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A new approach to the bicyclo[3.3.1]nonane framework of huperzine A-like molecules via palladium-catalyzed intramolecular γ-arylation

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In our synthetic studies toward huperzine A, a diastereoselective α′-alkylation of the α-amido-γ-methyl hexenone **4** was realized through a dianion intermediate which significantly enhanced the reactivity. Under the attempted Heck reaction conditions, an unexpected and unprecedented palladium-catalyzed intramolecular γ-arylation of **3** was observed, which generated **18** with bicyclo[3.3.1]nonane framework in satisfactory yield.

huperzine A, bicyclo[3.3.1]nonane, γ-arylation

Lycopodium alkaloid huperzine A (**1**, Figure 1) was isolated by Liu *et al*. from *Huperzia serrata*, a plant with a long history of being used in traditional Chinese medicine, and was identified to be a highly potent, selective and reversible AChE inhibitor [1]. Structurally, huperzine A contains a bicyclo[3.3.1]nonane carbon skeleton featured in lycodine family, which is further fused to a pyridone ring. The intriguing molecular architecture combined with the promise to become an anti-neurodegenerative agent [2] has aroused continuous interest from the synthetic community [3]. As part of our enduring interest in total synthesis of bioactive terpenoids [4], herein we report the results of our asymmetric synthetic studies toward huperzine A.

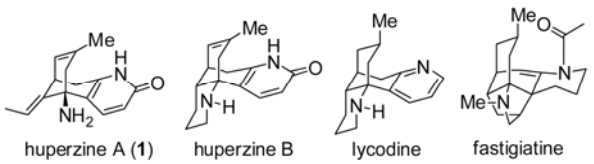
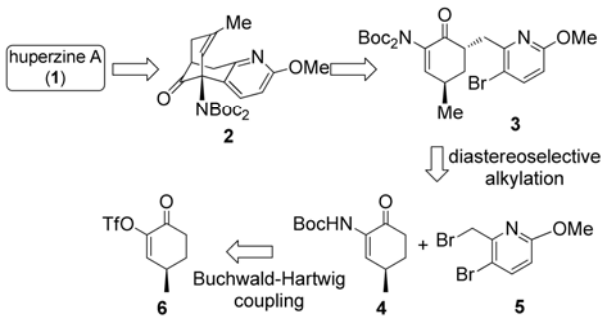


Figure 1 Huperzine A (**1**) and selected lycopodium alkaloids.

As outlined in Scheme 1, the *N*-protected α-aminoketone **2** was selected as the key precursor for the target molecule in the retrosynthetic analysis. A traceless convergent strategy was envisioned to construct the key precursor **2**, which was anticipated to be fashioned from **3** via an intramolecular Heck reaction [5] during which the initial chirality at the methyl group would vanish [6]. Enone **3** was envisaged to stem from α-amidocyclohexenone **4** and bromide **5** in a substrate-controlled diastereoselective alkylation process,



Scheme 1 Retrosynthetic analysis.

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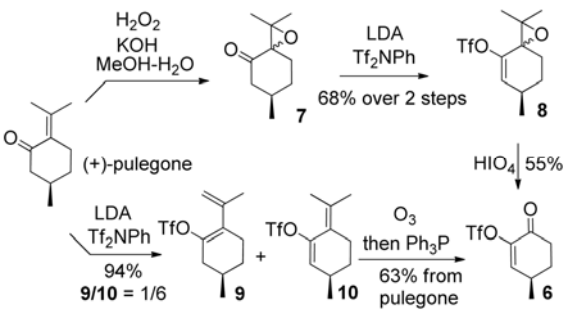
while **4** could further be reduced to **6** by using a coupling reaction to install the amido function. With the amido group to be introduced at an early stage of the synthesis, it was envisioned that the multistep procedure of Curtius rearrangement to fashion an amino group, which had always been employed in all the previous huperzine A synthetic routes, could be avoided.

Based on a chiral-pool strategy, the synthesis of **6** was achieved via two different procedures by employing (+)-pulegone as the starting material (Scheme 2). In the first procedure, pulegone was transformed into **6** in three steps with 37% overall yield. Treating pulegone with aqueous hydrogen peroxide in the presence of potassium hydroxide produced epoxide **7** as a mixture of two isomers [7], the exposure of which to LDA followed by treatment with $PhN(Tf)_2$ afforded triflate **8** in 68% yield over two steps. Subsequent cleavage of the epoxide with periodic acid produced ketone **6** in a moderate yield.

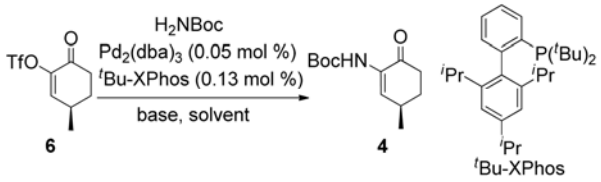
The alternative access to **6** was shorter and more efficient (Scheme 2). Thus, a site-selective deprotonation of pulegone with LDA was followed by treament with the triflating reagent to give the inseparable isomers **9** and **10** in ca. 1:6 ratio as determined by ^{1}H NMR spectroscopy with 94% overall yield. Subsequent selective ozonolytic cleavage of the more electron-rich olefinic double bond in **10** proceeded smoothly to generate **6** in 63% yield over two steps from pulegone. Compound **6** is properly functionalized and holds good potentials to become a versatile chiral building block in natural product synthesis [8].

