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[3+3] Benzannulations of benzenoid- and heteroaromatic-ring systems

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1. Introduction

Benzannulation of aromatic rings is an important process in organic synthesis since a wide range of organic molecules contain fused benzene rings. In theory, the construction of a fused benzene ring can be attained from a single cyclization or by the condensation of two, three, four and five components. In practice, the condensation of two components is the most useful, and classically [4+2] annulation has been widely used by organic chemists in Diels–Alder reactions of benzynes,[1–5] *o*-quinodimethanes,[6–8] isobenzofurans[9] and isoquinolinium salts.[10] However, in some cases, [4+2] cycloadditions suffer from lack of regioselectivity.

Recently, [3+3] benzannulation has become of considerable interest in many aspects of organic synthesis due to the ready availability of synthetic precursors and the well controlled regiochemistry. Rather than attempting a comprehensive survey, the purpose of the present review is to illustrate some of the available [3+3] benzannulations with an emphasis on our own work. It will mainly cover the

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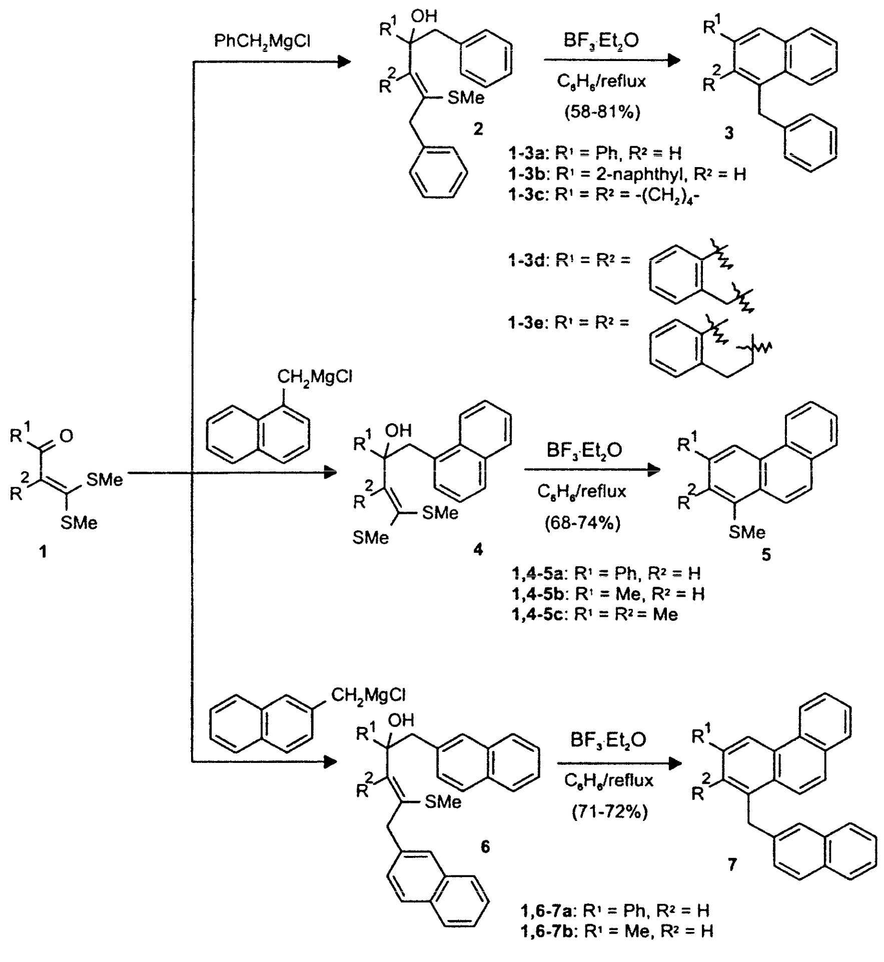


Ref. 11

Scheme 1.

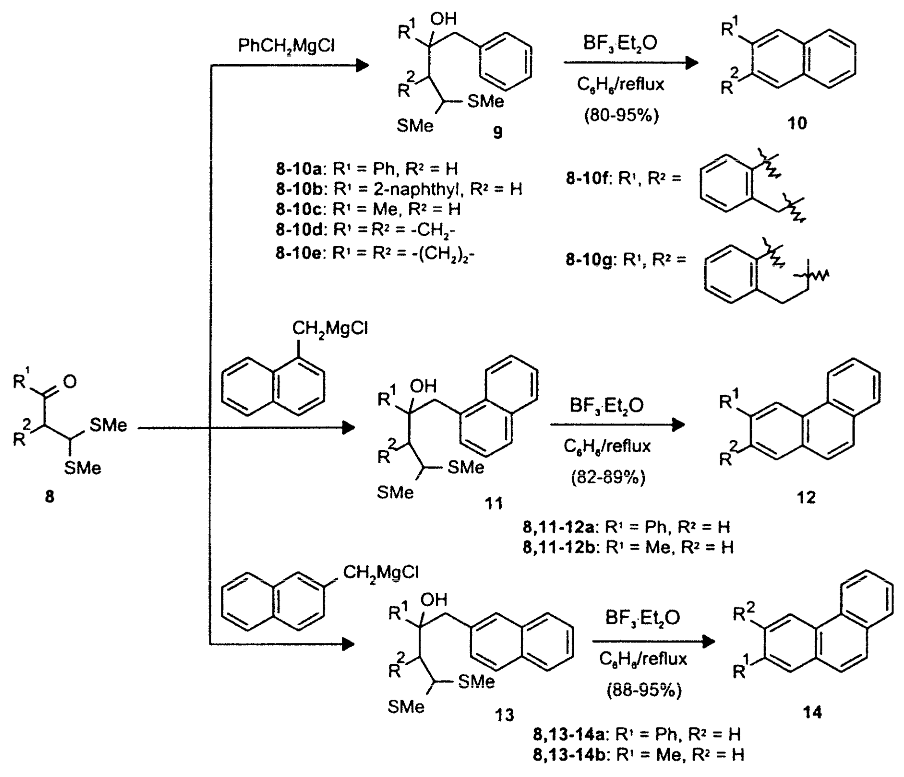
[3+3] benzannulation of aromatic hydrocarbons and important electron-rich heteroaromatic rings such as pyrroles, indoles, furans, benzofurans, thiophens and benzothiophens.

2. Nucleophilic Addition Followed by Cycloaromatization

Many [3+3] benzannulations involve three steps: (i) nucleophilic attack, (ii) cyclization that can proceed via a cationic, anionic or radical mechanism, and (iii) aromatization usually via elimination or oxidation. In sequences of this type, the initial nucleophiles can be an aryl- or heteroaryl-methyl derivative, aromatic ring carbon, or another nucleophile; and we consider these possibilities in turn.

2.1. Aryl- and heteroaryl-methyl nucleophiles

Due to the ready availability of the starting materials, the annulation of aryl- and heteroaryl-methyl nucleophiles and α,β-unsaturated carbonyl derivatives represents a general route for the synthesis of



Ref. 11

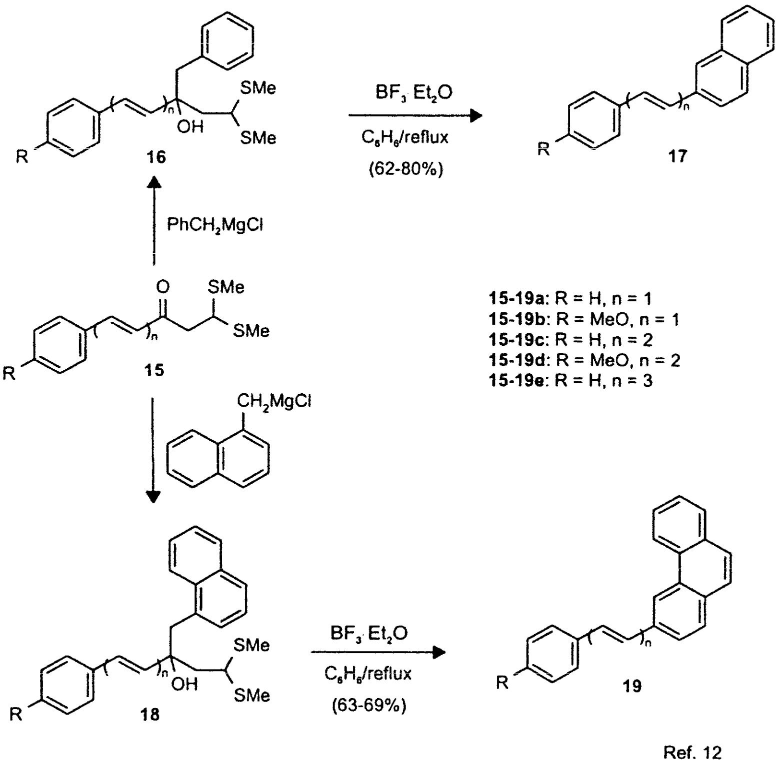
Scheme 2.

polynuclear aromatic hydrocarbons and heteroaromatic ring systems. Ila, Junjappa and coworkers found that a variety of substituted naphthalenes **3**, **10** and **17**; phenanthrenes **5**, **7**, **14** and **19**, and other polynuclear aromatic hydrocarbons, can be synthesized through 1,2-addition of either benzyl or 1- or 2-(naphthylmethyl) magnesium halides to α-oxoketene dithioacetals **1** or β-oxodithioacetals **8** or **15** followed by boron trifluoride-etherate catalyzed cycloaromatization of the resulting carbinols **2**, **4**, **6**, **9**, **11**, **13**, **16** or **18** (Schemes 1–3).[11,12] α-Oxoketene dithioacetals have been further used to prepare additional naphthalenes,[13] benz[*d*]isoxazoles,[14,15] quinazolinediones,[16] and carbazoles.[17] For a review of earlier work in this area see Junjappa et al.[18]

Olefination of naphthyl ketones **20** or **23** with benzyltriphenylphosphonium chloride and subsequent photochemical closure of the resultant naphthylstyrenes **21** or **24** (Scheme 4) provide key intermediates **22** or **25** for the synthesis of dihydrodiol and diol epoxide derivative of the carcinogenic benzo[*g*]chrysene (BgCh), which are used to probe structural factors involved in the carcinogenesis and mutagenesis of polycyclic aromatic hydrocarbons.[19] Notably, the photocyclization proceeds regiospecifically.

Base-catalyzed condensation of toluene derivatives **26** and **31** with diethyl ethylidenemalonate or 2-methyl-2-(2-oxo-ethyl)-1,3-dioxolane, respectively, and subsequent cycloaromatization has been used for the construction of naphthalenecarboxylic acid derivatives **30** and **35**, which are of biological interests (Schemes 5 and 6).[20]

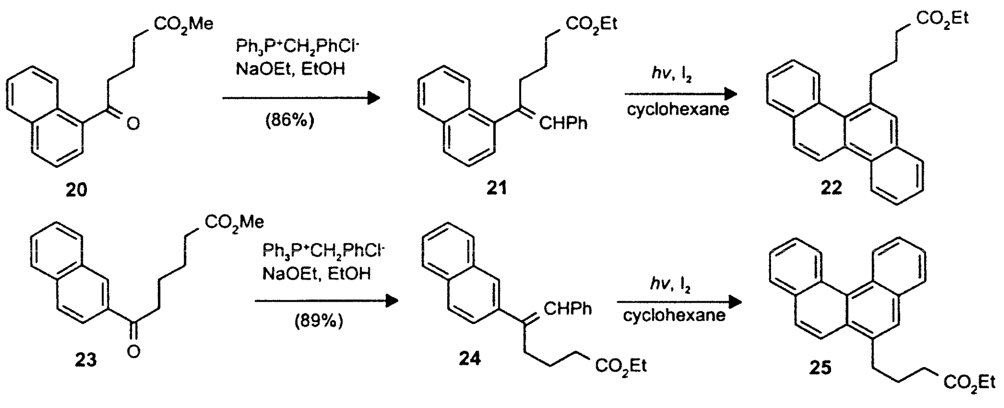
Reaction of benzanthrene **36** with 'vinamidinium salts' **37** in the presence of sodium methoxide furnished condensation products that underwent thermal electrocyclic ring closure with elimination of dimethylamine to afford the corresponding derivatives of benzo[*e*]pyrenes **38** regiospecifically



15-19a: R = H, n = 1
15-19b: R = MeO, n = 1
15-19c: R = H, n = 2
15-19d: R = MeO, n = 2
15-19e: R = H, n = 3

Ref. 12

Scheme 3.



