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COMMUNICATION

Synthesis of the Core Structure of Phalarine

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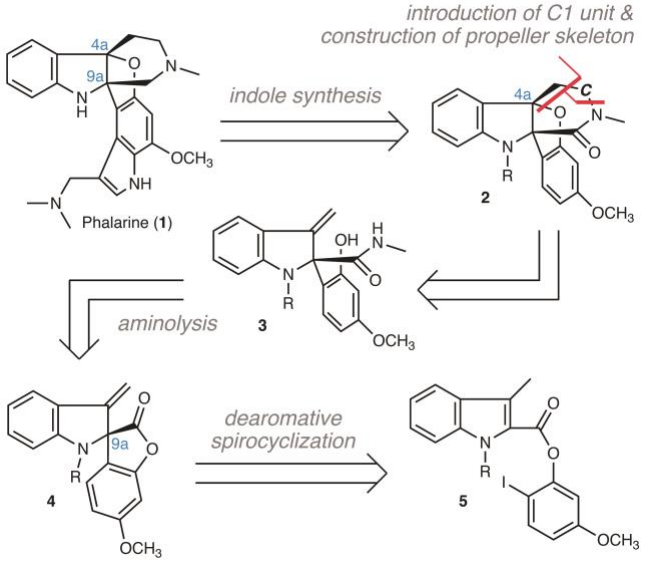
The core skeleton of phalarine was rapidly synthesised through a novel palladium-catalysed dearomative spirocyclisation and a palladium-catalysed Wacker–carbonylative cyclisation cascade. The two key steps allowed for the efficient construction of tricyclic propeller skeleton bearing contiguous tetrasubstituted carbon centres, within 3 steps from a topologically planar precursor.

Efficient access to architecturally complex molecules is a crucial challenge in modern organic synthesis. Especially, synthetic strategy for stereochemically diverse sp^3-rich polycyclic compounds are eagerly desired for devising an ideal tailor-made design of future drugs or advanced molecular materials.[1] Dearomative transformation has been one of the most important strategies for this purpose. It was often applied to the construction of three-dimensional molecular architecture by combining the efficient functionalisation of sp^2-rich planar aromatics and strategic saturations to efficiently deliver cubic sp^3-rich molecules.[2] In particular, transition metal-catalysed dearomatisation reaction has been intensively developed to enable rapid propagation of complexity from simple planar building blocks,[3] and these methodologies have been applied to various target-oriented syntheses.[4] Hereby we report the development of a new catalytic dearomatisation reaction and the application to the concise synthesis of the polycyclic core structure of unique propeller-shaped alkaloid, phalarine.

Phalarine (**1**) was isolated from the perennial grasses *Phalaris coerulescens* in 1999.[5] The structure was characterised by a unique tricyclic propeller core framework fused to a piperidine unit and a multiply functionalised indole moiety through the consecutive tetrasubstituted stereogenic centres at C4a and C9a. Although the biological activity of **1** have not been reported, the characteristic structure fascinated a number of synthetic chemists[6] and their endeavours have culminated in the seminal asymmetric total syntheses of **1** by Danishefsky[7] and Chen.[8] We herein aimed at the development of synthetic methodology to rapidly construct propeller-shaped core framework in racemic manner from achiral sp^2-rich precursor.

Scheme 1 shows our retrosynthetic analysis. Phalarine (**1**) would be derived by the late-stage construction of indole unit from simplified intermediate **2** bearing the core propeller-shaped framework. We have set this molecule without the indole moiety as the primary target of the current synthetic study. Removal of the C1 unit next to nitrogen functionality in **2** and the opening of cyclic ether moiety at C4a leads to amide **3**. This amide, in turn, could be derived by aminolysis of spirocyclic lactone **4** that was retrosynthetically excised at C9a to form the topologically planar aryl indole-2-carboxylate **5** via a pivotal dearomative spirocyclisation.



