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Palladium-Catalyzed, Modular Synthesis of Highly Functionalized Indoles and Tryptophans by Direct Annulation of Substituted *o*-Haloanilines and Aldehydes

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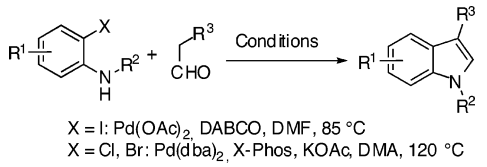
Received July 15, 2006



One-pot synthesis of indoles by a palladium-catalyzed annulation of *ortho*-haloanilines and aldehydes has been developed. Coupling of *ortho*-iodoaniline with aldehyde is realized under mild ligandless conditions [$Pd(OAc)_2$, DABCO, DMF, 85 °C], whereas X-Phos is found to be the ligand of choice for coupling reactions involving *ortho*-chloroanilines/*ortho*-bromoanilines and aldehydes. A variety of *ortho*-haloanilines with different electronic properties are suitable substrates, and aldehydes including chiral ones participated in this reaction without racemization. Coupling of (*S*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentanoate, derived from L-glutamic acid, with *ortho*-haloanilines provides a rapid access to the ring-A-substituted tryptophans in good to excellent yields.

Introduction

The indole nucleus is one of the most important heterocycles due to its presence in a vast number of bioactive natural products, pharmaceuticals, and agrochemicals.[1] Since the discovery of Fischer indole synthesis in 1883, synthesis and functionalization of indoles has been the subject of intensive research for over 100 years, and a variety of well-documented traditional and modern methods are now available.[2,3] However, the development of general and efficient methods for preparation of functionalized indoles from simple and easily accessible starting materials remains an active research field.[4] In this context, palladium-catalyzed transformations have had a major impact on indole synthesis, and indeed a range of catalytic protocols has been developed for the synthesis of functionalized indoles from simple starting materials.[5,6] Thus the intramolecular Heck reaction[7] involving 5-*exo* cyclization followed by double-bond isomerization has been widely used for the synthesis of substituted indole derivatives since the initial disclosure of Mori[8]

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10.1021/jo061471s CCC: $33.50
Published on Web 09/06/2006

and Hegedus.[9] Arguably, the palladium-catalyzed cyclization of *ortho*-alkynylanilines/anilides[10] and Larock annulation of *ortho*-haloanilines with internal alkynes[11] are among the most powerful synthetic methods recently developed for the construction of indoles. On the other hand, palladium-catalyzed cyclization of *ortho*-haloanilino enamines has also been developed since the initial report of Kibayashi.[12] In most cases, enamines are stabilized by conjugation with a carbonyl group (enaminones) and are synthesized in a separate step by one of the following methods: (a) condensation of *ortho*-haloanilines with 1,3-dicarbonyl compound[13] or α-keto ester;[14] (b) Michael addition of anilines to ethynyl ketone;[15] (c) palladium-catalyzed oxidative amination of electron-deficient olefins;[16] (d) Buchwald−Hartwig amination of vinylogous amides;[17] and (e) Wittig reaction of trifluoroanilides.[18] A breakthrough came in 1997 when Chen and co-workers at Merck Research Laboratories[19] reported a one-pot annulation process starting from the *ortho*-iodoaniline and cyclic ketones.[20,21] Surprisingly, aldehydes have not been used as a reaction partner in this annulation process, though this would produce highly demanding 2-unsubstituted indole derivatives. Indeed, it has been noted in Chen's original paper that this annulation works well with cyclic ketones, but less efficiently with acyclic ketones. To get the parent 2-unsubstituted indoles, the authors advocated the use of acylsilane or pyruvic acid since both carboxyl and silyl groups can be removed after the annulation reaction. In connection with a total synthesis project, we had occasion to examine this reaction, and we detail herein that *ortho*-iodoaniline reacted efficiently with a variety of aldehydes in the presence of palladium catalyst to afford the 2-*un*substituted indoles, including enantiomerically pure tryptophan derivatives.[22] We document also the development of conditions that allow the use of *ortho*-chloroaniline and *ortho*-bromoaniline as coupling partners, extending thus significantly the application scope of this reaction.

Results and Discussion

Annulation of *ortho*-Iodoanilines and Aldehydes. In the course of our efforts toward the total synthesis of complestatin (chloropeptin II),[23] we needed an efficient method for the preparation of benzenoid-substituted tryptophan. Literature search indicated that a variety of methodologies have been developed, including (a) enzymatic resolution of racemic compounds;[24] (b) tryptophan synthetase catalyzed alkylation of indole by L-serine;[25] (c) functionalization of the cyclic tautomer of tryptophan;[26] (d) enantioselective hydrogenation of dehydrotryptophan;[27] (e) diastereoselective[28] and enantioselective[29] alkylation of indole derivatives; (f) enantioselective ene reaction;[30] (g) The Fischer indole synthesis;[31] and (h) palladium-catalyzed Larock heteroannulation reaction.[32] However, most of these methodologies suffer from a number of disadvantages. Thus, the alkylation strategy is complicated by competitive nucleophilicity at C-3 versus C-2, N-1 and requires a presynthesis of the indole core,[33] whereas the traditional Fischer indole synthesis often failed to deliver indoles with electron-deficient hydrazines and *m*-substituted phenylhydrazines usually yielded a mixture of 4- and 6-substituted indoles.[34] The synthesis of substituted tryptophans by Larock annulation reaction required multistep synthesis of chiral internal silylalkynes.[32] The limitation of the current available synthetic approaches to access ring-A-substituted tryptophan derivatives prompted us to develop an alternative synthesis of this class of amino acids, and Chen's one-step annulation protocol seems to be highly promising in order to reach this goal.

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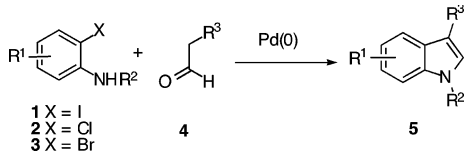
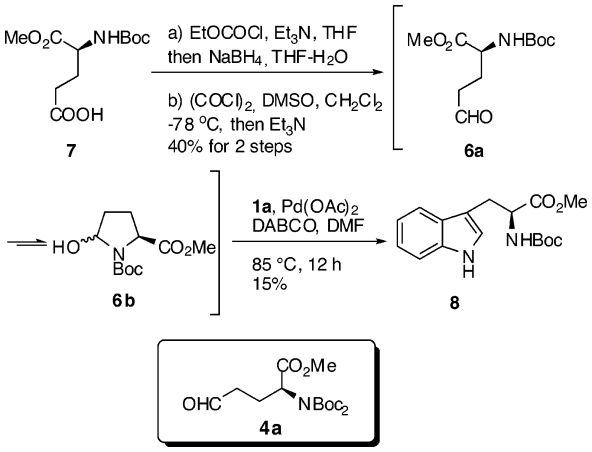
SCHEME 1



