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Syntheses of polyfunctional aromatic compounds from non-aromatic precursors

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Syntheses of polyfunctional benzene derivatives from both cyclic and acyclic non-aromatic precursors are reviewed. Such aromatizations include transformations that use Diels – Alder reactions, transition metal-catalyzed reactions, base mediated aldol or Michael addition reactions or electrocyclic and pericyclic reactions. This review is limited to research that has been published since the last reviews in 2006, 2008, 2015 and 2018 and is specifically focused on aromatic and heteroaromatic compounds synthesized by construction of the benzene ring. It excludes heterocyclic compounds that lack a monocyclic benzene core. Applications of such aromatization reactions for the total syntheses of natural products as well as potential medicinal chemical entities are included.
The bibliography includes 155 references.

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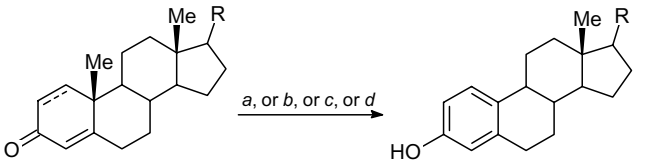
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1. Introduction

The classical methods for the synthesis of polyfunctional aromatic compounds depend on the use of a range of reactions including sequential electrophilic aromatic substitution reactions and *o*-metalation with addition or substitution reactions using electrophilic reagents. Additionally, transition metal-catalyzed substitution and C – H activation are also of considerable value in this regard. All these transformations depend on the conversion of an aromatic precursor to another aromatic compound of enhanced complexity. There is an alternative process: the conversion of a non-aromatic precursor, which may be cyclic or acyclic, into an aromatic compound; such transformations are complementary to classical approaches and are often used for the synthesis of arenes with ring substitution patterns not readily available by classical arene derivatizations.

An early example for this type of aromatization is the conversion of testosterone or androstadienedione into estradiol, both enzyme-catalyzed processes *in vivo* (Scheme 1, conditions *a*). Related bioinspired dehydrogenative aromatizations *via* transition metal-catalyzed oxidations have been reported in the first half of the 20th century.[1,2] Alternative reactions using oxidants such as iodine have since been extensively studied for the synthesis of many aromatic compounds mainly from functionalized cyclohexane or cyclohexanone precursors (see Scheme 1, conditions *b* – *d*).[3–8]

Scheme 1



R = OH (testosterone), (=O) (androstadienedione)

R = (=O) (estradiol)

(*a*) aromatase enzyme; (*b*) flash vacuum pyrolysis; (*c*) Fe-porphyrin, peroxide; (*d*) I_2, PPh_3

This review aims to complement an overview of these reactions by highlighting additional methods for ring formation and subsequent aromatization processes, which

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Current research interest of the authors: synthesis of bioactive natural, heterocyclic, organometallic compounds, macrocyclic ethers, lactones and porphyrazines, design of novel therapeutic agents for detection and treatment of cancers, catalytic sustainable organic synthesis, application of combinatorial chemistry and parallel synthesis for the development of pharmaceuticals, applications of microfluidic flow reactors in synthesis.

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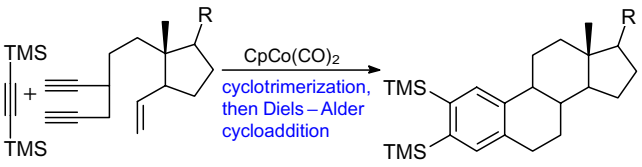
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allows for the synthesis of arenes with various functionalities otherwise not readily available from the derivatization of aromatic precursors. These alternative reactions possess a high degree of flexibility for the synthesis of polyfunctional arenes.

Such advantages are reported for the base-catalyzed benzannulation reactions,[9,10] Diels–Alder cycloadditions[11–16] and electrocyclic and pericyclic reactions followed by aromatization.[17–19] These strategies are often employed, since in addition to the above advantages, they can also reduce the costs of scale-up synthesis with the use of inexpensive building blocks and transformations with high atom economy.

The synthesis of aromatic compounds through transition metal-catalyzed reactions, such as ring-closing alkene metathesis (RCM) or cyclotrimerization of alkynes or alkenes and subsequent aromatization, often allows for the synthesis of aromatic compounds with a range of bespoke substituents that would not be easily accessible through other methods.[20–22] RCM shows remarkable functional group tolerance and can often be carried out under mild reaction conditions. Cyclotrimerization reactions are also often conducted under mild conditions and show broad functional group compatibility.[23] A highlight of this methodology is the Funk and Vollhardt's[24] estrone synthesis *via* a [2+2+2]-cyclotrimerization strategy to elaborate the aromatic ring complementing the biomimetic dehydrogenative processes described above (Scheme 2).

Scheme 2



R = OH, (=O); TMS = $SiMe_3$

The reaction strategies herein described have distinct advantages and disadvantages and are complementary to each other for the synthesis of aromatic compounds. The review covers a selection of methods for cyclization reactions and subsequent aromatizations published between 2016 and early 2020. For a more comprehensive and exhaustive selection of aromatization methods, the authors draw attention to the recently updated Chapter: Formation of Arenes by Aromatization in Comprehensive Organic Transformations by Larock and Pletnev † as well as various prior reviews.[25–33]

The following designations and abbreviations are used:

Ad — adamantyl,
All — allyl,
Atom Economy — ratio of atoms transferred from starting material to products,
BINAP — 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,
Boc — *tert*-butyloxycarbonyl,
[bmim][Cl] — 1-butyl-3-methylimidazolium chloride,
BMIDA — boronic acid *N*-methyliminodiacetic acid ester,
Bn — benzyl,
Cbz — carboxybenzyl,
CDI — 1,1′-carbonyldiimidazole,
Cy — cyclohexyl,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
DCE — 1,2-dichloroethane,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DEC — *N*,*N*-diethylcarbamoyl,
DMAD — dimethyl acetylenedicarboxylate,
DMP — Dess–Martin periodinane,
E_1CB — elimination unimolecular conjugate base,
FN — functionalized nanoparticle,
Fu — furyl,
FVP — flash vacuum pyrolysis,
HIV — human immunodeficiency virus,
IC — inhibitory concentration,
LC — median lethal dose,
LED — light-emitting diode,
Mes-Acr$^+ClO_4^-$ — 9-mesityl-10-methylacridinium perchlorate,
MIC — minimum inhibition concentration,
MOM — methoxymethyl,
Ms — methylsulfonyl (mesyl),
MTBE — methyl-*tert*-butyl ether,
MW — microwave,
NaBARF — sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate,
Naph — naphthyl,
p-NBA — 4-$O_2NC_6H_4COOH$,
NBS — *N*-bromosuccinimide,
NFSI — *N*-fluorobenzenesulfonimide,
NHC — *N*-heterocyclic carbene,
Ns — 4-nitrobenzenesulfonyl (nosyl),
o/n — overnight,
PG — protecting group,
PMB — *para*-methoxybenzyl,
Py — pyridyl,
RCM — ring closing alkene metathesis,
SET — single electron transfer,
TBAF — tetra-n-butylammonium fluoride,
TBD — 1,5,7-triazabicyclo[4.4.0]dec-5-ene,
TBS — *tert*-butyldimethylsilyl,
TEMPO — (2,2,6,6-tetramethylpiperidin-1-yl)oxyl,
TES — triethylsilyl,
Tf — trifluoromethanesulfonate (triflate),
TFA — trifluoroacetic acid,
TFP — tri-2-furylphosphine,
Th — thienyl,
THP — tetrahydropyranyl,
TIPS — triisopropylsilyl,
TMS — trimethylsilyl,
TMTU — tetramethylthiourea,
Ts — 4-toluenesulfonyl (tosyl),
w/u — work-up.

2. Diels–Alder reactions and subsequent aromatization

The Diels–Alder cycloaddition is an exceptionally powerful reaction for the synthesis of carbocycles, given the chemo-, regio- and stereoselectivity which is retained from the starting materials in addition to excellent atom economy. By employing a post-cycloaddition oxidation or an elimination reaction, aromatization can be carried out, thereby providing a range of heavily substituted aromatic com-

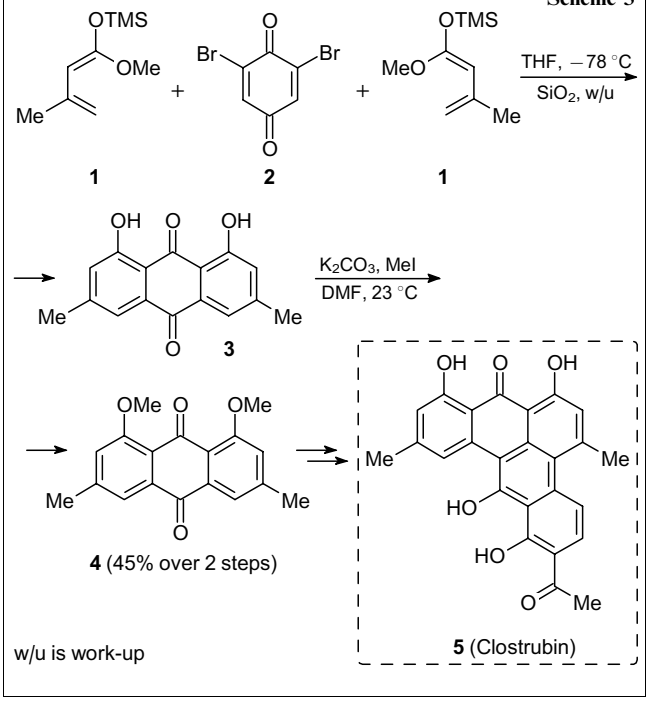
† R.C.Larock, A.Pletnev. In *Comprehensive Organic Transformations*. (Eds R.C.Larock). (Wiley, 2018).

pounds efficiently.[29, 34] These reactions may be sub-divided according to the diene or dienophile precursors.

2.1. Quinone precursors

Since previous reviews, Diels – Alder reactions of quinones and quinonimine ketals have been reported to be useful for the syntheses of aromatic compounds. Additionally, Brassard's, Danishefsky's and other related dienes remain particularly useful building blocks for the synthesis of α,β-unsaturated cyclohexenones, which are readily converted into phenols by oxidation using oxygen, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), *etc*. For example, Li and co-workers[35] reported that the reaction of dibromobenzoquinone **2** with diene **1** and subsequent dehydrobromination gave the northern anthraquinone fragment **3** of clostrubin (**5**) on a multi-gram scale (Scheme 3). The natural product was shown to have strong antibiotic activities with minimum inhibition concentrations (MIC's) at 0.12 μmol L^{-1} against methicillin-resistant *Staphylococcus aureus* and 0.97 μmol L^{-1} against vancomycin-resistant enterocci.

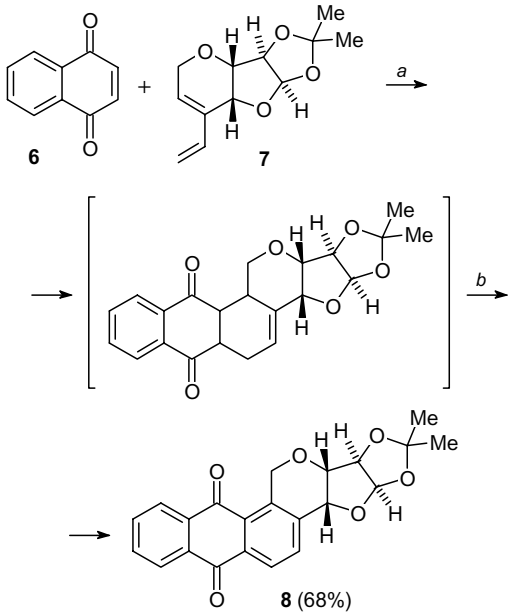
Scheme 3



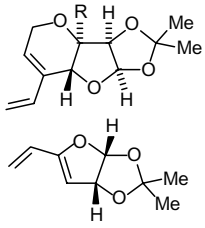
In 2017, Sayyad and Kaliappan[36] reported a Diels – Alder reaction and subsequent aromatization for the synthesis of the polycyclic anthraquinones **8** functionalized with delicate sugar moieties (Scheme 4). Other dienophiles that were employed in this sequence included various quinones as well as dimethyl acetylenedicarboxylate (DMAD) together with various sugar functionalized dienes followed by aromatization under aerobic, acidic conditions.

Khan and co-workers[37] recently reported the use of the Diels – Alder and aromatization strategy in their synthesis of magterpenoid C (**11**) *via* a key silica-gel mediated [4 + 2]-cycloaddition reaction followed by oxidative aromatization with manganese dioxide (Scheme 5). The magterpenoids A – C inhibit protein tyrosine phosphatase 1B, and thereby enhance insulin sensitivity in cells. An attempted synthesis of the more complex tricyclic magterpenoid B by the same methodology, however, was not successful.

Scheme 4

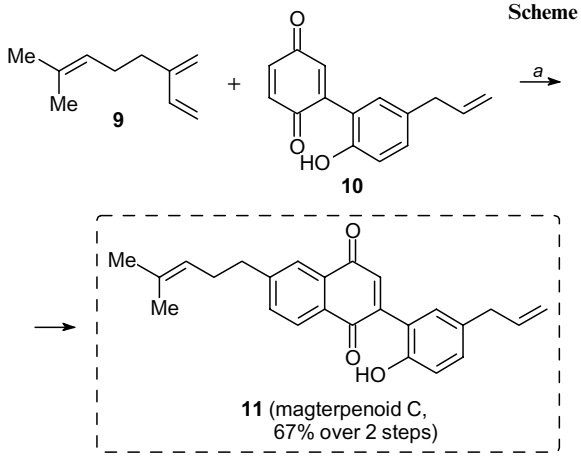


(*a*) PhMe, 110 °C, 12 h; (*b*) SiO_2, NEt_3, air, 23 °C, 2 h;

other dienes **7**:  (R = H, Me, Ph),

(52% – 89%, 26 examples)

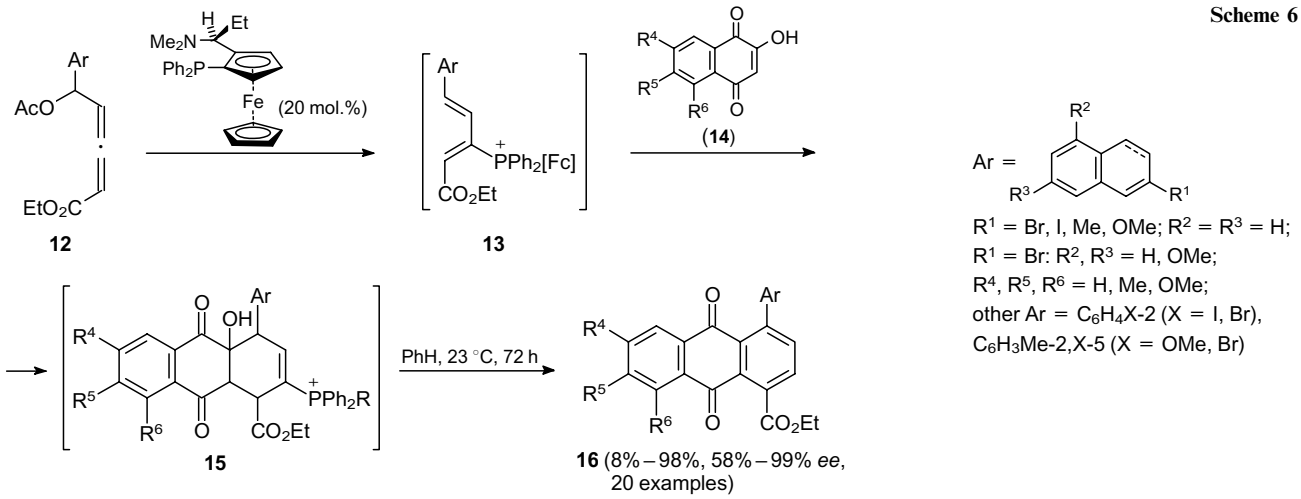
Scheme 5



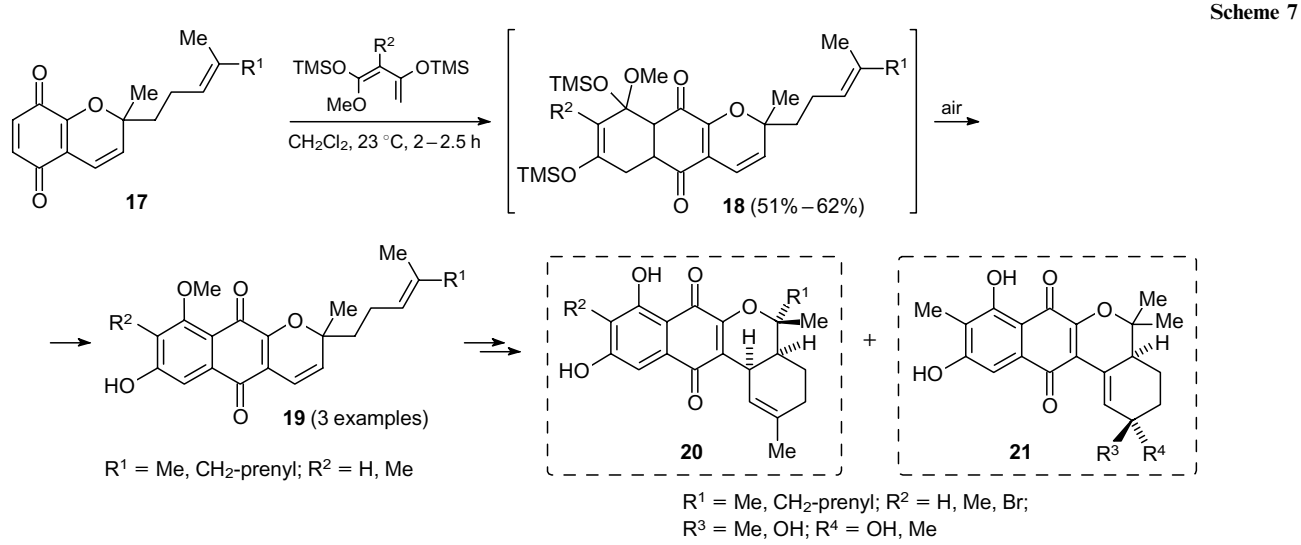
(*a*) 1) SiO_2, 2.5 h; 2) MnO_2, CH_2Cl_2, 39 °C, 4 h

Tong and co-workers[38] reported the first atropoisomerically-selective synthesis of conformationally stable 1,1′-naphthyl-anthraquinones **16** from the Diels – Alder reaction of (1-acetoxy-1-(1-naphthyl)methyl)allenoates **12** and 2-hydroxy-1,4-naphthoquinones **14** catalyzed by an enantiomerically pure ferrocene-based phosphine (Scheme 6). These reactions were extended to those of a range of substituted (1-acetoxy-1-(2-mono- and 2,6-disubstituted-phenyl)methyl)allenoates, mono- and disubstituted-2-hydroxy-1,4-benzoquinones and a hydroxybenzeno-anthracenequinone to provide the corresponding adducts

Scheme 6



Scheme 7



(**16**). The postulated mechanism involved phosphine addition to the allene and acetoxy elimination to form the diene **13**, which readily reacted with the dienophile **14** to produce the adduct **15**. Subsequent base mediated ylide formation, phosphine elimination and dehydration induced aromatization.

In his most recent meroterpenoid studies, George and co-workers[39] employed a Diels–Alder and aromatization sequence for the synthesis of the racemic aromatic core of the naphterpin and marinone natural products (Scheme 7). Quinones **17** and Brassard's diene (or derivative of Brassard's diene) and subsequent aerobic oxidation gave the tricyclic arenes **19**. Within one to three steps, these products **19** were converted into four different naphterpin (**20** and **21**) and marinone (**20**) natural products.

Hsu and Huang[40] employed a Diels–Alder reaction of naphthoquinone **22** with diene **23** in the presence of the Lewis acid boron triacetate, followed by methanol elimination, TMS-ether hydrolysis and aerobic oxidation to give anthraquinone **25**, furnishing three of the four rings of parimycin (**26**) (Scheme 8). The use of boron triacetate was critically important for the observed regioselectivity as well as enabling the reaction to proceed at room temperature. Anthraquinone **25** was subsequently converted into racemic parimycin (**26**) and its (*R*)-(−)-enantiomer (**27**) thereby defining the absolute stereochemistry of the natural product as the (*S*)-(+)-enantiomer, a potent antitumour compound with activities against stomach, lung, breast and skin cancers with IC_{70} values between 0.9 to 6.7 μg mL^{-1}.

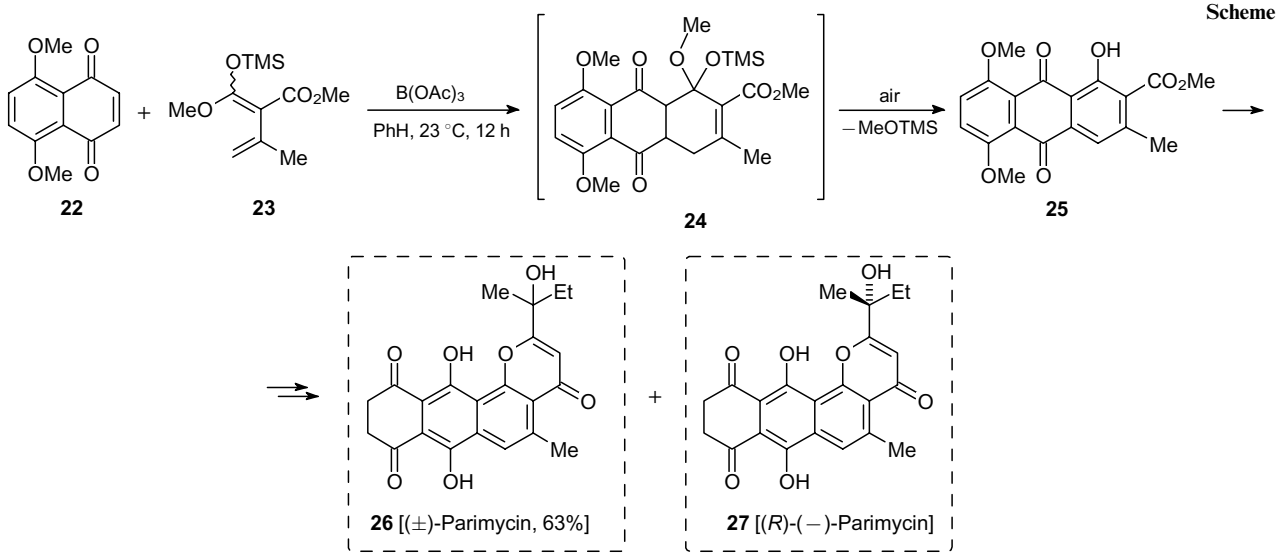
Chen and co-workers[41] showed that the formal Diels–Alder reaction of quinone imines **28** with dienals **29** catalyzed by the prolinol derivative **30** provided substituted aromatic compounds **33** with excellent relative and absolute stereochemical control following trimethylsilane mediated dehydroxylation of the carbinolamines **32** (Scheme 9). These products **33** included examples with a broad range of electron-withdrawing and -donating substituents. The method additionally showed good compatibility with a range of protecting groups (PG = Boc, Cbz, Ts) and proceeded with high enantioselectivities.

2.2. Thiophene and furan precursors

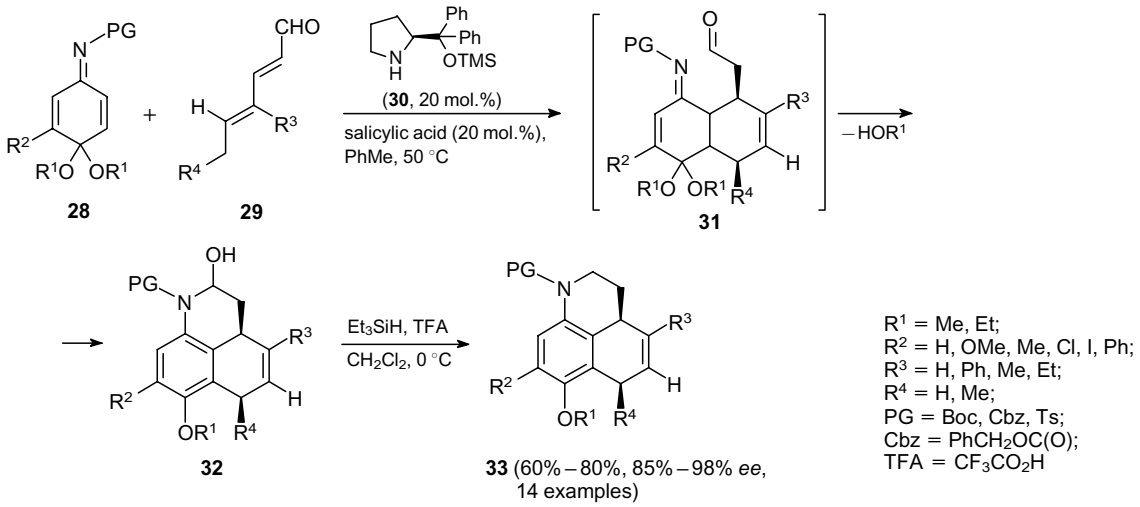
Kamimura and co-workers[42] reported the synthesis of phthalimides **38** from maleimides **35** and furfural hydrazones **34** under microwave irradiation (MW) in ionic liquids (Scheme 10). The only by-product of this reaction is water and the ionic liquids were shown to be repeatedly recyclable with no loss of functionality.

Jérôme and coworkers[43] described the synthesis of the *o*- and *m*-xylene derivatives **42** and **43** by allowing the

Scheme 8



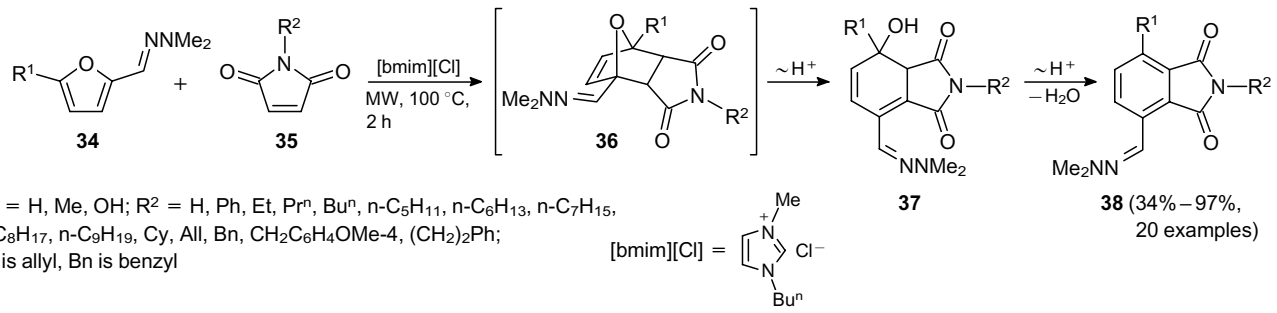
Scheme 9



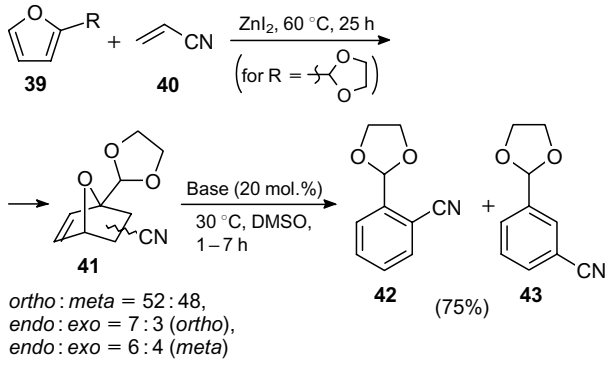
furfural acetal **39** to react with acrylonitrile **40** under Lewis acid catalysis to give the Diels–Alder adduct **41** (Scheme 11).[43] This Diels–Alder reaction showed modest selectivity towards the *o-endo*-adducts. Various bases were screened for the conversion of the Diels–Alder adducts into the aromatic compounds **42** and **43**, with regioselectivities ranging from 1.5–3.4 : 1 in favour of the *m*-product **43**. By prematurely quenching the base induced aromatization reaction of adduct **41**, the selectivity towards the *m*-xylene derivative **43** was further enhanced. Subsequent derivatization was used in a new route to *m*-xylenediamine, an important monomer in polymer chemistry.

Recently, Lei and co-workers[44] reported the conversion of thiophenes **44**, **45** and acetylenes **46**, **48** to aromatic compounds **47**, **49** under exceptionally mild photocatalytic conditions using 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$ClO$_4^-$), with the generation of elemental sulfur as a byproduct (Scheme 12). Related Diels–Alder reactions of thiophene were previously reported to proceed at very high temperatures (typically >220 °C)[45] but this was reduced to room temperature with photocatalysis. It was postulated

Scheme 10



Scheme 11

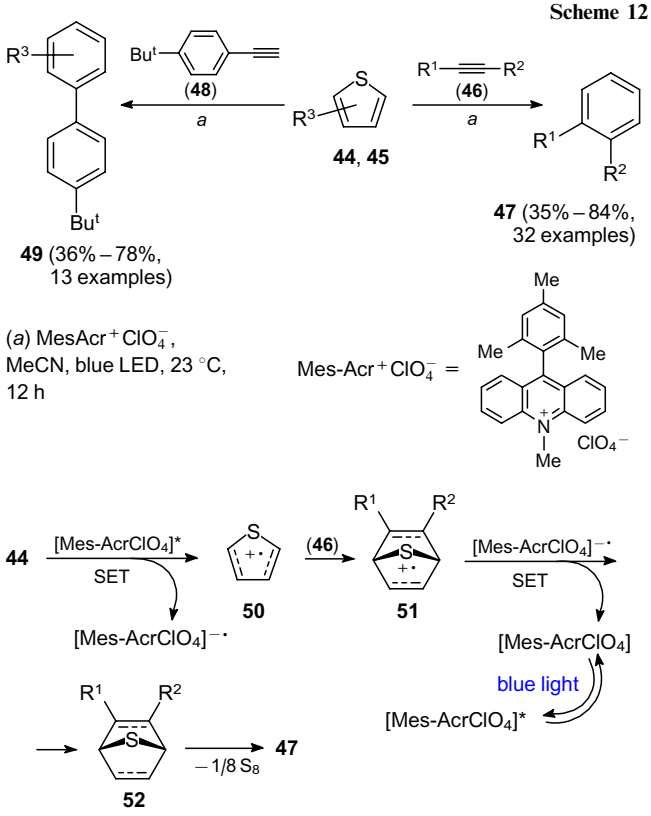


39 **40** **41** **42** **43**

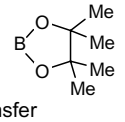
R = Me, CH_2OEt, CH_2OH (38%–86%, **42** : **43** = 1 : 1.5–1 : 3.4);
Base: NaOMe, $NaOBu^t$, KOH, NaOH, Amberlyst-26

that the formal [4 + 2] addition was initiated by the oxidation of thiophene (**44**) to the corresponding radical cation **50** by the excited state of the photocatalyst. Addition of this species to alkynes **46** gave the radical cation adduct **51**, which was reduced by a single electron transfer (SET) from the reduced photocatalyst, thereby regenerating the photocatalyst and forming the Diels–Alder adduct **52**, which subsequently underwent elimination of sulfur accompanied by aromatization. The authors reported related syntheses of aromatic compounds from the corresponding selenophenes.

