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*J. Am. Chem. Soc.*, **Just Accepted Manuscript** • Publication Date (Web): 11 May 2018

# Palladium-Catalyzed Asymmetric Allylic Alkylation of 3-Substituted-1*H*-Indoles and Tryptophan Derivatives with Vinylcyclopropanes

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**ABSTRACT:** Vinylcyclopropanes (VCPs) are known to generate 1,3-dipoles with a palladium catalyst that initially serve as nucleophiles to undergo [3 + 2] cycloadditions with electron-deficient olefins. In this report, we reverse this reactivity and drive the 1,3-dipoles to serve as electrophiles by employing 3-alkylated indoles as nucleophiles. This represents the first use of VCPs for the completely atom-economic functionalization of 3-substituted-1*H*-indoles and tryptophan derivatives via a Pd-catalyzed asymmetric allylic alkylation (Pd-AAA). Excellent yields and high chemo-, regio- and enantioselectivities have been realized, providing various indolenine and indoline products. The method is amenable to gram scale, and works efficiently with tryptophan derivatives that contain a diketopiperazine or diketomorpholine ring, allowing us to synthesize mollenine A in a rapid and ligand-controlled fashion. The obtained indolenine products bear an imine, an internal olefin, and a malonate motif, giving multiple sites with diverse reactivities for product diversification. Complicated polycyclic skeletons can be conveniently constructed by leveraging this unique juxtaposition of functional groups.

## INTRODUCTION

Naturally occurring indole alkaloids[1] display a broad range of anticancer, antibacterial, and antifungal properties (Figure 1).[2] For example, borreverine is strongly active against Gram-positive bacteria.[3] As a result, these molecules provide an attractive platform for structure-activity relationship studies and lead compound discovery in drug development.[4] Their indoline cores usually fuse with other hetero- or carbocyclic backbones, creating marvelous structural complexity and diversity (Figure 1, highlighted in red).

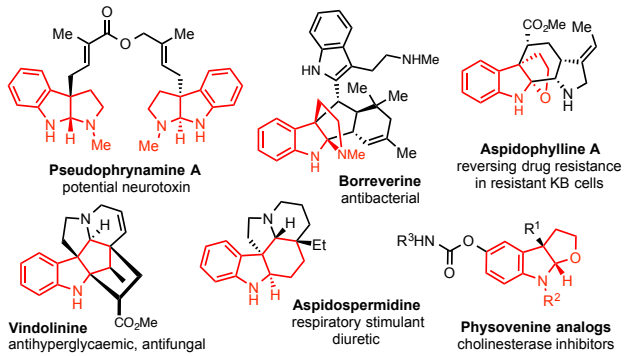



**Figure 1.** Bioactive molecules containing an indoline motif.

As many indoline-containing alkaloids possess C3 quaternary stereocenters, developing catalytic asymmetric methods to build these chiral centers is significant.[5] To address this synthetic challenge, early methods used an indirect approach of enantioselective preparation of 3,3-disubstituted oxindoles followed by further elaboration to the corresponding indolines.[6] More recent efforts have focused on tandem C3-functionalization/cyclization reactions of 3-substituted indoles,[5a] among which the Pd-AAA[7] of 3-substituted-1*H*-indoles represents an efficient way to achieve this goal.

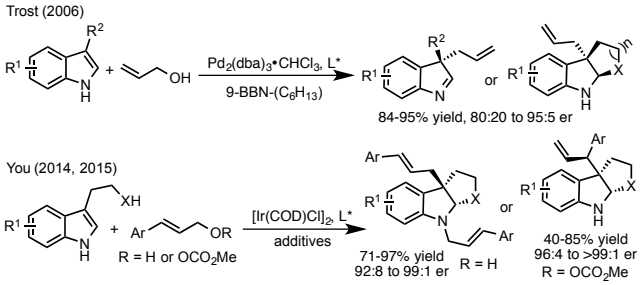



**Figure 2.** Previous partners for transition metal catalyzed asymmetric allylation of 3-substituted indoles are limited to allylic alcohols and carbonates.

In 2005, Tamaru reported a C3-selective palladium-catalyzed allylation of 1*H*-indoles using allylic alcohols,[8] in which the borane reagent facilitated the ionizations of allylic alcohols and thus promoted the catalytic process.[9] Subsequently, we developed the first catalytic asymmetric version of this transformation to obtain chiral indolenines and indolines bearing C3 quaternary stereocenters (Figure 2).[10] Allyl carbonates proved to be another type of effective reagents for the Pd-AAA of 3-substituted indoles.[11] Recently, You investigated the iridium-catalyzed intermolecular AAA of 3-substituted-1*H*-indoles using cinnamyl alcohols and carbonates.[12] In spite of these advances, the allylation partners for the asymmetric C3-functionalization of 3-substituted indoles have so far been limited to allylic alcohols and carbonates. Therefore, we were eager to see if the transition metal catalyzed AAA of 3-substituted indoles could be expanded to include other reaction partners as electrophiles so as to access indolenine/indoline

products bearing functionalized C3-allylic motifs for further synthetic elaborations.

