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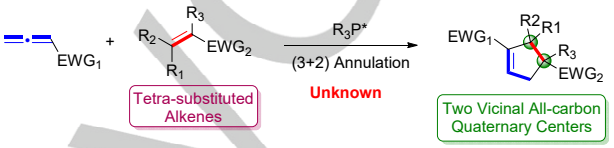
Phosphine-catalyzed (3+2) Annulation of Isoindigos with Allenes: Highly Enantioselective Creation of Two Vicinal Quaternary Stereogenic Centers

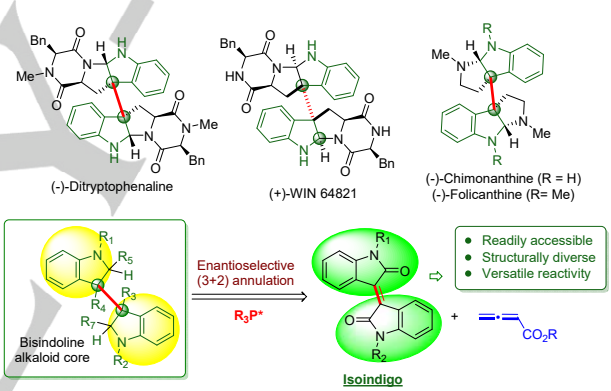
Wai-Lun Chan,[a] Xiaodong Tang,[a,b] Fuhao Zhang,[a,c] Glenn Quek,[a] Guang-Jian Mei[a]* and Yixin Lu[a,b]*

Abstract: Construction of contiguous all-carbon quaternary stereogenic centers is a long-standing daunting challenge in synthetic organic chemistry. In this report, we introduce a phosphine-catalyzed enantioselective (3+2) annulation reaction between allenes and isoindigos containing two identical/different oxindole moieties as a powerful strategy for the construction of spirocyclic bisindoline alkaloid core structures. The reported reactions are featured with high chemical yields, excellent enantioselectivities, and very good regioselectivities, and are highly useful for creating structurally challenging bisindoline natural products.

Even though seminal reports on phosphine-catalyzed reactions can be traced back to 1960s, the field of phosphine catalysis was dormant thereafter for a few decades. Two landmark discoveries in 1990s, Lu's (3+2) annulation[1a] and Trost's "umpolung" addition[1b] refueled the field and led to the renaissance of phosphine catalysis. It was the past decade that has witnessed tremendous advancement of asymmetric phosphine catalysis;[2] a kaleidoscope of phosphine-catalyzed enantioselective transformations, such as annulations, additions, Morita–Baylis–Hillman (MBH) reactions, Rauhut–Currier reactions, and so forth, have been intensively investigated. Among all the reactions that have been developed to date, phosphine-triggered annulation reactions are the most common reaction types. As the "signature" reaction, phosphine-promoted (3+2) annulations of allenes received enormous attention and have been most extensively studied.[3] With the invention of families of powerful chiral phosphine catalysts, numerous enantioselective (3+2) cyclization processes of allenes with activated alkenes or imines have emerged.[4] While mono-, di-, or tri-substituted activated alkenes are routinely used as a reaction partner for the creation of five-membered chiral carbocyclic systems, the utilization of tetra-substituted alkenes in phosphine-catalyzed (3+2) asymmetric annulation remains elusive (Scheme 1).[5] The synthetic challenges faced are intrinsic: the highly crowded nature of the tetra-substituted alkenes makes the addition of the phosphonium zwitterionic species extremely difficult. On the other hand, such reactions are highly interesting and rewarding from the synthetic point of view, since two vicinal all-carbon quaternary stereogenic centers can be created in a single-step operation.[6] We thus set our goal to develop enantioselective annulation reactions making use of tetra-substituted alkenes as a reaction partner, for the efficient construction of molecular architectures containing two contiguous all-carbon quaternary stereogenic centers.



Scheme 1. Tetra-substituted activated alkenes are challenging substrates in phosphine-catalyzed (3+2) annulation reactions with allenes.



Scheme 2. Selected HPI alkaloids with vicinal quaternary stereocenters and our proposed (3+2) annulation between isoindigos and allenes.

