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Palladium-Assisted Cyclization–Insertion Reactions. Synthesis of Functionalized Heterocycles

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Abstract: *o*-Allylbenzoic acids and N-substituted *o*-allylanilines undergo facile palladium-assisted cyclization/carbonylation to produce dihydroisocoumarin acetic acid esters and dihydroindolacetic acid esters in high yield. With *o*-allylanilines lacking β hydrogens in the cyclized intermediate σ-alkylpalladium(II) complex, conjugated enones such as methyl vinyl ketone and methyl acrylate insert, giving highly functionalized indolines. Intramolecular insertions of this type lead to tricyclic compounds of the pyrroloindole or pyridinoindole type.

Introduction

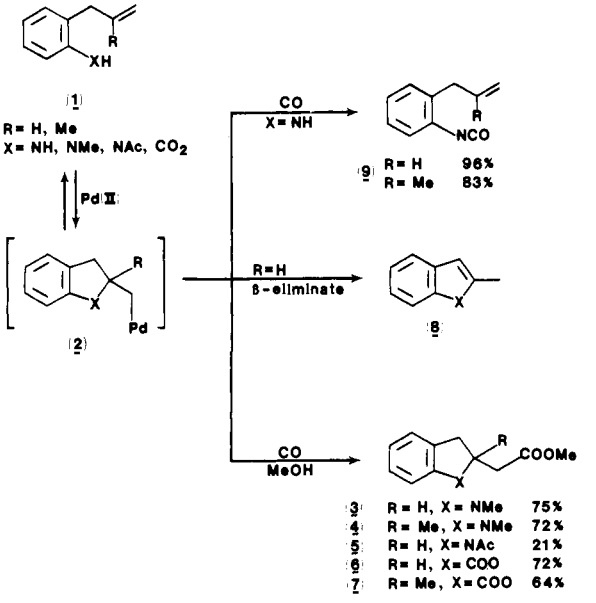
A typical reaction of σ-alkylpalladium(II) complexes is insertion of unsaturated molecules into the metal–carbon σ bond. Carbon monoxide inserts most readily, usually under mild conditions. Thus, σ-alkylpalladium(II) complexes arising from oxidative addition of organic halides to palladium(0) complexes,[1-6] from transmetalation reactions,[7] and from nucleophilic attack of methoxide,[8-11] amines,[12,13] and carbanions[14] on both chelating and simple olefin–palladium(II) complexes, react with CO to produce acylated organic products. Olefins, including conjugated enones, simple olefins, and enamides, also insert into σ-alkylpalladium(II) complexes. However, more severe experimental conditions are usually required, limiting this reaction to stable σ-alkyl complexes and/or those lacking β hydrogens.[1,15-20] A number of heterocyclic compounds were prepared by the insertion of conjugated enones into stable σ-alkylpalladium(II) complexes.[21-23] Similar chemistry was used in an elegant approach to the prostaglandins.[24]

We have recently reported the synthesis of indoles[25] and isocoumarins[26] by a palladium-assisted cyclization reaction. Herein we report insertion reactions of the unstable σ-alkylpalladium(II) complexes intermediate in these heterocyclization reactions.

Results and Discussion

Carbon Monoxide Insertion. The palladium-assisted cyclization of *o*-allylanilines and -benzoic acids to indoles and isocoumarins, respectively, is thought to proceed through σ-alkylpalladium(II) intermediates. While lacking sufficient stability to allow isolation, these complexes had sufficient lifetime to undergo CO insertion reactions (Scheme I). Several requirements must be met to accomplish the desired cyclization–carbonylation sequence, a process involving three distinct palladium-mediated reactions. First, the reaction must be carried out under conditions which will allow cyclization to occur, to produce the σ-alkylpalladium complex (**2**) required for subsequent insertion. Second, CO must insert under conditions sufficiently mild to preclude competitive β-hydride elimination reactions in systems having β hydrogens. Finally, carbonylation of the nucleophilic center itself, prior to cyclization, must be avoided.

Scheme I



With unsubstituted allylanilines, direct carbonylation of the

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Table I. Catalytic Cyclization-Carbonylation of 2-(2-Propenyl)-*N*-methylaniline

$$\mathbf{1} + BQ^{c} + X\text{LiCl} + Y\text{Na}_2\text{CO}_3 + \text{CO} \xrightarrow[\text{THF}]{5\%\ PdCl_2,\ MeOH} \mathbf{1} + \mathbf{3} + \mathbf{8}$$

(X = NMe, R = H) (X = NMe)

X	*Y*	CO pressure	products	% yield[a]
10	0	1 atm	**1**	94
10	1	1 atm	**3** + **8** (1:1)	100
5	2	1 atm	**3** + **8** (1:1)	70
2	1	25 psi	**1** + **3** + **8** (1:1:1)	100
1	1	25 psi	**1**	100
0.5	1	25 psi	**1**	90
5	0	25 psi	**1** + **3** (3:1)	100
5	1	25 psi	**1** + **3** + **8** (3:9:1)	100[b]

[a] Yields are of mixtures, purified but not separated. Ratios are by NMR integration of characteristic peaks. [b] Stannous chloride (5%) was added. [c] BQ = benzoquinone.

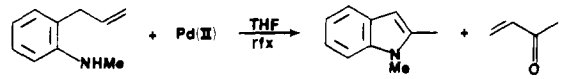
nitrogen could not be suppressed under a variety of conditions, even those for which ring closure had occurred to some extent. Thus, with both *o*-allylaniline and *o*-(2-methallyl)aniline, at temperatures between −78 and −10 °C and CO pressures between 1 and 2 atm, only carbonylation at nitrogen occurred, giving isocyanates (**9**) (or ureas). At temperatures above −10 °C significant amounts of indole, from β-hydride elimination of the cyclized σ-alkylpalladium complex, were obtained in addition. Thus, under mild conditions the cyclization process was reversed by CO addition,[27] while at higher temperatures β-hydride elimination proceeded more rapidly than CO insertion.