Scheme 1. Retrosynthetic Analysis

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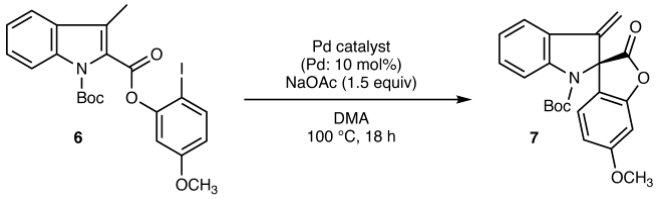
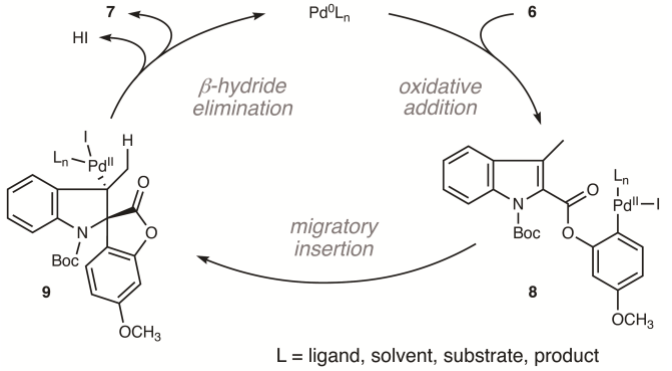
[c] *Electronic Supplementary Information (ESI) available: Experimental procedures and characterisation data. See DOI: 10.1039/x0xx00000x*

Table 1. Optimisation of the Reaction Conditions for Palladium-Catalysed Dearomative Spirocyclisation[a]



Entry	Pd catalyst	Yield (%)[b]
1	$Pd[P(t\text{-}Bu)_3]_2$	<1
2	$P(t\text{-}Bu)_3$ Pd G_2	25
3	$[Pd(IMes)(NQ)]_2$	75
4	$Pd_2(dba)_3{\cdot}CHCl_3$	77

[a]All reactions were carried out under standard reaction conditions: **6** (100 μmol), Pd catalyst (Pd: 10 mol%), NaOAc (1.5 equiv), DMA (1.0 mL), 100 °C, 18 h; [b]Determined by ^{1}H NMR analysis using dimethyl sulfone as an internal standard. NQ = naphthoquinone, dba = dibenzylideneacetone.

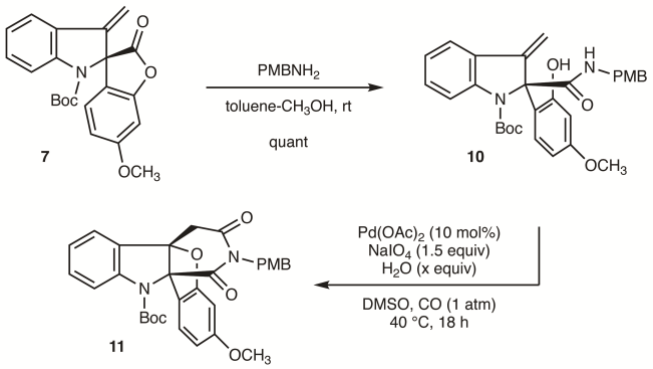


Scheme 2. Plausible Reaction Mechanism for Palladium-catalysed Dearomative Spirocyclisation.

Initially, Heck-type dearomative spirocyclisation from Boc-protected *o*-iodoaryl indole-2-carboxylate (**6**) to **7** was investigated (Table 1). A similar method with the amide linkage, using *o*-bromoaryl indole-2-carboxamide was reported by Jia.[9] The reaction was optimised by fixing our standard conditions as follows: **6** (100 μmol), palladium catalyst (10 mol%), NaOAc (1.5 equiv), DMA (1.0 mL), 100 °C, 18 h. Among the palladium species tested, $Pd[P(t\text{-}Bu)_3]_2$ showed insufficient reactivity (entry 1), while Buchwald's $P(t\text{-}Bu)_3$ Pd G_2 precatalyst[10] gave **7** in 25% yield (entry 2). To our delight, $[Pd(IMes)(NQ)]_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ catalysed the dearomative spirocyclisation and gave **7** in high yield (entry 3,4). Due to almost the same yields for these two conditions, the more easily available $Pd_2(dba)_3{\cdot}CHCl_3$ was employed in the current racemic scale-up synthesis.

Plausible mechanism for this transformation is shown in Scheme 2. Oxidative addition of **6** to palladium(0) species generates intermediate **8** that is then subjected to migratory insertion to form the spirocyclic centre.[9] Following β-hydride elimination from intermediate **9** releases olefin **7** in concomitant with hydrogen iodide to regenerate palladium(0) species.