Natural products encompassing two or more contiguous all-carbon quaternary stereogenic centers are prevalent scaffolds with a plethora of promising biological activities, and such molecular architectures pose a long-standing daunting synthetic challenge to organic chemists and stimulated intensive research activities.[7] In this context, we were attracted to dimeric and polymeric hexahydropyrroloindole (HPI) alkaloids,[8] a structurally and biologically fascinating class of cyclotryptamine alkaloids with a centerpiece bispyrrolidino[2,3-*b*]indoline bearing two sterically congested adjacent all-carbon quaternary stereogenic centers at the C_{3a} and $C_{3a'}$ positions. A few selected HPI alkaloids are illustrated in Scheme 2. Limited catalytic methods for efficient asymmetric construction of these motifs have been reported to date, including: radical dimerization,[9a–9i] and double functionalizations, i.e. double decarboxylative allylation,[9j,9k] double Michael addition,[9l] and double alkylation,[9m] among others.[9n–9s] Given the importance of HPI alkaloids family, there clearly exists a need to develop efficient catalytic asymmetric synthetic approaches for facile and versatile synthesis of these molecules and their structural analogues. In connection to our disclosure of amino acid-derived bifunctional phosphines and

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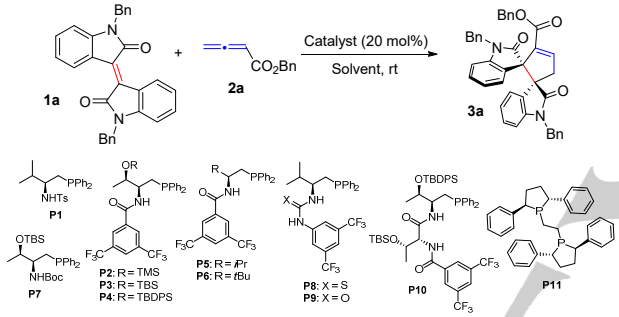
their applications in asymmetric synthesis,[10] we envisioned that the core bispyrrolidino[2,3-*b*]indoline structure in HPI alkaloids[11] may be conveniently constructed by employing an isoindigo as a starting substance, via a phosphine-catalyzed (3+2) annulation with an allene. Whereas the idea of installing two vicinal all-carbon quaternary stereocenters at the C_{3a} and $C_{3a'}$ through a single-step operation was very appealing to us, we were mindful that tetra-substituted alkenes are inherently sterically encumbered and have never been utilized in phosphine-catalyzed asymmetric (3+2) annulation processes. We reasoned that the two oxindole moieties may provide sufficient activations to the internally buried double bond, and the planar oxindole structures may be less sterically demanding that thus makes this otherwise extremely difficult reaction feasible. Herein, we document an unprecedented (3+2) annulation between isoindigos and allenes for highly enantioselective creation of structures containing two vicinal quaternary stereogenic centers.

Table 1: Optimization of the reaction conditions for phosphine-catalyzed (3+2) annulation between isoindigo **1a** and allene **2a**.[a]



Entry	Catalyst	Solvent	Time	Yield[b] (%)	*ee* (%)[c]
1	**P1**	Toluene	1 h	83	0
2	**P2**	Toluene	10 min	95	77
3	**P3**	Toluene	10 min	91	86
4	**P4**	**Toluene**	**15 min**	**94**	**92**
5	**P5**	Toluene	15 min	73	78
6	**P6**	Toluene	30 min	76	73
7	**P7**	Toluene	15 min	89	6
8	**P8**	Toluene	12 h	61	17
9	**P9**	Toluene	12 h	68	31
10	**P10**	Toluene	12 h	<30	N.D.
11	**P11**	Toluene	30 min	75	0
12	**P4**	**Et_2O**	**1 h**	**93**	**99**
13	**P4**	Dioxane	1 h	98	91
14	**P4**	CH_2Cl_2	1 h	87	86
15	**P4**	EtOAc	2 h	80	90
16	**P4**	CH_3CN	6 h	64	77
17	**P4**	THF	12 h	trace	N.D.
18	**P4**	CH_3OH	12 h	trace	N.D.

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.75 mmol), and the catalyst (20 mol%) in the solvent specified (1 mL) at room temperature. [b] Yields refer to isolated yields. [c] The *ee* values were determined by HPLC analysis on a chiral stationary phase. Bn: benzyl; rt: room temperature; N.D.: not determined.