Scheme 12



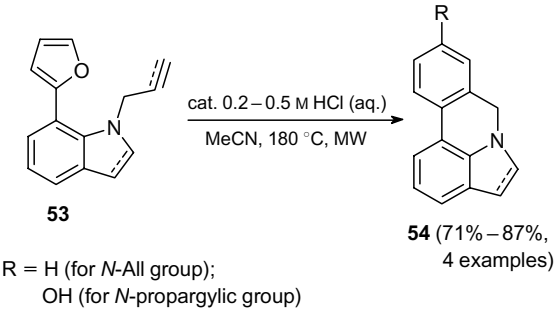
R^1 = Ph, C_6H_4X-4 (X = Bu^t, Me, Ph, OAc, OMe, F, Cl, Br, CHO, CO_2Me, CF_3, CN), C_6H_4Me-2(3), 3-Th (Th is thienyl), 4-NMe-pyrazole, 1-cyclohexenyl, $(CH_2)_2OTBS$, $(CH_2)_2Ph$, 3-biphenyl, Et, estrone, $C_6H_4[CH_2CH(NHAc)CO_2Me]$-4, sarcosine derivative, C_6H_4-4-$CH_2OC(O)C_6H_4(SO_2NPr^i_2)$-4; R^2 = H, Me, Et;
44: R^3 = H; **45**: R^3 = 2-X (X = Me, Cl), 4-X (X = Me, Et, n-C_6H_3, $(CH_2)_2OAc$, Cl, Br, I, CH_2OMe, 3-Bpin, 3-CO_2Me, C≡CH), 3,4-Me_2

TBS = $SiBu^tMe_2$, Bpin = , LED is light-emitting diode,

SET is single electron transfer

In 2019, Gundersen *et al.*[46] reported the conversion of *N*-allyl- or *N*-propargyl substituted indole or indoline derivatives **53** into the core of bioactive lycorine alkaloids **54** *via* a Diels–Alder reaction followed by acid-catalyzed dehydration and aromatization (Scheme 13). When the precursor **53** was functionalized with *N*-allyl groups, the reaction gave rise to arenes (**54**, R = H), whereas the use of precursors **53** with *N*-propargyl groups provided phenols (**54**, R = OH). The authors also reported related intramolecular Diels–Alder and aromatization sequences for *o*-(2-furyl)-*N*-allyl- and *N*-propargylaniline derivatives.

Scheme 13



In 2020, Zubkov and co-workers[47] reported an aromatization method that involves the formation of arenes **67** and **75** from 3-(2-furyl)-allylamines **56** and **73** and bromomaleic anhydride **55** (Scheme 14). The authors proposed the initial formation of amides **57** and **58**, which subsequently underwent an intramolecular Diels–Alder reaction, with *exo*-control. Amides **57** plausibly undergo reaction *via* intermediates **61**–**66** to produce the final lactams **67**. In a comparable way, amides **58** plausibly undergo reaction *via* intermediates **68**–**72** to produce the same final lactams **67**. The lactams **67** were obtained in moderate to good yields after recrystallization. When the authors used 3-(3-furyl)-allylamines **73**, the corresponding aromatization product **74** was shown to be sensitive to acidic conditions, which resulted in the opening of the dihydrofuran ring to yield phenols **75** in moderate yields after recrystallization.

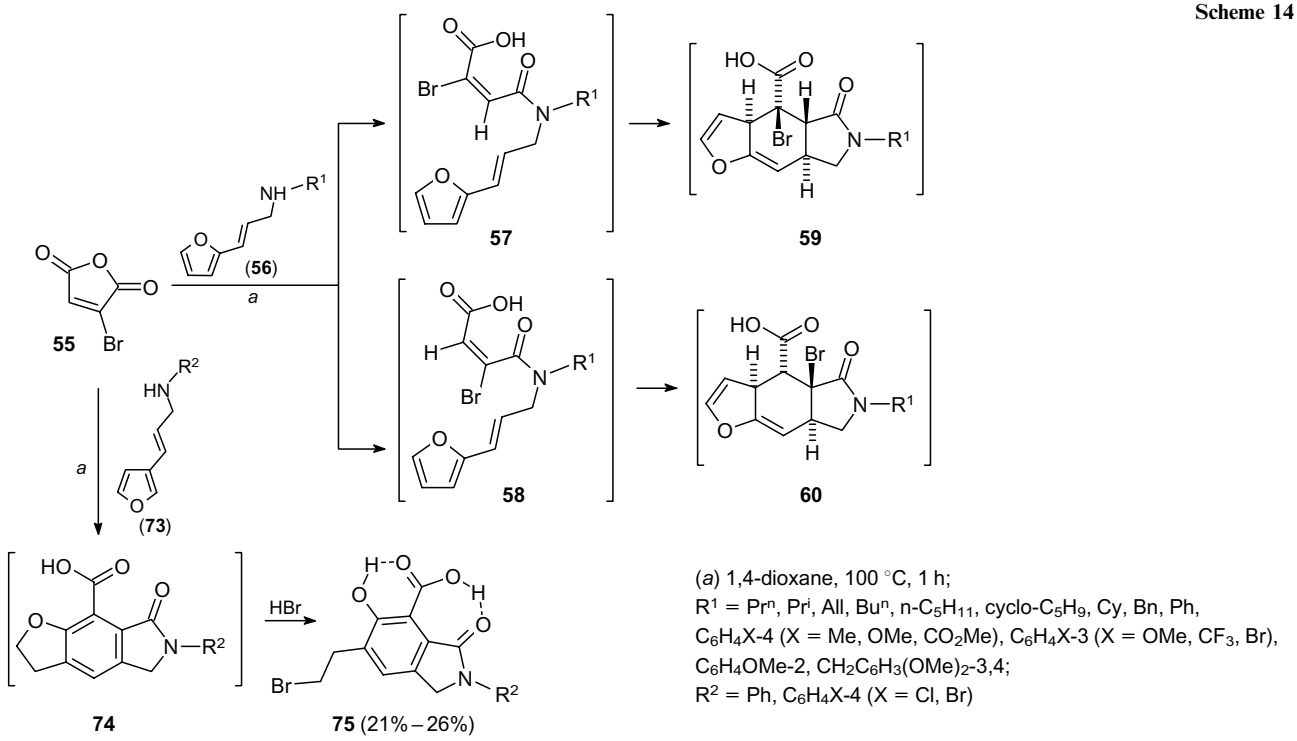
2.3. Pyrone starting material

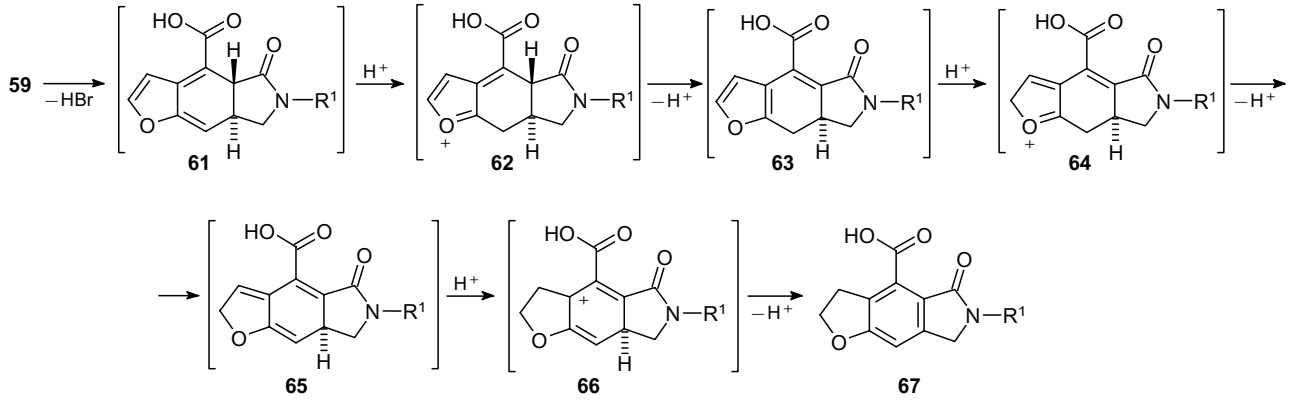
Pyrones are exceptionally good dienes for the synthesis of aromatic compounds since the initial cycloadducts **77** readily undergo loss of carbon dioxide in the aromatization step (Scheme 15). Snyder and co-workers[48] synthesized a range of indoline derivatives **78** in excellent yields using this method.

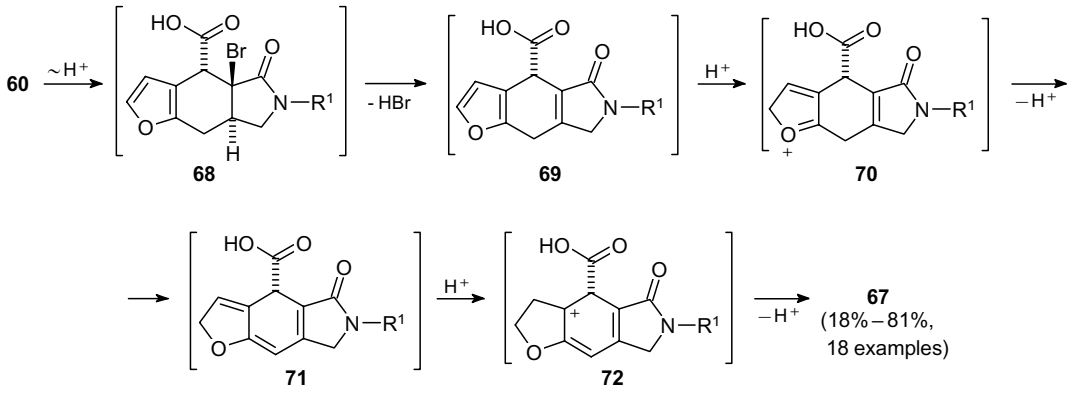
In 2017, Kraus and Wang[49] synthesized a range of differentially substituted aromatic compounds **82**, **84** by simple variation of the dienophile **80** in the Diels–Alder reaction step and subsequent aromatization by loss of carbon dioxide (Scheme 16). Interestingly in these examples, intermediate Diels–Alder-lactones **81** and **83** were stable and could be isolated.

Additionally, Yu and Kraus[50] expanded the substrate scope of this reaction by including various enamines **85**, **90**,

Scheme 14

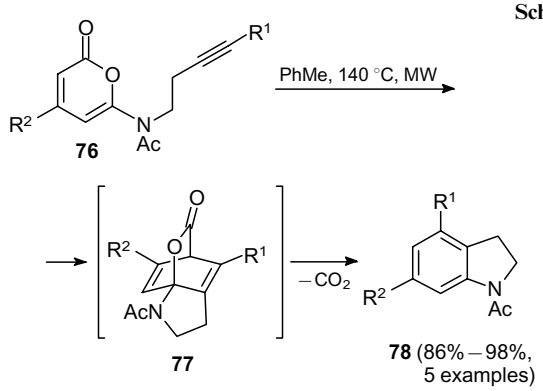






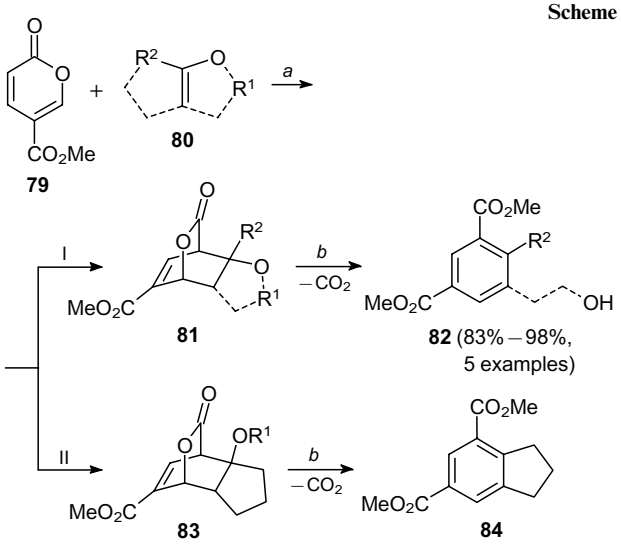
91 as dienophiles to provide the arenes **88**, **93** and **94** (Scheme 17). A range of enamine substrates bearing various alkyl and aryl groups as well as cyclic enamines were used in this reaction. Interestingly, the pyrrolidine enamine adducts **87** rapidly underwent elimination of both carbon dioxide and pyrrolidine and aromatization to provide the tetrahydronaphthalene **88**, whereas the morpholine adducts **92** were stable enough for purification but were aromatized using base-mediated elimination. When the cyclopentene derivative of enamine **86** was used, the reaction gave ketone **89** *via* a conjugate addition, carbon dioxide elimination and

Scheme 15



R^1 = H, Ph, TMS, CF_3; R^2 = Cl, SPh

Scheme 16

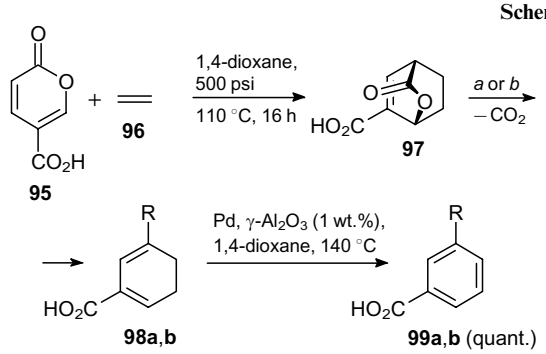


(*a*) MeCN, 75 °C; (*b*) TsOH, MeOH, 65 °C;
I: R^2 = H: R^1 = OBu^t, $(CH_2)_2$; R^1 = Me: R^2 = Me, Ph, 2-Th;
II: R^2 = $(CH_2)_2$: R^1 = OMe, OTMS; Ts is tosyl

hydrolysis of the enamine rather than the anticipated Diels – Alder product.

Methyl coumalates **79** (see Scheme 16) and coumalic acid **95** are feedstock chemicals accessible from malic acid through dimerization. Shanks and co-workers [51] investigated the transformation of acid **95** into the bulk chemicals benzoic (**99a**) and isophthalic acids (**99b**) (Scheme 18) *via* a Diels – Alder reaction of **95** with ethylene (**96**) which initially gave lactone **97**. The advanced cyclohexadiene moiety **98** was accessible through either Lewis acid mediated (R = H) or Brønsted acid (R = CO_2H) mediated lactone decarboxylation. Finally, catalytic dehydrogenation gave benzoic acid **99a** effectively from feedstock biomass.

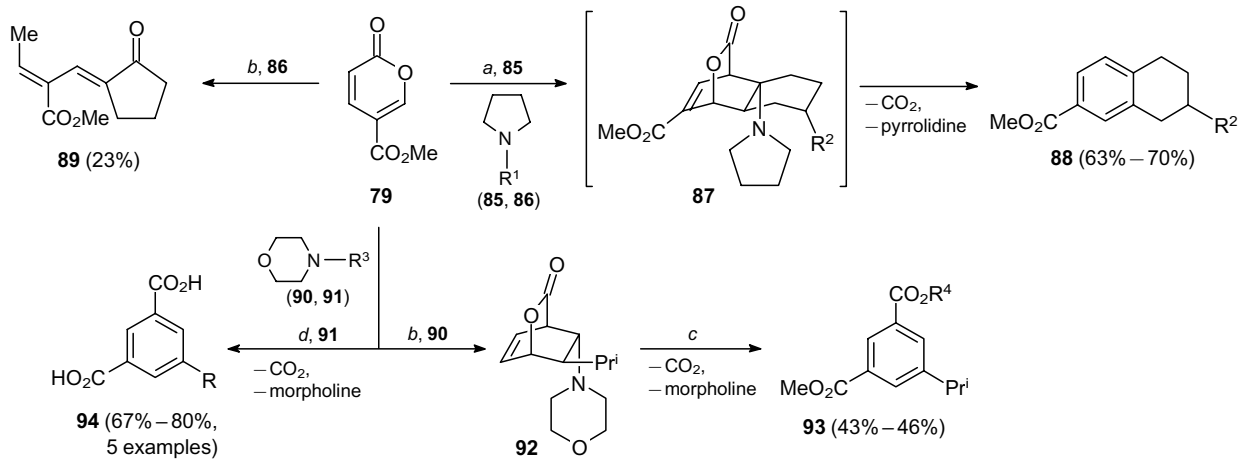
Scheme 18

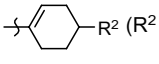
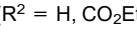
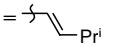


(*a*) γ-Al_2O_3, 1,4-dioxane, 120 °C (yield of **98a**, 58%);
(*b*) Amberlyst-45, 1,4-dioxane, 2 h, 120 °C (yield of **98b**, 39%);
R = H (method A) or CO_2H (method B); **98**, **99**: R = H (**a**), CO_2H (**b**)

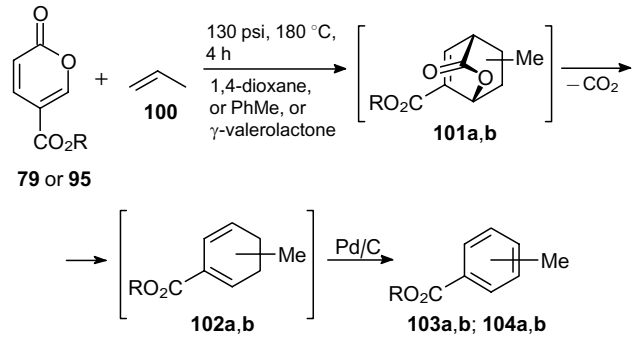
Subsequently, Shanks and co-workers [52] were able to expand this methodology to synthesize *p*- or *m*-toluic acids (**103a**, **104a**) or their esters (**103b**, **104b**) in excellent yields starting from methyl coumalate **79** or coumalic acid **95** and propylene (**100**) (Scheme 19). By raising the temperature, the reaction proceeded smoothly to the cyclohexadiene intermediates **102**, which upon addition of Pd/C could be dehydrogenated to compounds **103a**,**b**, **104a**,**b**.

Scheme 17



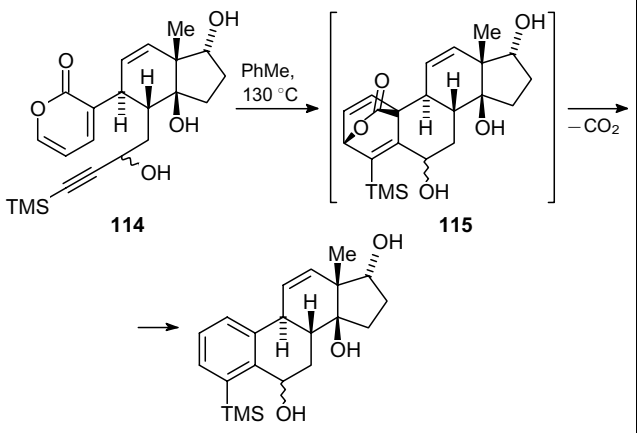
(*a*) MeOH; (*b*) CH_2Cl_2; R^1 =  (R^2 = H, CO_2Et, **85**, **87**, **88**),  (**86**); (*c*) K_2CO_3, MeOH; (*d*) 1) CH_2Cl_2; 2) KOH, MeOH – H_2O, reflux; 3) HCl; R^3 =  (**90**),  (R^5 = Et, Ph, C_6H_4OMe-4, C_6H_4Me-2, C_6H_4Br-3, **91**); R^4 = H, Me

Scheme 19



R = H (**a**), Me (**b**);
103 : **104** = from 4.2 : 1 to 4.8 : 1 (84% – 89%);
103 (*para*-substitution), **104** (*meta*-substitution)

Scheme 21



In 2018, Cui and co-workers[53] synthesized heavily substituted indole derivatives **109** as well as aniline derivatives **113** *via* a one-pot cascade sequence of alkyne (**106**, **111**, **112a**) and alkynyl-acid **110** coupling to produce pyrones **107**, which underwent a subsequent Diels – Alder and aromatization sequence (Scheme 20). A broad scope of various aliphatic and aromatic substituents were tolerated in these transformations.

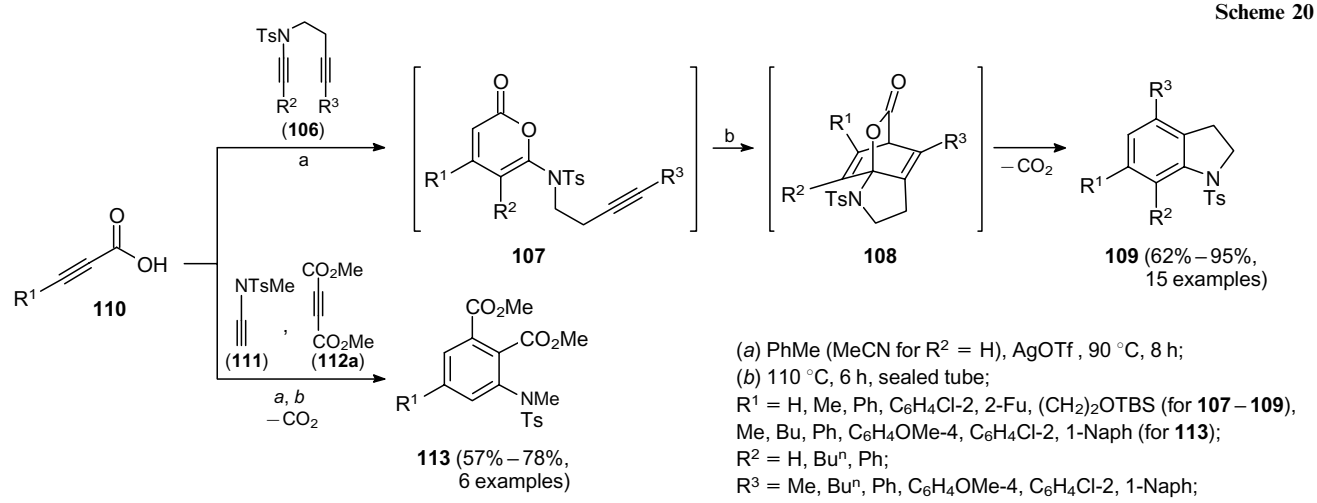
In 2019, Nakazaki and co-workers[54] reported the synthesis of an estrogen analogue **116** using an intramolecular pyrone – Diels – Alder and aromatization sequence of alkynyl-pyrone **114** in their studies on the potential medical chemistry applications of highly oxygenated steroids (Scheme 21).

Garg and co-workers[55] reported that electron-rich pyrones **121**, which can be synthesized from 6*H*-1,3,4-oxadiazin-6-one (**119**), reacted with the strained azacycloalkyne **118**, generated *in situ* from the silyl-triflate precursors **117** with caesium fluoride, to provide the heterocyclic compounds **123** and **124** after carbon dioxide elimination with concomitant aromatization. The initial cycloaddition with a ratio of precursors **117** : **119** of 1 : 2 and dinitrogen loss gave both regioisomers **121a**,**b** but the second adduct underwent selective decomposition with the excess caesium fluoride present to leave only the azapyrone **121a** (74%). When the reaction was carried out with a ratio of precursors **117** : **119** of 2 : 1, a double cycloaddition and carbon dioxide loss occurred giving both arenes **123** and **124**. The aza-pyrone **121a** was also converted into the corresponding derivatives by reaction with other strained cycloalkynes (cyclohexyne **125** and 4-oxacyclohexyne **126**). These reactions proceeded under mild conditions and in good yields [71% and 62% (**123** : **124** ratio is 1.5 : 1), respectively] (Scheme 22). Additional examples from the Garg group included related trapping reactions with arynes and heteroarynes but these are outside the scope of this review.

Recently, Wilson *et al.*[56] reported a cascade sequence of an intramolecular Diels – Alder reaction of the pyridones **127** followed by the elimination of isocyanic acid (**129**) instead of carbon dioxide to synthesize isoindolinones **130**; such heterocyclic compounds are common scaffolds in medicinal chemistry (Scheme 23).

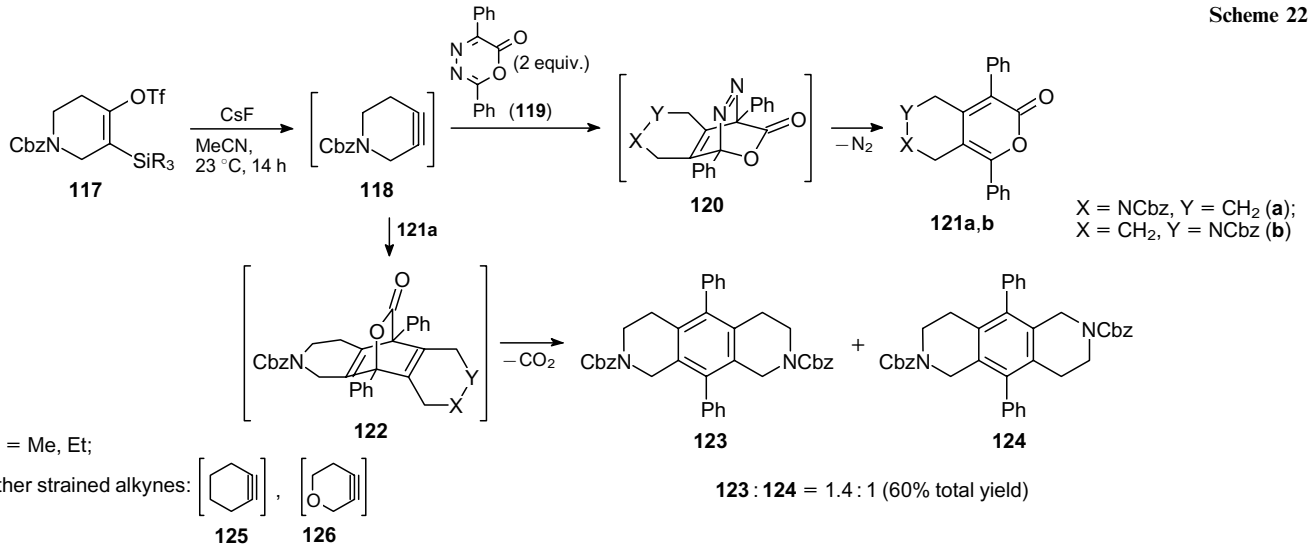
Wang and co-workers[57] reported the synthesis of benzoate esters **135** (Scheme 24). Initially, the synthesis provided lactones **133** at 120 °C, however raising the temperature to 150 °C resulted in smooth conversion to the cyclohexadienes **134**. Subsequently, this route was extended by addition of DDQ, thereby providing benzoate esters **135**. Finally, employing alkynes **136** instead of alkenes **132** gave the similar arenes **135**.

Scheme 20

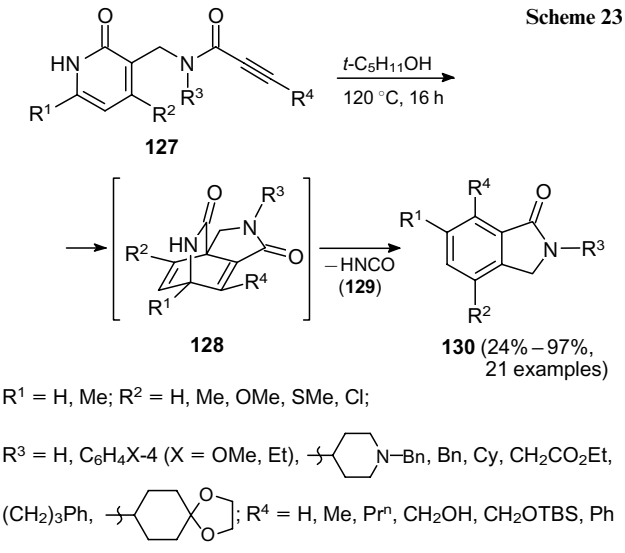


(*a*) PhMe (MeCN for R^2 = H), AgOTf , 90 °C, 8 h;
(*b*) 110 °C, 6 h, sealed tube;
R^1 = H, Me, Ph, C_6H_4Cl-2, 2-Fu, $(CH_2)_2OTBS$ (for **107** – **109**), Me, Bu, Ph, C_6H_4OMe-4, C_6H_4Cl-2, 1-Naph (for **113**);
R^2 = H, Bu^n, Ph;
R^3 = Me, Bu^n, Ph, C_6H_4OMe-4, C_6H_4Cl-2, 1-Naph;
Fu is furyl, Naph is naphthyl, Tf is triflate

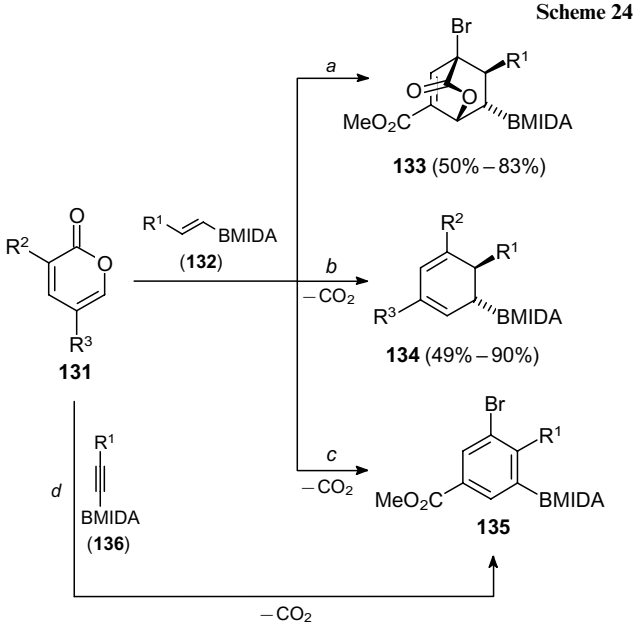
Scheme 22



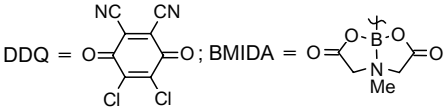
Scheme 23



Scheme 24



(*a*) DCE, 120 °C, 6 h; R^2 = Br, R^3 = CO_2Me:
R^1 = Ph, $C_6H_4CO_2Me$-4, $C_6H_2(OMe)_3$-3,4,5, $C_6H_3Me_2$-2,4, 2-fluorenyl, 2-Th;
(*b*) DCE, 150 °C, 3–9 h; R^1 = Ph, C_6H_4X-4 (X = CO_2Me, OMe, Cl), C_6H_4X-3 (X = Me, CF_3), C_6H_3F-4,Me-3, $C_6H_3Me_2$-2,4, 3-Th, 2-fluorenyl, 1-Naph; R^2 = H, Br, CO_2Me; R^3 = H, CO_2Me;
(*c*) 1) DCE, 150 °C, 5 h; 2) DDQ, 80 °C, 1 h; R^2 = Br, R^3 = CO_2Me: R^1 = Ph, C_6H_4X-4 (X = SMe, Bu^t, Cl, OMe), C_6H_4Me-3, 2-fluorenyl (21%–65%);
(*d*) DCE, 170 °C, 5 h; R^2 = Br, R^3 = CO_2Me; R^1 = Ph, C_6H_4X-4 (X = F, CO_2Me), C_6H_4OMe-3, 2-Th (40%–77%);
DCE = $Cl(CH_2)_2Cl$, DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone;



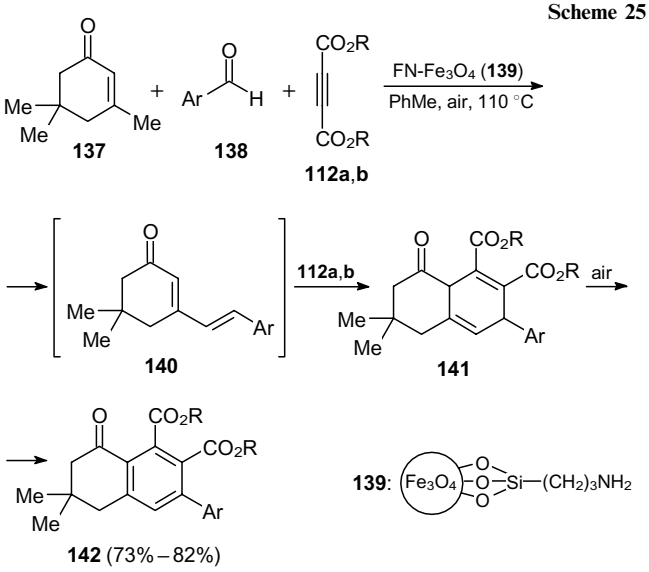
2.4. Miscellaneous substrates

Abaee *et al.*[58] reported a one pot procedure for the synthesis of bicyclic aromatic compounds **142** from enones **137**, aldehydes **138** and acetylenedicarboxylate esters **112a**,**b** using recyclable, silica-coated magnetite nanoparticle-based catalyst FN-Fe_3O_4 (**139**) followed by aerobic oxidative aromatization (Scheme 25).

