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Quaternary Stereocenters

Catalytic Enantioselective Decarboxylative Allylations of a Mixture of Allyl Carbonates and Allyl Esters: Total Synthesis of (−)- and (+)-Folicanthine

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This work is dedicated to Professor Richmond Sarpong

Abstract: A highly enantioselective decarboxylative allylation of a mixture of enol carbonates and allyl esters has been achieved. The strategic viability of this methodology has been demonstrated through the total synthesis of cyclotryptamine alkaloids (−)- and (+)-folicanthine (**1 a**) and the formal total synthesis of (−)-chimonanthine (**1 b**), (+)-calycanthine (**1 c**), and (−)-ditryptophenaline (**1 d**).

Introduction

Cyclotryptamine alkaloids (Figure 1)[1]that possess a bis-pyrrolidino-[2,3*b*]indoline moiety with a labile 3a–3a′ σ-bond constitute a large family of architecturally interesting alkaloids with a wide range of biological activities,[2] which makes their efficient total synthesis of notable importance. Recently, considerable effort has been devoted towards the development of oxidative dimerization methods for the construction of the core structure of these alkaloids.[3] As part of an alternative approach, the challenge of installing sterically congested vicinal all-carbon quaternary stereocenters[4] is of great synthetic interest among chemists; to achieve this in an asymmetric fashion would serve as a novel strategy in the synthesis of these alkaloids.[5]

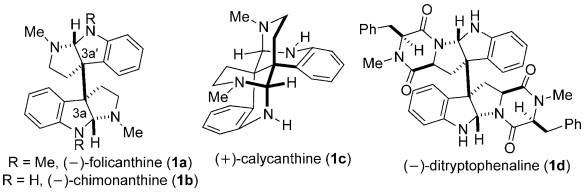
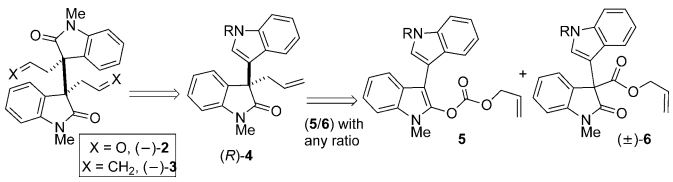


Figure 1. Selected bispyrrolidino-[2,3*b*]indoline alkaloids.

Towards this, elegant approaches include: Overman's first asymmetric synthesis of alkaloids **1 b** and **1 c** (Figure 1) by either a highly diastereoselective dialkylation or double Heck cyclizations to establish the quaternary stereocentres,[6] Movassaghi's biosynthetic approach by Co^{I}-promoted reductive homodimerization[7,8] and heterodimerization[9] reactions to construct various hexahydropyrroloindole alkaloids, a similar reductive homodimerization, which is catalyzed by Ni^{II} complexes,[10] and coupling reactions via 3a-phenylselenylpyrroloindoline.[11]

Prominent catalytic, enantioselective approaches include: the phosphoric-acid-catalyzed reactions of 3-hydroxy-2-oxindole with an enecarbamate by Gong,[12a] the decarboxylative alkylations by Ma,[12b] the Michael addition of indole onto isatylidene-3-acetaldehyde developed by Liu and Zhang,[13] a Michael reaction of *N*-Boc-protected bisoxindole with nitroethylene by Kanai and Matsunaga,[14] and the sequential Pd-catalyzed twofold decarboxylative allylations by Trost[15] and from our group[16] to afford C_2-symmetric bis-2-oxindole of type **3** (Scheme 1).



Scheme 1. Our retrosynthetic strategy.

