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Research Article

Dielectrophilic Allenic Ketone-Enabled [4 + 2] Annulation with 3,3′-Bisoxindoles: Enantioselective Creation of Two Contiguous Quaternary Stereogenic Centers

Xiaodong Tang, Chuan Xiang Alvin Tan, Wai-Lun Chan, Fuhao Zhang, Wenrui Zheng, and Yixin Lu*

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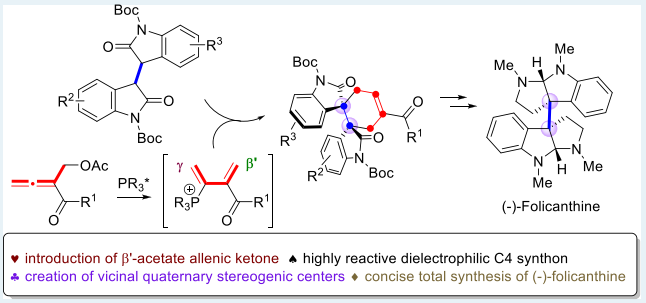
ABSTRACT: We introduced a type of allenic ketone as a dielectrophilic C4 synthon in phosphine-mediated reactions. The high electrophilicity of the advanced intermediates created upon phosphine activation empowered the utilization of 3,3′-bisoxindoles as a two-carbon reaction partner in a highly enantioselective [4 + 2] annulation, allowing for facile creation of spirocyclic bisindoline structures containing two contiguous quaternary stereogenic centers. Synthetic manipulations of the [4 + 2] annulation product led to concise total synthesis of (−)-folicanthine.



KEYWORDS: *allenic ketone, bifunctional phosphine, [4 + 2] annulation, quaternary stereogenic centers, dielectrophilic, dinucleophilic*

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INTRODUCTION

The past decade has witnessed remarkable progress of asymmetric phosphine catalysis.[1] Various phosphine-mediated cyclizations are certainly among the most investigated reaction types, which have been proven to be powerful for the construction of ring systems, especially for five- or six-membered cyclic structures. In 1995, Lu disclosed his seminal finding on phosphine-catalyzed [3 + 2] cyclization between nonsubstituted allenoate and activated alkenes in which the allene served as a C3 reaction partner (Figure 1, eq. a, R^1 = H).

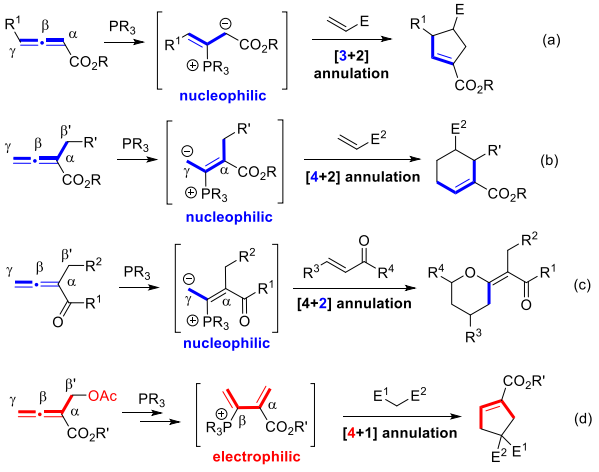

Figure 1. Utilization of allenes in phosphine-mediated annulations (some regioisomers and imine substrates are not shown).

Thereafter, such cyclization mode quickly gained popularity and received much attention from synthetic community, and a good number of excellent enantioselective [3 + 2] annulations employing simple allenes had been developed over the years.[2] Subsequently, the Kwon group made another seminal finding; they utilized γ-substituted allenoates and activated alkenes and discovered a new mode of [4 + 2] annulation. Notably, allenes served as C4 synthons in the Kwon [4 + 2] annulations (eq. b).[3] Recently, we discovered that when substituted allenic ketones reacted with unsaturated ketones or imines under the phosphine catalysis, a novel mode of [4 + 2] annulation took place in which allenic ketones acted as a C2 synthon (eq. c).[4] It is noteworthy that all the above [3 + 2] and [4 + 2] annulation reactions rely on the phosphine attack on allene substrates to generate active nucleophilic species, which then proceed to capture suitable electrophilic reaction partners to complete the cyclization events. In this context, Tong's [4 + n] annulation represents a remarkable breakthrough in phosphine catalysis.[5] Tong and co-workers designed a special type of allenoate containing a β′-acetate group, which upon reaction with a phosphine catalyst creates an electrophilic intermediate, suitable for reactions with nucleophilic reaction partners (eq. d). The reversal of electronic requirements for reaction