The Buchwald-Hartwig coupling reaction was next explored to install the amido group [9]. With $Pd_2(dba)_3$ as the catalyst and *t*-Bu-XPhos as the ligand, the base and the solvent were examined briefly (Table 1). The optimal conditions included cesium carbonate as the base and toluene as the solvent, which delivered the coupling product in 83% yield. To the best of our knowledge, this represents a rare example of palladium-catalyzed cross coupling reaction employing a simple α-trifloxy enone as the substrate [10], which provides facile access to α-amido-α,β-unsaturated ketone. Because (−)-pulegone is also commercially available, both enantiomers of the chiral building block **4** could be readily obtained in optically pure form according to the above protocol.



Scheme 2 Synthesis of **6** from (+)-pulegone.

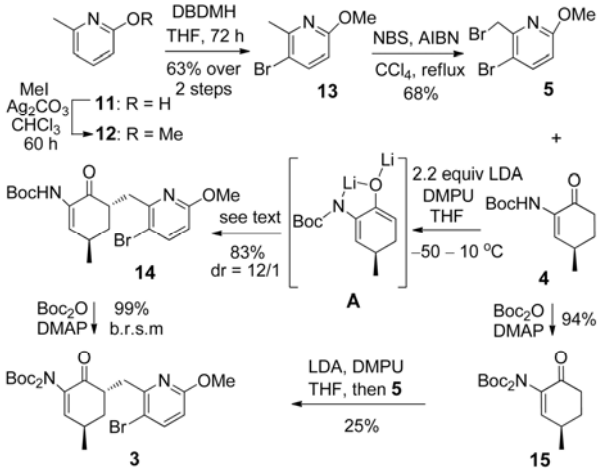
Table 1 Coupling of α-trifloxy enone **6** with $BocNH_2$



Entry	Base	Solvent	Temp., time	Yield (%)
1	K_2CO_3	*t*-BuOH	80 °C, 5 h	43
2	K_2CO_3	toluene	90 °C, 5 h	53
3	Cs_2CO_3	toluene	80 °C, 5 h	83

The bromopyridine **5** was readily prepared in three steps with 43% overall yield according to the known procedures [3i, 11] (Scheme 3). The diastereoselective alkylation reaction between **4** and **5** was then carefully studied with LDA as the base. After tremendous experimentations, it was found that the equivalent of the base was crucial for achieving satisfactory diastereoselectivity. Under the optimal conditions, **4** was exposed to 2.2 equiv LDA at −50 °C to form the putative intermediate dianion A and reacted with **5** before quenching at −10 °C to furnish the kinetically controlled coupling product **14** in 83% yield with 12:1 diastereoselectivity favoring the desired *trans* isomer [12]. No alkylation reaction took place when 1.0 equiv LDA was employed, while dimerization of **5** occurred when 4.0 eqivalent LDA was used. The reaction temperature also played a role. The diastereoselectivity eroded to 1:1 when the reaction was quenched at 20 °C. Amide **14** could be converted to imide **3** in a quantitative yield. It is noteworthy that the formation of dianion A contributed significantly to the observed reactivity of the alkylation process [13]. Actually, imide **15**, which precluded the formation of a dianion, could only generate **3** in 25% yield in the corresponding alkylating process.

With precursors **14** and **3** in hand, the stage was set for investigating the cyclization reaction. We first tried the intramolecular Heck reaction of **14**. Unfortunately, **14** gave



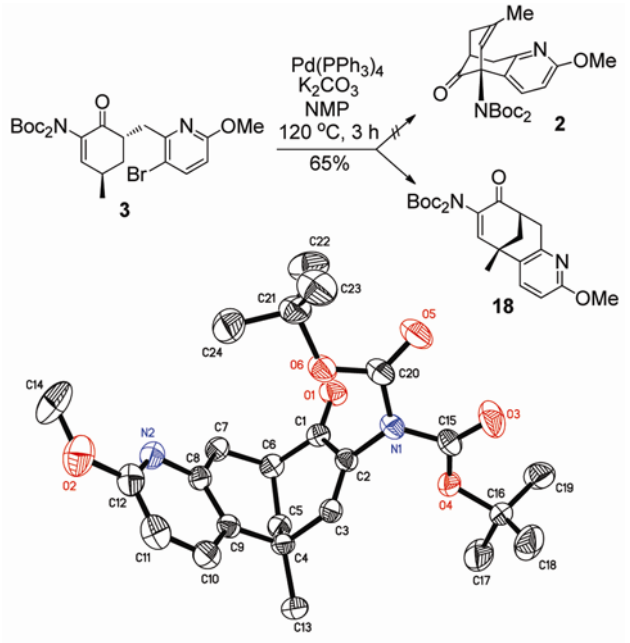
Scheme 3 Synthesis of **3** via diastereoselective alkylation.

either no reaction or decomposed products under tested conditions. We reasoned that the amide group, which might undergo deprotonation under the reaction conditions to render its coordinating ability further enhanced, along with the assistance of the vicinal carbonyl group, could associate the catalyst metal to engender a complex that probably deactivated the catalyst. With this assumption in mind, we turned our attention to the reaction of imide **3** in which such a complex was impossible to form.