Results and Discussion

We envisioned that a variety of cyclotryptamine alkaloids could easily be accessed by synthetic manipulation of a common enantioenriched intermediate **4**. In turn, this can be obtained through a Pd-catalyzed dynamic kinetic asymmetric transfor-

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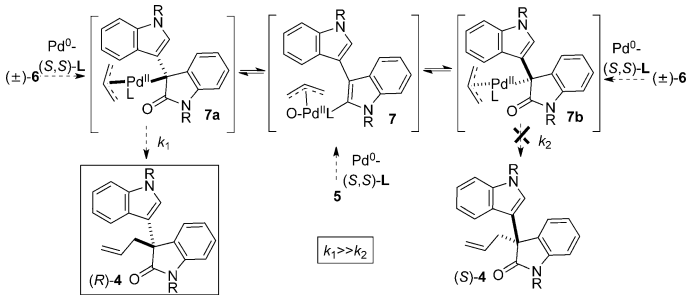
mation (DYKAT)[17,18] of *rac*-allyl ester (±)-**6**[19] and allyl carbonate **5**, either separately or as a mixture in any ratio. Herein, we report the use of the aforementioned strategy in the total synthesis of both enantiomers of folicanthine (**1a**).

However, as compounds (±)-**6** and **5** have different reaction rates for their Pd-catalyzed deallylation to form a common intermediate **7** (Scheme 2), the DYKAT of such a complicated



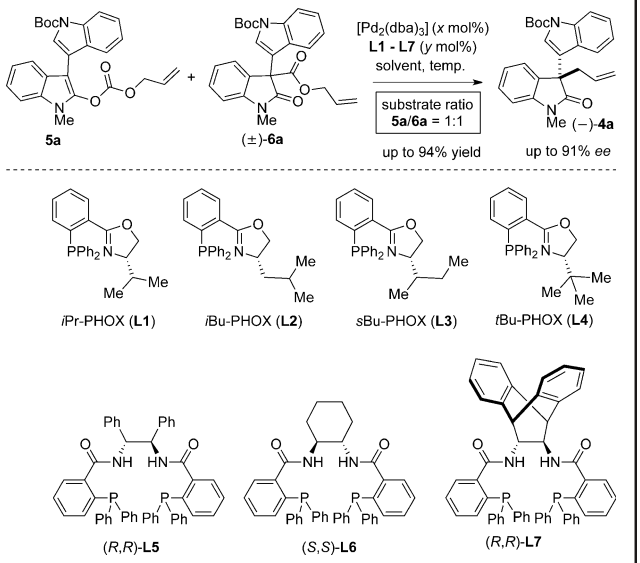
Scheme 2. DYKAT through rapid interconversion of intermediates **7a** and **b**.

mixture would be challenging and worth testing. The rationale for the sense of asymmetric induction is shown in Scheme 2. In our strategy, the DYKAT of compound (±)-**6** can be accomplished through a rapid interconversion of the two diastereomeric Pd^{II} intermediates **7a**–**b**.[18] Considering that the enantioselectivity arises from the kinetic reaction of one intermediate, this DYKAT requires a Curtin–Hammett condition to be established, in which the enantioselectivity is not dependent, in principle, upon the thermodynamic ratio of the intermediates.

In fact, the asymmetric induction arises from a selective reaction with one intermediate (**7a** in the case of [(*S*,*S*)-L-Pd^0]) through a selective differentiation of the enantiotopic faces of the nucleophile. In the reaction mixture, the Pd^{II} intermediate **7** would exist as an equilibrium of the two diastereomeric Pd^{II} intermediates **7a** and **b**, which have different energies of activation (Scheme 2). In the presence of an enatioenriched catalyst [(*S*,*S*)-L-Pd^0], one would expect the allylation of Pd^{II} intermediate **7a** (when $k_1 \gg k_2$) to afford a product with (*R*) stereochemistry ((*R*)-**4**), whereas, in case of the catalyst [(*R*,*R*)-L-Pd^0], the allylation of the Pd^{II} intermediate **7b** (if $k_2 \gg k_1$) should afford the enantioenriched product with (*S*)-stereochemistry ((*S*)-**4**).[18]

We chose the well-proved 2-phosphino-oxazoline (PHOX) ligands (*S*)-**L1**–**L4**[20] and 2-phosphino-carboxamide ligands **L5**–**L7**[20] alongside the allyl ester (±)-**6a**[21] and allyl carbonate **5a** substrates, which both contain orthogonal protecting groups (*N*-Me protection on the 2-oxindole moiety and Boc protection on the indole nucleus) to test in our Pd-catalyzed enantioselective DYKAT procedure[22] (Table 1). We carried out optimization of this reaction through the DYKAT of a mixture of allyl ester (±)-**6a** and allyl carbonate **5a** (1:1) in the presence of $[Pd_2(dba)_3]$ (5 mol%) in combination with ligands **L1**–**L7** (15 mol%) in diethyl ether at room temperature (entries 1–7). Interestingly, in almost all the cases, DYKAT afforded the expected product **4a** in excellent yield. Among various ligands that were screened, PHOX ligands (*S*)-**L1**–**L4** were found to be

Table 1. Optimization of the DYKAT of a 1:1 mixture of allyl carbonate **5** and allyl ester **6**.