To prevent isocyanate formation, N-monosubstituted allylanilines were examined. At temperatures below −25 °C *o*-allyl-*N*-methylaniline was smoothly converted to methyl 2,3-dihydro-1-methyl-1*H*-indole-2-acetate (**3**) in good yield, while at temperatures above −25 °C significant amounts of 1,2-dimethylindole (the β-hydride elimination product) were observed. Similarly, *o*-methallyl-*N*-methylaniline formed methyl 1,2-dimethyl-2,3-dihydro-1*H*-indole-2-acetate in good yield. Since this substrate lacks β hydrogens, the reaction was carried out successfully at room temperature. Finally, *o*-methallyl-*N*-acetylaniline underwent a similar reaction, but in low yield with substantial (71%) amounts of starting material being recovered.

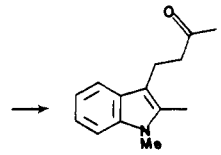
Related cyclization-carbonylation reactions with *o*-allylbenzoic acids to produce dihydroisocoumarin acetic esters were less complex, since acylation of the carboxylate group was not a competing reaction. Thus, both *o*-allylbenzoic acid and *o*-methallylbenzoic acid readily cyclized and carbonylated, producing methyl 3,4-dihydroisocoumarin-3-acetate (**6**) and methyl 3-methyl-(4*H*)-dihydroisocoumarin-3-acetate (**7**) in good yield. Reaction of the substrate having β hydrogens was carried out at low temperatures (−50 °C) to suppress competing β-hydride elimination.

Table I summarizes attempts to catalytically effect the conversion of *o*-allyl-*N*-methylaniline to **3**. For successful catalysis by palladium conditions must be adjusted to favor sequential olefin complexation by palladium(II), olefin amination, CO insertion, methanolysis, and reoxidation of palladium(0) to palladium(II), while suppressing CO-olefin competition for the palladium(II), β-hydride elimination from **2**, and methoxycarbonylation of the olefin. Under optimum conditions (5:1:1:1 LiCl-Na_2CO_3-benzoquinone-substrate, 25 psi CO, with 0.05 $PdCl_2/SnCl_2$ as catalyst) a 70% yield of **3** (14 turns of catalyst) was obtained. These conditions approximate the best conditions found for the cyclization reactions themselves (conversion of **1** to **8**).[25,26] Stannous chloride in amounts equivalent to the amount of $PdCl_2$ used greatly increased the yield of **3**.[28]

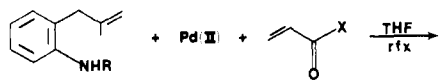
Olefin Insertions. The insertion of olefin compounds into σ-alkylpalladium complexes usually requires more severe conditions than does CO insertion. Thus these insertions are normally restricted to complexes which cannot competitively β-hydride eliminate.[15-24] When *o*-allyl-*N*-methylaniline was treated with Pd(II) in the presence of methyl vinyl ketone in refluxing THF, methyl vinyl ketone was indeed incorporated in the resulting indole, but at the 3 position. In this case, cyclization to indole occurred as usual (i.e., β-elimination rather than insertion resulted) and the thus-formed indole simply added to the unsaturated enone via the well-known Michael conjugate addition reaction of 2-methylindoles (eq 1).[29] To



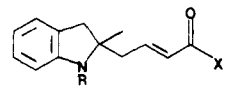
(1)



preclude this reaction, *o*-methallylanilines were studied, and were found to cyclize and then insert both methyl vinyl ketone and methyl acrylate in excellent yield (eq 2). The ester reacted



(2)

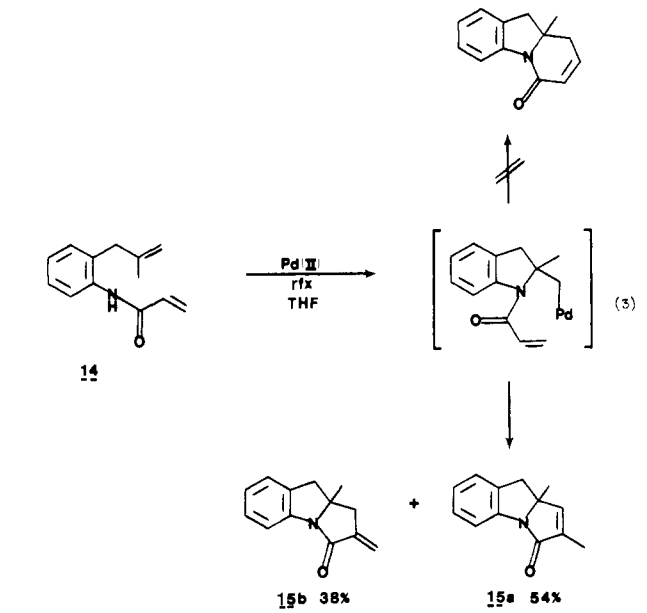


10	R = X = Me	91%	5:1 trans/cis
11	R = Me, X = OMe	75%	3.2:1 trans/cis
12	R = H, X = OMe	68%	trans
13	R = H, X = NHPh	35%	trans