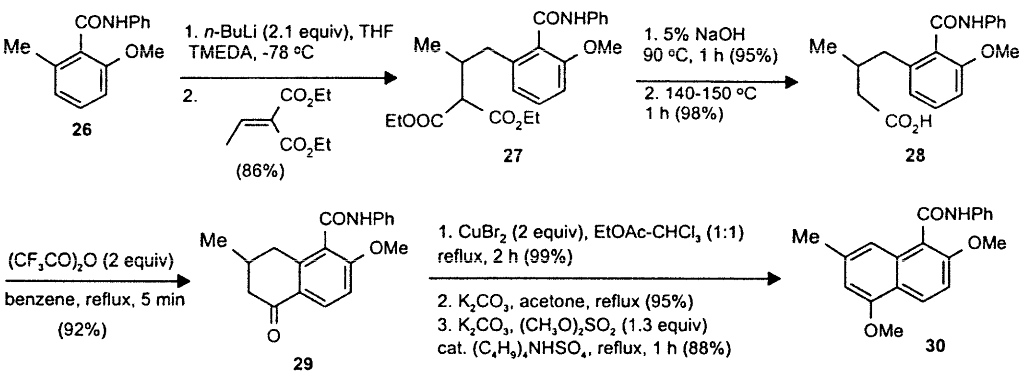
Ref. 19

Scheme 4.

(Scheme 7).[21] These reactions provide convenient synthetic access to benzo[*e*]pyrene derivatives that are otherwise difficult to obtain.

Sequential lithiation and alkylation of 1*H*-phenalene (**39**) with substituted 1,3-dibromopropanes followed by DDQ oxidation furnished a simple synthesis of methylated pyrenes **41** (Scheme 8).[22]

Recently, we found that polysubstituted naphthalenes **46** and **47** and phenanthrenes **49**, **51**, **53** and **54** can be readily prepared by annulation of (benzotriazol-1-ylmethyl)-benzenes **42** or -naphthalenes **48** or



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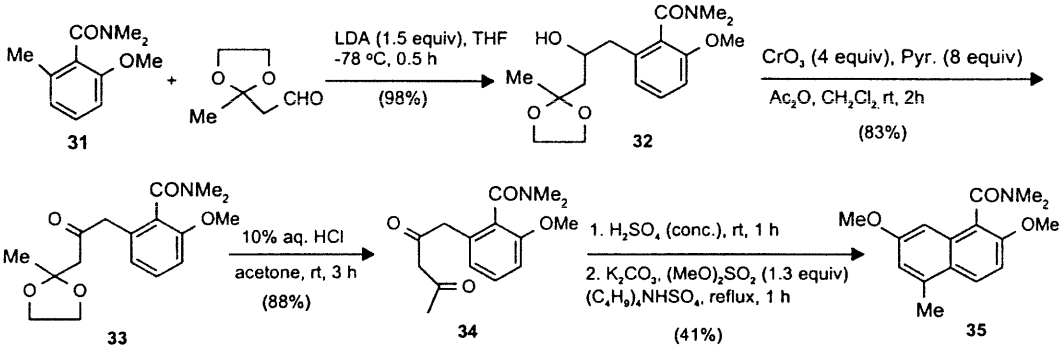
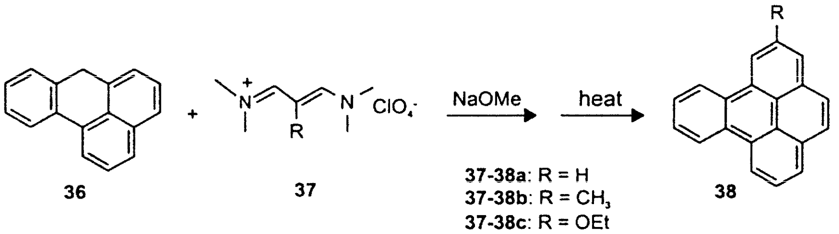
Scheme 5.



Ref. 20

Scheme 6.

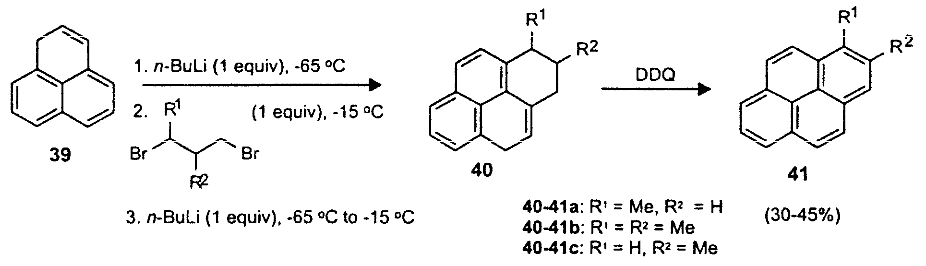


Ref. 21

Scheme 7.

52 with α,β-unsaturated aldehydes and ketones (Schemes 9 and 10).[23] The benzotriazolyl functionality acts as both an anion-stabilizing group and leaving group in the overall transformation.

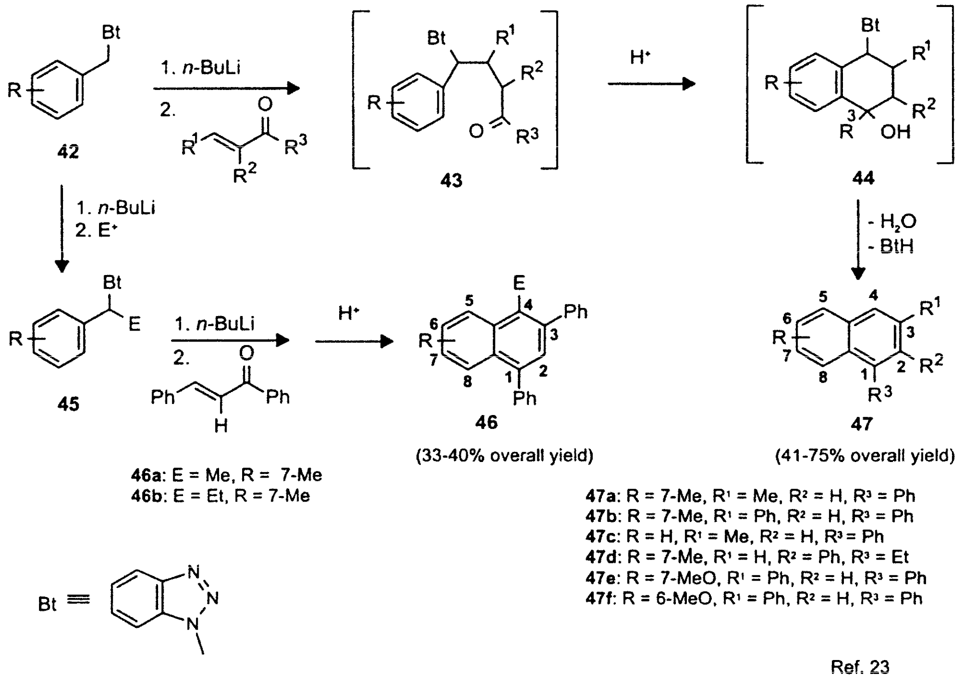
Similarly, the coupling of sulfonylmethylbenzene derivative **55** and methyl crotonate provided a convenient synthesis of 1-bromo-4,5-dimethoxy-7-methylnaphthalene (**60**), which is a useful intermediate for the construction of anti-HIV active naphthylisoquinoline alkaloids (Scheme 11).[24]



40-41a: R^1 = Me, R^2 = H
40-41b: R^1 = R^2 = Me
40-41c: R^1 = H, R^2 = Me

Ref. 22

Scheme 8.

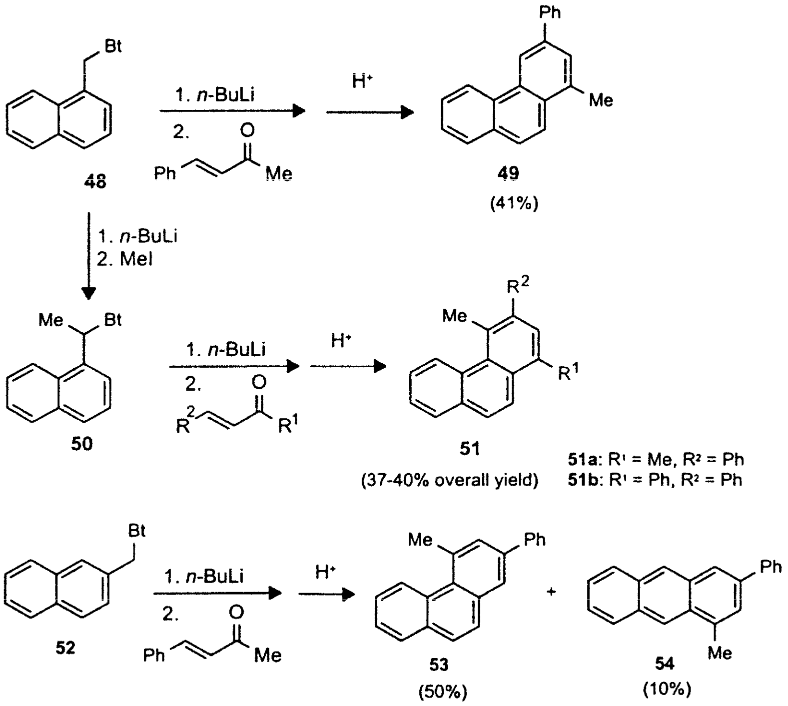


46a: E = Me, R = 7-Me
46b: E = Et, R = 7-Me

47a: R = 7-Me, R^1 = Me, R^2 = H, R^3 = Ph
47b: R = 7-Me, R^1 = Ph, R^2 = H, R^3 = Ph
47c: R = H, R^1 = Me, R^2 = H, R^3 = Ph
47d: R = 7-Me, R^1 = H, R^2 = Ph, R^3 = Et
47e: R = 7-MeO, R^1 = Ph, R^2 = H, R^3 = Ph
47f: R = 6-MeO, R^1 = Ph, R^2 = H, R^3 = Ph

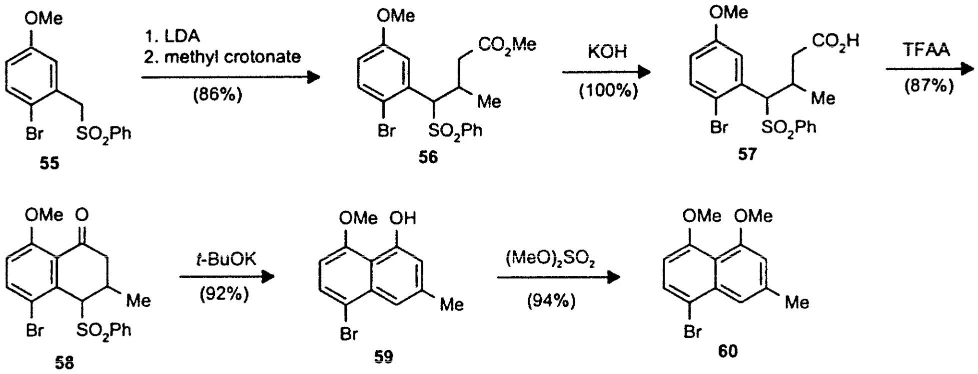
Ref. 23

Scheme 9.



Ref. 23

Scheme 10.



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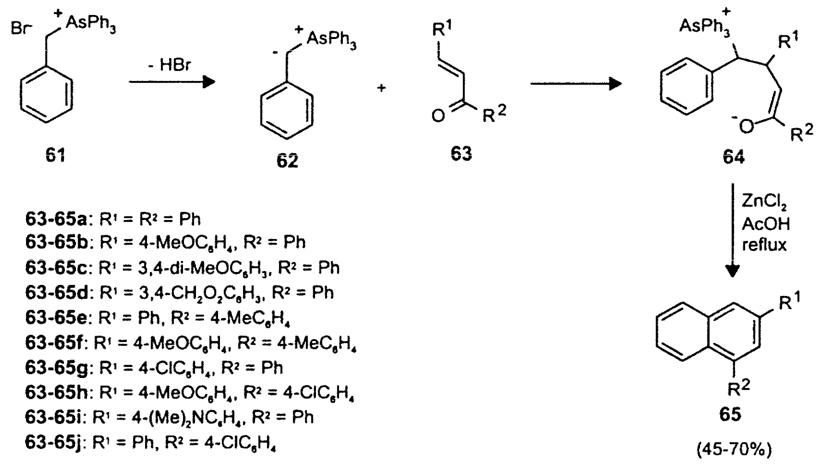
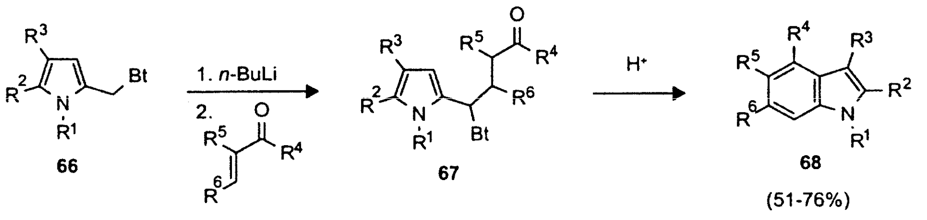
Scheme 11.