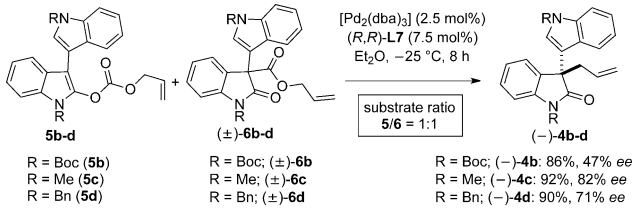
Entry[a]	$[Pd_2(dba)_3]$ [mol%]	Ligand ([mol%])	Solvent	Temp. [°C]	Time	Yield [%][b]	*ee* [%][c]
1	5	**L1** (15)	Et_2O	25	12 h	90	5
2	5	**L2** (15)	Et_2O	25	10 h	89	10
3	5	**L3** (15)	Et_2O	25	16 h	91	11
4	5	**L4** (15)	Et_2O	25	11 h	87	14
5	5	**L5** (15)	Et_2O	25	10 h	89	40
6	5	**L6** (15)	Et_2O	25	9 h	92	31
7	5	**L7** (15)	Et_2O	25	8 h	93	84
8	5	**L7** (15)	DCE	25	18 h	52	58
9	5	**L7** (15)	$CHCl_3$	25	36 h	30	50
10	5	**L7** (15)	DME	25	24 h	10	nd[d]
11	5	**L7** (15)	xylene	25	11 h	86	76
12	5	**L7** (15)	PhMe	25	11 h	87	79
13	5	**L7** (15)	THF	25	14 h	78	61
14	5	**L7** (15)	CH_2Cl_2	25	12 h	88	53
15	2.5	**L7** (7.5)	Et_2O	25	9 h	94	82
16	2.5	**L7** (7.5)	PhMe	25	12 h	88	74
17	5	**L7** (15)	Et_2O	−25	9 h	92	91
18	2.5	**L7** (7.5)	PhMe	−25	18 h	86	78
19	2.5	**L7** (7.5)	Et_2O	−25	9 h	93	90
20	1.25	**L7** (3.75)	PhMe	−25	24 h	74	76
21	1.25	**L7** (3.75)	Et_2O	−25	24 h	87	85
22	5	**L7** (15)	Et_2O	−40	48 h	86	90
23	2.5	**L7** (7.5)	Et_2O	−40	54 h	65	90
24	5	**L7** (15)	Et_2O	−60	5 d	75	72
25	2.5	**L7** (7.5)	Et_2O	−60	5 d	46	81

[a] Reactions were carried out on 0.04 mmol of substrates in 3 mL of solvent under an argon atmosphere. [b] Yield of isolated product after purification by column chromatography. [c] *ee*'s were determined by chiral HPLC analysis. [d] Not determined.

unsuitable because they afforded products in no more that 14% *ee*, whereas 2-phosphino-carboxamide ligands **L5**–**L6** yielded the product **4a** in up to 40% *ee* (entries 5 and 6). By using the sterically hindered anthracenyl ligand **L7**, which is rigidly held in a specific conformation, we were pleased to find that product (*S*)-**4a** was obtained in 84% *ee* (entry 7). Solvent screening showed that diethyl ether was the best choice over other organic solvents (entries 7–14). Interestingly, reduction of the catalyst loading to 2.5 mol% led to formation of the prod-