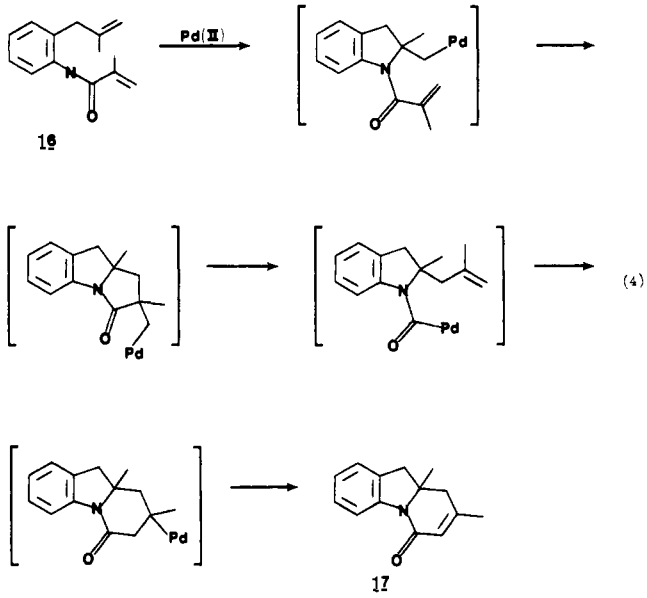
much more slowly than the ketone, and the insertion was facilitated by the addition of small amounts of iodine to promote oxidatively induced insertion.[30]

A number of olefins did not insert into the σ-alkylpalladium(II) complex formed by cyclization of *o*-methallylanilines under the above conditions. These included β-substituted enones such as cyclohexenone, methyl but-2-enoate, pent-3-en-2-one, electron-rich olefins such as vinyl acetate and *N*-vinylacetamide, and simple olefins such as ethene and styrene. These olefins are typically less reactive in insertion reactions and frequently require temperature in excess of 100 °C to react.

With substrates listed in eq 2, alkylation of the enone occurred exclusively at the β carbon. Anticipating similar behavior in intramolecular insertions, the acrylamide of *o*-methallylaniline was prepared and cyclized. Remarkably, only α-alkylation was observed (eq 3). Since the intermolecular version of this reaction (eq 2) went exclusively β, this observed α-alkylation must be due to steric restraints imposed by the cyclic nature of the insertion process in the intramolecular case.[31] In an attempt to force β-alkylation, the methacrylamide of *o*-methallylaniline was prepared and subjected to cyclization conditions. In all cases, the reaction was very sluggish. In the absence of added I_2 to oxidatively drive the insertion, unreacted starting material was recovered after 18 h at reflux (THF). Under the same conditions, but with added I_2, some ring closure (14%) had occurred, giving exclusively six-membered-ring product. However, the methyl group was in the β position of the cyclohexenone ring, indicating that direct cyclization to form a six-membered ring had not occurred. Instead, the recently reported[32] rearrangement involving closure to a five-

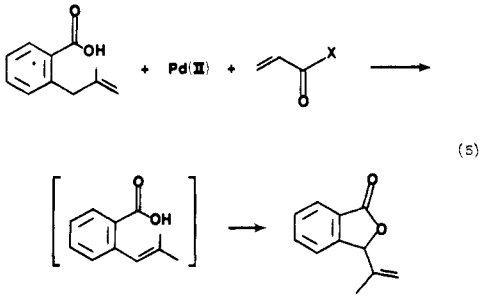


membered ring, β-aminocarbonyl elimination to form an aminocarbonylpalladium species, followed by a reverse readdition and β-hydride elimination, was observed (eq 4).[33]



Starting material (17%) and unidentified materials comprised the remainder of the crude product.

In contrast to the *o*-methallylanilines, *o*-methallylbenzoic acid failed to insert conjugated enones under all conditions tried. In all cases 3-(isopropenyl)phthalide from olefin rearrangement followed by cyclization and β-elimination was the sole cyclic product, obtained in up to 100% yield (eq 5).



Summary

The chemistry reported above results in the facile *di*functionalization of olefins in a one-pot procedure that is (potentially) catalytic in palladium. This allows the synthesis of complex, highly functionalized materials from relatively simple starting materials. Intramolecular cyclization insertion reactions produce polycyclic products cleanly. The application of this chemistry to the synthesis of heterocyclic natural products is currently under investigation.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded on either a Beckman Acculab 3 or Beckman 4240 spectrophotometer. ^{1}H NMR spectra were measured with either a Varian Model EM360 or JEOL FX100 using Me_4Si as an internal standard and are reported in δ. ^{13}C NMR spectra were recorded on a JEOL FX100. Analytical and preparative TLC were performed using Merck PF254 silica gel. Products were visualized by UV light. Analyses were performed by Midwest Microanalytical Labs, Indianapolis, Ind.

Materials. All solvents were freshly distilled and stored under an argon atmosphere. Immediately before use they were degassed and saturated with argon. THF (MCB, reagent grade) was refluxed over $LiAlH_4$ and distilled at atmospheric pressure. Ether (MCB, absolute reagent grade) was distilled at atmospheric pressure under a N_2 atmosphere from Na–benzophenone. *o*-Allylanilines[25] and *o*-allylbenzoic acids[26] were prepared by previously published procedures. Methyl vinyl ketone and methyl acrylate were purchased from commercial sources and used without further purification. Acryloyl chloride and methacryloyl chloride were distilled at reduced pressure. Hydroquinone was added to these distillations to retard polymerization. CO (commercial purity) was purchased from Matheson.