63-65a: $R^1 = R^2 = Ph$
63-65b: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = Ph$
63-65c: $R^1 = 3,4\text{-di-}MeOC_6H_3$, $R^2 = Ph$
63-65d: $R^1 = 3,4\text{-}CH_2O_2C_6H_3$, $R^2 = Ph$
63-65e: $R^1 = Ph$, $R^2 = 4\text{-}MeC_6H_4$
63-65f: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = 4\text{-}MeC_6H_4$
63-65g: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = Ph$
63-65h: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = 4\text{-}ClC_6H_4$
63-65i: $R^1 = 4\text{-}(Me)_2NC_6H_4$, $R^2 = Ph$
63-65j: $R^1 = Ph$, $R^2 = 4\text{-}ClC_6H_4$

Ref. 25

Scheme 12.



67-68a: $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = R^4 = Ph$, $R^5 = H$, $R^6 = Ph$
67-68b: $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = Ph$, $R^4 = H$, $R^5 = Ph$, $R^6 = Et$
67-68c: $R^1 = t\text{-}Bu$, $R^2 = H$, $R^3 = Ph$, $R^4 = Me$, $R^5 = R^6 = H$
67-68d: $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Me$, $R^5 = R^6 = H$
67-68e: $R^1 = MeO(CH_2)_2$, $R^2 = R^3 = Me$, $R^4 = Ph$, $R^5 = H$, $R^6 = Ph$
67-68f: $R^1 = MeO(CH_2)_2$, $R_2 = R^3 = Me$, $R^4 = H$, $R^5 = Ph$, $R^6 = Et$
67-68g: $R^1 = 4\text{-}MeOC_6H_4CH_2$, $R^2 = R^3 = Me$, $R^4 = Ph$, $R^5 = H$, $R^6 = Ph$
67-68h: $R^1 = n\text{-}Bu$, $R^2 = R^3 = Me$, $R^4 = Ph$, $R^5 = H$, $R^6 = Ph$

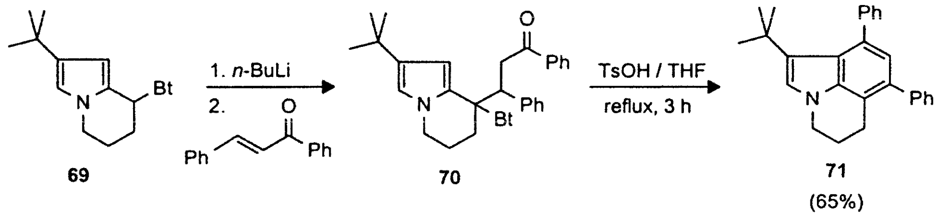
Ref. 26

Scheme 13.

Gupta and coworkers reported that benzyltriphenylarsonium bromide (**61**) reacted with substituted benzylideneacetophenones **63** in acetic acid in the presence of anhydrous $ZnCl_2$ and sodium acetate to give 1,3-diarylnaphthalenes **65** in a one-pot procedure (Scheme 12).[25]

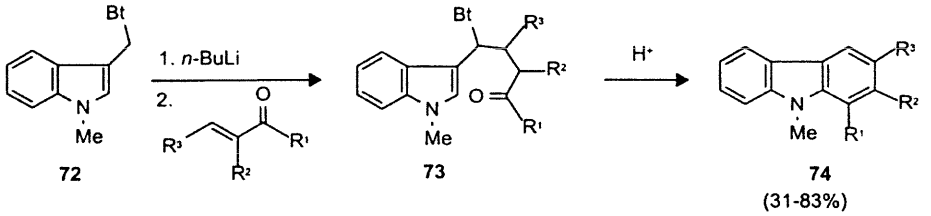
[3+3] Benzannulation of heterocyclic compounds has recently been developed as a new synthetic approach to many substituted heterocycles, including indoles, carbazoles, benzothiophenes and benzofurans. In particular, we have found that benzotriazolylmethyl substituted pyrroles **66** (Scheme 13),[26] and **69** (Scheme 14),[27] indoles **72** (Scheme 15),[28] thiophenes **75** (Scheme 16),[29] furans **80** (Scheme 17) and benzofuran **85** (Scheme 18)[30] all undergo base induced conjugate additions with α,β-unsaturated aldehydes and ketones followed by cyclization and elimination to afford the respective benzo-fused heterocycles. These benzannulations all start from readily available precursors and involve very simple synthetic manipulations with highly regiocontrolled ring formation and provide the desired products in good yields.

In a somewhat similar approach, Ila and coworkers reported the heteroaromatic annulation of indole-



Ref. 27

Scheme 14.

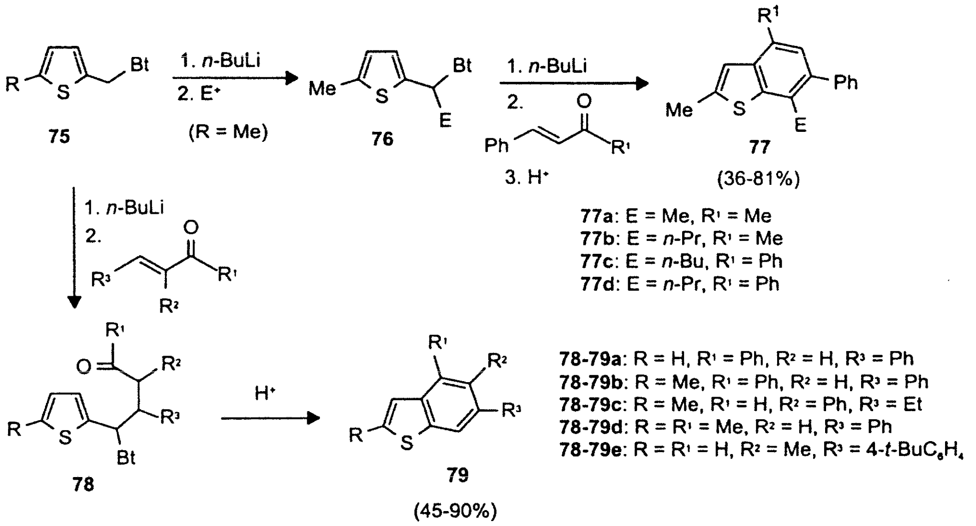


73-74a: R^1 = Ph, R^2 = H, R^3 = Ph
73-74b: R^1 = Me, R^2 = H, R^3 = Ph
73-74c: R^1 = PhCH=CH, R^2 = H , R^3 = Ph
73-74d: R^1 = Ph, R^2 = CN, R^3 = Ph
73-74e: R^1 = Me, R^2 = COOEt, R^3 = Ph

73-74f: R^1 = Me, R^2 = COOEt, R^3 = *n*-Pr
73-74g: R^1 = H, R^2 = Ph, R^3 = Me
73-74h: R^1 = H, R^2 = Ph, R^3 = Et
73-74i: R^1 = H, R^2 = Me, R^3 = Ph
73-74j: R^1 = H, R^2 = Ph, R^3 = *i*-Bu

Ref. 28

Scheme 15.

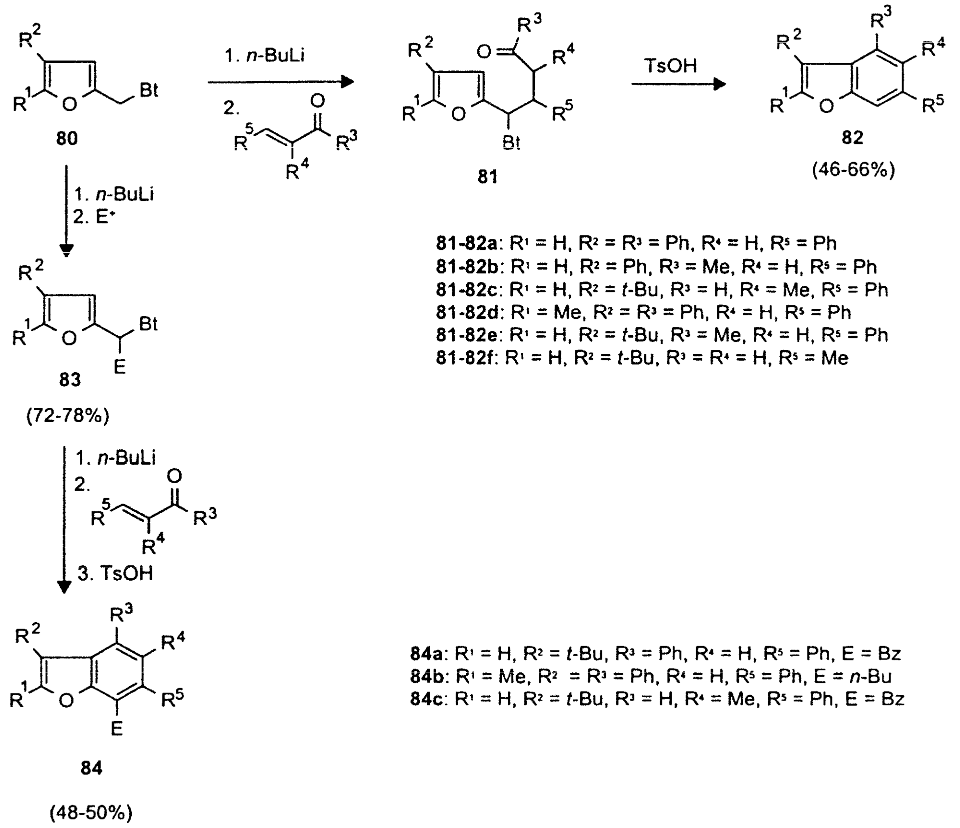


77a: E = Me, R^1 = Me
77b: E = *n*-Pr, R^1 = Me
77c: E = *n*-Bu, R^1 = Ph
77d: E = *n*-Pr, R^1 = Ph

78-79a: R = H, R^1 = Ph, R^2 = H, R^3 = Ph
78-79b: R = Me, R^1 = Ph, R^2 = H, R^3 = Ph
78-79c: R = Me, R^1 = H, R^2 = Ph, R^3 = Et
78-79d: R = R^1 = Me, R^2 = H, R^3 = Ph
78-79e: R = R^1 = H, R^2 = Me, R^3 = 4-*t*-BuC_6H_4

Ref. 29

Scheme 16.

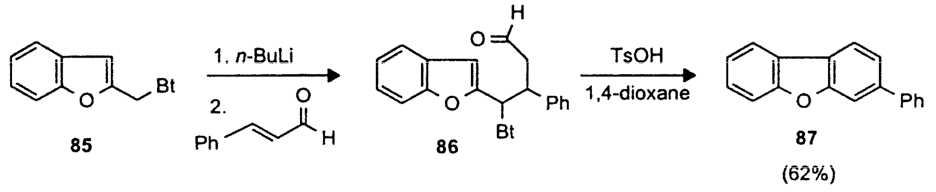


81-82a: $R^1 = H$, $R^2 = R^3 = Ph$, $R^4 = H$, $R^5 = Ph$
81-82b: $R^1 = H$, $R^2 = Ph$, $R^3 = Me$, $R^4 = H$, $R^5 = Ph$
81-82c: $R^1 = H$, $R^2 = t\text{-Bu}$, $R^3 = H$, $R^4 = Me$, $R^5 = Ph$
81-82d: $R^1 = Me$, $R^2 = R^3 = Ph$, $R^4 = H$, $R^5 = Ph$
81-82e: $R^1 = H$, $R^2 = t\text{-Bu}$, $R^3 = Me$, $R^4 = H$, $R^5 = Ph$
81-82f: $R^1 = H$, $R^2 = t\text{-Bu}$, $R^3 = R^4 = H$, $R^5 = Me$

84a: $R^1 = H$, $R^2 = t\text{-Bu}$, $R^3 = Ph$, $R^4 = H$, $R^5 = Ph$, $E = Bz$
84b: $R^1 = Me$, $R^2 = R^3 = Ph$, $R^4 = H$, $R^5 = Ph$, $E = n\text{-Bu}$
84c: $R^1 = H$, $R^2 = t\text{-Bu}$, $R^3 = H$, $R^4 = Me$, $R^5 = Ph$, $E = Bz$

Ref. 30

Scheme 17.



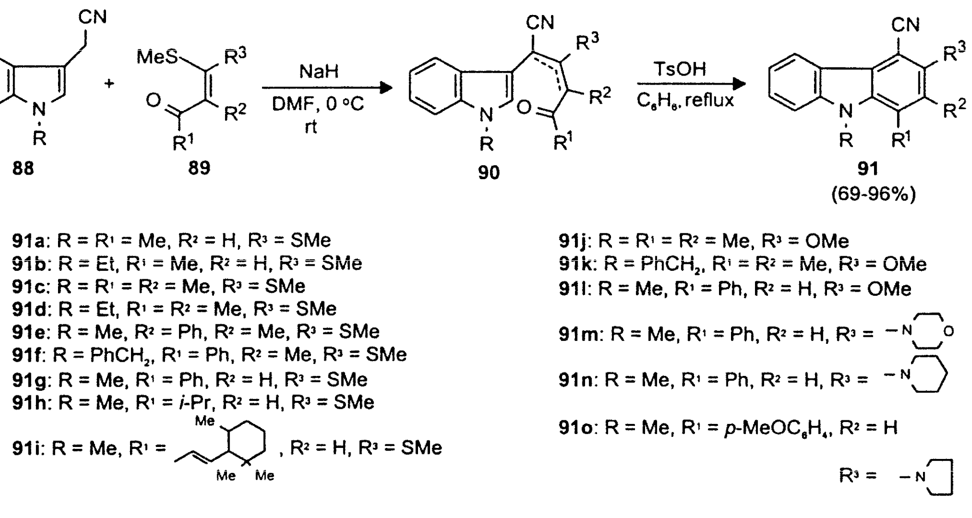
Ref. 30

Scheme 18.