To achieve this goal, we turned our attention to vinylcyclopropanes (VCPs). We previously used them in the presence of a palladium catalyst to generate 1,3-dipoles, which initially served as nucleophiles to attack electron-deficient olefins followed by an intramolecular electrophilic cyclization to give the formal [3 + 2] products (Figure 3).[13] However, using VCPs in a Pd-AAA reaction, which drives 1,3-dipoles to serve as electrophiles rather than nucleophiles, has not been realized before this work.[14] We wondered whether this challenge might be addressed by carefully choosing a reaction partner such as a 3-substituted indole. The strained C-C bond of the cyclopropane serves as a leaving group in this new version of transition metal catalyzed allylic alkylation, which is different from the previous cases using allylic alcohols or carbonates[9-12] and represents a completely atom economic approach.[15] More impressively, the obtained indolenine products would bear an imine, an internal olefin, and a 1,3-dicarbonyl motif, providing multiple sites with diverse reactivities for product diversification.

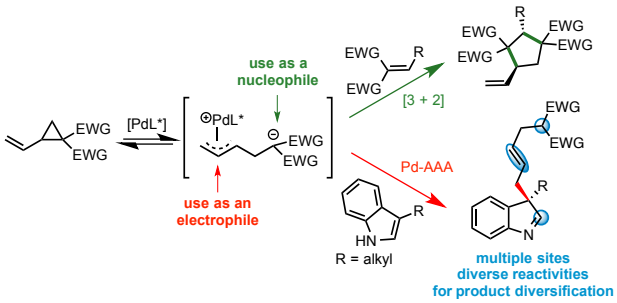



**Figure 3.** VCPs solely serve as electrophiles in Pd-AAA of 3-alkylated-1*H*-indoles.

Potential problems arising from the proposed Pd-AAA of 3-alkylated-1*H*-indoles would include chemo-, regio-, and enantioselectivity. As both *N* and C3 can undergo allylation,[16] we need to shut down the *N*-allylation process. With regard to the regioselectivity of attack on the π-allyl cation, the indole may attack the terminal position to give a linear product, or the internal position to yield the corresponding branched product. Previous studies using a Lewis acid catalyst showed that branched selectivity was dominant as indoles attacked the internal position of the π-allyl cation (Figure 4).[17] An interesting question arises if the C3-alkyl substituent of the indole is tethered to a nucleophile, since the pendant nucleophile and the nucleophilic site of the 1,3-dipole could compete for addition to the imine intermediate. This will especially become an issue if the two nucleophiles have similar nucleophilicity, leading to mixed product formation. Indeed, reactions between VCPs and indoles bearing a C3-pendant nucleophile are scarce seen. By using a palladium catalyst, we envisioned that this problem would be alleviated since the Pd-directed linear regioselectivity would give an imine intermediate that precludes competing intramolecular cyclization due to the *E*-olefin geometry. As a result, indoles bearing a pendant C3-nucleophile would be able to react with VCPs in a Pd-AAA fashion, cleanly providing the linear tricyclic indoline products.

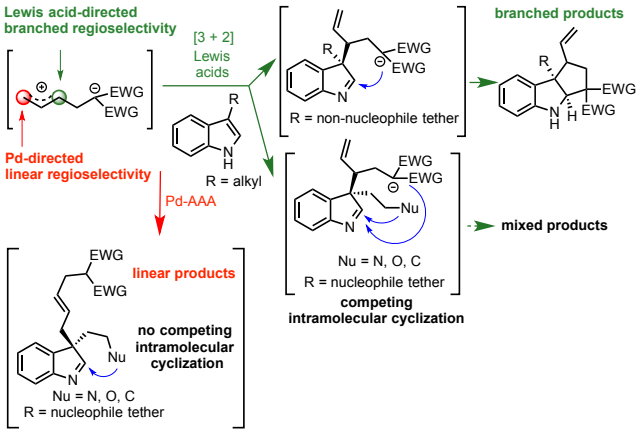


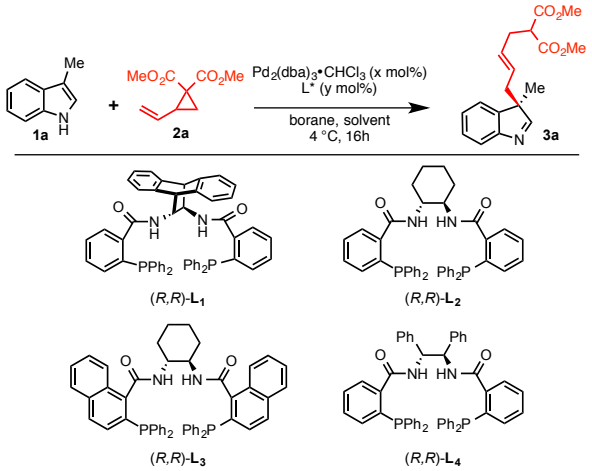

**Figure 4.** Lewis acids and palladium render different regioselectivity of the π-allyl cation within the 1,3-dipole.

Herein we report an asymmetric allylic alkylation using VCPs as electrophiles in which 3-substituted-1*H*-indoles and tryptophan derivatives are functionalized with high chemo-, regio-, and enantioselectivity and complete atom economy.