uct **4a** in 82% *ee* (entry 15). By decreasing the reaction temperature to −25 °C, we found that catalyst loadings of 5 mol% and 2.5 mol% provided the product **4a** in 91 and 90% *ee*, respectively (entries 17 and 19). In contrast, when reactions with a catalyst loading of 2.5 mol% at room temperature and −25 °C were carried out in toluene, we observed a reduced enatioselectivity to afford the product **4a** in 74 and 78% *ee*, respectively (entries 16 and 18). Further decreasing the catalyst loading of the reaction in diethyl ether to 1.25 mol% led to a loss in enantioselectivity to give product **4a** in 85% *ee* (entry 21). We also found that a further decrease in the reaction temperature to −40 °C and −60 °C led to slower reaction rates (entries 22–25). Thus, based on our optimization studies, we decided to proceed with an investigation into the substrate scope of this reaction by using 2.5 mol% of $[Pd_2(dba)_3]$ in combination with 7.5 mol% of the anthracenyl ligand **L7** in diethyl ether at −25 °C.

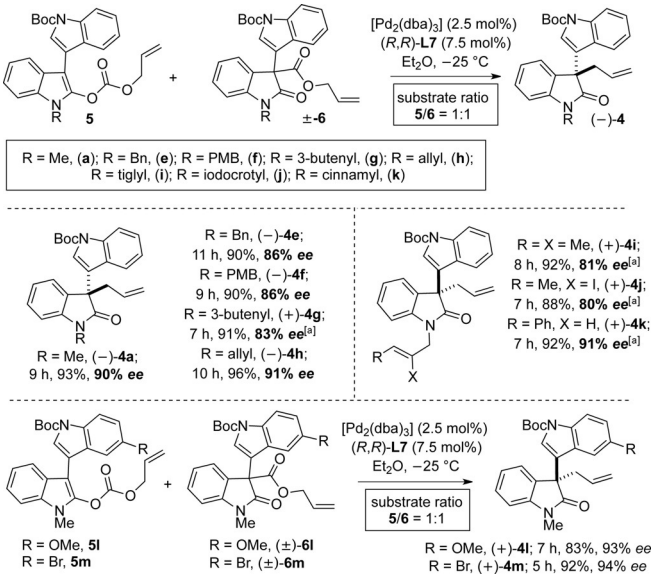
Firstly, we checked the effect of differently protected bisindole scaffolds on the enantioselectivity (Scheme 3). When we



Scheme 3. Effect of different protecting groups on the enantioselectivity. The reactions were carried out on 0.04 mmol of substrates in 3 mL of solvent under an argon atmosphere. The yield is that of the isolated product after purification by column chromatography. *ee* values were determined by chiral HPLC analysis.

used allyl ester (±)-**6b** and allyl carbonate **5b**, which have both N atoms protected with the bulky and electron-deficient Boc group, unfortunately, we obtained product **4b** in poor enantioselectivity (47% *ee*). However, when the N-protecting groups were changed to the less bulky and electron-rich methyl or benzyl groups, such as allyl esters (±)-**6c** and **d** and allyl carbonates **5c** and **d**, the enantioselectivity was enhanced to give the products **4c** and **d** in 82 and 71% *ee*, respectively. Thus, we proceeded to investigate the substrate scope of the allyl esters by using an electron-donating protecting group at the 2-oxindole or on the side of enol carbonate, such as substrate (±)-**6a**, and allyl carbonates that have an electron-withdrawing, bulky Boc group to protect the indole moiety, such as substrate **5a** (see Table 1).

A variety of substrates were tested under the optimized conditions to effect the Pd-catalyzed DYKAT of a mixture of substrates (±)-**6e**–**k** and **5e**–**k** (1:1) in the presence of $[Pd_2(dba)_3]$ (2.5 mol%) in combination with ligand **L7** (7.5 mol%) in diethyl ether at −25 °C to afford the products **4e**–**k** in good to excellent levels of enantioselectivity (up to 91% *ee*) (Scheme 4). Furthermore, substrates that had different functionality at the indole moiety, such as allyl esters (±)-**6l** and **m** and allyl carbonates **5l** and **m**, were tested under the optimized conditions;



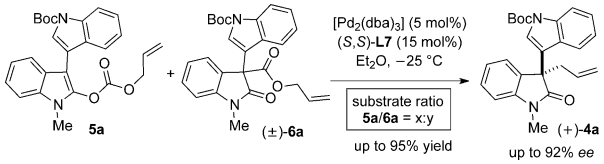
Scheme 4. Substrate scope of the DYKAT of a mixture of (±)-**6** and **5** (1:1). The reactions were carried out on 0.04 mmol of substrates in 3 mL of solvent under an argon atmosphere. The yield is that of the isolated product after purification by column chromatography. *ee* values were determined by chiral HPLC analysis. [a] (*S*,*S*)-**L7** was used as ligand.

to our delight, products **4l** and **m** were afforded in 93 and 94% *ee*, respectively, and high yields (Scheme 4).