3-acetonitriles **88** and 1-methylpyrrole-2-acetonitrile **93** with α-oxoketene acetals to form highly functionalized carbazoles **91** and indoles **95**, **98**, **100**, **102** and **104** (Schemes 19 and 20).[31,32]

2.2. *Aryl- and heteroaryl nucleophiles*

[3+3] Benzannulation commencing from aryl and heteroaryl ring carbanions as nucleophiles is less explored, perhaps due to the lesser availability of their precursors. Appropriate nucleophiles of this class already investigated include suitably *ortho*-substituted aryllithiums, aryl Grignard reagents, and electron-rich aromatic rings. As examples, benzamides **105** readily undergo *ortho*-lithiation to give intermediates that then couple with allyl bromides; subsequent methyllithium induced cycloaromatization afforded 1-



91a: R = R¹ = Me, R² = H, R³ = SMe
91b: R = Et, R¹ = Me, R² = H, R³ = SMe
91c: R = R¹ = R² = Me, R³ = SMe
91d: R = Et, R¹ = R² = Me, R³ = SMe
91e: R = Me, R² = Ph, R² = Me, R³ = SMe
91f: R = PhCH₂, R¹ = Ph, R² = Me, R³ = SMe
91g: R = Me, R¹ = Ph, R² = H, R³ = SMe
91h: R = Me, R¹ = *i*-Pr, R² = H, R³ = SMe
91i: R = Me, R¹ = , R² = H, R³ = SMe
91j: R = R¹ = R² = Me, R³ = OMe
91k: R = PhCH₂, R¹ = R² = Me, R³ = OMe
91l: R = Me, R¹ = Ph, R² = H, R³ = OMe
91m: R = Me, R¹ = Ph, R² = H, R³ =
91n: R = Me, R¹ = Ph, R² = H, R³ =
91o: R = Me, R¹ = *p*-MeOC₆H₄, R² = H
R³ =

Ref. 31

Scheme 19.

naphthols **108** (Scheme 21).[33] Deuterated cholanthrene is synthesized by condensation of indanone (**109**) with *o*-lithioarylamide (**110**) (Scheme 22).[34]

Aryl Grignard reagent **115** has been used for the synthesis of precursors for extended phenalenones. The reaction of 7*H*-benzo[*hi*]chrysen-7-one (**116**) with (5-methoxy-1-naphthyl)magnesium bromide (**115**) in toluene at 80°C and subsequent autoxidation in the presence of hydrochloric acid gave ketone (**118**), which underwent intramolecular polyphosphoric acid-catalyzed condensation to give 15*H*-benzo[*dc*]naphtho[1,2-*a*]perylen-15-one (**120**) in 78% yield (Scheme 23).[35]

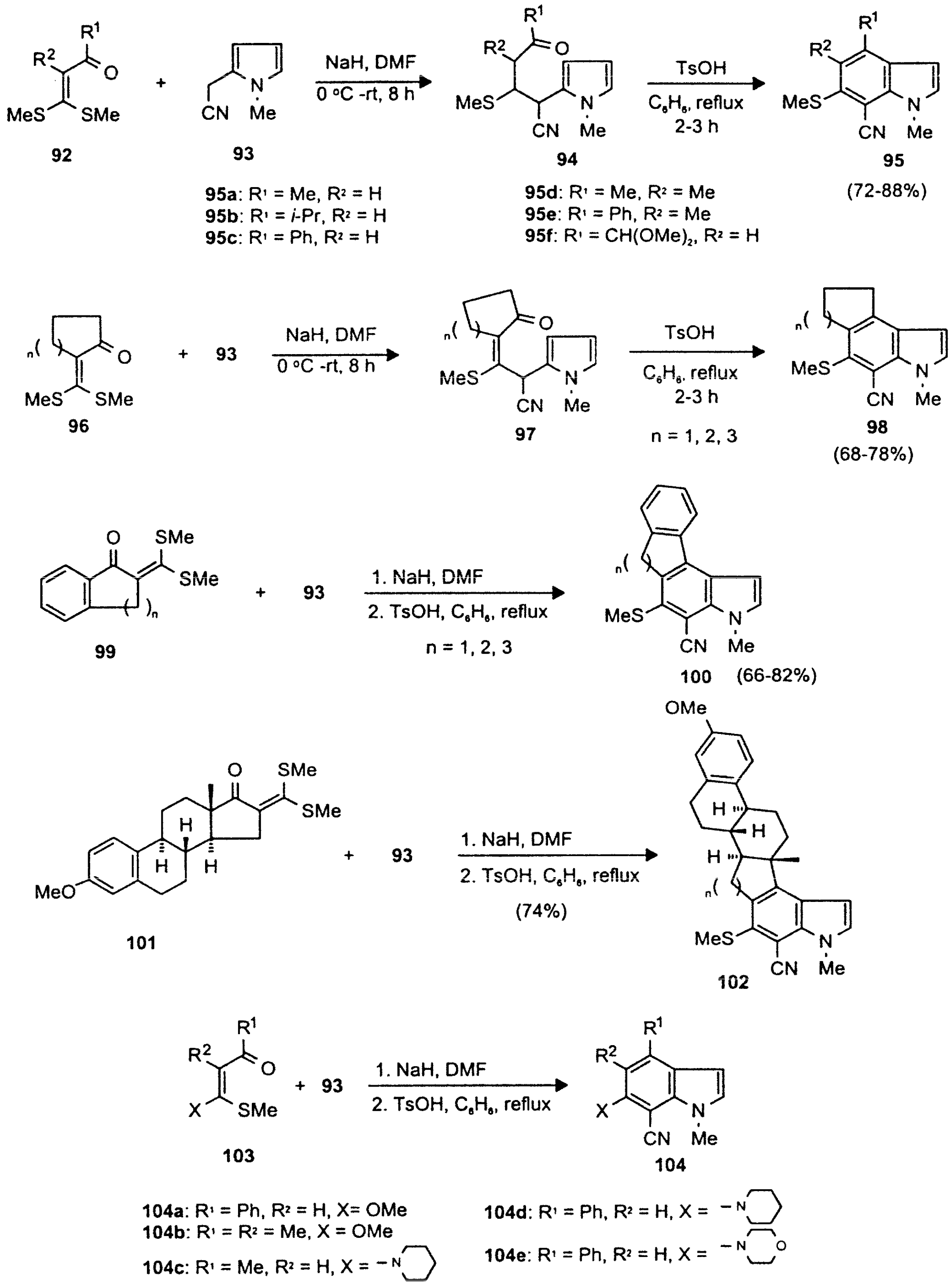
Although [3+3] benzannulation involving Friedel–Crafts coupling as the first step has been paid little attention, this approach can result in expeditious synthesis of complex molecules that otherwise are difficult to obtain. A notable example is the synthesis of resistomycin (**126**) reported by Kelly and Ghoshal as illustrated in Scheme 24.[36]

Lithium–halogen exchange is a potentially useful way to generate aromatic nucleophiles owing to the ready availability of halogenated aromatics. We found that 1-methyl-2-bromo-3-[(benzotriazol-1-yl)methyl]indole (**127**) underwent lithium–halogen exchange with *t*-BuLi and subsequently coupled with heterocyclic carboxaldehydes to give intermediates that underwent cycloaromatization to various heterocyclo[*b*]fused carbazoles **132**, which otherwise are difficult to prepare (Scheme 25).[37]

Bergman found 2-alkylindoles to be useful synthetic precursors in the synthesis of indole alkaloids and carbazoles.[38] The coupling of 2-ethylindole (**133**) with 2-methyl-3-formylpyridine (**134**) followed by thermolysis under reduced pressure yielded olivacine (**139**) directly (Scheme 26).[39] Condensation of 2-alkylindoles **140** with 2,3-unsaturated ketones **141** in the presence of Pd/C and molecular sieves provided a simple synthesis of substituted carbazoles **142** (Scheme 27).[40,41]

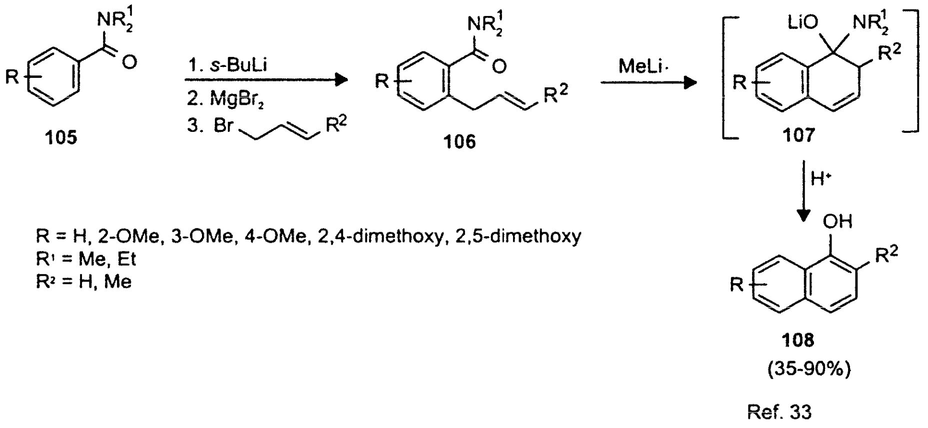
2.3. Other nucleophiles

Condensation of aromatic carbonyl compounds with other nucleophiles containing three of the carbon atoms to be incorporated in the newly annulated benzene ring of fused aromatic ring systems is of interest.



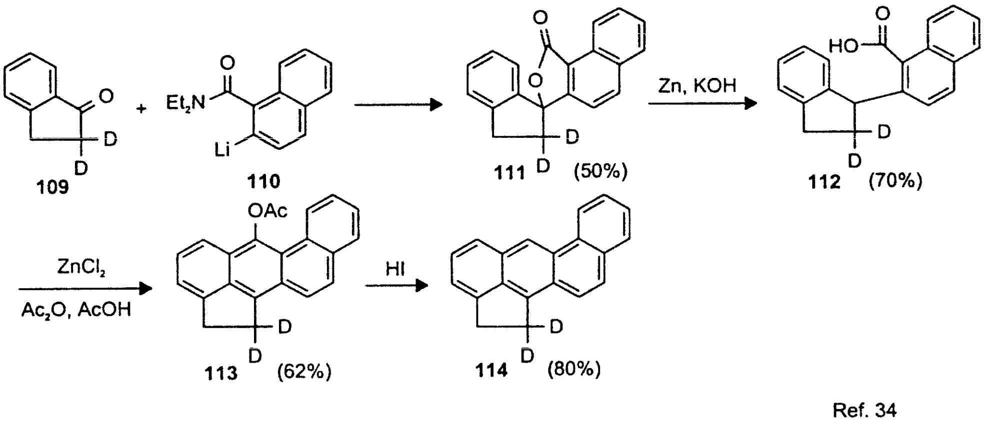
Ref. 32

Scheme 20.

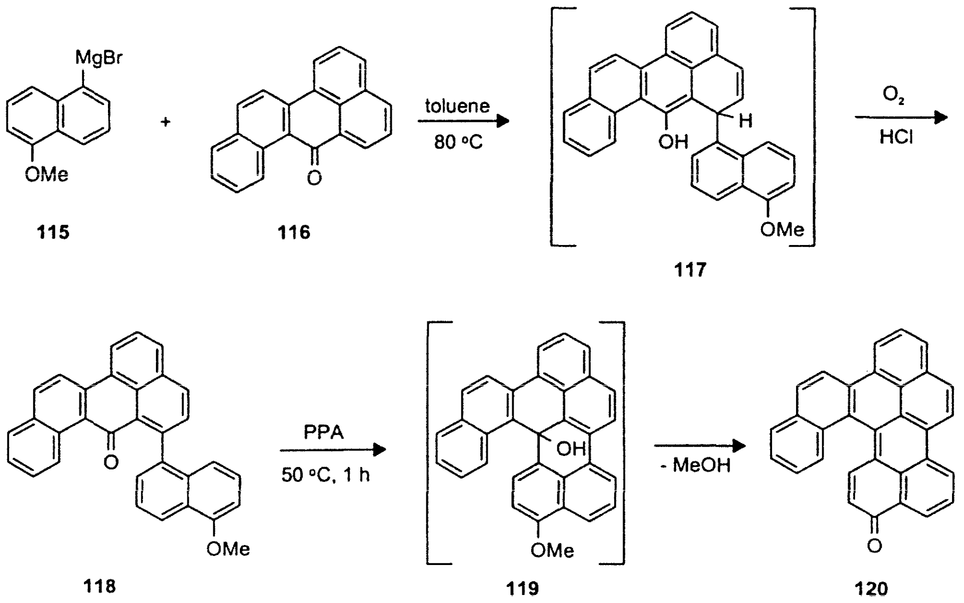


R = H, 2-OMe, 3-OMe, 4-OMe, 2,4-dimethoxy, 2,5-dimethoxy
R^1 = Me, Et
R^2 = H, Me

Scheme 21.