Table 2. Optimisation of the Amount of Water for Palladium-Catalysed Cyclisation Cascade[a]



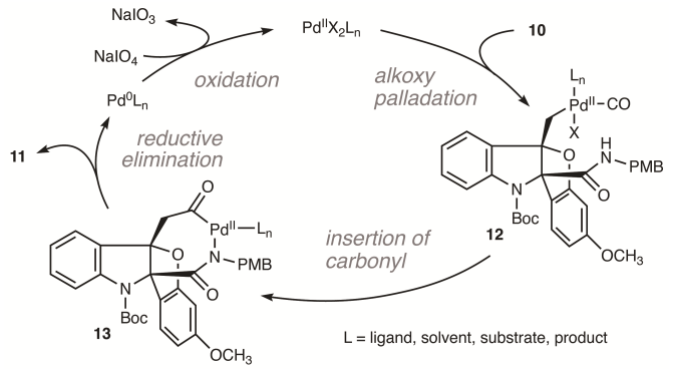
Entry	x (equiv)	Conversion (%)[b]	Yield (%)[b]
1	0	85	36
2	0.10	85	56
3	1.0	>99	81
4	10	85	70
5	100	8	<1

[a]All reactions were carried out under standard reaction conditions: **10** (100 μmol), $Pd(OAc)_2$ (10 mol%), reoxidant (1.5 equiv), DMSO (1.0 mL), CO (1 atm), 40 °C, 18 h; [b]Determined by ^{1}H NMR analysis using dimethyl sulfone as an internal standard. PMB = *p*-methoxybenzyl.

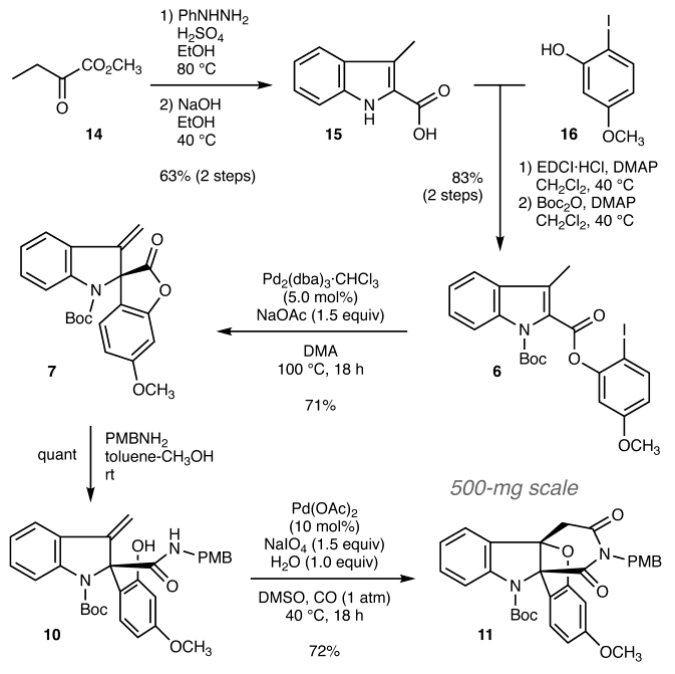
Subsequent transformation toward propeller architecture involved the ring-opening of spirocyclic lactone **7**, followed by sequential introduction of the C1 unit during the cyclisations of two heterocycles (Table 2). This transformation would facilitate the formation of 4a tetrasubstituted carbon centre. We eventually settled this task by Wacker-carbonylative cyclisation cascade on the exocyclic double bond, to afford a β-alkoxy carbonyl moiety.[11] An intriguing point for the current transformation was deemed the use of secondary amide as a terminal nucleophile for the formation of a cyclic imide. Thus, spirocyclic lactone **7** was subjected to the aminolysis with *p*-methoxybenzylamine, quantitatively affording the corresponding amide **10**.[12] Under various conditions, amide **10** were found to release an installed *p*-methoxybenzylamine to regenerate lactone **7**. Fortunately, this undesired cyclisation was suppressed specially in DMSO. The appropriate reoxidant for the reaction from **10** to **11** was eventually confirmed to be $NaIO_4$, a rare reoxidant for palladium catalyst.[13] Thus, the standard reaction conditions were fixed as follows: **10** (100 μmol), $Pd(OAc)_2$ (10 mol%), $NaIO_4$ (1.5 equiv), DMSO (1.0 mL), CO (1 atm), 40 °C, 18 h. Interestingly, the amount of water substantially affected the result of this transformation. Table 2 shows the summary of the effect of water to this reaction. Under strictly dehydrated conditions, low yield of **11** was observed due to the formation of various byproducts (entry 1). In the presence of 0.1 equiv of water, these undesired reaction path was suppressed and moderate yield (56%) of **11** was observed (entry 2). Exocyclic olefin **10** was consumed in the presence of 1.0 equiv of water, exclusively affording **11** in 81% yield (entry 3). The reactivity was reduced in the presence of 10 equiv of water and was sluggish with 100 equiv of water (entries

4, 5). The added water (<1 equiv) possibly inhibited the formation of potent highly oxidising species such as HIO_3-DMSO complex.[14] Instead, excess of water (>10 equiv) would reduce the Lewis acidity of palladium(II) species probably via the formation of inactive $Pd(OH)_2$ or PdO. Collectively, 1.0 equiv of water (entry 3) was determined to be the best additive to this catalytic cascade reaction.

