Palladium Catalysis

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Palladium-Catalyzed Asymmetric Construction of Vicinal All-Carbon Quaternary Stereocenters and its Application to the Synthesis of Cyclotryptamine Alkaloids**

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The cyclotryptamine alkaloids are a diverse group of natural products with a wide array of biological activities (Figure 1).[1] This family of alkaloids consists of hexahydropyrroloindole units linked to form oligomers of varying sizes. Cyclotryptamine alkaloids are found in a number of different types of plants and animals.

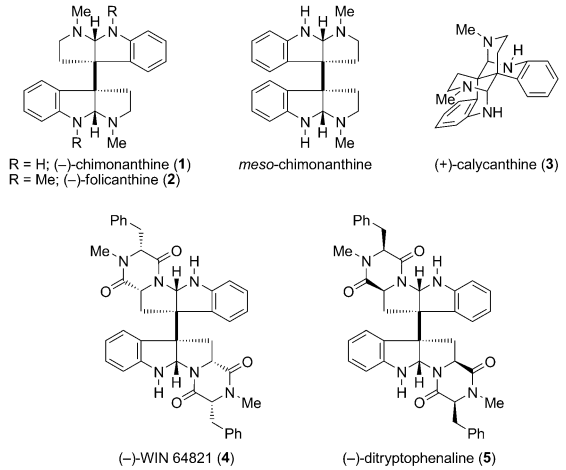

Figure 1. Representative cyclotryptamine alkaloids.

From a structural perspective, cyclotryptamines are found in both *meso* and optically active form. Because of their diverse biological profiles and unique structural features, the cyclotryptamine alkaloids have gained extensive attention from the synthetic community. Many elegant strategies have been devised to assemble these targets in enantiopure form.[2]

A pronounced feature found in these natural products is the presence of two vicinal quaternary stereocenters. Quaternary all-carbon stereocenters are present in a variety of natural products and biologically active compounds. The presence of this structural element greatly complicates the asymmetric assembly of such molecular architectures because of the steric congestion present when bringing four carbon substituents together. Over the last several decades, extensive research has been devoted to develop methods that can assemble quaternary all-carbon stereocenters in an asymmetric fashion, including cycloadditions, pericyclic reactions, and metal-catalyzed alkylation strategies.[3] When a second vicinal quaternary center is present in a synthetic target, the asymmetric assembly is complicated further. In fact, the construction of adjacent quaternary stereocenters has been referred to as "a daunting challenge in natural product synthesis".[4] Currently, few methods exist for the construction of vicinal quaternary carbon centers in a single synthetic operation; hence each stereocenter is typically assembled sequentially. Furthermore, relatively few examples have been reported for the assembly of this structural motif in a catalytic asymmetric manner.[5]

The Pd-catalyzed decarboxylative asymmetric allylic alkylation (Pd-DAAA) has proven to be a mild, robust, and functional-group-tolerant method for the construction of stereocenters with high levels of diastereo- and enantioselectivity.[6] This transformation has been performed with a variety of nucleophiles, including ketones, β-ketoesters, acyl imidazoles, *N*-acyl oxazolidinones, and 2-oxindoles.[7] Recently, the Pd-DAAA was used to construct two quaternary carbon stereocenters bearing a 1,4 relationship.[8] We sought to test the limits of the Pd-DAAA by constructing two vicinal quaternary carbon stereocenters in a single operation. Unlike two stereocenters in a distal 1,4 relationship, construction of two *vicinal* quaternary carbon stereocenters leads to sterically congested intermediates and products. Furthermore, the stereochemistry of the second stereocenter would likely be affected by the result of the first allylation; that is, substrate control will compete with chiral-catalyst control.

Our retrosynthetic strategy to access the cyclotryptamine core is outlined in Scheme 1. We envisioned that cyclotryptamines (−)-chimonanthine (**1**), (−)-folicanthine, (**2**) (+)-calycanthine (**3**), (−)-WIN 64821 (**4**), and (−)-ditryptophenaline (**5**) could be accessed by manipulation of the common intermediate **6**. This intermediate, which contains both vicinal quaternary stereocenters, would arise from a Pd-DAAA of dienol dicarbonate **7**. Compound **7** would be formed by treatment of bisoxindole **8** with allyl chloroformate under basic conditions.

