JOC*Note*

Catalytic Asymmetric Synthesis of Protected Tryptophan Regioisomers

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Abstract: Tryptophan **1** (Trp) is superior to all other naturally occurring peptide residues in its ability to bind cations (the cation−π interaction). In an effort to expand the toolbox of Trp-like amino acids, in this note we report catalytic asymmetric syntheses of Trp regioisomers **2a**−**e**, where the alanine unit is attached not to C-3 of indole but to C-2, C-4, C-5, C-6, or C-7. Excellent asymmetric induction is obtained in each case (generally >97% ee). Ab initio calculations suggest that the indole nuclei of **2a**−**e** will bind Na^+ with the same affinity as that of Trp.

The cation−π interaction is now known to be an important determinant of protein structure[1] and has been demonstrated to play critical roles in the function of acetylcholinesterase[2] and the nicotinic acetylcholine receptor.[3] Ab initio calculations by Dougherty show that among all the naturally occurring aromatic amino acids, the indole nucleus of Tryptophan (Trp) exhibits the strongest binding to Na^+ ion (32.6 kcal/mol, HF/6-31G**// HF/6-31G**).[4] A recent statistical analysis indicated that over 25% of all Trp residues in the Protein Data Base (PDB) experience an energetically significant cation−π interaction.[1]

We reasoned that unnatural indole-containing amino acids would prove to be valuable additions to the toolbox of available, effective cation−π donor amino acids.[5] Asymmetric syntheses of several indol-3-yl amino acids have been described.[6] One class of Trp analogues that we believe merit further exploration are regioisomers **2a**−**e**, where the alanine chain is attached not to C-3 of indole but to C-2, C-4, C-5, C-6, or C-7 (Scheme 1). A search of the CAS registry file reveals that **2d** and **2e** (both free and protected derivatives) have not yet been described in the literature; amino acid **2c** is known only in its racemic form (registry no. 3569-24-2). Asymmetric syntheses of (*S*)-**2a** ("isotryptophan")[6a] and **2b** ("neotryptophan")[7] based on stoichiometric use of the Schöllkopf auxiliary have recently been described. In this note, we report a general *catalytic* asymmetric synthetic route to protected derivatives of all five Trp regioisomers (*S*)-**2a**−**e**.

Our syntheses of the desired amino acids start with the corresponding known formylindoles. 2-Formylindole **3a** was prepared in two steps from indole-2-carboxylic acid.[8] 4- and 6-formylindoles **3b** and **3d** were prepared in three steps from 2-bromo-6-nitrotoluene and 4-bromo-2-nitrotoluene, respectively.[9] 5-Formylindole **3c** was prepared in one step from 5-bromoindole.[9] Finally, 7-formylindole **3e** was prepared in two steps from 2-nitrobenzaldehyde, using the Bartoli indole methodology.[10] Anticipating the need for indole-N-protected amino acids, *N*-Boc aldehydes **4a**−**d** were prepared in moderate to excellent yield. However, *N*-Boc derivative **4e** could not be prepared, perhaps due to the steric hindrance posed by the 7-formyl group (Scheme 2).

These aldehydes were then converted to the corresponding *N*-acetyl-dehydroamino acid methyl esters (*Z*)-**5a**−**e** and (*Z*)-**6b**−**d** using the standard Schmidt protocol.[11] The olefination reactions were slower than expected, and in the case of *N*-Boc aldehyde **4a**, none of the desired **6a** product could be obtained. Chromatography or crystallization of the olefination product yielded stereochemically pure (*Z*)-isomers; the alkene geometry was assigned using Schmidt's empirical rule (chemical shift of the β-proton).[11] Since the N^{α}-acetyl group can be difficult to remove from the final amino acid products, we explored olefination reactions with the *N*-Cbz Schmidt reagent. Reactions with *N*-Boc formyl indoles **4b**−**d** proceeded smoothly to give pure (*Z*)-**7b**−**d** after chromatography. However, reactions of unprotected **3c** with the *N*-Cbz Schmidt reagent gave a mixture of products. Reactions of **3a** and **3e** were followed in detail, revealing cyclic products **8**−**10** (Scheme 3).

