SYNTHESIS OF CONDENSED HETEROAROMATIC COMPOUNDS USING PALLADIUM-CATALYZED REACTION

Takao Sakamoto, Yoshinori Kondo, and Hiroshi Yamanaka*

Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

Abstract———The authors summarize the palladium-catalyzed synthesis of the key intermediates to condensed heteroaromatic rings such as indole, quinoline, isoquinoline, and their aza-analogs and also describe the palladium-catalyzed cyclization to condensed heteroaromatics.

CONTENTS

1. Introduction

One of the main methods to synthesize benzene-condensed heteroaromatics is the cyclization of monofunctional benzene derivatives. Fischer indole synthesis,[1] Bischler-Napieralski isoquinoline synthesis,[2] and Skraup quinoline synthesis[3] are representatives of this method. Although these cyclizations proceed smoothly in the carbocyclic aromatics such as benzene or naphthalene, the application of these cyclizations to synthesize aza- and diaza-analogs meets with some difficulties, because these cyclizations proceed by electrophilic reaction, and π-deficient nitrogen-heteroaromatics such as pyridines or pyrimidines in general have not enough reactivity toward electrophilic substitutions.

On the other hand, Reissert indole synthesis,[1] Friedländer quinoline synthesis,[4] and isoquinoline synthesis from homophthalic acid derivatives contain the cyclizations between two functional groups on the ortho-position of benzene ring. These cyclizations are considered to be independent of the electronic character of the parent nuclei.

Accordingly, the development of versatile synthesis for ortho-bifunctional heteroaromatics such as pyridine or pyrimidine derivatives, will provide a convenient way to the construction of aza- and diaza-analogs of indole, quinoline, or isoquinoline derivatives by cyclization. Classically established reactions, however, are not always pertinent to synthesize the starting compounds necessary for this subject. Recently, the progress of the palladium-catalyzed carbon-carbon bond formation in the field of aromatic and heteroaromatic chemistry[5] is removing the restriction as described above.

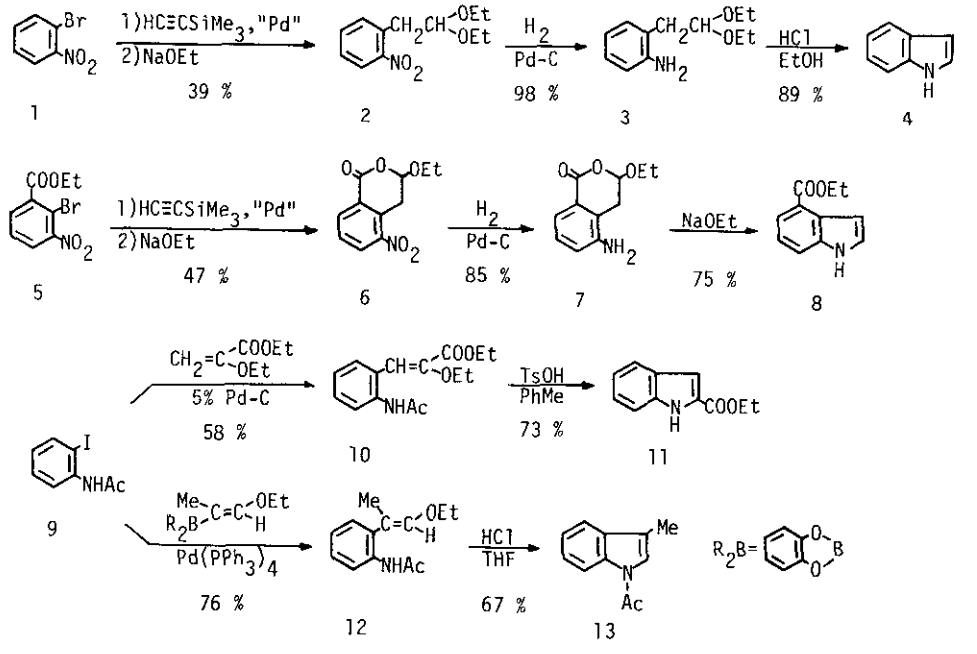
In this review, we summarize the palladium-catalyzed synthesis of key intermediates to the condensed heteroaromatic rings and the cyclization of the intermediates thus obtained as main subjects together with the palladium-catalyzed cyclizations leading directly to condensed heteroaromatics. The synthesis of monocyclic

and non-aromatic heterocycles by use of transition metals is omitted from this review, because the review dealing with this subject has been reported.[6]

2. Synthesis of Pyrrole-Condensed Heteroaromatics

2.1 Indoles from 2-Halonitrobenzenes

Intermediates of Reissert indole synthesis,[1] i.e. 2-nitrophenylacetaldehydes or 2-nitrobenzyl ketones, can be synthesized from 2-nitrotoluenes. Recently, a facile synthesis of 2-nitroarylacetaldehyde equivalent derivatives is achieved by using the condensation of 2-nitrotoluenes with dimethylformamide dimethyl acetal.[7] On the other hand, the intermediates of this type to indoles are synthesized from 2-nitro- or 2-aminohalobenzenes by palladium-catalyzed reaction with experimental simplicity. For example, 2-bromonitrobenzene (1) reacts with trimethylsilylacetylene in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine (In this review, this catalytic system is expressed by "Pd" in Schemes.) to yield 2-nitro(trimethylsilylethynyl)benzene which is smoothly converted into 2-(2,2-diethoxyethyl)nitrobenzene (**2**) by treatment with sodium ethoxide.[8] The catalytic reduction of **2** followed by treatment with hydrochloric acid causes intramolecular cylization to give indole (**4**).[9,10] By this method, the synthesis of ethyl indole-4-carboxylate (**8**) from ethyl 2-bromo-3-nitrobenzoate (5)



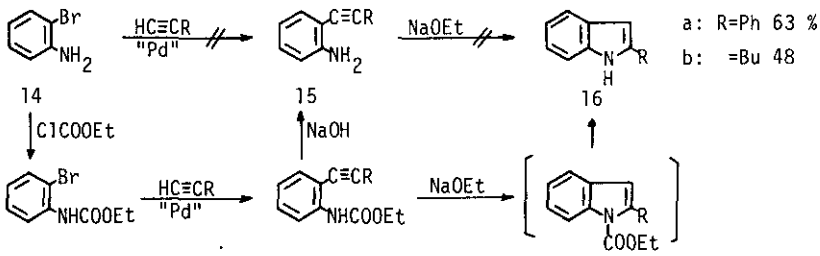
Scheme 1

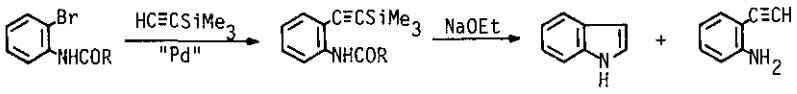
is also accomplished, while the intermediates (6 and 7) have bicyclic structures.[9,10] Indoles containing electron-withdrawing groups at the 6-position, which are difficult to synthesize by Fischer cyclization,[1] are also easily prepared according to a similar manner.[11]

Heck reaction[12] of 2-iodoacetanilide (9) with ethyl 2-ethoxyacrylate is prompted by palladium-charcoal to give ethyl 2-acetylamino-α-ethoxycinnamate (10) which is converted to ethyl indole-2-carboxylate (11) by deprotection.[13] It was also reported that the palladium-catalyzed reaction of 9 with organoborane enol ethers is applicable to synthesize indole derivatives (13) via a similar intermediate (12) to 10.[14]