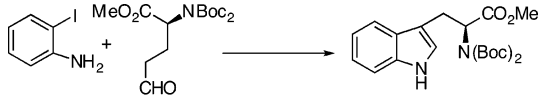
SCHEME 2



We initially examined the annulation reaction of *o*-iodoaniline **1a** ($R^1 = R^2 = H$) and (2*S*)-2-*N*-Boc-5-oxopentanoic acid methyl ester (**6a**). The aldehyde (**6a**) was synthesized from *N*-Boc-L-glutamic acid α-methyl ester **7** via a reduction/oxidation sequence and was found to exist mainly as the cyclic hemiaminal form **6b** (Scheme 2).[35] Submitting **6a**/**6b** and **1a** to Chen's conditions [$Pd(OAc)_2$, DMF, DABCO, 85 °C] afforded indeed the desired L-tryptophan (**8**) but in only 15% isolated yield. Although yield remained low, the result was nevertheless encouraging since it proved the feasibility of this approach, which constituted probably one of the shortest routes to **8**. Parallel to our work, Baran and co-workers reported a synthesis of racemic 6-hydroxytryptophan using a similar strategy in connection with their total synthesis of stephacidin A.[36]

Reasoning that hemiacetal **6b** may not react properly with aniline to produce the enamine intermediate required for the subsequent key C−C bond forming process, we turned our attention to the enantiomerically pure methyl (*S*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentanoate **4a** (Scheme 2), readily synthesized in four conventional steps from L-glutamic acid.[37] The reaction of **1a** and **4a** in DMF in the presence of palladium acetate was performed under a variety of conditions, and some representative results are summarized in Table 1. As it is seen, the choice of base is of utmost importance since no annulation product was formed when potassium carbonate (entry 1) and 1,2,2,6,6-pentamethylpiperidine (entry 2) were used as bases. However, in the presence of 1,4-diazabicyclo[2,2,2]octane (DABCO), the desired L-*N*,*N*-di-Boc-tryptophan methyl ester (**5a**) was produced in 81% yield. We have also briefly examined

TABLE 1. Palladium-Catalyzed Heteroannulation of *o*-Iodoaniline (1a, $R^1 = R^2 = H$) and *ω*-Amino Aldehyde 4a[a]



entry	base	additive	*T* (°C)	time (h)	yield (%)[b]
1	K_2CO_3		85	8	0
2	PMP		85	10	0
3	DABCO		85	8	81
4	DABCO	TBACl[c]	85	8	0
5	DABCO	TBAI[c]	85	20	48
6	DABCO	TBAI[c]	105	7	40
7[d]	DABCO		85	8	0

[a] General reaction conditions: concentration = 0.2 M in DMF, $Pd(OAc)_2$ (0.05 equiv) as palladium source except for entry 7, mole ratio = **1a**/**4a** = 1.1/1 in the presence of 3 equiv of base. [b] Isolated yield. [c] Three equivalents. [d] $Pd(PPh_3)_4$ was used as catalyst. Abbreviations: PMP = 1,2,2,6,6-pentamethylpiperidine; DABCO = 1,4-diazabicyclo[2,2,2]octane; TBACl = tetrabutylammonium chloride; TBAI = tetrabutylammonium iodide.

the effect of additives and found that the yield of **5a** decreased in the presence of tetrabutylammonium iodide (TBAI) or tetrabutylammonium chloride (TBACl) (entries 4−6).[38] The palladium source also played an important role since no desired product was isolated when $Pd(PPh_3)_4$ was used under otherwise identical conditions (entry 7). The enantiomeric purity of **5a** was determined to be higher than 92% by its conversion to **8** ($CeCl_3 \cdot 7H_2O$, NaI, MeCN)[39] and subsequent chiral HPLC analysis (cf. Supporting Information).

Having established the optimal reaction conditions, the scope of this reaction was examined with respect to anilines by varying systematically the electronic properties of the aromatic ring. As is shown in Table 2, the reaction turned out to be very general and is applicable to both electron-rich and electron-deficient *o*-iodoanilines. Thus, even with 4-nitroaniline (**1f**), the corresponding tryptophan **5f** was isolated in 74% yield, although the basicity of the amino function in **1f** was significantly reduced (entry 6). Steric hindrance was also well tolerated since both 4-methoxytryptophan **5c** (entry 3) and 7-methoxytryptophan **5i** (entry 9) can be synthesized by this methodology, although 2 equiv of aniline **1c** had to be used for the synthesis of **5c**. The reaction of *N*-methylanilines (**1b**, **1e**) with **4a** proceeded smoothly, leading to the corresponding tryptophan derivatives (**5b**, **5e**) in excellent yield. 6-Azatryptophan can be similarly prepared starting from 4-iodo-3-aminopyridine (entry 11). Furthermore, the reaction is site-selective since the reaction of 2-iodo-5-chloroaniline with **4a** afforded the corresponding 6-chlorotryptophan in 74% yield (**5l**, entry 12). The presence of a chlorine atom in **5l** provided a valuable handle for further functionalization by way of transition-metal-catalyzed processes.[40]

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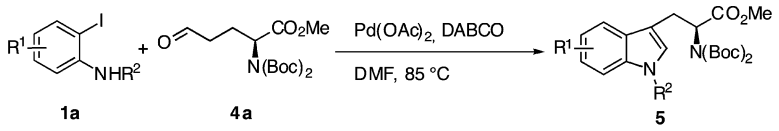
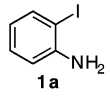
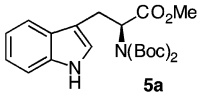
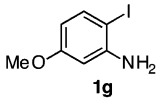
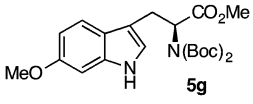
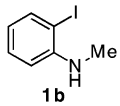
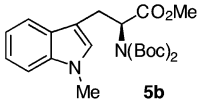
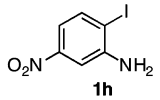
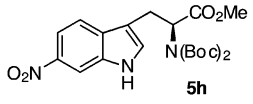
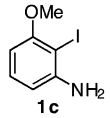
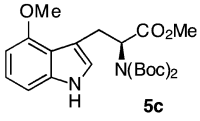
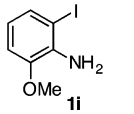
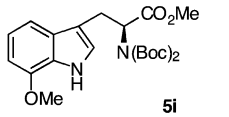
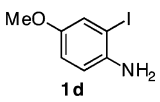
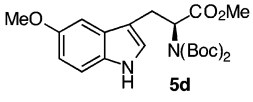
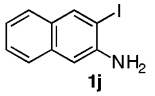
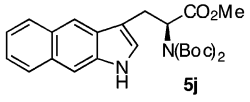
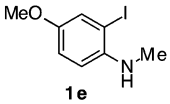
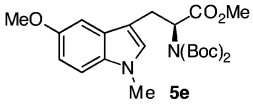
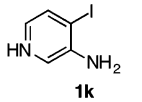
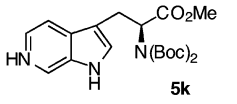
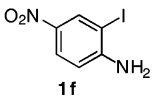
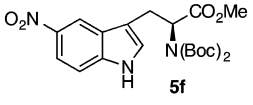
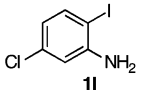
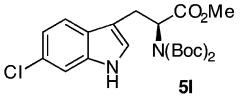
TABLE 2. Synthesis of Ring-A-Substituted Tryptophans by Palladium-Catalyzed One-Pot Annulation Reaction[a]



entry	*o*-iodoaniline	product	yield (%)[b]	entry	*o*-iodoaniline	product	yield (%)[b]
1	 **1a**	 **5a**	81	7	 **1g**	 **5g**	58
2	 **1b**	 **5b**	85	8	 **1h**	 **5h**	64
3	 **1c**	 **5c**	55	9	 **1i**	 **5i**	71
4	 **1d**	 **5d**	51	10	 **1j**	 **5j**	60
5	 **1e**	 **5e**	84	11	 **1k**	 **5k**	60
6	 **1f**	 **5f**	74	12	 **1l**	 **5l**	74

[a] General reaction conditions: concentration = 0.2 M in DMF, 0.05 equiv of $Pd(OAc)_2$, 1.1 equiv of *o*-iodoaniline **1**, 1.0 equiv of aldehyde **4a**, 3.0 equiv of DABCO, 85 °C. [b] Isolated yield.

