

# A Short Synthesis of Delavatine A Unveils New Insights into Site-Selective Cross-Coupling of 3,5-Dibromo-2-pyrone

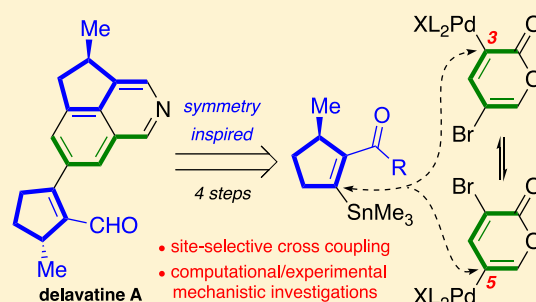
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**S** Supporting Information

**ABSTRACT:** The recognition of latent symmetry in delavatine A has enabled a short synthesis of the natural product starting from 3,5-dibromo-2-pyrone. The concise synthetic route features a cascade process involving a  $6\pi$  electrocyclization to construct the indane core of delavatine A. In addition, we have conducted detailed experimental and computational studies to gain an in-depth understanding of the mechanism of the observed site-selective cross-coupling of 3,5-dibromo-2-pyrone. This insight may provide new avenues to achieve the selective cross-coupling of multiply halogenated heteroarenes.



## INTRODUCTION

Plants of the *Incarvillea* genus, native to the Himalayas and Southwest China, have attracted considerable interest because of their use in traditional herbal medicine.<sup>1</sup> *Incarvillea delavayi* has been used as a medicinal plant to treat anemia, rheumatism, and dizziness.<sup>2</sup> Recently, a structurally unique alkaloid, delavatine A (**1**, Scheme 1a), was isolated from *I. delavayi* by Zhang and co-workers. This unusual isoquinoline-containing alkaloid displays micromolar antitumor activity against a number of human cancer cell lines.<sup>3</sup> Not surprisingly, the unique architecture and novel biological activity of **1** has made it an attractive synthetic target. An elegant total synthesis of **1** was recently reported by Li and co-workers that featured an asymmetric hydrogenation of an indenyl olefin group as well as the application of a triflamide-directed C–H olefination method (Scheme 1a).<sup>4a</sup>

Biosynthetically, it has been proposed that delavatine A (**1**) is derived from trisaldehyde **4** (Scheme 1b).<sup>3</sup> On this basis, our synthetic design targeted a final stage, bioinspired condensation of **4** with an ammonia source to yield the isoquinoline moiety in **1**. Furthermore, we recognized the latent symmetry in **4** (see the highlighted cyclopentenyls), which we envisioned could translate into an elegant and powerful retrosynthetic disconnection. Leveraging molecular symmetry (both hidden and overt) in total synthesis is especially powerful, as it may facilitate the identification of radically simplified precursors, and in this way enhance synthetic efficiency.<sup>5</sup>

By taking advantage of the latent symmetry of **4**, we also sought to devise a modular and convergent synthetic route to **4** through an ambitious cascade sequence starting from pseudosymmetric pyrone **7**. More specifically, it was anticipated that the indane core of **4** would be forged by  $6\pi$  electrocyclization<sup>6</sup> of cross-conjugated dienolate **5**, which in turn would arise from the highly conjugated polyene **6**. Given

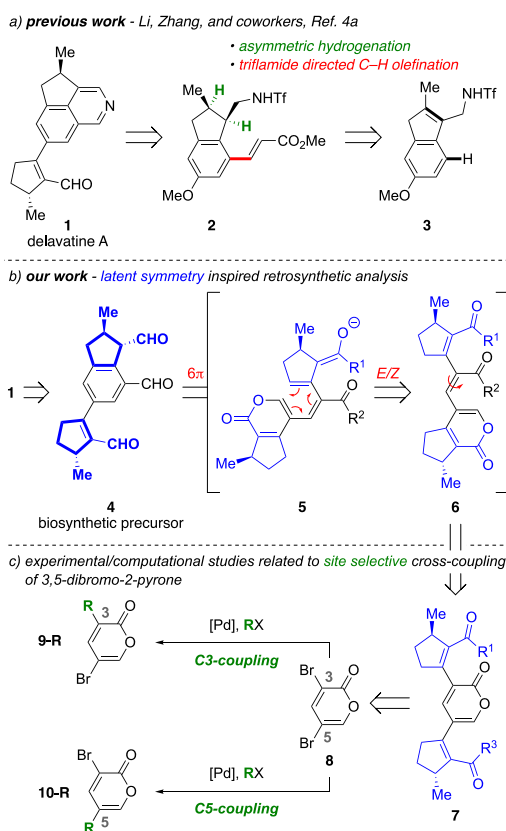
the inherent pseudosymmetry of pyrone **7**, this intermediate was traced back to known 3,5-dibromo-2-pyrone (**8**)<sup>7</sup> and the corresponding cyclopentenyl coupling partners (highlighted in blue in pyrone **7**) through site-selective cross-coupling reactions.