We started our investigation by examining the potential reaction between isoindigo **1a** and benzyl 2,3-butadienoate **2a** in the presence of various chiral phosphine catalysts. We initially employed isoindigo with an *N*-Boc protection; while the reactions went to completion within a minute and the desired (3+2) annulation products were formed in high yields, the stereoselectivities of the reaction was less satisfactory. We subsequently chose a less reactive isoindigo **1a** for further studies (Table 1). To our delight, L-Thr-derived phosphine–amide catalysts displayed remarkable catalytic effects, affording spirobisoxindole **3a** in high chemical yield and with good enantioselectivity. The best catalyst was O-TBDPS-L-Thr-derived **P4**,[12] furnishing the desired **3a** in 94% yield and 92% *ee* within 15 minutes (entry 4). All the other bifunctional phosphines bearing different hydrogen bond donating groups, i.e. sulfonamide (**P1**), carbamate (**P7**), thiourea (**P8**), urea (**P9**), and dipeptide phosphine **P10** were found to be ineffective, and so was mono-functional bisphosphine **P11** (entries 1, & 7–11). Solvent screening was then followed. In general, less polar aprotic solvents were better choices when *ee* values were concerned, suggesting the importance of hydrogen bonding interactions for the asymmetric induction (entries 12–16). Very poor reactivity was observed when the reaction was run in THF or methanol, as isoindigo **1a** was barely soluble in these solvents (entries 17, 18). Under the optimized reaction conditions, when the reaction was performed in diethyl ether in the presence of phosphine **P4**, spirobisoxindole **3a** was obtained in 93% yield and with 99% *ee* in 1 hour (entry 12). Moreover, γ-benzyl-substituted benzyl allenoate was also tested, and was found unreactive.[13]

With the optimal reaction conditions in hand, we subsequently proceeded to establish the scope of the reaction (Scheme 3). To allow for flexibility in the subsequent structural manipulations of the bisoxindole annulation products, we examined isoindigos with either an *N*-methyl or *N*-allyl group, and the corresponding annulation products were obtained in excellent yields and *ee* values (**3b** & **3c**). However, the isoindigo with an *N*-Ts protection was not suitable; messy reaction was observed without formation of any major products, and we suspect this may due to the substrate over-activation induced by the electron-withdrawing tosyl group. The ester moiety in the allenoate could also be varied; spirocyclic annulation products with different ester groups were obtained in very high yields and enantioselectivities, which is desirable if such esters are to be selectively manipulated in subsequent synthesis (**3d**, **3e**, **3f** & **3g**). Isoindigos containing oxindoles with different substituents were next investigated. However, it turned out that most substituted isoindigos were virtually insoluble in ether; after much experimentation, we adopted toluene as the solvent of choice and performed the reactions at –20 °C for the substituted isoindigos. The annulation reaction was applicable to the substrates with different halogen atoms on the oxindoles, and different substitution patterns were also well tolerated. In all the examples examined, high yields and excellent enantioselectivities were attainable (**3h**–**3n**). Moreover, the substrate containing oxindole moieties with an electron-