To determine whether the Pd-DAAA could be used to access the cyclotryptamine core in an enantio- and diastereoselective fashion, dienol dicarbonate **7** was prepared as

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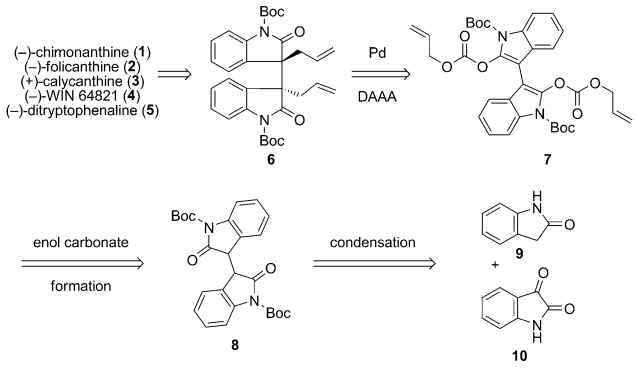
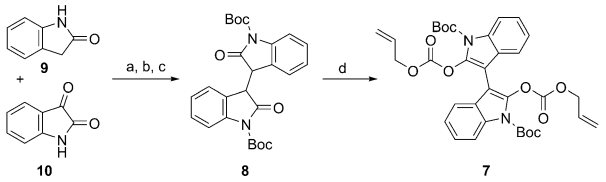


Scheme 1. Retrosynthesis of cyclotryptamine alkaloids. Boc = *tert*-butoxycarbonyl.

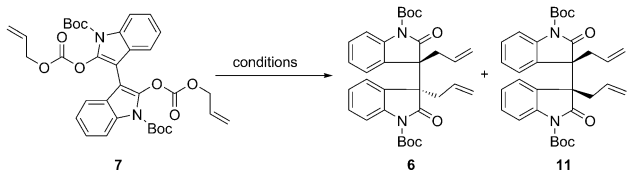
outlined in Scheme 2. Condensation of oxindole (**9**) and isatin (**10**) afforded isoindigo in 82% yield.[9] Isoindigo was treated with di-*tert*-butyl dicarbonate in THF followed by hydrogenation with Pearlman's catalyst to provide bisoxindole **8**. The reaction of bisoxindole **8** with allyl chloroformate and triethylamine facilitated smooth formation of dienol dicarbonate **7** in 90% yield.[10] Surprisingly, dienol dicarbonate **7** proved to be a bench-stable intermediate that could be accessed on a scale of more than 16 g in an overall yield of 63% from inexpensive commercially available starting materials **9** and **10** using the shown sequence.



Scheme 2. Synthesis of dienol carbonate **7**. Reagents and conditions: a) HCl, HOAc, reflux, 82%; b) Boc_2O, DMAP, NEt_3, THF, 0°C→RT, 89%; c) 10 wt% $Pd(OH)_2$/C, EtOH, RT, 96%. d) allyl chloroformate, NEt_3, THF, 0°C→RT, 90%. DMAP = 4-dimethylaminopyridine.

With key dienol dicarbonate **7** in hand, the Pd-DAAA was explored. Initial studies were performed using achiral ligands to determine the influence of the ligand structure on the diastereoselectivity of the reaction. Ideally, ligand control would override substrate control and could be used to favor either the D/L (**6**) or *meso* (**11**) products. This would provide access to both chiral and *meso* cyclotryptamine natural products. Treatment of the dienol dicarbonate **7** with [Pd_2(dba)$_3$·$CHCl_3$] and PPh_3 facilitated the desired allylation with greater than 95% conversion, but in a mere 2:1 d.r., favoring the chiral product **6** (Table 1, entry 1). Switching to the electron-deficient ligand tri-2-furylphosphine led to an improvement in the diastereoselectivity of the transformation and delivered the products in a 5.4:1 d.r., still favoring the C_2 symmetric product **6** (Table 1, entry 2). Employing the bulky *t*Bu-XPhos ligand resulted in further enhancement of the diastereoselectivity to 5.8:1, but continued to favor the C_2 symmetric product **6** (Table 1, entry 3). Bidentate ligands (Figure 2) were studied next in the transformation; utilizing dppf improved the d.r. to 6:1, still favoring the chiral product **6** (Table 1, entry 4). Xantphos led to a reduced 1.7:1 d.r., in favor of the chiral product **6** (Table 1, entry 5).