2.2 Indoles from Ethyl N-(2-Bromophenyl)carbamates

The copper-promoted cyclization of 2-ethynylanilines to indoles has been developed by Castro et al.,[15-19] and the starting materials are synthesized from 2-iodoanilines with copper(I) acetylides. Similar 2-ethynylaniline derivatives are prepared more conveniently by palladium-catalyzed reaction.[20-22] Namely, ethyl N-(2-bromophenyl)carbamate (17a) reacts smoothly with terminal acetylenes in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine, whereas 2-bromoaniline (14) does not. Ethyl N-(2-ethynylphenyl)-carbamates (18) thus obtained are easily converted to 2-subtstituted indoles (16) by treatment with sodium ethoxide. Among N-acyl-2-bromoanilines (17) tested,



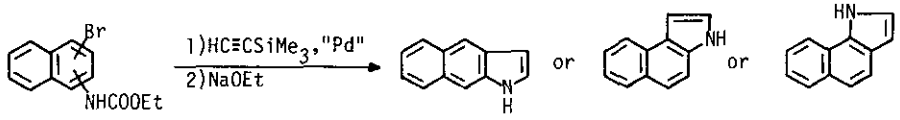


17		20	4	21
	a: R=OEt	77 %	93 %	0 %
	b: =H	45	17	52
	c: =Me	61	34	39
	d: $=CMe_3$	51	17	0
	e: =Ph	50	51	9

Scheme 2

ethyl N-(2-bromophenyl)carbamate (**17a**) is proved to be the most favorable substrate not only to the palladium-catalyzed condensation with acetylenes but also to the subsequent indole cyclization as listed in Scheme 2.[21]

In connection with the reaction pathway from **18** to indoles (**16**), 1-ethoxycarbonylindoles (**19**) are assumed to be likely intermediates, because the 2-ethynylanilines (**15**) prepared by the alkaline hydrolysis of **18** never cyclize to **16** under the basic conditions.[21] Using this method, the synthesis of three kinds of benzindoles (**23-25**) from the corresponding bromonaphthylcarbamates (**22**) has been reported,[23] while the synthesis of the linear compound (**23**) by Fischer indole cyclization is difficult.[24]

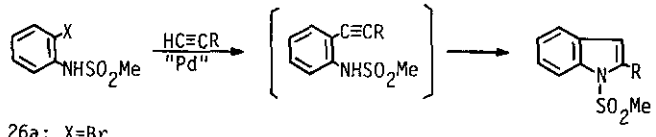


22 — 23: 48 % — 24: 54 % — 25: 53 %

Scheme 3

2.3 Indoles from N-(2-Halophenyl)methanesulfonamides

When N-(2-bromophenyl)- (**26a**) and N-(2-iodophenyl)methanesulfonamide (**26b**) are heated with terminal acetylenes in the presence of the palladium catalyst, the ethynyl intermediates (**27**) spontaneously cyclize to 1-methylsulfonylindoles (**28**).[22] The reaction of the corresponding 2-iodo derivative (**26b**) proceeds so smoothly that the reaction is convenient for the introduction of a carbon functional group into the 2-position of indole nucleus.



26a: X=Br
26b: =I

27 — 28

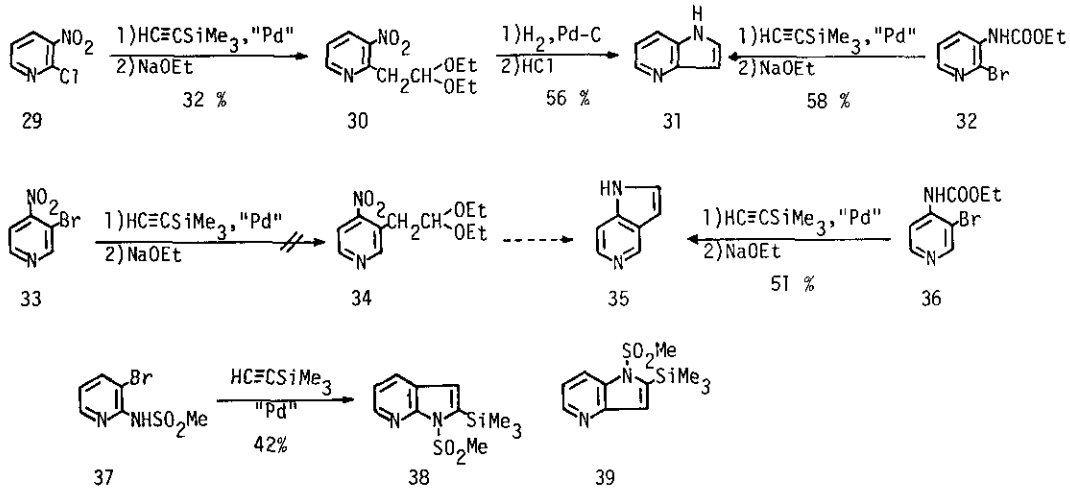
R=	X=Br:	X=I:
Ph	20 %	66 %
Bu	43	64
$SiMe_3$	58	31
CH_2OH	0	53
$(CH_2)_2OH$	47	59
CH_2OMe	12	71
$CH(OEt)_2$	0	63
$(CH_2)_2COOEt$	49	43

Scheme 4

2.4 Pyrrolopyridines

Pyrrolopyridines are synthesized by the application of the three methods described above to appropriate halopyridine derivatives. For example, the palladium-catalyzed reaction of 2-chloro-3-nitropyridine (**29**) with trimethylsilylacetylene followed by treatment with sodium ethoxide affords 2-(2,2-diethoxyethyl)-3-nitropyridine (**30**) which is derived to pyrrolo[3,2-c]pyridine (**31**).[10]

Since 4- and 2-nitropyridine derivatives are unstable under alkaline conditions, the reaction product of 3-bromo-4-nitropyridine (**33**) with trimethylsilyacetylene is not convertible to the desired compound (**34**).[10] On the other hand, ethyl N-(bromopyridine)carbamates (**32** and **36**)[21] and N-(bromopyridine)methanesulfonamides (e.g. **37**)[25] afford the corresponding pyrrolopyridines (**31**, **35**, **38**, and **39**).



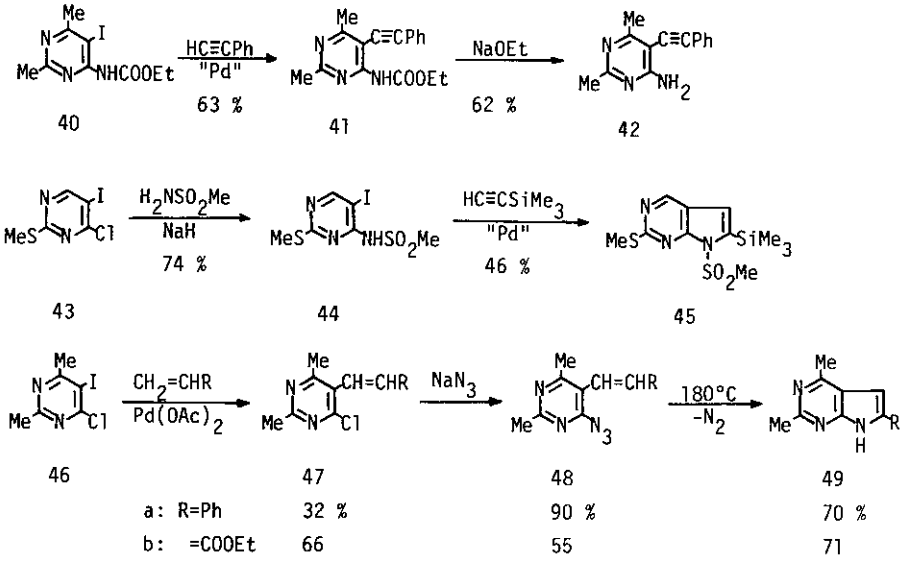
Scheme 5

2.5 Pyrrolopyrimidines

Differently from the synthesis of indoles or pyrrolopyridines, the cyclization of ethyl N-(5-ethynyl-4-pyrimidinyl)carbamate (**41**), prepared from **40**, to the pyrrolopyrimidine (**49a**) does not proceed.[25] On the contrary, the N-(5-iodo-4-pyrimidinyl)methanesulfonamide (**44**) is transformed to the pyrrolo[2,3-d]pyrimidine (**45**), where **44** is prepared by the nucleophilic substitution of the chloropyrimidine (**43**) with methanesulfonamide in place of sulfonylation of 4-amino-5-iodopyrimidines. Pyrrolo[2,3-d]pyrimidines (**45**) are synthesized by an alternative method. Namely, the 4-azido-5-ethenylpyrimidines (**48**) which are prepared by the Heck reaction of the chloroiodopyrimidine (**46**) with olefins and the subsequent reaction with sodium azide, are thermally transformed into **49** via the nitrene intermediates.[25,26]