General Procedure for the Carbonylation of Allylanilines and Allylbenzoic Acids. The $PdCl_2(CH_3CN)_2$ (1 equiv) was transferred to a 50-mL side-arm flask fitted with a stopcock, stir bar, and serum cap. The flask was alternately evacuated and filled with argon on a vacuum line. THF (10 mL/mmol complex) was added to the complex via syringe and allowed to stir for 2–3 min. The substrate (1 equiv) was taken up in THF (2 mL/mmol substrate) and added to the slurry of complex via syringe. The amber solution was stirred for 0.5–1 h. To this solution was added Et_3N (2 equiv), 1 equiv every 0.5–1 h. The cherry-red solution was carbonylated by attaching a CO-filled balloon to the stopcock and venting the flask. For carbonylations at pressures greater than 1 atm, a Fischer-Porter pressure vessel was used.

Preparation of Methyl 2,3-Dihydro-1-methyl-1*H*-indole-2-acetate (3). 2-(2-Propenyl)-*N*-methylaniline (147 mg, 1 mmol) and $PdCl_2(CH_3CN)_2$ (260 mg, 1 mmol) were combined in the usual manner. The temperature was lowered to −50 °C and Et_3N (276 μL, 2 mmol) (1 equiv/h) was added. After an additional 1 h, a CO-filled balloon was attached and MeOH (4 mL) was added to the reaction mixture. After stirring for 18 h, the solution was filtered and the solvent removed under vacuum. The indoline ester (**3**) was isolated by preparative TLC (SiO_2–6:1 benzene/hexane): R_f 0.27; 154 mg (75%); NMR ($CDCl_3$) δ 2.7 (s, 3, NCH_3), 2.9 (m, 2, CH_2CO), 3.2 (m, 2, $PhCH_2$), 3.7 (s, 3, OMe), 3.4–4.0 (m, 1, CHN), 6.4–7.3 (m, 4, ArH); IR (neat) 3070, 3050, 2980, 2920, 2880, 2840, 1740 (CO, ester), 1610, 1500, 900, 850, 750 cm^{-1}. Anal. ($C_{12}H_{15}NO_2$) C, H, N.

Preparation of Methyl 1,2-Dimethyl-2,3-dihydro-1*H*-indole-2-acetate (4). 2-(2-Methyl-2-propenyl)-*N*-methylaniline (133 mg, 0.83 mmol) and $PdCl_2(CH_3CN)_2$ (260 mg, 1 mmol) were combined in the usual manner. Et_3N (276 μL, 2 mmol) (1 equiv/0.25 h) was added at room temperature. After 20 min, a CO-filled balloon was attached and MeOH (0.5 mL) was added. The reaction mixture was stirred at room temperature for 18 h. The solution was filtered and the solvent removed under vacuum. Evaporative distillation gave 151 mg (72%) of a colorless oil: NMR ($CDCl_3$) δ 1.36 (s, 3, CH_3), 2.6 (s, 2, CH_2CO), 2.7 (s, 3, NCH_3), AB system δ_A 2.82, δ_B 3.40 (J_{AB} = 16 Hz, 2, diastereotopic $PhCH_2$), 3.6 (s, 3, OMe), 6.3–7.3 (m, 4, aromatic H); IR ($CHCl_3$) 3060, 3030, 2980, 2960, 2800, 2770, 1730 (vs, CO, ester), 1610 (vs), 1490 (vs), 1310, 840 cm^{-1} (w). Anal. ($C_{13}H_{17}NO_2$) C, H, N.

Preparation of Methyl 1-Acetyl-2,3-dihydro-1*H*-indole-2-acetate (5). 2-(2-Propenyl)-*N*-acetylaniline (75 mg, 0.43 mmol), $PdCl_2(CH_3CN)_2$ (112 mg, 0.43 mmol), and Na_2CO_3 (106 mg, 1 mmol) were placed in the standard reaction flask. THF (5 mL) and MeOH (1 mL) were added and a CO-filled balloon was attached to the flask. The solution turned red and within 10 min Pd(0) precipitated. After 18 h, the solution was filtered and the solvent removed under vacuum. Purification by preparative TLC (SiO_2, 10:1

$CHCl_3$/acetone) gave **5** (R_f 0.7, 20 mg, 21%): NMR ($CDCl_3$) δ 2.35 (s, 3, CH_3CO), 2.7 (m, 2, CH_2CO-), 3.4 (m, 2, $PhCH_2$), 3.65 (s, 3, OCH_3), 4.9 (m, 1, NCH-), 7.2 (m, 4, aromatic H); IR (neat) 3010, 2980, 2940, 2880, 1740 (CO, ester), 1660 (CO, amide), 1600, 1500, 1400, 1280, 1200, 750 cm^{-1}.

Preparation of Methyl 3,4-Dihydroisocoumarin-3-acetate (6). 2-(2-Propenyl)benzoic acid (134 mg, 0.83 mmol) and $PdCl_2(CH_3CN)_2$ (216 mg, 0.83 mmol) were combined in the usual manner. The temperature was lowered to −50 °C and Na_2CO_3 (90 mg, 0.85 mmol) was added to the solution. A CO-filled balloon was attached, MeOH (2 mL) was added, and the solution was allowed to stir for 18 h. During the course of the reaction Pd(0) was precipitated. The solution was filtered and solvent removed under vacuum. Purification by preparative TLC (SiO_2, 28:12:1 hexane/Et_2O/formic acid) gave the dihydroisocoumarin ester (**6**) as a white solid (mp 70–71 °C) (R_f 0.06, 132 mg, 72%): NMR ($CDCl_3$) δ 2.92, 2.96 (2 d, J = 7 Hz, 2, $PhCH_2$), 3.15 (d, J = 7 Hz, 2, CH_2CO), 3.80 (s, 3, OMe), 5.10 (quintet, 1, J = 7 Hz, methine), 7.42 (m, 3, ArH), 8.15 (m, 1, ArH); IR ($CHCl_3$) 3020 (m), 2980 (w), 2960 (w), 1730 (vs, CO, ester, lactone), 1610 (w), 1460, 1440, 1300, 1220, 1110 cm^{-1}. Anal. ($C_{12}H_{12}O_4$) C, H.