Table 1: Selected optimization studies.[a]



Entry	Ligand	Solvent	d.r.[b]	*ee* [%][c]
1[d]	PPh_3	THF	2.0:1	–
2[d]	(2-furyl)$_3$P	THF	5.4:1	–
3	*t*Bu-XPhos	THF	5.8:1	–
4	dppf	THF	6.0:1	–
5	Xantphos	THF	1.7:1	–
6	*i*Pr-PHOX	THF	7.0:1	24
7	(*S*,*S*)-**L1**	THF	1.6:1	89
8	(*S*,*S*)-**L2**	THF	1.6:1	26
9	(*S*,*S*)-**L3**	THF	3.3:1	87
10	(*S*,*S*)-**L4**	THF	3.0:1	47
11	(*S*,*S*)-**L3**	dioxane	2.7:1	58
12	(*S*,*S*)-**L3**	DME	3.0:1	83
13[e]	(*S*,*S*)-**L3**	THF	2.8:1	86
14[f]	(*S*,*S*)-**L3**	THF	3.5:1	88
15[e,f]	**(*S*,*S*)-L3**	**THF**	**3.2:1**	**92**

[a] All reactions were performed with [Pd_2(dba)$_3$·$CHCl_3$] (2.5 mol%), ligand (7.5 mol%), and dienol dicarbonate **7** (0.02 mmol) in the indicated solvent. All reactions proceeded with more than 95% conversion (determined by ^{1}H NMR spectroscopy of the crude reaction mixture). [b] d.r. determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] *ee* value determined by HPLC on a chiral stationary phase. [d] 22.5 mol% of ligand was used. [e] Reaction was conducted at 0°C. [f] (*n*-hex)$_4$NBr (10 mol%) was used as additive. Entry in bold highlights optimized reaction conditions. dba = dibenzylideneacetone, DME = 1,2-dimethoxyethane, dppf = 1,1′-Bis(diphenylphosphino)ferrocene.

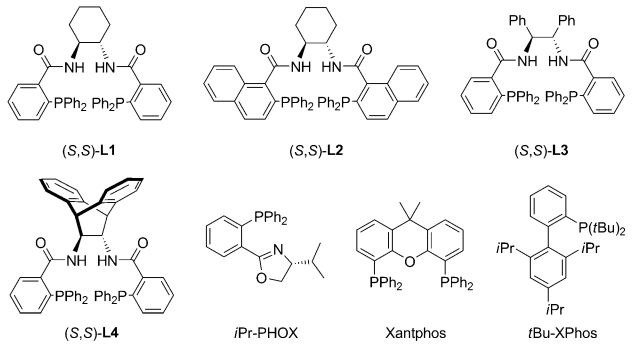
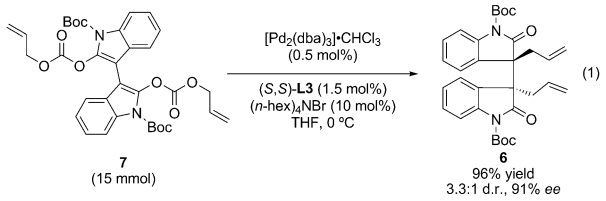


Figure 2. Ligands employed in the optimization studies.

Based on the results obtained by employing achiral ligands (Table 1, entries 1–5), it appeared that substrate control was favoring the C_2 symmetric product **6** over the *meso* product **11**, but the ligand structure still influenced this