Concerning the above reaction, it has been known that the photochemical reaction

of 4-azido-5-phenylpyrimidine affords pyrido[4,5-b]carbazole.[27]

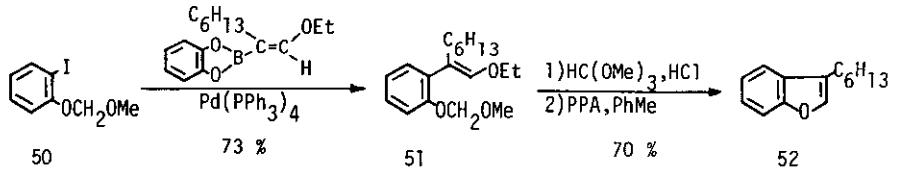


Scheme 6

3 Synthesis of Furan- and Thiophene-Condensed Heteroaromatics

3.1 Furan-Condensed Heteroaromatics

Similar to indole synthesis described in Section 2.1, the synthesis of 3-hexylbenzo[b]furan (**52**) from the 2-iodophenol derivative (**50**) has been reported. Namely, **51** derived by the palladium-catalyzed reaction of **50** with the organoborane derivative cyclizes to **52** in 70 % yield.[14]

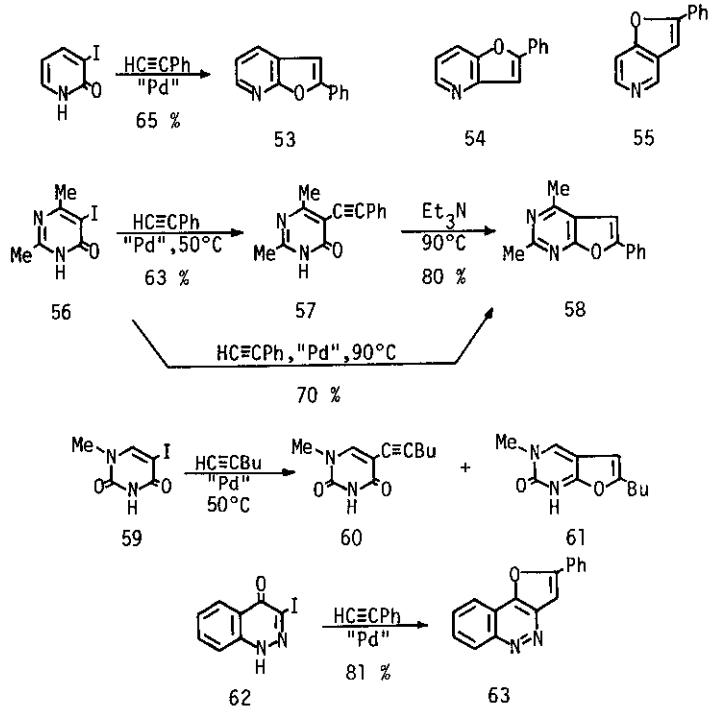


Scheme 7

It was reported[15-17] that the reaction of 2-iodophenol with copper(I) acetylides in dimethylformamide or pyridine affords 2-substituted benzo[b]furans, but the synthesis of benzo[b]furans from 2-halophenols using palladium-catalyzed reaction has not been reported.

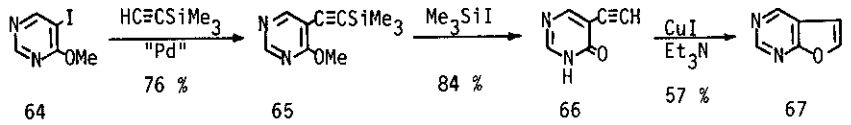
On the other hand, the reaction of 2-, 3-, and 4-pyridinols containing an iodine substituent with phenylacetylene in the presence of the palladium catalyst is accompanied with cyclization to give the corresponding furopyridines (**53-55**).[28] Similar results are observed on the reaction of 5-iodo-2,6-dimethyl-4(1H)-pyrimidinone (**56**),[26] 5-iodo-1-methyluracil (**59**),[29] and 3-iodo-4-cinnolinone (**62**).[30] In

the reaction of **56**, the intermediate (**57**) is isolated, when the reaction is carried out at lower temperature.



Scheme 8

Although the direct synthesis of unsubstituted furo[2,3-d]pyrimidine (**67**) by the palladium-catalyzed reaction of 5-iodo-4(1H)-pyrimidinone results in failure, this subject is accomplished by the reaction starting from 5-iodo-4-methoxypyrimidine (**64**) as illustrated below.[25]



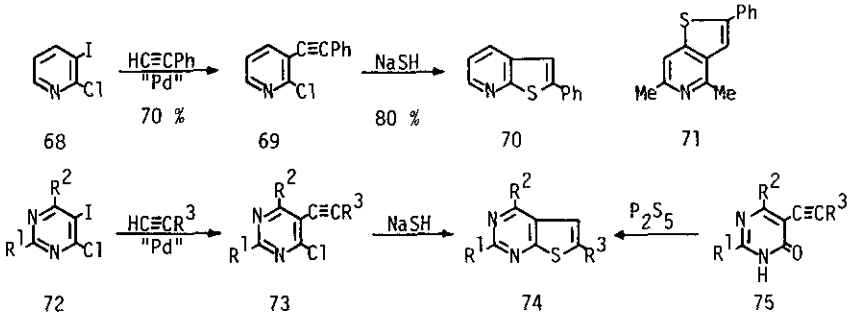
Scheme 9

3.2 Thiophene-Condensed Heteroaromatics

Similar to the synthesis of benzo[b]furans, the reaction of 2-bromothiphenol with copper(I) acetylides gives 2-substituted benzo[b]thiophenes,[31] but no report has been published on the synthesis of benzo[b]thiophenes using palladium-catalyzed reactions.