3,5-Dibromo-2-pyrone (**8**) is an  $\alpha$ -pyrone-derived polyhalogenated heterocycle bearing two chemically inequivalent C–Br bonds.<sup>8</sup> Site-selective modifications of **8**, leading to constitutional isomeric products, have been demonstrated by Cho and co-workers in various cross-coupling processes.<sup>9–11</sup> While certain experimental conditions have been established that enable site-selective coupling in **8**, the mechanistic rationale for this observed selectivity has not been unequivocally established. Site-selective cross-coupling reactions of polyhalogenated heterocycles<sup>12</sup> allow highly efficient retrosynthetic disconnections and have evolved to be invaluable transformations for both academic and industrial researchers.<sup>13</sup> While several studies aimed at understanding the basis of site-selective couplings have emerged over the past decade,<sup>14</sup> predicting and rationalizing the selectivity outcome has oftentimes remained challenging.<sup>8,12a</sup> In some polyhaloaromatic compounds, consideration of <sup>1</sup>H NMR chemical shifts of the C–H bonds in the corresponding nonhalogenated aromatic compounds can guide the prediction of site-selective transformations.<sup>15</sup> However, the cross-coupling of 3,5-dibromo-2-pyrone (**8**) gives rise to products that are contrary to this predicted outcome.<sup>8</sup> Hence, we sought to gather further mechanistic insight to guide predictable, site-selective couplings in **8**.

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## Scheme 1. Retrosynthetic Plan and Site-Selective Cross-Coupling of 3,5-Dibromo-2-pyrone



## MECHANISTIC STUDIES

On the basis of previous studies conducted by Cho and co-workers, we recognized that solvent choice, temperature, and addition of copper iodide appeared to have a marked influence on the observed coupling selectivity in **8**.<sup>9–11</sup> Table 1 summarizes our results of the site-selective Suzuki coupling of **8** and phenylboronic acid. Consistent with the results of Cho and co-workers,<sup>10</sup> we found that in nonpolar solvents, such as 1,2-dichloroethane, tetrahydrofuran, and toluene, C3-coupled product **9** was primarily formed. In these solvents,

Table 1. Suzuki Couplings with 3,5-Dibromo-2-pyrone

increasing polarity	$\epsilon^a$	Solvent	yield <sup>b</sup> (%) 9:10:11		
			$\Delta$ (w/o Cul)	rt (w/ Cul)	$\Delta$ (w/ Cul)
	47	DMSO	— <sup>c</sup>	nd:12:nd	8:13:nd
	38.25	DMF	tr:nd:nd	nd:18:nd	15:37:nd
	21.01	acetone	53:nd:nd	tr:32:nd	16:29:nd
	10.42	DCE	70:nd:nd	57:13:nd	58:tr:11
	7.52	THF	47:nd:19	27:8:nd	49:17:nd
	2.38	toluene	52:nd:nd	55:tr:nd	56:tr:tr

<sup>a</sup>Dielectric constant at 20 °C.<sup>18</sup> <sup>b</sup>Determined by <sup>1</sup>H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard; nd = not detectable, tr = trace. <sup>c</sup>Decomposition of **8**. Conditions: PhB(OH)<sub>2</sub> (1.2 equiv), Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %), CuI (1.0 equiv), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv), solvent (0.1 M).

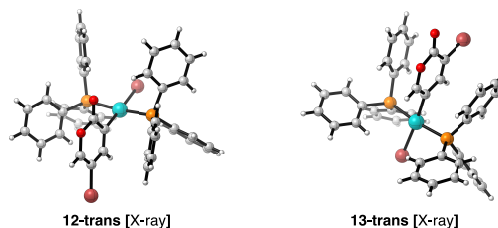
neither the addition of CuI nor conducting the reaction at elevated temperature affected the observed site-selectivity. Interestingly, in more polar solvents, such as dimethyl sulfoxide, dimethylformamide, and acetone, C5-coupled product **10** was generally formed as the major product. However, **9** was formed in the absence of CuI and when the reaction was conducted in acetone.<sup>16</sup> In contrast to the observations of Cho and co-workers,<sup>11</sup> we did not observe a switch in the site-selectivity upon increasing the reaction temperature from 23 to 50 °C. Overall, we found the selectivity of the cross-coupling reactions to be non-temperature-dependent and to proceed predominantly at the C3-position in nonpolar solvents, while coupling is favored at the C5-position in polar solvents in the presence of CuI.

To gain more insight into the effect of CuI in these cross-coupling reactions, we chose to revisit several oxidative addition experiments previously conducted by Cho and co-workers<sup>10,11</sup> and to analyze the relative stabilities of the resulting C3- and C5-Pd complexes (**12** and **13**, Table 2).<sup>17</sup>

Table 2. Oxidative Addition Experiments

Solvent	rt (w/o Cul)	yield <sup>a</sup> (%) 12:13		$\Delta$ (w/ Cul)
		$\Delta$ (w/o Cul)	rt (w/ Cul)	
DMF	31:nd	39:nd	11:20	14:23
toluene	32:nd	50:nd	29:nd	50:nd

L = PPh<sub>3</sub>, X = Br

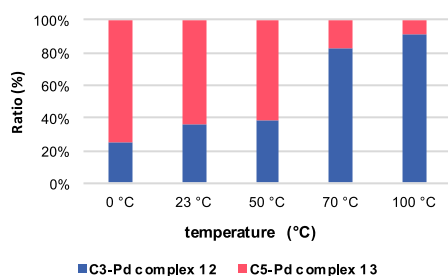


<sup>a</sup>Determined by <sup>1</sup>H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The NMR yields were calculated with respect to the amount of Pd(PPh<sub>3</sub>)<sub>4</sub> used (10 mol %); nd = not detectable. Conditions: Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %), CuI (1.0 equiv), solvent (0.1 M).