Apparently, after formation of the intended products, the indole NH is deprotonated and reacts with the *N*-Cbz protecting group, giving **8** and **10** with extrusion of benzyl alcohol. Compound **9** was formed as a significant side product in the reaction of **3a**, and its identity was confirmed by NOE difference, HMQC, and HMBC NMR experiments. The following experiments indicate that the methyl group in **9** originates from the Schmidt reagent: treatment of pure **8** with TMG and the Schmidt reagent

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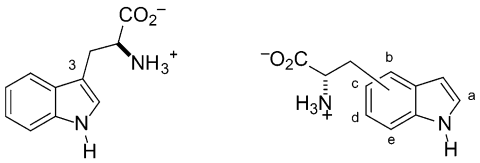
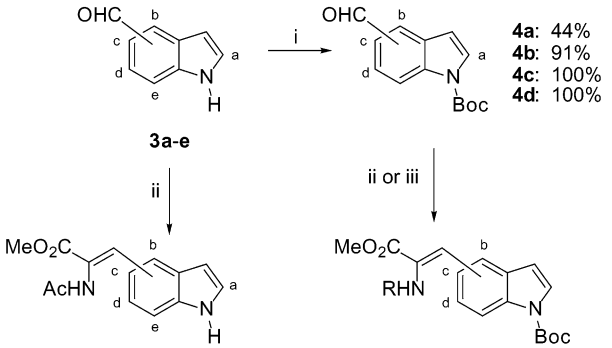
SCHEME 1. Tryptophan and Regioisomers (*S*)-2a−e



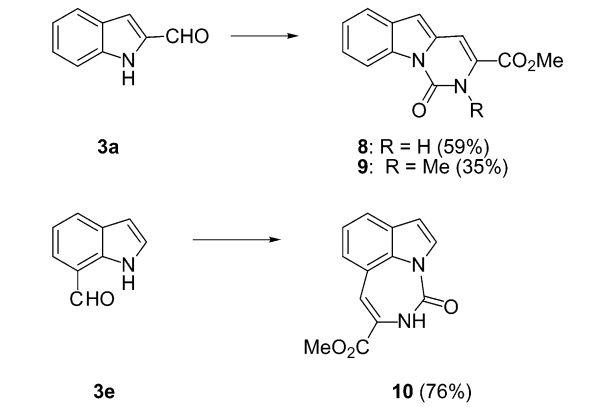
Trp (**1**) (*S*)-**2a-e**

SCHEME 2. Synthesis of Dehydroamino Acid Derivatives[a]



[a] Reagents and conditions: (i) 1.2 equiv of KO*t*-Bu, 1.5 equiv of Boc_2O, 0 °C → rt, 3 days. (ii) 1.5 equiv of $(MeO)_2P(O)CH-(NHAc)CO_2Me$, 1.5 equiv of TMG, THF, −78 °C → rt, 3 days. (iii) 1.5 equiv of $(MeO)_2P(O)CH-(NHCbz)CO_2Me$, 1.5 equiv of TMG, THF, −78 °C → rt, 3 days.

SCHEME 3. Ring-Closed Olefination Products of 3a and 3e[a]

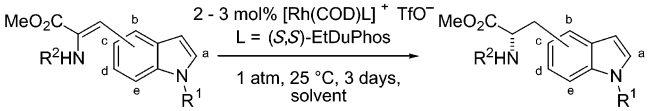


[a] Reagents and conditions: 1.5 equiv of $(MeO)_2P(O)CH-(NHCbz)CO_2Me$, 1.5 equiv of TMG, THF, −78 °C → rt, 3 days.

leads to formation of **9**; however, no new products form upon treatment of compound **8** with TMG alone.