It is well known[32] that iodides are much better substrates than chlorides in the palladium-catalyzed reactions. Further, the chlorine substituent on the α- and γ-position of π-deficient nitrogen-heteroaromatics is highly reactive to various

nucleophiles.[33] On the basis of these facts, the synthesis of thieno[2,3-b]pyridine,[28] thieno[2,3-d]pyridine,[28] and thieno[2,3-d]pyrimidines[26,28] is accomplished by the palladium-catalyzed reaction as a key step. For example, on treatment with sodium hydrosulfide, 2-chloro-3-phenylethynylpyrimidine (**69**) prepared from 2-chloro-3-iodopyridine (**68**) changed to 2-phenylthieno[2,3-b]pyridine (**70**) in good yield. Furthermore, thieno[2,3-d]pyrimidines (**74**) derived from **72** by a similar manner are alternatively synthesized by the reaction of the 5-ethynyl-4(1H)-pyrimidinones (**75**) with phosphorous pentasulfide.[26]



68 69 70 71

72 73 74 75

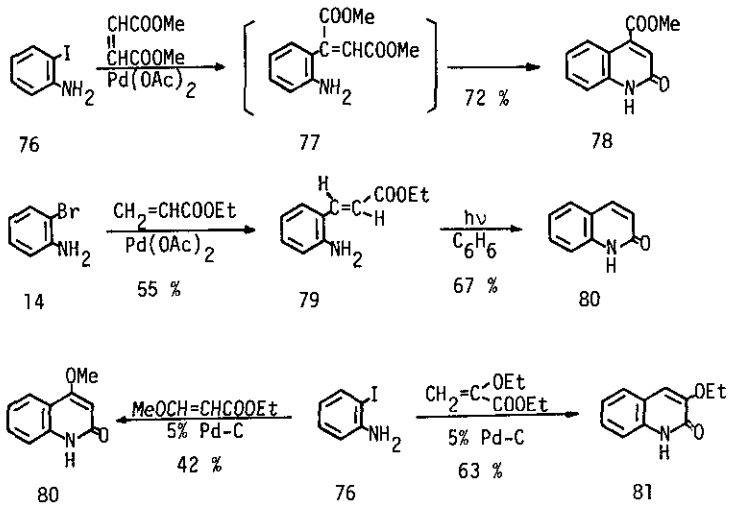
Scheme 10

4. Synthesis of Quinoline-Type Pyridine-Condensed Heteroaromatics

4.1 Quinolines

It is well known that the reduction of 2-nitrocinnamic acid followed by dehydroxycyclization provides 2(1H)-quinolinone. Since the palladium-catalyzed reaction of aryl halides with olefins (Heck reaction), is not retarded or inhibited, differently from the reaction with acetylenes (see Section 2.2), by the presence of an amino group, 2-aminocinnamic acid derivatives can be prepared by Heck reaction of 2-haloanilines. The first example of 2(1H)-quinolinone synthesis in this way is the direct formation of methyl 2-oxo-1,2-dihydroquinoline-4-carboxylate (**78**) in the palladium-catalyzed reaction of 2-iodoaniline (**76**) with dimethyl maleate.[34] Similarly, the reaction of 2-bromoaniline (**14**) with ethyl acrylate affords intermediary ethyl (E)-2-aminocinnamate (**79**) which is transformed into 2(1H)-quinolinone (**80**) under irradiation in moderate yield.[25]

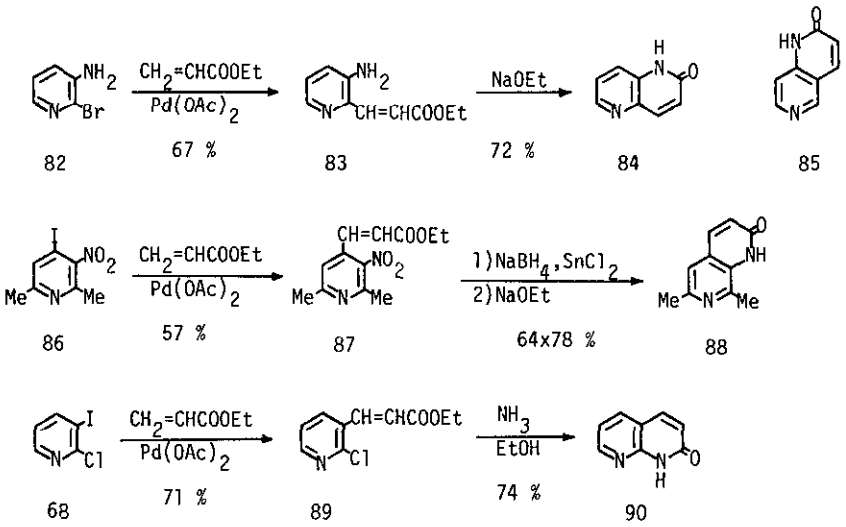
The reactions of 2-iodoaniline (**76**) with ethyl 3-methoxyacrylate or 2-ethoxyacrylate in the presence of 5 % palladium-charcoal are in the same category, and 4-methoxy- (**80**) or 3-ethoxy-2(1H)-quinolinone (**81**) are respectively obtained.[13,25]



Scheme 11

4.2 Carbostyril-Type Naphthyridinones and Related Heteroaromatics

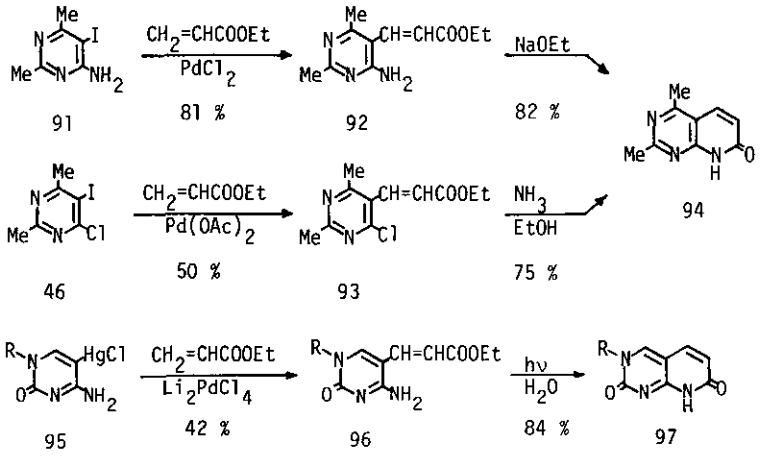
The application of Heck reaction to o-substituted halopyridines opened a way to versatile synthesis of four kinds of naphthyridinones, i.e. 1,5-, 1,6-, 1,7-, and 1,8-naphthyridinones.[35] Namely, ethyl 3-aminopyridine-2-acrylate (**83**) derived from 3-amino-2-bromopyridine (**82**) is transformed into 1,5-naphthyridin-2(1H)-one (**84**) by treatment with sodium ethoxide, and 1,6-naphthyridin-2(1H)-one (**85**) is synthesized by a similar route. 4-Iodo-3-nitro-2,6-dimethylpyridine (**86**) also reacts with ethyl acrylate to give **87** which cyclizes to the 1,7-naphthyridin-



Scheme 12

2(1H)-one (**88**) after the reduction of the nitro group. In the last example shown in Scheme 12, the amino group necessary to cyclization is introduced into ethyl 2-chloropyridine-3-acrylate (**89**), after the Heck reaction of 2-chloro-3-iodopyridine (**68**) with ethyl acrylate. In the cases of π-deficient nitrogen-heteroaromatic compounds containing an active halogen atom, the cyclizations of this type are frequently employed as an alternative method.

According to the procedure described above, the synthesis of the pyrido[2,3-d]-pyrimidinone (**94**) from the 4-amino- (**91**) and 4-chloro-5-iodopyrimidine (**46**) via the pyrimidine-5-acrylates (**92** and **93**) was reported.[36] It was also reported that 5-chloromercuricytidine (**95**) reacts with methyl acrylate in the presence of lithium tetrachloropalladate to give the ethyl (E)-cytidine-5-acrylate (**96**) which is transformed into the pyrido[2,3-d]pyrimidine derivative (**97**) under irradiation.[37]