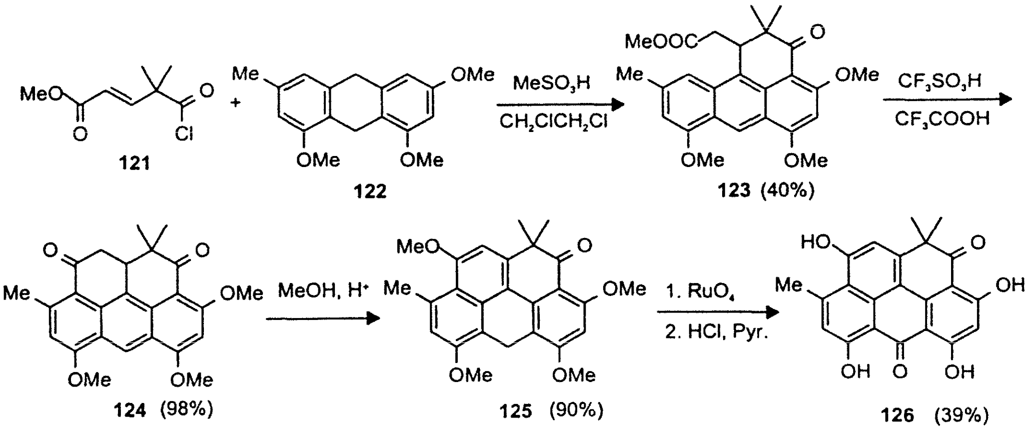


Scheme 22.



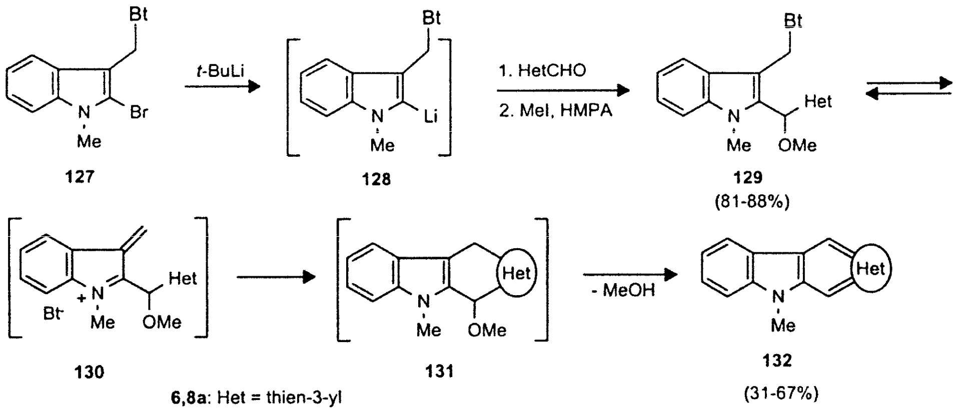
Ref. 35

Scheme 23.



Ref. 36

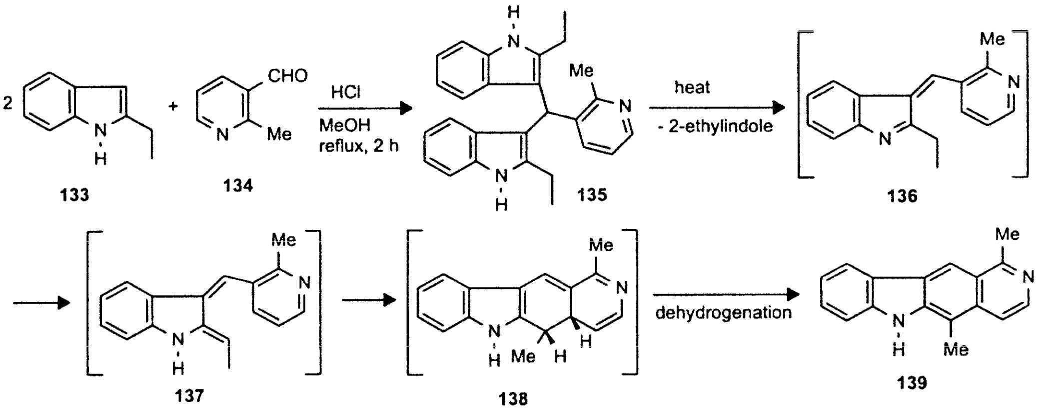
Scheme 24.



6,8a: Het = thien-3-yl
6,8b: Het = furan-3-yl
6,8c: Het = thien-2-yl
6,8d: Het = furan-2-yl
6,8e: Het = 1-methylindol-3-yl

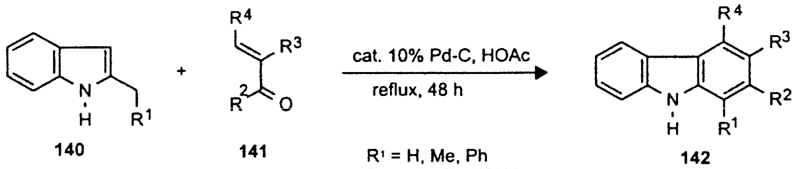
Ref. 37

Scheme 25.



Ref. 39

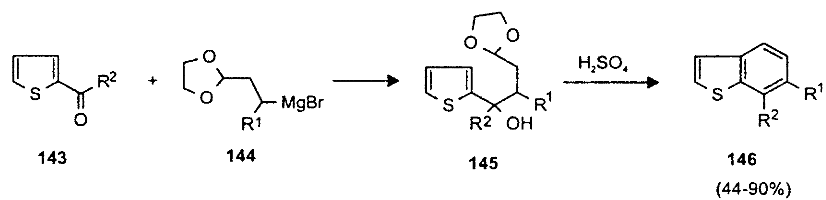
Scheme 26.



R^1 = H, Me, Ph
R^2 = Me, Et, -$(CH_2)_4$-
R^3 = H, -$(CH_2)_4$-
R^4 = H, Me, Ph, OMe

Refs. 40, 41

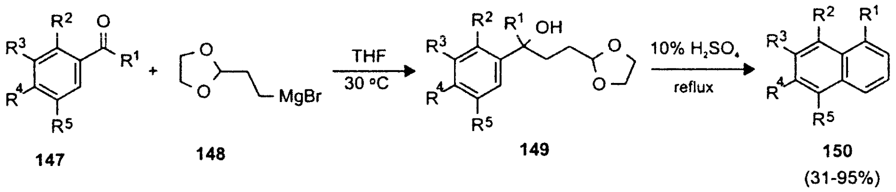
Scheme 27.



146a: $R^1 = R^2 = H$
146b: $R^1 = H$, $R^2 = Me$
146c: $R^1 = H$, $R^2 = Et$
146d: $R^1 = H$, $R^2 = i\text{-}Pr$
146e: $R^1 = R^2 = Me$
146f: $R^1 = Me$, $R^2 = Et$
146g: $R^1 = H$, $R^2 = CH_2CH_2CHO$

Ref. 42

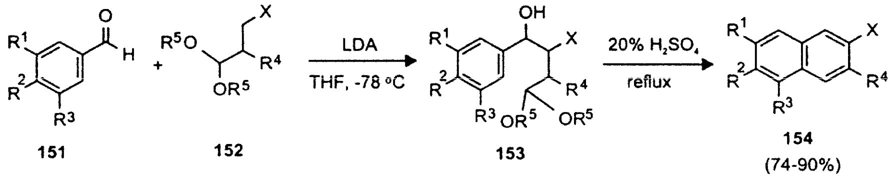
Scheme 28.



150a: $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = OMe$
150b: $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = OMe$
150c: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = OMe$
150d: $R^1 = R^2 = R^4 = H$, $R^3 = R^5 = OMe$
150e: $R^1 = R^2 = R^5 = H$, R^3, $R^4 = O\text{-}CH_2\text{-}O$
150f: $R^1 = Me$, $R^2 = R^4 = R^5 = H$, $R^3 = OMe$
150g: $R^1 = R^4 = R^5 = H$, $R^2 = OH$, $R^3 = OMe$
150h: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = OH$
150i: $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Me$
150j: $R^1 = R^2 = R^3 = R^4 = R^5 = H$

Ref. 43

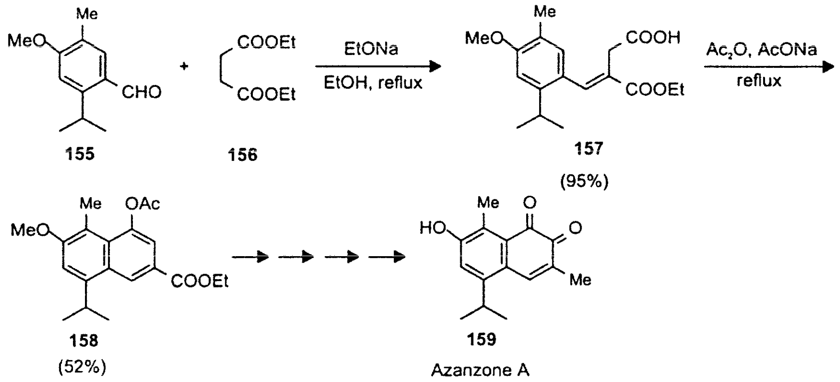
Scheme 29.



154a: $R^1 = R^2 = \text{-}OCH_2O\text{-}$, $R^3 = H$, $R^4 = H$, $R^5 = Et$, $X = CN$
154b: $R^1 = R^2 = \text{-}OCH_2O\text{-}$, $R^3 = H$, $R^4 = H$, $R^5 = \text{-}(CH_2)_3\text{-}$, $X = COOMe$
154c: $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = H$, $R^5 = Et$, $X = CN$
154d: $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = H$, $R^5 = \text{-}(CH_2)_3\text{-}$, $X = COOMe$
154e: $R^1 = R^2 = \text{-}OCH_2O\text{-}$, $R^3 = H$, $R^4 = R^5 = Me$, $X = CN$
154f: $R^1 = R^2 = \text{-}OCH_2O\text{-}$, $R^3 = H$, $R^4 = R^5 = Me$, $X = COOMe$
154g: $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = R^5 = Me$, $X = COOMe$
154h: $R^1 = R^2 = R^3 = OMe$, $R^4 = R^5 = Me$, $X = COOMe$
154i: $R^1 = R^2 = \text{-}OCH_2O\text{-}$, $R^3 = H$, $R^4 = R^5 = Me$, $X = CONMe_2$
154j: $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = R^5 = Me$, $X = CONMe_2$

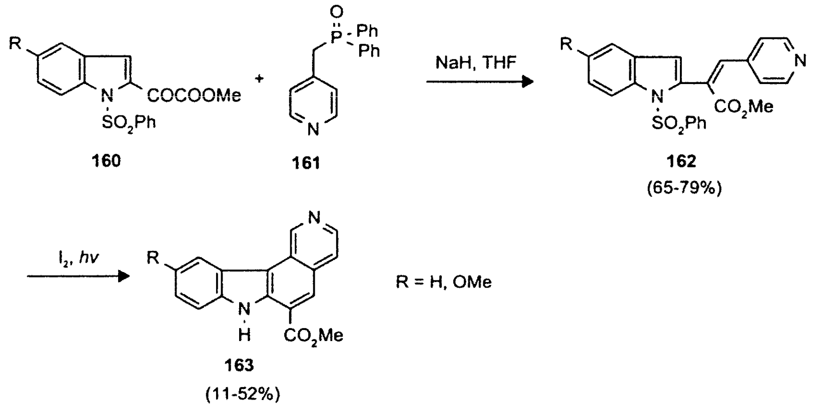
Ref. 44

Scheme 30.



Ref. 45

Scheme 31.



