

### Palladium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Vinyl Aziridines with Nitrogen Heterocycles: Rapid Access to Biologically Active Pyrroles and Indoles

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**Abstract:** We report that nitrogen heterocycles can serve as competent nucleophiles in the palladium-catalyzed dynamic kinetic asymmetric alkylation of vinyl aziridines. The resulting alkylated products were obtained with high regio-, chemo-, and enantioselectivity. Both substituted 1*H*-pyrroles and 1*H*-indoles were successfully employed to give exclusively the branched *N*-alkylated products. The synthetic utility of this process was demonstrated by applying this method to the preparation of several medicinal chemistry lead compounds and bromopyrrole alkaloids including longamide B, longamide B methyl ester, hanishin, agesamides A and B, and cyclooroidin.

#### Introduction

The Pd-catalyzed asymmetric allylic alkylation (Pd-AAA) has become a powerful tool for the construction of stereocenters and has engendered a number of versatile methods for the total synthesis of natural products and other biologically active targets.<sup>1</sup> Unlike other asymmetric reactions, the Pd-AAA is capable of constructing several different types of bonds in an enantioselective fashion, including C–C, C–N, C–O, and C–S bonds. Furthermore, this transformation is highly chemoselective and can be performed in the presence of a large number of functional groups. Despite its versatility, the Pd-AAA typically requires the use of soft stabilized nucleophiles such as malonates or imides and has been limited in its ability to accommodate hard nucleophiles. Our group has extended the scope of this reaction to include hard nucleophiles such as alkoxides, lithium enolates, and benzylic anions employing a family of diphenylphosphino benzoic acid-derived ligands (Figure 1).<sup>2</sup> However, hard nitrogen nucleophiles, specifically, nitrogen heterocycles, largely remain unexplored in this transformation (eq 1).<sup>3</sup> Likewise, the scope of electrophiles used in the Pd-AAA has been limited to allylic ester derivatives.<sup>1</sup> Other, unstabilized leaving groups, such as ethers and amines, are difficult to employ. By taking advantage of ring strain to facilitate ring-opening, vinyl epoxides have been successfully employed in

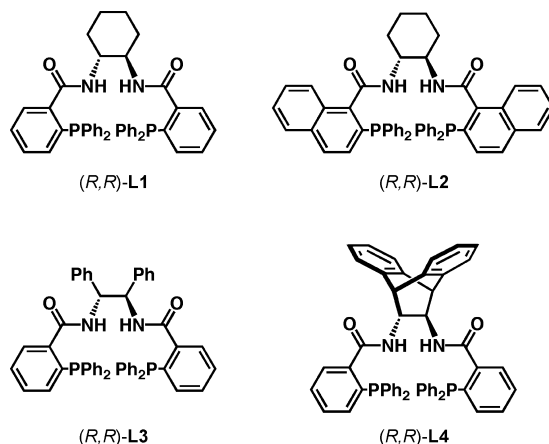
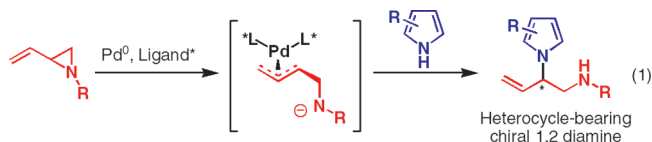


Figure 1. Diphenylphosphino benzoic acid-based ligands.

the Pd-AAA.<sup>4</sup> To date, the analogous vinyl aziridines have remained a challenge in this transformation despite their potential to construct chiral 1,2 diamines (eq 1).



Heterocycle-bearing chiral 1,2 diamines (see eq 1) are present in a large number of natural products and small molecule pharmaceuticals.<sup>5</sup> One important class of natural products containing this structural motif, the bromopyrrole alkaloids,

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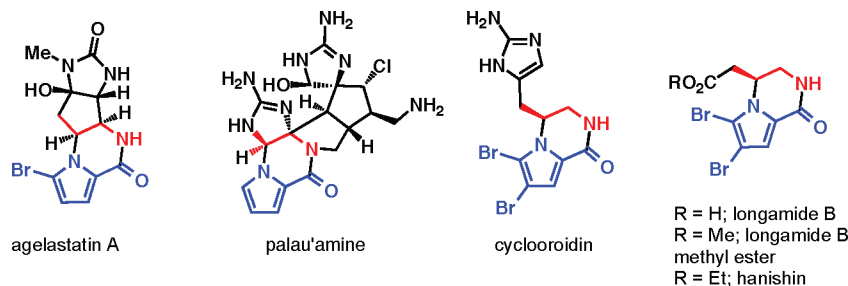


Figure 2. Representative bromopyrrole alkaloids.