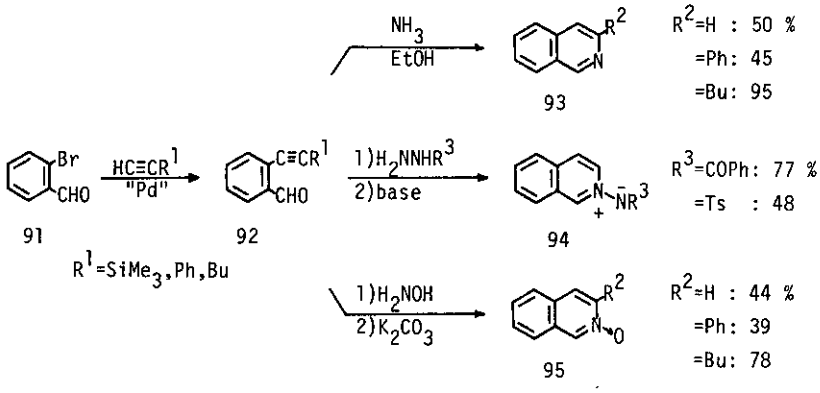


Scheme 13

5. Synthesis of Isoquinoline-Type Pyridine-Condensed Heteroaromatics

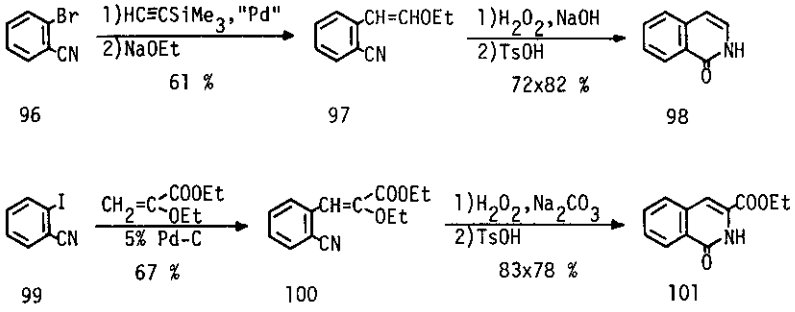
5.1 Isoquinolines and Their N-Oxides

As well as homophthaldehyde derivatives, 2-ethynylbenzaldehydes (**92**) are considered to be favorable substrates for isoquinoline cyclization. In fact, the 2-ethynylbenzaldehydes (**92**) derived from 2-bromobenzaldehyde (**91**) are converted into isoquinolines (**93**) on treatment with ammonia.[25] Further, the condensation of **92** with acylhydrazines and the subsequent intramolecular cyclization with a base gives isoquinoline 2-imides (**94**),[38] and the reaction of **92** with hydroxylamine followed by treatment with potassium carbonate provides isoquinoline 2-oxides (**95**).[39]



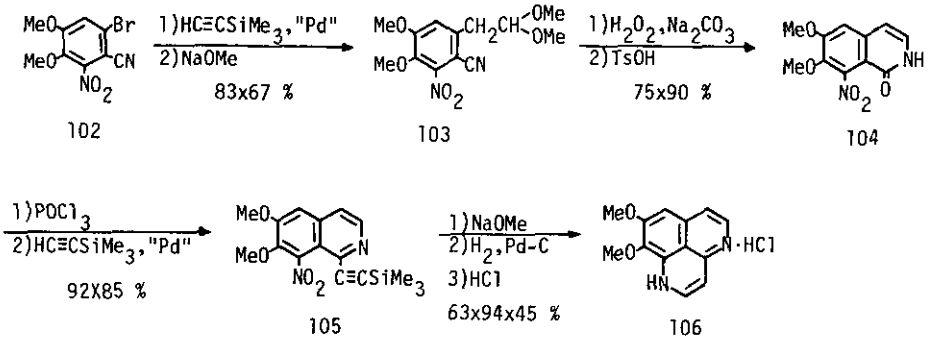
Scheme 14

In addition to the above, the synthesis of 1(2H)-isoquinolinone (**98**) from 2-(2-ethoxyethenyl)benzonitrile (**97**) was reported.[40] In this case, the intermediate (**97**) was prepared from 2-bromobenzonitrile (**96**) by the reaction with trimethylsilylacetylene and the subsequent treatment with sodium ethoxide. The Heck reaction of ethyl 2-iodobenzonitrile (**99**) with ethyl 2-ethoxyacrylate also provides ethyl α-ethoxy-2-cyanocinnamate (**100**) which analogously cyclized to ethyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylate (**101**).[13]



Scheme 15

In an alternative synthesis of aaptamine, a marine alkaloid, the isoquinoline formation mentioned above was employed as a key reaction, which is shown in Scheme 16.[41] The 2-bromobenzonitrile (**102**) is converted to the isoquinolinone (**104**) by an analogous route to synthesize **98** from **96**. After dehydroxychlorination of **104** with phosphoryl chloride, the palladium-catalyzed reaction with trimethylsilylacetylene gives **105** which is derived into aaptamine (**106**) by three steps.



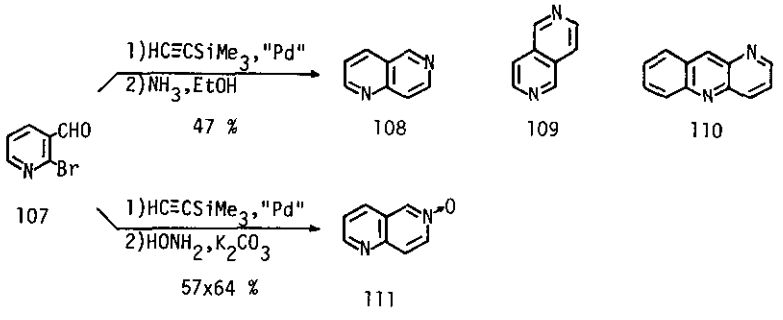
102 103 104 105 106

Scheme 16

5.2 Naphthyridines and Their N-Oxides

The isoquinoline cyclization from 2-ethynylbenzaldehydes described above is also applicable to the synthesis of naphthyridines. For example, the palladium-catalyzed reaction of 2-bromopyridine-3-carbaldehyde (**107**) with trimethylsilylacetylene followed by treatment with ammonia gives 1,6-naphthyridine (**108**).[25] Analogously, 2,7-naphthyridine (**109**) and benzo[b][1,6]naphthyridine (**110**) are obtained from the corresponding haloaldehydes.[25]

The isoquinoline N-oxide cyclization from 2-ethynylbenzaldehyde oximes described in Section 5.1 is used in the unequivocal synthesis of naphthyridine mono-N-oxides such as 1,6-naphthyridine 6-oxide (**111**).[25]