## RESULTS AND DISCUSSION

We initiated our studies using commercially available 3-methyl-1*H*-indole **1a** and readily prepared VCP derivative **2a** (Table 1). Simply subjecting the two compounds to 5 mol% of $Pd_2(dba)_3$•$CHCl_3$ and 15 mol% of anthracene-derived Trost ligand $\mathbf{L_1}$ in DCM at 4 °C for 16 h did not produce any detectable allylation product (entry 1). To our delight, the addition of 1.2 eq $BEt_3$ gave the linear allylation product **3a** in a moderate 76:24 er (entry 2). Neither branched nor *N*-allylation products were observed, suggesting that the triethylborane was at least partially responsible for both reactivity and chemoselectivity. We reasoned that the borane reagent, being tightly bound to the indole nitrogen during the allylation step, not only increased the nucleophilicity of the indole and accordingly promoted the reactivity, but also prevented the *N*-allylation and therefore benefited the chemoselectivity.[18] Unlike Lewis acid catalysts, the palladium catalyst enabled the indole **1a** to react at the terminal position of the 1,3-dipole, leading to exclusive formation of the linear product **3a**. This result confirmed our initial idea that a transition metal could be used to tune the regioselectivity of the 1,3-dipoles generated from VCP derivatives. Ligand examination revealed that using stilbene-derived Trost ligand $\mathbf{L_4}$ afforded a pleasing 95:5 enantiomeric ratio (entries 3-5). Switching to coordinating solvents like THF or MeCN was detrimental to the reactivity (entries 6-7), whereas using a nonpolar solvent like toluene gave full conversion (entry 8). Eventually, we found that using chloroform slightly boosted the er to 96:4 (entry 9). Although the more bulky 9-BBN-($C_6H_{13}$) marginally advanced the er, further increasing the steric size of the borane reagent dramatically impeded the reaction (entries 10-11). We chose triethylborane as it is commercially available as a solution in hexanes. Halving the catalyst loading maintained the full conversion and 96:4 er, and further decreasing the amount did not significantly affect the results (entries 12-13). Using 0.2 eq of $BEt_3$ still gave 75% conversion, suggesting that the role of the borane reagent was catalytic (entry 14).

**Table 1. Optimization of the Reaction Conditions.**[a]

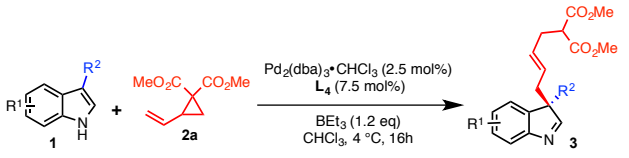


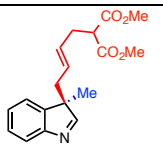
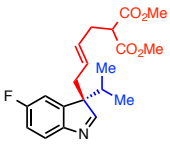
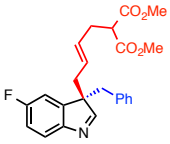
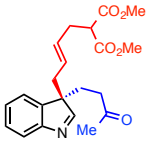
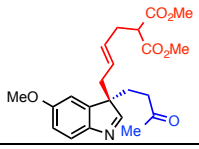

| entry | lig. | x/y | borane | solv | conv.[b] | er[c] |
|---|---|---|---|---|---|---|
| 1 | $L_1$ | 5/15 | none | DCM | <5% | nd |
| 2 | $L_1$ | 5/15 | $BEt_3$ | DCM | full | 76:24 |
| 3 | $L_2$ | 5/15 | $BEt_3$ | DCM | full | 92:8 |
| 4 | $L_3$ | 5/15 | $BEt_3$ | DCM | full | 94:6 |
| 5 | $L_4$ | 5/15 | $BEt_3$ | DCM | full | 95:5 |
| 6 | $L_4$ | 5/15 | $BEt_3$ | THF | 66% | 90:10 |
| 7 | $L_4$ | 5/15 | $BEt_3$ | MeCN | 85% | 95:5 |
| 8 | $L_4$ | 5/15 | $BEt_3$ | Tol | full | 93:7 |
| 9 | $L_4$ | 5/15 | $BEt_3$ | $CHCl_3$ | full | 96:4 |
| 10 | $L_4$ | 5/15 | 9-BBN-($C_6H_{13}$) | $CHCl_3$ | full | 97:3 |
| 11 | $L_4$ | 5/15 | $Sia_2B$-($C_6H_{13}$) | $CHCl_3$ | <10% | nd |
| 12 | $L_4$ | 2.5/7.5 | $BEt_3$ | $CHCl_3$ | full | 96:4 |
| 13 | $L_4$ | 1/3 | $BEt_3$ | $CHCl_3$ | full | 94:6 |
| 14[d] | $L_4$ | 2.5/7.5 | $BEt_3$ | $CHCl_3$ | 75% | nd |

[a]Reaction Conditions: 0.20 mmol of **1a**, x mol% of $Pd_2(dba)_3$•$CHCl_3$, y mol% of **L**, 0.24 mmol of $BEt_3$ and **2a**, in various solvent at 4 °C for 16h. [b]Determined by $^1H$ NMR analysis. [c]Determined by HPLC on a chiral stationary phase. [d]Reaction was performed with 0.2 eq of $BEt_3$.