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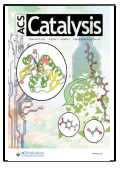

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components in Tong's [4 + n] annulation, as opposed to the [3 + 2]/[4 + 2] cyclizations discovered earlier by others, is especially noteworthy. Such reverse-electron-demand on substrates in phosphine-mediated reactions opens up new avenues for synthetic chemists to discover new reactions.

Over the past few years, we introduced a family of amino acid-based bifunctional phosphine catalysts and showed their values for a range of asymmetric transformations.[6] In an effort to continuously push the frontiers of phosphine catalysis, we reckon the importance of designing new reaction partners, which ideally would offer unprecedented reactivity, thus allowing novel reaction pathways to take place. To date, there are only three examples of utilizing allenoates as dielectrophilic reaction partners in asymmetric [4 + 1] annulations with a 1,1-dinucleophile, reported by us[5b] and the Fu group.[5c,d] On the other hand, phosphine-mediated asymmetric [4 + 2] annulation reaction between dielectrophilic allenes and 1,2-dinucleophiles is unknown.[7] It is rather striking to notice the substantially different modes of reaction for α-substituted allenoates and simple allenoates. Furthermore, reverse-electron-demand substrates in phosphine catalysis are currently very limited. Thus, we devised a new allenic ketone with a β'-acetate group, which was anticipated to be a valuable synthon in phosphine catalysis (Figure 2). We

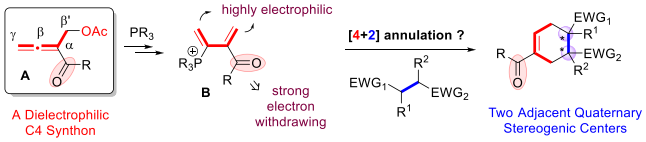

Figure 2. Design of a novel dielectrophilic C4 synthon: our hypothesis.

envisioned that exposure of such an allenic ketone (**A**) to a phosphine catalyst will lead to the elimination of the acetate group, resulting in an advanced dielectrophilic intermediate (**B**). The presence of the ketone functionality is expected to endow **B** with high electrophilicity, permitting subsequent reactions with relatively weak nucleophiles. If a dinucleophile containing two methine hydrogens is employed, a potential [4 + 2] annulation may readily deliver a six-membered ring system containing two adjacent quaternary carbon centers. Herein, we report the first enantioselective [4 + 2] annulation between C4-dielectrophiles and dicarbon nucleophiles.

RESULTS AND DISCUSSION

Establishing Reactivity of Allenic Ketones. To start our investigation, we first wanted to find out whether allenic ketone[8] **1a** would possess desirable reactivity toward a variety of different nucleophiles, especially in comparison with Tong's β'-acetate allenoate **1b**. Therefore, [4 + 1] annulation of **1a** with C1 reaction partners possessing two electron-withdrawing groups was chosen to establish the reactivity profile, and the results are summarized in Figure 3. When allenic ketone **1a** was employed, the [4 + 1] annulation with various dinucleophilic C1 synthons proceeded very smoothly, affording annulation products in high to nearly quantitative yields (**3a** to **3f**). In contrast, the [4 + 1] annulation with allenoate **1b**, under otherwise identical reaction conditions, afforded the desired products only in moderate to good yields (**3a'** to **3f'**). It is noteworthy that allenic ketone **1a** displayed improved reactivity compared to allenoate **1b** in its reactions