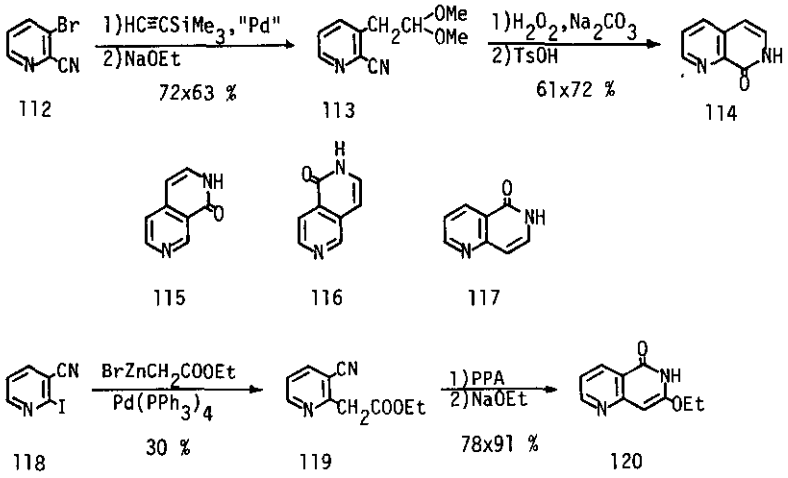
107 108 109 110 111

Scheme 17

5.3 Isocarbostyril-Type Naphthyridinones and Related Heteroaromatics

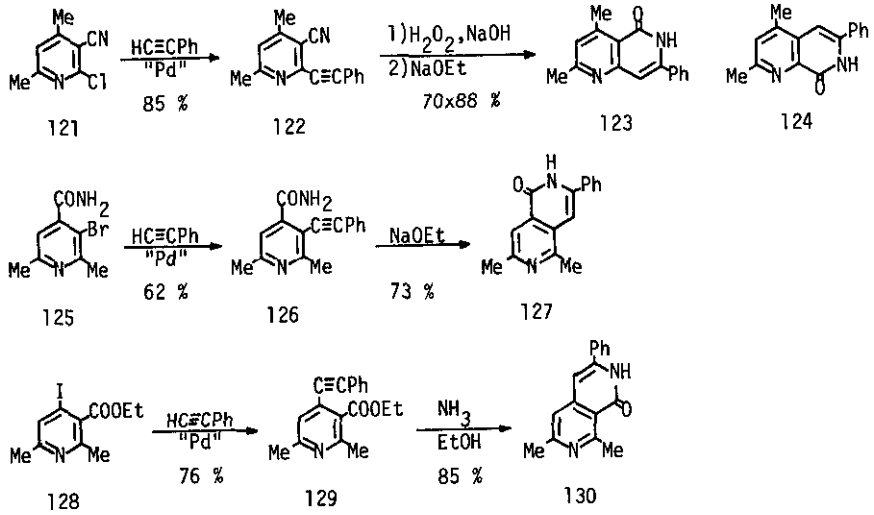
The conversion of 2-ethynylbenzonitrile to 1(2H)-isoquinolinone shown in Scheme 15 is a good model to synthesize isocarbostyril-type naphthyridinones. Thus, the following four kinds of naphthyridinones (**114-117**) are obtained from the corresponding bromopyridinecarbonitriles (e.g. **112**) by the palladium-catalyzed reaction with trimethylsilylacetylene and the subsequent reactions as illustrated in Scheme 21.[40]

Similar to this naphthyridinone synthesis, the application of the palladium-catalyzed reaction of heteroaryl halides with Reformatsky reagent[42] to 2-iodopyridine-3-carbonitrile (**118**) provides ethyl 3-cyanopyridine-2-acetate (**119**) which is reasonably transformed into 7-ethoxy-1,6-naphthyridin-5(6H)-one (**120**).[25]



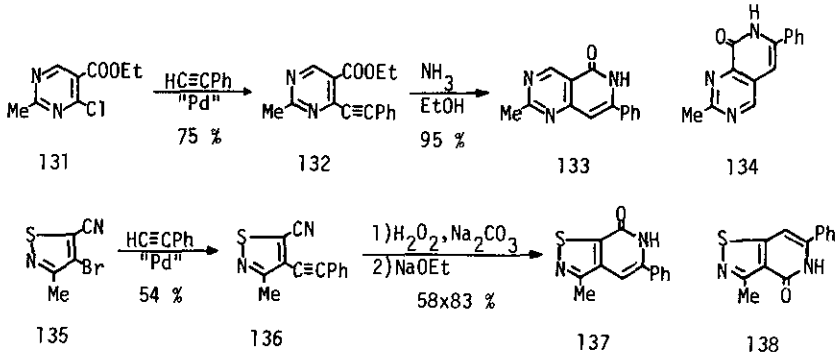
Scheme 18

A very close method to the above naphthyridine synthesis was reported,[40] that is, the 2-phenylethynylpyridine-3-carbonitrile (**122**) synthesized from the 2-chloropyridine-3-carbonitrile (**121**) is converted to the corresponding amide which is cyclized to the 1,6-naphthyridinone (**123**) under basic conditions. The final example in Scheme 22 is a modification of this method in which the ethyl pyridine-3-carboxylate (**129**) is treated with ammonia to give the 2,7-naphthyridinone (**130**).



Scheme 19

As shown in the next Scheme, the method mentioned above appears to have wide generality. Namely, the synthesis of the pyrido[4,3-d]pyrimidinone (**133**),[36] the pyrido[3,4-d]pyrimidinone (**134**),[36] the isothiazolo[4,5-d]pyridinone (**137**),[25] and the isothiazolo[4,5-c]pyridinone (**138**)[25] are accomplished in a similar fassion to the naphthyridinone synthesis.

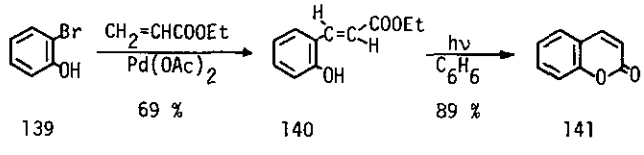


Scheme 20

6. Synthesis of Pyrone-Condensed Heteroaromatics

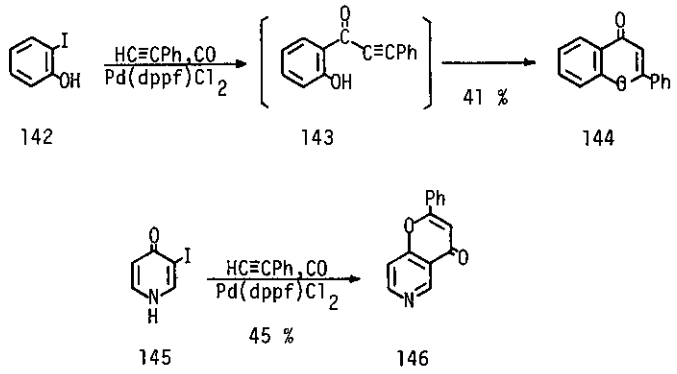
6.1 Coumarins and Chromones

Ethyl (E)-2-hydroxycinnamate (**140**) like ethyl 2-aminocinnamate cyclizes to coumarin under irradiation in good yield,[25] and the synthesis of **140** is accomplished by the Heck reaction of 2-bromophenol (**139**) with ethyl acrylate.[25] The reaction seems to have considerable generality, but the synthesis of pyranopyridinones (aza-coumarins) from the corresponding pyridine derivatives by this method has not yet been reported.



Scheme 21

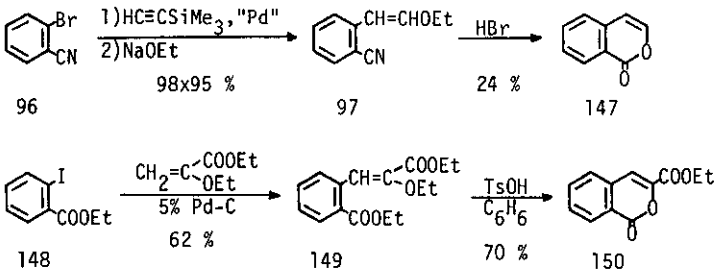
When the palladium-catalyzed reaction of aryl halides with terminal acetylenes is carried out in the presence of carbon monoxide, a carbonyl insertion reaction takes place, and aryl ethynyl ketones are obtained.[43] Using this reaction, the following chromone and pyranopyridinone (aza-chromone) are synthesized,[25] but the prospect of this reaction is uncertain at present.



Scheme 22

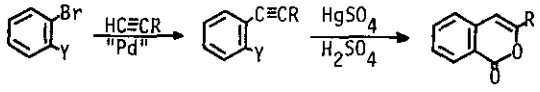
6.2 Isocoumarins and Pyranopyridinones

As described with the synthesis of 1(2H)-isoquinolinone (see Section 5.1), 2-bromobenzonitrile (**96**) is transformed into 2-(2-ethoxyethenyl)benzonitrile (**97**) in good yield, which is cyclized with hydrogen bromide to isocoumarin (**147**).[44] Intermediate (**149**) like **97** is also prepared by the Heck reaction of ethyl 2-iodobenzoate (**148**) with ethyl 2-ethoxyacrylate, and **149** is derived to ethyl isocoumarin-3-carboxylate (**150**) under acidic conditions.[13]



Scheme 23

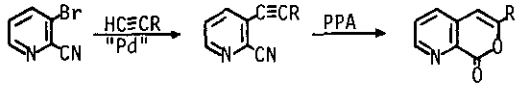
The palladium-catalyzed reaction products (**152**) obtained from 2-bromobenzoic acid derivatives (**96** and **151**) with phenylacetylene and 1-hexyne cyclize to 3-substituted isocoumarin (**153**) by treatment with mercuric sulfate in dilute sulfuric acid.[44] Based on the results illustrated in Scheme 27, ethyl 2-bromobenzoate (**151**) is a better substrate for the isocoumarin cyclization.