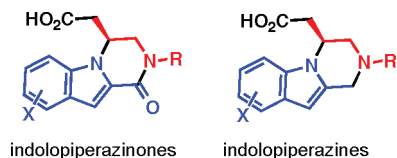


Figure 3. Representative medicinal chemistry lead compounds.

present a significant synthetic challenge due to the presence of numerous contiguous stereocenters, nitrogen-rich polar functional groups, and sensitive pyrrole nuclei (Figure 2). Due to their intriguing structures and biological activities, the bromopyrrole alkaloids have been the target of numerous total syntheses.<sup>6</sup> The agelastatins contain a fused tetracyclic structure and possess a variety of interesting biological activities including nanomolar activities against several cancer cell lines.<sup>7</sup> Palau'amine possesses a strained hexacyclic skeleton, flanked by eight contiguous stereocenters and nine nitrogen atoms and has shown antibiotic, antifungal, as well as immunosuppressant activity.<sup>8</sup> Other bromopyrrole alkaloids, including longamide B and its methyl ester, hanishin, agesamides A and B, and cyclooroidin contain pyrrole-fused piperazinones, and possess significant antibiotic and cytotoxic activities.<sup>9</sup>

Like the piperazinones found in pyrrole alkaloids, indole-fused piperazinones and piperazines (Figure 3) have also shown a broad array of biological activities.<sup>10</sup> Indole-fused piperazinones are known for their ability to act as conformationally rigid peptidomimetics and have been shown to act as antagonists of the histamine 3 (H3) receptor, which is expressed in the central nervous system and controls histamine levels in the brain.<sup>10</sup>

These indole-fused heterocycles are present in a large number of drug candidates as well as medicinal chemistry lead compounds.<sup>11</sup> Recently, these compounds have been patented for their H3 antagonist activity, which can be used to treat obesity, cardiovascular disorders, Alzheimer's disease, and other neurological disorders.<sup>10</sup>

Due to the abundance of biologically active compounds that contain a heterocycle-bearing 1,2 diamine (see eq 1 and Figures 2 and 3), the development of catalytic asymmetric methods to generate these moieties is an important challenge. While many asymmetric alkylation methods exist for functionalizing heterocycles at the carbon atom,<sup>12</sup> relatively few examples are known for the direct asymmetric alkylation at nitrogen. Chen and co-workers reported an organocatalytic intermolecular asymmetric *N*-alkylation of various substituted indoles with Morita Baylis-Hillman carbonates.<sup>13</sup> Likewise, Bandini et al. have disclosed that cinchona alkaloid-derived catalysts can facilitate enantioselective *N*-alkylations of indoles in an intramolecular fashion.<sup>14</sup> Most recently, Hartwig et al. reported an elegant Ir-catalyzed chemo-, regio- and enantioselective allylation of indoles with linear allyl carbonates.<sup>15</sup> Our group has utilized heterocycles as nitrogen nucleophiles in the Pd-AAA in the context of natural product total syntheses.<sup>3</sup> However, no general method has yet been disclosed utilizing these molecules as nucleophiles in the Pd-AAA.

The Pd-AAA can operate through a variety of mechanisms to induce chirality. Unlike many other asymmetric transformations, the Pd-AAA can convert racemic starting materials to enantioenriched products through a dynamic kinetic asymmetric transformation (DYKAT).<sup>16</sup> In contrast to a kinetic resolution, which is limited to a maximum theoretical yield of 50% and involves consumption of only one enantiomer of the starting material, a DYKAT has a theoretical yield of 100%. In this transformation, both enantiomers of the starting material are

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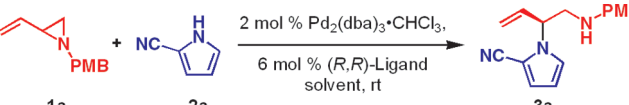
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**Table 1.** Selected Optimization Conditions<sup>a</sup>


entry	ligand	solvent	% yield <sup>b</sup>	% ee <sup>c</sup>
1	<b>L1</b>	DCE	73	61
2	<b>L2</b>	DCE	99	89
3	<b>L3</b>	DCE	77	72
4	<b>L4</b>	DCE	<5	9
5	<b>L2</b>	PhMe	50	89
6	<b>L2</b>	PhCF <sub>3</sub>	52	88
7	<b>L2</b>	THF	52	89
8	<b>L2</b>	DME	44	89
9	<b>L2</b>	Dioxane	60	93

<sup>a</sup> All reactions were performed with 1.0 equiv of **2a** and 1.1 equiv of **1a** at ambient temperature at 0.25 M in the designated solvent. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC.

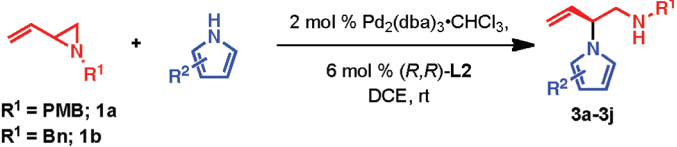
converted into a single, optically active, product. This type of process is desirable, as it minimizes waste and increases the overall synthetic efficiency and atom economy of a reaction by employing all of the starting material.<sup>16</sup>

While racemic vinyl epoxides have been shown to undergo a Pd-catalyzed DYKAT with a number of carbon and heteroatom nucleophiles, examples with vinyl aziridines remain scant.<sup>17</sup> Typically, vinyl aziridines require a strong electron-withdrawing group on the nitrogen atom to increase the electrophilicity of the adjacent carbon atoms.<sup>18</sup> The necessity of such a group imposes a limitation on the system, and ideally