To evaluate the application scope of this one-pot annulation protocol with respect to aldehydes, coupling of *ortho*-iodoaniline with different aldehydes was next investigated, and the results are summarized in Table 3. As expected, the annulation reaction proceeded without event to afford the corresponding ring-A-functionalized C-3-substituted indoles in good yields. The presence of a free hydroxy group was well tolerated since 5-hydroxypentanal can be used directly in the annulation reaction to afford indole **5r** (entry 6). The 3-phenyl-substituted indole **5o** was prepared in good yield from the corresponding phenylacetaldehyde.[41] Indole **5p** bearing an asymmetric center adjacent to the C-3 carbon was obtained by annulation of (*S*)-citronellal with *ortho*-iodoaniline without racemization (cf. Supporting Information). The synthesis of this type of indole has been the recent focus, and most of the reported methods called for the asymmetric functionalization of indole, requiring thus the presynthesis of the substituted indole nucleus.[42−45] The *N*-methyl *ortho*-iodoaniline (**1b**) reacted with 3-phenylpropinaldehyde efficiently to provide **5s** in 76% yield (entry 7).

Annulation of *ortho*-Chloroanilines and Aldehydes. With these results in hand, we were interested in exploring the possibility of replacing the *ortho*-iodoaniline with much cheaper and readily accessible *ortho*-chloroaniline and *ortho*-bromoaniline as the reaction partners of the present annulation process. Although remarkable progress has been achieved in palladium-catalyzed coupling reactions of aryl chlorides,[40] examples using highly deactivated chloroanilines remained relatively rare. As a model reaction, the union of *o*-chloroaniline **2a** with 3-(3,4,5-trimethoxyphenyl)propanal **4b** in DMA with (t-Bu_3P)HBF_4 (**9**) as a supporting ligand[20,46] was examined in the presence of a variety of bases and palladium sources. As shown in Table 4, potassium acetate turned out to be the base of choice (entry 1), and DABCO was also capable of promoting the reaction but

(41) (a) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363−1366. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057.

(42) For a review of stereoselective Friedel−Crafts alkylation reaction, see: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550−556.

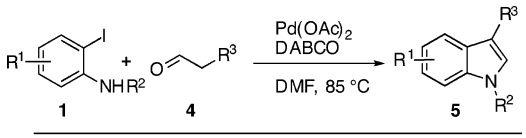
(43) For metal-catalyzed additions of indoles to α,β-unsaturated systems, see: (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780−10781. (b) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309−1320. (c) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154−4155. (d) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943.

(44) For organo-catalyzed additions of indoles to α,β-unsaturated systems, see: (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172−1173. (b) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437−3440. (c) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576−6579.

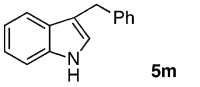
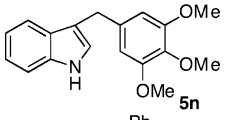
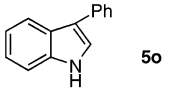
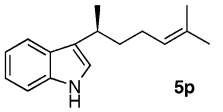
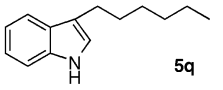
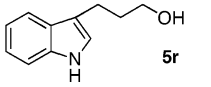
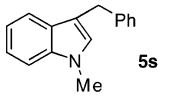
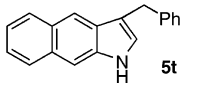
(45) (a) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, 1759−1762. (b) Dardennes, E.; Kovacs-Kulyassa, A.; Renzetti, A.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **2003**, *44*, 221−223.

(46) (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (b) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (c) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298. (d) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348.

TABLE 3. Synthesis of Indoles by Palladium-Catalyzed One-Pot Annulation Reaction[a]



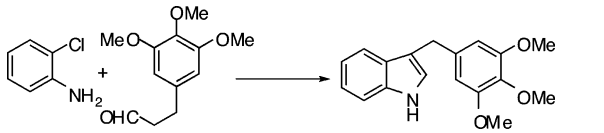
1 4 5

entry	o-iodoaniline	product	yield (%)[b]
1	**1a**	 **5m**	55
2	**1a**	 **5n**	67
3	**1a**	 **5o**	78
4	**1a**	 **5p**	43
5	**1a**	 **5q**	55
6	**1a**	 **5r**	41[c]
7	**1b**	 **5s**	76
8	**1j**	 **5t**	45

[a] General reaction conditions: concentration = 0.2 M in DMF, 0.05 equiv of $Pd(OAc)_2$, 1.1 equiv of *o*-iodoaniline **1**, 1.0 equiv of aldehyde **4**, 3.0 equiv of DABCO, 85 °C. [b] Isolated yield. [c] 5-Hydroxypentanal (open-chain form) was used as coupling partner.

with low conversion (entry 7). On the other hand, potassium phosphate, potassium carbonate, cesium carbonate, and PMP were less effective as bases. The addition of magnesium sulfate as dehydrating agent did not exert any positive effect. Palladium acetate can also act as palladium source, albeit with slightly reduced yield and longer reaction time (entries 11 and 12). Overall, under optimum conditions [$Pd(dba)_2$, (t-Bu_3P)HBF_4, KOAc, DMA, 120 °C], the desired indole **5n** was isolated in 57% yield. It has to be noted that, in the absence of (t-Bu_3P)-HBF_4, no reaction occurred under otherwise identical conditions (entry 13). To further optimize the reaction conditions, a screening of ligands was carried out (Table 5). The electron-rich but sterically less demanding monophosphines (tricyclohexyl phosphine (**10**), tri-^{n}butyl phosphine (**11**), and dicyclohexyl-(2,4,6-triisopropylphenyl)phosphine (**12**)) were found to be ineffective for the present transformation (entries 1−3). The bulky electron-rich biphenyl phosphines, such as **13** (cyclohexyl JohnPhos), **14** (JohnPhos), and **15** (DavePhos), gave inferior results relative to those of (t-Bu_3P)HBF_4 (entries 4−6), while ligand **16** (2-dicyclohexylphosphino-2′-methylbiphenyl) was as efficient as (t-Bu_3P)HBF_4. The best result was obtained when X-phos **17** was employed as supporting ligand affording indole