With the desired protected dehydroamino acids (*Z*)-**5**−**7** in hand, we explored asymmetric hydrogenation using both Rh and Ru catalysts. In the end, the most generally useful catalyst system was the Burk DuPhos system,[12] with the EtDuPhos ligand affording slightly higher % ee than the MeDuPhos analogue.[13] The best reaction conditions proved to be 2−3 mol % catalyst, atmospheric pressure, for 3 days: under these conditions, 100% conversion and greater than 97% ee was normally obtained (Table 1). The high catalyst loading is undesirable, but at less than 1 mol % catalyst, the enantiomeric excess decreased significantly and reactions would not go to completion.[14] At 2−3 mol % catalyst, the hydrogenation was insensitive to solvent: methanol, ethanol, ethyl acetate, dichloromethane, and acetone all gave acceptable yields and % ee. To improve reaction rates, the use of higher pressures (40 psi) was explored. However, under these conditions, N^{in}-Boc-dehydroamino acid esters **6** and **7**, as well as **5e**, gave significant amounts of byproducts resulting from hydrogenation of the pyrrole portion of the indole. N^{in}-Boc-N^{α}-Cbz dehydroamino ester **7c** proved to be susceptible to overhydrogenation even at atmospheric pressure; however, in this case, use of dichloromethane or acetone as a solvent successfully prevented overhydrogenation.

TABLE 1. Asymmetric Hydrogenation of Dehydroamino Acid Derivatives 5−7



entry	dehydro-amino acid	R^1	R^2	regio-isomer	amino acid[a]	% ee (column)[b]	solvent
1	**5a**	H	Ac	2-yl	**11a**[c]	98.6 (AD)	ethyl acetate
2	**5b**	H	Ac	4-yl	**11b**	99.1 (OD)	MeOH
3	**5c**	H	Ac	5-yl	**11c**	98.0 (OD)	MeOH
4	**5d**	H	Ac	6-yl	**11d**	96.7 (AD)	MeOH
5	**5e**	H	Ac	7-yl	**11e**	99.5 (OD)	MeOH
6	**6b**	Boc	Ac	4-yl	**12b**	98.9 (OD)	MeOH
7	**6c**	Boc	Ac	5-yl	**12c**	98.6 (OD)	CH_2Cl_2
8	**6d**	Boc	Ac	6-yl	**12d**	98.5 (OD)	MeOH
9	**7b**	Boc	Cbz	4-yl	**13b**[d]	98.9 (OD)	MeOH
10	**7c**	Boc	Cbz	5-yl	**13c**[e]	97.5 (AD)	CH_2Cl_2
11	**7d**	Boc	Cbz	6-yl	**13d**[e]	96.9 (OD)[f]	MeOH

[a] Protected amino acid products were isolated in quantitative yield, except where indicated. The absolute configuration of products derived from (*S*,*S*)-DuPhos ligands is assumed to be *S*. [b] Determination of % ee was carried out by HPLC on a Daicel Chiralcel OD or Chiralpak AD column, as indicated. [c] Only 92% conversion after 4 days. [d] (*S*,*S*)-MeDuPhos catalyst was used. [e] (*R*,*R*)-MeDuPhos catalyst was used, giving the (*R*)-product. [f] This product was converted to the 2′,3′-dihydro-N^{α}-acetyl derivative (H_2, Pd/C, 4:1 MeOH/Ac_2O, 12 h) for % ee determination.

We envision that amino acids **2a**−**e** will prove to be useful as substitutions for the naturally occurring cation−π donor amino acids Trp, tyrosine (Tyr), and phenylalanine (Phe). Substitution of **2b** for Tyr11 in neurotensin(8−13) analogues was shown to greatly improve affinity for the human neurotensin (type 1) receptor.[15] Regioisomer **2a** is sterically much like Trp; **2c** and **2d** combine a Phe-like steric presence close to the peptide backbone with the cation−π binding superiority of Trp. All of these unnatural regioisomers may also confer a

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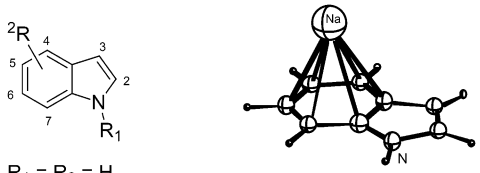
TABLE 2. Calculated Na^+ Binding Energies of Indole (14A) and Methylated Indoles (15A−21A)



14a: $R_1 = R_2 = H$
15a: R_1 = Me, $R_2 = H$
16a-21a: $R_1 = H$, R_2 = 2-Me to 7-Me

η^6-indole•Na^+ (**14b**)