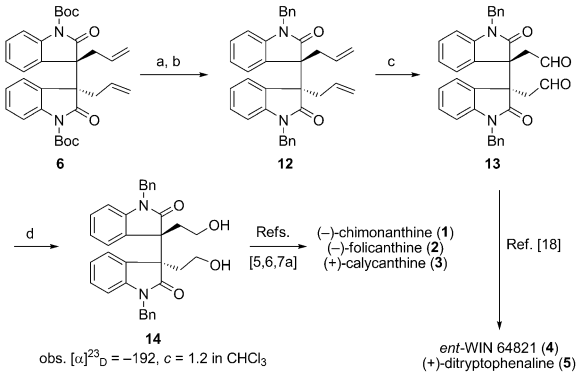
selectivity as can be deduced from the varying diastereomeric ratios. With this bias, we were interested in determining if chiral ligands could provide the C_2 symmetric product **6** with high levels of enantioselectivity. Employing *i*Pr-PHOX[11] in the transformation provided the products **6** and **11** with an excellent 7:1 d.r., but in only 24% *ee* (Table 1, entry 6). A screening of our modular ligands **L1**–**L4** (Table 1, entries 7–10) showed that (*S*,*S*)-**L3**, which contains a stilbene backbone, performed best, both in terms of diastereo- and enantioselectivity, thus facilitating the allylation, which resulted in 3.3:1 d.r. and 87% *ee* (Table 1, entry 9). Continuing with (*S*,*S*)-**L3** as the ligand, a solvent screen revealed that the Pd-DAAA was best performed in THF (Table 1, entries 9, 11, and 12). Temperature and additives were examined for the effect on the diastereo- and enantioselectivity of the transformation. Performing the reaction at reduced temperature led to a slightly diminished diastereoselectivity, but a slight increase in enantioselectivity (Table 1, entry 13). The addition of $(n\text{-hex})_4NBr$ (10 mol%) to the reaction led to an increase in both diastereoselectivity and enantioselectivity (Table 1, entry 14). It has been demonstrated that addition of $(n\text{-hex})_4NBr$ to the Pd-catalyzed allylic alkylations can have a beneficial effect on enantioselectivity by decreasing the rate of the nucleophilic attack.[12] In the hope of seeing a synergistic effect on selectivity, the Pd-DAAA was conducted at 0°C in the presence of $(n\text{-hex})_4NBr$ (10 mol%). To our delight, running the reaction under these conditions resulted in greater than 95% conversion, 3.2:1 d.r., and 92% *ee* (Table 1, entry 15).

With optimized conditions in hand, the scalability of the Pd-DAAA was explored. The transformation proved quite amenable to scale-up, and was easily conducted on a scale of more than 9 g [Eq. (1)]. When conducted on this scale, the Pd



and ligand loading could be reduced five-fold, and only 0.5 mol% of $[Pd_2(dba)_3{\cdot}CHCl_3]$ and 1.5 mol% of (*S*,*S*)-**L3** were needed to drive the transformation to completion. Under these reaction conditions, the isolated products could be obtained in a 96% yield, 3.3:1 d.r., and 91% *ee*.

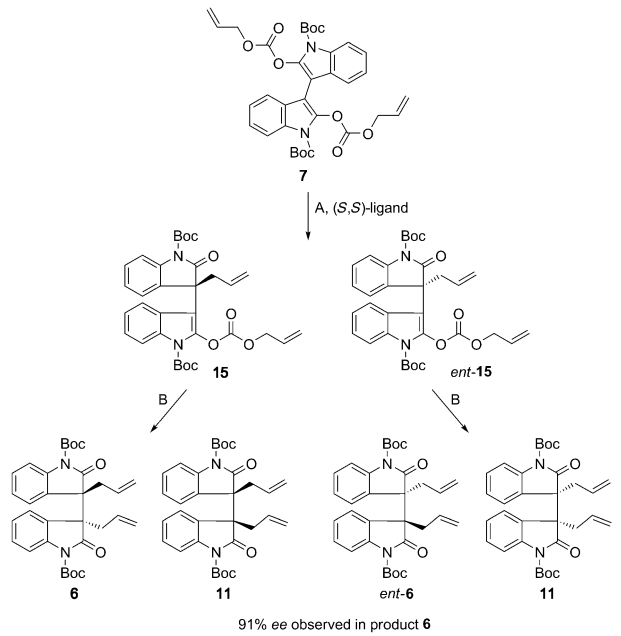
With gram quantities in hand, chiral bisallyl oxindole **6** was transformed into diol **14** (Scheme 3). Treatment of bisallyl oxindole **6** with TFA in CH_2Cl_2 followed by benzylation with BnBr provided alkylated oxindole **12** in near quantitative yield. Oxidative cleavage of the alkylated oxindole **12** under modified Johnson–Lemieux conditions afforded unstable bisaldehyde **13**. Reduction of bisaldehyde **13** with $NaBH_4$ provided diol **14**. At this stage, optical rotation was used to determine the absolute configuration of diol **14**. Previously, Overman and co-workers have used the (+) enantiomer of diol **14** to complete the syntheses of (+)-chi-



Scheme 3. Completion of the formal syntheses. Reagents and conditions: a) TFA, CH_2Cl_2, RT; b) NaH, DMF, 0°C, then BnBr and warming to RT, 95% over two steps; c) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O, RT; d) $NaBH_4$, MeOH, 0°C, 52% over two steps. DMF = *N*,*N*-dimethylformamide, TFA = trifluoroacetic acid.