Preparation of Methyl 3-Methyl-3,4-dihydroisocoumarin-3-acetate (7). 2-(2-Methyl-2-propenyl)benzoic acid (180 mg, 1.02 mmol) and $PdCl_2(CH_3CN)_2$ (260 mg, 1 mmol) were combined in the usual manner. The temperature was lowered to −25 °C and Na_2CO_3 (106 mg, 1 mmol) was added to the solution. A CO-filled balloon was attached and MeOH (1 mL) was added. The reaction mixture was stirred for 3 h at −25 °C, then 18 h at room temperature. The solution was filtered and the solvent removed. The crude material was taken up in ether and washed with dilute acid. The ether layer was dried over $MgSO_4$, the solution filtered, and the solvent removed. Purification by preparative TLC (SiO_2, 4:1 hexane/ether) gave 150 mg (64%) of the dihydroisocoumarin ester (**7**) (R_f 0.09): NMR ($CDCl_3$) δ 1.65 (s, 3, CH_3), 2.85 (s, 2, CH_2CO), AB system, δ_A 3.20, δ_B 3.46, J_{AB} = 16 Hz (2, $PhCH_2$), 3.80 (s, 3, OCH_3), 7.5 (m, 3, ArH), 8.2 (m, 1, ArH); IR ($CHCl_3$) 3020 (s), 2980, 1730 (vs, CO, ester, lactone), 1610 (s), 1475 (s), 1450 (s), 1230, 1170, 1130, 1100 cm^{-1}. Anal. ($C_{13}H_{14}O_4$) C, H.

General Procedure for Catalytic Carbonylation of 2-(2-Propenyl)-*N*-methylaniline (Benzoquinone as Oxidant). 2-(2-Propenyl)-*N*-methylaniline (1 equiv) was added to 10 mL of a THF/MeOH (3:1) solution of $PdCl_2(CH_3CN)_2$ (10 mol %), benzoquinone (1 equiv), Na_2CO_3 (0–2 equiv), and LiCl (1–10 equiv). Carbon monoxide (0–50 psi) was introduced and the reaction mixtures were allowed to stir overnight. The solvent was removed under vacuum and the residue triturated with ether. The ether solution was decanted and the solvent removed to yield crude material. From the NMR spectra the relative amounts of the products (starting material, 1,2-dimethylindole, and indoline ester) were determined. The results are found in Table I.

Synthesis of 4-[3′-(1,2-Dimethylindolyl)]butan-2-one. *N*-Methyl-2-propenylaniline (44.9 mg, 0.30 mmol) was dissolved in 10 mL of THF and LiCl (259.0 mg, 6.1 mmol) and Na_2CO_3 (64.7 mg, 0.61 mmol) were added. $PdCl_2(CH_3CN)_2$ (79.2 mg, 0.30 mmol) and methyl vinyl ketone (214.1 mg, 3.0 mmol, 0.25 mL) were then added and the solution was heated at the reflux temperature for 5 min. A dilute I_2 solution (1 mL) was added and the reaction mixture was heated at reflux overnight. The heterogeneous black reaction mixture was filtered and the solvent removed under reduced pressure. The product (28 mg, 43%) was isolated by preparative TLC (SiO_2, 5:1 hexane/acetone, R_f 0.25), yielding 28.3 mg (43%): NMR ($CDCl_3$) δ 2.09 (s, 3, $COCH_3$), 2.35 (s, 3, C=CCH_3), 3.0 (m, 4, CH_2CH_2), 3.62 (s, 3, NCH_3), 7.10 (m, 3, ArH), 7.45 (m, 1, ArH); ^{13}C NMR ($CDCl_3$) 10.16 ($COCH_3$), 18.63 (C=CCH_3), 29.37, 30.13 (CH_2CH_2), 44.43 (NCH_3), 108.36, 109.47, 117.41, 118.46, 120.27, 126.93, 132.71, 136.27 (8 sp^2 carbons, 4 nonprotonated), 208.50 ppm (C=O); IR (neat) 3050 (w), 2915 (br, CH_2), 1710 (s, C=O), 1610 (w), 1565 (w), 1472 (s), 1435 (m), 1410 (m), 1372 (s), 1332 (m), 1298 (w), 1160 (m), 1014 (w), 740 cm^{-1} (s). Anal. ($C_{14}H_{17}NO$) C, H, N.

Preparation of 2,3-Dihydro-1,2-dimethyl-2-(2-penten-3-one)-1*H*-indole (10). 2-(2-Methyl-2-propenyl)-*N*-methylaniline (152 mg, 0.95 mmol) and $PdCl_2(CH_3CN)_2$ (246 mg, 0.95 mmol) were combined in the usual manner. Et_3N (262 μL, 1.90 mmol) was slowly added and the reaction mixture was allowed to stir for 0.5 h. Methyl vinyl ketone (308 μL, 3.8 mmol) was added dropwise and the solution refluxed for 7 h. Purification by preparative TLC (SiO_2, 4:1 hexane/ether) gave two products. Compound A (R_f 0.36, 30 mg, 16%) was characterized by NMR and IR as *cis*-**10**: FX100 NMR ($CDCl_3$) δ 1.19 (s, 3, CH_3), 2.23 (s, 3, CH_3CO), 2.65 (s, 3, NCH_3), 2.69–3.24 (m, 4, CH_2), 6.18 (m, 2, ArH), 6.29 (d, 1, J = 7.3 Hz, cis CO-CH=CH), 6.50 (d of t, J = 7.32, 0.98 Hz, 1, cis COCH=CH), 6.95–7.13 (m, 2, ArH); FX100 ^{13}C NMR ($CDCl_3$) 23.03 (CH_3), 27.87 (CH_2), 31.64 (CH_2), 36.69 ($COCH_3$), 40.46 (NCH_3), 66.91 (tetrasubstituted C), 127.3 (=CHCO-), 116.32, 123.83, 127.22, 105.24 (aromatic carbons), 143.57 (=CH), 199.01 ppm (CO); IR (neat) 3080 (w), 3050 (w), 2980 (m), 2950, 2890, 2840, 1700 (s, C=O), 1620 (s), 1500 (vs), 1185 (s), 750 cm^{-1} (s). Anal. ($C_{15}H_{19}NO$) C, H, N.