With the optimized conditions in hand, we started to explore the scope of this transformation using 3-alkylated 1*H*-indoles **1a-e** (Table 2). High yields were obtained in all cases. Substrates bearing electron-withdrawing or -donating groups all smoothly delivered the corresponding 3,3-disubstituted indolenines, with enantiomeric ratio ranging from 95:5 to 99:1. These indolenine products **3a-e** are exceptional acceptors for various nucleophiles, as we demonstrated later when derivatizing these products. Additionally, indoles containing a carbonyl functional group were also tolerated (entries 4-5), which provided an extra handle to elaborate the products.

**Table 2. Scope of C3-allylation of 3-Subsituted-1*H*-indoles.[a]**

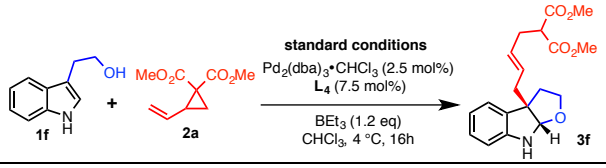



| entry | 3 | product structure | yield[b] | er[c] |
|---|---|---|---|---|
| 1 | **a** |  | 93 | 96:4 |
| 2 | **b** |  | 90 | 99:1 |
| 3 | **c** |  | 91 | 97:3 |
| 4 | **d** |  | 96 | 96:4 |
| 5 | **e** |  | 92 | 95:5 |

[a]Reaction Conditions: 0.20 mmol of **1**, 2.5 mol% of $Pd_2(dba)_3$•$CHCl_3$, 7.5 mol% of $L_4$, 0.24 mmol of $BEt_3$ and **2a**, in $CHCl_3$ at 4 °C for 16h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

We next moved onto substrates bearing a pendant nucleophile that could intercept the formed imines under the reaction conditions to generate varied tricyclic skeletons. Employing our previously established standard conditions, tryptophol **1f** efficiently delivered the anticipated furoindoline **3f** in 93% yield with 96:4 er (Table 3, entry 1). This result confirmed our prior assumption that using a palladium catalyst would enable indoles bearing a pendant C3-nucleophile to cleanly react with VCPs, while employing a Lewis acid might have generated mixed products. Replacing the solvent with DCM, using 9-BBN-($C_6H_{13}$) as borane reagent, warming up the reaction to ambient temperature, or lowering the catalyst loading did not considerably change the yield or enantioselectivity (entries 2-5).

**Table 3. Optimization with Tryptophol 1f.[a]**

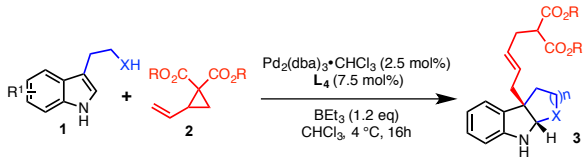


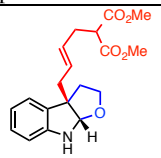
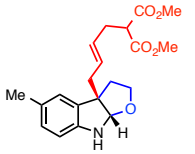
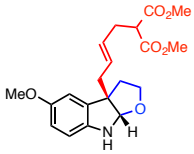
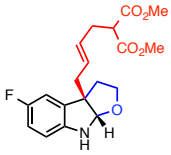
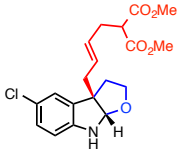
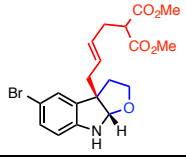
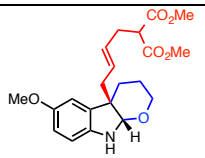
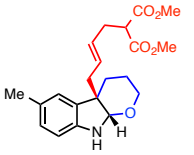
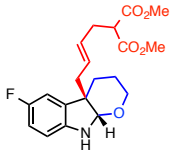
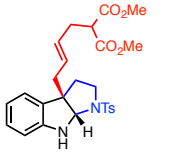
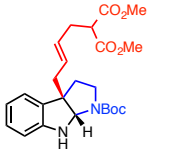
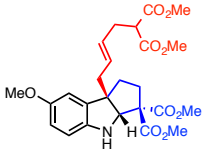
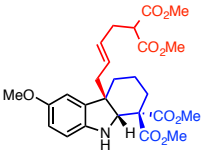
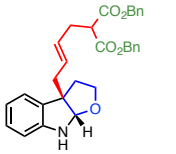
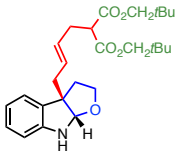

| entry | deviation from standard conditions | yield[b] | er[c] |
|---|---|---|---|
| 1 | none | 93 | 96:4 |
| 2 | DCM as solvent | 88 | 96:4 |
| 3 | reaction at rt | 91 | 94:6 |
| 4 | 9-BBN-($C_6H_{13}$) as the borane | 91 | 97:3 |
| 5 | 1 mol% of $Pd_2(dba)_3$•CHCl3 and 3 mol% of $L_4$ | 88 | 94:6 |