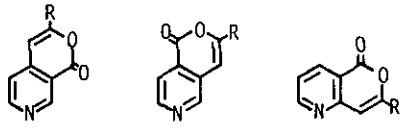
96: R=CN 151: =COOEt		152	153
Y=CN	,R=Ph	86 %	76 %
=COOEt,	=Ph	95	97
=CN	, =Bu	77	64
=COOEt,	=Bu	70	92

Scheme 24

The method is applied to the synthesis of pyranopyridinones (aza-isocoumarins) (**155-158**) from the ethynylpyridinecarbonitriles (e.g. **154**) using polyphosphoric acid as a condensing reagent.[45]



112		154	155
	R=Ph	83 %	54 %
	=Bu	93	62



156 157 158

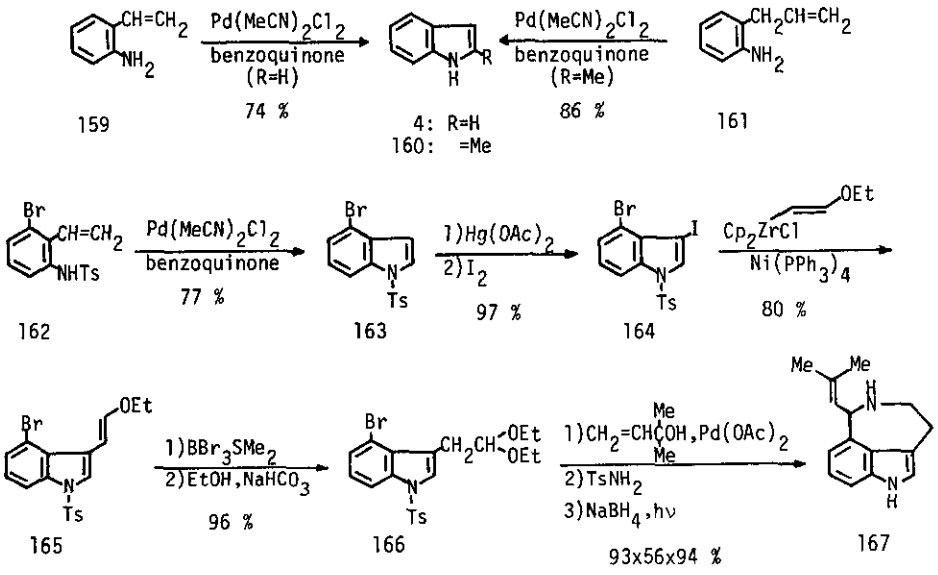
Scheme 25

7. Synthesis of Condensed Heteroaromatics by Palladium-Catalyzed Cyclization

Prior to this Chapter, we described the construction of condensed heteroaromatic ring systems, in which palladium-catalyzed reaction is efficiently used for the synthesis of the key intermediates concerned. On the other hand, there are many papers dealing with the palladium-catalyzed cyclization of appropriate open-chain compounds to give condensed heteroaromatic compounds. In this Chapter, we summarize briefly the synthesis of heteroaromatics in these manner.

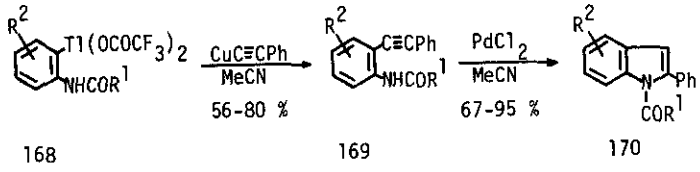
7.1 Indoles

When 2-vinyl- (**159**) and 2-allylaniline (**161**) are heated in the presence of dichlorobis(acetonitrile)palladium and benzoquinone, the cyclization to indole (**4**) and 2-methylindole (**160**) occurs in good yields.[46] By use of the transition metal-catalyzed reactions including the reaction from **159** to **4**, an elegant synthesis of the ergot alkaloids, e.g. (±)-aurantioclavine (**167**), was reported[47-49] as shown in Scheme 26.



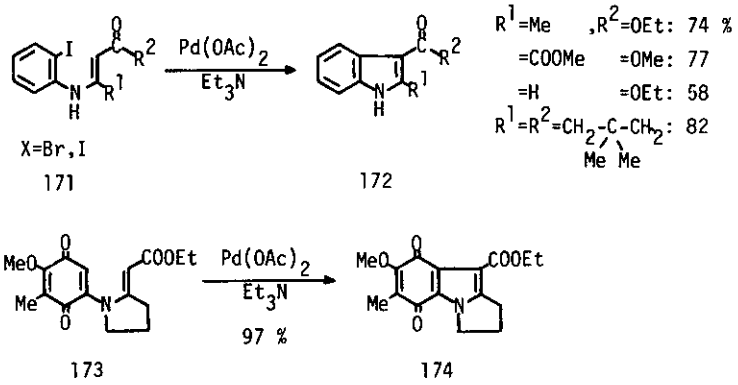
Scheme 26

Another palladium-catalyzed indole cyclization by N^1-C^2 bond formation was reported. Namely, the conversion of 2-phenylethynyl-N-acylaniline (**169**) prepared 2-acylaminophenylthallium(III) derivatives (**168**) with copper(I) phenylacetylide to 2-phenylindoles (**170**) was achieved by the catalytic action of palladium chloride.[50]



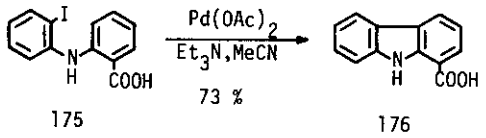
Scheme 27

On the other hand, intramolecular Heck reaction is used as an alternative method for the synthesis of indoles containing electron-withdrawing groups at the 3-position. Namely, N-(2-halophenyl)enamines (**171**) are converted to indoles (**172**) in the presence of palladium(II) acetate.[25,51] Using this reaction, 7-methoxymitosene is synthesized from the bromo-p-benzoquinone (**173**) via **174**.[52]



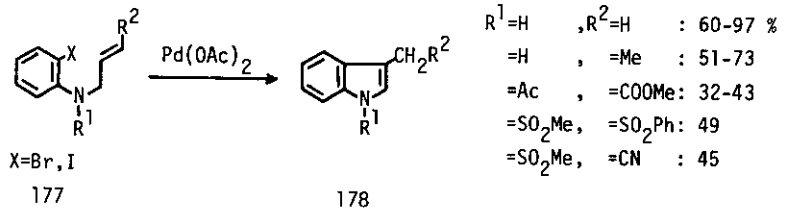
Scheme 28

Treatment of N-(2-iodophenyl)anthranilic acid (**175**) with palladium(II) acetate provides carbazole-1-carboxylic acid (**176**) in 73 % yield.[53] This carbazole formation is considered to be analogous one to the above reaction.



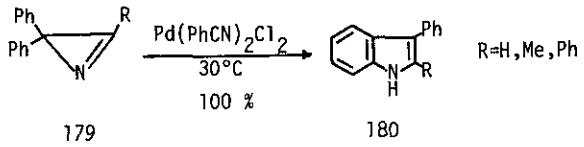
Scheme 29

It was reported by several groups[25,54-56] that N-allyl-2-haloanilines cyclize to 3-substituted indoles by the action of palladium catalyst. This reaction is a versatile method to synthesize indoles containing alkoxycarbonylmethyl, cyanomethyl, or phenylsulfonylmethyl group at the 3-postion.