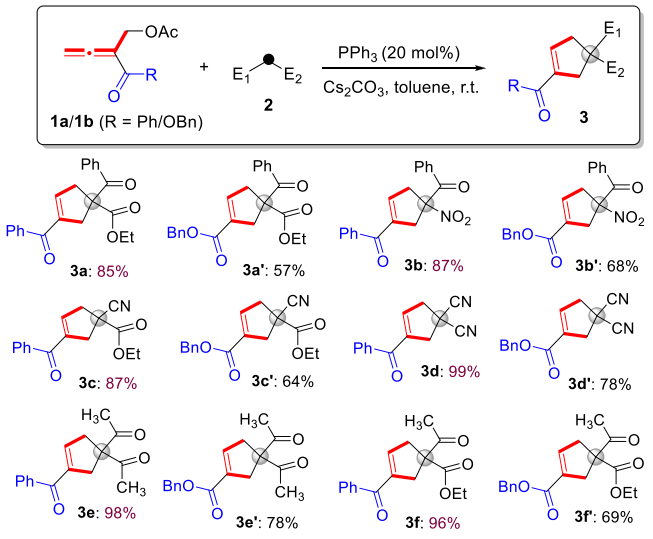

Figure 3. Evaluation of allenic ketone 1a and allenic ester 1b in PPh_3-catalyzed [4 + 1] annulation. Reactions were performed with **1** (0.12 mmol), **2** (0.1 mmol), Cs_2CO_3 (0.12 mmol), and PPh_3 (0.02 mmol) in toluene (2 mL) at room temperature for 5 h. Both allenic ketone and allenoate were fully consumed; yields refer to isolated products.

with different nucleophilic reaction partners. Our next goal is to explore practical values of this newly designed β'-acetate allenic ketone in the context of asymmetric phosphine catalysis, aiming to develop new reactions and address challenging synthetic problems.

Novel [4 + 2] Annulation of Allenic Ketones with 3,3′-Bisoxindoles. We recently became interested in effective enantioselective construction of dimeric hexahydropyrroloindole (HPI) alkaloids,[9] a class of natural products containing two adjacent quaternary stereogenic centers.[10] With our ongoing medicinal chemistry program toward efficient asymmetric synthesis of HPI alkaloids, we questioned whether a phosphine-based catalytic methodology may be applied to the total synthesis of (−)-folicanthine, a member of HPI alkaloids possessing potential anticancer and antifungal activities. We envisioned that the core structure of (−)-folicanthine can be conveniently constructed from a bisoxindole and allenic ketone **1a**; dielectrophilic allenic ketone and dinucleophilic bisoxindoles are anticipated to undergo [4 + 2] annulation readily to deliver a spirocyclic product bearing two adjacent quaternary stereogenic centers (Figure 4). It should be noted that the proposed reaction represents the first example of utilizing allenes as a dielectrophilic reaction partner in enantioselective [4 + 2] cycloaddition with a 1,2-dinucleophile.

The viability of our proposal was first evaluated. When bisoxindole **4a** was exposed to allenic ketone **1a** under the catalysis of triphenylphosphine, a [4 + 2] annulation took place smoothly, quantitatively furnishing the desired annulation product containing two sterically highly congested quaternary carbon centers. In stark contrast, when allenoate **1b** was employed, the annulation product was only obtained in 35% yield.[11] Such comparison studies firmly established that the high electrophilicity of the advanced intermediate rendered by incorporating a ketone moiety in the allene structure indeed is crucial, especially for promoting reactions with weaker nucleophiles, which are otherwise synthetically less viable.

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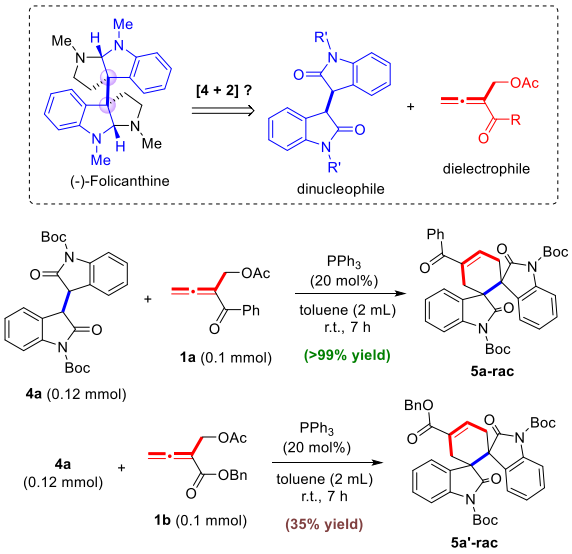
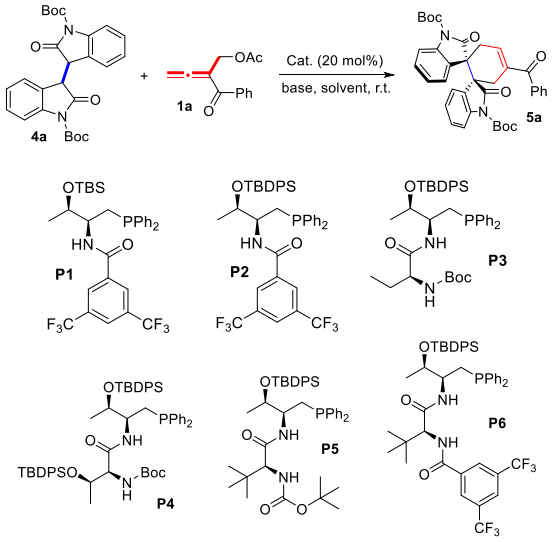