10.1002/anie.201900758

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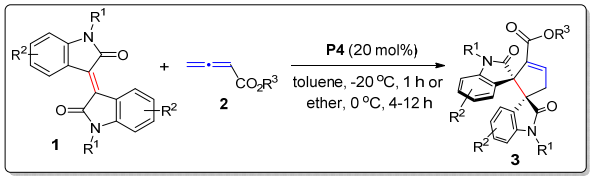
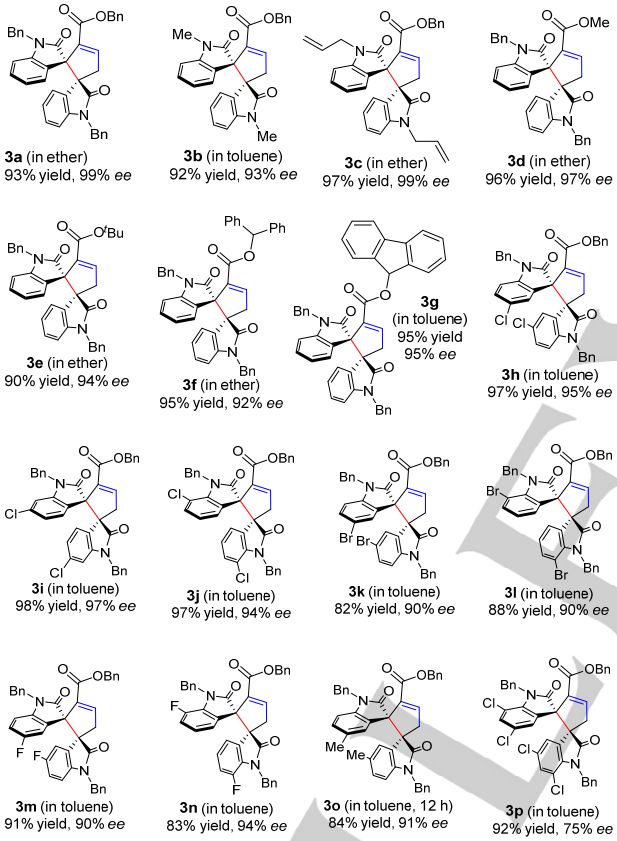
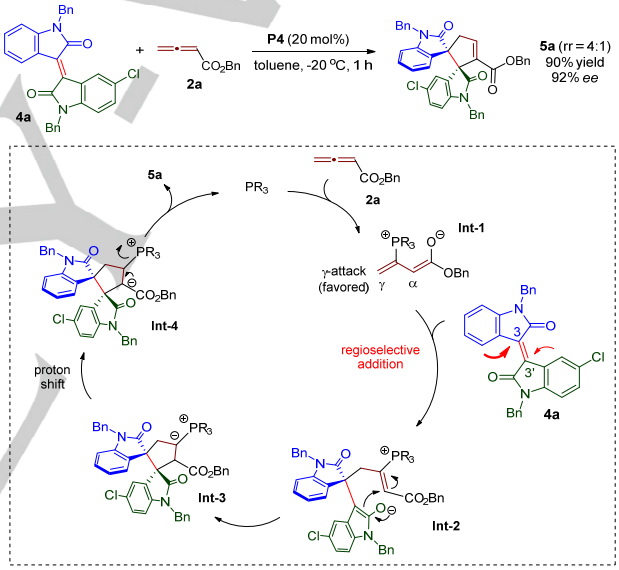
donating methyl group was found to be suitable as well (**3o**). However, when isoindigo bearing a 5,7-dichloro-oxindoles was employed in the reaction, even though the chemical yield was excellent, the enantioselectivity of the reaction was only modest (**3p**). The structures of the (3+2) annulation products were assigned on the basis of X-ray crystallographic analysis of product **3a**.





Scheme 3. Substrate scope of phosphine-catalyzed (3+2) annulation of symmetric isoindigos **1** with allenes **2**. Reaction conditions: **1** (0.05 mmol), **2** (0.75 mmol), and **P4** (20 mol%) in diethyl ether (1 mL) at 0 °C or in toluene (1 mL) at –20 °C. Isolated yields are reported. The *ee* values of **3** were determined by HPLC analysis on a chiral stationary phase. The absolute configurations of the annulation products were assigned based on X-ray crystallographic analysis of **3a** (CCDC 1874573).

Apart from isoindigos containing two identical oxindole moieties, isoindigo building blocks may also be constructed from different oxindole subunits, i.e. unsymmetric isoindigos could potentially be employed in the annulation. This perspective is truly exciting: we envisaged that the employment of unsymmetric isoindigos may create intriguing regioisomers of the annulation products bearing two structurally similar oxindole motifs. We hypothesized that such delicate structural variation could be conveniently realized by selecting oxindoles with different electronic and steric properties. To embark on our investigation, we chose isoindigo **4a** and explored its annulation with allene **2a**. Indeed, the annulation proceeded smoothly in a regioselective manner, and product **5a** was obtained in excellent yield, with a 4:1 regioisomeric ratio (rr) and 92% *ee* (for the major regioisomer). The observed regioselectivity could be rationalized following mechanistic pathway illustrated in Scheme 4. Phosphine attack on allene **2a** creates zwitterionic intermediate **Int-1**. Between the two possible regioisomeric attacks, the less hindered γ-attack is apparently more favored for the subsequent addition to structurally encumbered activated C–C double bond in **4a**. The presence of 5-chlorine atom in one of the oxindoles in **4a** makes C_3 more electron-deficient than $C_{3'}$, thus leading to regioselective formation of **Int-2**. The subsequent cyclization, followed by proton transfer and regeneration of phosphine catalyst, yields the final annulation product **5a**.