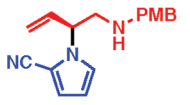
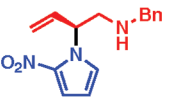
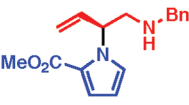
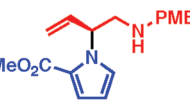
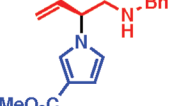
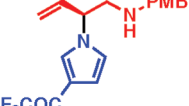
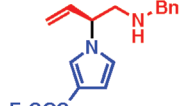
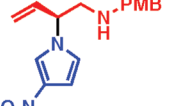
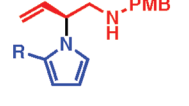
both electron-rich and electron-deficient vinyl aziridines could be used. Our group has studied these compounds in the Pd-AAA but required the use of isocyanates to activate the vinyl aziridine.<sup>17a</sup> Thus, the utility with these useful, nitrogen-containing electrophiles has been limited, and nucleophiles such as nitrogen heterocycles have remained understudied. The reactions of vinyl aziridines with nitrogen heterocycles, such as pyrrole and indole, would provide access to useful, enantioenriched, heterocycle-bearing diamine products, which comprise the core of several biologically relevant compounds.

## Results and Discussion

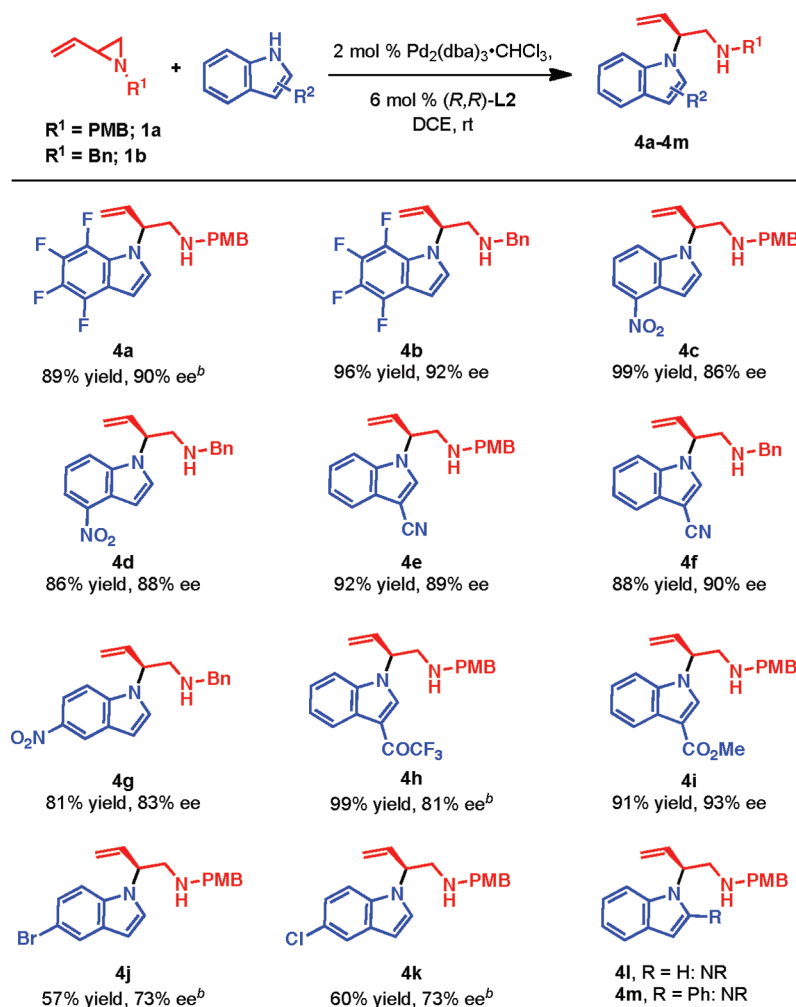
**Reaction Optimization.** To determine conditions under which nitrogen heterocycles could serve as competent nucleophiles in the Pd-AAA, we studied the reaction of 1*H*-pyrrole-2-carbonitrile (**2a**) with vinyl aziridine **1a**<sup>17a</sup> (Table 1). Treatment of this system with 2 mol % Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, and 6 mol % of ligand **L1** in 1,2-dichloroethane (DCE) provided the desired *N*-alkylated product **3a** in a promising 73% yield and 61% ee (entry 1). Previous work with vinyl aziridines showed that changing the ligand had a profound impact on both reactivity and selectivity of the transformation.<sup>17a</sup> Further screening (entries 2–4) revealed that ligand **L2**, containing a naphthyl moiety, provided the desired product **3a** in 99% yield and 89% ee. Additionally, the choice of solvent (Table 1, entries 5–8) was found to have a dramatic effect on the course of this transformation: conducting the reaction in aromatic solvents (entries 5 and 6) or polar solvents (entries 7–9) had a detrimental effect on the reactivity while showing little impact on the levels of enantioselectivity.