monanthine,[2a,b] (+)-folicanthine,[2c] and (−)-calycanthine.[2a,b] Our synthetic sample of **14** had a rotation of −192 ($c = 1.2$ in $CHCl_3$), indicating the formation of the shown enantiomer. This result corresponds with the formal syntheses of (−)-chimonanthine (**1**), (−)-folicanthine (**2**), and (+)-calycanthine (**3**).[2a] Likewise, bisaldehyde **13** has been used by Overman and co-workers to complete the total synthesis of (−)-WIN 64821 (**4**) and (−)-ditryptophenaline (**5**)[13] and constitutes a formal synthesis of these targets with the same absolute configuration.

The described Pd-DAAA is intriguing from a mechanistic perspective, because the process proceeds through two independent allylation steps (Scheme 4). The first allylation (**A**) is enantiodetermining in the transformation, and gives rise to two intermediates, **15** and *ent*-**15**, which are not observed. Instead, the enantiomeric mixture of **15** and *ent*-**15**



Scheme 4. Mechanistic rationale for double Pd-DAAA.

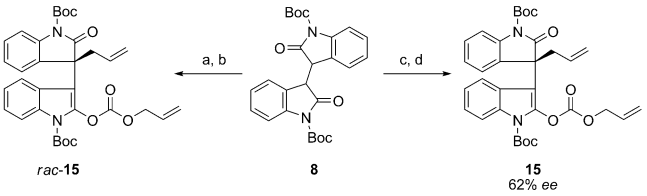
undergoes a second, diastereoselective allylation step (**B**), which affords the observed products **6** and **11** in 95% yield, 3.3:1 d.r., and 91% *ee* [Eq. (1)].

Several outcomes for allylations **A** and **B** are possible that can provide the enantio- and diastereoselectivity observed in the double allylation process. For instance, the first allylation (**A**) can proceed with lower levels of enantioselectivity than what is observed at the end of the transformation (91% *ee*), while the second allylation (**B**) can enhance the % *ee* to 91% by transforming the minor intermediate enantiomer *ent*-**15** to the *meso* product **11**. Conversely, the first allylation (**A**) can proceed with higher levels of enantioselectivity than that observed at the end of the transformation (91%), and the second allylation (**B**) could be eroding the % *ee* observed by transforming the major intermediate enantiomer **15** to the *meso* product. Additionally, the second allylation step (**B**) can occur in a matched sense, where the stereocenter constructed in allylation step **A** reinforces the formation of the second stereocenter in step **B** to favor the C_2 symmetric product **6**. Conversely, the second allylation (**B**) can occur in a mismatched fashion, such that the first stereocenter leads to unfavorable interactions in the transition state in step **B**, which would disfavor the formation of the C_2 symmetric product **6**.

To probe the effect the allylation step **B** has on the % *ee* and d.r. of the transformation, monoallylated enol carbonates **15** and *rac*-**15** were studied in the Pd-DAAA. Monoallylated enol carbonate **15** is the intermediate obtained in the double allylation process after the enantiodetermining allylation step (**A**). Subjecting this intermediate (**15**) with known enantiopurity to the reaction conditions of the Pd-DAAA would reveal the effect the second allylation step (**B**) has on the enantioselectivity and diastereoselectivity of the overall reaction.

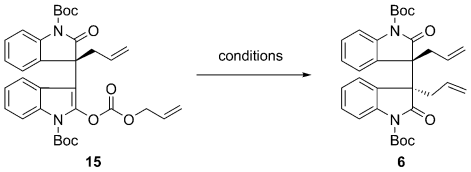
Enantioenriched (62% *ee*) monoallylated enol carbonate **15** was prepared by treatment of oxindole dimer **8** with a single equivalent of allyl acetate and (*S*,*S*)-**L1**[14] under Pd catalysis followed by enol carbonate formation with allyl chloroformate (Scheme 5). Racemic monoallylated enol carbonate *rac*-**15** was prepared in an analogous fashion.