Scheme 30

In addition to the reactions mentioned above, 2-substituted 3,3-diphenylaziridines (**179**) transforms to 2-substituted 3-phenylindoles (**180**) by the action of dichlorobis(benzonitrile)palladium at 30°C in quantitative yields, while the ring-transformation proceeds at 170°C without the palladium catalyst.[57]

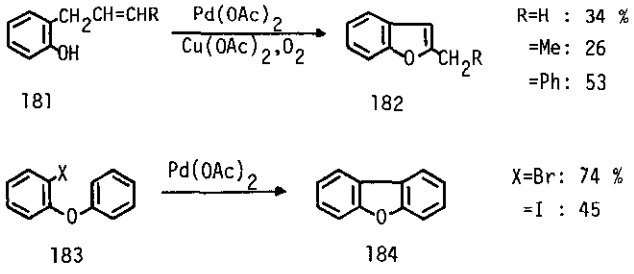


179 180

Scheme 31

7.2 Benzo[b]furans

There are relatively few papers dealing with the palladium-catalyzed cyclization to benzo[b]furans, but the basically same reaction to the indole cyclization mentioned in Section 7.1 is anticipated as a reasonable one. In fact, 2-allylphenols (**181**) or 2-halodiphenyl ethers (**183**) are derived to the corresponding benzo[b]furans (**182**)[58] or dibenzofuran (**184**)[53,59] by the catalytic action of palladium(II) acetate.



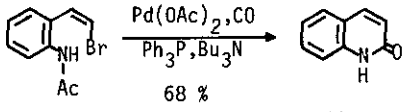
181 182

183 184

Scheme 32

7.3 Quinolines and Isoquinolines

Carbon monoxide is frequently used as a component of the palladum-catalyzed reactions with vinyl and aryl halides. The reaction of (Z)-2-(2-bromoethenyl)acetanilide (**185**) with carbon monoxide in the presence of palladium(II) acetate forms 2(1H)-quinolinone (**80**) in 68 % yield, while the same reaction of E-isomer gives **80** in low yield.[60]



185 80

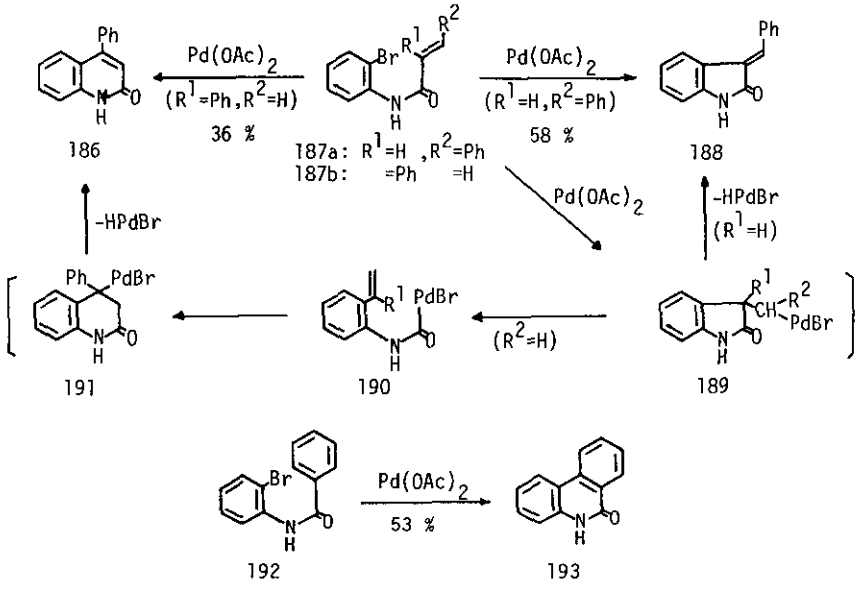
Scheme 33

The cyclization of aniline derivatives containing three carbon units on the amino group is one of fundamental procedures for the construction of quinoline rings. Skraup reaction, Döbner-Miller reaction, and Gould-Jacobs reaction are classical representatives of the procedure. The examples illustrated in the following

Schemes may be looked upon as modern modifications of these reactions.

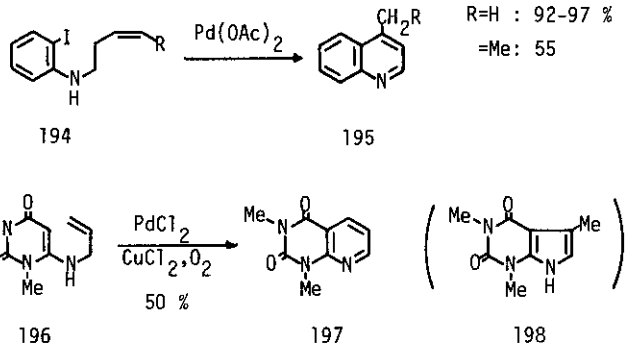
Similar to the reaction illustrated in Scheme 33, the palladium-catalyzed reaction of N-(2-bromophenyl)cinnamide (**187a**) provides 3-benzylideneoxindole (**188**), but N-(2-bromophenyl)-2-phenylacrylamide (**187b**) yields unexpected 4-phenyl-2(1H)-quinolinone (**186**).[61] While the former product (**188**) is considered to form via usual intermediate (**189**), the latter product (**186**) forms by the ring-opening of **189** and the ring-closure of **190**.

The reaction of N-(2-bromophenyl)benzamide (**192**) which can not form the above intermediate (**189** and **190**) under the same reaction conditions affords the normal product (**193**).[53]



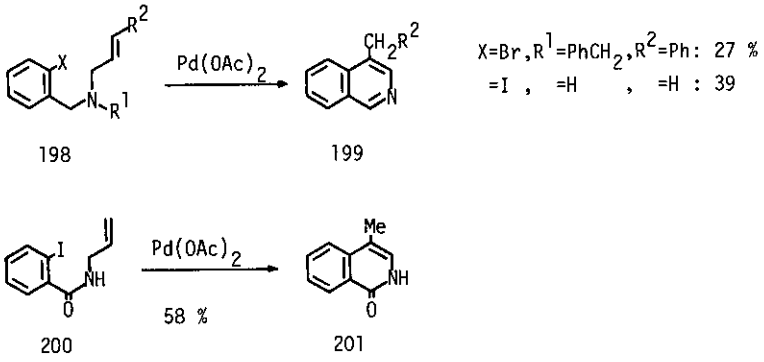
Scheme 34

As shown in Scheme 33, N-(2-halophenyl)allylamine yields indoles by palladium-catalyzed cyclization, but the corresponding homoallylamines afford quinolines. Namely, N-(3-butenyl)- (**194a**) and N-(3-pentenyl)-2-iodoaniline (**194b**) give 4-methyl- (**195a**) and 4-ethylquinoline (**195b**) by the catalytic action of palladium (II) acetate.[55] Analogous result is found in the palladium-catalyzed cyclization of the 6-allyaminouracil (**196**). Although this reaction does not start from the corresponding halide, it proceeds via the arylpalladium-complex to give the pyrido[2,3-d]pyrimidine (**197**) instead of the pyrrolo[2,3-d]pyrimidine (**198**).[62]



Scheme 35

Analogous cyclizations of N-allyl-2-halobenzylamine (**198**)[55,56] and N-allyl-2-iodobenzamide (**200**)[55] in the presence of palladium(II) acetate form the corresponding isoquinoline derivatives (**199** and **201**).



Scheme 36

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