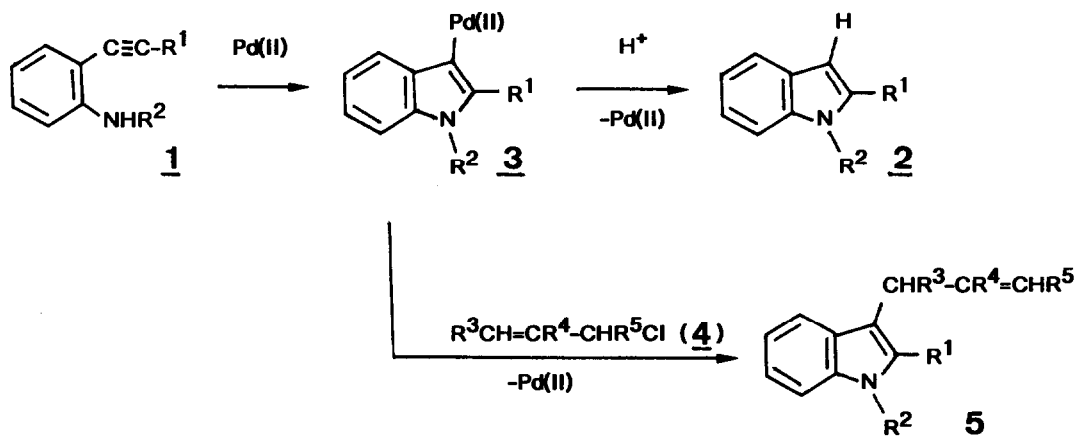


**PALLADIUM CATALYZED REACTION OF 2-ALKYNYLANILINES WITH ALLYL CHLORIDES.
 FORMATION OF 3-ALLYLINDOLES**

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Summary: Pd(II) catalyzed reaction of N-carbomethoxy-2-alkynylanilines with allyl chlorides produces 2-alkyl-3-allyl-N-carbomethoxyindoles in the presence of oxiranes; Aminopalladation of a N-carbomethoxy-2-alkynylaniline gives 3-(N-carbomethoxyindolyl)palladium intermediate, which regioselectively attacks on the γ position of allyl chlorides to give 3-allyl-2-alkylindoles with concurrent regeneration of Pd(II) catalyst.

Palladium catalyzed organic reactions of olefinic as well as aromatic substrates have been extensively studied and utilized as powerful tool in organic synthesis.^{1,2,3} Palladium-catalyzed reactions utilizing acetylenic substrates, on the other hand, have been little reported,⁴ until recently reported intramolecular amino- or oxy-palladation affording various heterocycles as well as the reactions of intermediary vinylpalladium species.⁵⁻⁸ Although preparation of pyrroles from alkynylamines⁸ has induced analogous cyclization of alkynylanilines into indoles,^{9,10,13} allylative cyclization^{14,15} of alkynylamines into allylated heterocycles has been little studied. This paper describes novel preparation of N-carbomethoxy-3-allyl-2-alkylindoles by the reaction of N-carbomethoxy-2-alkynylanilines with allyl chlorides under palladium catalysis.



2-Alkynylanilines are easily prepared by several methods; Reaction of N-benzyl-N-trimethylsilyloxylaniline with trialkynylaluminum,¹² treatment of ortho-selectively thallated N-acylanilines with alkynylcopper reagents,⁹ and reaction of ortho-iodoaniline with 1-alkynes.¹⁶

Treatment of 2-hexynylaniline (**1**, $R^1 = \text{Bu}$, $R^2 = \text{H}$) with PdCl_2 in refluxing MeCN afforded 2-butylindole (**2**, $R^1 = \text{Bu}$, $R^2 = \text{H}$) in 81% yield. Use of $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ as catalyst afforded the same product in better yield. N-Substituted anilines also reacted analogously to give N-substituted indoles in good yields. Combination of substituents, catalysts, and yields of the products are summarized in Table 1.¹⁷