In 2017, Philkhana and Reddy[59] reported the synthesis of fregenedadiol (**146**) and fregenedadiol acetate (**147**) using a Diels–Alder cycloaddition and oxidative (DDQ) aromatization sequence as key steps to elaborate the arene core **145** (Scheme 26). Reaction of diene **143** with dimethylacetylenedicarboxylate **112a** gave the cycloadduct **144** and this was oxidatively aromatized with DDQ to provide the arene **145**, which was converted to the natural products **146** and **147** respectively in two (reduction, hydrogenolysis) and three (reduction, hydrogenolysis, acylation) steps.

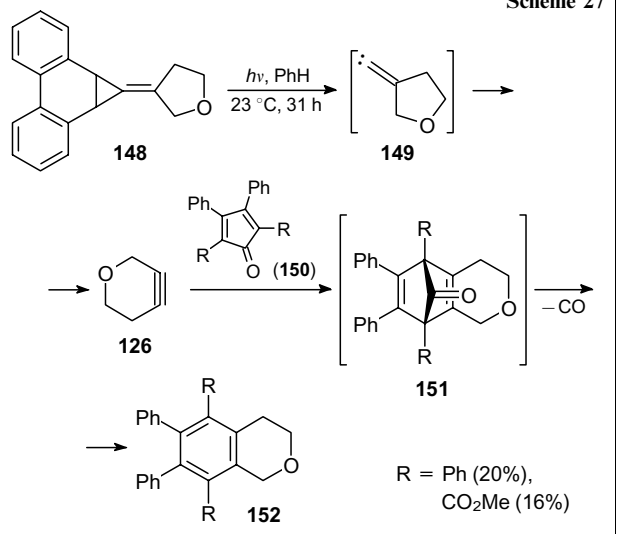
Thamattoor and co-workers[60] reported the synthesis of the reactive intermediate, 3-oxacyclohexyne (**126**), *via* an unusual photochemical rearrangement reaction (Scheme 27).[60] In this study, the phenanthrene derived precursor **148** underwent photolytic cleavage and thereby formed carbene **149**, which, in turn, rearranged to the reactive species **126**. Its generation *in situ* in the presence of cyclopentadienones **150** gave the Diels–Alder adduct **151** and this underwent a retro [4 + 1] reaction with loss of carbon monoxide and aromatization to provide the isochromanes **152** in moderate yields.

Scheme 25



R = Me (**a**), Et (**b**); Ar = Ph, C_6H_4X-3 (X = Me, OMe), C_6H_4X-4 (X = Me, OMe, Cl), 2-Th

Scheme 27



In 2019, Carreira and co-workers[61] reported the completion of the total synthesis of (−)-merochlorin A (**160**) by a late stage introduction of the aromatic core (Scheme 28). Dehydrogenation of ketone **153** by reaction of the derived enolate with imino-sulfenyl chloride **154** gave the enone **155**, which underwent a Diels–Alder reaction with Brassard's diene **156** with hydrolytic cleavage to produce the core cyclohexenone unit **157**. This was converted into the enol trimethylsilyl ether **158**, which underwent Saegusa–Ito oxidation to form the resorcylate **159**. Subsequent de-*O*-methylation of ether **159** completed the synthesis of (−)-merochlorin A (**160**), a potent antibiotic with MIC's of 0.15–0.3 μmol L^{-1} against *C. dificile* and 2–4 μmol L^{-1} against *S. aureus*.

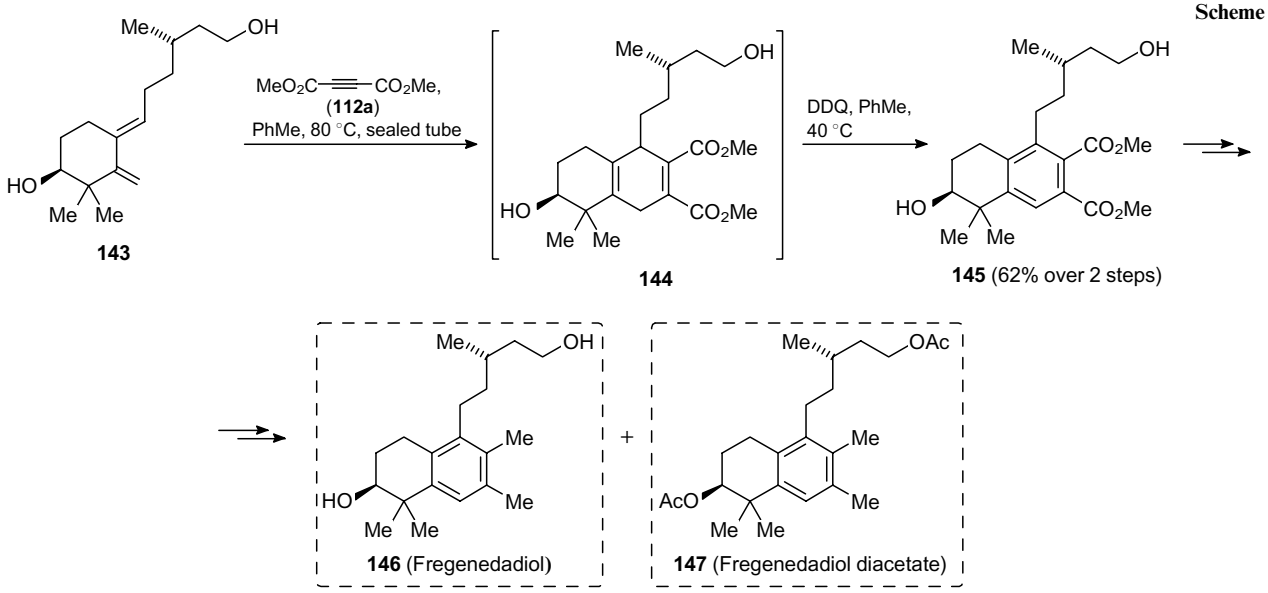
In 2019, Liang and co-workers[62] synthesized the ABCE ring system of daphenylline **165** using a Diels–Alder reaction of amine-borane complex **161** with dimethyl acetylenedicarboxylate (**112a**) and subsequent aerobic oxidation to produce the arene **163**, which was purified as the amine-borane salt (Scheme 29). Without amine coordination with borane as in the complex **161**, the critical Diels–Alder reaction did not occur. Additionally, diverse alternative oxidants for the aromatization reaction of diene **162** to arene **163** were unsuccessful.

Recently, Yu and co-workers[63] synthesized the aromatic core of psymberin (**170**, irciniastatin A) by the reaction of alkynyl-ester **166** with diene **167** and subsequent aromatization by the expulsion of isobutylene following earlier Danishefsky and co-workers[64–66] precedent (Scheme 30). Psymberin was shown to have high cytotoxic activities against breast cancer, colon cancer and melanoma (LC_{50} values $< 2.5 \times 10^{-9}$ mol L^{-1}).

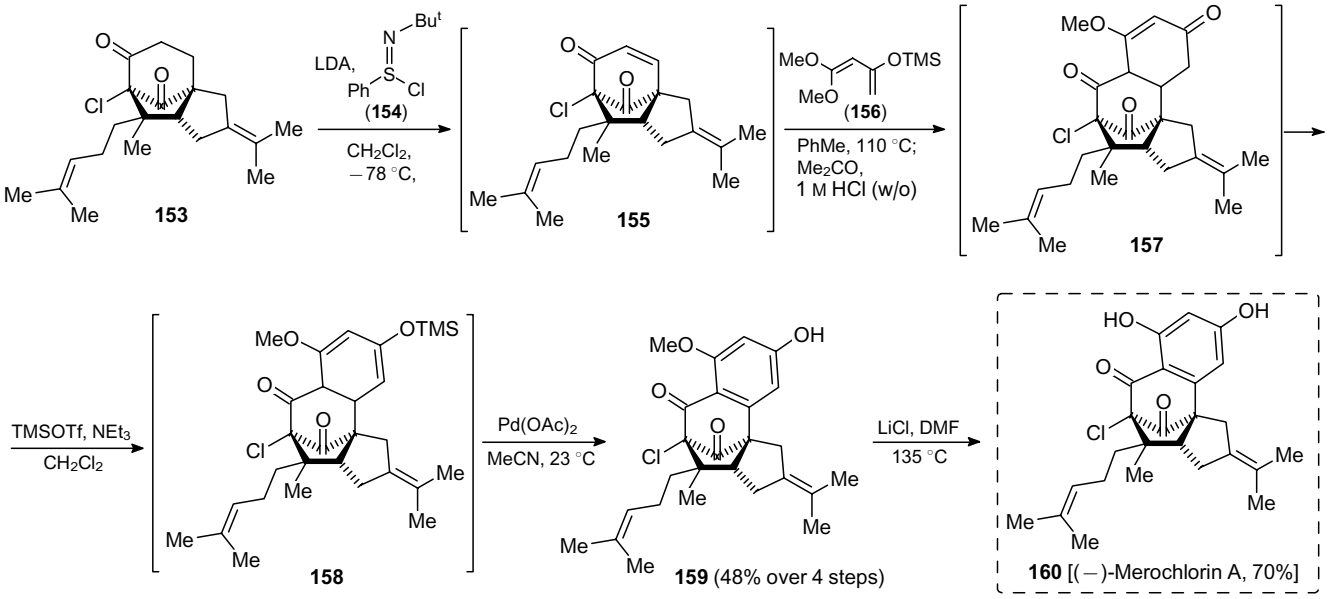
Moreover, Yuan and co-workers[67] synthesized a range of bioactive sesquiterpenes **173** through the key intramolecular Diels–Alder and oxidative aromatization sequence of alkyne **171** (Scheme 31) *via* diene **172**. Further functionalization of the ketone at the α-position was used to readily synthesize a range of natural products **174**–**178**.

Some benzochromenes exhibit interesting biological properties including antibacterial, antioxidative and anti-

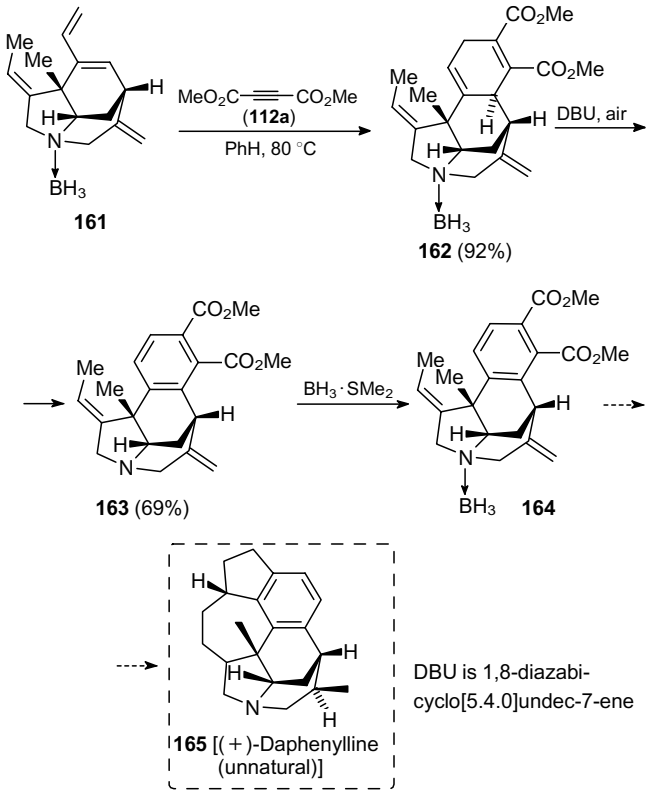
Scheme 26



Scheme 28



Scheme 29



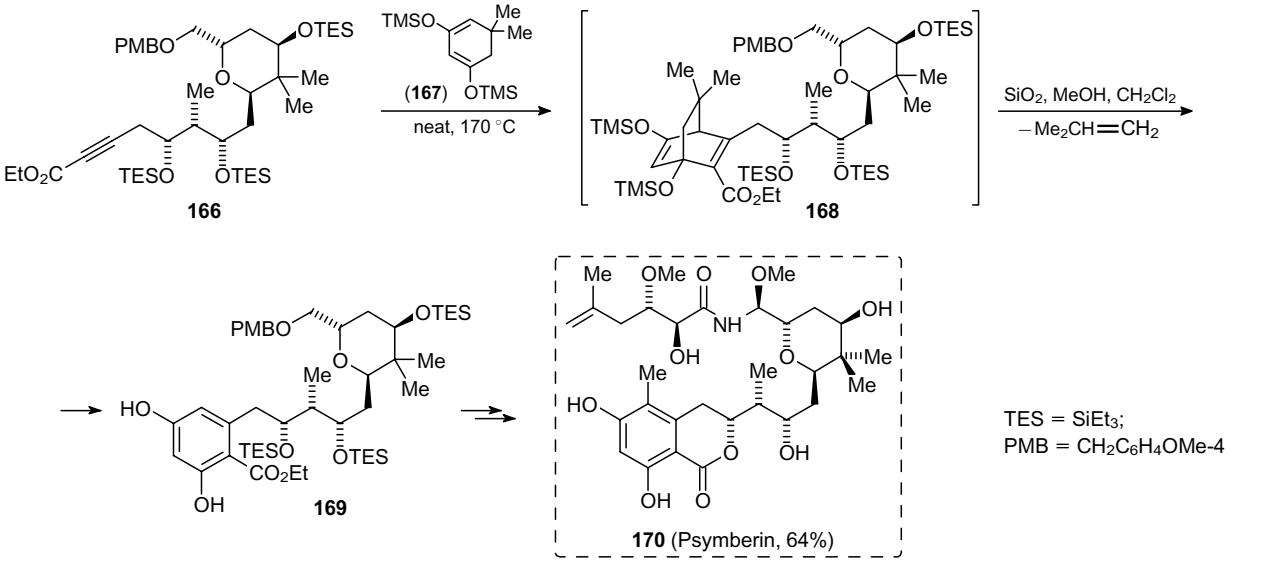
microbial activities and possess material properties useful for the fabrication of photovoltaic devices. Xu and co-workers[68] reported a synthesis of these heterocyclic compounds through a Wolf-rearrangement of a diazoacetoacetate derivative **179** to the corresponding ketene-based diene **180** (Scheme 32). This reactive intermediate gave 6*H*-benzo[*c*]chromene derivatives **182** following an intramolecular Diels–Alder reaction and subsequent aromatization through tautomerization.

Zhang and co-workers[69] reported that bifunctional ligands **L**, with a Lewis-basic phosphine coordinating to the metal catalyst as well as a Brønsted-basic amine to act as a proton shuttle, together with a π-Lewis acid such as gold(I) chloride mediated the rearrangement of acetylenic amides **183** into amino-furans **185** (Scheme 33). These highly electron-rich intermediates were trapped, *in situ*, with a dienophile in an inter- or intra-molecular Diels–Alder reaction. Ring opening of the resultant dihydrofuran intermediates **187** and elimination of water gave the tetra-substituted arenes **188** and **190**. The intramolecular reaction affording the latter arene was extended with variation in the tether.

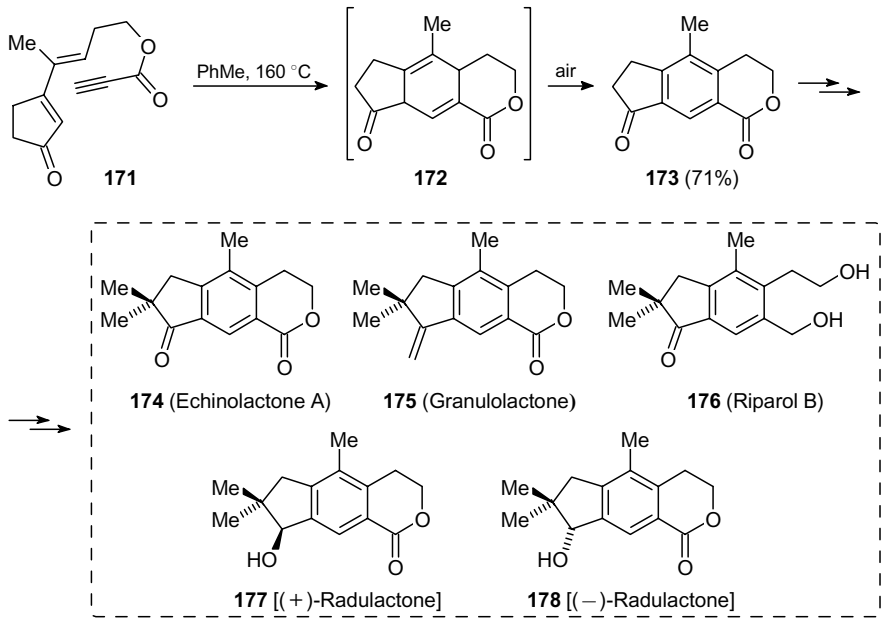
Kirschning and co-workers[70] reported three different routes to synthesize chromanes, a heterocyclic unit found in various biologically active natural products (Scheme 34). Reaction of vinyl-dihydropyran **191** with nitroalkenyl sulfoxide **192** gave cyclohexadiene **194** by Diels–Alder reaction and subsequent elimination of phenylsulfenic acid. Without the need of further oxidants, cyclohexadiene **194** underwent aromatization by elimination to yield alcohol **195**. Diels–Alder reaction of vinyl-dihydropyran **196** with keto-acetylene **197** gave cyclohexadienes **198** and **199**, which were subsequently converted into chromane **200** *via* DDQ mediated oxidation. Reaction using excess DDQ resulted in cleavage of the silyl-ether and oxidation of the benzylic alcohol giving the corresponding ketone. Other acetylenes and additives were examined, but the yield of the Diels–Alder reaction was not significantly better. Subsequently, the use of high pressure was investigated, which gave dihydrobenzenes **198**, **199** in combined 35% yield. In addition, chromane **202** was formed under these conditions, presumably due to a second Diels–Alder reaction of dihydrobenzene **199** with keto-acetylene **197** and subsequent elimination of ethylene from **201** to produce chromane **202**.

The pyrone Diels–Alder reaction was investigated by Kirschning and co-workers[70] initially on a model system, which gave lactones **204** and **205**. Subsequent loss of carbon dioxide gave cyclohexadiene **206** and this was aromatized with DDQ to produce chromane **207** (Scheme 35). Optimum yields were obtained at room temperature and high pressure

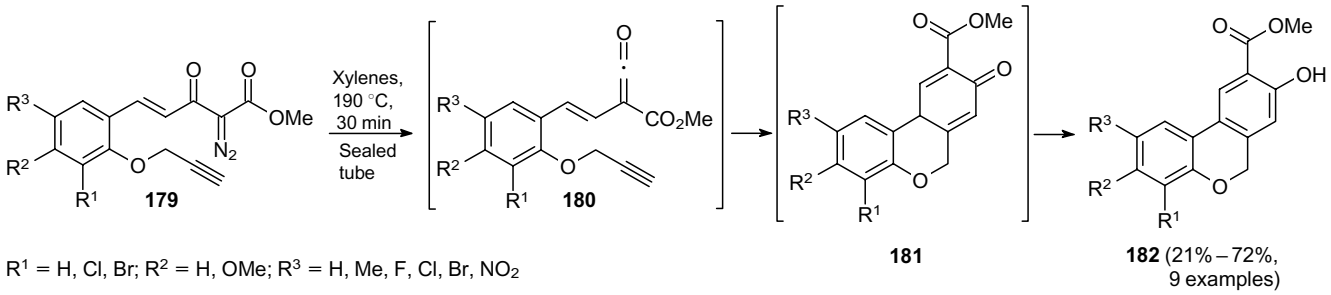
Scheme 30



Scheme 31



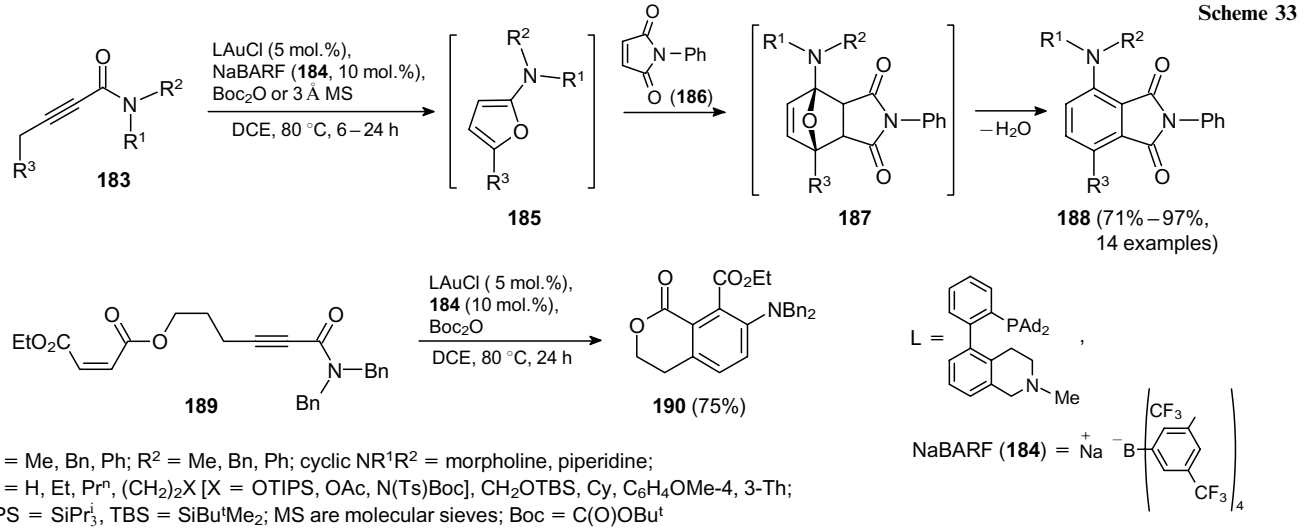
Scheme 32



over prolonged reaction times. This method was successfully applied to dihydropyran **208** and methyl coumalate **79** in an inverse electron demand Diels–Alder reaction followed by the loss of carbon dioxide and DDQ mediated oxidative aromatization.

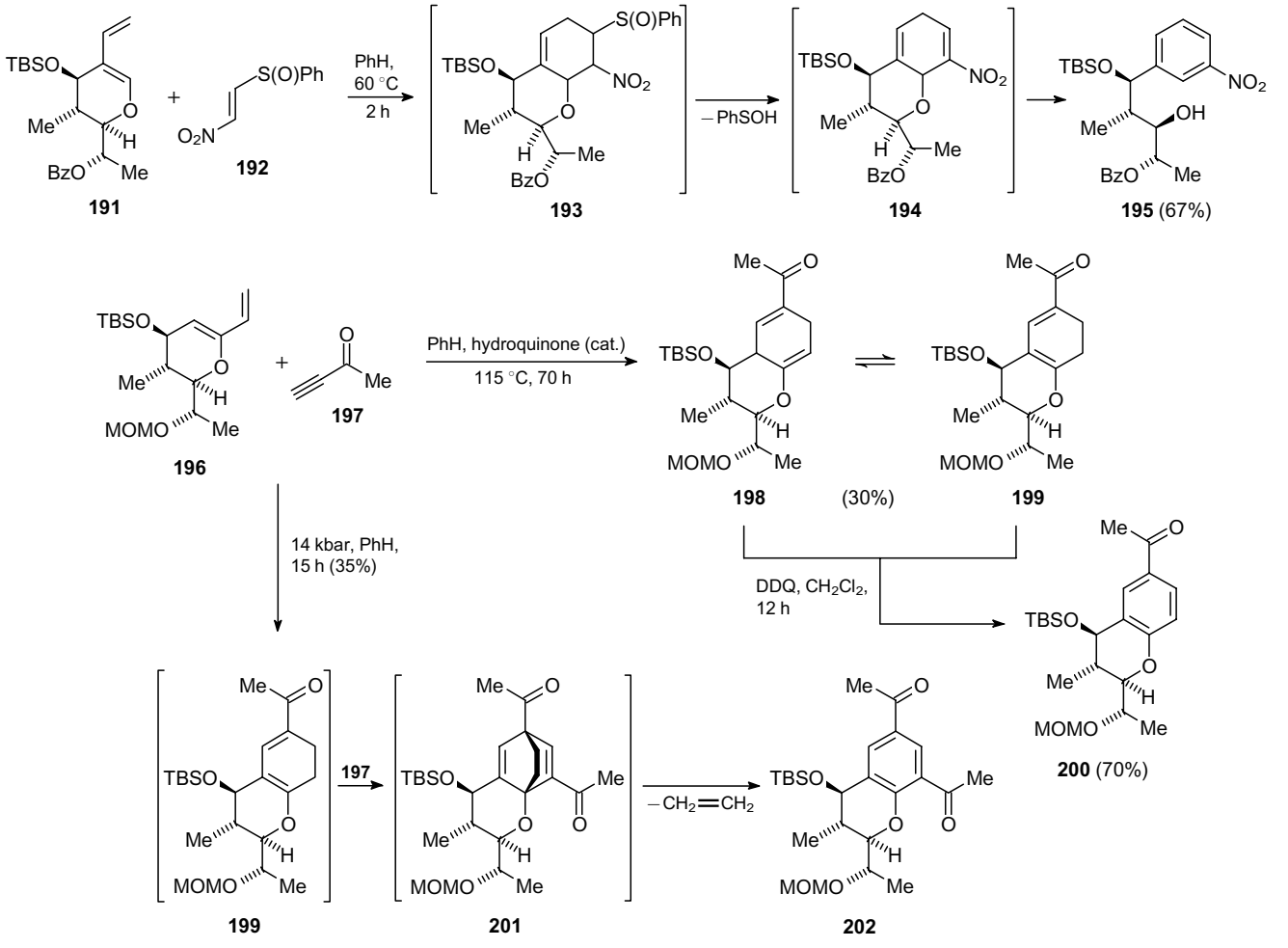
In recent studies on the synthesis of biphenyl and heterobiaryls, Temperini *et al.*[71] employed a Diels–Alder reaction of the enol acetate derived from **211**, *via* transacylation with *iso*-propenyl acetate (**213**), with acetylene **212** (Scheme 36).[71] Yields were better at 145 °C than 110 °C, and elevated pressure in a closed metal vessel gave dihy-

Scheme 33



R^1 = Me, Bn, Ph; R^2 = Me, Bn, Ph; cyclic NR^1R^2 = morpholine, piperidine;
R^3 = H, Et, Pr^n, $(CH_2)_2X$ [X = OTIPS, OAc, N(Ts)Boc], CH_2OTBS, Cy, C_6H_4OMe-4, 3-Th;
TIPS = $SiPr^i_3$, TBS = $SiBu^tMe_2$; MS are molecular sieves; Boc = $C(O)OBu^t$

Scheme 34



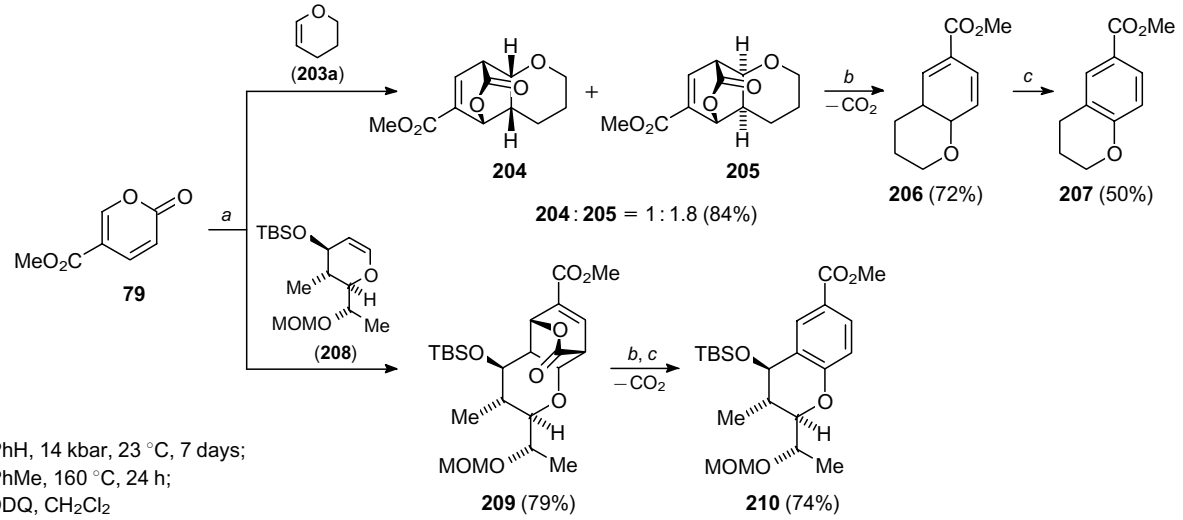
MOM = CH_2OMe, Bz = $C(O)C_6H_4$

drobenzenes **214**, which upon DDQ mediated oxidative aromatization furnished biaryls and heterobiaryls **215** in moderate to good yields.

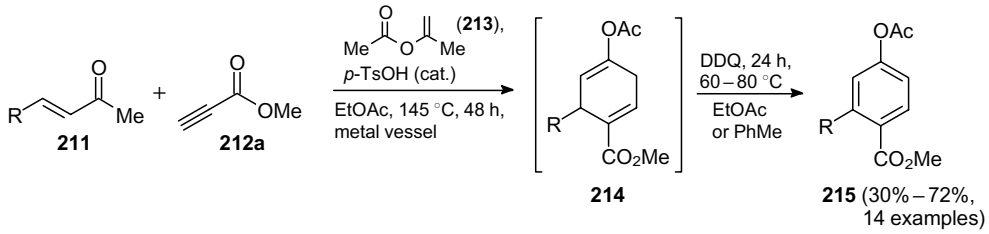
Recently, Hu and co-workers [72] reported that tetra-ynes **216** underwent cyclization *via* the arynes **217**, **218**, which were trapped by reaction with oxazolines **219** to give arenes **223**. The authors suggested a plausible mechanism *via* intermediates **220** to **222** (Scheme 37). Equivalent reactions using oxazolines **224** gave the indoles **228**, which were formed presumably *via* the intermediates **225**–**227**.