η^5-indole•Na^+ (**14c**)

ligand	Na^+ binding energies (kcal/mol)[a] η^6-(benzo)	η^5-(pyrrolo)	ΔE (kcal/mol)
indole (**14a**)	−32.6	−29.0	−3.6
N-methylindole (**15a**)	−33.7	−30.0	−3.7
2-methylindole (**16a**)	−34.2	−30.2	−4.0
3-methylindole (**17a**)	−33.2	−30.0	−3.2
4-methylindole (**18a**)	−33.5	−29.8	−3.8
5-methylindole (**19a**)	−33.4	−30.3	−3.1
6-methylindole (**20a**)	−33.4	−30.4	−3.0
7-methylindole (**21a**)	−33.6	−29.8	−3.8

[a] Binding energies are calculated from HF/6-31G**//HF/6-31G** energies, without zero-point vibrational energy correction (see Experimental Section).

degree of peptidase resistance to peptides in which they are incorporated. Furthermore, it is likely that the alternative placement of the indole ring in **2a**−**e** relative to Trp will in some cases geometrically facilitate cation−π interaction, either in the normal benzo-face mode[4] or in the pyrrolo-face mode recently observed by Gokel.[16] To determine if the position of the attachment of the alanine chain would affect the cation-binding ability of the indole ring, we calculated Na^+ binding energies of indole **14a**, *N*-methylindole **15a**, and the corresponding C-methylated isomers **16a**−**21a** at the HF/6-31G**//HF/6-31G** level, as recommended by Dougherty[17] (Table 2).

Vibrational frequency analysis confirmed that all of the η^6-(benzo) Na^+ complexes (**14b**−**21b**) and η^5-(pyrrolo) Na^+ complexes (**14c**−**21c**) were local minima. The calculated Na^+ η^6-binding energy of indole (−32.6 kcal/mol)[4] matches Dunbar's recent experimental value (−34 ± 3 kcal/mol)[18] quite well. As reported previously at the B3LYP/6-31G* level, η^6-binding of indole **14a** is preferred to η^5-binding by about 4 kcal/mol,[19] and this energy difference is maintained for the methylated indoles **15a**−**21a**. Finally, Na^+ η^6-binding energies of the C-methylated indoles **16a**−**21a** vary by only 1 kcal/mol (i.e., <3%). We thus conclude that there will be no intrinsic difference in cation-binding ability between Trp and regioisomers **2a**−**e**. The catalytic asymmetric syntheses presented here are offered in the hope that they will facilitate further exploration of (*S*)- and (*R*)-Trp-regioisomers **2a**−**e** for peptide modification, de novo peptide design, and as fluorescence probes.[20]

Experimental Section

General. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. Acetone, ethyl acetate, and methanol were reagent grade and used as received. Formyl indoles were prepared according to the literature: 2-formylindole **3a**,[8] 4-, 5-, and 6-formylindoles **3b**−**d**, respectively,[9] and 7-formylindole **3e**.[10] *N*-Acetyl-α-phosphonoglycine trimethyl ester was prepared according to the literature.[21] *N*-Cbz-α-Phosphonoglycine trimethyl ester was purchased commercially. The DuPhos ligands and $Rh(COD)_2(OTf)$ were also purchased commercially. Rh Catalysts derived from (*S*,*S*)-EthylDuPhos, (*S*,*S*)-MethylDuPhos, and (*R*,*R*)-MethylDuPhos were prepared using Schlenk techniques according to the literature.[12] Catalysts were stored and dispensed in a nitrogen-filled drybox.