Figure 4. Feasibility study of the projected [4 + 2] annulation. Reactions were performed with **1** (0.1 mmol), **4** (0.12 mmol), Na_2CO_3 (0.12 mmol), and PPh_3 (0.02 mmol) in toluene (2 mL) at room temperature for 7 h. Both allenic ketone and allenoate were fully consumed; yields refer to isolated products.

To develop an asymmetric version of [4 + 2] annulation between allenic ketone **1a** and bisoxindole **4a**, we screened the catalytic effects of different amino acid-based bifunctional phosphines, and the results are summarized in Table 1. L-Threonine-derived phosphine−amide catalysts **P1** and **P2** led to the formation of the desired annulation product in quantitative yields; however, the enantioselectivities were poor (entries 1 and 2). While dipeptide phosphines **P3** and **P4** offered enhanced enantioselectivities (entries 3 and 4), L-Thr-L-*tert*-Leu-derived **P5** was found to be an excellent catalyst (entry 5). Surprisingly, structurally similar L-Thr-L-*tert*-Leu-derived **P6** gave the product with extremely low *ee* values (entry 6). We subsequently examined effects of different bases and also screened a number of solvents, and the results could not be further improved (entries 7−12). Under the optimized reaction conditions, the [4 + 2] annulation between allenic ketone **1a** and bisoxindole **4a** occurred smoothly under the catalysis of **P5** and Na_2CO_3, and annulation product **5a** was obtained in 98% yield and with 96% *ee* (entry 5).

With the optimal conditions in hand, we next explored the substrate scope (Figure 5). The reaction was applicable to symmetric bisoxindoles containing different aryl substituents, and the spirocyclic products were formed in very high yields and with excellent *ee* values (**5b** to **5f**). When the unsymmetric bisoxindoles bearing different aryl moieties were employed, the reaction proceeded in a regioselective and enantioselective manner, forming the desired products in high yields (**5g** to **5m**). Such regioselectivity can be rationalized mechanistically: the more efficiently stabilized oxindole anion is formed preferentially, which then attacks the dielectrophilic phosphonium intermediate at the *β*′-position,[5e] finally producing a specific regioisomer favorably. It is apparent that the electronic property difference of the two aryl moieties in bisoxindoles determines the level of regioselectivity, e.g., unsymmetric substrate containing a simple oxindole and an oxindole with a para-fluoro-substitution led to the formation of annulation products in a highly regioselective manner (**5 L**, rr > 20:1).[12] We also tested aryl allenic ketones with a methyl group at

Table 1. Reaction Screening[a]



entry	cat.	solvent	base	t [h]	yield (%)[b]	*ee* (%)[c]
1	**P1**	toluene	Na_2CO_3	4	99	15
2	**P2**	toluene	Na_2CO_3	4	99	40
3	**P3**	toluene	Na_2CO_3	6	99	50
4	**P4**	toluene	Na_2CO_3	8	98	77
5	**P5**	toluene	Na_2CO_3	8	98	96
6	**P6**	toluene	Na_2CO_3	8	98	10
7	**P5**	toluene	K_2CO_3	3	77	96
8	**P5**	toluene	Li_2CO_3	20	85	96
9	**P5**	THF	Na_2CO_3	8	30	96
10	**P5**	CH_2Cl_2	Na_2CO_3	8	90	96
11	**P5**	CH_3CN	Na_2CO_3	8	trace	
12	**P5**	1,4-dioxane	Na_2CO_3	8	-[d]	-[d]