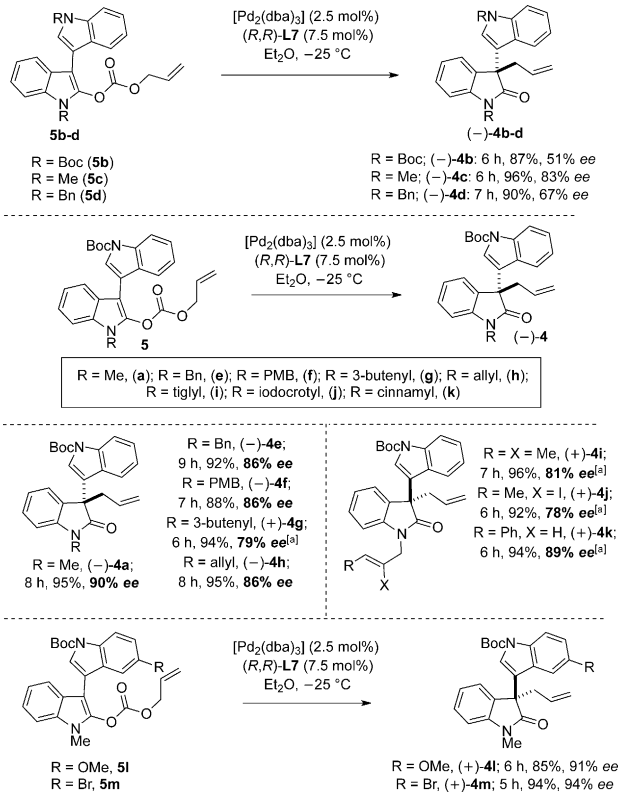
Next, as per our hypothesis (Scheme 2), the enantioselective Pd-catalyzed decarboxylative allylation by DYKAT was also carried out with allyl esters (±)-**6** and carbonates **5**, independently. We observed that in both cases the enantioselectivities of the reactions were good to excellent (Scheme 5 and 6).

In accordance with our proposal (Scheme 2), we then investigated the effect that different ratios of the substrates (±)-**6a** and **5a** had on the enantioselectivity of the reaction (Table 2). Interestingly, all of the possible mixtures that we tried were equivalently good with respect to the yield and enantioselectivity (entries 1–5). Gratifyingly, a gram-scale reaction of a mixture of substrates (±)-**6a** and **5a** also afforded (+)-**4a** in 89% yield with 90% *ee* (entry 6).

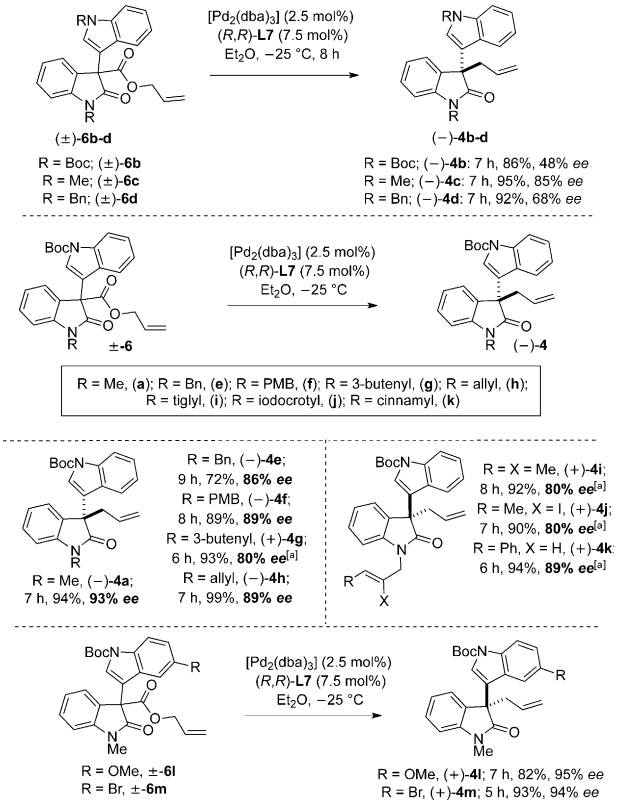
Table 2. Effect of different ratios of **5a** and (±)-**6a** on the enantioselectivity of the DYKAT.