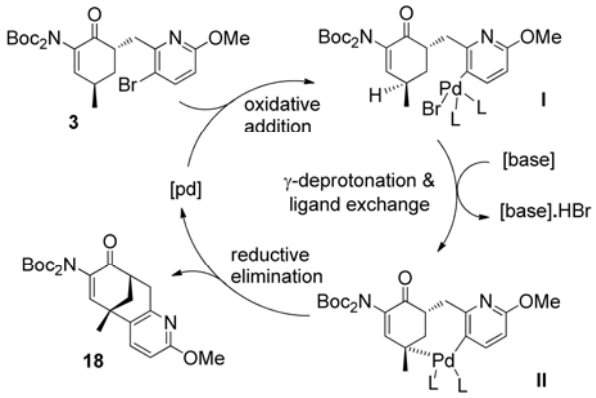
After numerous attempts, it was found that a cyclization product could be obtained in as high as 65% yield (Scheme 4) [14]. Although this cyclization product was initially mistakenly assigned as the expected **2** based on spectroscopic studies including ^{1}H NMR, COSY, and NOESY, we were surprised to find that the real product was **18** with a 1-methylbicyclo[3.3.1]nonane skeleton stemming from an unprecedented intramolecular γ-arylation, as revealed by the X-ray crystallographic structure [15]. The X-ray data also disclosed that the compound was not optically pure, which suggested that partial racemization of the substrate had occurred under the reaction conditions [16]. Interestingly, we did not detect any Michael addition product which was dominant in Mann's relevant studies [11], indicating the α-amido group played a crucial role in the current reaction.

Our proposed mechanism of the observed γ-arylation is depicted in Scheme 5. Under the reaction conditions, **3** underwent oxidative addition with the Pd(0) catalyst to furnish the palladium species **I**, which proceeded to give **II** via γ-deprotonation and ligand exchange. The subsequent reductive elimination produced **18** with concomitant regeneration of Pd(0) catalyst.

In conclusion, an unexpected and unprecedented palladium-catalyzed intramolecular γ-arylation was observed,



Scheme 4 Palladium catalyzed γ-arylation of **3**.



Scheme 5 Proposed mechanism for the palladium catalyzed γ-arylation of **3**.

which generated bicyclo[3.3.1]nonane framework **18** in satisfactory yield. The synthesis of the precursor for the arylation reaction featured a diastereoselective alkylation, which was powered by the formation of a dianion intermediate. The new chiral building blocks **4** and **6** could find applications in natural product synthesis. To divert the cyclization process away from the current γ-arylation pathway, fine-tunings of the electronic and/or steric properties of the substrates are entailed. Alternative reactions, such as oxidative Heck reaction [17], may also be explored to achieve the huperzine skeleton. Efforts along these lines are currently being actively pursued and will be reported in due course.

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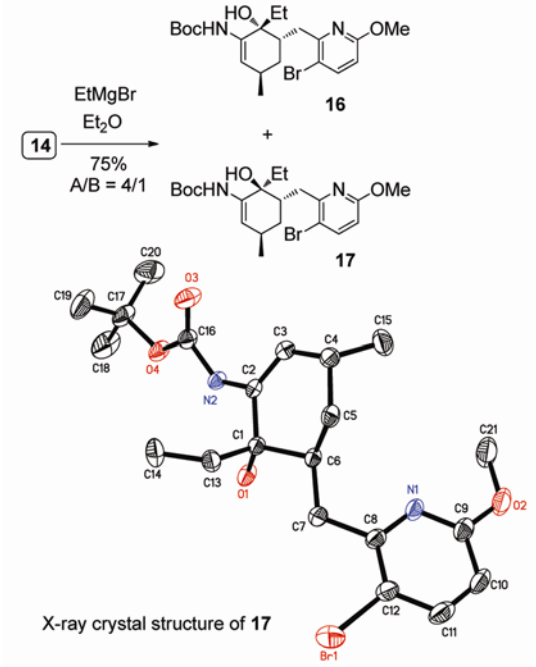
12 The stereochemistry was elucidated via the X-ray structure of **17** obtained through the addition reaction of **14** with Grignard reagent



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14 See Supporting Information for details

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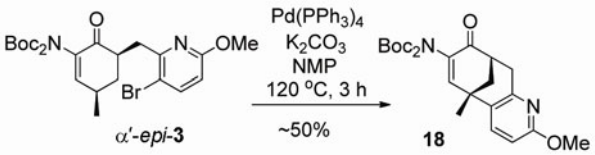
16 We reasoned that if racemization was intervening, α′-*epi*-**3** should also be capable of generating **18**. This was exactly what we observed. When α′-*epi*-**3** was subjected to the identical reaction conditions, product **18** was obtained in comparable yield.



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