TABLE 4. Annulation Reaction of *o*-Chloroaniline 2a and Aldehyde 4b, Conditions Survey[a]



2a **4b** **5n**

entry	Pd cat.	base	additive	time (h)	yield (conv.)[b]
1	$Pd(dba)_2$	KOAc		5	57
2	$Pd(dba)_2$	KOAc		5	51[c]
3	$Pd(dba)_2$	KOAc	$MgSO_4$	7	57
4	$Pd(dba)_2$	K_3PO_4	HOAc	7	51
5	$Pd(dba)_2$	K_3PO_4		8	14
6	$Pd(dba)_2$	K_2CO_3		4	38
7	$Pd(dba)_2$	DABCO		5	58 (46)
8	$Pd(dba)_2$	Cs_2CO_3		6	17
9	$Pd(dba)_2$	PMP		20	33 (56)
10	$Pd(Ph_3P)_4$	KOAc		25	15
11	$Pd(OAc)_2$	KOAc		12	47
12	$Pd(OAc)_2$	DABCO		20	51(78)
13	$Pd(OAc)_2$	DABCO		10	0[d]

[a] General reaction conditions: concentration = 0.2 M in DMA, 0.10 equiv of palladium source, 0.20 equiv of (t-Bu_3P)HBF_4, 1.0 equiv of *o*-chloroaniline **2a**, 1.0 equiv of aldehyde **4b**, 3.0 equiv of base, 120 °C. [b] Isolated yield. [c] 1.5 equiv of KOAc. [d] No ligand used. Abbreviations: PMP = 1,2,2,6,6-pentamethylpiperidine; DABCO = 1,4-diazabicyclo[2,2,2]octane.

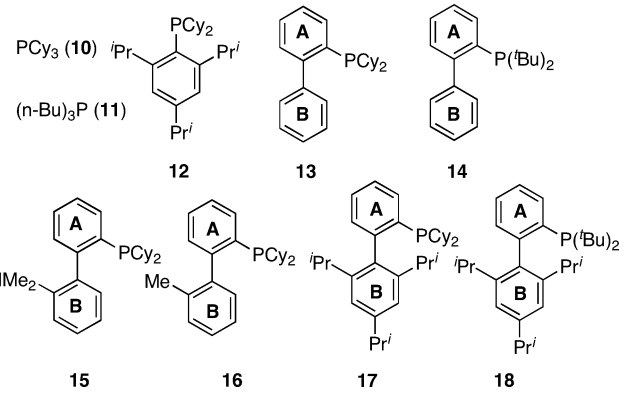
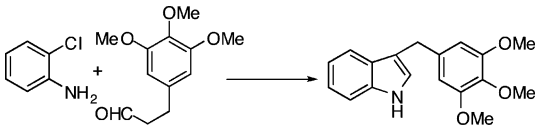


FIGURE 1. Structure of ligands screened for the annulation of *ortho*-chloroaniline (**2a**) and 3-(3,4,5-trimethoxyphenyl)propanal (**4b**).

5n in 83% yield (entry 7). As for many other palladium-catalyzed transformations, the present annulation process is very sensitive to the ligand structure. Thus switching from X-Phos to the structurally very similar but bulkier ligand **18** (*tert*-butyl XPhos) completely suppressed the desired transformation (entry 9). It is evident that the ability of these biphenyl phosphines as supporting ligands to catalyze, in association with palladium, the annulation reaction relied on the proper combination of two steric factors: the substituent at the phosphorus center and the *ortho* substituents on the ring B. Moderately encumbered dicyclohexylphosphinyl substituent (ring A) in combination with a hindered 2′,4′,6′-triisopropylphenyl (ring B) was apparently optimum as a supporting ligand for the present transformation.

While 0.1 equiv of palladium was used in the above survey of reaction conditions, we were pleased to find that catalyst loading can be decreased. Thus performing the annulation of **2a** and **4b** in the presence of 0.025 equiv of $Pd(dba)_2$ and 0.050 equiv of ligand **17** provided the desired indole **5n** in 85% yield. It is worthy noting that X-Phos is known to be an excellent

TABLE 5. Ligand Screening for Annulation Reaction of *o*-Chloroaniline 2a with Aldehyde 4b[a]



2a **4b** **5n**

entry	ligand	time (h)	yield (%)[b]
1	PCy_3	25	<5
2	$(n\text{-}Bu)_3P$	20	<5
3	12	20	5
4	13	20	40
5	14	20	30
6	15	20	53
7	16	5	59
8	17	4	83
9	18	10	<5
10	17	5	85[c]

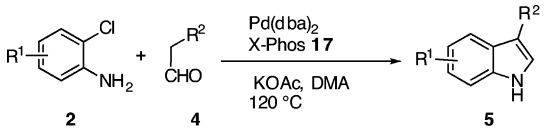
[a] General reaction conditions: concentration = 0.2 M in DMA, 0.10 equiv of $Pd(dba)_2$, 0.20 equiv of ligand, 1.0 equiv of *o*-chloroaniline **2a**, 1.0 equiv of aldehyde **4b**, 3.0 equiv of KOAc, 120 °C. [b] Isolated yield. [c] With 0.025 equiv of $Pd(dba)_2$ and 0.05 equiv of ligand.

ligand for the palladium-catalyzed amination reaction.[47] However, under the present reaction conditions, products resulting from the potentially competitive dimerization or oligomerization of *ortho*-chloroaniline **2a** were not observed.[11d,48] This may indicate that the condensation of aniline and aldehyde preceded the oxidative addition of palladium(0) to the aryl chloride.[49]

To illustrate the generality of this new protocol, annulation of a variety of *o*-chloroanilines and aldehydes was examined, and the results are depicted in Table 6. In most cases, the yield of desired indole is comparable with that obtained from *o*-iodoaniline, except for the reaction of **2d** with phenylacetaldehyde. In this latter case, the desired indole was obtained in only 24% yield together with the dehalogenated product, the methyl 4-amino-2-methoxybenzoate, in 55% yield. Tryptophan derivatives can be similarly prepared, and indeed yield of **5g** obtained from annulation of 2-chloro-5-methoxyaniline with **4a** (73%, entry 5) is higher than that obtained from 2-iodo-5-methoxyaniline (58%, entry 7, Table 2).

Annulation of *ortho*-Bromoanilines and Aldehydes. Without further optimization, the catalytic conditions developed for *o*-chloroanilines were directly applied to *o*-bromoanilines. As is seen from Table 7, good to excellent yields of indoles were obtained from *o*-bromoanilines with different electronic properties. 6-Phenyltryptophan and related aromatic-substituted tryptophans have previously been synthesized via a multistep sequence.[50] Thus a one-step synthesis of **5z** from 2-bromo-5-phenylaniline and aldehyde **4a** is particularly attractive. The presence of a nitro group has an adverse effect on the reaction as it is seen from entry 5. Nevertheless, one might keep in mind that, as in most palladium-catalyzed processes, fine-tuning of reaction conditions may be necessary for an individual substrate in order to optimize the reaction outcome.