Representative Procedure for Synthesis of *N*-Boc-Formylindoles: *N*-Boc-5-Formylindole (4c).[22] A 250 mL round-bottom flask was charged with potassium *t*-butoxide (0.79 g, 7 mmol) and freshly distilled THF (100 mL). After dissolution of the base, 5-formylindole **3c** (1.02 g, 7 mmol) was added and stirred, cooled to 0 °C, and di-*tert*-butyl-dicarbonate (1.81 g, 8.3 mmol) was added to the solution. Following stirring at 0 °C for 1 h, the ice bath was removed and the reaction was allowed to stir at room temperature overnight. Water (100 mL) was added, and the product was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried with Na_2SO_4, filtered, concentrated in vacuo, and purified by flash chromatography to yield the desired *N*-Boc-5-formylindole **4c** (1.7 g, 100%) as a yellow solid: mp 58−60 °C; ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 9H), 6.69 (d, ^3J = 3.8 Hz, 1H), 7.69 (d, ^3J = 3.7 Hz, 1H), 7.85 (dd, ^3J = 8.6 Hz, ^4J = 1.5 Hz, 1H), 8.09 (d, ^4J = 1.0 Hz, 1H), 8.29 (d, ^3J = 8.6 Hz, 1H), 10.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.08, 84.61, 107.78, 115.55, 124.18, 125.11, 127.65, 130.64, 131.67, 138.70, 149.18, 192.08; MS (CI) *m*/*z* 246 $[M + H]^+$. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.51; H, 6.12; N, 5.70.

Representative Procedure for Schmidt Olefinations: (*Z*)-N^{α}-Acetyl-N^{in}-Boc-2,3-dehydro-3-(indol-5-yl)-alanine, Methyl Ester (6c). The following procedure is based on Schmidt:[11] a 10 mL round-bottom flask was charged with *N*-acetyl-α-phosphonoglycine trimethyl ester (1.44 g, 6 mmol) and THF (5 mL) and cooled to −78 °C. 1,1,3,3-Tetramethylguanidine (TMG, 0.753 mL, 6 mmol) was added and stirred for 5 min, followed by *N*-Boc-5-formylindole **4c** (0.98 g, 4 mmol). After stirring at −78 °C for 1 h, the dry ice bath was removed, and the reaction was allowed to stir at room temperature over 3 days, at which point TLC analysis indicated substantial conversion of starting material. Water (10 mL) was then added, the product was extracted with ethyl acetate (2 × 40 mL). The

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combined organic extracts were washed with water, dried with Na_2SO_4, and concentrated in vacuo. Recrystallization from ethyl acetate gave pure (*Z*)-**6c** (1.02 g, 71%): mp 161−162 °C; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 9H), 2.16 (s, 3H), 3.85 (s, 3H), 6.56 (br s, 1H), 7.07 (br s, 1H), 7.45 (d, ^3J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.60 (s, 1H), 7.68 (s, 1H), 8.11 (^3J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.33, 28.12, 52.53, 84.05, 107.36, 115.05, 122.79, 123.05, 125.69, 126.66, 128.01, 130.52, 133.59, 135.30, 149.26, 165.80, 169.09; MS (CI) *m*/*z* 359 [M + H]$^+$. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.46; H, 6.19; N, 7.84.

(*Z*)-*N*$^\alpha$-Acetyl-2,3-dehydro-3-(indol-7′-yl)-alanine, Methyl Ester (5e). Compound **5e** was isolated as a yellow solid by recrystallization from ethyl acetate and flash chromatography (diethyl ether) of the remaining mother liquor (90% yield): mp 148−149 °C; ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H), 3.83 (s, 3H), 6.48 (d, ^3J = 3.2 Hz, 1H), 7.05 (t, ^3J = 7.7 Hz, 1H), 7.25 (d, ^3J = 3.2 Hz, 1H), 7.46 (d, ^3J = 7.6 Hz, 1H), 7.59 (d, ^3J = 7.9 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.55, 52.80, 102.68, 117.00, 119.37, 122.36 (2C), 124.90 (2C), 128.39, 129.43, 133.70, 165.59, 169.94; MS (CI) *m*/*z* 259 [M + H]$^+$. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.86; H, 5.51; N, 10.78.

(*Z*)-*N*$^\alpha$-Cbz-*N*^{in}-Boc-2,3-Dehydro-3-(indol-6′-yl)-alanine, Methyl Ester (7d). Compound **7d** was isolated by flash chromatography (20% ethyl acetate in hexane) as a yellow oil (47% yield): ^{1}H NMR (CD_3OD) δ 1.63 (s, 9H), 3.79 (br s, 3H), 5.14 (br s, 2H), 6.60 (d, ^3J = 3.7 Hz, 1H), 7.21−7.54 (m, 7H), 7.67 (d, ^3J = 3.8 Hz, 1H), 8.51 (br s, 1H); ^{13}C NMR (CD_3OD) δ 28.40, 52.94, 68.13, 85.32, 108.19, 117.72, 121.84, 125.12, 126.05, 128.73, 128.84, 129.24, 130.72, 133.07, 135.96, 136.42, 137.78, 150.55, 156.93, 167.58 (20 C found); MS (CI) *m*/*z* 451 [M + H]$^+$. Anal. Calcd for $C_{25}H_{26}N_2O_6$: C, 66.66; H, 5.82; N, 6.22. Found: C, 66.43; H, 5.88; N, 6.15.