Compound B (R_f 0.21, 98 mg, 75%) was characterized by NMR and IR as *trans*-**10**: FX-100 NMR ($CDCl_3$) δ 1.25 (s, 3, CH_3), 2.08 (s, 3, CH_3CO), AB system δ_A 2.40, δ_B 2.61 (J_{AB} = 8 Hz, 2, CH_2C=C), 2.68 (s, 3, NCH_3), AB system δ_A 2.71, δ_B 2.97 (J_{AB} = 16 Hz, 2, $PhCH_2$), 6.01 (d of t, J = 15.8, 1.2 Hz, 1, trans CH=CHCO), 6.31 (d, J = 7.6 Hz, 1, aromatic H), 6.59 (m, 1, aromatic H), 6.67 (m, 1 CH=CHCO), 6.95–7.12 (m, 2, aromatic); FX100 ^{13}C NMR ($CDCl_3$) 23.15 (CH_3), 26.42 (CH_2), 28.03 (CH_2), 40.67 (CH_2CO), 40.75 (NCH_3), 67.11 (tetrasubstituted carbon), 133.10 (=CHCO), 116.80, 123.72, 127.31, 105.36 (aromatic CH), 126.90 (substituted aromatic), 143.63 (CH), 151.42 (amine substituted aromatic), 198.02 ppm (CO); IR (neat) 3070 (m), 3040 (m), 2980 (s), 2950, 2920, 2890, 2830, 1710 (s, CO), 1685 (vs, CO), 1640 (s, C=C), 1620 (vs, C=C), 1500 (vs), 1380 (vs), 1260, 750 cm^{-1} (vs) (doubling of C=O and C=C bonds due to presence of s-trans and s-cis-trans enone). Anal. ($C_{15}H_{19}NO$) C, H. N.

Preparation of 2,3-Dihydro-1,2-dimethyl-2-(methyl 2-buten-4-oate)-1*H*-indole (11). *N*-Methyl-2-(2-methyl-2-propenyl)aniline (116.4 mg, 0.72 mmol) was dissolved in 10 mL of THF. $PdCl_2(CH_3CN)_2$ (187.5 mg, 0.72 mmol) was added and the reaction mixture stirred for 5 min, giving an orange, homogeneous solution. Triethylamine (146.3 mg, 1.44 mmol, 0.2 mL) was added dropwise and the solution stirred for 0.5 hr. Methyl acrylate (622.4 mg, 7.23 mmol, 0.65 mL) was added followed by 15 drops of a dilute iodine solution (made by dissolving two crystals of iodine in 1 mL of THF). The solution was then heated at reflux for 18 h and filtered and the solvent removed under reduced pressure. The product was isolated by preparative TLC (SiO_2, 4:1 petroleum ether/ether). Compound A (R_f 0.52) is *cis*-**11** (32 mg, 18%): NMR ($CDCl_3$) δ 1.25 (s, 3, CH_3), 2.7 (s, 3, NCH_3), 2.75–3.4 (m, 4, CH_2), 3.75 (s, 3, OCH_3), 5.72 (d, J = 12 Hz, 1, cis CH=CHCO), 5.90–7.0 (m, 5, ArH, CH=CHCO); IR (neat) 3060, 3030, 2960, 2930, 2875, 2810, 1730 (vs, CO, ester), 1650 (C=C), 1610, 1490, 1200, 1175, 750 cm^{-1}. Anal. ($C_{15}H_{19}NO_2$) C, H, N. Compound B (R_f 0.31, 100 mg, 57%) was assigned as *trans*-**11** by NMR and IR: NMR ($CDCl_3$) δ 1.23 (s, 3,CH_3), AB quartet, δ_A 2.2, δ_B 2.6 (J_{AB} = 16 Hz, 2, CH_2C=C), 2.65 (s, 3, NCH_3), AB quartet, δ_A 2.52, δ_B 2.80 (J_{AB} = 16 Hz, 2, $PhCH_2$), 3.75 (s, 3, OCH_3), 5.72 (d, J = 17 Hz, 1, trans CH=CHCO), 6.1–7.2 (m, 5, ArH and CH=CHCO); IR (neat) 3080, 3060, 2980, 2960, 2890, 2820, 1730 (CO, ester), 1655 (C=C), 1615, 1490, 1200, 1180, 750 cm^{-1}. Anal. ($C_{15}H_{19}NO_2$) C, H, N.