[a]Standard Conditions: 0.20 mmol of **1f**, 2.5 mol% of $Pd_2(dba)_3$•$CHCl_3$, 7.5 mol% of $L_4$, 0.24 mmol of $BEt_3$ and **2a**, in $CHCl_3$ at 4 °C for 16h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

The scope of this tandem C3-allylation/cyclization process was then investigated (Table 4). Electron-deficient tryptophols afforded better enantioselectivity compared to electron-rich ones, but in all cases >92:8 er was realized (entries 1-5). Homologating the C3-alcoholic chain of the indoles delivered the corresponding *cis*-[4,3,0]-*N*,*O*-tricyclic products **3l-n** in 87-90 yields with enantiomeric ratios from 86:14 to 98:2 (entries 7-9). Using tryptamine derivatives afforded pyrroloindolines **3o-p** with outstanding enantioselectivity (entries 10-11). It is worth noting that *N*-Ts and *N*-Boc protected tryptamines work equally well for this transformation. The malonate-containing side chain could also effectively trap the initially formed indolenines, providing the respective indolines featuring five- or six-membered carbocycle (entries 12-13). Lastly, VCP derivatives bearing sterically more hindered ester groups were tested. These bulky ester groups not only better guide the enantioselectivity, but also offer an opportunity for ester cleavage using other conditions if necessary (entries 14-15).

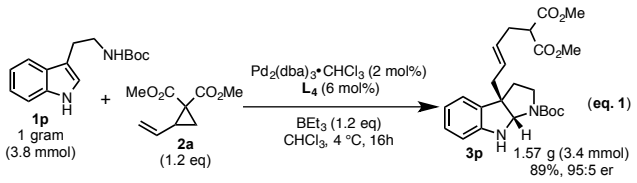
**Table 4. Scope of Tandem C3-allylation/Cyclizations of 3-Substituted-1*H*-indoles.**[a]




| entry | **3** | product structure | yield[b] | er[c] |
|---|---|---|---|---|
| 1 | **f** |  | 93 | 96:4 |
| 2 | **g** |  | 83 | 92:8 |
| 3 | **h** |  | 89 | 92:8 |
| 4 | **i** |  | 95 | 96:4 |
| 5 | **j** |  | 89 | 94:6 |
| 6 | **k** |  | 92 | 92:8 |
| 7 | **l** |  | 88 | 91:9 |
| 8 | **m** |  | 87 | 86:14 |
| 9 | **n** |  | 90 | 98:2 |
| 10 | **o** |  | 80 | 96:4 |
| 11 | **p** |  | 85 | 95:5 |
| 12[d] | **q** |  | 80 | 94:6 |
| 13[d] | **r** |  | 82 | 95:5 |
| 14 | **s** |  | 93 | 97:3 |
| 15 | **t** |  | 90 | 98:2 |

[a]Reaction Conditions: 0.20 mmol of **1**, 2.5 mol% of $Pd_2(dba)_3$•$CHCl_3$, 7.5 mol% of $\mathbf{L_4}$, 0.24 mmol of $BEt_3$ and **2**, in $CHCl_3$ at 4 °C for 16h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase. [d]The cyclization onto the imine intermediate smoothly occurred by addition of ethanolamine to the crude indolenine products.

To demonstrate the scalability and practicality of this newly developed method, the reaction was performed using one gram of the *N*-Boc protected tryptamine **1p** with decreased catalyst loading (eq. 1). To our delight, employing 2 mol% palladium catalyst and 6 mol% of the Trost ligand $\mathbf{L_4}$ provided the pyrroloindoline **3p** in 89% isolated yield and 95:5 er.




Tryptophan-originated alkaloids are ubiquitous in nature, mostly as diketopiperazines (DKPs) or diketomorpholines (DKMs) (Figure 5, highlighted in red).[19] Early efforts to construct these natural products usually employed an indirect approach through diastereoselective seleno- or halocyclization of tryptophan derivatives followed by Stille coupling to install the desired allyl motifs.[20] More recently, Tamaru showed that a Pd-catalyzed allylation of *L*-tryptophan methyl ester using triethylborane exclusively provided the *endo*-pyrroloindoline product[8] while Carreira found that a Ir-catalyzed reverse prenylation of the same starting material led to the preferential formation of the *exo*-pyrroloindoline product, both in a diastereoselective manner.[21] Later, Stark reported the first and only diastereodivergent reverse prenylation of tryptophan derivatives, in which the borane reagents mysteriously played a key role in determining the *exo*- and *endo*-selectivity.[22] A ligand-controlled enantioselective allylation of tryptophan derivatives can hypothetically provide convenient access to either *exo*- or *endo*-selective pyrroloindoles, but the pre-existing chirality of the starting material might display a match-mismatch effect with the chiral ligand and consequently hamper the *exo*- or *endo*-selectivity.[12b] Building upon the encouraging results of asymmetric allylation of 3-substituted-1*H*-indoles using VCPs, we were curious to examine the more challenging tryptophan derivatives, in the hope of accessing pyrroloindoline products with the corresponding *exo*- and *endo*-selectivity being well controlled by the chiral ligands.