Both enol carbonates **15** and *rac*-**15** were subjected to the Pd-DAAA reaction conditions using different enantiomers of **L3** (Table 2). The reaction of enantioenriched monoallyl enol carbonate **15** under optimized conditions employing (*S*,*S*)-**L3**, which is the enantiomer of the ligand that is present in the double allylation, resulted in formation of the desired product **6** with greater than 95% conversion, 3.6:1 d.r., and 57% *ee* (Table 2, entry 1). The d.r. obtained in this reaction was comparable to the d.r. obtained in the double Pd-DAAA [compare to Eq. (1)], and the *ee* value decreased by 5% in comparison to the starting material. The result in Table 2, entry 1, suggests that the first allylation step (**A**) proceeds with higher enantioselectivity (>91%) than what is observed at the end of the double allylation process (91%), because the *ee* value decreased by 5% from **15** to **6**. Enantioenriched monoallyl enol carbonate **15** was next treated under the optimized reaction conditions with (*R*,*R*)-**L3**, the antipode of the ligand present in the Pd-DAAA. This reaction resulted in formation of the desired product **6** with greater than 95% conversion, 6.5:1 d.r., and 69% *ee* (Table 2, entry 2). The d.r. obtained in this reaction was significantly higher than the d.r. obtained in the Pd-DAAA [compare Table 2, entry 2, to Eq. (1)], and a 7% increase in the *ee* value was observed. The increased enantiopurity of the product observed in Table 2, entry 2 supports the notion that the first allylation step (**A**) proceeds with greater than 91% *ee*. Additionally, the results in Table 2, entry 2, suggest that the second allylation step (**B**), is mismatched with (*S*,*S*)-**L3**, the enantiomer of the ligand that is present in the double Pd-DAAA, because the d.r. is improved when (*R*,*R*)-**L3** is used. The reaction of enantioenriched monoallyl enol carbonate **15** employing (*rac*)-**L3** resulted in formation of the desired product with greater than 95% conversion, 5.4:1 d.r., and 62% *ee* (Table 2, entry 3). In this reaction, the d.r. was slightly higher than the d.r. obtained in the double Pd-DAAA [compare Table 2, entry 3, with Eq. (1)], and no change in the *ee* value was observed. Finally, treatment of racemic monoallyl enol carbonate *rac*-**15** under optimized conditions employing (*S*,*S*)-**L3** resulted in formation of the desired product **6** with greater than 95% conversion, 4:1 d.r., and −8% *ee*, favoring the *opposite* enantiomer to the one that is observed in the double allylation process with (*S*,*S*)-**L3** (Table 2, entry 4). This result supports the notion that the second allylation (**B**) is



Scheme 5. Preparation of monoallyl enol carbonates **15** and *rac*-**15**. Reagents and conditions: a) $[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.5 mol%), (*rac*)-**L1** (7.5 mol%), allyl acetate, Cs_2CO_3, THF, RT; b) allyl chloroformate, NEt_3, THF, 0°C, 95% over two steps; c) $[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.5 mol%), (*S*,*S*)-**L1** (7.5 mol%), allyl acetate, Cs_2CO_3, THF, RT; d) allyl chloroformate, NEt_3, THF, 0°C, 95% over two steps.

Table 2: Pd-DAAA of monoallyl enol carbonate **15**.[a]



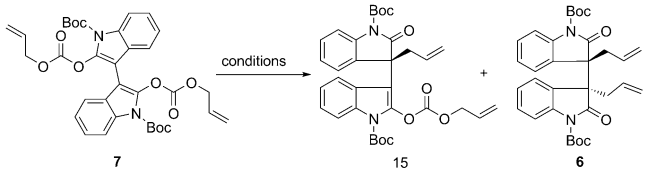
Entry	*ee* [%] of **15**	Ligand	d.r.[b]	*ee* [%][c] of **6**
1	62	(*S*,*S*)-**L3**	3.6:1	57
2	62	(*R*,*R*)-**L3**	6.5:1	69
3	62	(*rac*)-**L3**	5.4:1	62
4	0	(*S*,*S*)-**L3**	4.0:1	-8

[a] All reactions were performed with $[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.5 mol%), ligand (7.5 mol%), $(n\text{-hex})_4NBr$ (10 mol%), and dienol dicarbonate **7** (0.02 mmol) in THF (0.1 M) at 0°C. All reactions proceeded with more than 95% conversion (determined by ^1H NMR spectroscopy of the crude reaction mixture). [b] d.r. determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] *ee* value determined by HPLC on a chiral stationary phase.

mismatched, because the *minor* enantiomer of the product is favored from what is expected when (*S*,*S*)-**L3** is used for the double Pd-DAAA.