**Table 2.** Reaction Scope of Pyrroles with Vinyl Aziridines<sup>a</sup>


R<sup>1</sup> = PMB; **1a**  
R<sup>1</sup> = Bn; **1b**

		
<b>3a</b> 99% yield, 89% ee	<b>3b</b> 77% yield, 89% ee	<b>3c</b> 76% yield, 96% ee
		
<b>3d</b> 86% yield, 94% ee	<b>3e</b> 86% yield, 94% ee	<b>3f</b> 92% yield, 93% ee
		
<b>3g</b> 95% yield, 93% ee	<b>3h</b> 85% yield, 90% ee <sup>b</sup>	<b>3i</b> , R = Et: NR <b>3j</b> , R = H: NR

<sup>a</sup> All reactions were performed with 1.0 equiv of pyrrole nucleophile and 1.1 equiv of **1** at ambient temperature. Isolated yield. % ee was determined by chiral HPLC. <sup>b</sup> Cs<sub>2</sub>CO<sub>3</sub> (1.1 equiv) was added.

**Table 3.** Reaction Scope of Indoles with Vinyl Aziridines<sup>a</sup>

<sup>a</sup> All reactions were performed with 1.0 equiv of indole nucleophile and 1.1 equiv of **1** at ambient temperature. Isolated yield. % ee was determined by chiral HPLC. <sup>b</sup> Cs<sub>2</sub>CO<sub>3</sub> (1.1 equiv) was added.

The combination of ligand **L2** in DCE was found to be optimal for this transformation. Under all the conditions that were evaluated, the branched, *N*-alkylated product was observed exclusively, demonstrating the profound chemo- and regioselectivity of the transformation.

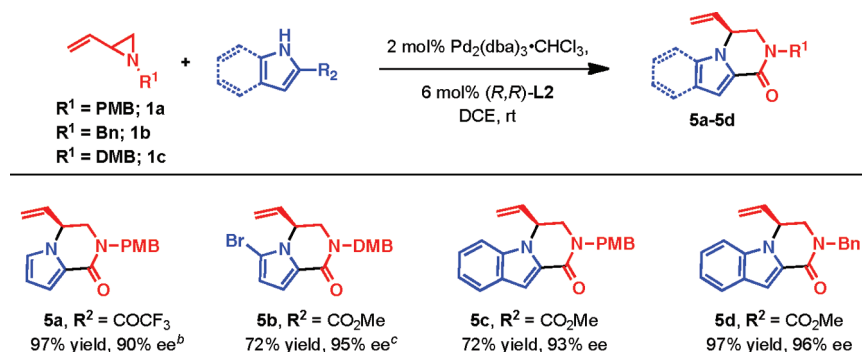
**Substrate Scope.** With optimized conditions in hand, we next studied the scope of this transformation using other substituted pyrroles and vinyl aziridines (Table 2). Vinyl aziridines substituted at R<sup>1</sup> with either PMB (**1a**) or Bn (**1b**) groups reacted smoothly and typically resulted in similar levels of enantioselectivity. A variety of functional groups were tolerated on the pyrrole nucleus at both the C2- and C3-positions and afforded the branched *N*-alkylated products in high yield and % ee. The presence of an electron-withdrawing group on the pyrrole ring

was necessary for the reaction to proceed, and only starting materials were recovered when an electron-rich or unsubstituted pyrrole was used as the nucleophile (**3i,j**). To investigate whether C-alkylation could occur, *N*-methyl pyrrole was subjected to the optimized reaction conditions but resulted in only slight decomposition of the starting materials. The reaction between methyl 1*H*-pyrrole-2-carboxylate with vinyl aziridines **1a** and **1b** afforded homoallyl amines **3c** and **3d**, respectively, as acyclic products which could be stored at −20 °C for several weeks without appreciable cyclization to the piperazinone. The cyclic pyrrole-fused piperazinones could be accessed by heating the acyclic products to 40 °C for 16 h. In cases where lower yields were obtained, such as **3b** and **3c**, only unreacted pyrrole was observed, with little to no decomposition. On the other hand, unreacted vinyl aziridine was rarely observed at the end of the reaction. When 3-nitro-1*H*-pyrrole was used, the addition of 1.1 equiv of Cs<sub>2</sub>CO<sub>3</sub> was needed to facilitate the reaction (**3h**). However, no base was required in other cases, and the amide anion in the  $\pi$ -allyl Pd intermediate (see eq 1) was sufficiently basic to deprotonate the pyrrole N–H and facilitate the transformation.

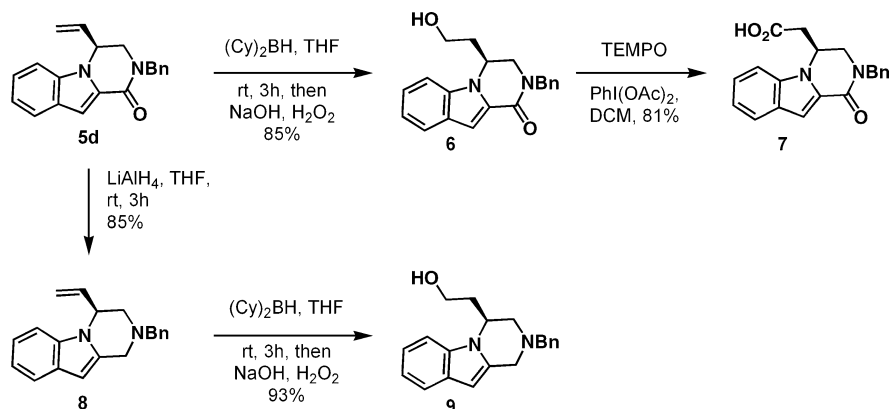
To further expand the generality of this process, indoles were employed as nucleophiles in the transformation. Like pyrroles,