We observed that when the oxidative addition was conducted in nonpolar solvents (toluene), only C3-Pd complex **12** was formed, irrespective of the reaction temperature or whether CuI was added.

In polar solvents (DMF), we observed the formation of **12** when the reaction was conducted in the absence of CuI, while C5-Pd complex **13** was formed as the major product in the presence of CuI. The structures of **12** and **13** were unambiguously confirmed by single-crystal X-ray analysis.<sup>19</sup> Notably, these oxidative addition experiments are also supported by the observed position selectivity in Suzuki coupling of **8** (Table 1), where the C5-coupled product (**10**) was only formed in polar solvents and in the presence of CuI.

Next, the oxidative addition experiments were carried out at different reaction temperatures in the presence of CuI with DMF as the solvent (Figure 1). It was observed that C5-Pd oxidative adduct **13** was favored at lower temperatures, whereas at elevated temperature, C3-Pd oxidative adduct **12** was formed as the major product. Further experiments revealed



**Figure 1.** Influence of temperature on ratios of C3- to C5-Pd complexes. Conditions: Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %), CuI (1.0 equiv), DMF (0.1 M).

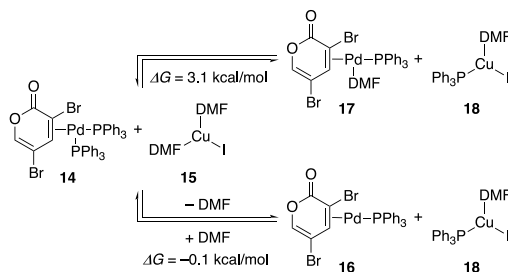
that C5-Pd oxidative adduct **13** converts to C3-Pd oxidative adduct **12** in DMF in the presence of CuI at elevated temperatures and over prolonged reaction periods.<sup>20</sup>

Interestingly, when a mixture of Pd oxidative adducts **12** and **13** was treated with tributylphenylstannane in DMF, only the C5-coupled product (**10**) was formed,<sup>20</sup> indicating that **12** can also interconvert to **13** prior to cross-coupling. In summary, our observations indicate that, in the presence of CuI in DMF, C5-Pd complex **13** is the *kinetic* oxidative adduct, whereas C3-Pd complex **12** is the *thermodynamic* oxidative adduct. Moreover, **12** and **13** can interconvert, and the rate of transmetalation/reductive elimination is faster for C5-Pd complex **13** when compared to that of C3-Pd complex **12**. This describes a Curtin-Hammett scenario<sup>21</sup> wherein rapid interconversion of the Pd complexes (**12** and **13**) occurs and where the ratio of the resulting cross-coupled products (i.e., **9:10**) is solely dependent on the energy difference between the two respective rate-limiting transition states of transmetalation/reductive elimination.

## COMPUTATIONAL INSIGHT

We sought to gain additional insight into the origins of the effects of CuI and solvent on the kinetic and thermodynamic selectivities of the oxidative addition through computational studies. Density functional theory (DFT) calculations were performed at the M06/6-311+G(d,p)-SDD/SMD(DMF)//B3LYP/6-31G(d)-SDD level of theory.<sup>20</sup> We first computationally considered the Lewis acid activation of the pyrone through coordination of CuI or cationic (DMF)Cu<sup>+</sup> to the carbonyl group of **8**. However, these results indicated that the CuI or Cu<sup>+</sup> coordination has a minimal impact on the site-selectivity of oxidative addition<sup>20</sup> and thus cannot explain the experimentally observed site-selectivity trend under the different conditions. Additionally, we considered the pathway involving oxidative addition of pyrone **8** to CuI<sup>22</sup> ( $\Delta G^\ddagger = 27.2$  kcal/mol, with respect to the pyrone-CuI  $\pi$ -complex). This pathway requires a higher barrier than the oxidative addition to Pd(0) and does not support the observed reversal of site-selectivity in the presence of CuI.<sup>20</sup> As such, we surmised that in the presence of CuI the oxidative addition may occur through an alternative mechanism with a different active Pd catalyst. Because previous computational studies have suggested that a bisphosphine ligated Pd complex is more favored for oxidative addition with PPh<sub>3</sub> as ligand,<sup>23</sup> the oxidative addition in the absence of CuI is expected to occur via tricoordinated (PPh<sub>3</sub>)<sub>2</sub>Pd(0)-pyrone complex **14** (Scheme 2). Additionally, on the basis of empirically established precedent supporting the ability of CuI to promote phosphine ligand exchange at Pd,<sup>24</sup> we hypothesized that CuI could have