TABLE 6. Synthesis of Indoles from *ortho*-Chloroanilines[a]



2 **4** **5**

entry	o-chloroaniline	product	yield (%)[b]
1	**2a**	**5n**	85
2	**2a**	**5o**	70
3	**2a**	**5r**	63
4	**2b**	**5u**	56
5	**2b**	**5g**	73
6	**2c**	**5v**	31
7	**2d**	**5w**	24

[a] General reaction conditions: concentration = 0.2 M in DMA, 0.05 equiv of $Pd(dba)_2$, 0.10 equiv of X-Phos **17**, 1.0 equiv of *o*-chloroaniline **2**, 1.0 equiv of aldehyde, 3.0 equiv of KOAc, 120 °C. [b] Isolated yield.

Conclusions

In summary, we have developed an efficient synthesis of highly functionalized indoles by a palladium-catalyzed annulation reaction between *ortho*-haloanilines and aldehydes. The reaction is very general, and a variety of *o*-haloanilines with different electronic properties and aldehydes, including chiral ones, can be used to afford indoles in good to excellent yield. Coupling of *ortho*-iodoaniline with aldehyde is realized under mild ligandless conditions [$Pd(OAc)_2$, DABCO, DMF, 85 °C], whereas X-Phos is found to be the ligand of choice for coupling reactions involving *ortho*-chloroanilines/*ortho*-bromoanilines and aldehydes [$Pd(dba)_2$/ligand **17** (X-Phos), KOAc, DMA at 120 °C]. Coupling of (*S*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentanoate, derived from L-glutamic acid, with *ortho*-haloanilines provides the corresponding ring-A-substituted tryptophans in good to excellent yields. This represents one of the shortest routes for the synthesis of tryptophan derivatives. Further application of this chemistry to the synthesis of natural products is currently in progress.

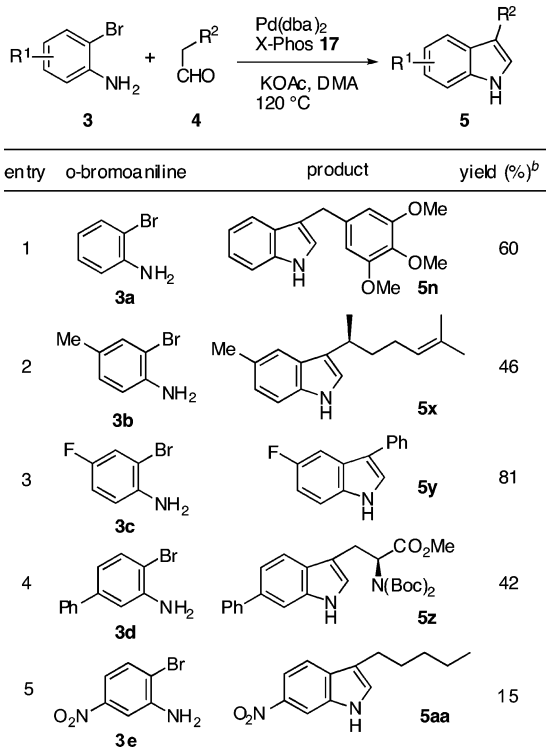
(47) (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819. (c) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synthesis* **2005**, 3229−3234.

(48) For N-arylation of *ortho*-chloroaniline, see: Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310−2311.

(49) For synthesis of indole via arylation of *ortho*-halonitroarenes followed by reductive cyclization, see: Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168−15169.

(50) Wang, W.; Xiong, C.; Zhang, J.; Hruby, V. J. *Tetrahedron* **2002**, *58*, 3101−3110.

TABLE 7. Synthesis of Indoles from *ortho*-Bromoanilines[a]



[a] General reaction conditions: concentration = 0.2 M in DMA, 0.05 equiv of $Pd(dba)_2$, 0.10 equiv of X-Phos **17**, 1.0 equiv of *o*-bromoaniline **3**, 1.0 equiv of aldehyde, 3.0 equiv of KOAc, 120 °C. [b] Isolated yield.