Preparation of 2,3-Dihydro-2-methyl-2-(methyl 2-buten-4-oate)-1*H*-indole (12). 2-(2-Methyl-2-propenyl)aniline (82.3 mg, 0.56 mmol), $PdCl_2(CH_3CN)_2$ (145.2 mg, 0.56 mmol), and Na_2CO_3 (118.6 mg, 1.12 mmol) in 20 mL of THF were heated at reflux for 1 h. The solution was cooled and methyl acrylate (0.5 mL, 482.0 mg, 5.6 mmol) was added, followed by a dilute I_2 solution. This mixture was heated at reflux overnight and filtered and the solvent removed under reduced pressure. The product was isolated by preparative layer TLC (SiO_2, 2:1 petroleum ether/ether). The R_f 0.43 band contained the product (88.0 mg, 68%): NMR ($CDCl_3$) δ 1.40 (s, 3, CH_3), 2.46 (d, J = 8 Hz, 2, C=CCH_2), 2.86 (s, 2, benzylic CH_2), 3.73 (s, 3, CH_3O), 5.86 (d, J = 16 Hz, 1, trans CH=CHCO), 6.48–7.3 (m, 5, CH=CHCO, ArH); IR (neat) 3255 (m, N-H), 3045 (w), 2950 (m), 1740 (s, C=O), 1652 (m), 1619 (s), 1485 (s), 1463 (s), 1433 (m), 1399 (w), 1375 (w), 1335 (m), 1320 (m), 1265 (s), 1196 (s), 1170 (s), 1145 (m), 982 (m), 745 cm^{-1} (s). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

Preparation of *N*-Acryloylaniline. Aniline (0.49 mL, 500 mg, 5.4 mmol) was dissolved in 75 mL of ether. Pyridine (0.8 mL, 785 mg, 9.9 mmol) was added and the solution cooled to 0 °C. The reaction mixture was stirred for 10 min at 0 °C and acryloyl chloride (0.44 mL, 485.9 mg, 5.3 mmol) was added dropwise. After a few drops a white precipitate formed. The reaction mixture was stirred for 10 min at 0 °C, allowed to warm to room temperature, and then stirred for 4 h. The ether solution was washed (2 × 10 mL) with dilute Na_2CO_3, dried

over $MgSO_4$, and filtered. The solvent was removed under reduced pressure giving a pink solid. Recrystallization from toluene gave a pink solid (441.9 mg, 56%): NMR ($CDCl_3$) δ 5.68 (m, 1, C=CHCO), 6.33 (m, 2, COCH=CH_2), 7.4 (m, 5, ArH), 8.1 (br s, 1, O=CNH): IR (KBr) 3300 (s, N-H), 3220 (s, C-H), 3120 (s, CH), 1670 (s, C=O), 1610 (s), 1550 (s), 1500 (s), 1445 (s), 1410 (s), 1330 (s), 1254 (s), 1200 (s), 1065 (m), 985 (m), 955 (m), 945 (m), 940 (m), 895 (m), 839 (m), 790 (m), 750 (s), 680 cm^{-1} (s). Anal. (C_9H_9NO) C, H, N.

Preparation of 2,3-Dihydro-2-methyl-2-(*N*-phenylbut-2-en-4-amide)-1*H*-indole (13). 2-(2-Methyl-2-propenyl)aniline (49.1 mg, 0.33 mmol), $PdCl_2(MeCN)_2$ (84.9 mg, 0.33 mmol) and Na_2CO_3 (69.3 mg, 0.65 mmol) in THF were heated at reflux for 1.5 h. The solution was cooled to room temperature and *N*-acryloylaniline (57.8 mg, 0.39 mmol) added. The solution was then heated at reflux overnight and filtered, and the solvent was removed under reduced pressure. The product (32.9 mg, R_f 0.55, 34.5%) was isolated by preparative TLC (SiO_2, 4:1 benzene/methanol): NMR ($CDCl_3$) δ 1.20 (s, 3, CH_3), 2.34 (d, J = 8 Hz, 2, C=CCH_2), 2.75 (s, 2, $PhCH_2$), 3.39 (s, 1, NH), 5.92 (d, J = 15 Hz, 1, trans CH=CHCO), 6.42-7.78 (m, 10, ArH, CH=CHCO); ^{13}C NMR ($CDCl_3$) 26.85 (CH_3), 42.46, 44.5 (benzylic CH_2, allylic CH_2), 62.33 (NC<), 108.24, 119.80, 124.08, 124.69, 127.2, 127.46, 128.70, 137.77, 141.00, 149.62 (11 protonated sp^2 C), 163.62 ppm (C=O); IR (neat) 3310 (br s, N-H), 3145 (w), 3060 (m), 3030 (m), 2980 (m), 2940 (m), 1680 (s, C=O), 1650 (s), 1620 (s), 1554 (s), 1509 (s), 1495 (s), 1470 (m), 1450 (s), 1381 (m), 1362 (m), 1265 (s), 755 cm^{-1} (s). Anal. ($C_{19}H_{20}N_2O$) C, H, N.

Preparation of *N*-Acryloyl-2-(2-methyl-2-propenyl)aniline (14). 2-(2-Methyl-2-propenyl)aniline (70.3 mg, 0.48 mmol) was dissolved in 10 mL of ether. Pyridine (49.1 mg, 0.62 mmol) was added and the solution cooled to 0 °C. The reaction mixture was stirred for 5 min and acryloyl chloride (43.3 mg, 0.48 mmol) dissolved in 1 mL of ether was added dropwise. A white precipitate formed immediately. The reaction mixture was then warmed to room temperature and stirred for 4 h. The precipitate dissolved giving a pale yellow solution, which was washed with 3 × 10 mL of dilute Na_2CO_3. The ether extract was dried over $MgSO_4$ and the solvent removed under reduced pressure, giving a yellow solid (71.3 mg, 74%): IR (KBr) 3280 (s, N-H), 1660 (s, C=O), 1630 (m, aromatic), 1590 (m), 1530 (s), 1450 (s), 1410 (m), 1310 (m), 1250 (m), 1205 (m), 1000 (m), 950 (m), 890 (m), 800 (m), 750 (s), 735 cm^{-1} (m); NMR ($CDCl_3$) δ 1.7 (s, 3, CH_3C=C), 3.32 (s, 2, $PhCH_2$), 4.83 (m, 2, -C=CH_2), 5.7 (m, 1, CH=CHCO), 6.21 (m, 2, CH_2=CHCO), 7.13 (m, 3, ArH), 7.50 (br s, 1, NH), 7.95 (m, 1, ArH). Anal. ($C_{13}H_{15}NO$) C, H, N.