Ref. 48

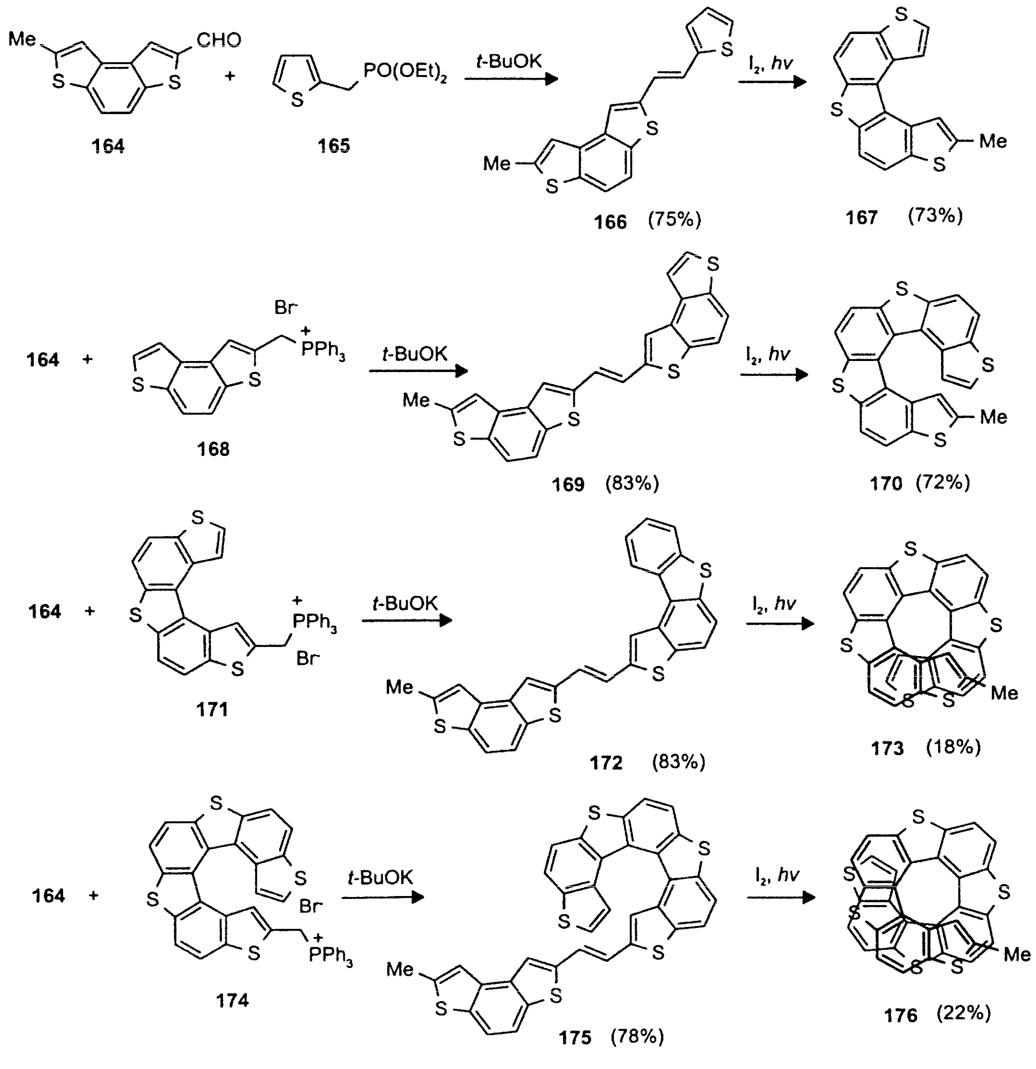
Scheme 32.

The reaction usually commences with attack of the nucleophile on a carbonyl group and subsequent intramolecular cycloaromatization.

In an earlier example, Loozen reported the facile synthesis of benzo[*b*]thiophenes **146** and naphthalenes **150** by annulation of thienyl aldehyde or ketones **143** and strongly activated benzaldehydes **147** with Grignard reagents **144** and **148** bearing an acetal group (Schemes 28 and 29).[42,43] Later, Tergue and Toth developed this method using lithium reagents to synthesize highly functionalized naphthalene derivatives **154** (Scheme 30).[44]

The Stobbe condensation of substituted benzaldehyde (**155**) with diethyl succinate (**156**) gave butanedioic acid mono-ester **157**, which readily cyclized to give naphthoate (**158**). Further elaboration of **158** gave azanzone A, a naturally occurring *o*-naphthoquinone (**159**) (Scheme 31).[45] Similar Stobbe condensation of pyrrole and indole aldehydes have been used by El-Raynes to prepare indoles[46] and carbazoles,[47] respectively.

The core structure **163** of 6-substituted 7*H*-pyrido[4,3-*c*]carbazoles, a class of antitumor agents, was conveniently synthesized by the Wittig reaction of *N*-(phenylsulfonyl)-2-methoxalylindoles **160** with diphenyl(4-pyridylmethyl)phosphine oxide (**161**) and subsequent oxidative photocyclization (Scheme 32).[48] Similar [3+3] benzannulations using heteroaromatic aldehydes and Wittig reagents have been reported for the preparation of annulated 2-methylheterohelicenes and optically pure heterohelicenes (Schemes 33 and 34).[49,50]

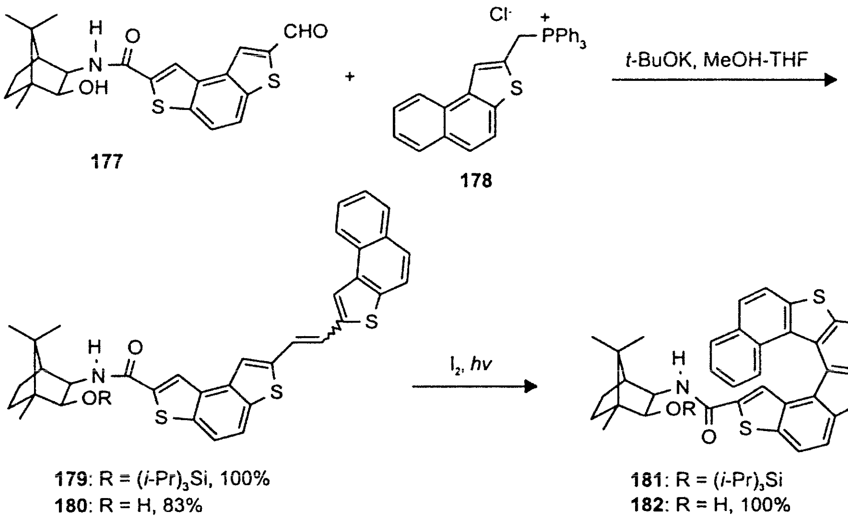


Ref. 49

Scheme 33.

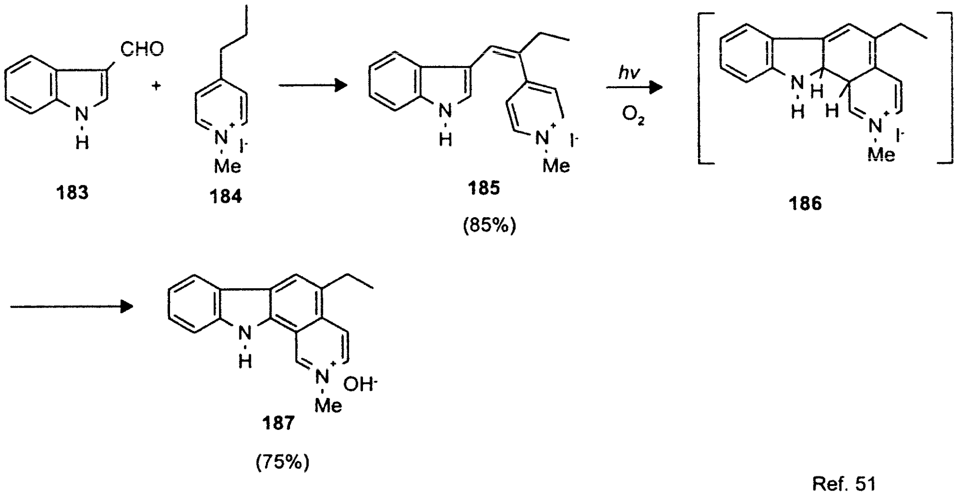
The naturally occurring alkaloid **187** was synthesized via condensation of 3-indolecarbaldehyde (**183**) with pyridinium salt (**184**) (Scheme 35).[51] Benzo[*a*]acridines were similarly prepared based on condensation of 4-hydroxy-2-methylquinoline derivatives with aryl aldehydes and photochemical transformation of the condensed intermediates **190** (Scheme 36).[52]

Oda and Machida reported the benzannulation of heteroaromatics by photoreaction of arenethiocarbamides **192** with 2-methoxyfuran (**193**) as illustrated in Scheme 37, which indicates the likely reaction mechanism.[53]



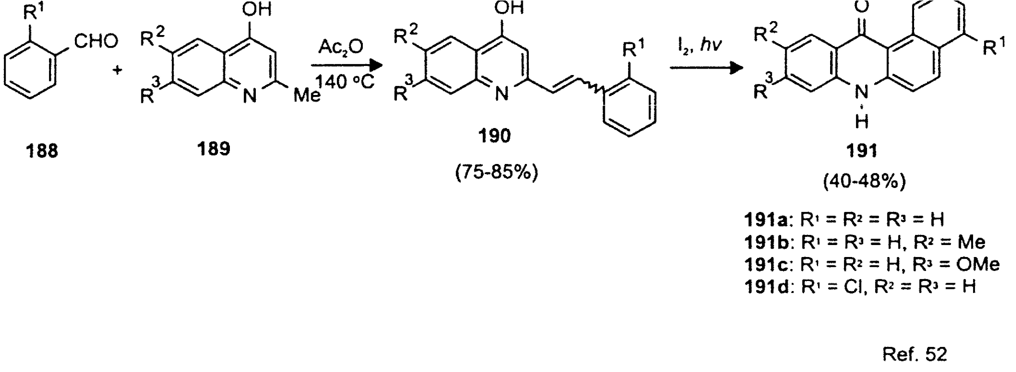
Ref. 50

Scheme 34.



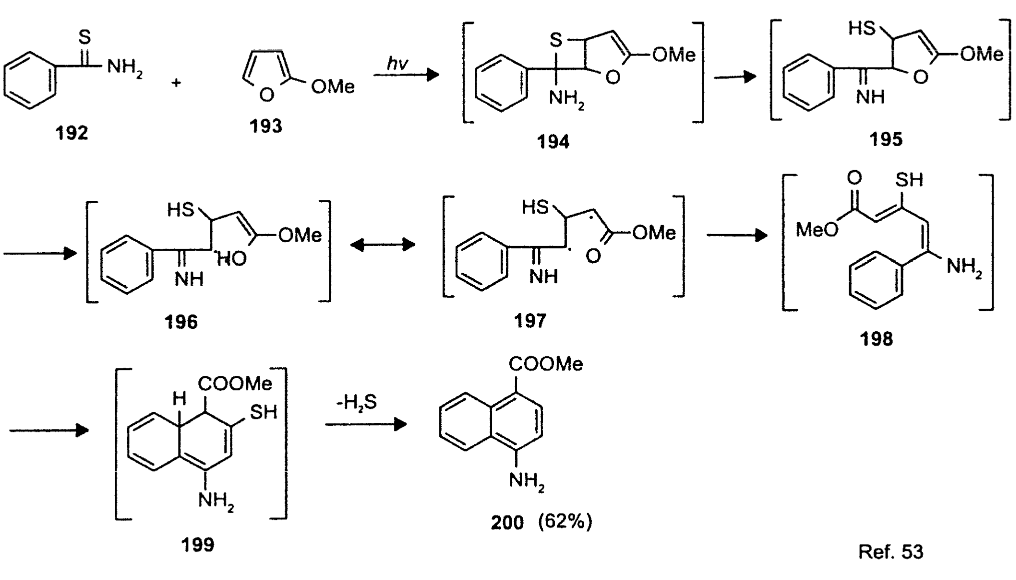
Ref. 51

Scheme 35.

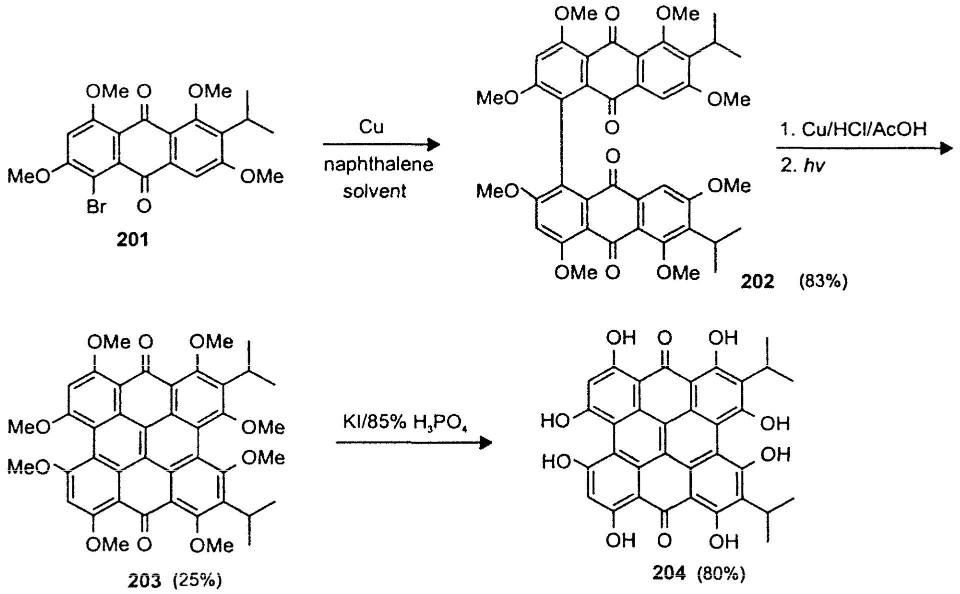


191a: $R^1 = R^2 = R^3 = H$
191b: $R^1 = R^3 = H$, $R^2 = Me$
191c: $R^1 = R^2 = H$, $R^3 = OMe$
191d: $R^1 = Cl$, $R^2 = R^3 = H$

Scheme 36.