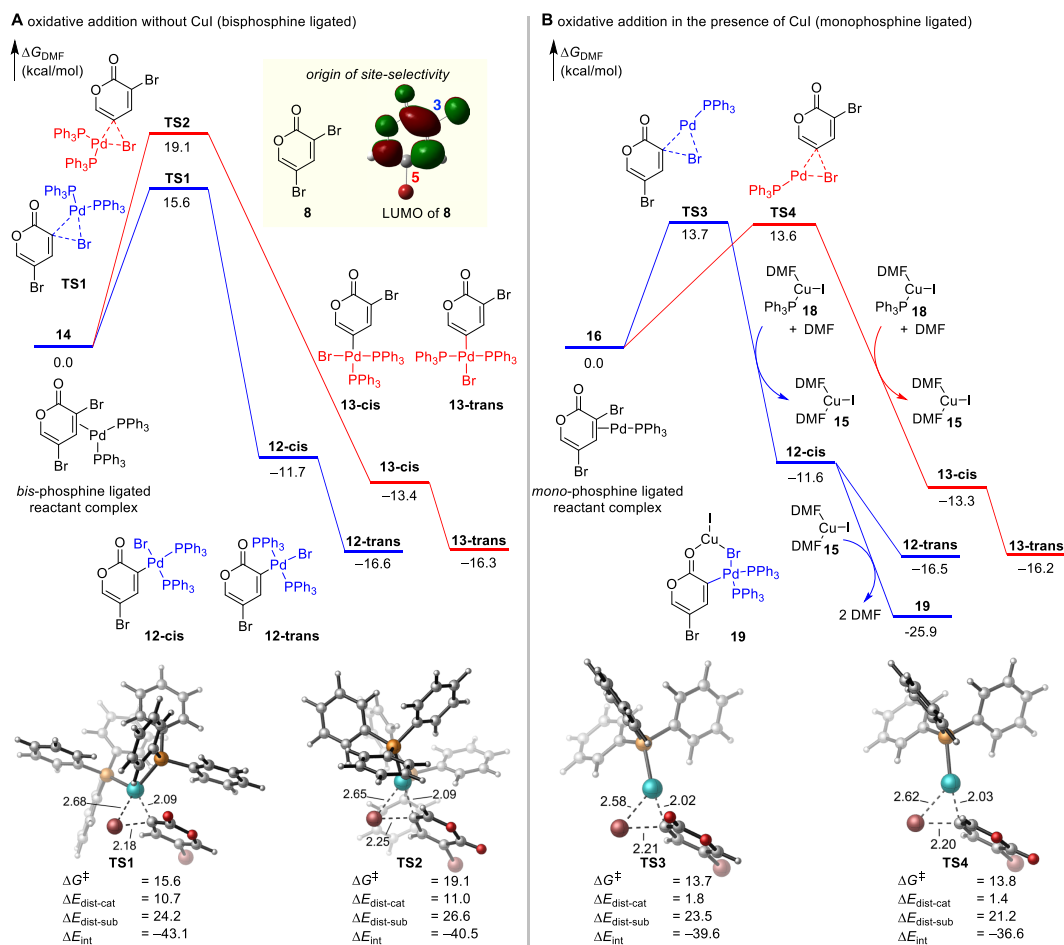
## Scheme 2. Computed Ligand Exchange Energies from the Bisphosphine Ligated Pd Complex **14** To Form Monophosphine Ligated Pd Complexes **16** and **17**



a similar effect on this system. In this way, CuI could promote phosphine ligand dissociation from **14** to form a monophosphine ligated Pd complex (**16** or **17**, Scheme 2) as the operative intermediate in the catalytic cycle, which has been reported to be relatively more reactive toward oxidative addition.<sup>25</sup> Indeed, our DFT calculations show that exchanging one of the PPh<sub>3</sub> ligands in **14** with (DMF)<sub>2</sub>CuI (**15**) to form both monophosphine ligated Pd complexes **17** and **16** is thermodynamically feasible,<sup>26</sup> indicating an equilibrium between the bis- and monophosphine ligated Pd complexes before the oxidative addition step. Furthermore, in the absence of CuI, formation of the monophosphine ligated Pd complexes is highly endergonic ( $\Delta G \geq 13$  kcal/mol),<sup>20</sup> indicating that the bisphosphine ligated Pd complex **14** is operative under these conditions.

Therefore, we computed the oxidative addition pathways from complexes **14** (Figure 2A), **16** (Figure 2B), and **17** (Figure S3A in the Supporting Information). Interestingly, the oxidative additions of **14** and **16** have very different site-selectivity outcomes. In the bisphosphine ligated Pd complex pathway, the barrier for the oxidative addition at C3 (TS1; Figure 2A) is 3.5 kcal/mol lower than that at C5 (TS2). Following *cis/trans* isomerization of the phosphine ligands on the oxidative addition complexes (i.e., **12-cis** and **13-cis**, respectively), the C3-adduct (**12-trans**) is slightly (0.3 kcal/mol) more stable than the C5-adduct (**13-trans**). These results are consistent with the experimentally observed C3-selectivity for oxidative addition in DMF and toluene in the absence of CuI (see Table 2). To understand the factors governing the C3 site-selectivity, we performed a distortion/interaction analysis to investigate the distortion energies of the catalyst ( $\Delta E_{\text{dist-cat}}$ ) and the pyrone substrate ( $\Delta E_{\text{dist-sub}}$ ) to reach their transition state geometries, as well as the stabilizing interaction energy ( $\Delta E_{\text{int}}$ ) between the two fragments (Figure 2A).<sup>27</sup> Although the C3-oxidative addition has an earlier transition state, as evidenced by the smaller substrate distortion energy ( $\Delta E_{\text{dist-sub}}$ ) and the shorter C-Br bond distance in TS1, the interaction between the catalyst and the substrate in TS1 ( $\Delta E_{\text{int}}$ ) is still stronger than that in TS2 by 2.6 kcal/mol. The stronger catalyst-substrate interaction is due to a more favorable frontier molecular orbital (FMO) interaction between the LUMO ( $\pi^*$ ) of **8** and the HOMO ( $d_{xy}$ ) of the Pd in TS1.<sup>14a</sup> The computed LUMO of **8** showed a much larger coefficient at the C3-position than at the C5-position (Figure 2A, inset).<sup>28</sup>