Table 1. Indoles **2** from Alkynylanilines **1**

| Entry | R^1 | R^2 | Catalyst ^a | Solvent | Temp | Time (h) | Yield (%) |
|-------|------------------------|-------|------------------------------|---------|--------|----------|-----------------|
| 1 | Bu | H | PdCl_2 | MeCN | reflux | 1 | 81 |
| 2 | ^t Bu | H | PdCl_2 | MeCN | reflux | 0.5 | 77 |
| 3 | CH(Me)Hex | H | PdCl_2 | MeCN | reflux | 0.5 | 83 |
| 4 | Ph | H | PdCl_2 | MeCN | reflux | 0.5 | 52 |
| 5 | Me_3Si | H | PdCl_2 | MeCN | reflux | 16 | -- ^b |
| 6 | Bu | Ac | PdCl_2 | MeCN | reflux | 4 | 74 |
| 7 | Bu | COOMe | PdCl_2 | MeCN | reflux | 2 | 78 |
| 8 | Bu | H | $\text{NaAuCl}_4^{\text{c}}$ | THF | r.t. | 2 | 87 |
| 9 | ^t Bu | H | NaAuCl_4 | THF | reflux | 0.5 | 90 |
| 10 | Ph | H | NaAuCl_4 | THF | r.t. | 0.5 | 62 |
| 11 | Me_3Si | H | NaAuCl_4 | THF | reflux | 3 | 31 |
| 12 | CH(Me)Hex | H | NaAuCl_4 | THF | r.t. | 45 | 87 |
| 13 | Bu | Ac | NaAuCl_4 | THF | reflux | 1 | 88 |
| 14 | Bu | COOMe | NaAuCl_4 | THF | reflux | 1 | 72 |

a) Employed 0.05 equiv of catalyst. b) Recovery of starting material.

c) $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ was used.

As indole formation could be explained by the protonolysis of the intermediary 3-indolypalladium (**3**) or 3-indolylaurate species, effective use of the intermediates for organic synthesis was examined. We have already shown the coupling reaction of allyl chlorides with oxygen or nitrogen substituted vinylpalladium species prepared by intramolecular addition of alcohol or amine to acetylenes.^{14,15} Analogous to these vinylpalladium species, 3-indolypalladium species (**3**) are conceivable to react with allyl chlorides (**4**) regioselectively on γ -position. When above described indole formations from 2-alkynylanilines (**1**, $R^2 = \text{COOMe}$) are carried out in the presence of allyl chlorides (**4**) and methyloxirane under the catalytic action of $\text{PdCl}_2(\text{MeCN})_2$, N-carbomethoxy-3-allyl-2-alkylindoles (**5**, $R^2 = \text{COOMe}$) are obtained in good yields.¹⁸ Results are summarized in Table 2.

Trap of the intermediary organopalladium species without oxiranes afforded fruitless results. Effective work of oxiranes as proton scavenger has been reported in the coupling of allyl chlorides with 3-furylpalladium intermediate.¹⁹ When the reaction was carried out without methyloxirane (Table 2, entry 2), about 30% of allylated product and 20-35% of protonated one

were obtained. The reaction employing KOAc, in place of methyloxirane, did not give any cyclized product. Application of proton sponge as proton scavenger also resulted recovery of the starting material.

In contrast to the successful cyclization of 2-alkynylanilines (**1**) to give indoles (**2**) by NaAuCl₄ catalysis, trapping of the assumed intermediary 3-indolyaurate with allyl chlorides was unsuccessful even using oxiranes as proton scavenger; 2-alkylindole (**2**) was obtained mainly and allylated one (**5**) was isolated only a few yield.

Table 2. 3-Allylindole (**5**) by Allylative Cyclization of Alkynylaniline (**1**)