[a]Reactions were performed with **1a** (0.12 mmol), **4a** (0.1 mmol), Na_2CO_3 (0.12 mmol), and the catalyst (0.02 mmol) in the solvent specified (2 mL) at room temperature. [b]Yields of isolated products. [c]Determined by HPLC analysis on a chiral stationary phase. [d]No reaction.

different positions of the phenyl ring, and the corresponding products were obtained in excellent chemical yields and *ee* values (**5n** to **5p**). Furthermore, aliphatic allenic ketone could also be employed, and the [4 + 2] annulation product was formed in a highly enantioselective manner (**5q**). The absolute configuration of **5g** was determined based on X-ray crystal structure analysis,[13] and the regioisomerism and the configurations of other [4 + 2] annulation products were assigned by analogy.

Mechanism Insight. The proposed reaction mechanism is illustrated in Figure 6. Phosphine first attacks the allenic ketone, eliminating acetate and generating the diene intermediate **I**. The anionic bisoxindole attacks dielectrophilic **I** at the *β*′-position, creating advanced intermediate **II**. The subsequent intramolecular proton transfer gives anionic **III**, which undergoes cyclization with the alkene moiety to afford cyclized intermediate **IV**. Finally, another intramolecular proton transfer followed by regeneration of the phosphine catalyst furnishes the desired [4 + 2] annulation product. To rationalize asymmetric induction, we believe that amide and carbamate moieties of the catalyst interact with the bisoxindole substrate through hydrogen bonding interactions and thus direct the addition of anionic bisoxindole to phosphonium

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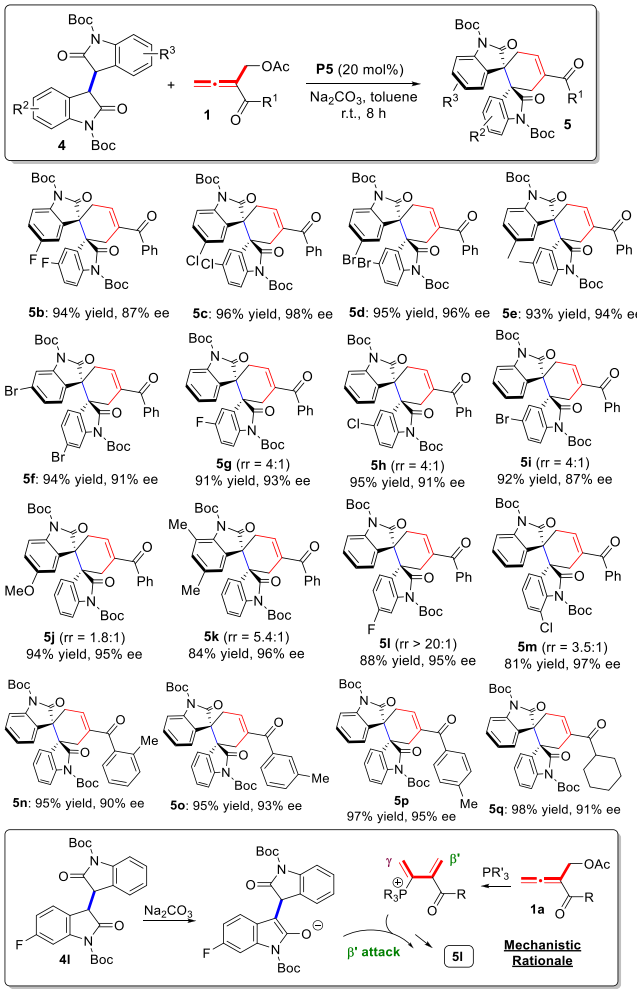


Figure 5. Scope of the reaction. Reactions were performed with **1** (0.1 mmol), **4** (0.12 mmol), Na_2CO_3 (0.12 mmol), and **P5** (0.02 mmol) in toluene (2 mL) at room temperature. Yields are for isolated products. The *ee* values were determined by HPLC analysis on a chiral stationary phase. The regioisomer ratios (rr) were determined by ^1H NMR analysis. The reaction time was 12 h for **5j** and **5 k**.