Also, it was reported that reaction using oxazolines **229** without a substituent at the imine carbon atom gave adducts **232** in good yields (Scheme 38). These reactions

Scheme 35

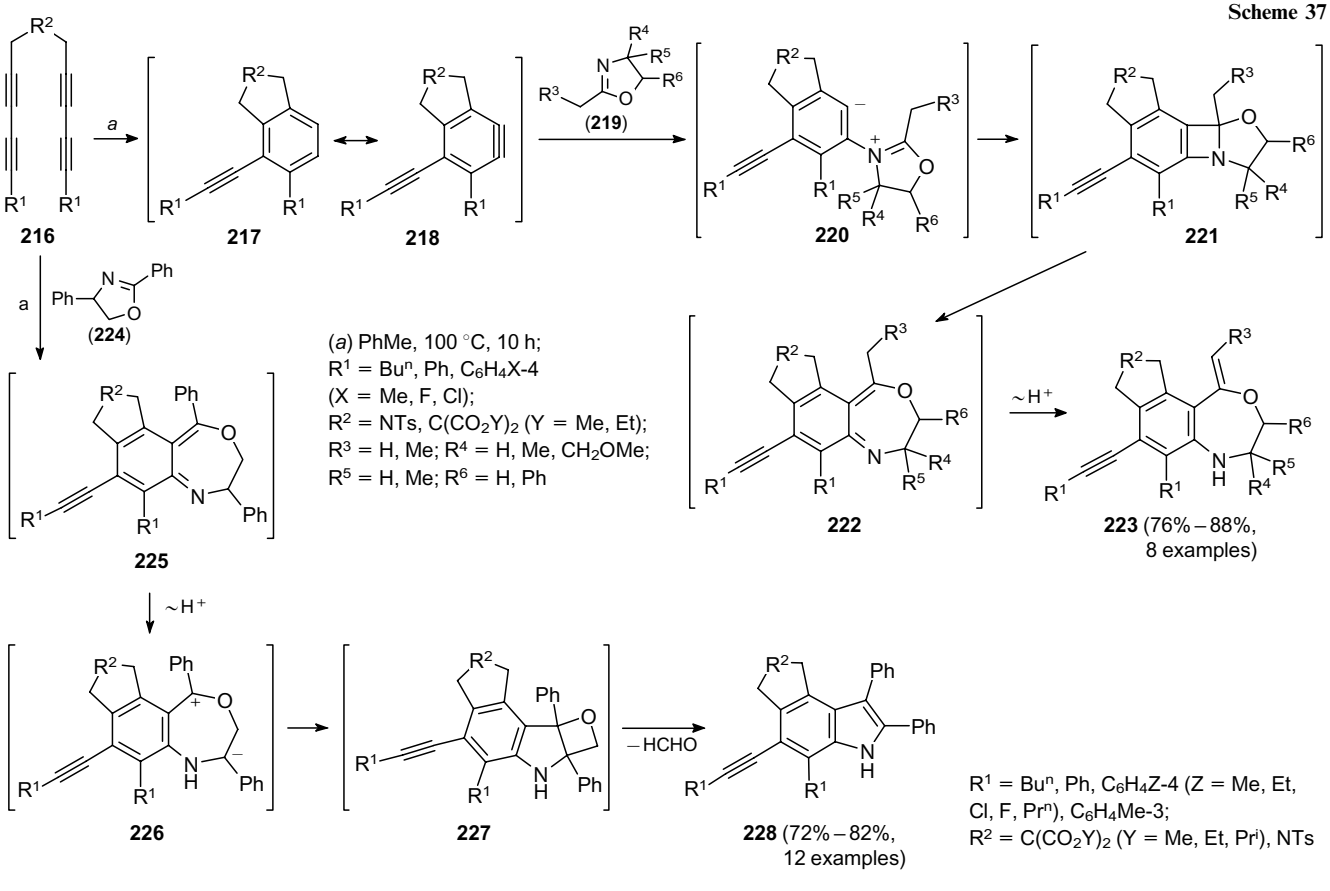


Scheme 36

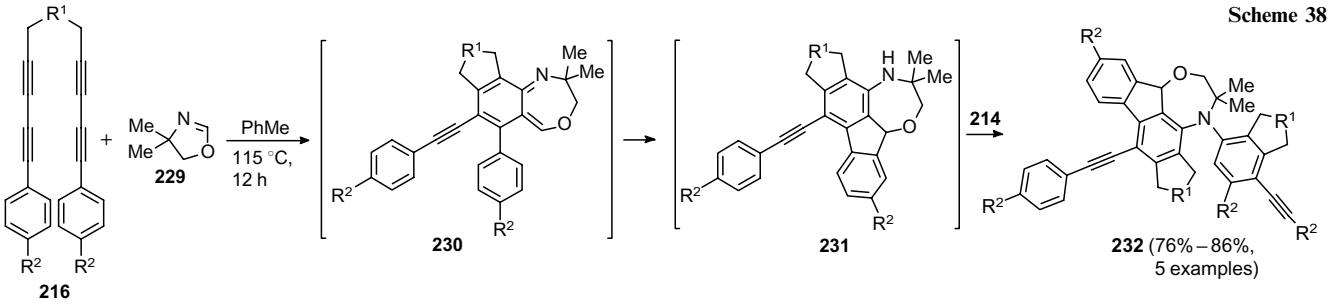


R = Ph, C_6H_4F-2, $C_6H_4NO_2$-3, C_6H_4X-4 (X = OMe, CN), $C_6H_3(MeO)_2$-2,5, $C_6H_2(Br)_2$-2,5,OMe-4, 4-Br-thien-2-yl, 1-Ts-1*H*-pyrrol-2-yl, 2-phenylthiazol-4-yl, 1-Ts-1*H*-indol-3-yl, 5-bromo-1-Ts-1*H*-indol-3-yl, 5-methoxy-1-Ts-1*H*-indol-3-yl, benzo[*b*]thien-2-yl

Scheme 37



Scheme 38



R^1 = $C(CO_2X)_2$ (X = Me, Et, Pr^i); R^2 = H, Me

were again suggested to proceed *via* intermediates **230** and **231**.

3. Electrocyclic(pericyclic) reactions and aromatization

6π-Electrocyclic and pericyclic reactions are governed by orbital-symmetry, which controls their mode of cyclization (disrotatory or conrotatory). This stereoelectronic control has been used in highly regioselective and stereoselective syntheses of carbocycles or heterocycles through the simple use of heat or light. Aerobic oxidation or the addition of oxidants was used for aromatization to provide arenes with various substitution patterns with broad functional group compatibility and atom economy.

1,3-Cyclohexadienes are the initial product of 6π-electrocyclization reactions and were found to be convenient precursors for the synthesis of benzene derivatives by oxidation. Additionally, 6π-electrocyclizations have been proposed as possible pathways in the biosynthesis of natural products. In conjunction with other *n*π-electrocyclic (n = 4, 8) or pericyclic reactions, these cascade reactions have been applied photochemically for the rapid assembly of complex products.[73] UV irradiation or thermally initiated 6π-electrocyclic and pericyclic reactions are therefore useful for the conversion of acyclic precursors into benzene derivatives. This chapter will exclusively focus on the synthesis of all carbon aromatic compounds; equivalent methods for heteroarene syntheses have been reviewed by Ding and Kaufman.[74, 75]

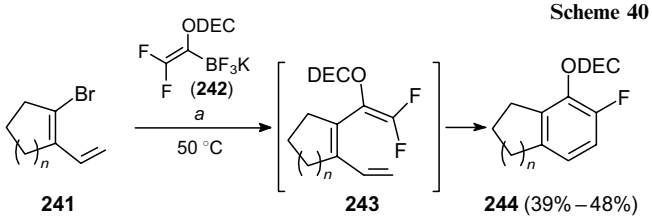
Chuang and co-workers[76] reported that the (formal) electrocyclization of polyfunctional triene ylides **236**, which were synthesized from enyne-esters **234**, triarylphosphines **235** and imines or aldehydes **233**, gave stabilized ylides **237** and subsequently oxindole and benzofuranone ylides **238** (X = NR, O, respectively). These were further derivatized to produce isatins **239** and isooxazolinones **240** (Scheme 39).

In 2016, Wilson and co-workers[77] reported that reaction of bromodienes **241** and trifluoroborate **242** under Molander–Suzuki–Miyaura conditions gave trienes **243**, which underwent sequential thermal 6π-electrocyclization and dehydrofluorination reactions to give indanes, tetralins and benzosuberans **244** (Scheme 40).[77]

Huang and co-workers[78] applied a 6π-electrocyclization and aromatization sequence by the addition of amines **246** to ynedienyl-amines **245** and **248** followed by siloxane elimination to synthesize variously substituted 1,3-diaminobenzene derivatives **247**, **249** (Scheme 41). The reaction conditions tolerated a range of amine substituents with both cyclic and acyclic amines as defined below.

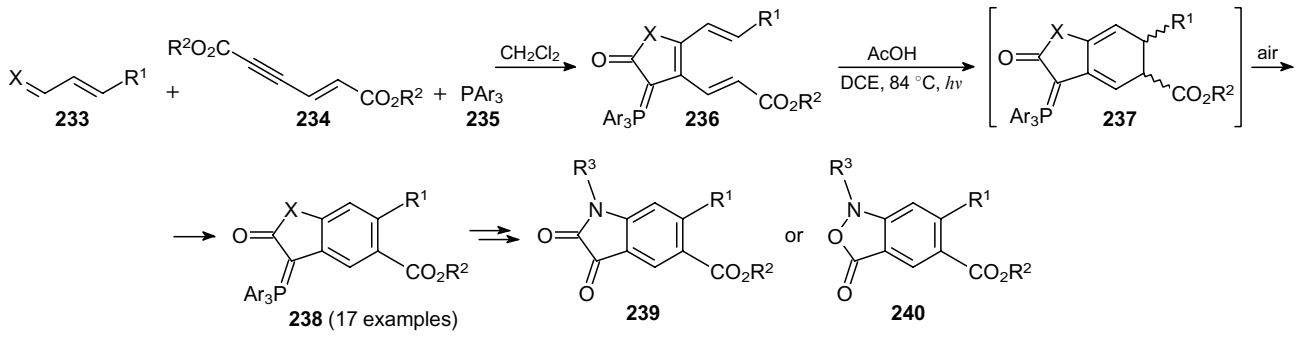
Delavatine A (**254**) and (−)-incarviatone A (**255**) are two secondary metabolites from *Incarvillea delavayi*. These plants are found in Southwest China and the Himalayas and have been used in traditional Chinese medicine to treat anemia and dizziness. Both have intriguing biological activities with delavatine A (**254**) possessing anti-cancer activity against several human cancer cell lines. Sarpong and co-

Scheme 40



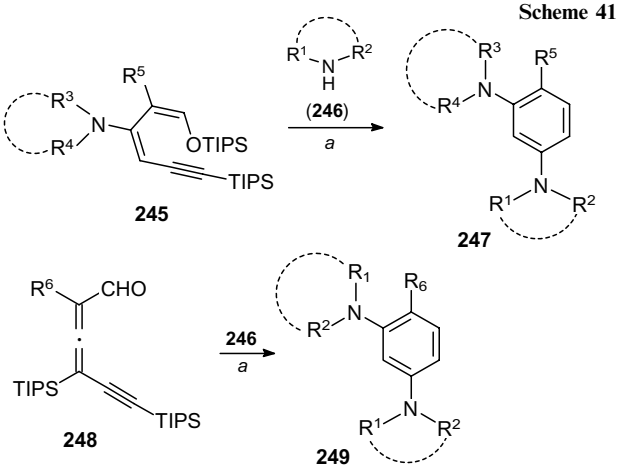
(*a*) $(Ph_3P)_2PdCl_2$, Cs_2CO_3, Bu^tOH, H_2O; n = 1–3; DEC = $Et_2NC(O)$

Scheme 39



X = NR^3 (81%–89%), O (62%); Ar = Ph, C_6H_4Y-4 (Y = OMe, Cl, F, Me); R^1 = C_6H_4Z-4 (Z = NO_2, CN); R^2 = Me, Et; R^3 = Ts, Bs; Bs = $PhSO_3^-$

Scheme 41



(*a*) NaOAc, 4-$O_2NC_6H_4CO_2H$, 4 Å MS, PhCl, 120 °C;
$HNR^1R^2 = HN(CN_2)_4$: R^3, R^4 = Me, Et; HNR^3R^4 = 1-pyrrolidine, piperidine, morpholine, 3-pyrroline, 4-OH-piperidine, *N*-Me piperazine, tetrahydroisoquinoline, azepane, azocane; R^5 = Bn, $(CH_2)_4OBn$, $(CH_2)_4OTBS$, $(CH_2)_2O$-prenyl, n-C_6H_{13} (**247**: 52%–85% yields);
$R^1 = R^2$ = Et; HNR^1R^2 = 1-pyrrolidine;
HNR^3R^4 = 3-OH-pyrrolidine, 3-pyrroline, isoindoline, piperidine, azepane, azocane; R^5 = Bn (**247**: 51%–74%);
HNR^1R^2 = pyrrolidine, azepane , azocane; R^6 = Bn, n-C_6H_{13}, $(CH_2)_4OBn$ (**249**: 52%–82%)

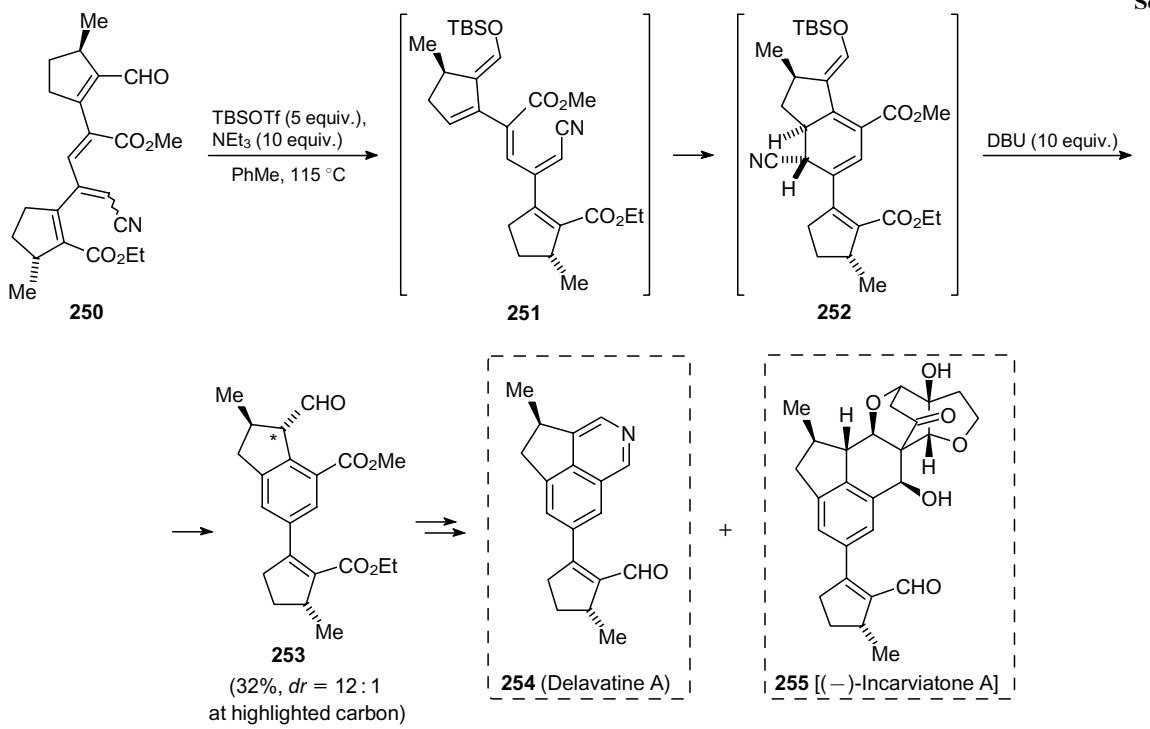
workers[79] have developed a unified approach for the synthesis of these two natural products as they share a common molecular scaffold (Scheme 42). The polyene precursor **250** upon silylation with TBSOTf or TIPSOTf gave penta-ene **251** with a core triene with the (*Z*,*Z*,*E*)-geometry. This polyene **251** underwent a 6π-electrocyclization reaction and subsequent DBU-mediated aromatization of intermediate **252** to give the polyfunctional indane **253**. Subsequently, it was found that this transformation worked well in a one-pot procedure with precise base stoichiometry (10 equiv.) to provide indane **253** as a 12 : 1 mixture of diastereoisomers. Within three steps this indane **253** was subsequently converted into delavatine A (**254**) and also used to complete a formal total synthesis of (−)-incarviatone A (**255**).

Coffin and Ready[80] reported the preparation of the advanced intermediate **262** in their enantioselective synthesis of (+)-dysoline (**263**) (Scheme 43). A highly regioselective Danheiser benzannulation between diazoketone **257** and alkyne **256** was used to synthesize the core chromenone **262**. Irradiation with blue light induced a Wolf-rearrangement of diazo-ketone **257** to provide ketene **258**, which, in turn, underwent a selective [2 + 2] addition with alkyne **256** to produce cyclobutenone **259**, followed by a retro-4π-electrocyclic opening and subsequent 6π-electrocyclization of triene **260** and aromatization through tautomerization to give the advanced intermediate **262**. The natural product **263** was shown to have cytotoxic activity against HT1080 fibrosarcoma cell lines (IC_{50} 0.21 μmol L^{-1}).

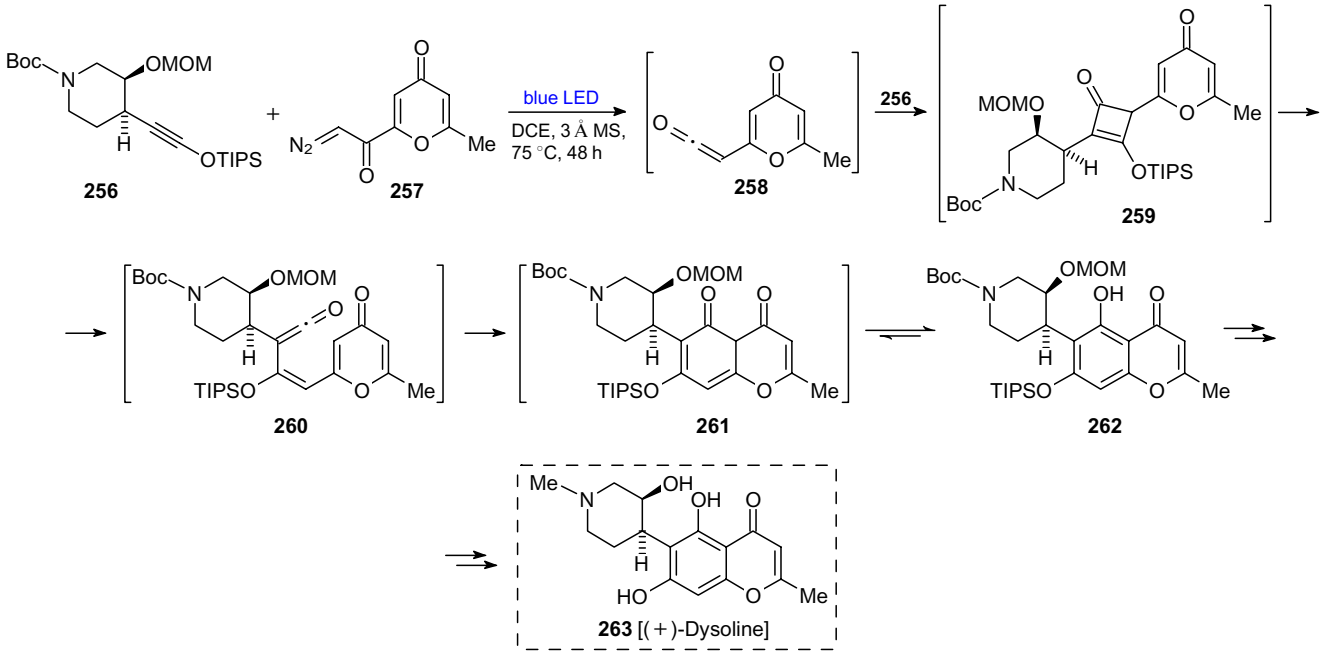
In 2015 and 2018, the group of Magauer[81,82] reported a unified approach for the synthesis of variously substituted phenols **268**, anilines and phenol ethers **269** and polycyclic compounds **271** and **272** through the 2π-disrotatory electrocyclic ring opening of bicyclo[3.1.0]hexan-2-ones **264** and **270** (Scheme 44). The optimal reaction conditions were applied to the synthesis of phenols **268** tolerating various electron-donating and electron-withdrawing substituents. In addition, a penta-substituted derivative of phenol **268** was synthesized in reasonable yield (53%) after a [1,2]-shift.

In 2017, Zhu and co-workers[83] developed a gold-catalyzed ring expansion including a 6π-electrocyclization-aromatization sequence to prepare a selection of mono- and bicyclic aromatic compounds **278** (Scheme 45). The authors' proposed mechanism of reaction involved enyne-activation and ring expansion to provide nonacycle **275**, followed by a formal 6π-electrocyclization of the intermediate hexatriene **276** and subsequent aromatization.

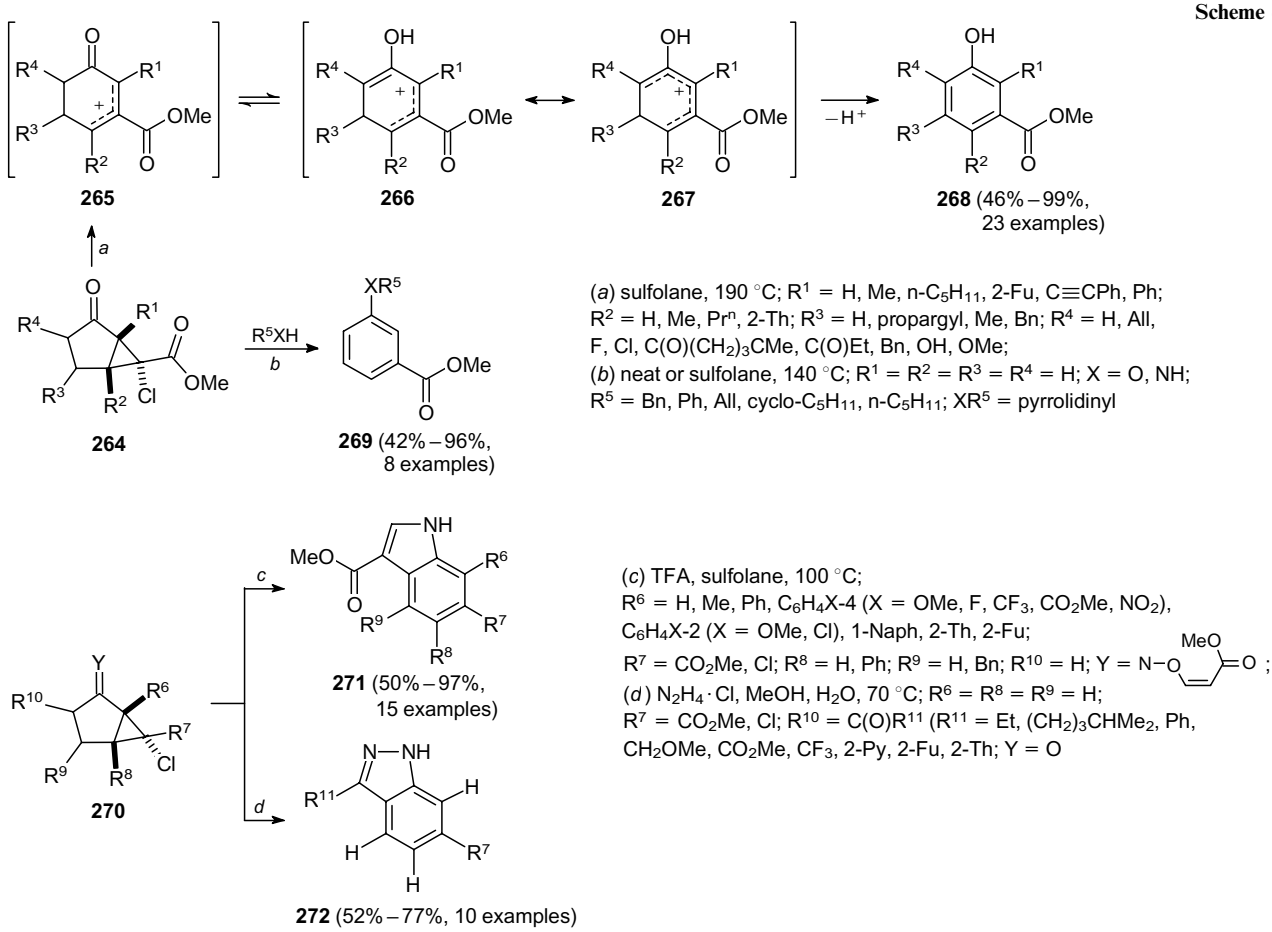
Scheme 42



Scheme 43

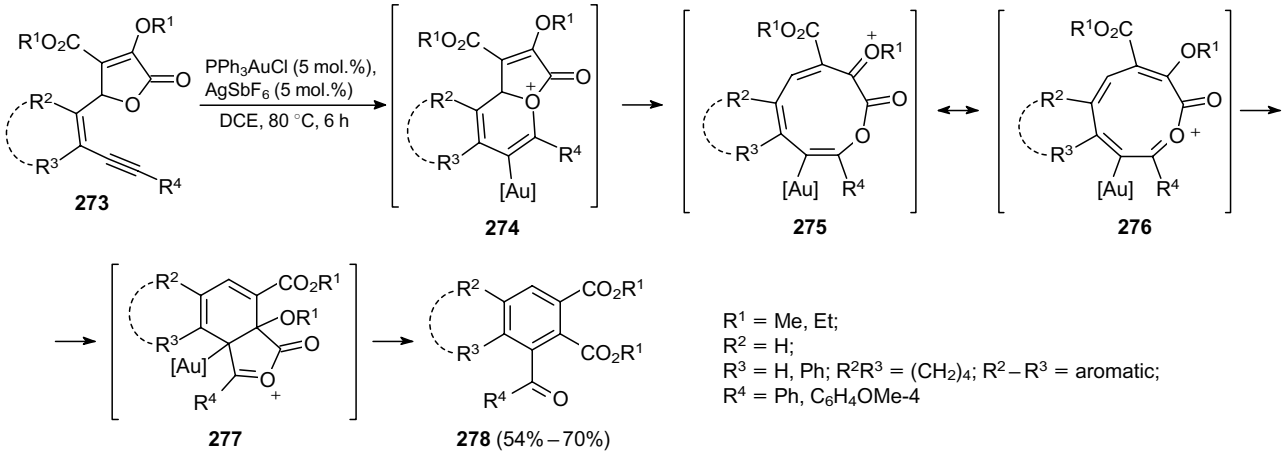


Scheme 44

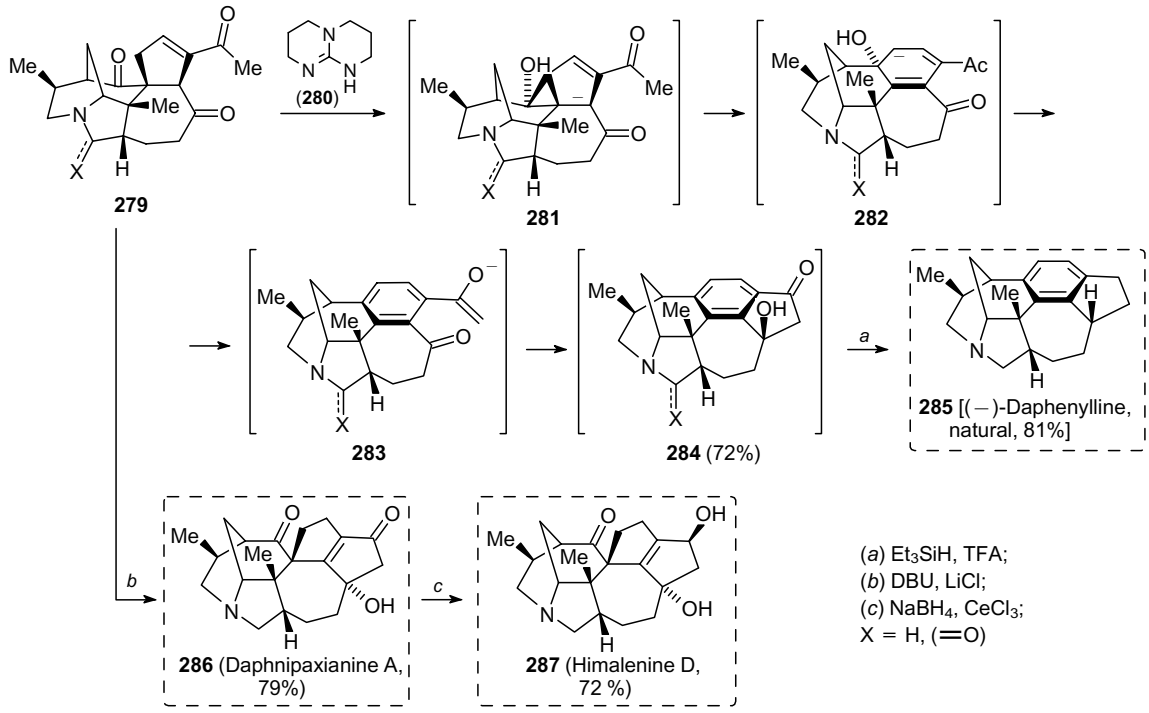


In 2018, Li and co-workers [84] reported a divergent total synthesis of three *Daphniphyllum* alkaloids, namely, (−)-daphenylline (**285**), daphnipaxianine A (**286**) and himalenine D (**287**) using a late stage aromatization of the common intermediate **279** (Scheme 46). The natural products have been used in traditional Chinese medicine and have a range of biological activities, including antitumour and antiviral properties. Their synthesis of the central aromatic ring of the daphenylline precursor **284** applied a formal 6π-electrocyclization and aromatization sequence.

Scheme 45



Scheme 46



Pentacyclic triketone **279** was allowed to react with guanidine **280** (triazabicyclodecene, TBD), which induced a vinylogous aldol reaction with the adjacent ketone to produce the cyclopentene-anion **281**. This set the stage for a 6π-electrocyclic ring expansion, which upon elimination of hydroxide from **282** produced the aromatic core of daphenylline **283**, followed by an additional aldol reaction of the acetophenone moiety with the proximal ketone. This elegant reaction cascade sequence led to the formation of one aromatic and 2 different ring systems in one procedure. Reductive deoxygenation completed the synthesis of the natural product (**285**).

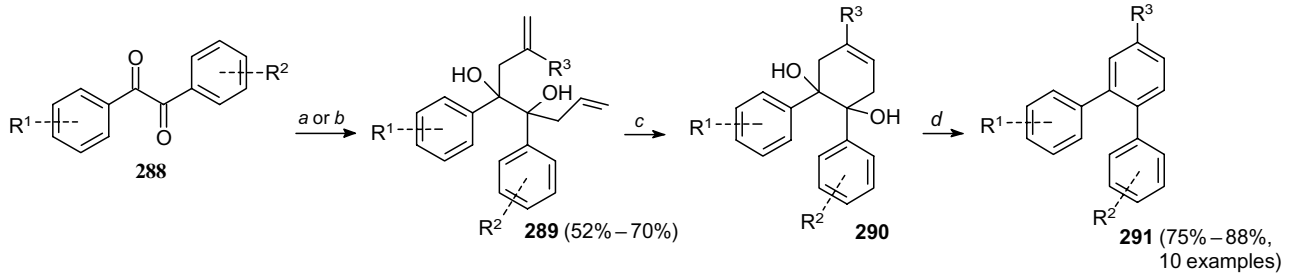
4. Transition metal-catalyzed reactions and aromatization

A series of *ortho*-terphenyl derivatives **291** were prepared by Dash and co-workers[85] utilizing a ring closing alkene metathesis (RCM) reaction as a key step (Scheme 47). Treatment of diketones **288** with allylmagnesium bromide or sequentially with $(allyl)_{1\text{-}2}-XBr$ (X = Zn, In) and allylmagnesium bromide provided the diallylated compounds **289**, which were subjected to RCM with Grubb's 2nd generation catalyst thereby providing tricyclic diols **290**. Subsequent reaction of these diols **290** with *p*-toluenesulfonic acid resulted in aromatization *via* double dehydration to provide the arenes **291**.