| Entry | R ¹ | R ² | Allyl Chloride 4 | Reaction Conditions | | Yield (%) | |
|-------|----------------------|----------------|-----------------------------------------------------|---------------------|----------|-----------------|-----------------------------------|
| | | | | Temp | Time (h) | 5 | 2 |
| 1 | Bu | H | H ₂ C=CHCH ₂ Cl | reflux | 1 | 15 ^a | 21 ^b (59) ^c |
| 2 | Bu | Ac | H ₂ C=CHCH ₂ Cl | reflux | 9 | 51 | 5 |
| 3 | Bu | COOMe | H ₂ C=CHCH ₂ Cl | r.t. | 20 | 73 | 5 |
| 4 | Bu | COOMe | H ₂ C=CHCHMeCl | r.t. | 5.5 | 80 ^d | 5 |
| 5 | Bu | COOMe | H ₂ C=OMeCH ₂ Cl | r.t. | 2.5 | 74 | 12 |
| 6 | Bu | COOMe | MeCH=CHCH ₂ Cl | r.t. | 48 | 69 | 10 |
| 7 | Bu | COOMe | H ₂ C=CHCHEtCl | r.t. | 72 | 31 | 6 |
| 8 | Bu | COOMe | H ₂ C=CHCH(Cl)CH ₂ Cl | r.t. | 1 | 71 ^e | 6 |
| 9 | Bu | COOMe | H ₂ C=C(Cl)CH ₂ Cl | r.t. | 20 | 52 | 9 |
| 10 | Bu | COOMe | ClCH ₂ CH=CHCH ₂ Cl | r.t. | 5 | 51 | 20 |
| 11 | Bu | COOMe | H ₂ C=C(CH ₂ Cl) ₂ | r.t. | 1 | 72 | 9 |
| 12 | ^t Bu | COOMe | H ₂ C=CHCH ₂ Cl | reflux | 5 | 33 | 5 |
| 13 | Ph | COOMe | H ₂ C=CHCH ₂ Cl | r.t. | 48 | 82 | 0 |
| 14 | Ph | COOMe | H ₂ C=CHCH ₂ Cl | reflux | 0.5 | 82 | 0 |
| 15 | H ₂ C=OMe | COOMe | H ₂ C=CHCH ₂ Cl | reflux | 5 | 47 | 0 |
| 16 | HexCH(Me) | COOMe | H ₂ C=CHCH ₂ Cl | r.t. | 20 | 81 | 8 |
| 17 | Bu | COOMe | H ₂ C=CHCH=CHCH ₂ Cl | reflux | 1 | 30 ^f | 22 |

a) Obtained N-allylated product. b) 2-Butylindole. c) N-Allyl-2-butylindole.

d) E/Z Ratio is 77/23. e) A mixture of E- and Z-isomer. f) 3-(2,4-Pentadienyl)-2-butylindole was obtained.

Coupling of the 3-indolypalladium intermediates with bromoethene afforded unsatisfactory results; Reaction of N-carbomethoxy-2-hexynylaniline with bromoethene in the presence of 2,2-dimethyloxirane under PdCl₂(MeCN)₂ catalysis afforded mainly N-carbomethoxy-2-butylindole accompanied by a trace amount of N-carbomethoxy-2-butyl-3-vinylindole.

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- 17) Typical procedure for cyclization; To an acetonitrile solution of 2-hexynylaniline (173 mg, 1 mmol in 5 mL solution), PdCl₂ (13 mg, 0.05 mmol) was added under argon atmosphere, and the whole was heated under reflux for 1 h. The reaction mixture was poured onto ice-water and extracted with ethyl acetate. Organic layer was washed with sat. NaCl, dried over Na₂SO₄, and concentrated. Chromatography (silica gel/hexane-ethyl acetate) of the crude product gave 140 mg (81% yield) of 2-butyldiole.
- 18) Typical procedure for allylative cyclization; To a THF solution of N-carbomethoxy-2-hexynylaniline (230 mg, 1 mmol in 5 mL solution), methyloxirane (0.73 mL, 10 mmol) and 3-chloro-1-propene (1.7 mL, 10 mmol), PdCl₂(MeCN)₂ (13 mg, 0.05 mmol) are added under argon atmosphere, and the whole was stirred overnight at room temperature. Aqueous workup, extraction with ether, concentration, and chromatographic purification (silica gel) of the reaction mixture gave N-carbomethoxy-3-allyl-2-butyldiole (210 mg, 73% yield) and N-carbomethoxy-2-butyldiole (5% yield). Analogous results are obtained by the use of 2,2-dimethyloxirane, in place of methyloxirane.
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