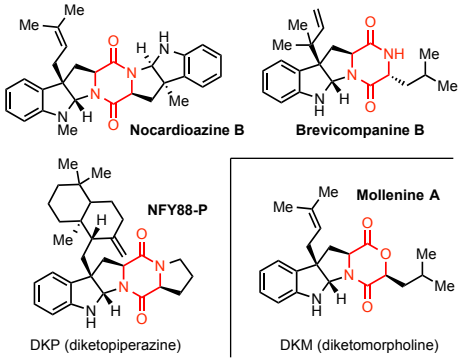
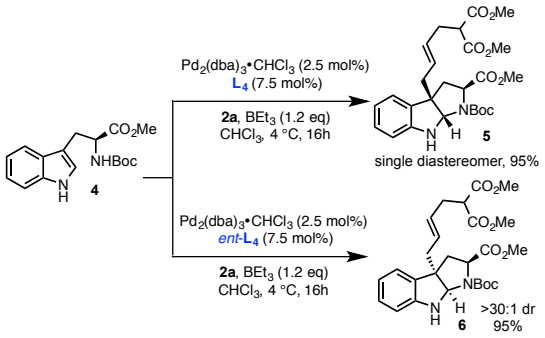



**Figure 5.** Bioactive molecules bearing DKP and DKM motifs.

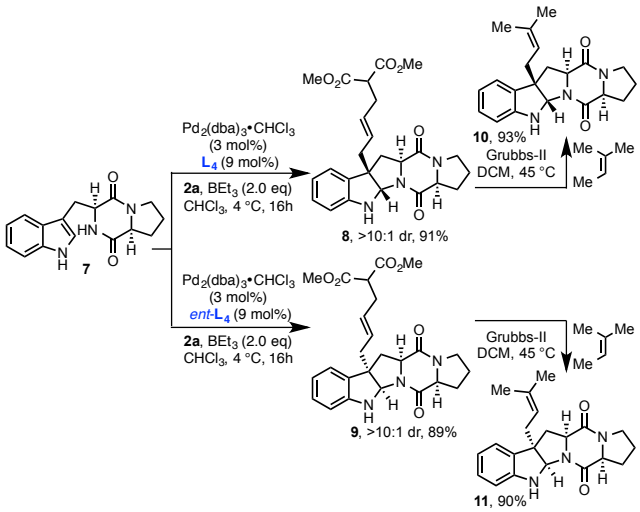
We first studied the Pd-catalyzed asymmetric allylation of commercial *N*-Boc-*L*-tryptophan methyl ester **4** with VCP derivative **2a** using triethylborane and stilbene-derived Trost ligand $\mathbf{L_4}$ [(*R*,*R*)] (Scheme 1). To our delight, the *exo*-pyrroloindoline product **5** was obtained as a single diastereomer in 95% yield. Switching to *ent*-$\mathbf{L_4}$ [(*S*,*S*)] led to exclusive formation of the *endo*-selective product **6**. In stark contrast, using DPPF as a ligand delivered a 1:1 mixture of products **5** and **6**. These outcomes suggested that the product distribution during the Pd-AAA was guided by the chiral ligand. Accordingly, no match-mismatch effect was seen, which is different from prior observations in the iridium-catalyzed system using a cinnamyl carbonate as the electrophile.[12b]

**Scheme 1. Pd-AAA of the *N*-Boc-*L*-Tryptophan Methyl Ester Using a VCP.**




We next turned our attention to the DKP-containing tryptophan derivative **7** (Schemes 2).[23] This cyclic dipeptide underwent the desired asymmetric allylation with slightly increased catalyst loading to provide the corresponding pentacyclic products **8** and **9** in high yield. The ligand effectively controlled the product formation during this transformation. Interestingly, the obtained products could further participate in a cross-metathesis reaction[24] with 2-methylbut-2-ene to deliver the corresponding prenylated products **10** and **11** that are known precursors for the cell cycle inhibitor tryprostatin B.[25]