Scheme 37.



Ref. 54

Scheme 38.

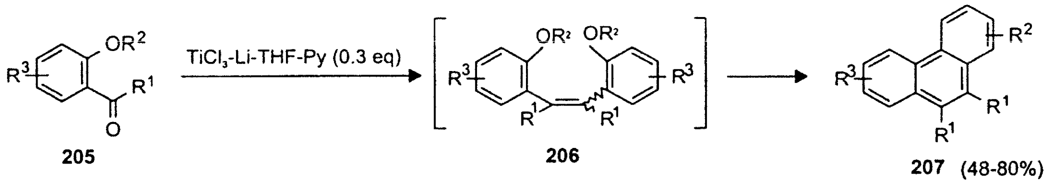
3. Dimerization Followed by Aromatization

[3+3] Dimerization is an effective way to construct symmetrical molecules and [3+3] benzannulations by dimerization have been reported for the synthesis of many biologically interesting compounds and important synthetic intermediates. These annulations are usually initiated by radical coupling induced by reducing reagents such as metals.

Iio et al. reported a facile synthesis of stentorin (**204**), the photoreceptor of *stentor coeruleus*: using the Ullmann coupling of 5-bromo-2-isopropyl-1,3,6,8-tetramethoxyanthraquinone (**201**) promoted by copper gave intermediate **202** which, upon treatment with 'Cu/HCl/HOAc', underwent reductive coupling of the carbonyl groups to form a double bond and subsequent photocyclization afforded **203**. Demethylation with KI/85% H_3PO_4 yielded stentorin (**204**) (Scheme 38).[54]

In 1991, Banerji and Nayak disclosed that phenanthrenes can be synthesized by low valent titanium (LVT)-induced double coupling of *ortho*-alkoxyaromatic aldehydes and ketones.[55] Recently, they found that use of the LVT-pyridine reagent system improved yields of phenanthrenes **207** by as much as two-fold[56] (Scheme 39). Dibenzo[*b,f*]suberone (**208**) underwent LVT-promoted reductive coupling to give tetrahydrobis(benzocyclohept)anthracene (**213**) (Scheme 40).[57] Similarly, the treatment of fluorenone (**214**) with magnesium gave highly pure rubicene (**215**) (Scheme 41).[58]

The naturally occurring perylenequinones are of interest due to their significant biological potential. An important feature of this class of compounds is their symmetrical structures. Therefore, the dimerization method represents a most effective approach for their synthesis. Zhang and his coworkers described two closely related routes to perylenequinone (**223**) in which the fused benzene rings were formed by Ullmann coupling followed by further elaboration (route 1) or by a double oxidative coupling (route 2) (Scheme 42).[59,60] Based on the above results, Diwu and Lown demonstrated a short-cut for the preparation of perylenequinone (**223**) via double coupling of 1,2-naphthoquinone (**228**) promoted by $FeCl_3$/MeCN (Scheme 43).[61] Hauser et al. found that no external oxidizing agent was required for the dimerization process in their total synthesis of optically active calphostin D (**232**) (Scheme 44).[62]

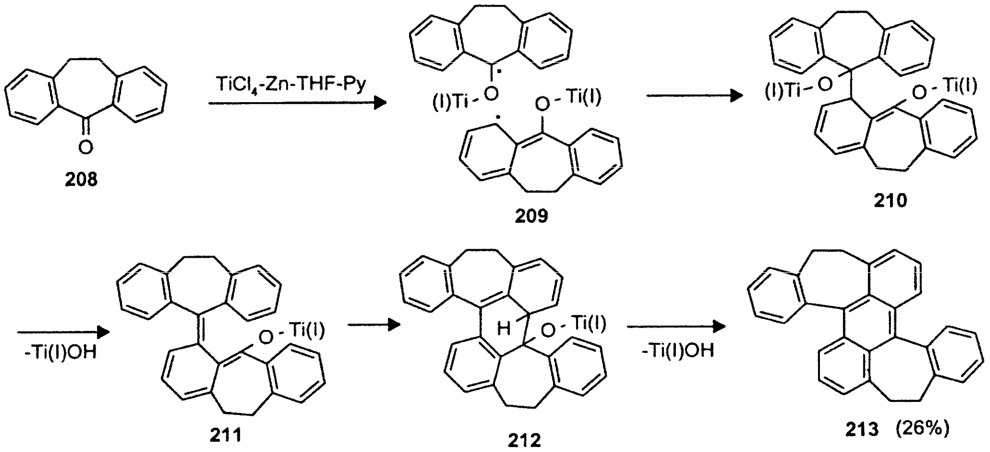


205-206a: R^1 = Me, R^2 = Et, R^3 = H
205-206b: R^1 = H, R^2 = Me, R^3 = H
205-206c: R^1 = R^2 = Me, R^3 = 5-Me

207a: R^1 = Me, R^2 = R^3 = H
207b: R^1 = R^2 = R^3 = H
207c: R^1 = Me, R^2 = 2-Me, R^3 = 7-Me

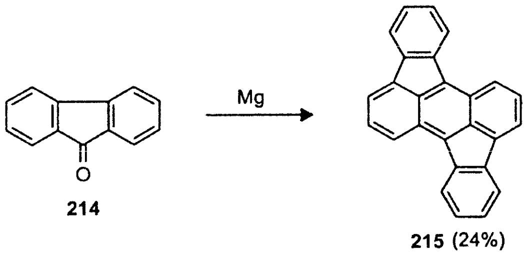
Ref. 56

Scheme 39.



Ref. 57

Scheme 40.



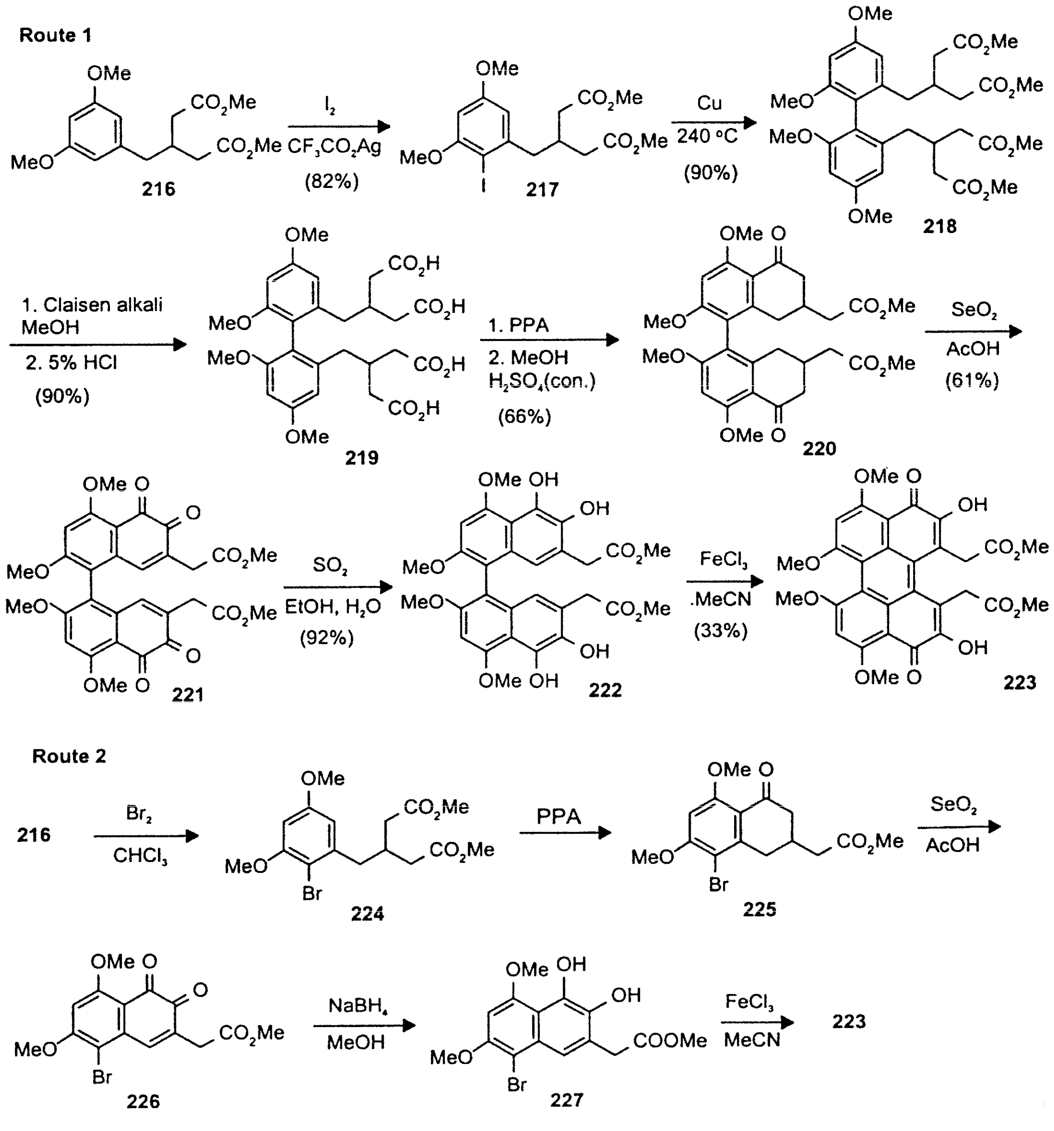
Ref. 58

Scheme 41.

Perlenequinone (**234**) and its dimethyl ether derivatives (**235** and **236**) were similarly synthesized (Scheme 45).[63]

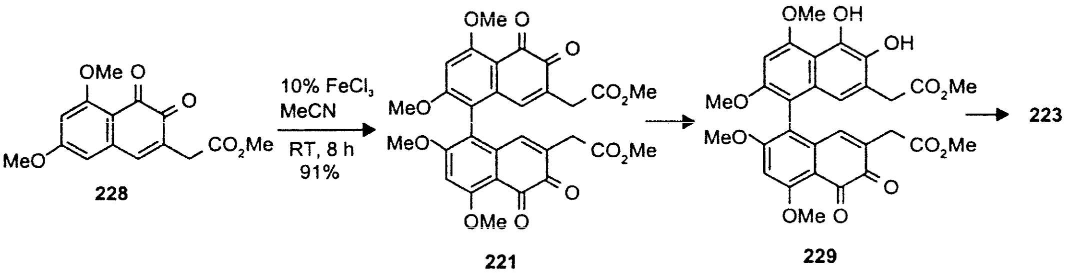
In 1973, Steglich and Arnold discovered that isohypericin (**242**) can be synthesized by base catalyzed condensation of emodin (**237**) (Scheme 46).[64]

Recently, we found that in the presence of zinc chloride 2-(benzotriazol-1-ylalkyl)-indoles **243** and **246** readily underwent dimerization followed by dehydrogenation on exposure to air to furnish indolo[3,2-*b*]carbazoles **245** and **247** (Scheme 47).[27,65]



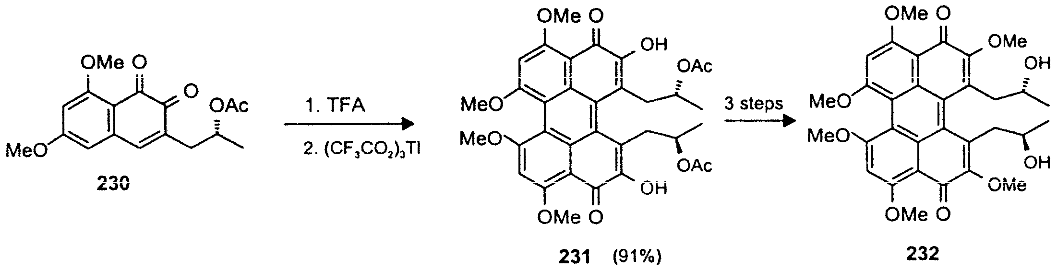
Refs. 59 and 60

Scheme 42.



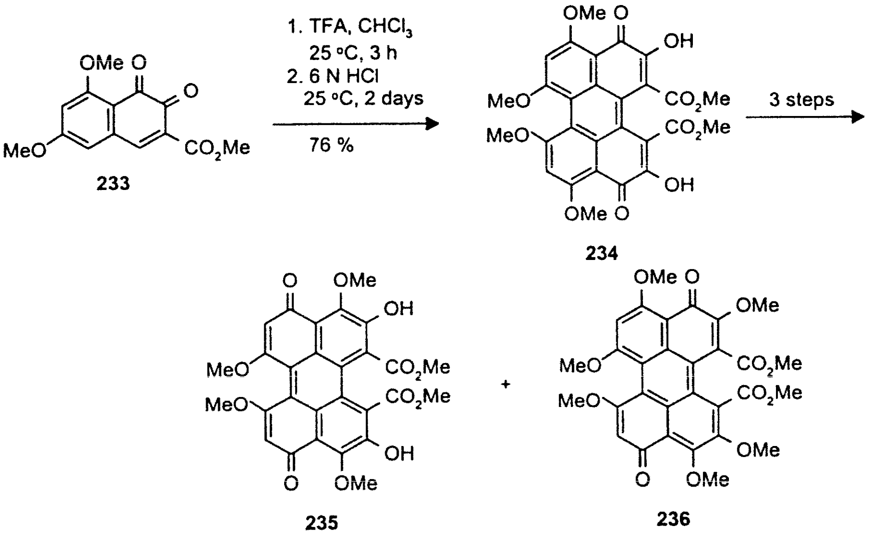
Ref. 61

Scheme 43.