Experimental Section

A Typical Experimental Procedure for Annulation of *o*-Iodoanilines with Aldehydes: A mixture of *o*-iodoaniline **1** (0.33 mmol), aldehyde **4** (0.30 mmol), and DABCO (101.0 mg, 0.90 mmol) in dry DMF (1.5 mL) was degassed for 20 min. $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) was added to the reaction, and the resulting reaction mixture was heated at 85 °C until the reaction was complete (usually 6−12 h; the progress of the reactions was monitored by TLC). The reaction mixture was cooled to room temperature and was diluted with water. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Purification of crude product by flash column chromatography provided the desired product **5**.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(1*H*-indol-3-yl)propionic acid methyl ester 5a: Yellow oil; yield 81%; $[\alpha]_D^{23}$ −60° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3348, 2980, 1782, 1741, 1457, 1369, 1273, 1140, 1092, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.15 (dt, J = 1.2, 7.7 Hz, 1H), 7.09 (dt, J = 1.2, 7.9 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 5.20 (dd, J = 4.7, 10.3 Hz, 1H), 3.77 (s, 3H), 3.62 (dd, J = 4.7, 14.9 Hz, 1H), 3.40 (dd, J = 10.3, 14.9 Hz, 1H), 1.28 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 151.5, 136.3, 127.5, 123.2, 121.7, 119.2, 118.5, 111.2, 82.8, 59.0, 52.1, 27.6 (6C), 25.8; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{30}N_2O_6Na$ (M + Na)$^+$ 441.2002; found 441.1975.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(1-methyl-1*H*-indol-3-yl)propionic acid methyl ester 5b: Colorless oil; yield 85%; $[\alpha]_D^{23}$ −72° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2978, 1790, 1742, 1695, 1473, 1366, 1324, 1269, 1137, 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.19 (ddd, J = 1.1, 7.9, 8.1 Hz, 1H), 7.09 (ddd, J = 1.1, 7.9, 8.1 Hz, 1H), 6.87 (s, 1H), 5.16 (dd, J = 4.7, 10.1 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.60 (dd, J = 4.7, 14.9 Hz, 1H), 3.38 (dd, J = 10.1, 14.9 Hz, 1H), 1.29 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 151.6 (2C), 136.9, 128.0, 127.7, 121.4, 118.8, 118.8, 110.1, 109.0, 82.7 (2C), 59.1, 52.1, 32.5, 27.6 (6C), 25.7; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_6Na$ (M + Na)$^+$ 455.2158; found 455.2144.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-methoxy-1*H*-indol-3-yl)propionic acid methyl ester 5c: Yellow oil; yield 55%; $[\alpha]_D^{23}$ −102° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3344, 2980, 2952, 1782, 1745, 1697, 1508, 1456, 1383, 1368, 1277, 1257, 1140, 1094, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.02 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.44 (d, J = 7.6 Hz, 1H), 5.39 (dd, J = 4.0, 10.8 Hz, 1H), 3.88 (s, 3H), 3.88−3.83 (m, 1H), 3.77 (s, 3H), 3.27 (dd, J = 10.8, 14.2 Hz, 1H), 1.22 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 154.7, 151.4, 138.2, 122.5, 122.2, 117.4, 111.5, 104.7, 99.2, 82.5, 59.7, 55.1, 52.0, 27.9, 27.5 (6C); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_7Na$ (M + Na)$^+$ 471.2107; found 471.2119.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(5-methoxy-1*H*-indol-3-yl)propionic acid methyl ester 5d: Colorless oil; yield 51%; $[\alpha]_D^{23}$ −62° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3348, 2977, 1781, 1736, 1696, 1486, 1455, 1438, 1382, 1367, 1271, 1216, 1136, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 2.4, 8.8 Hz, 1H), 5.18 (dd, J = 4.7, 10.1 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.57 (dd, J = 4.7, 14.9 Hz, 1H), 3.35 (dd, J = 10.1, 14.9 Hz, 1H), 1.29 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 154.0, 151.6 (2C), 131.4, 127.8, 123.9, 112.3, 111.8, 111.3, 100.4, 82.9 (2C), 59.0, 55.9, 52.2, 27.7 (6C), 25.9; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_7Na$ (M + Na)$^+$ 471.2107; found 471.2117.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(5-methoxy-1-methyl-1*H*-indol-3-yl)propionic acid methyl ester 5e: Colorless oil; yield 84%; $[\alpha]_D^{23}$ −72° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2978, 1790, 1743, 1697, 1492, 1366, 1270, 1225, 1171, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 2.3 Hz, 1H), 6.87−6.83 (m, 2H), 5.15 (dd, J = 4.7, 9.9 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.56 (dd, J = 4.7, 14.9 Hz, 1H), 3.32 (dd, J = 9.9, 14.9 Hz, 1H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 153.8 (2C), 151.6, 132.3, 128.3, 128.2, 111.9, 109.8, 109.7, 100.7, 82.7 (2C), 59.1, 55.9, 52.1, 32.7, 27.7 (6C), 25.8; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{34}N_2O_7Na$ (M + Na)$^+$ 485.2264; found 485.2262.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(5-nitro-1*H*-indol-3-yl)propionic acid methyl ester 5f: Yellow solid; yield 74%; mp 55−57 °C (heptane/EtOAc); $[\alpha]_D^{23}$ −52° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3307, 2979, 1779, 1745, 1697, 1519, 1472, 1456, 1434, 1368, 1334, 1273, 1230, 1140, 1097, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (br s, 1H), 8.56 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 2.1, 9.0 Hz, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 1.9 Hz, 1H), 5.19 (dd, J = 4.8, 10.5 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, J = 4.8, 14.9 Hz, 1H), 3.42 (dd, J = 10.6, 14.9 Hz, 1H), 1.26 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.5, 141.4, 139.4, 126.9 (2C), 117.4, 116.0, 113.5, 111.5, 83.6, 58.7, 52.4, 27.6 (6C), 25.6; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{29}N_3O_8Na$ (M + Na)$^+$ 486.1852; found 486.1827.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(6-methoxy-1*H*-indol-3-yl)propionic acid methyl ester 5g: Yellow oil; yield 58%; $[\alpha]_D^{23}$ −69° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3353, 2980, 1782, 1742, 1631, 1456, 1369, 1306, 1255, 1143, 1092, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.43 (d, J = 8.6 Hz, 1H), 6.86−6.85 (m, 2H), 6.76 (dd, J = 2.2, 8.6 Hz, 1H), 5.18 (dd, J = 4.8, 10.3 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.56 (dd, J = 4.7, 14.8 Hz, 1H), 3.34 (dd, J = 10.3, 14.8 Hz, 1H), 1.28 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 156.4, 151.5, 137.0, 122.1, 122.0, 119.1, 111.1, 109.3, 94.8, 82.9, 59.0, 55.7, 52.2, 27.7 (6C), 25.9; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_7Na$ (M + Na)$^+$ 471.2107; found 471.2105.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(6-nitro-1*H*-indol-3-yl)propionic acid methyl ester 5h: Yield 64%; mp 75−77 °C; $[\alpha]_D^{23}$ −68° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3307, 2979, 1779, 1747,

1696, 1508, 1458, 1369, 1331, 1272, 1143, 1129, 1095, 1059, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.91 (br s, 1H), 8.41 (d, J = 1.9 Hz, 1H), 7.99 (dd, J = 1.9, 8.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 5.18 (dd, J = 5.0, 10.3 Hz, 1H), 3.79 (s, 3H), 3.62 (dd, J = 5.0, 14.9 Hz, 1H), 3.41 (dd, J = 10.3, 14.9 Hz, 1H), 1.28 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.5, 143.0, 134.7, 132.0, 129.6, 118.3, 114.6, 111.8, 108.7, 83.6, 58.6, 52.3, 27.6 (6C), 25.5; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{29}N_3O_8$Na $(M + Na)^+$ 486.1852; found 486.1858.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(7-methoxy-1*H*-indol-3-yl)propionic acid methyl ester 5i: Yellow solid; yield 71%; mp 133−135 °C (heptane/EtOAc); $[\alpha]_D^{23}$ −65° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3374, 2979, 1787, 1742, 1697, 1579, 1502, 1451, 1368, 1258, 1149, 1131, 1091, 1057, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (br s, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 5.19 (dd, J = 4.8, 10.1 Hz, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.59 (dd, J = 4.7, 14.9 Hz, 1H), 3.38 (dd, J = 10.1, 14.9 Hz, 1H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 151.6, 146.1, 128.9, 126.6, 122.6, 119.7, 112.0, 111.5, 101.8, 82.7, 59.0, 55.3, 52.1, 27.6 (6C), 25.9; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_7$Na $(M + Na)^+$ 471.2107; found 471.2091.

(2*S*)-3-(1*H*-Benzo[*f*]indol-3-yl)-2-(di-*tert*-butoxycarbonylamino)propionic acid methyl ester 5j: Yield 60%; mp 64−66 °C (heptane/EtOAc); $[\alpha]_D^{23}$ −69° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3348, 2978, 1781, 1732, 1693, 1428, 1385, 1367, 1271, 1225, 1130, 1087, 906, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (br s, 1H), 8.06 (s, 1H), 7.92 (dd, J = 2.1, 7.1 Hz, 1H), 7.84 (dd, J = 2.1, 7.1 Hz, 1H), 7.75 (s, 1H), 7.37−7.28 (m, 2H), 7.19 (d, J = 2.4 Hz, 1H), 5.32 (dd, J = 4.7, 10.3 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, J = 4.7, 14.9 Hz, 1H), 3.52 (dd, J = 10.3, 14.9 Hz, 1H), 1.24 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 151.6 (2C), 137.0, 130.2, 129.5, 128.4, 128.1, 127.3, 127.2, 123.5, 122.4, 115.9, 110.5, 106.4, 82.9 (2C), 58.9, 52.2, 27.6 (6C), 26.0; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{32}N_2O_6$Na $(M + Na)^+$ 491.2158; found 491.2172.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)propionic acid methyl ester 5k: Yield 60%; mp 52−54 °C (CH_2Cl_2); $[\alpha]_D^{23}$ −66° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3318, 2979, 1780, 1741, 1694, 1460, 1383, 1366, 1271, 1251, 1136, 1091, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 8.74 (s, 1H), 8.14 (d, J = 5.5 Hz, 1H), 7.46 (d, J = 5.5 Hz, 1H), 7.17 (s, 1H), 5.09 (dd, J = 4.9, 10.1 Hz, 1H), 3.71 (s, 3H), 3.53 (dd, J = 4.9, 14.9 Hz, 1H), 3.34 (dd, J = 10.1, 14.9 Hz, 1H), 1.21 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 151.6 (2C), 137.2, 134.1, 133.7, 132.4, 128.2, 113.5, 110.5, 83.2 (2C), 58.9, 52.2, 27.6 (6C), 25.5; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{30}N_3O_6$ $(M + H)^+$ 420.2135; found 420.2119.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(6-chloro-1*H*-indol-3-yl)propionic acid methyl ester 5l: Yield 74%; $[\alpha]_D^{23}$ −73° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3334, 2978, 1779, 1737, 1693, 1455, 1384, 1367, 1271, 1230, 1140, 1128, 1089, 905, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (br s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 1.8, 8.5 Hz, 1H), 6.94 (d, J = 2.2 Hz, 1H), 5.16 (dd, J = 4.8, 10.3 Hz, 1H), 3.77 (s, 3H), 3.57 (dd, J = 4.8, 14.9 Hz, 1H), 3.36 (dd, J = 10.3, 14.9 Hz, 1H), 1.28 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 151.5 (2C), 136.6, 127.5, 126.0, 124.1, 119.8, 119.3, 111.3, 111.1, 83.1 (2C), 58.8, 52.2, 27.6 (6C), 25.7; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{29}N_2O_6$NaCl $(M + Na)^+$ 475.1612; found 475.1609.