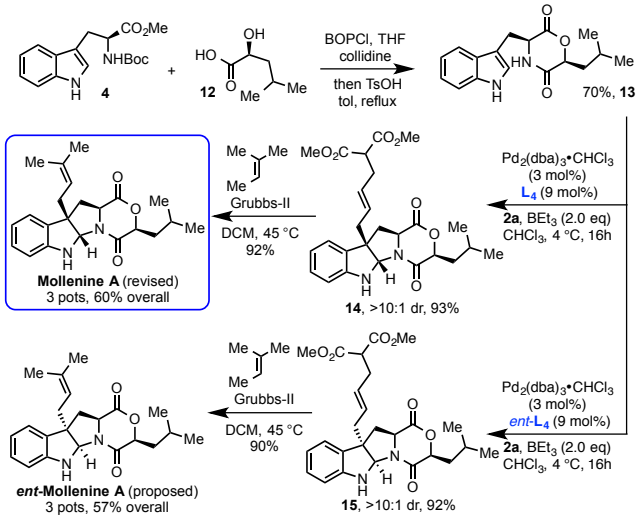
**Scheme 2. Pd-AAA of the Cyclo(*L*-Trp-*L*-Pro) (DKP motif) Using a VCP.**




Our motivation to examine the DKM-containing tryptophan derivative **13** arose from the desire to quickly access and verify the absolute stereochemistry of mollenine A using our newly established method (Scheme 3). Chan recently reported the first total synthesis of this molecule in 9 steps and 11.4% overall yield, using the aforementioned indirect approach of diastereoselective bromo-cyclization of *N1*-Boc-protected **4** followed by a Stille allylation and olefin cross-metathesis to install the prenyl moiety.[26] During the preparation of this manuscript, Ishikawa realized the synthesis of mollenine A in three steps and 16.5% overall yield through a direct yet uncontrolled prenylation of *D*-tryptophan ethyl ester under strong acidic conditions.[27] The desired prenylated intermediate was obtained in 22% yield along with six side products. As a result, we believed that our ligand-controlled allylation process would provide a better approach to synthesize mollenine A. Starting from *L*-tryptophan drivative **4** and (*S*)-2-hydroxy-4-methylpentanoic acid (HMA) **12**, the DKM **13** was prepared in

70% yield in one pot.[28] Subjecting this material to the allylation conditions using ligand **L$_4$** [(*R,R*)] and *ent*-**L$_4$** [(*S,S*)] provided the tetracyclic pyrroloindolines **14** and **15** respectively in high yields and >10:1 dr, showcasing the ligand control for the transformation. Subsequent olefin cross-metathesis provided mollenine A (revised structure) as well as the enantiomer of its proposed structure. This allowed us to verify the absolute configuration of mollenine A and also establish the absolute stereochemistry of the Pd-AAA products **14** and **15**. The three-pot synthesis enabled us to obtain the mollenine A in an impressive 60% overall yield, demonstrating the utility of our method to build DKP- and DKM-containing natural products.

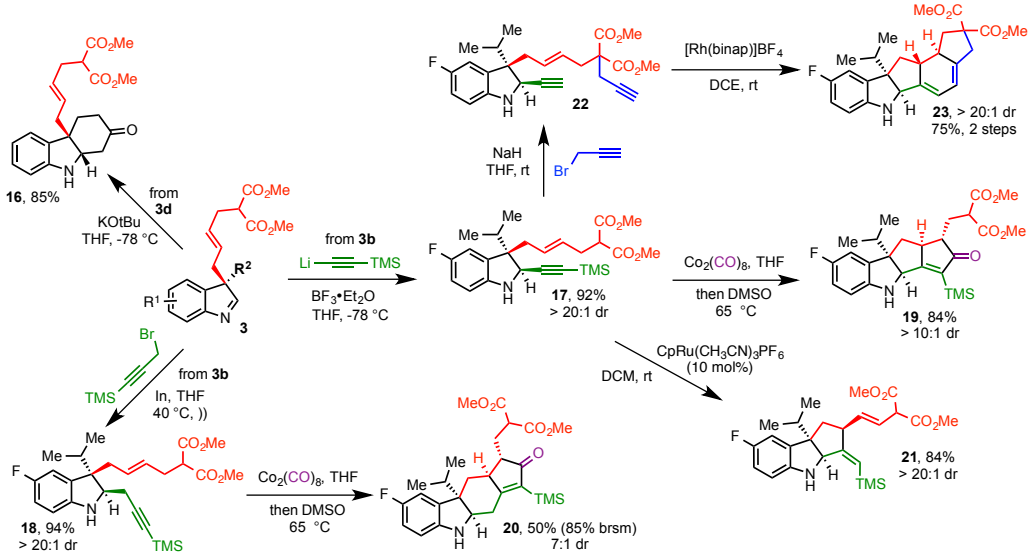
**Scheme 3. Pd-AAA of the Cyclo(*L*-Trp-*S*-HMA) (DKM motif) Using a VCP; Total Synthesis of Mollenine A.**