General Procedure for Asymmetric Hydrogenations. In a nitrogen-filled drybox, a Schlenk tube was charged with catalyst (1 mg), sealed with a septum, and brought out of the drybox. Unless otherwise noted, the catalyst used was [Rh(COD)L]$^+$ TfO$^-$ (L = (*S*,*S*)-EtDuPhos). The dehydroamino acid (20 mg) was weighed into a 5 mL round-bottom flask, dissolved in 3 mL of MeOH (unless otherwise noted), capped with a septum, and ultrasonicated. After three vacuum/N_2 cycles, the substrate was cannulated to the Schlenk tube. After three vacuum/H_2 cycles, the tube was set to an initial pressure of 1 atm H_2. Assuming use of EtDuPhos, catalyst loadings are thus 1.8, 2.6, and 3.2% for dehydroamino acids **5**, **6**, and **7**, respectively. The reactions were allowed to continue at room temperature for 3 days. Afterward, the reactions were concentrated in vacuo; the residue was dissolved in ethyl acetate, and the solution was passed through a short SiO_2 column to remove the catalyst. ^{1}H and ^{13}C NMR analyses and the enantiomeric excesses were determined directly with the crude products thus obtained. For each substrate below, hydrogenations were performed with both (*S*,*S*)- and (*R*,*R*)-catalysts. Comparison of the respective HPLC traces thus allowed enantiomeric peaks to be assigned. Unless otherwise noted, reactions went to 100% conversion, with no overhydrogenation of the pyrrole portion of the indole ring.

(*S*)-*N*$^\alpha$-Acetyl-*N*^{in}-Boc-3-(indol-5′-yl)-alanine, Methyl Ester [(*S*)-12c]. The hydrogenation was performed in CH_2Cl_2. HPLC analysis (OD column) indicated 98.6% ee: $[\alpha]^{25}_D$ +26.9 (*c* 0.95, MeOH); ^{1}H NMR (CD_3OD) δ 1.65 (s, 9H), 1.89 (s, 3H), 3.01 (dd, ^2J = 13.8 Hz, ^3J = 8.8 Hz, 1H), 3.21 (dd, ^2J = 13.8 Hz, 5.8 Hz, 1H), 3.67 (s, 3H), 4.68 (dd, ^3J = 8.8 Hz, 5.8 Hz, 1H), 6.55 (d, ^3J = 3.8 Hz, 1H), 7.13 (dd, ^3J = 8.5 Hz, ^4J = 1.7 Hz, 1H), 7.38 (d ^4J = 1.1 Hz, 1H), 7.57 (d, ^3J = 3.7 Hz, 1H), 8.01 (d ^3J = 8.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 22.27, 28.40, 38.43, 52.64, 55.68, 84.83, 108.14, 115.76, 122.24, 126.24, 127.01, 132.08, 132.32, 135.41, 150.81, 172.91, 173.43; MS (CI) *m*/*z* 361 [M + H]$^+$; HRMS (FAB) calcd for $C_{19}H_{25}N_2O_5$ [M + H]$^+$ 361.1763, found 361.1744.