Entry	**5a**/**6a**	Scale	Time [h]	Yield [%]	*ee* [%]
1	50:50	100 mg	10	90	91
2	100:0	100 mg	8	95	90
3	0:100	100 mg	10	94	92
4	25:75	100 mg	9	92	91
5	75:25	100 mg	8	93	90
6	50:50	1 g	11	89	90

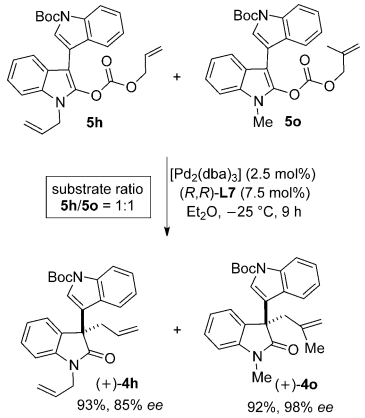


Scheme 5. Substrate scope of DYKAT only using allyl carbonate **5**. The reactions were carried out on 0.04 mmol of substrates in 3 mL of solvent under an argon atmosphere. The yield is that of the isolated product after purification by column chromatography. *ee* values were determined by chiral HPLC analysis. [a] (*S*,*S*)-**L7** was used as ligand.



Scheme 6. Substrate scope of DYKAT only using (±)-allyl ester **6**. The reactions were carried out on 0.04 mmol of substrates in 3 mL of solvent under an argon atmosphere. The yield is that of the isolated product after purification by column chromatography. *ee* values were determined by chiral HPLC analysis. [a] (*S*,*S*)-**L7** was used as ligand.

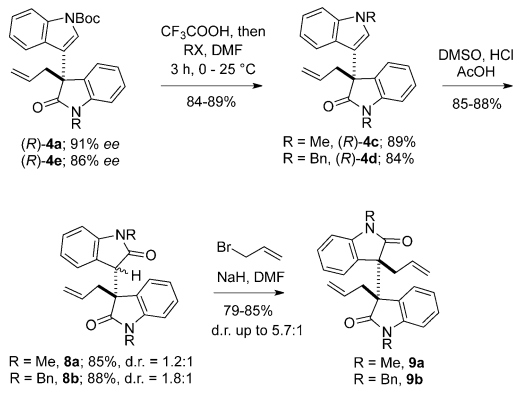
We hypothesized that these reactions might proceed via either a tight-ion-pair-type Pd^{II}-π-allyl complex that is linked with the nucleophile, such as **7**, or a separate Pd^{II}-π-allyl complex and an enolate species. To test this hypothesis, we performed a Pd^0-catalyzed DYKAT in the presence of two different enol carbonates **5h** and **o** (1:1) in the presence of $[Pd_2(dba)_3]$ (2.5 mol%) in combination with (*S*,*S*)-**L7** (7.5 mol%), and we found that no scrambling occurred during the course of the DYKAT. From this reaction, we isolated only the enantioenriched allylated product (+)-**4h** and methallylated product (+)-**4o** in 93% (85% *ee*) and 92% (98% *ee*) yield, respectively without any other side products (Scheme 7). This observation clearly supports the probable involvement of a tight ion pair in the DYKAT process and the intramolecular nature of the reaction (Scheme 2).



Scheme 7. Decarboxylative allylation of a mixture of **5h** and **o** (1:1).