To gain further insight into the first allylation (**A**) of the double Pd-DAAA process, we were interested in isolating and assaying the intermediate monoallyl enol carbonate **15** by stopping the double Pd-DAAA reaction at partial conversion. Monoallyl enol carbonate **15** could be observed using TLC analysis after running the double Pd-DAAA reaction for 10 min. However, attempts to stop the reaction at partial conversion after 5, 10, 15, 30, and 60 min by dilution of reaction aliquots with oxygenated diethyl ether led only to the double allylation products **6** and **11**, which were observed by ^{1}H NMR spectroscopy. This unexpected result indicated that the double Pd-DAAA was occurring more quickly than the catalyst oxidation with molecular oxygen. To overcome this limitation, aliquots of the reaction mixture were loaded directly onto preparatory TLC plates at 0, 5, 10, and 15 min reaction times (Table 3), and the monoallyl enol carbonate **15**

Table 3: Isolation of monoallyl enol carbonate **15**.



7 **15** **6**

Entry	*t* [min]	*ee* [%][b] of **15**	*ee* [%][b] of **6**
1	0[c]	–	–
2	5	93	91
3	10	93	91
4	15	93	91

[a] All reactions were performed with $[Pd_2(dba)_3{\cdot}CHCl_3]$ (2.5 mol%), ligand (7.5 mol%), $(n\text{-hex})_4NBr$ (10 mol%), and dienol dicarbonate **7** (0.02 mmol) in THF (0.1 M) at 0°C. [b] *ee* value determined by HPLC on a chiral stationary phase. [c] Only traces of **15** and **6** were observed.

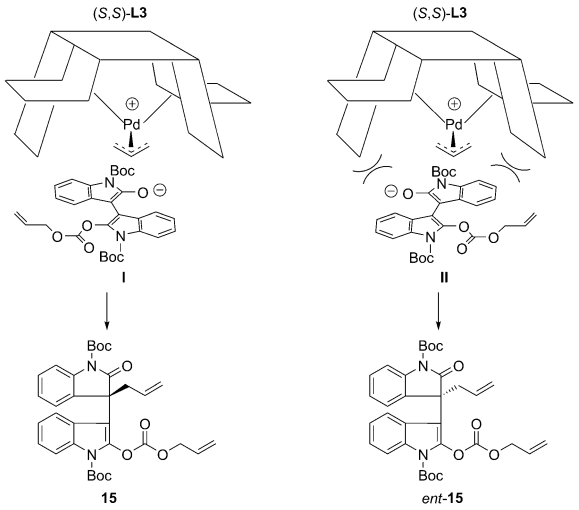
and the double allylation products **6** and **11** were separated from the active catalyst species. The enantiopurities of **15** and **6** were assayed by HPLC on a chiral stationary phase to determine if the conclusions drawn from Table 2 were valid. At $t = 0$ min, only traces of **15** and **6** were observed. At $t = 5$, $t = 10$, and $t = 15$ min on the other hand, **15** and **6** could be isolated and assayed by HPLC on a chiral stationary phase. At these time intervals, both the intermediate monoallyl enol carbonate **15** and the double allylation products **6** and **11** were detected, indicating that the second, mismatched allylation step (**B**) had a rate comparable to the first, enantiodetermining allylation (**A**). Monoallyl enol carbonate **15** was observed in 93% *ee* at $t = 5$, $t = 10$, and $t = 15$ min, while the double allylation product **6** was isolated with 91% *ee* at $t = 5$, $t = 10$, and $t = 15$ min. As suggested by the result shown in Table 2, the enantiopurity of monoallyl enol carbonate **15** is higher than the *ee* value of the double allylation product **6**.

Based on the results obtained from Tables 2 and 3, several conclusions can be drawn about enantioselectivity of the double allylation process (Scheme 4). The first, enantiodetermining allylation (**A**) provides intermediates **15** and *ent*-**15** with greater enantiopurity ($\approx$93% *ee*) than that observed at the end of the transformation (91% *ee*). The second allylation (**B**) is more substrate controlled than ligand controlled and occurs in a mismatched fashion. This event reduces the enantiopurity of intermediate **15** to that of product **6** from 93% to 91% *ee*. This occurs because the second mismatched allylation step (**B**) proceeds at different rates for **15** and *ent*-**15** to give the *meso* and chiral products. Both **15** and *ent*-**15** react in the second allylation to form the chiral products **6** and *ent*-**6** with a greater rate than the *meso* product.