In 2016, Xie and co-workers[86] reported studies on the total synthesis of (–)-rubriflordilactone B (**295**), a natural product which showed bioactivity against HIV-1 replication (Scheme 48). The key aromatization step in their approach involved a rhodium-catalyzed formal [2 + 2 + 2] cycloaddition of triynes **292** to produce arene **293**, which was subsequently allowed to react with *p*-toluenesulfonic acid to give an advanced lactone intermediate **294**.

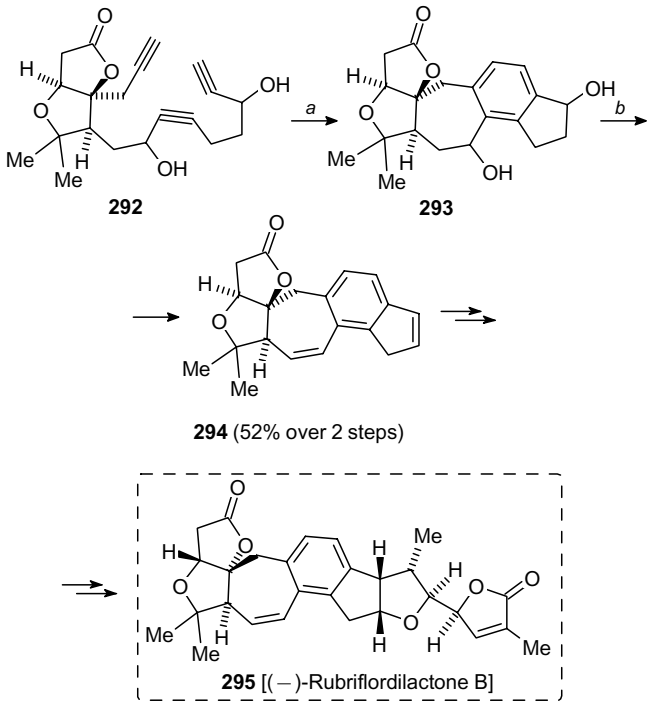
Matsuda and Matsumoto[87] reported a rhodium(I) catalyzed approach for the synthesis of arenes **301** (Scheme 49). It was found that Wilkinson's catalyst $[(Ph_3P)_3RhCl]$ medi-

Scheme 47



(*a*) AllMgX, THF, from 0 °C to 23 °C, 6 h; (*b*) AllBr, NaI, Zn or In, THF: H_2O (4 : 1), 23 °C, 6 h; (*c*) Grubbs II (5 mol.%), CH_2Cl_2, 23 °C, 15 h; (*d*) TsOH, PhH, 80 °C, 3 h; $R^1 = R^2 = H$, 2-F, 4-F, 4-Cl, 4-Me, 3-OMe, 2,5-$(OMe)_2$; $R^1 = H$: $R^2 = I$, OMe; $R^3 = H$, Me

Scheme 48



(*a*) $[RhCl(PPh_3)_3]$, DCE, 23 °C; (*b*) *p*-TsOH, PhH

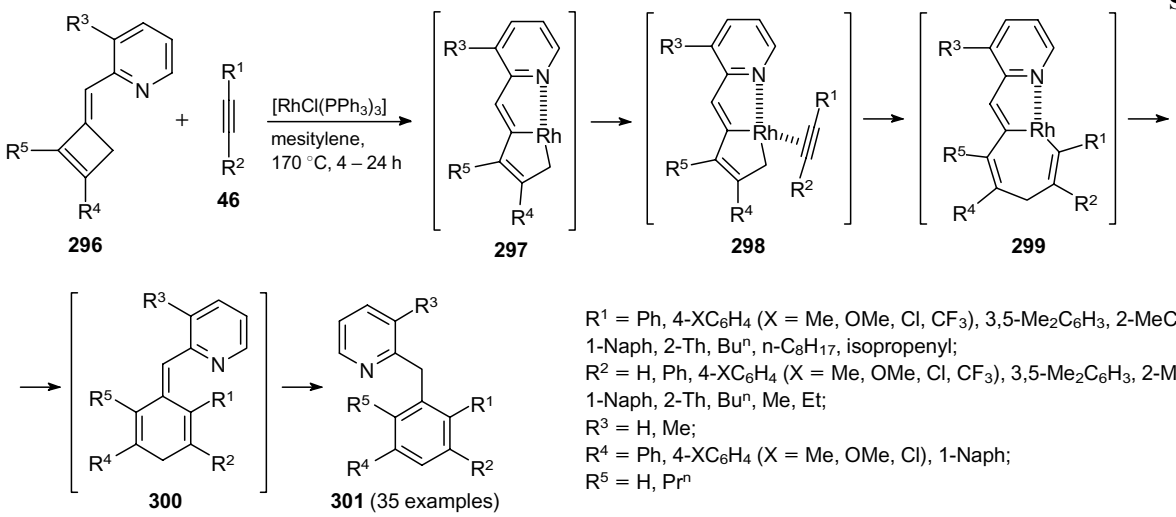
ated the insertion of alkyne **46** into the C – C bond of cyclobutenes **296** to give a range of tetra- and pentasubstituted arenes **301**.

Benzocyclobutenes are valuable synthetic intermediates in organic chemistry. Recently Shi and co-workers[88] reported a gold(I)-catalyzed dehydrogenative cycloisomerization of 1,5-enynes **302** to produce disubstituted benzocyclobutenes **305** after oxidative aromatization using DDQ (Scheme 50). Furthermore, cyclobutane and cyclohexane but not cyclopentane tethered 1,5-enynes **306** were also aromatized under the reaction conditions to produce arenes **307** as well as enynes with the $R^1R^2C{=}CH_2$ tethers (where $R^1 = R^2$ = Me, Et; R^1 = Me; R^2 = Ph, C_6H_4Cl-4).

A new method for the synthesis of aryl triazoles was reported by Fan and co-workers[89] (Scheme 51). This involved one pot cascade reactions of alkynes **308** with aliphatic keto-azides **309** and allenic ketones **311**. Firstly, the alkynes **308** and azides **309** underwent copper-catalyzed Huisgen cycloaddition reactions to give triazole intermediates **310**, which were subsequently allowed to react with allenic ketones **311** *via* Michael addition and intramolecular condensation to yield the aromatic compounds **313**.

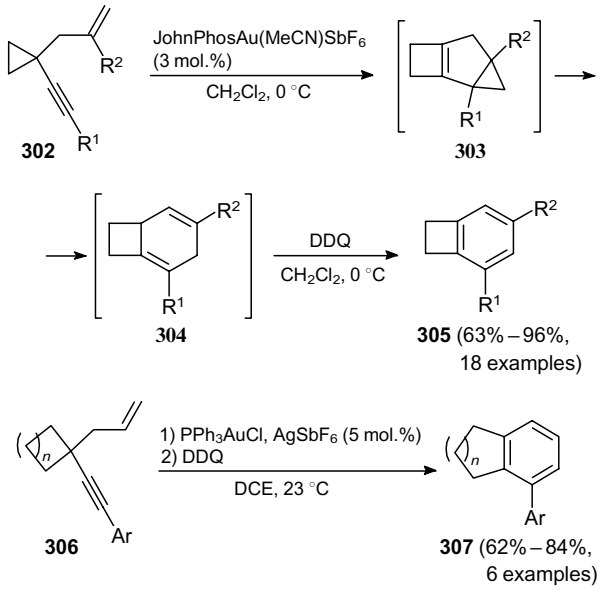
Chan and co-workers[90] reported that in the presence of DDQ or *N*-fluorobenzenesulfonimide (NFSI) as an oxidant, the known cycloisomerization of 1,4-enyne esters **314** to cyclopropanated cyclopentene-derivatives **315** occurred with oxidative ring expansion to provide phenol derivatives **317** in moderate to good yields (Scheme 52). The reaction tolerated various aliphatic and aromatic substituents in the *meta*-position thereby highlighting the value of synthesizing

Scheme 49



R^1 = Ph, 4-XC_6H_4 (X = Me, OMe, Cl, CF_3), 3,5-$Me_2C_6H_3$, 2-MeC_6H_4, 1-Naph, 2-Th, Bu^n, n-C_8H_{17}, isopropenyl;
R^2 = H, Ph, 4-XC_6H_4 (X = Me, OMe, Cl, CF_3), 3,5-$Me_2C_6H_3$, 2-MeC_6H_4, 1-Naph, 2-Th, Bu^n, Me, Et;
R^3 = H, Me;
R^4 = Ph, 4-XC_6H_4 (X = Me, OMe, Cl), 1-Naph;
R^5 = H, Pr^n

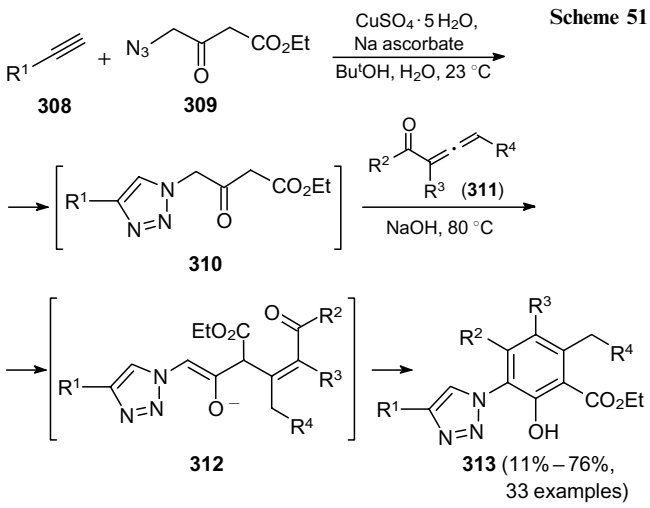
Scheme 50



302, **303**, **304**, **305** (63% – 96%, 18 examples), **306**, **307** (62% – 84%, 6 examples)

R^1 = Ph, 4-XC_6H_4 (Me, OMe, Ph, Br, Cl, F, Ac, CF_3), 3-XC_6H_4 (X = Me, OMe), 3,5-$Me_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 2-Th, *N*-Boc-5-indolyl, 2-Naph, 6-MeO-2-Naph, 9-phenanthryl; R^2 = H, Me; Ar = Ph, 4-$MeOC_6H_4$; *n* = 1, 2 (complex mixtures), 3; JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl

Scheme 51



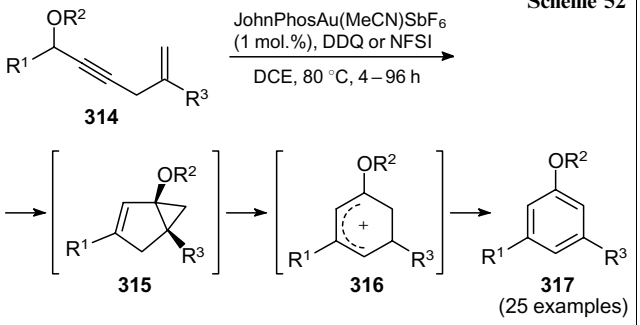
308, **309**, **310**, **311**, **312**, **313** (11% – 76%, 33 examples)

R^1 = Ph, C_6H_4X-4 (X = Cl, F, Br, OMe, Me), C_6H_4Me-3, CH_2OH, CH(OH)Ph, CH(OH)$CH_2C_6H_4$Br-2, Bn, 3-Th, 3-Py;
R^2 = Ph, C_6H_4Br-2, C_6H_4X-4 (X = Me, CF_3), Bn, Me, CH_2Bn, $C_6H_3(MeO)_2$-3,4, $C_6H_3Br_2$-2,5, C_6H_3Br-2,F-5;
R^3 = H, Me; R^4 = H, Ph

aromatic compounds from acyclic precursors given the preference for *ortho*- and *para*-substitution of phenols on reaction with electrophiles or *via ortho*-lithiation based processes.

Zi and co-workers[91] reported a *de novo* synthesis of substituted phenols **320** *via* oxidative cycloaromatizations of dienynes **318** (Scheme 53).[91] The key step involved their rhodium-catalyzed conversion into the corresponding metal vinylidenes, which were subsequently oxidized to provide metal ketenes **319**. These reactive intermediates **319** underwent cycloaromatization to provide phenols **320** in fair to good yields.

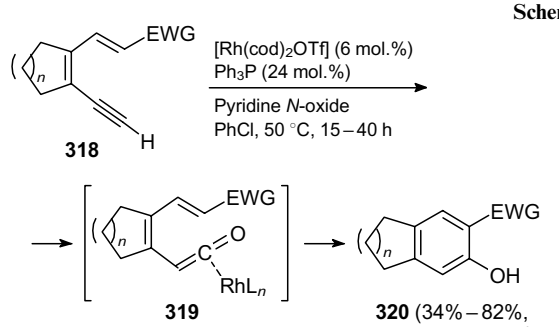
Scheme 52



314, **315**, **316**, **317** (25 examples)

R^1 = Ph, C_6H_4X-4 (X = Me, Br, Ph), C_6H_4X-2 (X = Br, I), 3-(6-Br-benzodioxolyl), $C_6H_2(MeO)_2$-4,5,Br-2, 1-Naph, 2-Naph, *N*-Ts-indolyl, cyclo-Pr, cyclo-C_5H_9, Cy, $CHEt_2$, $(CH_2)_2Bn$, n-C_6H_{13};
R^2 = Ac, $C_6H_4C(O)NO_2$-4;
R^3 = Ph, CH_2OPh, CH_2OAc, Me, NTsPh, $CH_2CMe(CO_2Et)_2$, steroid

Scheme 53



318, **319**, **320** (34% – 82%, 9 examples)

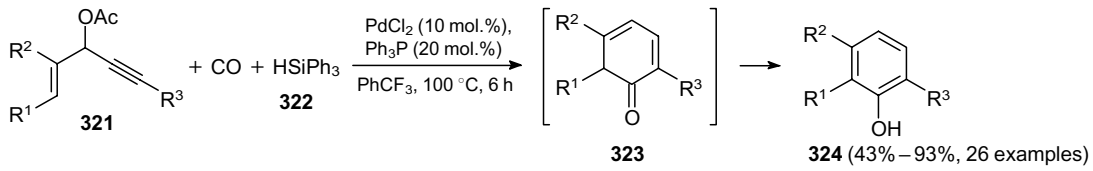
EWG = CO_2Me, CO_2Et, Weinreb amide, C(O)Bu^n, C(O)Ph, C(O)Me; *n* = 1, 2

In 2018, Li and co-workers[92] reported a palladium-catalyzed carbonylative benzannulation approach to synthesize substituted phenols **324** (Scheme 54). Hydrosilane **322** was used to mediate the palladium-catalyzed reductive [5 + 1] cycloaddition of enynes **321** with carbon monoxide to provide a range of substituted phenols **324** with excellent functional group tolerance.

The gibberellins are a family of tetracyclic *ent*-kaurenoid diterpenes that exhibit multiple biological activities including promoting plant germination and growth. When Zhang and co-workers[93] prepared triazole derivatives of allogibberic acid **326**, they utilized two different aromatization approaches to elaborate the arene core (Scheme 55). Aromatization of gibberellin **325** with hydrochloric acid provided arene **326**, which was subsequently esterified to produce methyl ester **327**. On the other hand, sequential esterification and Dess Martin periodinane (DMP)-mediated oxidation of gibberellin **325** gave enone **328**, which was subsequently aromatized using quinone **329** and $Pd(PPh_3)_4$ in aqueous DMSO to give phenol **330**.

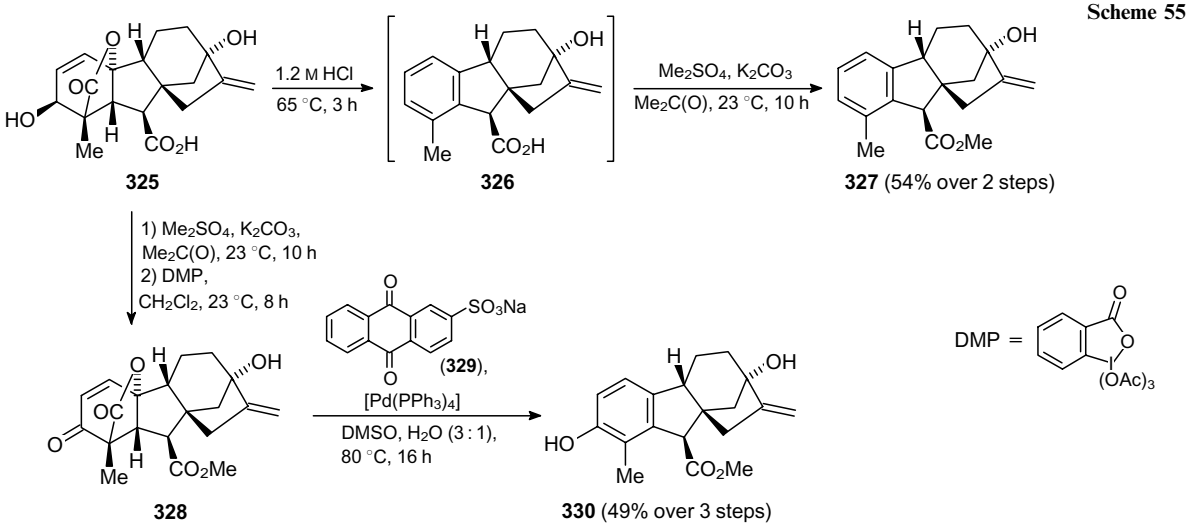
In 2018, Loh and co-workers[94] reported the synthesis of highly substituted salicylaldehydes **336** starting from dialkenyl ketones **331** and diazoketones **332** using rhodium catalysis (Scheme 56, conditions *a*). The authors proposed that the reaction proceeded *via* intermediates **333** – **335**. This reaction tolerated various alkyl, aryl and alkenyl substituents and was also useful for the synthesis of a series of arylene-spaced bic(salicylaldehydes) in moderate yields.

Scheme 54

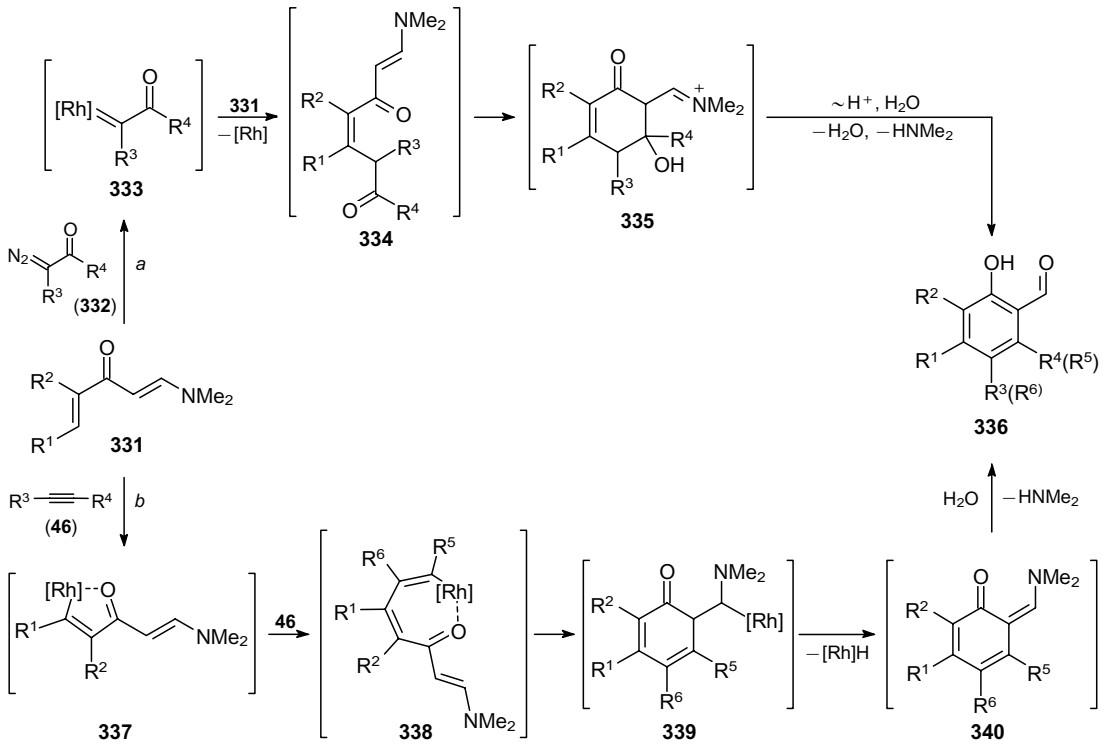


R^1 = H, 4-XC_6H_4 (X = Me, OMe, Cl, CF_3), 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, Pr^n, Ph; R^2 = H, Me, Et, Ph; R^3 = Ph, 4-XC_6H_4 (X = Me, OMe, Cl, Br, Ph) , 3-XC_6H_4 (X = Me, OMe, F, CF_3), 2-XC_6H_4 (X = Me, Cl), 3,5-$Me_2C_6H_3$, 2-Th, Me, Bu^n, n-C_6H_{13}, cyclo-Pr

Scheme 55



Scheme 56

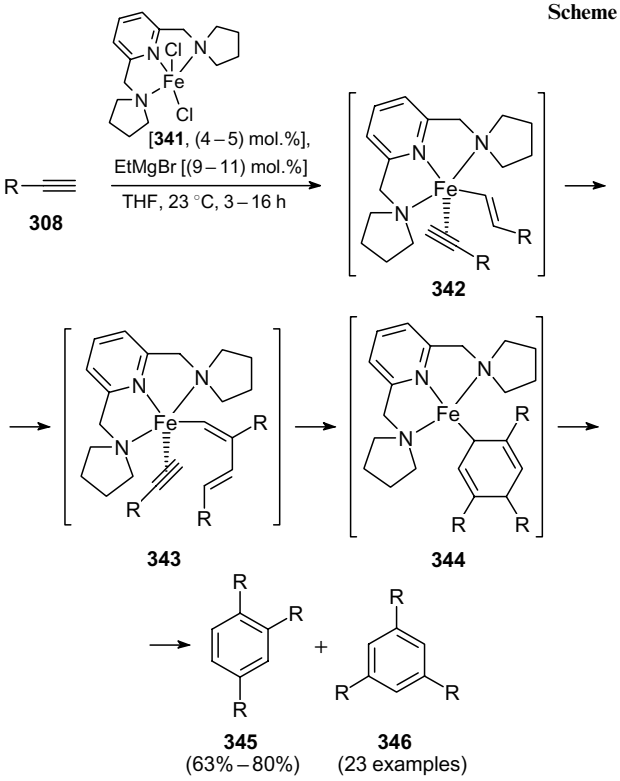


(*a*) [$(RhCp^*Cl_2)_2$] (2 mol.%), CF_3CO_2Ag (8 mol.%), $Zn(OAc)_2$, Ac_2O, CF_3CH_2OH, 40 °C, 12 h; R^1 = Me, Bu^n, Ph, C_6H_4X-2, C_6H_4X-3 (X = Me, F), C_6H_4X-4 (X = Me, OMe, F, Cl, Br, CF_3, NO_2, CH = CHAc), $C_6H_3(OMe)_2$-3,4, 5-(2,3-dihydro)benzofuryl, 2-Fu, 2-Th, Fe, styryl, 2-propenyl, 1,3-pentadienyl; $R^1–R^2$ = $(CH_2)_4$; R^2 = H, C_6H_4F-4; R^3 = CO_2Me, CO_2Et, CO_2All, Ac; R^4 = H, Me, Pr^i, cyclo-Pr, CH_2OMe, Ph, C_6H_4X-4 (X = F, OMe) [**336**: 34 examples, 24%–87% yields; 4 additional examples with polybenzene formation (52%–68%)];
(*b*) [$(RhCp^*Cl_2)_2$] (2.5 mol.%), $AgSbF_6$ (10 mol.%), AgOAc, H_2O, DCE, 90 °C, 15–24 h; R^1 = H, C_6H_4Me-4; R^2 = C_6H_4X-4, (X = OMe, Ph), 2-(7-MeO)-naphthyl, $C_6H_3(OCH_2O)$-3,4; R^5 = R^6 = Ph, C_6H_4X-4 (X = Me, OMe, F, Cl, Br, Ac, CO_2Et, NO_2), C_6H_4X-3 (X = Me, OMe, F, CO_2Me), 2-Naph, 2-Th, 2-(5-Me)-thienyl; R^5 = Ph: R^6 = Me, Et (**336**: 50%–92%, 24 examples)

Gao and co-workers[95] reported the synthesis of the same structures **336** *via* rhodium catalyzed reaction of similar dienamides **331** with acetylenes **46** (Scheme 56, conditions *b*). The authors suggested that the process proceeded *via* the organo-rhodium intermediates **337** to **339**, quinomethide **340** and its hydrolysis.

Gawali and Gunanathan[96] reported that iron-pincer complex **341** catalyzed a regioselective cyclotrimerization to yield trisubstituted benzene derivatives **345**, **346** (Scheme 57). Activation of the iron dichloride in the **341** with ethylmagnesium bromide produced iron(I)-hydride, which was the active catalytic species for the reaction and mediated the stepwise formal [2 + 2 + 2] cycloaddition of aryl alkynes **308** *via* intermediates **342**–**344** to provide arenes **345** and **346**. The authors also reported that aliphatic alkynes reacted in a similar fashion to yield the corresponding arenes.

Scheme 57

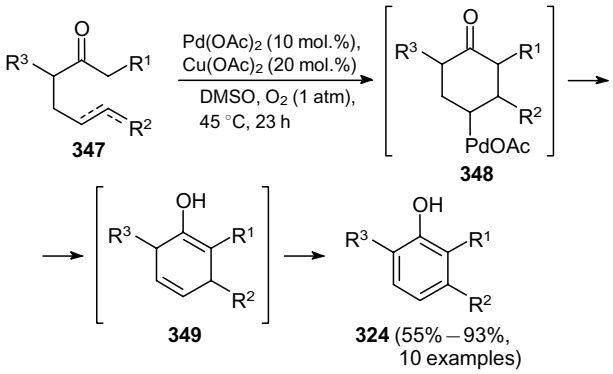


R = n-C_5H_{11}, $(CH_2)_2Pr^i$, cyclo-C_5H_9, CH_2Cy, Bu^t, Bn, CH_2Bn, CH_2OAll, CH_2OPh, CH_2NMeBn, $CH_2OSiMe_2Bu^t$, $(CH_2)CH_2OSiMe_2Bu^t$, $SiMe_3$, Ph, C_6H_4X-4 (X = Me, OMe, F), C_6H_4Me-3, C_6H_4X-4 (X = OMe, CF_3), $C_6H_2Me_3$-2,4,5, $C_6H_3(CF_3)_2$-3,5

Toyota and co-workers[97] reported a palladium-mediated aromatization of various alkenyl-β-keto-esters **347** to produce substituted phenols **324** (Scheme 58). The authors proposed that the reaction proceeded with the enolate attack of the terminal carbon to form an acetoxy palladium intermediate **348**. Subsequent β-elimination and oxidative aromatization gave phenols **324**.

In 2019, Gong and co-workers[98] described the total synthesis of dehydrobotrydienal (**355**), dehydrobotrydienol (**356**) and 10-oxodehydrodihydrobotrydial (**357**). These botryanes are structurally diverse sesquiterpenoids that are isolated from the phytopathogenic fungus *Botrytis cinerea*

Scheme 58



R^1 = CO_2Me, CO_2Et, Ac; R^2 = H, Me; R^3 = H, Me, Bn

(Scheme 59). Co-tetramethylthiourea (**351**, TMTU)-catalyzed tandem Pauson–Khand and 6π-electrocyclization reactions of trienyne **350** gave the tricyclic ketone **353**. Subsequent oxidative aromatization mediated by DDQ gave the aromatic ketone **354**, which was subsequently transformed into the above-mentioned botryanes **355**–**357**.

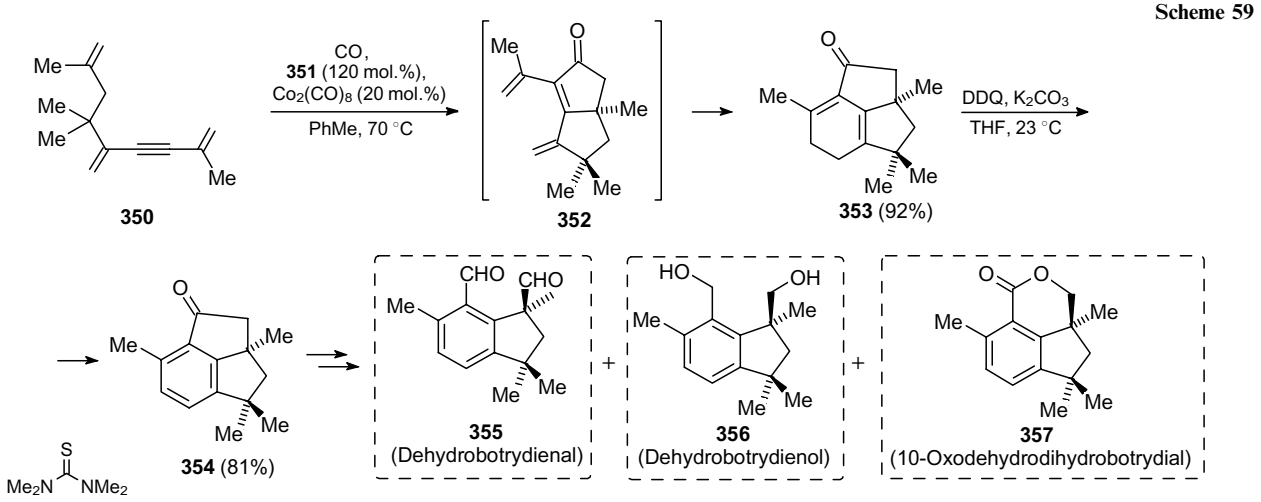
Aryl triazenes are versatile synthetic intermediates since they can be transformed into many different compounds on reaction of the derived arenediazonium salts with different oxygen- and nitrogen-containing nucleophiles. Recently, Cramer and co-workers[99] reported the synthesis of heavily substituted aromatic triazenes **363** and **365**, which utilized a ruthenium-catalyzed cyclization reaction (Scheme 60). Reaction of tethered diynes **358** with alkynyl triazenes **359** in the presence of a Ru^{II} complex resulted in formal [2 + 2 + 2] cyclotrimerization reactions, producing aryl triazenes **363**. Similarly, 1-diynyl triazenes **364** and alkynes **46** underwent a related [2 + 2 + 2] cycloadditions to produce aryl triazenes **365**. The retention of the triazine unit during these aromatization reactions is noteworthy.

Ma and co-workers[100] reported a palladium-catalyzed synthesis of 1,3-dihydroisobenzofurans **371**, **372** and **374**, **375** (Z = O) and isoindolines **374** and **375** (Z = NTs) (Scheme 61). The authors found that palladium acetate and tri-2-furylphosphine (TFP) promoted the cyclization of dienyl carbonates **367** with terminal alkynes **366** to produce dihydroisobenzofurans **371** and **372**, favouring regioisomers **371** due to regioselective double alkyne insertion reactions. Furthermore, a range of oxygen- or nitrogen-tethered carbonates **373** were also cyclized with terminal alkynes **366** to produce arenes **374** and **375**.