Scheme 4. Formation of specific regioisomers from unsymmetric isoindigos: mechanistic rationale.

We next prepared a range of unsymmetric isoindigos and subjected them to **P4**-promoted (3+2) annulation reactions with allene **2a**, and the results are shown in Scheme 5. While the presence of 5-Cl or 6-Cl in one of the oxindole rings led to the formation of the annulation product with good regioselectivity (**5a** or **5b**), isoindigos containing an oxindole with two chlorine atoms exerted stronger electronic effects, and only one regioisomer was observed (**5c** & **5d**). In comparison with 5-Cl oxindole-containing substrate, isoindigo with 6-Cl oxindole had enhanced regioselectivity in the cyclization, and such observation is correlated well with the electronic effects induced by the chlorine atom at these two positions (**5a** vs. **5b**). Isoindigo with 5-Br displayed similar selectivity to the 5-Cl analogue, likely due to the interplay of both electronic and steric factors (**5e** vs. **5a**). Introducing an electron-donating group in one oxindole moiety led to anticipated electronic differentiation of isoindigo, resulting in the

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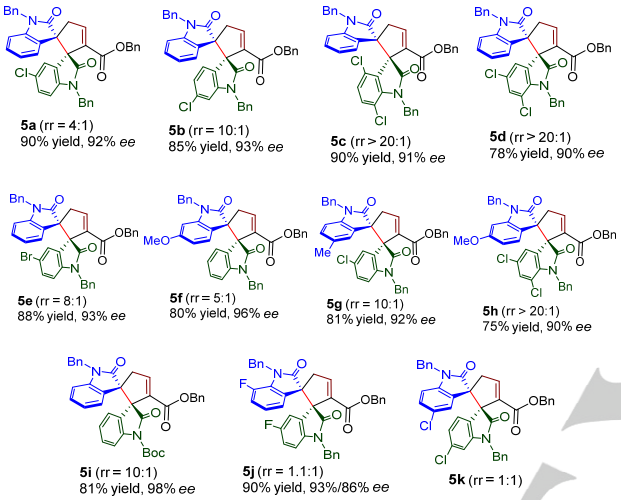
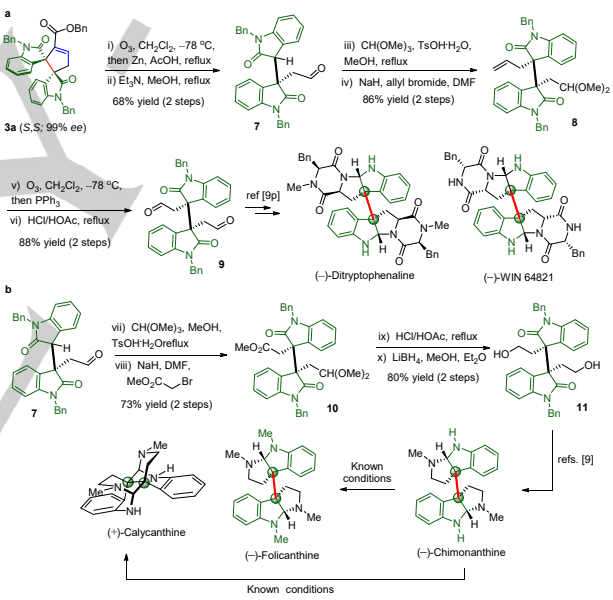
formation of the corresponding regioisomer (**5f**). When isoindigoes containing one electron-rich oxindole moiety and another electron-poor oxindole subunit were employed, regioselective products were formed as expected (**5g** & **5h**). Interestingly, electronic differentiation could also be achieved by utilizing different protective groups on the oxindole nitrogen (**5i**). We also strived to test the limit of electronic-differentiating strategy; isoindigo containing 5-F and 7-F oxindole moieties, as well as isoindigo bearing 5-Cl and 6-Cl oxindole units were examined in the annulation. In both cases, electronic difference was too subtle to be differentiated, and products were obtained with virtually no regioselectivity (**5j** & **5k**).