3-Benzyl-1*H*-indole 5m: Yellow solid; yield 55%; mp 105−106 °C ($CHCl_3$), [mp[51] 104−106 °C]; IR ($CHCl_3$) 3415, 3025, 2918, 2847, 1665, 1618, 1600, 1493, 1453, 1418, 1337, 1224, 1090, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.38−7.23 (m, 7H), 7.10 (t, J = 7.8 Hz, 1H), 6.91 (s, 1H), 4.16 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 136.4, 128.7, 128.3, 127.4, 125.8, 122.3, 122.0, 119.3, 119.1, 115.8, 111.0, 31.6; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{13}$NNa $(M + Na)^+$ 230.0946; found 230.0970.

3-(3,4,5-Trimethoxybenzyl)-1*H*-indole 5n: Yellow solid; yield 67%; mp 128−130 °C (heptane/EtOAc); IR ($CHCl_3$) 3365, 2929, 1589, 1505, 1455, 1418, 1329, 1227, 1119, 1005, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 (dt, J = 1.2, 7.0 Hz, 1H), 7.11 (dt, J = 1.1, 8.0 Hz, 1H), 6.93 (s, 1H), 6.55 (s, 2H), 4.08 (s, 2H), 3.85 (s, 3H), 3.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 137.0, 136.4, 136.1, 127.3, 122.4, 122.0, 119.3, 119.0, 115.5, 111.1, 105.7, 60.8, 56.0, 31.9; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}NO_3$Na $(M + Na)^+$ 320.1263; found 320.1277.

3-Phenyl-1*H*-indole 5o: Yield 78%; mp 86−88 °C; [mp[52] 86−87 °C]; IR ($CHCl_3$) 3415, 3393, 3056, 3035, 2925, 1597, 1538, 1486, 1456, 1416, 1338, 1259, 1237, 1186, 1121, 1014, 954, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.58 (dd, J = 1.5, 7.9 Hz, 2H), 7.35 (t, J = 7.9 Hz, 2H), 7.28 (dd, J = 1.7, 7.5 Hz, 1H), 7.22−7.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 135.5, 128.7, 127.4, 125.9, 125.7, 122.4, 121.8, 120.3, 119.8, 118.2, 111.4.

3-((1*S*)-1,5-Dimethylhex-4-enyl)-1*H*-indole 5p: Colorless oil; yield 43%; $[\alpha]_D^{23}$ 5.6° (*c* 0.80, $CHCl_3$); IR (neat) 3414, 2959, 2919, 2852, 1455, 1417, 1374, 1336, 1224, 1094, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 1.1, 8.0 Hz, 1H), 7.11 (dt, J = 1.1, 7.9 Hz, 1H), 6.96 (d, J = 2.3 Hz, 1H), 5.17 (m, 1H), 3.07 (m, 1H), 2.03 (m, 2H), 1.86 (m, 1H), 1.70 (s, 3H), 1.66 (m, 1H), 1.56 (s, 3H), 1.37 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 131.3, 126.9, 124.8, 122.6, 121.7, 119.9, 119.4, 118.9, 111.1, 37.6, 30.4, 26.2, 25.7, 21.4, 17.7; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{22}N$ $(M + H)^+$ 228.1752; found 228.1758.

3-Hexyl-1*H*-indole 5q: Colorless oil; yield 55%; IR (neat) 3414, 2923, 2852, 1455, 1418, 1337, 1225, 1089, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.19 (dt, J = 1.4, 8.1 Hz, 1H), 7.14 (dt, J = 1.2, 7.9 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 2.78 (t, J = 7.6 Hz, 2H), 1.79−1.69 (m, 2H), 1.46−1.29 (m, 6H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 127.6, 121.8, 120.9, 119.0 (2C), 117.2, 111.0, 31.8, 30.1, 29.3, 25.2, 22.7, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}N$ $(M + H)^+$ 202.1596; found 202.1585.

3-(1*H*-Indol-3-yl)propan-1-ol 5r:[53] Colorless oil; yield 41%; IR (neat) 3409, 2933, 1455, 1338, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.21 (dt, J = 1.2, 8.1 Hz, 1H), 7.13 (dt, J = 1.2, 7.9 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 3.74 (t, J = 6.4 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 2.00 (m, 2H), 1.53 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 127.4, 121.9, 121.3, 119.1, 118.8, 115.9, 111.1, 62.6, 32.9, 21.3; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}$NONa $(M + Na)^+$ 198.0895; found 198.0881.

3-Benzyl-1-methyl-1*H*-indole 5s: Yield 76%; IR ($CHCl_3$) 3024, 2910, 1600, 1492, 1473, 1452, 1423, 1373, 1326, 1250, 1153, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 7.9 Hz, 1H), 7.45−7.24 (m, 7H), 7.18 (m, 1H), 6.83 (s, 1H), 4.21 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 137.1, 128.6, 128.3, 127.8, 127.1, 125.8, 121.5, 119.2, 118.7, 114.3, 109.1, 32.5, 31.5; HRMS (MALDI) *m*/*z* calcd for $C_{16}H_{16}N$ $(M + H)^+$ 222.1275; found 222.1282.

3-Benzyl-1*H*-benzo[*f*]indole 5t: Yield 45%; IR ($CHCl_3$) 3422, 3024, 1630, 1600, 1537, 1493, 1469, 1446, 1423, 1359, 1274, 1260, 1085, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.96−7.24 (m, 11H), 7.09 (s, 1H), 4.25 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 137.3, 130.4, 129.5, 128.7, 128.4, 128.3, 127.6,

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127.3, 126.4, 126.0, 123.8, 122.5, 116.6, 115.0, 106.3, 31.7; HRMS (MALDI) *m*/*z* calcd for $C_{19}H_{15}N$ (M^+) 257.1204; found 257.1202.