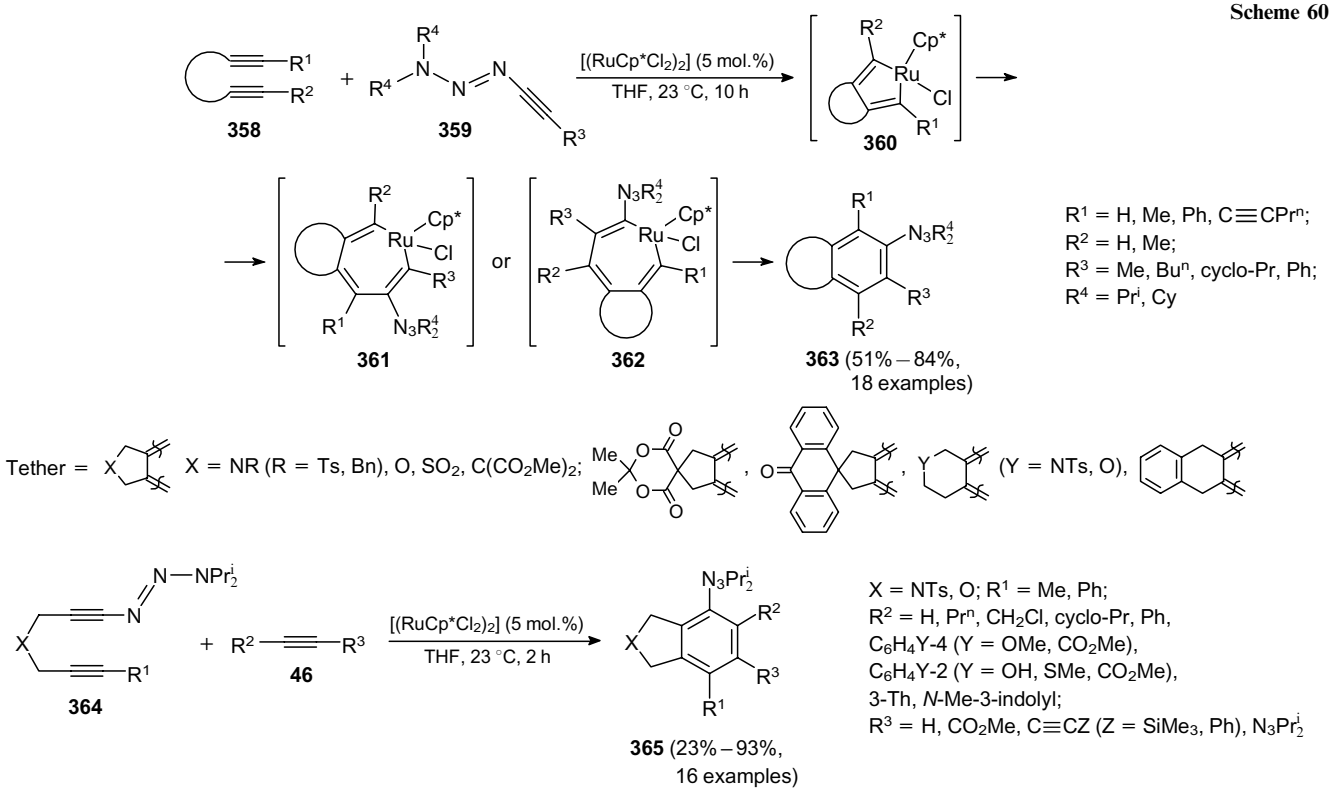
Yang and co-workers[101] reported a simple formal [3 + 3] cycloaddition approach to produce polysubstituted terphenyls **382** from vinylethylene carbonates **376** (Scheme 62). With palladium catalysis, the latter compounds were converted into the corresponding α,β-unsaturated aldehydes **377**, which were subsequently allowed to react with allylic sulfones **378** to induce a regioselective [3 + 3] oxidative cycloaddition in the presence of DBU to give terphenyl compounds **382**.

Kale and Liu[102] reported that the cyclohexene-bridged diyne **383** underwent gold-catalyzed aromatization reactions with *para*-substituted nitrosobenzenes **384** to give tetrahydronaphthaldehyde derivatives **388** (Scheme 63). It was found that the propargylic oxygen substituent of the 1,6-diyne substrate influenced the reaction outcome with

Scheme 59



Scheme 60



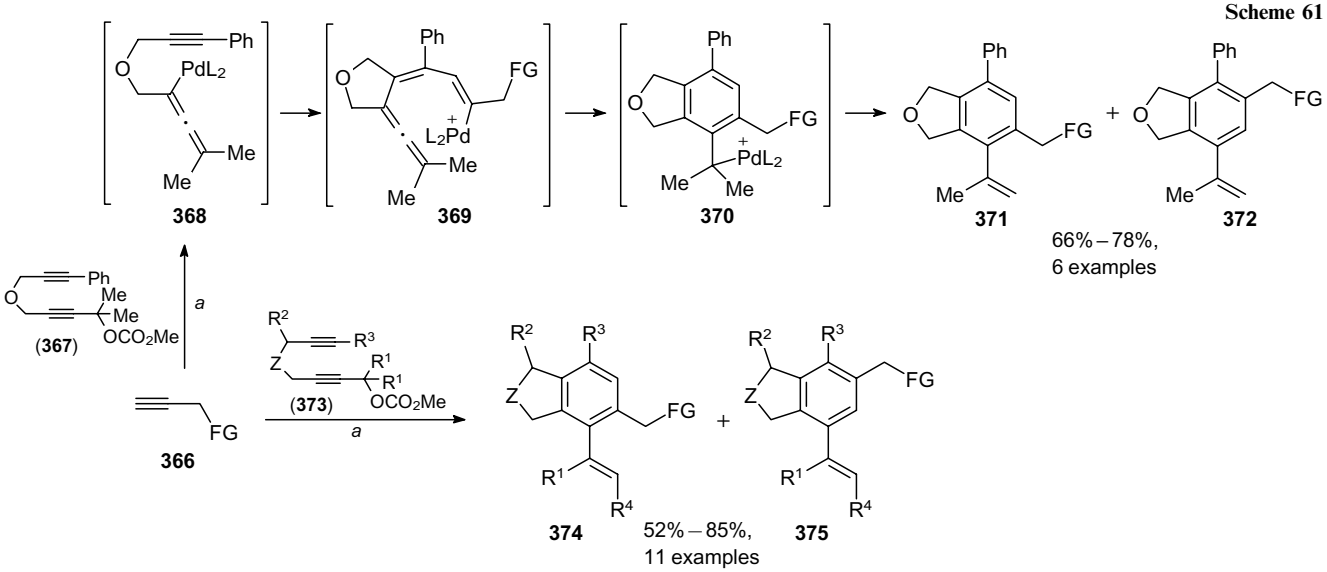
larger silyl groups leading to higher reactivity due to the operation of the Ingold – Thorpe effect.

Deng and co-workers [103] reported a palladium-catalyzed aerobic benzannulation approach for the preparation of highly functionalized anilines **396** (Scheme 64). It was found that these anilines were formed *via* palladium-catalyzed formal [3 + 2 + 1] cycloadditions between amines **389**, aldehydes **138** and β-dicarbonyl compounds **390**. It is important to note that the addition of acetic acid was essential to promote both the condensation process as well as in the oxidative dehydrogenation step.

Ghorai and Lee [104] reported aryne-based multicomponent coupling reactions for the preparation of highly functionalized aromatic compounds **402** – **406** (Schemes 65, 66). They reported the hexadehydro Diels – Alder reaction of the tetra-ynes **214**, **397** to produce aryne intermediates **398**, which readily underwent reaction with aryl isocyanides to form nitrilium intermediates **399**. Subsequent trapping of these species with carboxylic acids gave the corresponding imides **401** after Mumm rearrangement. This method was further extended for the syntheses of imidate **404**, amidine **405** and amide **406** by respectively replacing the carboxylic acid with an alcohol, sulfonamide or water (see Scheme 66). All these 3-component coupling reactions were generalized by variation in the tetra-yne, alcohol and sulfonamide. Also, the processes could be catalyzed using silver(I) hexafluoroantimonate but yields were better in its absence.

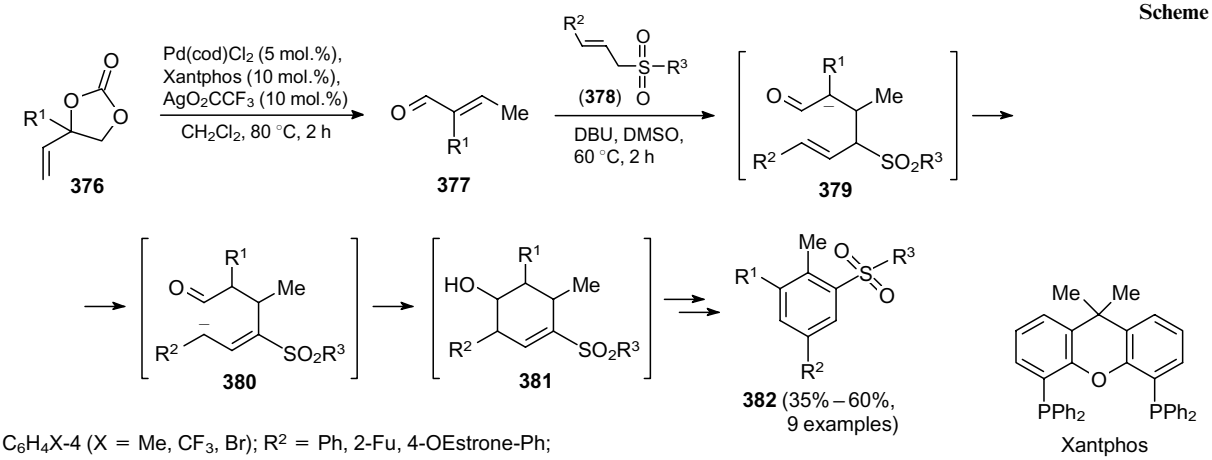
(–)-Rubriflordilactone B (**295**) is a highly functionalized polycyclic nortriterpenoid extracted from the plants of the *Schisandra sp.* and, as mentioned above, displays antiviral and anticancer activities. Recently, Anderson and coworkers [105] reported a convergent strategy for the total synthesis of this natural product in which the aromatic core was elaborated from a non-aromatic precursor

Scheme 61



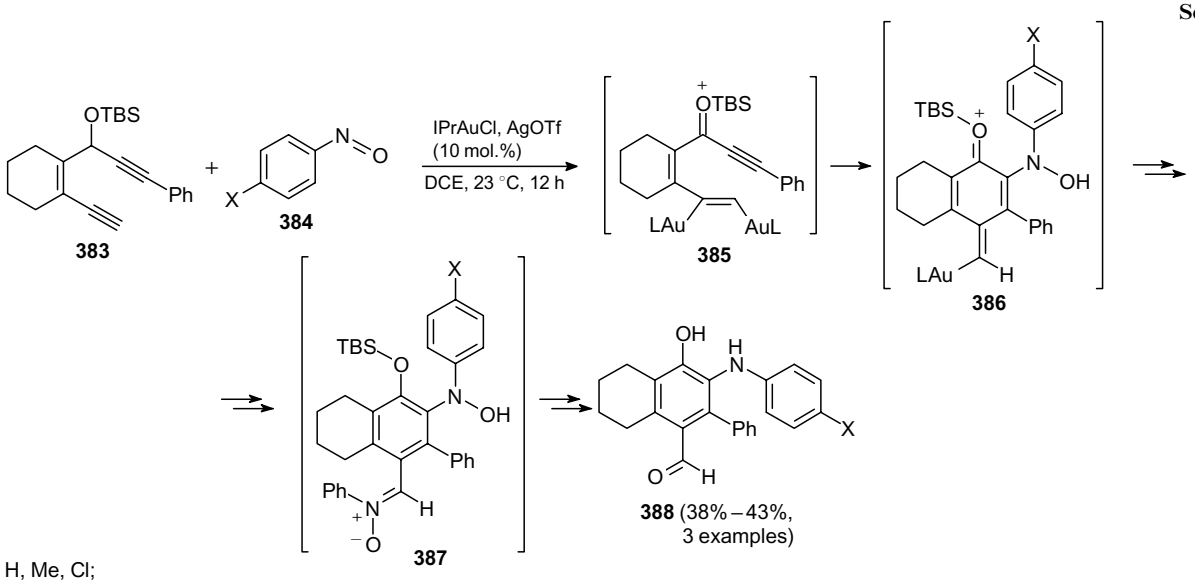
(*a*) $Pd(OAc)_2$ (5 mol.%), TFP (10 mol.%) [TFP = P(2-Fu)$_3$], Na_2CO_3, H_2O, N_2, MeCN, 30 °C; FG = NHTs, OH, 1-indolyl, 2-indolyl, 3-formyl, 6-Br-, 5-Me-1-indolyl; Z = O, NTs; R^1 = Me; R^2 = H, Pr^n; R^3 = Ph, C_6H_4X-4 (X = Me, OMe, Cl), C_6H_4Me-2, 3-Th, Bu^n, $SiMe_3$; R^4 = H; $R^1 – R^4$ = $(CH_2)_3$, $(CH_2)_4$

Scheme 62



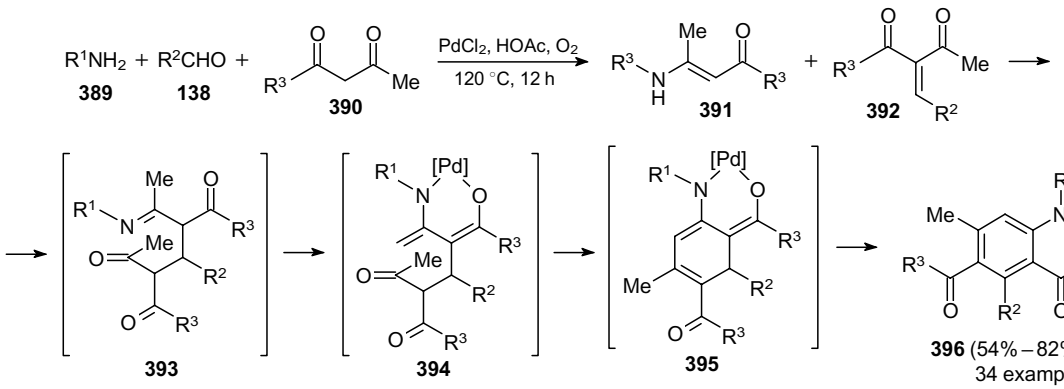
R^1 = Ph, C_6H_4X-4 (X = Me, CF_3, Br); R^2 = Ph, 2-Fu, 4-OEstrone-Ph;
R^3 = Ph, C_6H_4X-4 (X = Me, OMe, F)

Scheme 63



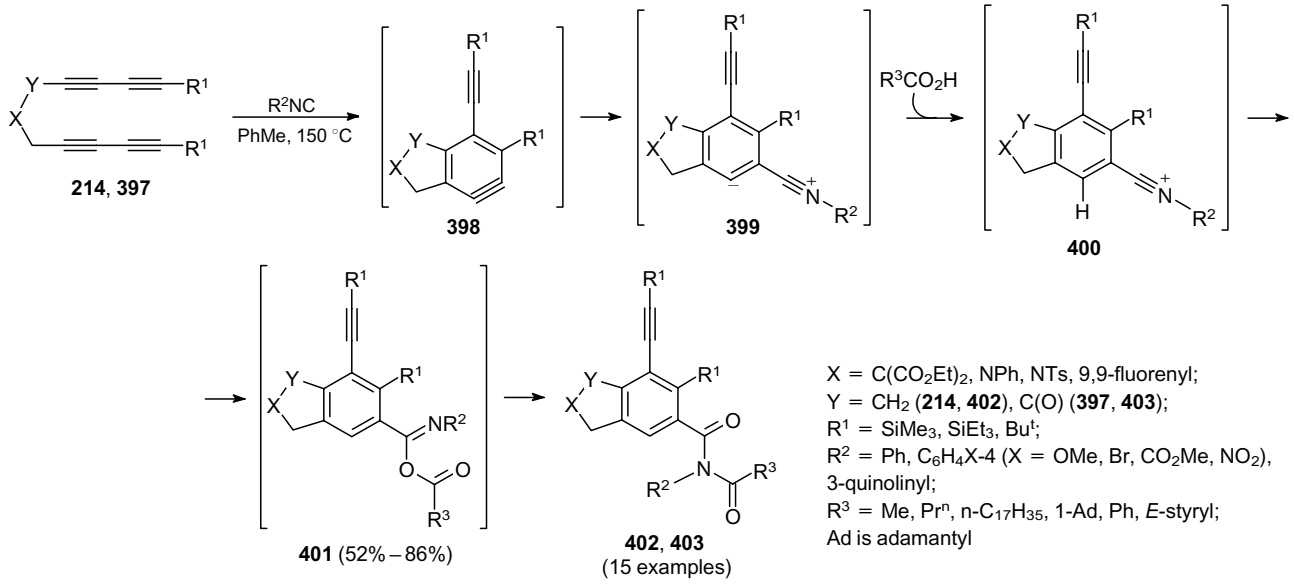
X = H, Me, Cl;
IPr is 1,3-bis(diisopropylphenyl)imidazol-2-ylidene

Scheme 64



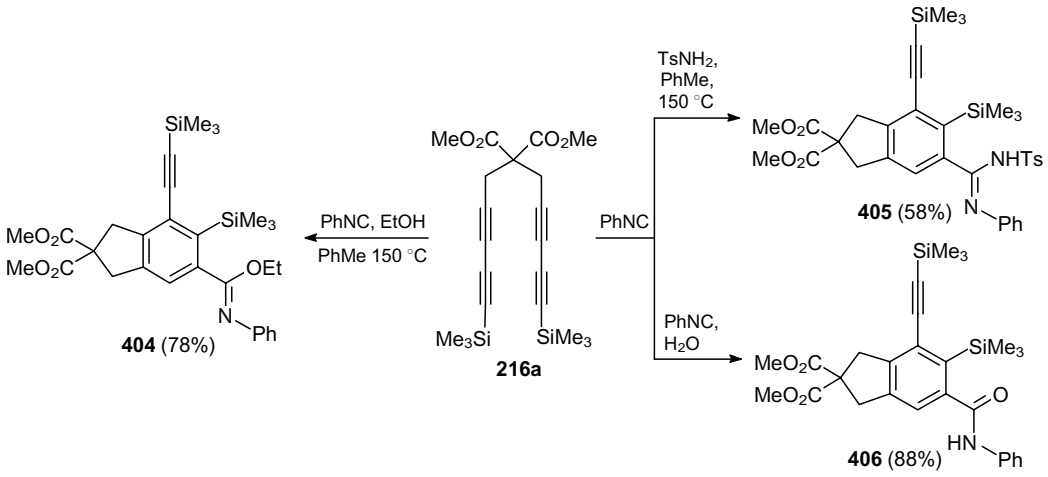
R^1 = Ph, C_6H_4X-4 (X = Me, Pr^i, Bu^t, CF_3, OMe, OCF_3, F, Cl, Br, Ph), C_6H_4X-3 (X = Me, Cl), C_6H_4X-2 (X = Me, F, Cl), 2-Py, CH_2-2-Th;
R^2 = Ph, C_6H_4X-4 (X = Me, Bu^t, OMe, Cl, Br, Ph), C_6H_4X-3 (X = Me, F, Br), C_6H_4F-2, 2-Fu; R^3 = Me, OMe, OEt; MeC_6H_4Y (Y = 4-Cl, 3-Cl, 2-Br)

Scheme 65



X = $C(CO_2Et)_2$, NPh, NTs, 9,9-fluorenyl;
Y = CH_2 (**214**, **402**), C(O) (**397**, **403**);
R^1 = $SiMe_3$, $SiEt_3$, Bu^t;
R^2 = Ph, C_6H_4X-4 (X = OMe, Br, CO_2Me, NO_2), 3-quinolinyl;
R^3 = Me, Pr^n, n-$C_{17}H_{35}$, 1-Ad, Ph, *E*-styryl;
Ad is adamantyl

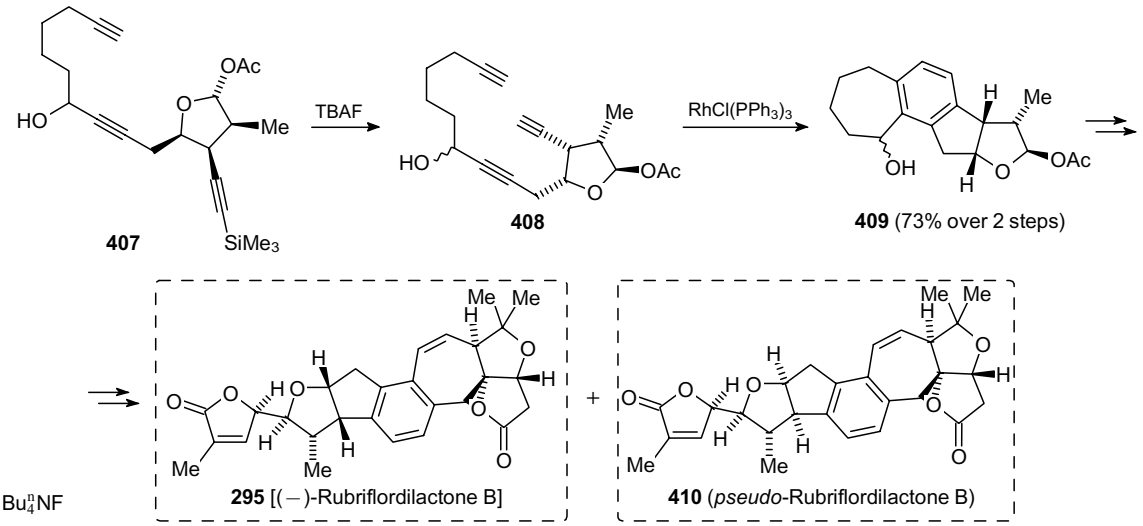
Scheme 66



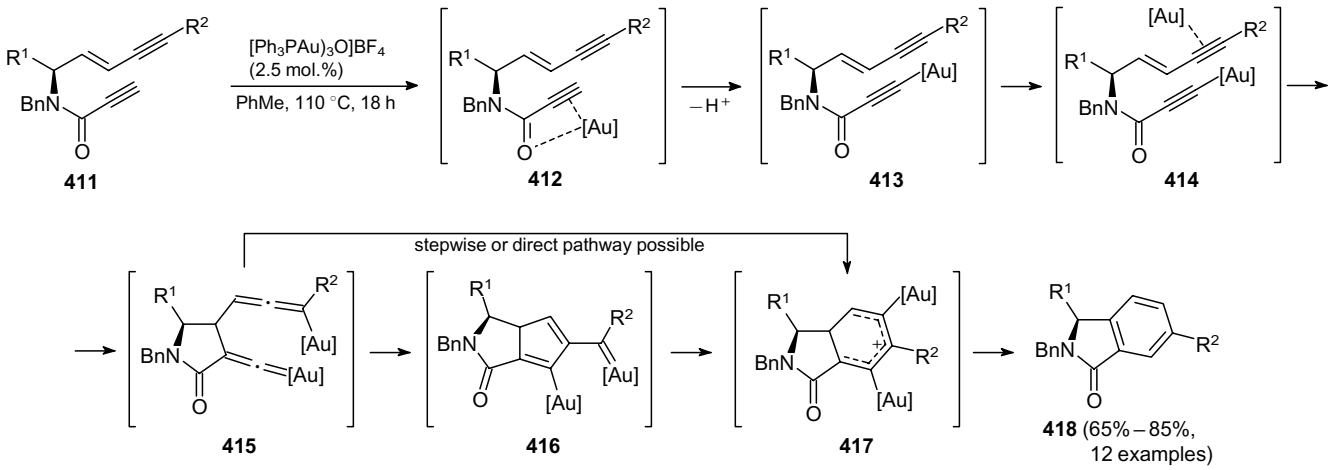
(Scheme 67). Triyne **408**, derived from triyne **407** by desilylation, underwent a rhodium-catalyzed cyclotrimerization reaction in the presence of Wilkinson's catalyst [$(Ph_3P)_3RhCl$] to give the arene core of alcohol **409**, an advanced intermediate which was further converted into (−)-rubriflordilactone B (**295**) and (−)-*pseudo*-rubriflordilactone B (**410**).

Hyland and co-workers[106] disclosed the synthesis of isoindolinones **418** *via* a gold catalyzed cycloisomerization and aromatization of diyne **411** (Scheme 68). The authors

Scheme 67



Scheme 68



suggested that the reaction proceeded *via* gold acetylides **412** and **413**, a second gold incorporation as acetylene complex **414**, and cyclization *via* intermediates **415**–**417**.

As a follow up publication from the earlier dihydroisobenzofuran synthesis (see Scheme 61), Ma and co-workers [107] reported that the use of α-disubstituted propargylic alcohols **420** gave tricyclic arenes **424** with only minor amounts of the β-elimination products (Scheme 69). The authors suggested a mechanism where Pd-coordination induced the elimination of the carbonate and gave the reactive intermediate **421**, which reacted with propargylic alcohol **420** to give the allene **422**. Arene **423** formation was followed by nucleophilic displacement of the catalyst to release the benzoisofuran derivatives **424** in fair to good yields. The use of enantiomerically pure diynes **367a**,**b** gave the arenes **424a**,**b** with retention of configuration at the propargylic position.

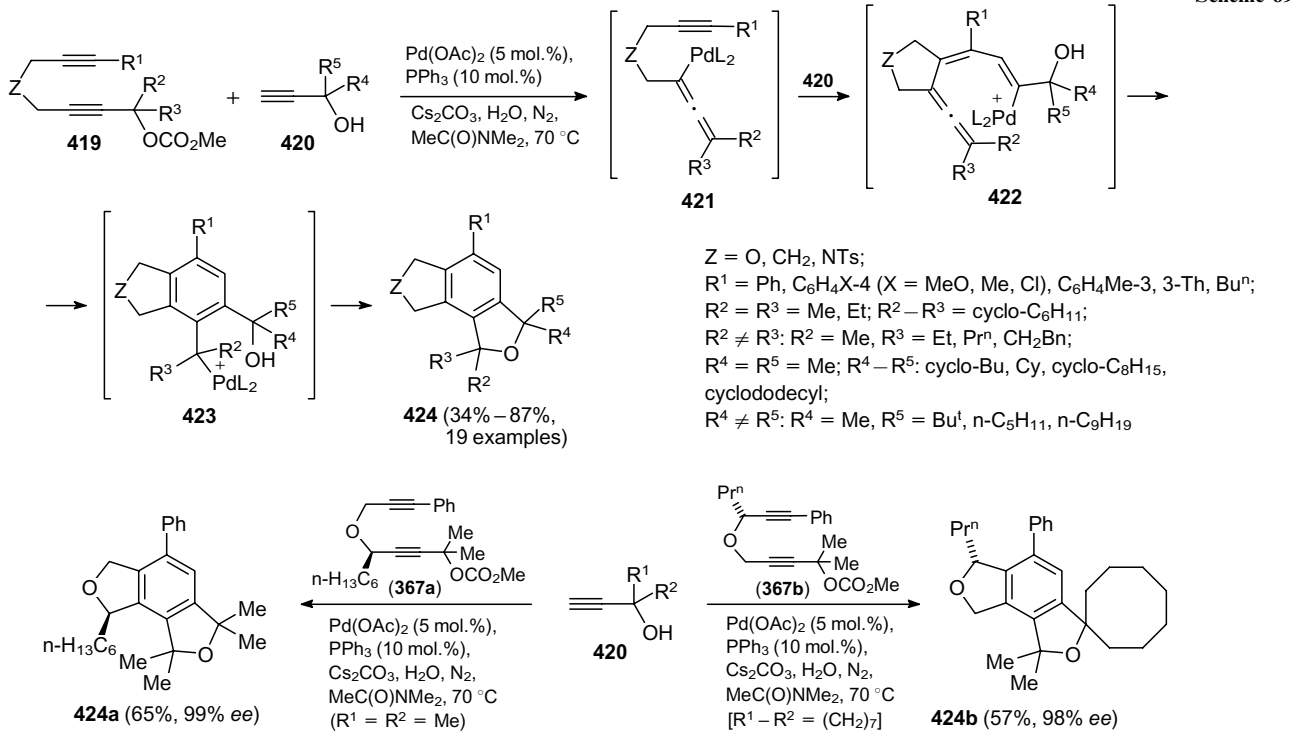
Recently, Zhu and co-workers [108] showed that diynes **425** on reaction with a catalytic amount of cobalt dichloride and pinacolborane **426** in the presence of phenanthroline gave vinyl boranes **427** in moderate to good yields (Scheme 70). Vinyl borane **427a** was subsequently converted into cyclohexadienes **428**, employing a Suzuki–Miyaura coupling reaction followed by a thermal 6π-electrocyclization. Oxidative aromatization mediated by DDQ gave indanes **429** in good yields.

Lee and co-workers [109] expanded their earlier work [104] on imides **401**, imidates **404**, amidines **405** and amides **406** (see Schemes 65, 66) by trapping the aryne intermediate **432** from triynes **430** by nitriles in the presence of a silver catalyst (Scheme 71). Silver complexed aryne **433** gave rise to two regioisomeric nitrilium ions **434** and **437**, which underwent conversion into the two isomeric quinazolines **436** and **439** on treatment with a second equivalent of nitrile. The observed regioselectivity was controlled by the steric bulk of the R^5 group with *tert*-butyl favouring nitrilium ion **434** whereas nitrilium ion **437** was favoured with the smaller TMS group. Aromatic substituents resulted in a slight preference of **434** over **437**.

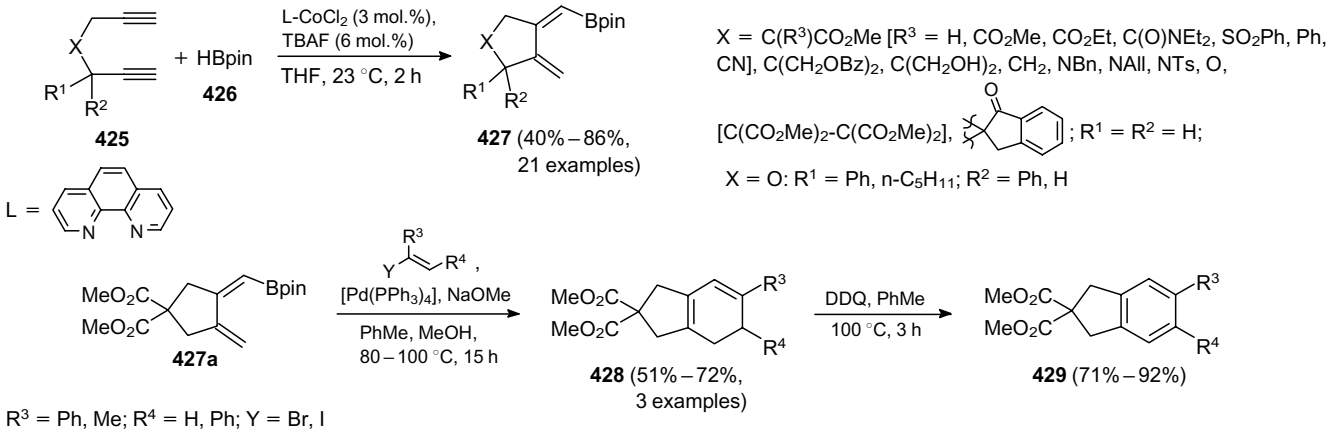
Additionally, the same group [110] reported that arynes of type **434** derived from **440** were trapped with isonitriles to give benzocyclobutene-diimines **441** in moderate yields (Scheme 72). Mixed additions of both nitriles and isonitriles were also performed. In this case, reactions gave indolimines **442** in fair yields, as well as the derived hydrate **443** in moderate yields in some cases.