To further validate the synthetic utility of our newly developed method, the obtained indolenine products **3** were elaborated to complex polycycles via atom-economic addition processes (Scheme 4). Upon treatment with base,[29] indolenine **3d** underwent an intramolecular 1,2-addition to give the tricyclic cyclohexanone **16** in 85% yield. Meanwhile, the intermolecular 1,2-additions of indolenine **3b** with lithium (trimethylsilyl)acetylide in the presence of $BF_3$•$Et_2O$[30] and propargyl bromide/In under sonication [31] diastereoselectively installed the corresponding alkynyl and propargyl motifs, providing the indolines **17** and **18** both in >90% yield and >20:1 dr. Both the obtained indolines could participate in a Pauson-Khand reaction [32] to deliver the respective 6,5,5,5- and 6,5,6,5-tetracyclic compounds **19** and **20** with good control of diastereoselectivity. In addition, the Ru-catalyzed alkene-alkyne coupling of indoline **17** provided the tricyclic 1,4-diene **21** in 84% yield and >20:1 dr, whose stereochemistry was determined by NOE analysis. These powerful transformations take advantage of the newly furnished imine and allyl motifs, demonstrating the benefits of functionalizing C3-substituted-1*H* indoles via Pd-AAA. Using VCPs for this tranformation also introduces a malonate group, which can serve as an excellent nucleophile for additional product decorations. For instance, propargylation of indoline **17** using propargyl bromide and NaH provided the enediyne **22**, which smoothly underwent a Rh-catalyzed [2 + 2 + 2] reaction[33] to deliver the 6,5,5,6,5-pentacyclic product **23** in 75% yield over 2 steps and >20:1 dr, the stereochemistry of which was determined by NOE analysis. The obtained product **23** bears a diene motif that has the potential to participate in various [4 + 2] reactions to further increase its structural complexity if needed. These interesting elaborations demonstrate the rewards of employing VCP derivatives rather than the previously used allylic alcohols or carbonates to functionalize C3-substituted-1*H* indoles.

The proposed catalytic cycle is depicted in Figure 6.[34] The palladium(0) catalyst opens the VCP derivative **2a** to generate the zwitterionic π-allylpalladium complex **I**. Meanwhile, triethylborane readily binds to the indole **1a** to form the complex **II**, dramatically increasing the acidity of the indole proton. As a result, it protonates the malonate anion of **I**, which consequently shuts down the nucleophilic reactivity of the malonate site and allows the obtained π-allylpalladium complex **III** to solely serve as an electrophile for the following allylation reaction. The high-energy π-allylpalladium species **III** might be stabilized via a possible intramolecular coordination to one of the ester groups. The newly generated *N*-indolyltriethylborate **IV** regioselectively attacks the complex **III** at the terminal

**Scheme 4. Derivatization of Indolenines 3.**



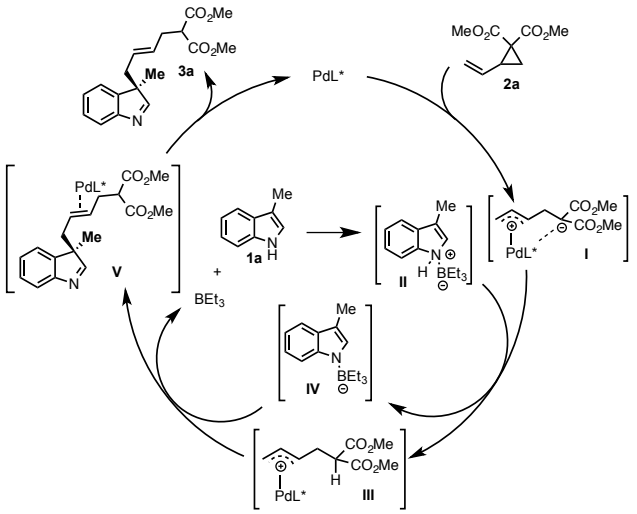



**Figure 6.** Proposed catalytic cycle.

position to deliver the indolenine/palladium complex **V** and releases the triethylborane for next association cycle with the starting indole **1a**. As the borane strongly binds to the indole nitrogen of **IV**, the *N*-allylation process is inhibited. Finally, decomplexation of complex **V** liberates the product **3a** and then turns over the catalytic cycle.

## CONCLUSION

In summary, we have reported the first use of VCP derivatives as electrophiles for the asymmetric allylation of C3-substituted-1*H* indoles and tryptophan derivatives. Utilizing $Pd_2(dba)_3$•$CHCl_3$ and stilbene-derived Trost ligand $\mathbf{L_4}$, a broad range of 3,3-disubstituted- indolenines and indolines has been prepared in a highly chemo-, regio-, and enantioselective fashion. This completely atom-economic transformation enables indoles bearing a pendant C3-nucleophile to cleanly react with VCPs, whereas employing a Lewis acid might be problematic. The reaction can be performed on gram scale. The stereochemical outcomes of asymmetric functionalizations of tryptophan derivatives are well controlled by the chiral ligands, allowing us to expeditiously synthesize mollenine A. The indolenine products can be elaborated to intricate polycyclic compounds by making use of the newly installed imine and internal olefin motifs. More importantly, VCPs, like no other allylation reagents, introduce a nucleophilic malonate substituent through the Pd-AAA, providing an excellent handle for additional product derivatization.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, compound characterization data, and spectra (PDF)

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENT

We appreciate the NIH (GM-033049) and the NSF (CHE-1360634) for their generous support of our programs.

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