Scheme 5. Substrate scope of phosphine-catalyzed (3+2) annulation of unsymmetric isoindigos **4** with allene **2a**. Reaction conditions: isoindigo **4** (0.05 mmol), **2** (0.75 mmol), and **P4** (20 mol%) in toluene (1 mL) at – 20 °C. Isolated yields are reported. The *ee* values of **5** were determined by HPLC analysis on a chiral stationary phase. The regioisomer ratios (rr) were determined by ^{1}H NMR analysis.

The aforementioned highly enantioselective phosphine-catalyzed (3+2) cyclization between isoindogos and allenes allows for quick creation of challenging bisindoline alkaloid core structures, which are amenable for further synthetic transformations (Scheme 6). Spirocyclic annulation product **3a** (99% *ee*) was subjected to ozonolysis;[14] decarboxylation took place to afford bisoxindole **7**. The subsequent acetal formation and allylation afforded **8** in high yield. Another ozonolysis and cleavage of the acetal deprotection furnished bisoxindole aldehyde **9**, which can be converted to (–)-Ditryptophenaline and (–)-WIN 64821 following literature procedures.[9j] Alternatively, intermediate **7** was transformed to compound **10**, via a convenient acetalation and alkylation reaction sequence. Cleavage of the acetal, followed by reduction then yielded bisoxindole diol **11**, which can be transformed to (–)-Chimonanthine using the procedures that were described in the literature.[9n] Furthermore, by utilizing known reaction conditions, (–)-Chimonanthine can be elaborated to (–)-Folicanthine[9a,9l] and (+)-Calycanthine[9a,9l].

In summary, we have developed the first phosphine-catalyzed highly enantioselective (3+2) annulation between allenes and tetra-substituted alkenes, for the creation of structural motifs containing two contiguous all-carbon quaternary stereogenic centers. By employing isoindigos bearing two identical oxindole moieties and utilizing amino acid-derived bifunctional phosphines, various challenging dimeric spirocyclic bisindoline alkaloid motifs were efficiently constructed in high chemical yields and with excellent enantiomeric excesses. Moreover, structurally distinct spirocyclic molecules bearing two different oxindole moieties were conveniently derived from the corresponding unsymmetrical isoindigo precursors. To the best of our knowledge, regioselective annulation reaction making use of substrates bearing two similar moieties with subtle structural difference is unprecedented. The synthetic values of our methodology and annulation products were demonstrated by concise formal total syntheses of (–)-Ditryptophenaline, (–)-WIN 64821, (–)-Chimonanthine, (–)-Folicanthine, and (+)-Calycanthine, using phosphine-catalyzed enantioselective (3+2) annulation between isoindigos and allenes as the key step. Currently, we are intensively developing other phosphine-catalyzed enantioselective processes, which will be broadly applied to the total syntheses of families of bisindoline alkaloids.



Scheme 6. Formal total syntheses of (–)-Ditryptophenaline, (–)-WIN 64821, (–)-Chimonanthine, (–)-Folicanthine, and (+)-Calycanthine.[9]

Acknowledgements

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Keywords: chiral phosphines • annulations • quaternary stereocenters • indole alkaloids • enantioselective syntheses

[1] a) C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906; b) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* **1994**, *116*, 3167.

[2] For selected most recent reviews on phosphine catalysis, see: a) H. Ni, W.-L. Chan, Y. Lu, *Chem. Rev.* **2018**, *118*, 9344; b) H. Guo, Y. C. Fan, Z. Sun, Y. Wu, O. Kwon, *Chem. Rev.* **2018**, *118*, 10049.

[3] a) Z. Wang, X. Xu, O. Kwon, *Chem. Soc. Rev.* **2014**, *43*, 2927; b) Y. Wei, M. Shi, *Org. Chem. Front.* **2017**, *4*, 1876.