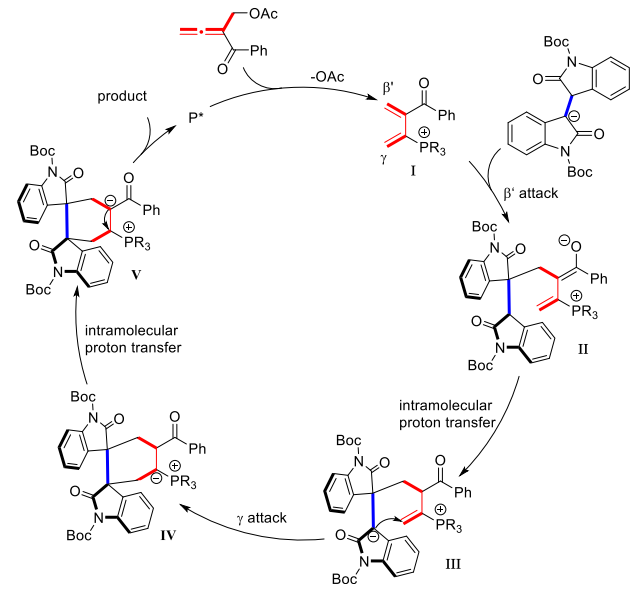


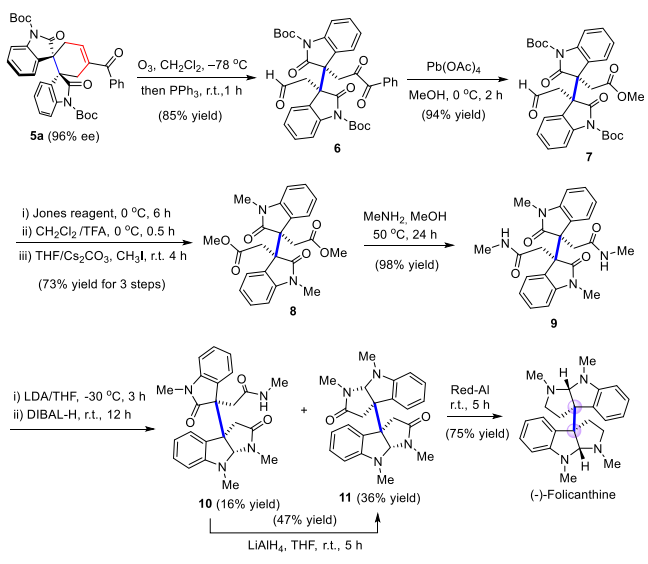
Figure 6. Proposed mechanism.

intermediate **I**, leading to the formation of the observed stereoisomer.[14]

To gain better mechanistic understanding of this [4 + 2] annulation process, preliminary mechanistic investigations were carried out. The phosphorus species involved in the reaction process were monitored by ^{31}P NMR. Two new resonances at 31.7 and 28.5 ppm were observed during the course of the reaction, which are different from the resonances of phosphine catalyst **P5** (−23.9 ppm), phosphine oxide (33.8 ppm), and phosphonium diene intermediate **I** (22.7 ppm). These results suggested that the steps of phosphonium **I** formation and the addition of anionic bisoxindole to phosphonium diene **I** are fast reaction steps and thus not rate-determining for the overall reaction. Our kinetic studies showed that the annulation reaction is first-order in the phosphine catalyst and in the allenic ketone and also is first-order in the bisoxindole nucleophile (see the Supporting Information for details). Furthermore, we preformed deuterium-labeling experiments, the result which is shown in eq 1. Under the otherwise identical reaction conditions, the rate of reaction employing **4a-D** was much slower than that of **4a**; the kinetic isotope effect was observed (KIE = 4). Taken together, all the experimental evidence we have collected so far is consistent with our proposed mechanism, whereby the proton transfer processes are likely to be rate-determining steps. Given the fact that allenic ketones are more reactive in the annulation reaction than the allenic ester counterparts, the second intramolecular proton transfer (from **IV** to **V**) in the proposed catalytic cycle is likely to be crucial for rate determination.