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**Table 4.** Reactions of Nitrogen Heterocycles with Vinyl Aziridines to Access Piperazinones<sup>a</sup>

<sup>a</sup> All reactions were performed with 1.0 equiv of heterocyclic nucleophile and 1.1 equiv of **1** at ambient temperature. Isolated yield. % ee was determined by chiral HPLC. <sup>b</sup>  $\text{Cs}_2\text{CO}_3$  (1.1 equiv) was added. <sup>c</sup> Performed using 2.5 mol %  $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$  7.5 mol %  $(R,R)\text{-L1}$ , in  $\text{CH}_2\text{Cl}_2$  at rt.

**Scheme 1.** Synthesis of Medicinal Chemistry Lead Compounds

electron-deficient indoles reacted smoothly under the optimized reaction conditions providing the desired products in high yield and % ee (Table 3). Although indoles have a high propensity to undergo substitution at C3 in the presence of a Pd source and an allylic electrophile, only the *N*-alkylated, branched products were observed.<sup>19</sup> We postulated that *N*-alkylation could be suppressed in favor of C3 alkylation in the absence of an electron-withdrawing group, or in the presence of an electron-donating group at C2. However, using 2-methyl-1*H*-indole or unsubstituted indole (**4l**) led to only unreacted starting materials. Substitution on either the azole, or benzene portion of the indole moiety, was sufficient to facilitate the reaction. However, a strong electron-withdrawing group was necessary to obtain high levels of reactivity and enantioselectivity. When weak electron-withdrawing groups were employed, such as Cl or Br, both the yield and % ee of the product decreased (**4j,k**); 2-phenyl-1*H*-indole only afforded trace quantities of the desired product (**4m**). As for the cases with pyrroles, nitrile (**4e,f**), ester (**4i**), halide (**4j,k**), ketone (**4h**), and nitro (**4c,d,g**) functional groups were all tolerated in the transformation and little to no decomposition of the indole nucleophile was observed, demonstrating the high functional group compatibility of this transformation.

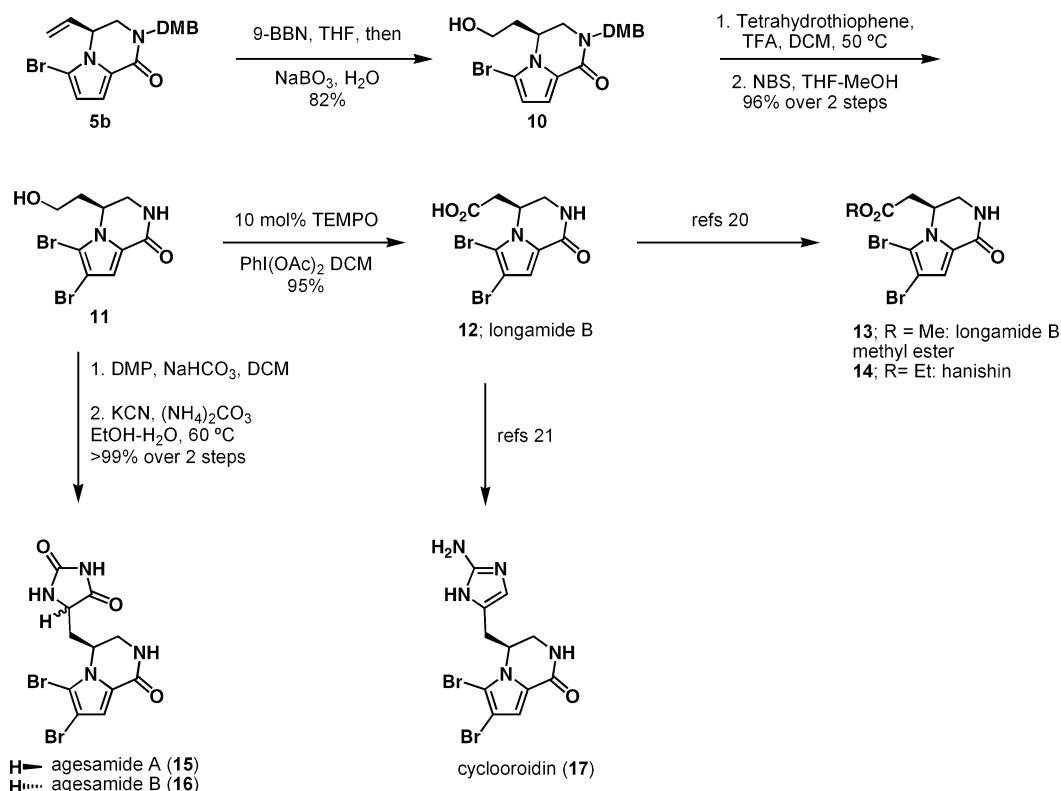
**Piperazinone Functionalization and Synthesis of Medicinal Chemistry Leads.** When heterocycles containing certain acyl substituents at the 2-position were employed in the transformation, a cyclization occurred, providing access to enantioenriched piperazinones (Table 4). For instance, pyrrole-fused piperazinone