[4] a) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836; b) J. E. Wilson, G. C. Fu, *Angew. Chem. Int. Ed.* **2006**, *45*, 1426; *Angew. Chem.* **2006**, *118*, 1454; c) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988; d) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660; e) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *J. Am. Chem. Soc.* **2008**, *130*, 14030; f) H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang, G. Zhao, *Angew. Chem. Int. Ed.* **2010**, *49*, 4467; *Angew. Chem.* **2010**, *122*, 4569; g) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726; h) Y. Fujiwara, G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 12293; i) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2012**, *51*, 767; *Angew. Chem.* **2012**, *124*, 791; j) D. Wang, G.-P. Wang, Y.-L. Sun, S.-F. Zhu, Y. Wei, Q.-L. Zhou, M. Shi, *Chem. Sci.* **2015**, *6*, 7319; k) I. P. Andrews, O. Kwon, *Chem. Sci.* **2012**, *3*, 2510; l) L. Cai, K. Zhang, O. Kwon, *J. Am. Chem. Soc.* **2016**, *138*, 3298; m) X. Han, W.-L. Chan, W. Yao, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2016**, *55*, 6492; *Angew. Chem.* **2016**, *128*, 6602; n) M. G. Sankar, M. Garcia-Castro, C. Golz, C. Strohmann, K. Kumar, *Angew, Chem. Int. Ed.* **2016**, *55*, 9709; *Angew. Chem.* **2016**, *128*, 9861.

[5] a) For a (3+2) annulation to synthesize carbocyclic [60]fullerene derivatives, see: J. Marco-Martínez, V. Marcos, S. Reboredo, S. Filippone, N. Martín, *Angew. Chem. Int. Ed.* **2013**, *52*, 5115; *Angew. Chem.* **2013**, *125*, 5219; b) X.-C. Zhang, S.-H. Cao, Y. Wei, M. Shi, *Org. Lett.* **2011**, *13*, 1142.

[6] K. W. Quasdorf, L. W. Overman, *Nature* **2014**, *516*, 181.

[7] For selected reviews on contiguous quaternary stereocenters in natural product syntheses, see: a) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943; b) R. Long, J. Huang, J. Gong, Z. Yang, *Nat. Prod. Rep.* **2015**, *32*, 1584; c) M. Büschleb, S. Dorch, S. Hanessian, D. Tao, K. B. Schenthal, L. E. Overman, *Angew. Chem. Int. Ed.* **2016**, *55*, 4156; *Angew. Chem.* **2016**, *128*, 4226; For asymmetric preparations of quaternary stereocenters, see: d) C. Uyeda, A. R. Rötheli, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2010**, *49*, 9753; *Angew. Chem.* **2010**, *122*, 9947; e) H. Zhang, L. Hong, H. Kang, R. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 14098; f) K. Ohmatsu, N. Imagawa, T. Ooi, *Nat. Chem.* **2014**, *6*, 47; g) A. Khan, L. Tang, J. Xu, L. Y. Jin, Y. J. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 11257; *Angew. Chem.* **2014**, 126, 11439; h) J. Zheng, L. Lin, L. Dai, W. Tang, X. Liu, X. Feng, *Angew. Chem. Int. Ed.* **2017**, *56*, 13107; *Angew. Chem.* **2017**, *129*, 13287; i) Y. Liu, Q.-S. Gu, X. Meng, G.-C. Chen, X.-Y. Liu, *Nat. Commun.* **2018**, *9*, 227; j) J. Caleb Hethcox, S. E. Shockley, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2018**, *57*, 8664; *Angew, Chem.* **2018**, *130*, 8800.

[8] P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, *Chem. Eur. J.* **2011**, *17*, 1388.