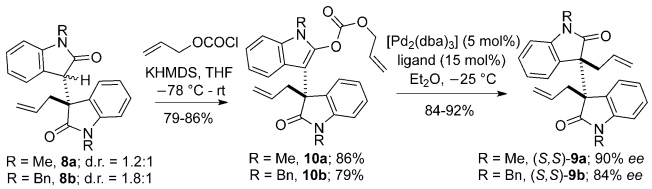
To show the synthetic viability of our methodology, we undertook the total synthesis of (−)-folicanthine (**1a**). Towards this, we carried out the DYKAT of a mixture of compounds (±)-**6a** and **5a** (1:1) in the presence of Pd^0-(*S*,*S*)-**L7** to afford (*R*)-**4a** in 93% yield with 91% *ee* (Scheme 8). In a similar manner, we also synthesized (*R*)-**4e** in 90% yield with 86% *ee*. Starting from (*R*)-**4a** and **e**, we synthesized the bis-2-oxindoles **8a** and **b** (up to ≈1.8:1 d.r.), respectively, in three steps: removal of the Boc-group, *N*-alkylation, and reaction with DMSO in the presence of HCl. At this stage, we anticipated that the diastereoselective allylation with allyl bromide could afford the C_2-symmetric product (*S*,*S*)-**9a** and **b** in high d.r. by manipulation of the reaction temperature (Table in Scheme 8, entries 1–5). However, we only achieved the product (*S*,*S*)-**9a** in a maximum 5.7:1 d.r. by carrying out the allylation at −50 °C (entry 3).

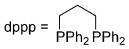
Therefore, we adopted an alternative pathway for the synthesis of (*S*,*S*)-**9a** and **b**, which employs a Pd^0-catalyzed diastereoselective decarboxylative allylation of (*S*)-**10a** and **b** (Scheme 9). These enol carbonates (*S*)-**10a** and **b** were syn-



Entry	8a-b	T [YC]	t [h]	Product	Yield [%][a,b]	ee [%][c]	d.r.[d]
1	8a	0 - 25	1	(S,S)-9a	81 (39)[e]	91% (99)[f]	3.6:1 (>20:1)[g]
2	8a	−25	2	(S,S)-9a	79	91%	5.4:1
3	8a	−50	2	(S,S)-9a	82	91%	5.7:1
4	8b	0 - 25	1	(S,S)-9b	83 (37)[e]	84% (97)[f]	4.4:1 (>20:1)[g]
5	8b	−25	2	(S,S)-9b	85	84%	4.6:1

Scheme 8. Synthesis of C_2-symmetric bis-allyl compounds. [a] Reactions were carried out on a 0.10 mmol scale of **8a** and **b** in 1 mL of DMF. [b] Yield of isolated product after purification. [c] *ee*'s were determined by chiral HPLC analysis. [d] d.r.'s were determined by ^{1}H NMR spectroscopy of unpurified product. [e] Yields after recrystalization. [f] *ee*'s after recrystalization. [g] d.r.'s after recrystalization.



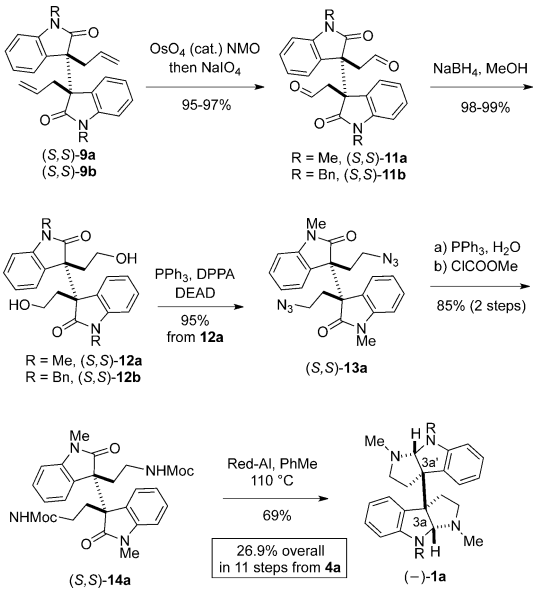
dppp = 

Entry	(S)-10a-b	Ligand	T [°C]	t [h]	Product	Yield [%][a,b]	ee [%][c]	d.r.[d]
1	(S)-10a	dppp	0	2	(S,S)-9a	91	91	5.4:1
2	(S)-10a	dppp	−25	4	(S,S)-9a	90	91	6.3:1
3	(S)-10a	(R,R)-L7	−25	5	(S,S)-9a	84	91	1.4:1
4	(S)-10a	(S,S)-L7	−25	4	(S,S)-9a	92 (79)[e]	91 (99)[f]	>20:1[g]
5	(S)-10b	(S,S)-L7	−25	6	(S,S)-9b	90 (72)[e]	86 (97)[f]	11:1[g] (>20:1)[h]