**5a** was obtained in 97% yield and 90% ee from vinyl aziridine **1a** and pyrrole containing a trifluoromethyl ketone at the 2-position. Switching  $\text{R}^2$  from a trifluoromethyl ketone to a methyl ester also afforded the desired cycloadduct **5b**. Like pyrroles, indoles could also be employed as nucleophiles, to afford indole-fused piperazinones utilizing either **1a** or **1b** as the vinyl aziridine. Piperazinones containing a pyrrole moiety like the one found in **5b**, represent the core structure of a number of bromopyrrole alkaloids including longamide B, agesamides A and B, hanishin and cyclooroidin.<sup>9</sup> Piperazinones containing indole moieties such as **5c** and **5d** have also found broad use in medicinal chemistry and show significant biological activities.<sup>10</sup>

The indole products isolated from this cyclization were readily transformed into the core of several patented piperazinones (Scheme 1).<sup>10</sup> Hydroboration of compound **5d** followed by oxidation afforded primary alcohol **6** as the only product, in 85% yield. Oxidation of the alcohol **6** with  $\text{PhI}(\text{OAc})_2$  in the presence of catalytic TEMPO provided the known carboxylic acid **7** in 81% yield. The sign and magnitude of the optical rotation of this acid was in agreement with previous reports, confirming the absolute configuration from the Pd-AAA.<sup>10,14</sup>

Compound **5d** was easily reduced upon treatment with  $\text{LiAlH}_4$  to give the corresponding piperazine **8** in 85% yield. Indole-fused piperazines of this general structure are also found in a large number of medicinal chemistry leads, and have been shown to be useful in treating central nervous system disorders, gastrointestinal disorders, diabetes, obesity, and sleep apnea.<sup>10</sup> Hydroboration of piperazine **8**, followed by oxidation, provided the known alcohol **9** in 93% yield. Although we only show the

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**Scheme 2.** Concise Synthesis of Bromopyrrole Alkaloids

elaboration of a simple indole into the core of biologically active piperazinone **7** and piperazine **8**, utilizing substituted indoles should provide access to more complex members of this substrate class.

**Concise Synthesis of Bromopyrrole Alkaloids.** Bromopyrrole alkaloids are an important class of natural products with a range of biological activities.<sup>6</sup> Many of these alkaloids contain a piperazinone core that can be accessed through the Pd-AAA of a vinyl aziridine with a bromopyrrole nucleophile. To demonstrate the versatility of the method described herein, the syntheses of several bromopyrrole alkaloids were pursued (Scheme 2). Piperazinone **5b** served as a scaffold that was elaborated to a common intermediate from which many bromopyrrole alkaloids were synthesized. Hydroboration of **5b** with 9-BBN, followed by oxidation, provided the desired primary alcohol **10** in 82% yield. Cleavage of the dimethoxybenzyl (DMB) group with tetrahydrothiophene followed by bromination with NBS furnished alcohol **11** in 96% over two steps. Alcohol **11** was readily oxidized to longamide B (**12**) with PhI(OAc)<sub>2</sub> in the presence of catalytic TEMPO. Longamide B (**12**) could then be converted to three additional natural products. Esterification of the free acid in longamide B (**12**) under known literature conditions<sup>20</sup> with either a methyl or ethyl group affords longamide B methyl ester (**13**), and hanishin (**14**) respectively. Two additional bromopyrrole alkaloids, agesamides A and B, were readily accessed from alcohol **11**. Oxidation of **11** with Dess-Martin periodinane, followed by treatment with potassium cyanide and ammonium carbonate, lead to both agesamides A (**15**) and B (**16**). Likewise, installation of the amino-imidazole moiety onto the free acid, affords cyclooroidin (**17**).<sup>21</sup>

**Mechanistic Discussion and Rationalization of Asymmetric Induction.** We propose the following mechanistic rationale for the observed stereochemistry based on the “wall and flap” model previously reported.<sup>1d,22</sup> Initial ionization of the two enantiomers of the vinyl aziridine **1** (Scheme 3) with the (*R,R*)-enantiomer of the Pd-ligand complex proceeds rapidly in both a matched and mismatched manner to provide two possible zwitterionic  $\pi$ -allyl Pd complexes **18** and *ent*-**18**, respectively. These two intermediates can interconvert through a rapid  $\pi$ - $\sigma$ - $\pi$  equilibration. Nucleophilic attack of the pyrrole nucleophile **2** on the  $\pi$ -allyl palladium species **18**, at the more substituted terminus, provides the desired product **3**.