In the presence of CuI, the C3 and C5 oxidative additions of the monophosphine ligated Pd complex **16** (TS3 and TS4, respectively, Figure 2B) both require lower barriers as compared to those of bisphosphine ligated Pd complex **14**.



**Figure 2.** (A) Oxidative addition of the bisphosphine ligated Pd complex **14** at the C3-position (shown in blue) and C5-position (in red) of 3,5-dibromo-2-pyrone **8** in the absence of CuI. (B) Oxidative addition of the monophosphine ligated Pd complex **16** in the presence of CuI. The distortion energies of the PdL<sub>n</sub> catalyst ( $\Delta E_{\text{dist-cat}}$ ) and the pyrone substrate ( $\Delta E_{\text{dist-sub}}$ ) and the interaction energies between these two fragments in the oxidative addition transition states ( $\Delta E_{\text{int}}$ ) are provided. All energies in Figure 2A are with respect to **14**. All energies in Figure 2B are with respect to **16**, **18**, and DMF.

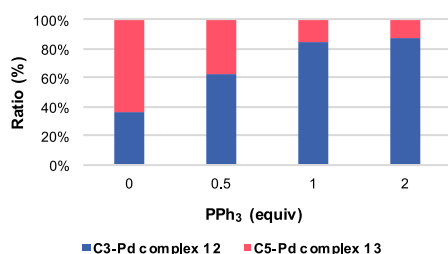
Notably, the monophosphine ligated Pd complex oxidative addition no longer kinetically favors the formation of C3–Pd complex **12** and the barriers for TS3 and TS4 are comparable. This is consistent with the low selectivity for the site of oxidative addition observed empirically in the presence of CuI in DMF (Table 2). Distortion/interaction analysis of TS3 and TS4 reveals that TS3 has a more favorable interaction energy as compared to TS4. However, TS3 is a later transition state with greater distortion penalty of the substrate ( $\Delta E_{\text{dist-sub}}$ ), which compensates for the interaction energy difference and leads to similar barriers for the two oxidative addition transition states. In this monophosphine ligated Pd complex pathway, Pd is less nucleophilic due to a lower-lying HOMO.<sup>29</sup> Therefore, the FMO interaction between the Pd center and the substrate is less prominent and the preference for the C3 oxidative addition selectivity is diminished.

We also considered the oxidative additions of the DMF-coordinated monophosphine ligated Pd complex **17**. From **17**, the selectivity between the C3 and C5 oxidative addition transition states is also diminished ( $\Delta\Delta G^\ddagger = 0.8$  kcal/mol).<sup>20</sup> Overall, these results highlight the significant effect of the number of PPh<sub>3</sub> ligands on the selectivity of oxidative addition. While oxidative addition of bisphosphine ligated Pd complex **14** is strongly preferred at C3, the site-selectivity is diminished

in reactions with the monophosphine ligated Pd complexes (**16** or **17**).

Following oxidative addition, the more-electron-deficient Pd(II) adduct binds another PPh<sub>3</sub> through ligand exchange with the CuI–phosphine complex to form tetracoordinated Pd(II) complexes **12** and **13** (Figure 2B). The cis-isomer of the C3 adduct (**12-cis**) can bind to CuI to form a relatively stable complex (**19**) in which the Cu center is coordinated to both the pyrone carbonyl oxygen and the bromide attached to the Pd center. It should be noted that similar chelating complexes cannot be formed from **13-cis** or either of the trans-isomers.<sup>20</sup> Because of the greater stability of **19** compared to other C3- and C5-adducts, the C3 oxidative addition pathway is thermodynamically more favorable.<sup>20</sup> This is consistent with the experimentally observed trend that increasing temperature leads to the C3-adduct as the major product (Figure 1).

With computational results in hand that explain the role of CuI in facilitating formation of a monophosphine ligated Pd complex (**16** or **17**), which in turn kinetically favors the formation of C5–Pd complex **13**, we sought experimental evidence to support this pathway. Toward this end, we analyzed the ratio of the generated C3–Pd to C5–Pd complexes when the oxidative addition was carried out with varying concentrations of triphenylphosphine (Figure 3).