Intramolecular Cyclization and Insertion of *N*-Acryloyl-2-(2-methyl-2-propenyl)aniline. Compound **14** (43.7 mg, 0.21 mmol) was dissolved in 15 mL of THF. $PdCl_2(CH_3CN)_2$ (56.4 mg, 0.21 mmol) was added and the solution stirred for 5 min giving an orange, homogeneous solution. Na_2CO_3 (23.0 mg, 0.21 mmol) was added, the solution stirred overnight, then brought to reflux and stirred for an additional 1 day at reflux. After cooling and filtering, the solvent was removed under reduced pressure giving a brown solid. Preparative layer chromatography yielded 23.7 mg (54.8%) of **15a** (R_f 0.63) and 16.6 mg (38.5%) of **15b** (R_f 0.54).

15a: NMR ($CDCl_3$) δ 1.42 (s, 3, CH_3CN), 1.88 (d, J = 2 Hz, 3, CH_3C=C), AB quartet, δ_A 2.10, δ_B 3.10 (J_{AB} = 16 Hz, 2, $PhCH_2$), 6.88 (d, J = 2 Hz, 1, CH=CCH_3), 7.1-7.5 (m, 4, ArH); IR (neat) 2960 (m, CH), 2930 (m, CH), 2860 (m, CH), 1702 (s, C=O), 1605 (m), 1480 (m), 1460 (m), 1355 (s), 760 cm^{-1} (m). Anal. ($C_{13}H_{13}NO$) C, H, N.

15b: NMR ($CDCl_3$) δ 1.35 (s, 3, CH_3CN), 2.89 (t, J = 2 Hz, 2, CH_2C=CH), AB quartet, δ_A 2.95, δ_B 3.20 (J_{AB} = 16 Hz, 2, $PhCH_2$), 5.45 (t, J = 2 Hz, 1, CH=CCO), 6.10 (t, J = 2.5 Hz, 1, CH=CCO), 7.20 (m, 3, ArH), 7.80 (m, 1, ArH); IR (neat) 2970 (m, CH), 2930 (m, CH), 2860 (m, CH), 1702 (s, C=O), 1660 (m), 1610 (m), 1485 (s), 1400 (s), 1315 (m), 1265 (m), 755 cm^{-1} (m). Anal. ($C_{13}H_{13}NO$) C, H, N.

Preparation of *N*-Methacryloyl-2-(2-methyl-2-propenyl)aniline (16). 2-(2-Methyl-2-propenyl)aniline (88.2 mg, 0.6 mmol) was dissolved in 15 mL of ether. Pyridine (57.0 mg, 0.72 mmol) was added and the solution cooled to 0 °C. Freshly distilled methacryloyl chloride (58 mL, 62.7 mg, 0.6 mmol) was added and a white precipitate formed immediately. The solution was stirred for 1 day. The ether solution was washed with 3 × 10 mL of dilute Na_2CO_3, dried over $MgSO_4$, and filtered. The ether was removed under reduced pressure, giving a colorless oil (131.6 mg, 100%): NMR (CCl_4) δ 1.7 (s, 3, CH_3), 1.96 (d, J = 1 Hz, 3, CH_3C=C), 3.28 (s, 2, $PhCH_2$), 4.7 (m, 2, C=CH_2), 5.30 (m, 1, CH=CCO), 5.65 (m, 1, CH=CCO), 7.05 (m, 3, aromatic), 7.65 (s, 1, NH), 8.05 (m, 1, ArH); IR (neat) 3380 (s, NH), 3080 (m), 2980 (s), 2940 (s), 1745 (s, C=O), 1690 (s), 1590 (s), 1525 (br), 1450 (s), 1380 (s), 1295 (s), 1250 (s), 1180 (s), 1110 (m), 1095 (m), 1050 (s), 991 (s), 890 (s), 750 cm^{-1} (s). Anal. ($C_{14}H_{17}NO$) C, H, N.

Cyclization and Insertion of *N*-Methacryloyl-2-(2-methyl-2-propenyl)aniline. *N*-Methacryloyl-2-(2-methyl-2-propenyl)aniline (65.5 mg, 0.30 mmol), $PdCl_2(CH_3CN)_2$ (79.0 mg, 0.3 mmol), and Na_2CO_3 (32.3 mg, 0.3 mmol) were heated at reflux in 10 mL of THF for 45 min. To the hot solution was added 15 drops of a dilute iodine solution (two small crystals in 1 mL of THF). The reaction mixture was then heated at reflux overnight. The resulting black solution was filtered and the solvent removed under reduced pressure. Purification by preparative layer chromatography (silica gel, 1:1 hexane/ether, twice, R_f 0.25) gave 10 mg (14%) of **17**: NMR (CCl_4) δ 1.22 (s, 3, CH_3), 2.00 (d, J = 1 Hz, 3, C=CCH_3), 2.5 (m, 2, C=CCH_2), 2.96 (s, 2, $PhCH_2$), 5.78 (s, 1, C=CH-), 7.1 (m, 3, aromatics), 8.2 (m, 1, aromatic). Anal. ($C_{14}H_{15}NO$) C, H, N.

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