In 2020, B.Wang and co-workers [111] reported the rhodium catalyzed annulation of heterocyclic amides **444** with

Scheme 69



Scheme 70



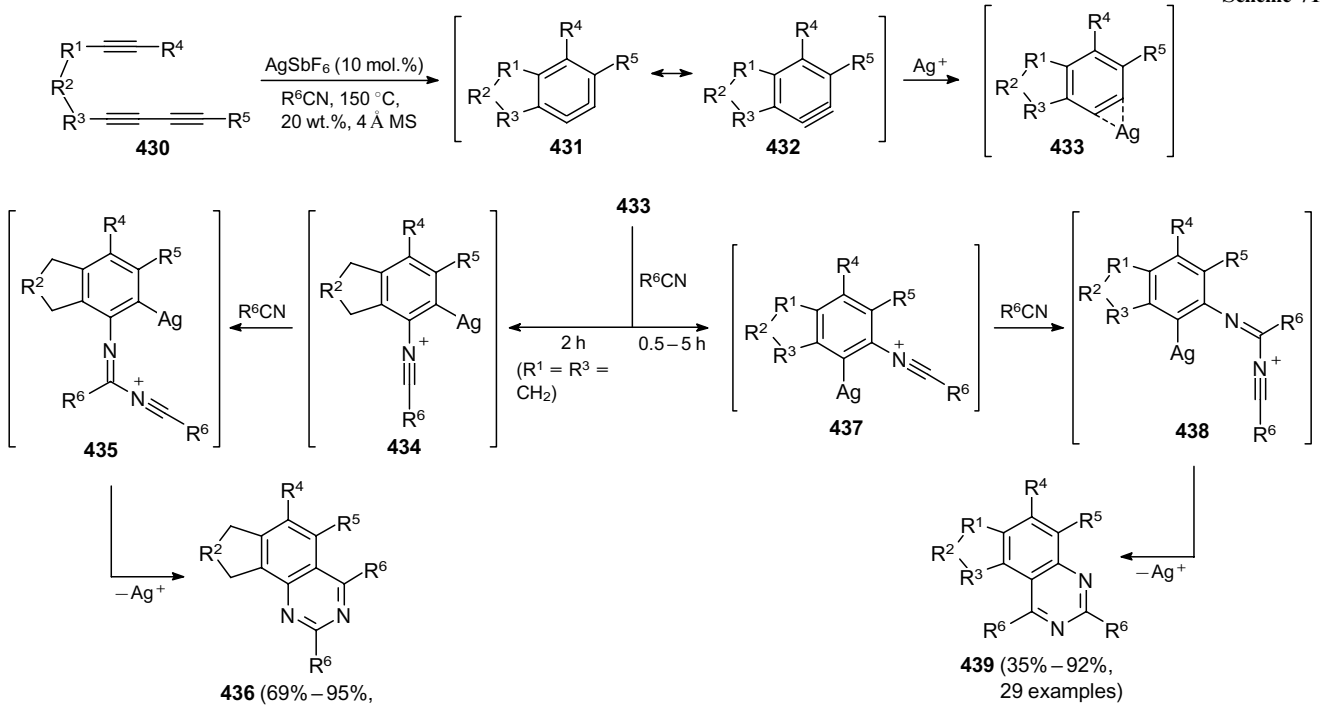
diynes **445** (Scheme 73). As a directing group, the amide functionality is known to facilitate Rh–C–H insertion to intermediate **446**, which reacted with diyne **445**. Subsequently, a five-membered rhodacycle **448** was formed, which in the presence of a nucleophile lost the directing group. Concomitant insertion into the other alkyne gave the metallacycle **449**, followed by rhodium elimination to give arenes **450** in low to good yields.

Activation of diynes **451** with rhodium in the presence of 2 equivalents of quinones **452** gave naphthoquinones **457** (Scheme 74).[112] Initially, the metallacycle **454** was formed, which reacted with quinone **452** in a cycloaddition type fashion to give diene **456** after rhodium elimination. The intermediate cyclohexadiene **456** was aromatized by reaction with a second equivalent of quinone **452** giving naphthoquinones **457** in fair to good yields. Hexasubstituted arenes were accessible *via* this procedure in moderate yields.

Foubelo and co-workers[113] investigated strategies for the conversion of diynes and enynes into arenes. Firstly, rhodium catalyzed [2+2+2]-cyclotrimerization of diyne **458** and acetylenes **112** gave tetrahydroisoquinolines **463** (Scheme 75). In addition, enynes **464**, **465** were cyclized using the Hoveyda–Grubbs catalyst to give dienes **466** and **469**. Finally, Diels–Alder reaction of these compounds with dimethyl acetylenedicarboxylate (**112a**) and subsequent DDQ mediated oxidative aromatization gave tetrahydroisoquinolines **468** and **470**.

Li and co-workers[114] reported the oxidative coupling of primary alcohols **472** with differently substituted cyclohexanones **471** on Pd/C for the synthesis of *o*-substituted phenols **478** (Scheme 76). Oxidation of the alcohols **472** to the corresponding aldehydes **473** followed by base catalyzed aldol reaction gave alcohols **474**. Dehydration and alkene isomerization gave cyclohexanone **476**, which on aerobic oxidation and tautomerization gave phenols **478** in reasonable yields. Intriguingly, reaction with a steroid triol occurred with regioselective oxidation of the primary alcohol and gave the steroidal phenol **479**.

Scheme 71

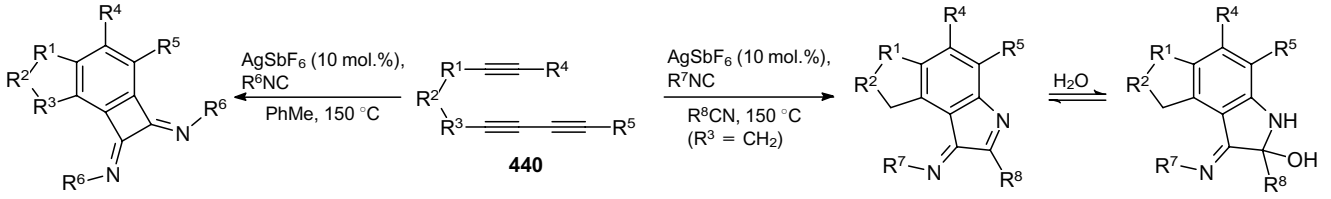


430, **431**, **432**, **433**, **434**, **435**, **436** (69% – 95%, 5 examples), **437**, **438**, **439** (35% – 92%, 29 examples)

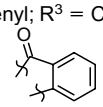
R^2 = $C(CO_2Me)_2$, $C(CO_2Et)_2$, CH_2;
R^4 = C≡CX (X = Bu^t, $CH_2C_6H_4OMe$-4, Ph);
R^5 = Bu^t, $CH_2C_6H_4OMe$-4, Ph; R^6 = Ph

R^1 = C(O), CH_2; R^2 = NTs, O, CH_2, NPh, $C(CO_2Me)_2$;
R^2 = 9,9-fluorenyl; R^3 = CH_2, NTs;
$R^1-R^2-R^3$ =  ; R^4 = H, $SiMe_3$, C≡CX (X = $SiMe_3$, Bu^n);
R^5 = $SiMe_3$, $SiEt_3$; R^6 = Ph, C_6H_4X-4 (X = OMe, NMe_2, F), piperidyl, morpholyl, vinyl, styryl, Me, Et, Pr^i, cyclo-Pr, 2-Naph

Scheme 72



440, **441** (42% – 76%, 15 examples), **442** (36% – 74%, 9 examples), **443** (32% – 55%)

R^1 = CH_2, C(O); R^2 = $C(CO_2Me)_2$, NTs, NPh, O;
R^2 = 9,9-fluorenyl; R^3 = CH_2;
$R^1-R^2-R^3$ =  ; R^4 = H, C≡CTMS; R^5 = TMS, TES;
R^6 = Ph, C_6H_4X-4 (X = Me, OMe, NMe_2, CO_2Me, NO_2, Br), 2-Naph, 3-quinolyl

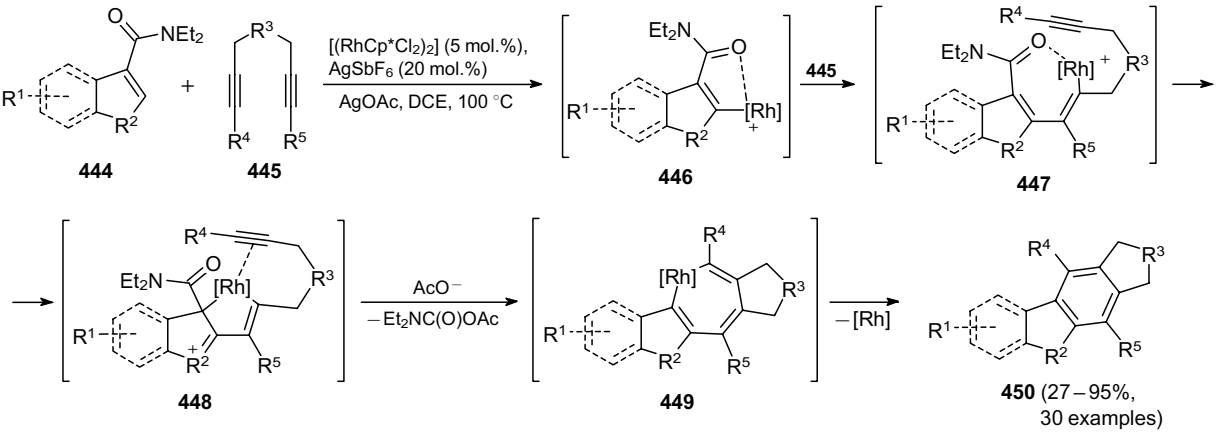
R^1 = CH_2, C(O);
R^2 = $C(CO_2Me)_2$, NPh;
R^4 = H, C≡CTMS;
R^5 = TMS, TES;
R^7 = Ph, C_6H_4X-4 (X = Me, Br, CO_2Me, NO_2);
R^8 = Ph, Pr^i

R^1 = CH_2, C(O);
R^2 = $C(CO_2Me)_2$, NPh;
R^4 = H, C≡CTMS;
R^5 = TMS, TES;
R^7 = Ph, C_6H_4X-4 (X = Me, Br, CO_2Me);
R^8 = Me, Et

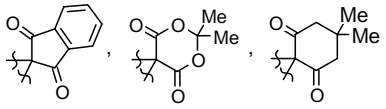
Recently, Deng and co-workers[115] reported the synthesis of heavily substituted phenols **487** from allenyl diazo ketones **480** (Scheme 77). Upon mixing with a silver salt, allene **481** was cycloisomerized to diazofuran **483**. Under rhodium catalysis conditions, this compound was converted into the rhodium-carbene **484**, which underwent cyclopropanation and ring expansion to give the cyclohexanone **486**. When R^1 = Ar, R^2 = OEt these underwent tautomerization under the reaction conditions and gave phenols **487** in good yields. In ten other examples when R^2 = Ph, OEt the products isolated were the cyclohexenones **486**. Addition of a second Lewis acid mediated the aromatization of seven of those examples (R^2 = OEt, 50% – 86%) while three (R^2 = Ph or R^1 = H and R^2 = OEt) did not undergo conversion into the phenols **487**. Further attempts to transform this reaction into a one-pot procedure were unsuccessful since the reaction stopped at the furan **483** stage.

Toyota and co-workers[116] reported the conversion of enamines **488** into anilines **491** in moderate to good yields by reaction with copper(II) and palladium(II) acetates in

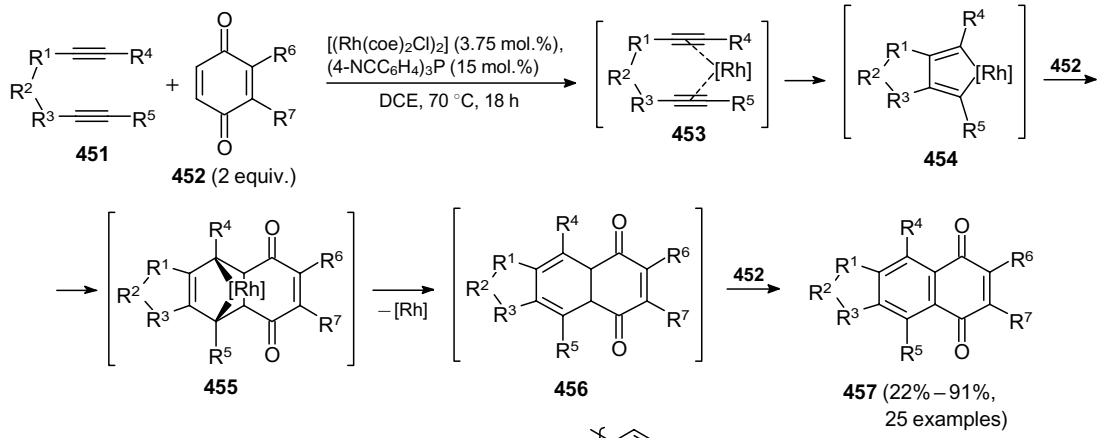
Scheme 73

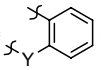


Ar = indole, benzothiophene, thiophene; R^2 = NMe: R^1 = H, 4-OMe, 5-X (X = Br, Me, OMe, F, NO_2), 6-Cl, 7-Me, 7-Cl; R^2 = NBn, NH, S: R^1 = H, R^3 = $C(CO_2Et)_2$, $C(Ac)_2$, NTs, $C(Ac)CO_2Et$, $C(CN)_2$, O; R^4 = R^5 = Ph, CC_6H_4X-4 (X = Me, OMe, F, Cl), 2-Th, Me; R^4 = C_6H_4Cl-4, R^5 = C_6H_4MeO-4 (major); R^4 = C_6H_4OMe-4, R^5 = C_6H_4Cl-4 (minor);

other tethers: 

Scheme 74



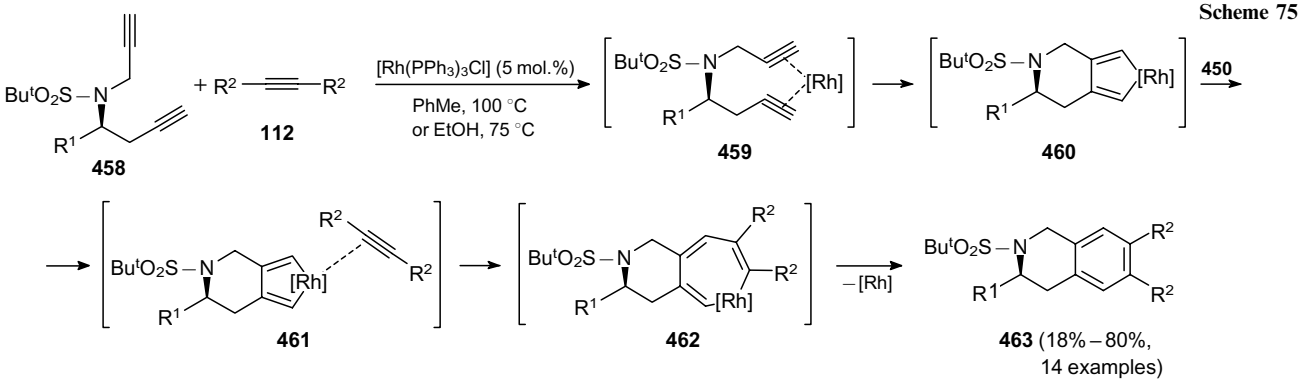
R^1 = CH_2; R^2 = $C(CO_2Me)_2$, CH_2, O, NTs; R^3 = CH_2; R^1–R^2–R^3 =  (Y = NTs, O); R^4 = H, Me, Bu^n, CH_2OTBS, Ph, C_6H_4X-4 (X = OMe, F); R^5 = H, Me, Bu^n, Ph, C_6H_4X-4 (X = OMe, F); R^6 = H, Me, OMe, N(Me)Ph, Cl, Br, I, Ph, C_6H_4X-2 (X = OMe, Br), $C_6H_4CF_3$-4; R^7 = H, Me; coe is cyclooctene

DMSO (Scheme 78). The transformation by $Pd(OAc)_2$ mediated cyclization to the palladated cyclohexane derivative **489** and subsequent reductive elimination gave cyclohexadiene **490**, which was subsequently converted into the anthranilic acid ester derivatives **491** by further oxidation with $Pd(OAc)_2$. In these cases, $Cu(OAc)_2$ was the best co-oxidant. When the amine **488** was only monosubstituted and the alkene was terminal, a mixture of the cyclohexanone imine **489** and the corresponding pyrrolidine was obtained, which gave rise to a mixture of anilines and pyrroles slightly favouring the aniline. Additionally, the authors showed that the procedure was amenable to a one-pot process starting with the acetoacetate and the amine (with oxygen as the oxidant).

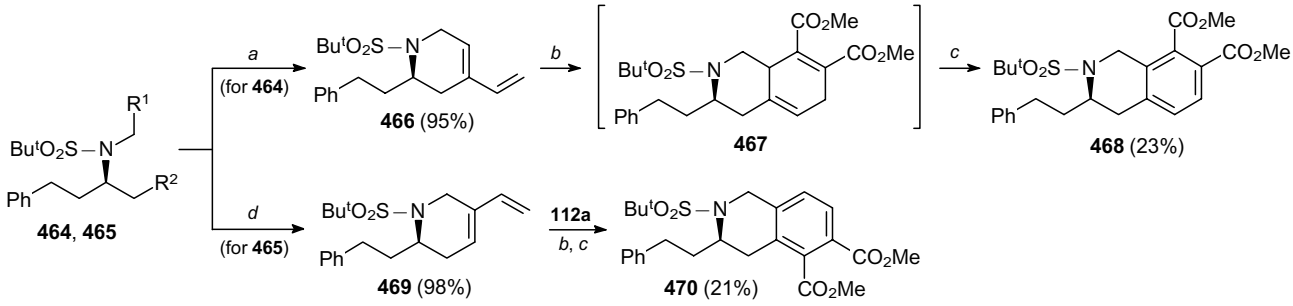
5. Other aromatization strategies

This final section of the review will focus on alternative methods that are not classified according to the sections above. This includes aromatization reactions that depend on applications of organo-catalysis, base-mediated reactions (Aldol-reactions, Mannich-reactions, *etc.*) and oxidative cyclohexane- or cyclohexanone halide–halonium addition–elimination reactions to form phenols. These methods are highly versatile and applicable for the synthesis of heavily substituted phenols from readily available starting materials. As shown in this chapter, new developments in phenol syntheses have facilitated the synthesis of *m*-substituted derivatives through pre-functionalization and subsequent aromatization. These approaches overcome the limitations of electrophilic aromatic substitution reactions or *ortho*-lithiation reactions of phenols and phenol derivatives, which strongly favour *ortho*- or *para*-substitution reactions and not *meta*. These reactions may be sub-divided according to their reaction type.

Scheme 75

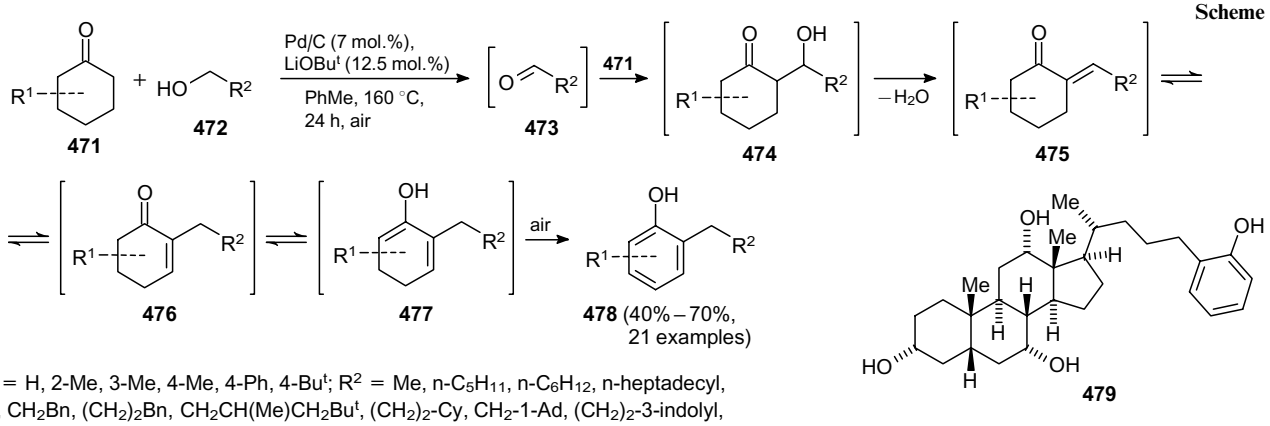


R^1 = CH_2Bn, Ph, n-C_9H_{19}, $(CH_2)_4OTHP$, Bu^i; R^2 = Et, CH_2OH, CO_2Me; R^2–R^2 = Bu^n, H gives 1 : 1 mixture; THP is tetrahydropyranyl



(a) H-G II (10 mol.%), 1,7-octadiene, CH_2Cl_2, 40 °C; (*b*) $MeO_2C{\equiv}{-}CO_2Me$ (**112a**), PhMe, 100 °C; (*c*) DDQ, PhMe, 80 °C;
(*d*) H-G I (20 mol.%), 1,7-octadiene, CH_2Cl_2, 40 °C (H-G is Hoveyda–Grubbs 1st (I) or 2nd (II) generation catalyst);
464: R^1 = CH═CH_2, R^2 = C≡CH; **465**: R^1 = C≡CH, R^2 = C═CH_2

Scheme 76



R^1 = H, 2-Me, 3-Me, 4-Me, 4-Ph, 4-Bu^t; R^2 = Me, n-C_5H_{11}, n-C_6H_{12}, n-heptadecyl, Ph, CH_2Bn, $(CH_2)_2Bn$, $CH_2CH(Me)CH_2Bu^t$, $(CH_2)_2$-Cy, CH_2-1-Ad, $(CH_2)_2$-3-indolyl, $(CH_2)_3$-2-benzofuranyl, $(CH_2)_3$-2-Th, 2,6-dimethylheptanyl, 11-hydroxyheptadecyl

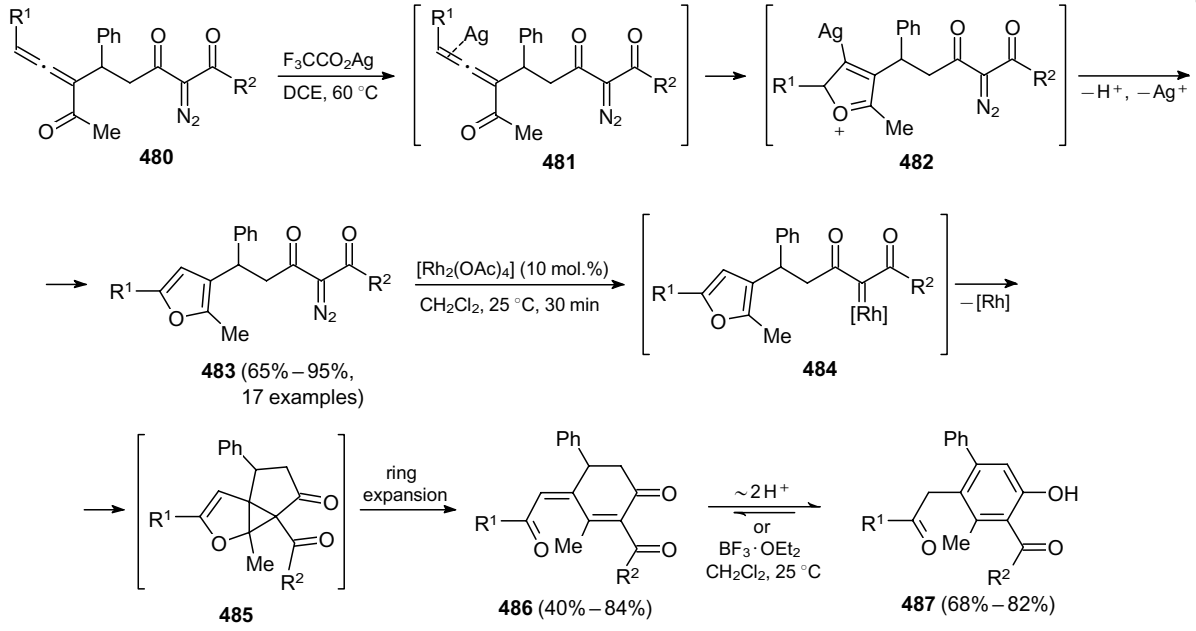
5.1. Halogen-mediated reactions

Luo *et al.*[117] showed that substituted cyclohexenones **492** reacted with iodine in DMSO under air to provide phenols **493** (Scheme 79). This procedure was applicable to a broad range of different substitution patterns including for the elaboration of tetra-substituted phenols **493**.

Kang and co-workers[118] reported the trimethylsilyl triflate-catalyzed aromatization of Hagemman's esters **494** with NBS as the stoichiometric oxidant. Sixteen examples of phenol derivatives **495** were synthesized *via* this route by simple variation of the aldehyde precursor (RCHO) used in the preparation of the starting cyclohexanone **494** (Scheme 80) from ethyl acetoacetate.

Luo and co-workers[119] reported the conversion of α,β-unsaturated oximes **496** with iodine under air to provide anilines **500** (Semmler–Wolf type reaction) (Scheme 81). Improving on recent findings, this method excluded strong acids or transition metal catalysis. A range of aromatic substituents were tolerated with the R^1 and R^2 substituents and the reaction provided the desired products with overall moderate to good yields. The authors suggested that the reaction proceeded *via* the imine radical **497**, its tautomerization to radical **498**, C-iodination and elimination to the aniline tautomer **499** and aromatization. Whilst the authors have shown by reaction inhibition with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) that the process involves radicals, the authors of this review consider that the imine

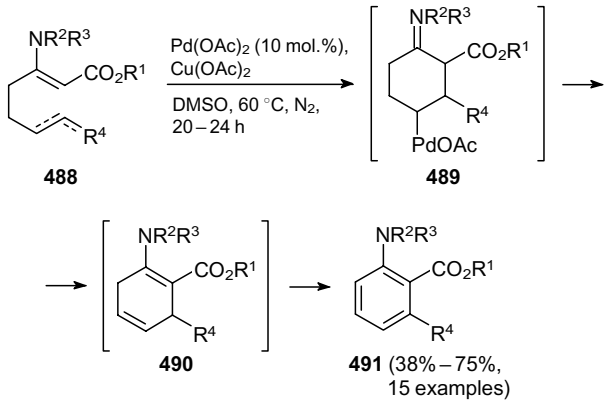
Scheme 77



10 other examples stopped at **486**, 7 examples could be converted to **487** with BF_3;
R^1 = Ph, C_6H_4F-4, Bu^n, Bu^t;
R^2 = OEt, Ph

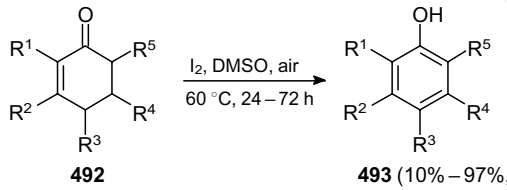
5 examples formed **487** directly;
R^1 = C_6H_4X-4 (X = Me, OMe, Br, Cl), 3-Th;
R^2 = OEt (50% – 86%)

Scheme 78



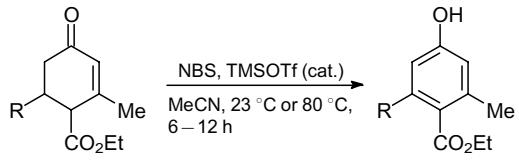
R^1 = Me, Et; R^2 = H, NR^2R^3: pyrrolidine, piperidine, morpholine, *N*-Me-piperazine, *N*-Ac-piperazine; R^3 = Bn, $CH_2C_6H_4X$-4 (X = MeO, Me, F), CH_2Bn, n-C_6H_{13}; R^2 = R^4 = H, R^3 = Bn or $CH_2C_6H_4OMe$-4 2 : 1 to 5 : 3 mixture between aniline and pyrrole; R^4 = H, Me

Scheme 79



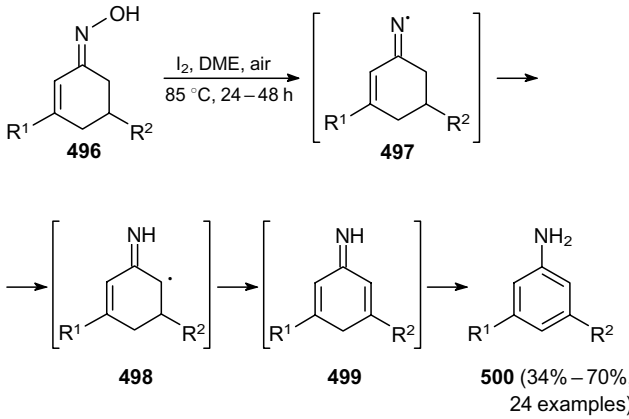
R^1 = H, Me; R^2 = Ph, C_6H_4X-4 (X = OMe, Cl, Me, Br, NHBoc, OH), 2-Fu; R^3, R^5 = H, Me, CO_2Et; R^4 = Ph, $C_6H_4NO_2$-3, $C_6H_3OCH_2O$-3,4, 2-Naph, C_6H_4Br-4, CO_2H, CO_2Et, C(O)NHBn, C(O)NHPh, $C(O)NHC_6H_4OMe$-4

Scheme 80



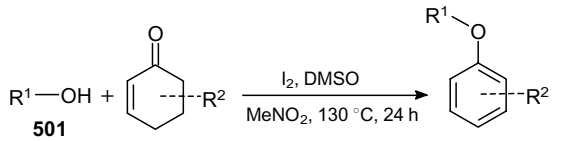
R = Me, Et, Pr^n, Pr^i, Bu^s, CO_2Et, 2-Fu, Ph, 2-Naph, C_6H_4X-4 (X = Me, SMe, OMe, CN, NO_2, Br, Cl)

Scheme 81



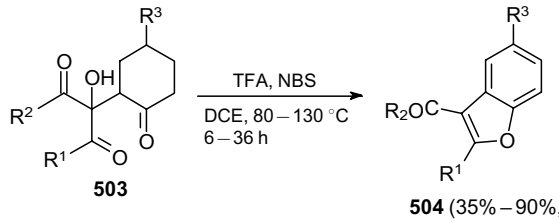
R^1 = H, Me, Ph, C_6H_4X-4 (X = OMe, Me, Cl, SMe, SO_2Me), 2-Th, 2-Fu, 2-Naph, cyclohex-2-enone oximes;
R^2 = H, CO_2H, CO_2Et, C(O)NHBn, C(O)NHPh, Ph, C_6H_4X-4 (X = Me, OMe, NO_2, Cl, Br), $C_6H_3OCH_2O$-3,4

Scheme 82



R^1 = $(CH_2)_2$-1-Naph, CH_2Bn, $(CH_2)_2C_6H_4X$-4 (X = Bu^t, OMe, OBn, Br, F, OH), $(CH_2)_2C_6H_4Y$ (Y = 2-Br, 3-Br), $CH_2CH(Ph)_2$, $CH_2C_6H_4X$-4 (X = CO_2H, C≡CH), $(CH_2)_2Bn$, $(CH_2)_2C{\equiv}CH$, $CH_2C{\equiv}CPh$, cyclo-C_5H_9, $CH(Et)_2$, CHMe-cyclo-Pr, 2-C_6H_{13}, Cy, $C_6H_{10}Me$-4, $C_6H_{10}Pr^i$-2, $(CH_2)_2$(4-Me)thiazole, menthyl, citronellyl, cholesteryl, borneoyl;
R^2 = H, 3-Me, 3-Ph, 3-(2-Th), 3-(1-Naph), 3-CO_2Me, 3,5-Ph_2, 3-(5-phenyl)thienyl, 2-(C_6H_4Me-4), 3-(SC_6H_4Cl-4)

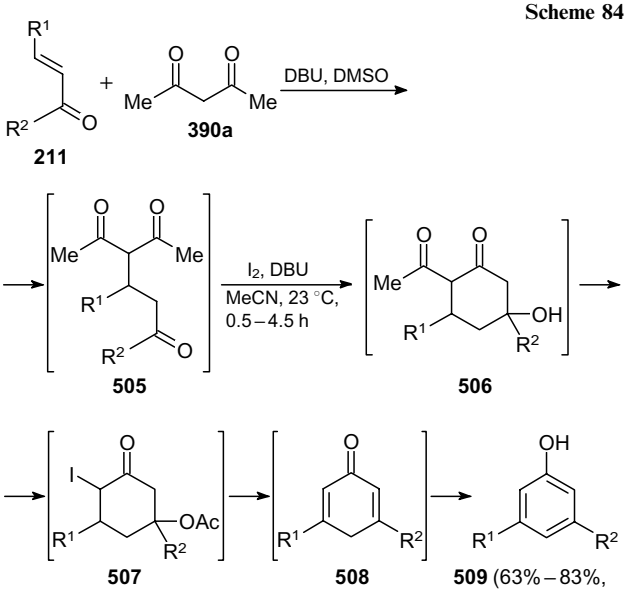
Scheme 83



R^1 = Me, Pr^n, Pr^i, Bn, Et, Ph, 2-Naph, 2-Th, C_6H_4X-4 (X = Cl, Br);
R^2 = OBn, OMe, OEt, OC_5H_{11}-n, OBu^s, $MeO(CH_2)_2O$, Me;
R^3 = H, Me, Et, Pr^n, Bu^t, Ph, CO_2Me, NHC(O)Me

radical **497** is an unlikely intermediate and the reaction more likely proceeds *via* an alternative radical pathway and intermediacy of the dihydroaryl hydroxylamine and dehydrative aromatization.