**Figure 3.** Effect of  $\text{PPh}_3$  on the observed ratio of C3–Pd to C5–Pd complex. Conditions:  $\text{Pd}(\text{PPh}_3)_4$  (10 mol %),  $\text{CuI}$  (1.0 equiv),  $\text{PPh}_3$ , DMF (0.1 M), 23 °C.

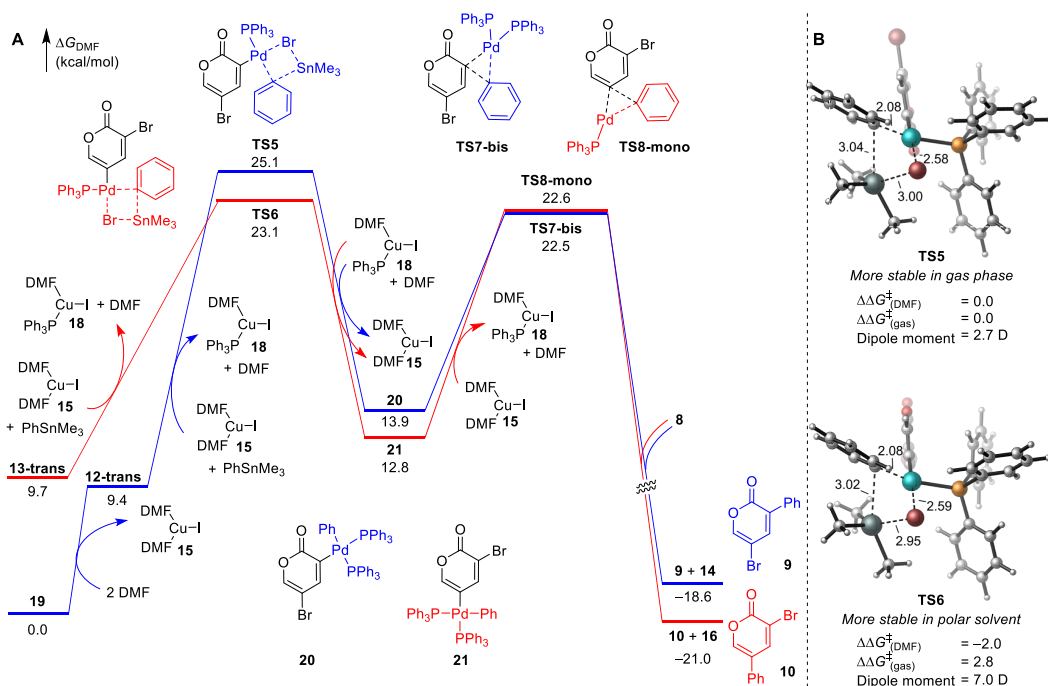
Interestingly, we observed that when the concentration of triphenylphosphine was increased, C3–Pd complex **12** was predominantly formed. Hence, we postulated that higher concentrations of  $\text{PPh}_3$  favor the oxidative addition pathway involving a bisphosphine ligated Pd complex, which leads to formation of C3–Pd complex **12**, in concert with our computational studies.

Furthermore, we repeated the oxidative addition studies in the presence of other phosphine ligands.<sup>20</sup> We observed a preference for the formation of C5–Pd complex **13** when the oxidative addition was carried out using bulky phosphine ligands. This observation supports the rationale that the C5–Pd complex **13** is generated when the oxidative addition proceeds via a monophosphine ligated Pd complex, which is favored at lower  $\text{PPh}_3$  concentrations or in the presence of bulkier phosphine ligands. The conclusions drawn from these experiments are in good agreement with our computationally derived results.

We next sought to gain computational insight into the origin of the C5 site-selectivity of the Stille coupling reactions under conditions where oxidative addition has been established to be

reversible (see Table S6 of the Supporting Information for experimental details).<sup>30</sup> In these cases, the selectivity is expected to be determined in the subsequent transmetalation or reductive elimination steps. We calculated the C3- and C5-selective pathways for the transmetalation and reductive elimination steps from the oxidative adducts **12** and **13** using trimethylphenylstannane as a model coupling partner (Figure 4). We located the cyclic transmetalation transition states where the substrate and bromide are either cis- or trans-disposed. In accordance with previous computational studies,<sup>31</sup> the trans-transmetalation transition states (TS5 and TS6) are about 5–6 kcal/mol more favorable than the corresponding cis-TS. The transition state associated with the transmetalation of the C5-adduct (TS6) is 2.0 kcal/mol more favorable than that of the C3-adduct (TS5) (Figure 4A).

These computational results are consistent with the empirically observed preferable coupling of **13** over **12**, when this mixture is exposed to tributylphenylstannane.<sup>20</sup> To better understand the origin of this preference, we considered the polarity of the transmetalation transition states. We hypothesized that since TS6 is significantly more polar than TS5 due to the greater separation of the partial positive (on Pd and Sn) and negative (on the pyrone carbonyl oxygen) charges, more favorable stabilization of this transition state would occur in a polar solvent. In support of this hypothesis, we calculated the gas-phase energies for TS5 and TS6. These calculations show that the relative stability is reversed in the gas phase, where TS5 is favored by 2.6 kcal/mol (Figure 4B). Therefore, the polar solvent plays an important role in determining the selectivity for transmetalation. The transmetalation and subsequent ligand exchange with  $\text{CuI}(\text{PPh}_3)(\text{DMF})$  **18** leads to a four-coordinate  $\text{Pd}^{\text{II}}$  species (**20** or **21**), which then undergoes reductive elimination via either a bisphosphine or