The proposed reaction mechanism (Scheme 3) proceeds through alkoxypalladation on the exocyclic double bond to form alkyl palladium intermediate **12**, to which carbon monoxide would be installed. Resultant carbonyl group was attacked by the nitrogen atom of the amide to lead to palladacycle **13**. Reductive elimination would provide the product **11** in concomitant with the palladium(0) species, that would be oxidised by $NaIO_4$ to regenerate the palladium(II) species to finish the cycle.



Scheme 3. Plausible Reaction Mechanism for Wacker–Carbonylative Cyclisation Cascade.



Scheme 4. Scale-up Synthesis of the Core structure of Phalarine (**1**). EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

Synthesis of the propeller core **11** thus have been established was scaled up to verify its efficiency (Scheme 4). Methyl-2-oxobutyrate (**14**) was converted to 3-methylindole-2-carboxylic acid (**15**) in 63% yield in 2 steps.[15] Condensation of **15** with 2-iodo-5-methoxy phenol (**16**)[16] followed by installation of Boc group gave **6** in 83% yield in 2 steps. Palladium-catalysed dearomative spirocyclisation on **6** efficiently proceeded even on a 5-g scale, and provided **7** in 71% isolated yield. Aminolysis of lactone **7** by *p*-methoxybenzylamine quantitatively gave amide **10**, which was subjected to catalytic Wacker-carbonylative cyclisation cascade using the established $Pd(OAc)_2$-$NaIO_4$-DMSO system with 1.0 equiv of water. These transformations successfully provided **11** with the propeller architecture on a 500-mg scale.

Conclusions

We have efficiently constructed the propeller-shaped core structure of phalarine (**1**). Our synthesis consisted of two unique transformations: 1) a palladium-catalysed dearomatisation transformation of topologically planar indole **6** to indoline **7** with the formation of the tetrasubstituted C9a centre, and 2) a palladium-catalysed Wacker–carbonylative cyclisation cascade on olefin **10** to construct the core structure bearing contiguous C4a–C9a tetrasubstituted carbon centres. These processes eventually provided the 3-step transformation of aryl indole carboxylate **6** to tricyclic propeller framework of **11** on 500 mg scale. Development of a catalytic asymmetric dearomative spirocyclisation and further transformation of **11** to phalarine (**1**) will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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12 Use of methyl amine or ammonia would seem more straightforward for total synthesis of phalarine. The use of these aminolysis products, however, was obstructed by the undesired transformations during Wacker-carbonylative cyclisation cascade or further reductive transformations, thus was not employed in the current research project.

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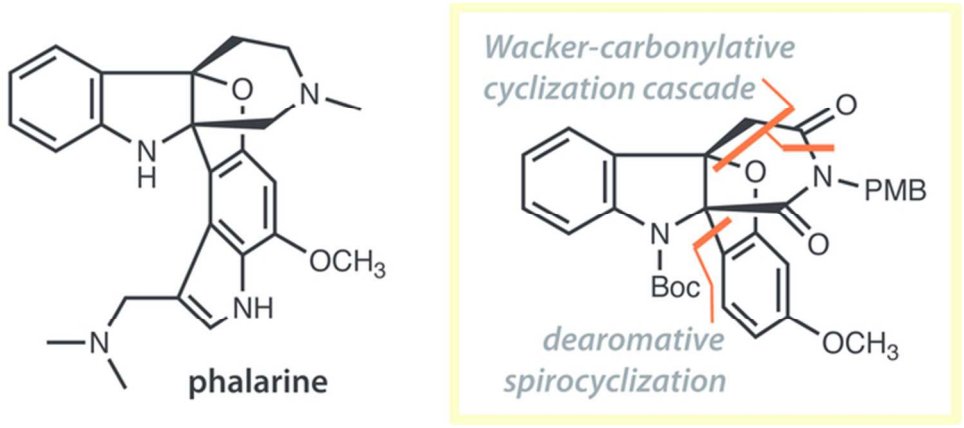
Two new palladium-catalyzed reactions enabled the synthesis of the core structure of phalarine.



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