A Typical Experimental Procedure for Annulation of *o*-Chloroanilines/*o*-Bromoanilines with Aldehydes. A mixture of *o*-chloroaniline/*o*-bromoaniline (0.30 mmol), aldehyde **4** (0.30 mmol), and KOAc (88 mg, 0.90 mmol) in dry DMA (1.5 mL) was degassed for 20 min. $Pd(dba)_2$ (8.0 mg, 0.015 mmol) and X-Phos (14.3 mg, 0.03 mmol) were added to the reaction, and the resulting reaction mixture was heated at 120 °C until the reaction was complete (usually 2−6 h; the progress of the reactions was monitored by TLC). The reaction mixture was cooled to room temperature and was diluted with water. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Purification of crude product by flash column chromatography provided the desired product **5**.

3-Benzyl-6-methoxy-1*H*-indole 5u: Yield 56%; mp 102−104 °C (heptane/CH_2Cl_2); IR ($CHCl_3$) 3386, 3025, 2922, 2833, 1627, 1553, 1501, 1451, 1348, 1302, 1250, 1199, 1162, 1122, 1084, 1051, 1023, 941, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.20−7.16 (m, 4H), 7.11 (m, 1H), 6.71−6.64 (m, 3H), 3.98 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 141.2, 137.1, 128.6, 128.3, 125.8, 121.9, 121.1, 119.7, 115.6, 109.2, 94.6, 55.6, 31.6; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{16}NO$ $(M + H)^+$ 238.1232; found 238.1241.

3-Hexyl-7-methyl-1*H*-indole 5v: Yield 31%; IR ($CHCl_3$) 3418, 3050, 2954, 2923, 2853, 1614, 1454, 1432, 1340, 1275, 1223, 1166, 1094, 1063, 932 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.98 (s, 1H), 2.77 (t, J = 7.5 Hz, 2H), 2.49 (s, 3H), 1.73 (m, 2H), 1.45−1.28 (m, 6H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 127.1, 122.3, 120.7, 120.1, 119.2, 117.7, 116.7, 31.8, 30.2, 29.3, 25.3, 22.7, 16.6, 14.1; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{22}N$ $(M + H)^+$ 216.1752; found 216.1747.

6-Methoxy-3-phenyl-1*H*-indole-5-carboxylic acid methyl ester 5w: Yield 24%; mp 163−165 °C (heptane/EtOAc); IR ($CHCl_3$) 3287, 2923, 1713, 1624, 1601, 1566, 1546, 1462, 1434, 1404, 1344, 1266, 1231, 1201, 1172, 1125, 1103, 1068, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 8.44 (s, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.46 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 6.88 (s, 1H), 3.92 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 156.3, 139.8, 134.8, 128.8, 127.4, 126.3, 124.4, 121.8, 119.3, 119.2, 114.2, 94.3, 56.2, 51.9; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{15}NO_3Na$ $(M + Na)^+$ 304.0950; found 304.0924.

3-((1*S*)-1,5-Dimethylhex-4-enyl)-5-methyl-1*H*-indole 5x: Yield 46%; $[\alpha]_D^{23}$ 0.2° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3412, 2960, 2919, 2854, 1480, 1455, 1419, 1374, 1225, 1094, 984, 867 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.45 (s, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.93 (d, J = 2.3 Hz, 1H), 5.19 (m, 1H), 3.05 (m, 1H), 2.49 (s, 3H), 2.04 (m, 2H), 1.86 (m, 1H), 1.72 (s, 3H), 1.67 (m, 1H), 1.58 (s, 3H), 1.38 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 131.3, 128.0, 127.1, 124.8, 123.3, 122.1, 120.0, 119.1, 110.7, 37.6, 30.4, 26.2, 25.7, 21.6, 21.4, 17.7; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{24}N$ $(M + H)^+$ 242.1909; found 242.1918.

5-Fluoro-3-phenyl-1*H*-indole 5y: Yield 81%; IR ($CHCl_3$) 3417, 3027, 1627, 1601, 1578, 1543, 1478, 1453, 1416, 1351, 1311, 1291, 1274, 1261, 1231, 1176, 1105, 1072, 923, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.68−7.61 (m, 3H), 7.49 (t, J = 7.4 Hz, 2H), 7.39 (d, J = 2.6 Hz, 1H), 7.37−7.31 (m, 2H), 7.03 (dt, J = 2.5, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4 (d, J = 235 Hz), 135.0, 133.1, 128.8, 127.2, 126.1, 126.1, 123.4, 118.4, 112.0 (d, J = 9.8 Hz), 110.8 (d, J = 26.4 Hz), 104.7 (d, J = 24.1 Hz); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{10}NF$ (M^+) 211.0783; found 211.0797.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(6-phenyl-1*H*-indol-3-yl)propionic acid methyl ester 5z: Yield 42%; mp 177−179 °C (CH_2Cl_2); $[\alpha]_D^{23}$ −67° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3342, 2978, 1780, 1742, 1695, 1456, 1384, 1367, 1257, 1133, 1091, 909, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 7.66−7.61 (m, 3H), 7.55 (d, J = 1.2 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.37 (dd, J = 1.5, 8.3 Hz, 1H), 7.31 (m, 1H), 7.03 (d, J = 2.0 Hz, 1H), 5.22 (dd, J = 4.8, 10.2 Hz, 1H), 3.78 (s, 3H), 3.63 (dd, J = 4.8, 14.9 Hz, 1H), 3.43 (dd, J = 10.2, 14.9 Hz, 1H), 1.30 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 151.6, 142.4, 136.8, 135.5, 128.6, 127.3, 126.9, 126.5, 123.8, 119.3, 118.9, 111.5, 109.7, 82.9, 59.0, 52.2, 27.7 (6C), 25.9; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{34}N_2O_6Na$ $(M + Na)^+$ 517.2315; found 517.2322.

3-Hexyl-6-nitro-1*H*-indole 5aa: Yield 12%; mp 95−98 °C (heptane/EtOAc); IR ($CHCl_3$) 3358, 2921, 2854, 1501, 1462, 1324, 1274, 1208, 1101, 1056, 876, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 8.33 (d, J = 1.9 Hz, 1H), 8.01 (dd, J = 1.9, 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.28 (s, 1H), 2.77 (t, J = 7.5 Hz, 2H), 1.70 (m, 2H), 1.42−1.25 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 134.6, 132.3, 127.1, 118.9, 118.3, 114.7, 108.0, 31.7, 30.1, 29.2, 24.8, 22.6, 14.1; HRMS (MALDI) *m*/*z* calcd for $C_{14}H_{19}N_2O$ $(MH - O)^+$ 231.1490; found 231.1497.

Acknowledgment. Financial support from CNRS and the Institut de Chimie des Substances Naturelles is gratefully acknowledged. We thank Dr. G. Mignani of Rhodia, Lyon, for the generous gift of ligands **12**−**18**.

Supporting Information Available: Copies of ^1H NMR, ^{13}C NMR spectra of compounds **5a**−**5z**−**5aa**, and HPLC diagram of chiral indoles **5p**, **5x**, chiral N-Boc tryptophan **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061471S