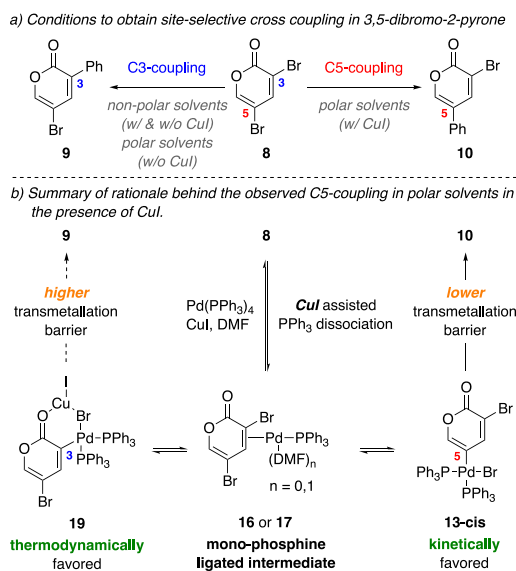
**Figure 4.** (A) Transmetalation and reductive elimination steps in the Pd-catalyzed Stille cross-coupling reaction of 3,5-dibromo-2-pyrone. The C3- and C5-selective pathways are shown in blue and in red, respectively. (B) Relative activation energies of transmetalation in an implicit solvent ( $\Delta\Delta G_{\text{DMF}}^{\ddagger}$ ) and in the gas phase ( $\Delta\Delta G_{\text{gas}}^{\ddagger}$ ). All energies in part A are with respect to **19**, two DMF molecules, and  $\text{PhSnMe}_3$ . The energies in part B are with respect to TS5.

monophosphine ligated transition state to form coupling products **9** and **10**.<sup>20</sup>

### SUMMARY OF CROSS-COUPLING STUDIES

Scheme 3a provides an overview of our observations regarding the site-selective cross-coupling in 3,5-dibromopyrone. In

#### Scheme 3. Summary of Experimental/Computational Results That Rationalize the Observed Site-Selectivity in 3,5-Dibromo-2-pyrone



summary, cross-coupling of **8** gave rise to the C3-coupled product (**9**) as the major product in nonpolar solvents (with or without CuI) and in polar solvents in the absence of CuI. The formation of C5-coupled product **10** was favored by conducting the reaction in polar solvents in the presence of CuI. Under these conditions, it was determined that C5 Pd

complex **13-cis** is kinetically favored and gives rise to C5-coupled product **10** following a relatively low barrier for transmetalation.

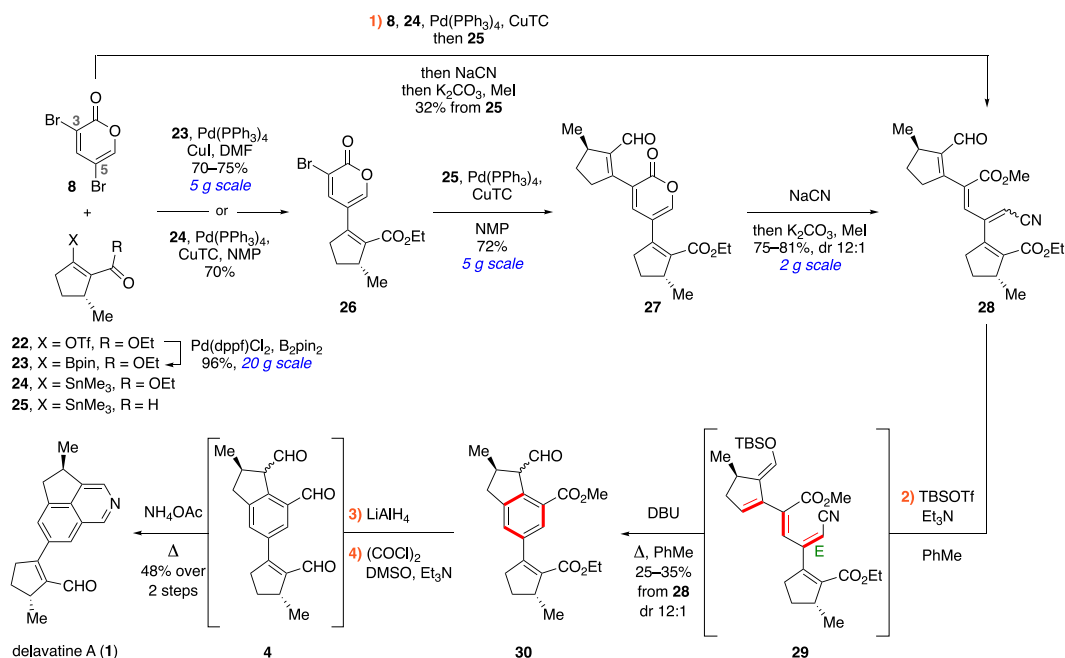
This latter selectivity was computationally established to arise from an initial CuI-assisted PPh<sub>3</sub> dissociation from bisphosphine ligated Pd complex **14** to give monophosphine ligated Pd complex **16** or **17** (Scheme 3b), which has a lower activation barrier to furnish the C5-Pd complex **13-cis**. In addition, when the coupling is conducted in polar solvents in the presence of CuI, the isomeric Pd complexes were found to interconvert. The C3-Pd complex **19** was established to be the thermodynamic oxidative adduct and possesses a higher transmetalation barrier compared to its C5-analog **13-cis**.