(*S*)-*N*$^\alpha$-Acetyl-3-(indol-7′-yl)-alanine, Methyl Ester [(*S*)-11e]. HPLC analysis (OD column) indicated 99.5% ee: $[\alpha]^{25}_D$ −1.61 (*c* 1.055, MeOH); ^{1}H NMR (CD_3OD) δ 1.89 (s, 3H), 3.25 (dd, ^2J = 14.2 Hz, ^3J = 7.9 Hz, 1H), 3.34 (dd, ^2J = 14.2 Hz, ^3J = 6.9 Hz, 1H), 3.59 (s, 3H), 4.78 (t, ^3J = 7.4 Hz, 1H), 6.44 (d, ^3J = 3.1 Hz, 1H), 6.88 (dd, ^3J = 7.1 Hz, ^4J = 1.2 Hz, 1H), 6.93 (t, ^3J = 7.4 Hz, 1H), 7.22 (d, ^3J = 3.2 Hz, 1H), 7.43 (dd, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H); ^{13}C NMR (CD_3OD) δ 22.31, 34.64, 52.60, 54.17, 102.80, 120.01, 120.16, 120.49, 122.79, 125.46, 129.58, 136.40, 173.01, 173.59; MS (CI) *m*/*z* 261 [M + H]$^+$; HRMS (FAB) calcd for $C_{14}H_{17}N_2O_3$ [M + H]$^+$ 261.1239, found 261.1241.

(*R*)-*N*$^\alpha$-Cbz-*N*^{in}-Boc-3-(indol-6′-yl)-alanine, Methyl Ester [(*R*)-13d]. The (*R*,*R*)-MeDuPhos catalyst was used: $[\alpha]^{25}_D$ +8.50 (*c* 0.20, MeOH); ^{1}H NMR (CD_3OD) δ 1.62 (s, 9H), 3.05 (dd, ^2J = 13.8 Hz, ^3J = 8.7 Hz, 1H), 3.24 (dd, ^2J = 13.7 Hz, ^3J = 5.6 Hz, 1H), 3.68 (s, 3H), 4.50 (dd, ^3J = 8.7 Hz, 5.6 Hz, 1H), 4.96 (d, ^2J = 12.6 Hz, 1H), 5.02 (d, ^2J = 12.6 Hz, 1H), 6.54 (d, ^3J = 3.7 Hz, 1H), 7.05 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1H), 7.19−7.27 (m, 5H), 7.43 (d, ^3J = 8.0 Hz, 1H), 7.54 (d, ^3J = 3.8 Hz, 1H), 8.01 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.15, 38.70, 52.32, 55.14, 66.94, 83.62, 107.03, 115.92, 120.94, 123.92, 125.98, 128.04, 128.10, 128.47, 129.59, 131.70, 135.51, 136.25, 142.47, 155.65, 172.03; MS (CI) *m*/*z* 453 [M + H]$^+$; HRMS (FAB) calcd for $C_{25}H_{29}N_2O_6$ [M + H]$^+$ 453.2026, found 453.2022.

Computational Method. Equilibrium geometries of all indoles and their η^5- and η^6-Na$^+$ complexes were determined at the HF/6-31G** level using Spartan '02 Windows.[23] All geometries were characterized as local minima by vibrational frequency analysis (no imaginary frequencies). Zero-point vibrational energies (ZPVE) were scaled by 0.8992,[24] and ZPVE values were found to be very similar (95.8 ± 0.1 kcal/mol) for all the η^5- and η^6-complexes of methylated indoles **15a**−**21a**; these data are reported in Supporting Information. ZPVE correction reduced calculated binding energies by approximately 1.1 kcal/mol, as has been noted previously by other investigators.[17,19] Basis set superposition error (BSSE) corrections have been shown to reduce calculated cation−π binding energies by 0.2−4 kcal/mol.[17,19,25] However, we did not perform BSSE corrections, since the appropriate BSSE computational model is unresolved,[18,19] and since published studies[17,25] show that BSSE corrections to cation−π binding energies are very similar across a series of related compounds. Binding energies reported in Table 2 are derived from uncorrected HF/6-31G** energies, since Dougherty has shown that uncorrected HF/6-31G** energies match well experimentally determined binding enthalpies.[17] Dougherty has also shown that MP2/6-31G** energies are too high but approach experimental values when ZPVE and BSSE corrections are applied.[17]

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Supporting Information Available: ^{1}H and ^{13}C NMR and MS data for all new compounds; enantiomeric excess determination protocols for protected amino acid derivatives **11**−**13**; and absolute energies, ZPVE, and equilibrium geometries for indoles **14a**−**21a** and their corresponding η^6- and η^5-Na$^+$ complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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