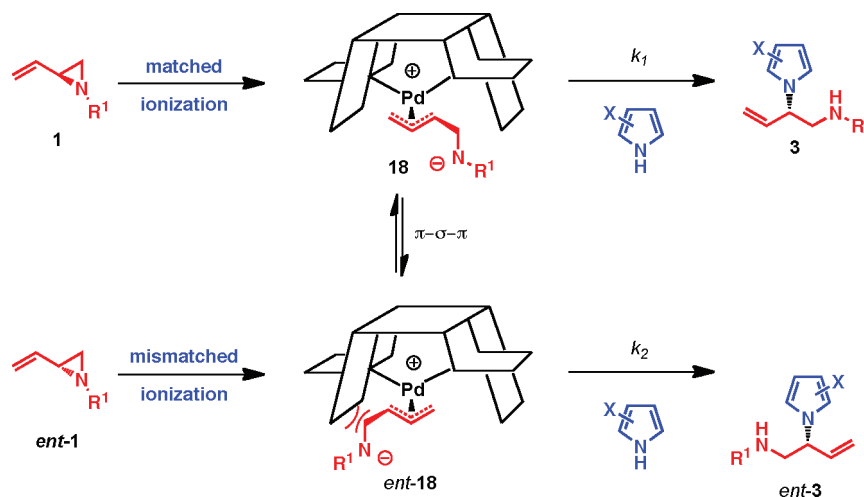
To obtain high levels of enantioselectivity, a Curtin-Hammett situation must be established such that  $\pi$ - $\sigma$ - $\pi$  interconversion is rapid and much faster than the subsequent nucleophilic attack. By using a larger ligand, **L2**, a more sterically encumbered environment is established, which slows down the rate of nucleophilic attack and increases the time allowed for  $\pi$ - $\sigma$ - $\pi$  interconversion. An unfavorable steric interaction between one of the two diastereomeric  $\pi$ -allyl Pd intermediates determines which enantiomer of the product is formed, such that  $k_1$  is much larger than  $k_2$ . The absolute configuration of the product from this transformation, as well as related reactions with vinyl epoxides, support this model.<sup>4</sup>

Pd-catalyzed allylic alkylation of monosubstituted  $\pi$ -allyl-Pd intermediates typically favors the achiral, linear product. To rationalize the exclusive regioselectivity for the branched product, we propose that nucleophilic attack proceeds through a five-membered transition state (Scheme 4). In this transition

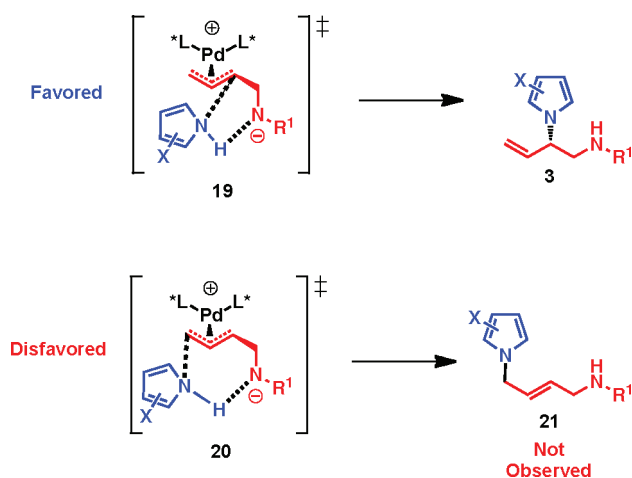
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Scheme 3. Mechanistic Rationale



Scheme 4. Rationale for Observed Regioselectivity



state, the amide anion of the vinyl aziridine directs the pyrrole nucleophile through a hydrogen bond with the pyrrole N–H, to the proximal end of the  $\pi$ -allyl-Pd moiety. Thus nucleophilic attack proceeds through the favored five-membered transition state **19**, leading to the observed branched product. This would preclude the reaction proceeding through a strongly disfavored seven-membered transition state **20**, which contains a trans-olefin and leads to the achiral linear product.

## Conclusion

In conclusion, a highly chemo-, regio-, and enantioselective palladium-catalyzed asymmetric allylic alkylation between nitrogen heterocycles and vinyl aziridines has been developed. Both substituted pyrroles and indoles can be utilized as nucleophiles in the transformation to afford the *N*-alkylated branched products exclusively in high yield and % ee. The presence of an electron-withdrawing group on the nitrogen heterocycle was necessary for this reaction to proceed, but many functional groups on the pyrrole and indole nuclei were tolerated. No electron-withdrawing groups were needed on the vinyl aziridine to facilitate its opening, adding to the high generality of this process.

By substituting the heterocycles at the C2 position with an ester derivative, piperazinones were accessed readily through a formal asymmetric [3 + 3] cycloaddition. The indole-fused

piperazinones were used as synthetic building blocks to access a series of drug leads that have received extensive attention from the medicinal chemistry community. Likewise, pyrrole-fused piperazinones were used as synthetic building blocks to rapidly assemble the bromopyrrole alkaloids longamide B, longamide B methyl ester, hanishin, agesamides A and B, and cyclooroidin.

