of **4** with Bz group provided **18** in 95% yield. With **18** and **20** in hand, the key oxidative coupling reaction was performed under the optimized condition. The reaction

proceeded smoothly to provide the desired benzofuroindoline **19** as the sole product. Attempts to introduce the two carbon-unit for indolization by Sonogashira coupling of **19** with trimethylsilylacetylene failed. To our delight, Suzuki-Miyaura coupling of **19** with potassium vinyltrifluoroborate afforded nitrostyrene **22** in 93% yield.[22] Cadogan reductive cyclization of **22** with $P(OEt)_3$ at 210 °C successfully gave indole **23** in 56% yield.[23] Attempts to direct reduction of carbamate group to Me and removal of Bz in **23** with $LiAlH_4$ led to the decomposition of **23** at room temperature or 0 °C, but no reaction occurred at -40 °C. After considerable experimentation, we were pleased to find that Red-Al was the best choice and the desired product **24** was obtained in 68% yield.[24] Finally, reaction of **24** with *N,N*-dimethylmethylene iminium chloride in the presence of AcOH provided **1** in 68% yield.[25] The physical data of our synthesized phalarine (**1**) are identical to those reported in the literature.[1,4c] Thus, we achieved the total synthesis of **1** in only eight steps (longest linear sequence) with 5.5% overall yield from commercially available tryptamine.

In summary, we have addressed the challenge of the regioselectivity of the direct oxidative coupling reaction between indoles and phenols to construct the benzofuro[3,2-*b*]indolines. The resulting method enabled us to accomplish the total synthesis of phalarine in only eight steps from commercially available tryptamine. This synthesis represents the shortest pathway for the total synthesis of phalarine to date.

Acknowledgements

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Keywords: alkaloids • total synthesis • oxidative coupling • regioselectivity • natural products

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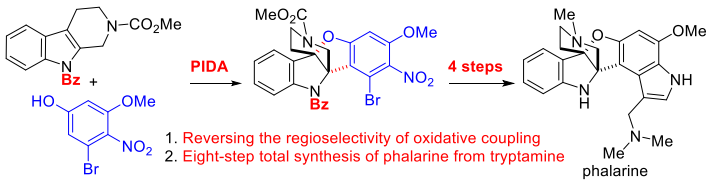

A new method for the synthesis of benzofuro[3,2-*b*]indolines was developed by a PIDA-mediated direct oxidative coupling of 2,3-disubstituted-indoles with phenols. Application of this chemistry allows for an eight-step total synthesis of phalarine from commercially available tryptamine.

*Lei Li, Kuo Yuan, Qianlan Jia, and Yanxing Jia**

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Eight-Step Total Synthesis of Phalarine via Bioinspired Oxidative Coupling of Indole and Phenol