[9] a) M. Movassaghi, M. A. Schmidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 3725; *Angew. Chem.* **2007**, *119*, 3799; b) M. Movassaghi, M. A. Schmidt, J. A. Ashenhurst, *Angew. Chem. Int. Ed.* **2008**, *47*, 1485; *Angew. Chem.* 2008, *120*, 1507; c) J. Kim, J. A. Ashenhurst, M. Movassaghi, *Science* **2009**, *324*, 238; d) J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2010**, *132*, 14376; e) E. Iwasa, Y. Hamashima, S. Fujishiro, E. Higuchi, A. Ito, M. Yoshida, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4078; K. Foo, T. Newhouse, I. Mori, H. Takayama, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 2716; *Angew. Chem.* **2011**, *123*, 2768; g) S. Tadano, Y. Mukaeda, H. Ishikawa, *Angew. Chem. Int. Ed.* **2013**, *52*, 7990; *Angew. Chem.* **2013**, *125*, 8148; h) W. Xie, G. Jiang, H. Liu, J. Hu, X. Pan, H. Zhang, X. Wan, Y. Lai, D. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 12924; *Angew. Chem.* **2013**, *125*, 13162; i) E. C. Gentry, L. J. Rono, M. E. Hale, R. Matsuura, R. R. Knowles, *J. Am. Chem. Soc.* **2018**, *140*, 3394; j) B. M. Trost, M. Osipov, *Angew. Chem. Int. Ed.* **2013**, *52*, 9176; *Angew. Chem.* **2013**, *125*, 9346; k) S. Ghosh, S. Bhunia, B. N. Kakde, S. De, A. Bisai, *Chem. Commun.* **2014**, *50*, 2434; l) H. Mitsunuma, M. Shibasaki, M. Kanai, S. Matsunaga, *Angew. Chem. Int. Ed.* **2012**, *51*, 5217; *Angew. Chem.* **2012**, *124*, 5307; m) S.-K. Chen, W.-Q. Ma, Z.-B. Yan, F.-M. Zhang, S.-H, Wang, Y.-Q. Tu, X.-M. Zhang, J.-M. Tian, *J. Am. Chem. Soc.* **2018**, *140*, 10099; n) L. W. Overman, D. V. Paone, B. A. Stearns, J. Am. Chem. Soc. 1999, 121, 7702; o) L. E. Overman, J. F. Larrow, B. A. Stearns, J. M. Vance, *Angew. Chem. Int. Ed.* **2000**, *39*, 213; *Angew. Chem.* **2000**, *112*, 219; p) L. W. Overman, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 9465; q) C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 1046; *Angew. Chem.* **2012**, *124*, 1070; r) D.F. Chen., F. Zhao, Y. Hu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2014**, *53*, 10763; *Angew. Chem.* **2014**, *126*, 10939; s) C. R. Jamison, J. J. Badillo, J. M. Lipshultz, R. J. Comito, D. W. C. MacMillan, *Nat. Chem.* **2017**, *9*, 1165.

[10] T. Wang, X. Han., F. Zhong, W. Yao, Y. Lu, *Acc. Chem. Res.* **2016**, *49*, 1369.

[11] a) J. T. Link, L. E. Overman, *J. Am. Chem. Soc.* **1996**, *118*, 8166; b) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas, *ACS Catal.* **2014**, *4*, 743; c) G.-J. Mei, F. Shi, *Chem. Commun.* **2018**, *54*, 6607.

[12] We believe the OTBDPS group in **P4** may be engaged in π–π interactions with the substrates, aside from exerting a steric effect, making it the best catalyst.

[13] The reactions between γ-benzyl-substituted benzyl allenoate and isoindigo **1a** in the presence of cinchona alkaloid-based amine catalysts were examined, and no reaction was observed. For an interesting related example, see: C. T. Mbofana, S. J. Miller, *J. Am. Chem. Soc.* **2014**, *136*, 3285.

[14] F.-Z. Li, S. Li, P.-P. Zhang, Z.-H. Huang, W.-B. Zhang, J. Gong, Z. Yang, *Chem. Commun.* **2016**, *52*, 12426.

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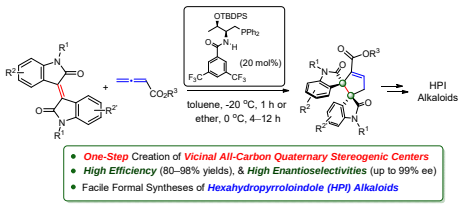

Phosphine-catalyzed enantioselective (3+2) annulation reaction between allenes and isoindigos was introduced for the first time as a powerful strategy for the construction of structural motifs containing two vicinal quaternary stereogenic centers. The reactions documented are featured with high chemical yields, excellent enantioselectivities, and very good regioselectivities, and are highly useful for creating structurally challenging bisindoline natural products.

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Page No. – Page No.

Phosphine-catalyzed (3+2) Annulation of Isoindigos with Allenes: Highly Enantioselective Creation of Two Vicinal Quaternary Stereogenic Centers

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