## Experimental Section

**Typical Procedure for the Pd-Catalyzed Asymmetric Allylic Alkylation of Pyrroles with Vinyl Aziridines.** To a flame-dried microwave vial equipped with a magnetic stir bar was added 1*H*-pyrrole-2-carbonitrile **2a** (18.4 mg, 0.2 mmol) and vinyl aziridine **1a** (48.2 mg, 0.22 mmol). The system was evacuated and filled with argon (3 $\times$ ) and dry degassed DCE (0.4 mL) was then added. In a separate flame-dried microwave vial equipped with a magnetic stir bar was added Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (4.1 mg, 4.0  $\times$  10<sup>−3</sup> mmol) and (*R,R*)-**L2** (9.5 mg, 0.012 mmol). The system was evacuated and filled with argon (3 $\times$ ), and DCE (0.4 mL) was added. This vial was stirred at rt for 15–20 min until a bright orange color persisted and its contents were then cannulated to the first vial. The reaction mixture was stirred for 48 h at rt, diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and then poured onto water (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated *en vacuo*. The crude reaction mixture was purified by flash column chromatography on silica gel (30% ethyl acetate in petroleum ether) to provide 56 mg of a yellow oil (**3a**) (99% yield, 89% ee by HPLC, OJ-H column, 9:1 heptane/*i*-propanol, 1.0 mL/min, 254 nm, rt = 27.4, 30.2 min). *R*<sub>f</sub> = 0.30 (30% ethyl acetate/petroleum ether). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.20–7.17 (m, 2H), 6.92 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.86–6.84 (m, 2H), 6.82 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.22 (dd, *J* = 3.9, 2.8 Hz, 1H), 5.97 (ddd, *J* = 17.1, 10.5, 5.9 Hz, 1H), 5.28 (ddd, *J* = 10.5, 1.3, 0.7 Hz, 1H), 5.10 (ddd, *J* = 17.2, 1.5, 0.7 Hz, 1H), 4.97–4.92 (m, 1H), 3.79 (s, 3H), 3.72 (q, *J* = 12.2 Hz, 2H), 3.13–3.03 (m, 2H), 1.35 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz):  $\delta$  159.2, 135.3, 132.2, 129.7, 124.7, 120.5, 119.0, 114.4, 114.3, 110.3, 104.3, 61.5, 55.7, 53.1, 52.5. IR (film): 3335, 3123, 2917, 2836, 2214, 1610, 1511, 1457 cm<sup>−1</sup>. [ $\alpha$ ]<sub>D</sub>: −31.7 (CH<sub>2</sub>Cl<sub>2</sub>, c 1.00). HRMS (C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>ONa): calculated (M + Na) 304.1426, found (M + Na) 304.1428.

**Typical Procedure for the Pd-Catalyzed Asymmetric Allylic Alkylation of Indoles with Vinyl Aziridines.** To a flame-dried microwave vial equipped with a magnetic stir bar was added methyl 1*H*-indole-3-carboxylate (35.0 mg, 0.2 mmol) and vinyl aziridine **1b** (48.2 mg, 0.22 mmol). The system was evacuated and filled with argon (3 $\times$ ) and dry degassed DCE (0.4 mL) was then

added. In a separate flame-dried microwave vial equipped with a magnetic stir bar was added  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (4.1 mg,  $4.0 \times 10^{-3}$  mmol) and (*R,R*)-**L2** (9.5 mg, 0.012 mmol). The system was evacuated and filled with argon ( $3\times$ ), and DCE (0.4 mL) was added. This vial was stirred at rt for 15–20 min until a bright orange color persisted and its contents were then cannulated to the first vial. The reaction mixture was stirred for 48 h at rt, diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL) and then poured onto water (10 mL). The organic layer was separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10$  mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and concentrated *en vacuo*. The crude reaction mixture was purified by flash column chromatography on silica gel (35% ethyl acetate in petroleum ether) to provide 66.0 mg of a clear oil (**4i**) (91% yield, 93% ee by HPLC, IA column, 95:5 heptane/*i*-propanol, 0.8 mL/min, 254 nm,  $r_t = 28.6, 32.8$  min.).  $R_f = 0.3$  (45% ethyl acetate/petroleum ether).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.21–8.18 (m, 1H), 7.93 (s, 1H), 7.39–7.34 (m, 1H), 7.30–7.23 (m, 2H), 7.13–7.10 (m, 2H), 6.84–6.80 (m, 2H), 6.00 (ddd,  $J = 17.3, 10.6, 5.7$  Hz, 1H), 5.27–5.24 (m, 1H), 5.10–5.06 (m, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 3.73–3.66 (m, 2H), 3.16 (qd,

$J = 14.2, 6.8$  Hz, 2H), 1.40 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz):  $\delta$  165.9, 159.2, 137.1, 135.2, 132.5, 132.1, 129.6, 127.0, 123.2, 122.5, 122.2, 118.7, 114.3, 110.8, 108.1, 59.2, 55.7, 53.7, 51.8, 51.5. IR (film): 2995, 2948, 2835, 1697, 1612, 1532, 1512, 1460  $\text{cm}^{-1}$ .  $[\alpha]_D: -19.4$  ( $\text{CH}_2\text{Cl}_2$ ,  $c$  1.03). HRMS ( $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3\text{Na}$ ): calculated ( $M + \text{Na}$ ) 387.1676, found ( $M + \text{Na}$ ) 387.1685.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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