However, the relative rate of the formation of *ent*-**6** to **11** is greater than the rate of formation for **6** to **11**, which leads to a greater portion of *meso* product to come from **15**, and leads to the observed reduction in enantiopurity in the product from monoallyl enol carbonate intermediate **15**. These conclusions are supported by the result shown in Table 2, entry 1, where the starting material **15** (62% *ee*) was treated under the optimized reaction conditions with (*S*,*S*)-**L3**, the same enantiomer of the ligand that is present under the optimized reaction conditions in Eq. (1), and produced the product with a reduced 57% *ee*. The result shown in Table 2, entry 2, also supports this conclusion, because treatment of the monoallyl enol carbonate **15** with (*R*,*R*)-**L3**, the opposite enantiomer of the ligand that is present in the reaction mixture, resulted in an improvement in enantiopurity from 62% to 69% *ee*. The result shown in Table 2, entry 4, also supports these conclusions, because treatment of racemic monoallyl enol carbonate *rac*-**15** with (*S*,*S*)-**L3** produced a product with −8% *ee*, favoring the opposite enantiomer of that observed under the optimized reaction conditions employing (*S*,*S*)-**L3** as the ligand [Eq. (1)]. Finally, direct isolation of the monoallyl enol carbonate **15** from the double Pd-DAAA also supports this conclusion, because this intermediate was observed in 93% *ee*, which is higher than the 91% *ee* obtained in product **6**.

Based on the mechanistic experiments in Tables 2 and 3, several conclusions can be drawn about the diastereoselectivity of the Pd-DAAA. Under the optimized reaction conditions, monoallyl enol carbonate **15** reacts with the catalyst in a mismatched fashion and produces a greater quantity of *meso* product **11** than the reaction of catalyst with *ent*-**15**. This occurs because the monoallyl enol carbonate intermediate **15** is present in much greater quantity than *ent*-**15**. (at 62% *ee*, the ratio of **15** to *ent*-**15** is 81:19) This conclusion is supported by the results shown in Table 2, entry 2, where the monoallyl enol carbonate was treated with (*R*,*R*)-**L3** to produce the chiral product **6** in a 6.5:1 d.r., which is higher than the 3.3:1 d.r. observed under the optimized reaction conditions [Eq. (1)]. Under the conditions shown in Table 2, entry 2, the allylation is conducted with the opposite enantiomer of the ligand that is present under the optimized reaction conditions, and is therefore matched for monoallyl enol carbonate **15** and is mismatched for the enantiomer *ent*-**15**. Because the matched monoallyl enol carbonate **15** is now present in much greater quantity than the mismatched monoallyl enol carbonate *ent*-**15**, the diastereoselectivity of the reaction increases from what is observed under the optimized reaction conditions [Eq. (1)].

The observed stereochemical outcome for the double Pd-DAAA can be rationalized using a "wall and flap" mnemonic,



Scheme 6. Rationale for the observed absolute configuration.

which represents the chiral π-allyl palladium species (Scheme 6).[15] Approach of the oxindole enolate under the "flap" of the chiral-ligand environment in trajectory **I** is favored and minimizes steric clash with the "walls". On the other hand, approach of the oxindole enolate from the opposite face as depicted in trajectory **II** leads to several unfavorable steric interactions. Trajectory **I** leads to the formation of monoallyl enol carbonate **15**, the enantiomer observed in the double Pd-DAAA.

In conclusion, we have successfully developed a scalable twofold Pd-DAAA of oxindole dienol dicarbonate **7** to construct two vicinal carbon quaternary stereocenters in near quantitative yield and high levels of diastereo- and enantioselectivity. The bisoxindole product (**6**) of this challenging transformation was elaborated into known intermediates to complete the formal synthesis of the cyclotryptamine alkaloids (−)-chimonanthine (**1**), (−)-folicanthine, (**2**) (+)-calycanthine (**3**), (−)-WIN 64821 (**4**), and (−)-ditryptophenaline (**5**). Detailed mechanistic studies on the twofold allylation process showed that the reaction proceeds through an enantiodetermining allylation step (**A**) in 93 % *ee* followed by a mismatched second allylation step (**B**) to arrive at the chiral product in 3.3:1 d.r. and 91 % *ee*.

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