### TOTAL SYNTHESIS OF DELAVATINE A

Our enhanced mechanistic understanding of the site-selective cross-coupling of 3,5-dibromo-2-pyrone (**8**) positioned us well to complete a synthesis of delavatine A (Scheme 4). In a first step, known vinyl triflate<sup>32</sup> **22** was subjected to Miyaura borylation<sup>33</sup> to furnish vinyl boronate ester **23** in high yield. Next, the conditions initially established by Cho and co-workers for the site-selective Suzuki coupling of **8** efficiently yielded C5 monocoupled pyrone **26** in 70–75% yield on a 5 g scale. Alternatively, a site-selective Stille coupling of **8** and stannane ester<sup>34</sup> **24** gave **26** in comparable yield. Stille coupling of **26** with known stannane aldehyde<sup>4a</sup> **25** then delivered pseudosymmetric pyrone **27**.

With bis-coupled pyrone **27** in hand, we initially sought to open the lactone moiety with an alkoxide in order to induce the desired cascade sequence (cf. **7** → **5**, Scheme 1b). However, under a variety of reaction conditions, the pyrone opening was not successful and resulted merely in decomposition of **27**. Eventually, we discovered that pyrone **27** could be cleanly opened in a 1,6-fashion using sodium cyanide,<sup>35</sup> and the resulting carboxylate was alkylated to furnish methyl ester **28**. Impressively, sequential Stille coupling of **8**, **24**, and **25**, followed by pyrone opening, could also be achieved to furnish

#### Scheme 4. Total Synthesis of Delavatine A



methyl ester **28** directly from **8** in a single pot and in comparable overall yield. A number of conditions were next investigated to convert **28** into a suitable dienolate-like species (cf. **5**, Scheme 1). While deprotonation of the  $\gamma$ -hydrogen of enal **28** using strong bases was unsuccessful, softer enolization conditions cleanly converted **28** to silyl enol ether **29**, providing a precursor for the envisioned  $6\pi$ -electrocyclization. The major olefin diastereomer in **29** was established as the *E*-isomer. We then began exploring conditions for the  $6\pi$ -electrocyclization and were delighted to find that the desired transformation occurred at elevated temperature in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to furnish the desired cyclized product (**30**). The entire sequence (silyl enol ether formation, *E/Z* isomerization,  $6\pi$ -electrocyclization, desilylation, and aromatization) can be carried out in a single pot to directly deliver **30** in 25–35% overall yield.<sup>36</sup> Tricycle **30** was then reduced using lithium aluminum hydride, and the corresponding triol was subjected to global Swern oxidation to provide the proposed biosynthetic intermediate **4**. Finally, treatment of trisaldehyde **4** with ammonium acetate led to formation of the isoquinoline moiety to provide delavatine A (**1**), which possessed analytical data (<sup>1</sup>H and <sup>13</sup>C NMR, HRMS, IR, [ $\alpha$ ]<sub>D</sub>) in full agreement with those reported for the naturally occurring material.

## CONCLUSION

In summary, we have employed computational analysis as a powerful tool to gain insight into the observed site-selective cross-coupling in 3,5-dibromo-2-pyrone. The calculations show that bisphosphine ligated palladium complexes promote oxidative addition at C3 of 3,5-dibromopyrone as a result of more favorable FMO interactions between the HOMO ( $d_{xy}$ ) of the Pd complex and the pyrone LUMO ( $\pi^*$ ). Additionally, combined experimental and computational investigations suggest that the oxidative addition in the presence of CuI proceeds via a pathway that involves a monophosphine ligated Pd complex. In this case, the site-selectivity for oxidative addition is diminished and the C5 cross-coupling is preferred due to a more facile transmetalation step. This outcome is attributed to more favorable solvation effects that stabilize the more polar transition state in the C5-selective pathway. These insights may prove valuable in developing a more general understanding of the effects of solvents and CuI additives in site-selective cross-couplings in other polyhalogenated heterocycles. The site-selective cross-coupling has enabled a short total synthesis of delavatine A that takes advantage of a strategy inspired by the inherent symmetry of this natural product. The synthesis of **1** proceeds in only four steps from known 3,5-dibromo-2-pyrone **8** [or in the longest linear sequence of 10 steps from commercially available (*R*)-pulegone] and features a cascade sequence involving five transformations occurring in a single pot. Our concise and modular route to delavatine A sets the stage for the synthesis of a library of structurally related analogues to facilitate biological studies.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13012.

Experimental details and spectroscopic data (PDF)

Crystallographic data for **12-trans** in CIF format (CIF)

Crystallographic data for **13-trans** in CIF format (CIF)

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### Notes

The authors declare no competing financial interest.

CCDC 1882829 and 1882830 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44 1223 336033).

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