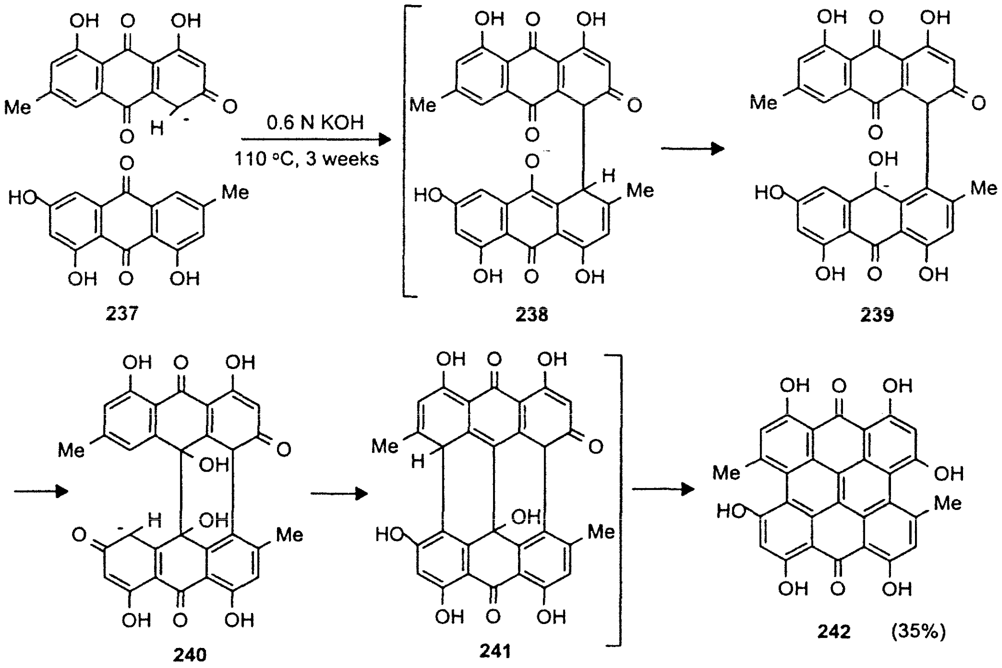
Ref. 62

Scheme 44.



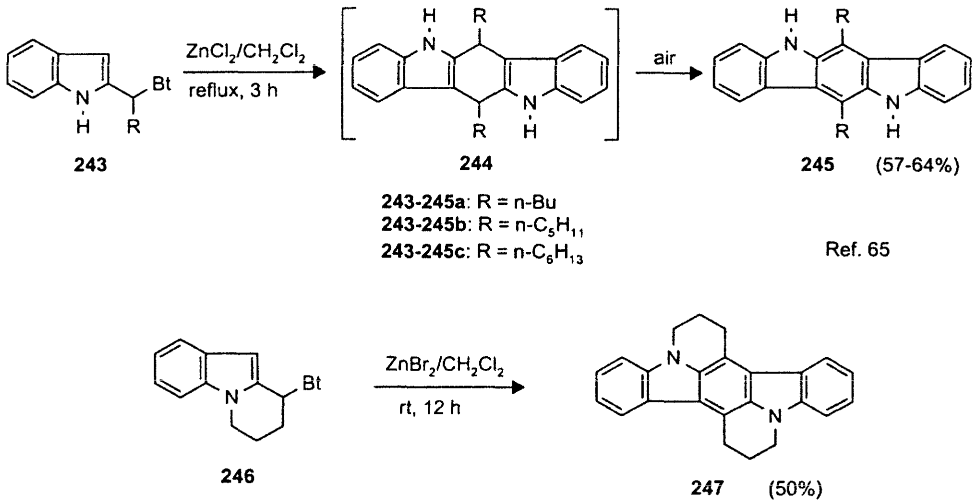
Ref. 63

Scheme 45.



Ref. 64

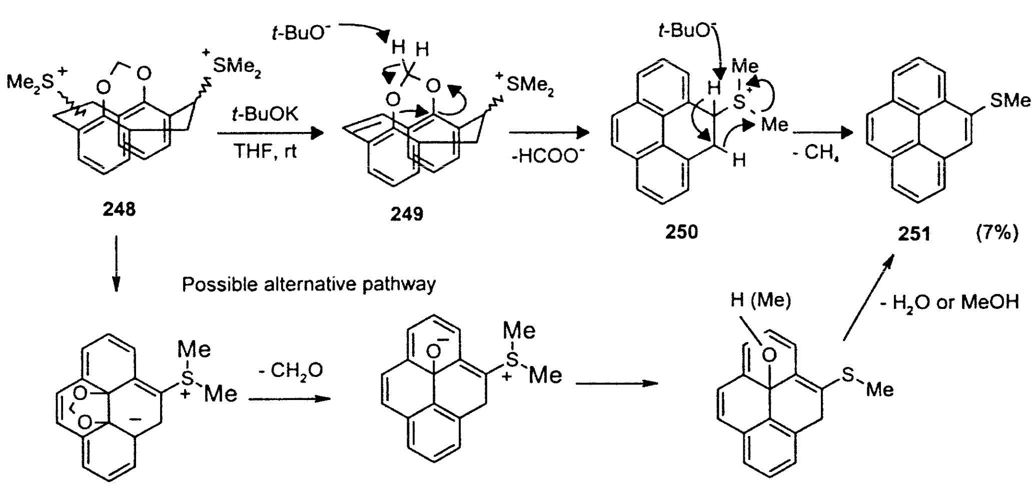
Scheme 46.



Ref. 65

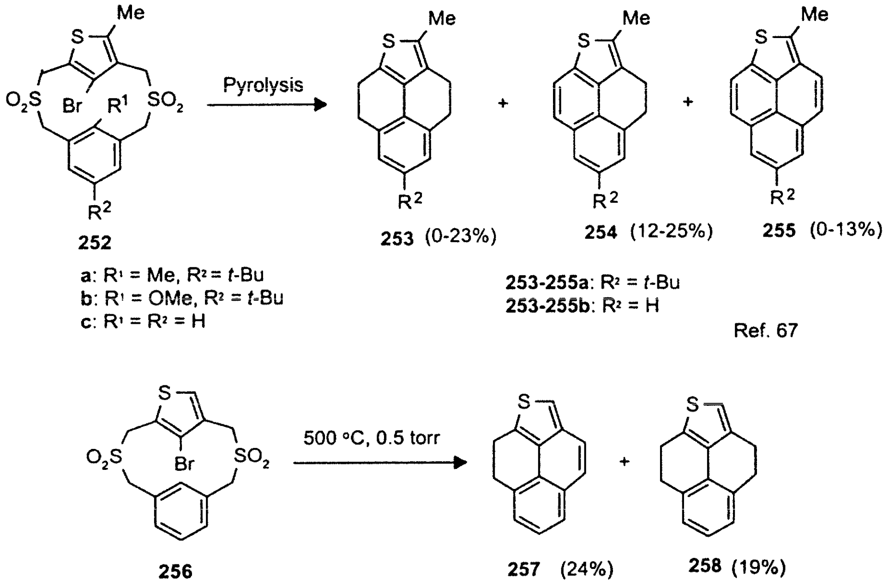
Ref. 27

Scheme 47.



Ref. 66

Scheme 48.

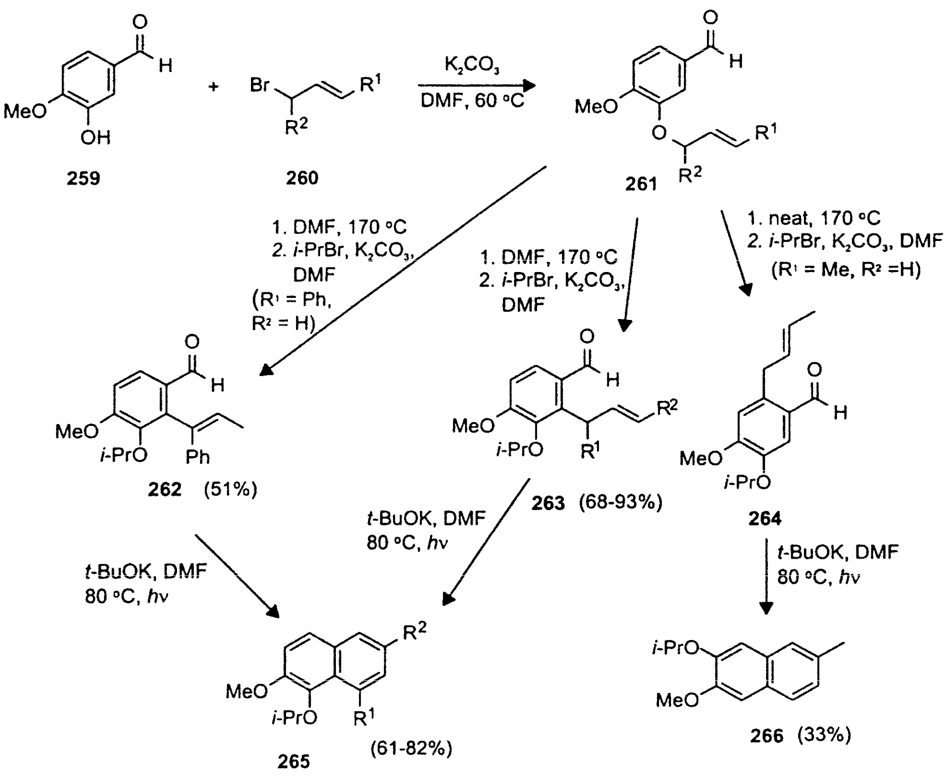


Ref. 68

Scheme 49.

4. Intramolecular [3+3] Benzannulation

Intramolecular [3+3] benzannulations have not been well explored and their synthetic utility has not yet been recognized. Nevertheless, these reactions have been described in several papers. In an investigation toward the synthesis of 17,19-dioxa[2.2.3](1,2,3)cyclophanediene, Lai and Eu demonstrated the formation of 4-methylthiopyrene (**251**) which was explained by invoking a novel base-induced ring cyclization of **249** resulting in elimination of formate anion from the methylenedioxy bridge to form **250**. This was suggested to be followed by a novel 1,4-hydride shift resulting in the elimination of methane (Scheme 48);[66] an alternative pathway is also shown in the scheme.

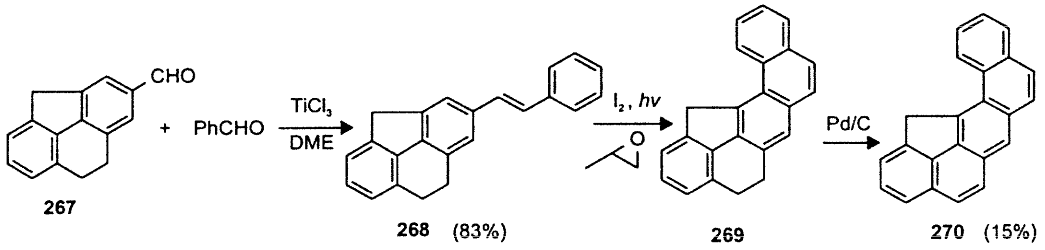


260-261, 265a: $R^1 = R^2 = H$
260-261, 265b: $R^1 = Me, R^2 = H$
260-261, 265c: $R^1 = H, R^2 = Me$
260-261, 265d: $R^1 = Ph, R^2 = H$

263a: $R^1 = R^2 = H$
263b: $R^1 = Me, R^2 = H$
263c: $R^1 = H, R^2 = Me$

Ref. 69

Scheme 50.



Ref. 70

Scheme 51.

In the synthesis of [2]metacyclo[2]thiophenophanes, Takeshita and Tashiro isolated unexpected benz-annulation products (Scheme 49).[67,68]

5. Miscellaneous Benzannulation

Koning and coworkers recently reported a novel synthesis of substituted naphthalenes **265–266** involving coupling of allyl bromides **260** with isovanilin (**259**), subsequent Claisen rearrangement and then cycloaromatization induced by irradiation (Scheme 50).[69]

Yang and Harvey synthesized methylene-bridged polycyclic aromatic hydrocarbons **270** using McMurry coupling of **267** with benzaldehyde in the presence of $TiCl_3$ and followed by single-step oxidative photocyclization in the presence of I_2 and propylene oxide (Scheme 51).[70]

6. Summary

[3+3] Benzannulation reactions have found a wide range of applications in organic synthesis. A crucial feature of [3+3] benzannulation is its regioselectivity. We hope that this review will be a useful reference for synthetic organic chemists and will generate increased attention for this methodology.

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