Total Synthesis of (−)-Folicanthine. (−)-Folicanthine was isolated from *Calycanthus floridus*[15] and also the seeds of *Chimonanthus praecox*.[16] It belongs to a big family of HPI alkaloids and possesses prominent biological activities.[9b] In the reported total synthesis of (+)-folicanthine, the challenging two vicinal quaternary stereogenic centers were constructed in a stepwise fashion.[17] We envisioned that our [4 + 2] annulation product, which contains two contiguous quaternary stereogenic centers, could be readily elaborated to the core structure of (−)-folicanthine (Scheme 1). We started our synthesis by subjecting **5a** to ozonolysis, which yielded aldehyde **6** in 85% yield, and the two quaternary stereogenic

Scheme 1. Concise Total Synthesis of (−)-Folicanthine



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centers in **6** were intact. In the presence of the aldehyde functionality, selective oxidation of the di-ketone moiety with lead tetraacetate furnished ester **7** in excellent yield. Subsequently, Jones oxidation, removal of the Boc protective group, and simultaneous methylation on oxindole nitrogens and the carboxylic acid were carried out, which delivered diester **8** in good chemical yield. Treatment of **8** with methylamine yielded diamide **9** in a virtually quantitative manner. The following cyclization via reductive amination was carried out by treating **9** with LDA/DIBAL.[18] While mono- and bis-cyclized products were both formed, the former was converted to the latter by reacting with $LiAlH_4$. The final reduction of the lactam moiety by Red-Al then completed the total synthesis of (−)-folicanthine.

CONCLUSIONS

In summary, we introduced a new type of allenic ketone as a dielectrophilic C4 synthon in phosphine catalysis. The presence of the ketone functionality endowed the advanced dielectrophilic C4 species with high reactivity, allowing for efficient reaction with weak nucleophiles. The value of our newly developed C4 synthon was demonstrated in an asymmetric [4 + 2] annulation with dinucleophilic bisoxindoles. Remarkably, spirocyclic bisoxindole scaffolds containing two contiguous quaternary stereogenic centers were constructed in a simple one-step operation, in very high chemical yields and with excellent enantioselectivities. Furthermore, the power of the synthetic strategy reported herein was demonstrated in a concise total synthesis of (−)-folicanthine. The high electrophilicity observed for the allenic ketone-derived C4 synthon will empower many new transformations to take place, which were previously not possible under phosphine-catalyzed conditions. We are currently working in this direction, and our findings will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05225.

Experimental procedure, optimization tables, and characterization data for all the products (PDF)

crystal data for JS79 (CIF)

AUTHOR INFORMATION

Corresponding Author

Yixin Lu − *National University of Singapore (Suzhou) Research Institute, Suzhou, Jiangsu 215123, China; Department of Chemistry, National University of Singapore, 117543, Singapore; Graduate School for Integrative Sciences & Engineering (NGS), National University of Singapore, 117456, Singapore; Joint School of National University of Singapore and Tianjin University, International Campus of Tianjin University, Binhai New City, Fuzhou 350207, China;* orcid.org/0000-0002-5730-166X; Email: chmlyx@nus.edu.sg

Authors

Xiaodong Tang − *National University of Singapore (Suzhou) Research Institute, Suzhou, Jiangsu 215123, China; Department of Chemistry, National University of Singapore, 117543, Singapore*

Chuan Xiang Alvin Tan − *Department of Chemistry, National University of Singapore, 117543, Singapore; Graduate School for Integrative Sciences & Engineering (NGS), National University of Singapore, 117456, Singapore*

Wai-Lun Chan − *Department of Chemistry, National University of Singapore, 117543, Singapore;* orcid.org/0000-0002-3995-5985

Fuhao Zhang − *Department of Chemistry, National University of Singapore, 117543, Singapore; Department of Chemistry, Southern University of Science and Technology, Shenzhen 518000, China*

Wenrui Zheng − *National University of Singapore (Suzhou) Research Institute, Suzhou, Jiangsu 215123, China; Department of Chemistry, National University of Singapore, 117543, Singapore*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.0c05225

Author Contributions

X.T. performed and analyzed the experiments. W.C., F.Z., W.Z., and A.T. participated in the early development of the project. X.T. and Y.L. conceived and designed the project. Y.L. overall supervised the project. X.T. and Y.L. prepared this manuscript.

Notes

The authors declare no competing financial interest.

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