Scheme 9. Highly diastereoselective synthesis of (*S*,*S*)-**9a** and **b**. [a] Reactions were carried out on a 0.10 mmol scale of **10a** and **b** in 2 mL of Et_2O. [b] Yield of isolated product after purification. [c] *ee*'s were determined by chiral HPLC analysis. [d] d.r.'s were determined by ^{1}H NMR spectroscopy of unpurified product. [e] Yields after single recrystalization. [f] *ee*'s after single recrystalization. [g] d.r.'s were determined in these cases by chiral HPLC analysis as well. [h] d.r. after single recrystalization.

thesized from bis-2-oxindoles **8a** and **b** by the reaction of allyl chloroformate in the presence of KHMDS at −78 °C. To our delight, a highly diastereoselective synthesis of the C_2-symmetric products can be realized in the presence of (*S*,*S*)-**L7** at −25 °C to afford (*S*,*S*)-**9a** and **b** in high yields with >20:1 and 11:1 d.r., respectively (entries 4 and 5). Furthermore, a single recrystalization of these compounds afforded (*S*,*S*)-**9a** and **b** both in >20:1 d.r. and with 99% (79% yield) and 97% *ee* (72% yield), respectively (entries 4 and 5).

Following the oxidative degradation of bis-allyl groups, we synthesized the C_2-symmetric bis-aldehydes (*S*,*S*)-**11a** and **b** in 95 and 97% yield, respectively (Scheme 10). Then, bis-aldehyde



Scheme 10. Total synthesis of (−)-folicanthine **1a**.

(*S*,*S*)-**11a** was reduced with $NaBH_4$ to afford the diol intermediate (*S*,*S*)-**12a**, which in turn underwent a Mitsunobu reaction in the presence of diphenylphosphoryl azide to afford the bis-azide (*S*,*S*)-**13a** in 94% yield over the 2 steps. The latter was then reduced by using triphenylphosphine in water, and subsequent protection with chloromethylformate provided the bis-Moc-protected compound (*S*,*S*)-**14a** in 85% yield over two steps. Finally, compound (*S*,*S*)-**14a** was reduced in the presence of Red-Al in toluene at 110 °C to complete the total synthesis of (−)-folicanthine (**1a**) in 26.9% overall yield from compound **4a**. In fact, the synthesis of bis-aldehyde (*S*,*S*)-**11b** represents the formal total synthesis of (−)-chimonanthine (**1b**),[6b] (+)-calycanthine (**1c**),[6b] and (−)-ditryptophenaline (**1d**)[23] (Figure 1).

For the total synthesis of (+)-folicanthine (*ent*-**1a**), we carried out the Pd-catalyzed DYKAT of (±)-**6a** in the presence of Pd^0-(*R*,*R*,)-**L7**, which afforded (*S*)-**4a** in 94% yield with 91% *ee*. By following a similar sequence of reactions shown in Scheme 8–10, we also completed the total synthesis of (+)-folicanthine (*ent*-**1a**) (see the Supporting Information).

Conclusion

We have reported an enantioselective, Pd-catalyzed decarboxylative allylation protocol, which proceeds through a DYKAT of a mixture of allyl ester (±)-**6** and allyl carbonate **5** (1:1) to afford the enantioenriched, advanced intermediate (*R*)-**4** in up to 98% *ee* with excellent yields. We also achieved intermediate (*S*)-**4** in similar efficiencies when (*R*,*R*)-**L7** was used. We applied

our asymmetric protocol to the enantioselective total synthesis of (−)- and (+)-folicanthine (**1a**). Further application of this strategy for the total synthesis of higher analogues of cyclotryptamine alkaloids is under active investigation.

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