Scheme 84

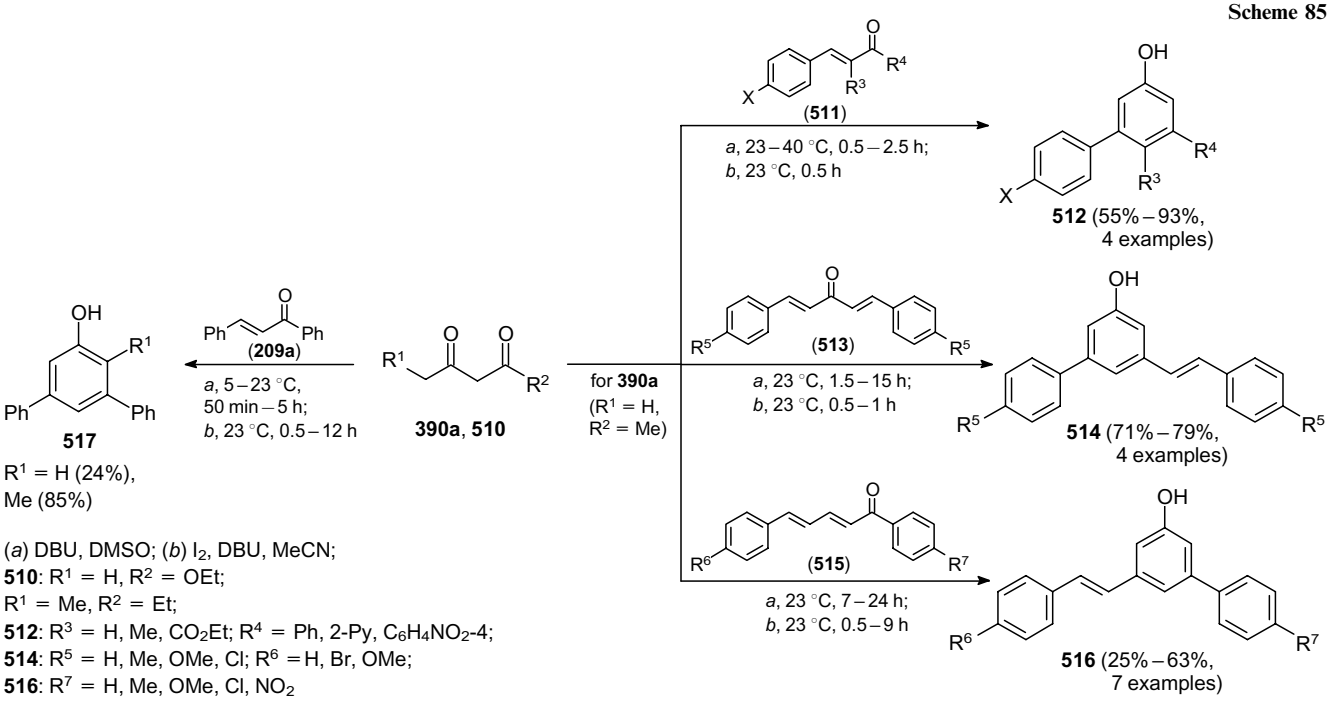


R^1 = Ph, C_6H_4X-4 (X = Me, OMe, NMe_2, Cl, NO_2), $C_6H_3OCH_2O$-3,4, 2-Fu, 2-Th; R^2 = Me, Ph, C_6H_4X-4 (X = OMe, Me, Cl)

Jiao and co-workers [120] reported the coupling of cyclohexenones **201** with primary, secondary, terpene based, cyclic, and benzylic alcohols **501** to afford phenol ethers **502** (Scheme 82). The reaction tolerated different substituents on the cyclohexanone scaffold as well, giving trisubstituted phenol ethers in fair to excellent yields.

Sha and Liu [121] discovered a Paal-Knorr based benzofuran synthesis starting from the readily available 2-hydroxy-1,4-diketones **503** (Scheme 83). With the use of trifluoroacetic acid-catalysis, the diketones were converted into the furans; subsequent NBS oxidation resulted in aromatization to produce benzofurans **504**.

Scheme 85



(*a*) DBU, DMSO; (*b*) I_2, DBU, MeCN;
510: R^1 = H, R^2 = OEt;
R^1 = Me, R^2 = Et;
512: R^3 = H, Me, CO_2Et; R^4 = Ph, 2-Py, $C_6H_4NO_2$-4;
514: R^5 = H, Me, OMe, Cl; R^6 = H, Br, OMe;
516: R^7 = H, Me, OMe, Cl, NO_2

Scheme 86



471, **201a** → **518** (12%–86%, 17 examples)

R^1 = H, Me, Et, 4-oxocyclohexyl, CO_2H, CO_2Et, Pr^n, Bu^t, n-C_5H_{11}, $C(Me)_2Et$, OH, OMe, NHAc; R^2 = H, Me; R^3 = H, Me, Bu^s

Yang and co-workers [122] reported a general method for the syntheses of phenols **509** with a varying substitution patterns starting from 1,3-diketone **390a** and enones **209** (Scheme 84). Self-condensation of 1,3-diketones **505** mediated by iodine as catalyst followed by transacylation (*C* to *O*) of intermediate **506** and subsequent iodine promoted oxidation, presumably *via* iodides **507**, provided a variety of biaryl-phenols **509**.

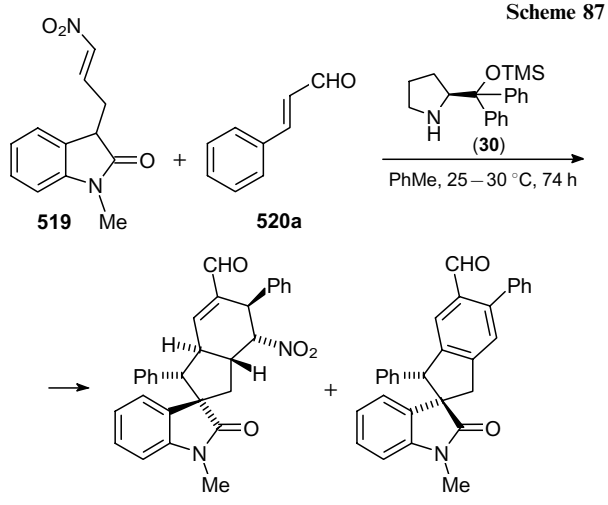
Additionally, the authors showed that 1,3-diketones **390a**, **510** were general precursors for the synthesis of biaryl phenols **512**, **514**, **516** and **517** using α,β-unsaturated ketones **511**, **513**, **515** and **209a**, respectively (Scheme 85). Both symmetrical **513** as well as unsymmetrical ketones (**511**, **515**, **209a**) were found to readily react to produce the corresponding phenols in moderate to good yields using this iodine mediated reaction.

In 2019, Wu *et al.*[123] reported the oxidization of cyclohexanones **471** with iodine in the presence of DMSO for the synthesis of 2-sulfanyl-catechols **518** (Scheme 86). This method proved to be general and worked with a range of alkyl and carboxylate substituents in the 2, 3 and 4 position of the cyclohexanones **471** and the reaction was also applicable to 2-cyclohexenones (*e.g.*, **201a**) as starting materials.

5.2. Organocatalyst-mediated reactions

In 2017, Lee and co-workers [124] reported the reaction of the nitroalkene **519** and cinnamaldehyde (**520a**) with the prolinol catalyst **30** to produce the heavily substituted spirocyclic oxindole derivative **521** as well as the arene **522** (Scheme 87). This reaction proceeded through a catalyst **30** mediated Michael–Michael–Michael–Aldol reaction cascade, a multistep process that proceeded with remarkable enantioselectivity (>96% *ee*) to provide oxindole **521** and presumably its spirane epimer, which underwent spontaneous aromatization by the elimination of nitrous acid under the reported reaction conditions and directly gave the spiro-arene **522**. The authors noted that other organocatalytic reactions of cinnamaldehyde derivatives with nitroalkenes structurally related to nitroalkene **519** gave spirocyclic oxindole derivatives corresponding to oxindole **521** as mixtures of spirane-epimers and no arene products corresponding to arene **522**. Presumably these cyclohexenes *e.g.*, **521** could be aromatized by reactions at the nitro-group.

Scheme 87

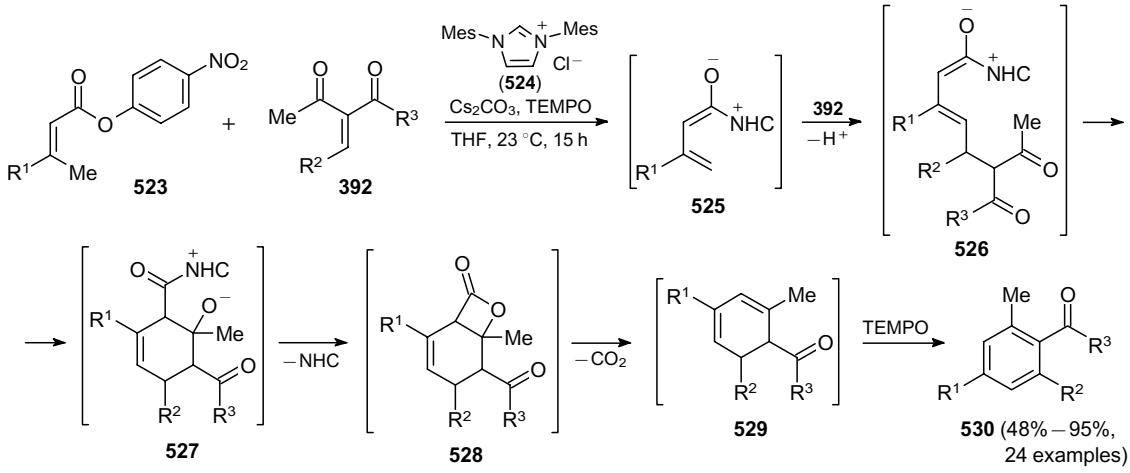


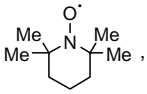
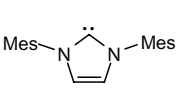
521 (93% *ee*) + **522** (97% *ee*)

(**521** : **522** = 3 : 2 *dr*, total 52% yield)

In 2018, Chi and co-workers [125] reported that an *N*-heterocyclic carbene (NHC) derived from a precatalyst **524**

Scheme 88



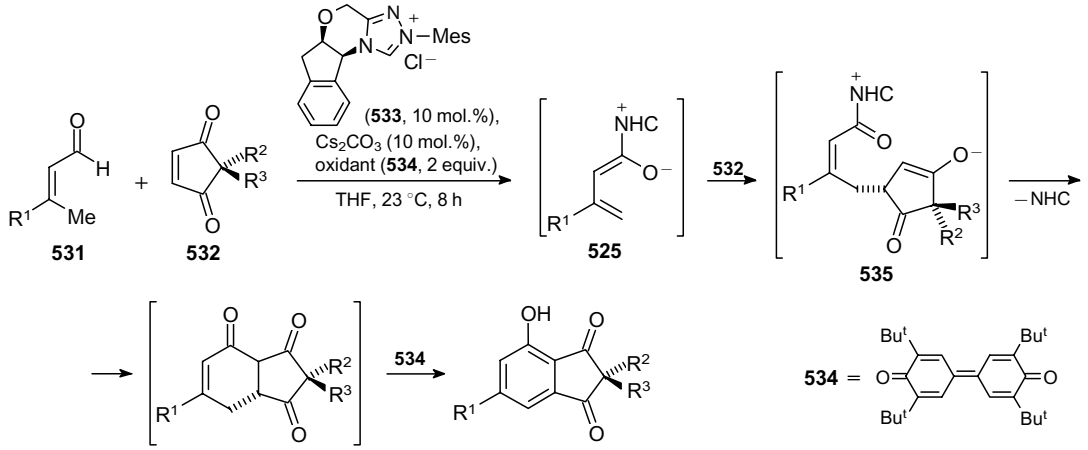
R^1 = Ph, C_6H_4X-4 (X = Me, OMe, F, Br, Cl), C_6H_4X-2 (X = OMe, Cl, F), C_6H_4X-3 (Me, OMe, Cl, F), 2-Fu, 2-Th, 2-Naph; R^2 = Ph, C_6H_4F-2, C_6H_4X-4 (X = Me, Cl), C_6H_4Br-3, 2-Naph, 2-Th, 1-E-pentenyl; R^3 = Me, Ph; TEMPO = , NHC = 

catalyzed the aromatization condensation reaction of α,β-unsaturated *p*-nitrophenol esters **523** with enediones **392** to produce tetrasubsituted benzene derivatives **530** (Scheme 88). The authors proposed that the reaction proceeded *via* the Michael and aldol adducts **526** and **527**, lactone **528** formation and elimination of carbon dioxide to provide cyclohexadiene **529**, with final aromatization carried out with TEMPO as the oxidant. With this method, a broad variety of different biaryl systems **530** were synthesized in moderate to excellent yields.

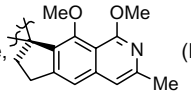
After their successful synthesis of tetrasubstituted arenes **530** from α,β-unsaturated esters **523** under NHC catalysis, the Chi group [126] expanded this methodology to prepare stereodefined indane derivatives **537** in good yields and enantiomeric ratios (up to 96 : 4 *er*) (Scheme 89). The reaction followed a similar pathway as above, however, using the stereodefined NHC-based catalyst **533**, gave the products **537** with high enantioselectivities (up to 91% *ee*). The scope of reaction allowed for variation of the different substituents R^1, R^2 and R^3 in substrates **531**, **532**. In addition, several spirocyclic 1,3-dienones **532** gave the corresponding derivatives in good yields and moderate to excellent enantiomeric ratios.

In addition to the synthesis of arenes **530** and stereodefined indanes **537**, Chi and co-workers [127] showed that the method was useful for the synthesis of biaryls such as phenyl benzothiazoles **543** (Scheme 90). Reaction of enal **531** and enone **538** gave phenyl benzothiazoles **543**, which were formed *via* a NHC catalyzed Michael-addition and aldol reaction pathway, followed by lactone formation and loss of carbon dioxide to give **542**. Oxidation with 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (**534**) gave the phenyl benzothiazoles **543** in moderate to excellent yields. Benzothiazoles have been shown to act as directing groups in

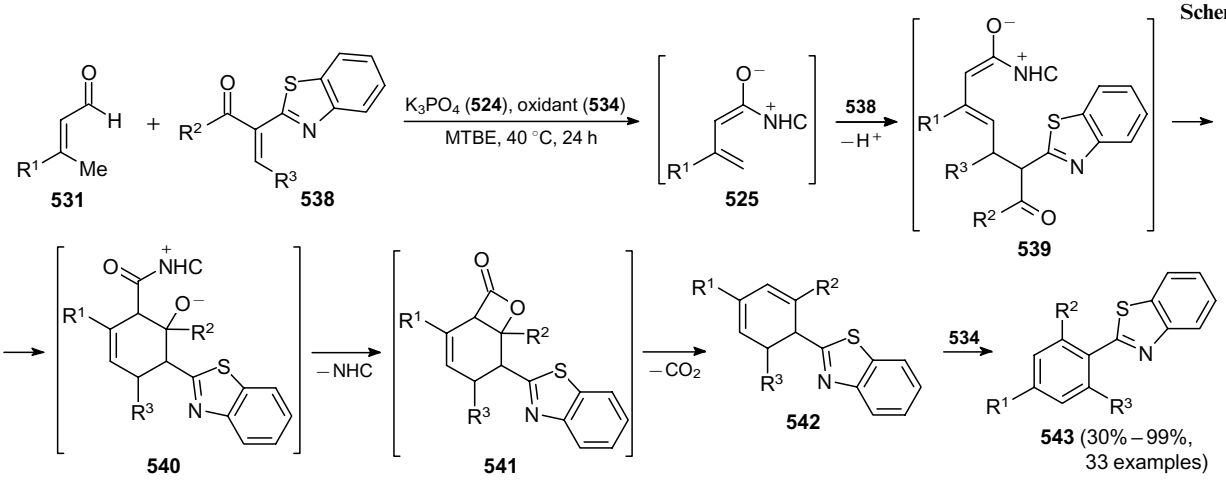
Scheme 89



R^1 = Ph, C_6H_4X-4 (X = Me, OMe, F, Cl, Br), C_6H_4MeO-3, C_6H_4MeO-2, $C_6H_3OCH_2O$-3,4, 1-Naph, 2-Naph, 2-Fu, 2-Th; R^2 = Me; R^3 = Bn, $CH_2C_6H_4X$-4 (X = Me, OMe, F, Cl, Br), $CH_2C_6H_4X$-3, $CH_2C_6H_4X$-2 (X = Me, NO_2), CH_2(3-Naph), CH_2(2-Th), $CHPh_2$;

R^2R^3C = 1,2,3,4-tetrahydro-5-naphthylidene; 1-indanylidene,  (DEF ring-system of fredericamycin A)

Scheme 90



R^1 = Ph, C_6H_4X-4, C_6H_4X-2 (X = Me, OMe, Br), C_6H_4X-3 (X = Me, OMe), $C_6H_3Me_2$-2,6, 2-Th, cyclo-Pr, 2-Naph;
R^2 = Ph, C_6H_4X-4 (X = Br, F, Me); R^3 = Ph, C_6H_4X-4 (X = Me, F, Cl, Br, NO_2, CN), C_6H_4X-3 (X = F, Cl), C_6H_3Cl-3,X-4 (X = F, Br), C_6H_3F-2,Br-5, 3-Th, 3-Py, Me, CH_2Bn; MTBE = $MeOBu^t$

transition metal-catalyzed C–H activation reactions and are thus useful intermediates for late-stage functionalization.

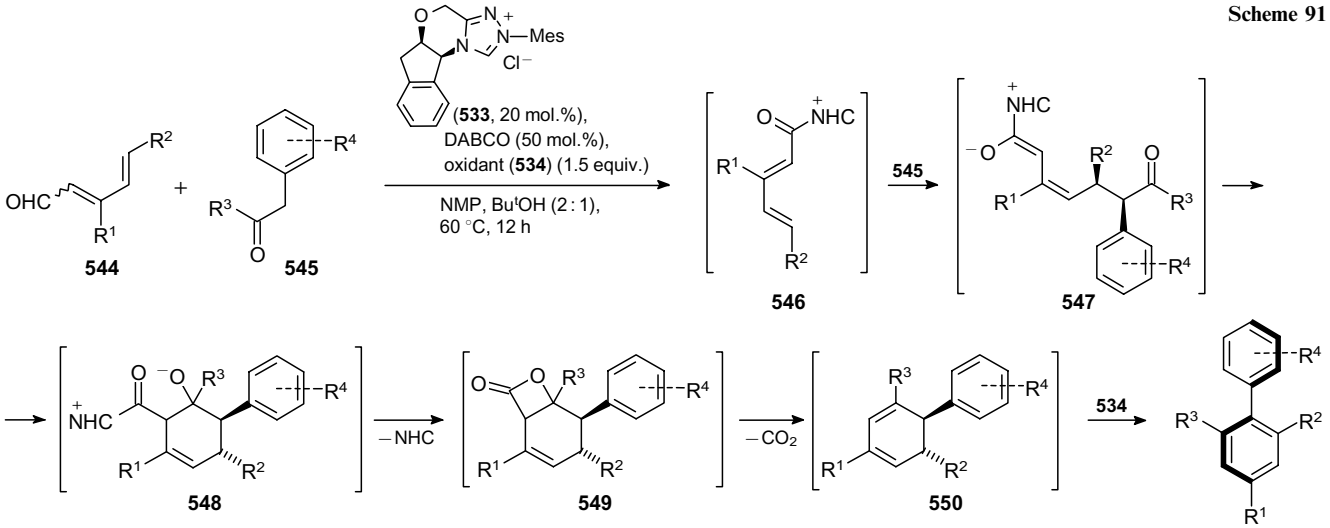
Additionally, Zhu and co-workers [128, 129] applied the same stereodefined NHC based catalyst for the synthesis of biaryls **551** with good levels of atropoisomeric control (98% *ee*) (Scheme 91). The reaction proceeded *via* a similar mechanistic pathway as postulated by Chi and co-workers [125–127] and also tolerated various functional groups in the *ortho* and *para* positions. The resultant biaryls **551** were isolated in good to excellent yields and enantioselectivities.

In 2019, Wang and co-workers [130] extended the stereoselective NHC catalysed indanone syntheses by employing a stereodefined catalyst to bring about the coupling of various cyclopentene-1,3-diones **532** with α,β-unsaturated enals **531** (Scheme 92). The mechanism, as postulated above, involved a Michael–aldol–aromatization cascade to elaborate the aromatic indanone framework followed by protection of the phenol as the methyl ether. The reaction was shown to tolerate various substituents on the starting cyclopentenediones **532** as well as different aromatic substituents on the enal **531**.

Recently, Han and co-workers [131] published a prolinol catalyzed coupling of acrylonitriles **554** with enals **520** to prepare tetrasubstituted arenes **561** (Scheme 93). Michael-addition of the resonance stabilized anion **555** with the iminium ions **556** gave adducts **557**. Proton transfer and Mannich-type addition gave the cyclohexene derivative **559**, which upon elimination of the catalyst gave cyclohexadiene **560**, which easily underwent oxidation under aerobic conditions to give arene **561**. The authors applied the method to synthesize various trisubstituted R_F containing arenes in an efficient manner.

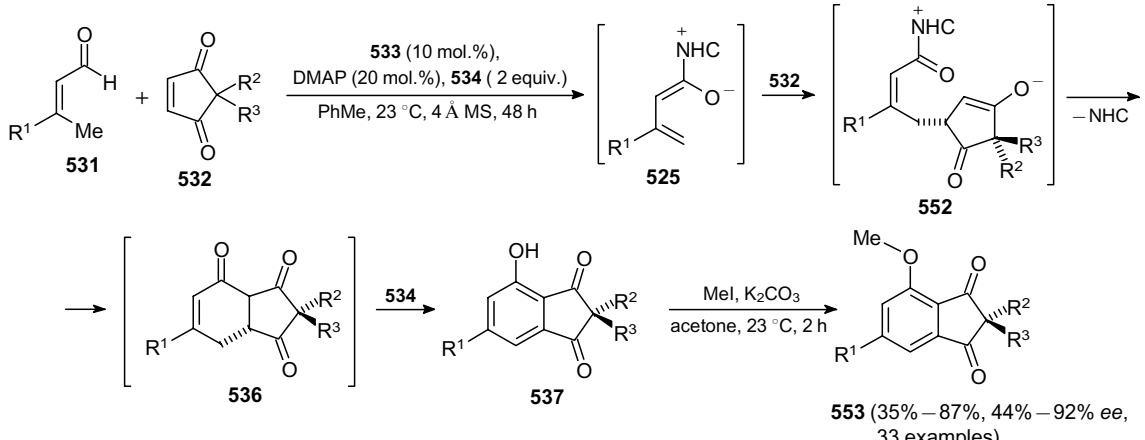
In addition, Han and co-workers [131] showed that prolinol **30** catalyzed the reaction of β-trifluoromethyl-enones **562** and enals **520** and gave tetrasubstituted benzaldehydes **568** (Scheme 94). A similar reaction pathway as described above gave intermediate **565**, which underwent a prolinol catalyzed aldol reaction to give the cyclohexene core **566**.

Scheme 91



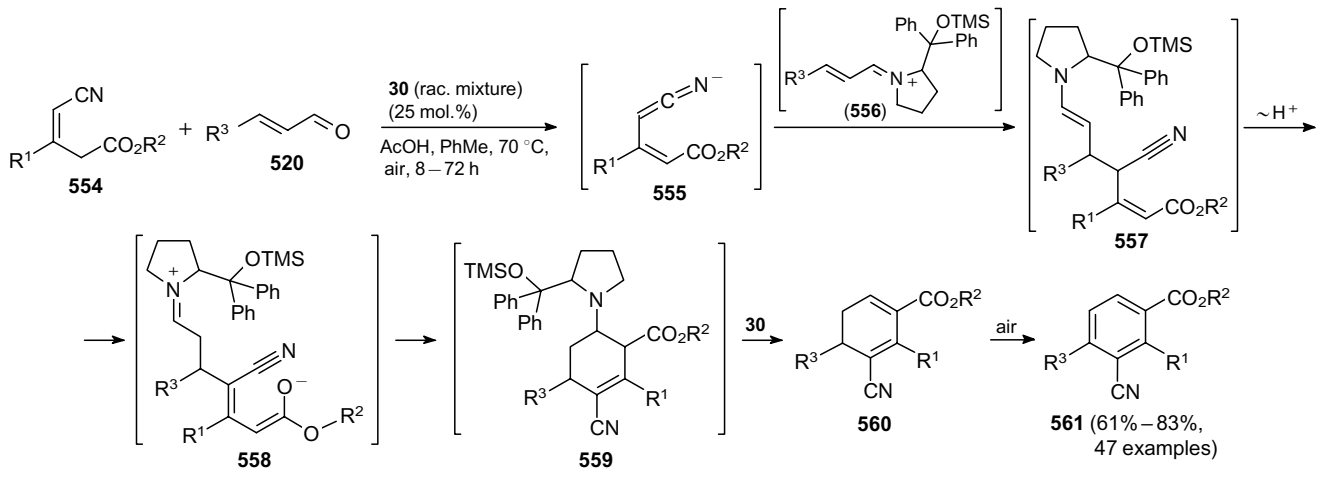
R^1 = Ph, 1-Naph, C_6H_4X-4 (X = Cl, Br, CF_3, OMe, Me), C_6H_4Me-3, C_6H_4Me-2; R^2 = Ph, C_6H_4X-2 (X = Cl, F, Me), C_6H_4Cl-3; R^3 = Me, C_6H_4X-4 (X = Me, CF_3, Br, NO_2, CN), $C_6H_4NO_2$-2, 3-Py, 2-Th; R^4 = 2-NO_2, 4-NO_2, 4-Me, 2-CF_3, 4-CF_3, 2-CN, 2-Br, 2-P(O)Ph_2; DABCO is 1,4-diazabicyclo[2.2.2]octane, NMP is *N*-methyl-2-pyrrolidone

Scheme 92



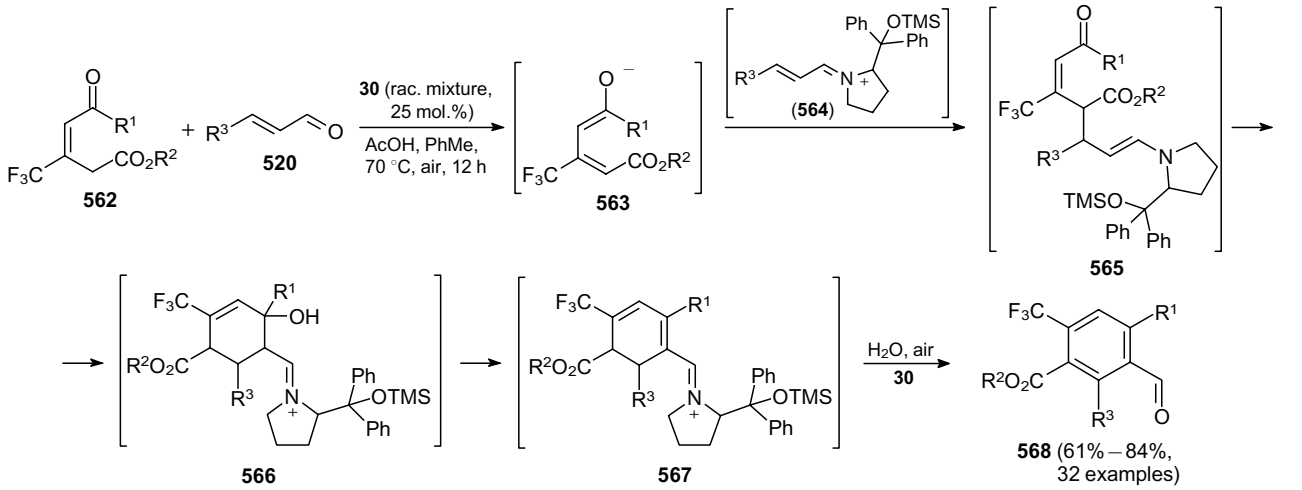
R^1 = Ph, C_6H_4X-4 (X = F, Cl, Br, I, Me), C_6H_4X-3 (X = F, Me), $C_6H_4O_2N$-3, 2-Naph, 2-Fu, 2-Th; R^2 = Me, Et; R^3 = Bn, $CH_2C_6H_4X$-4 (X = F, Cl, Br, Me, CF_3, NO_2), $CH_2C_6H_4X$-3 (X = Cl, Br, OMe, Me), $CH_2C_6H_4X$-2 (X = F, Cl, Br, Me), 2-Naph, 1-Naph, All, CH_2CO_2Me, CH_2(2-Th); DMAP is 4-dimethylaminopyridine

Scheme 93



R^1 = CF_3, CF_2H, C_2F_5, Ph, C_6H_4X-4 (X = F, NO_2); R^2 = Me, Et, Bn, Pr^i; R^3 = Ph, C_6H_4X-2 (X = Cl, Br, F, NO_2, OMe), C_6H_4X-3 (X = Cl, Br, F, CF_3), C_6H_4X-4 (X = Cl, Br, F, NO_2, Me, OMe), $C_6H_3Cl_2$-2,4, $C_6H_3Cl_2$-2,5, $C_6H_3Cl_2$-3,4, C_6H_3Cl-2,F-5, C_6H_3Br-2,Cl-4, C_6H_3Br-2,Cl-5, C_6H_3Br-4,F-2, C_6H_3-Br-5,F-2, $C_6H_3(OMe)_2$-3,4, 2-Fu, 1-Naph, 2-Naph, 1-(2-OMe)Naph

Scheme 94



R^1 = Ph, C_6H_4X-4 (X = Br, F, OMe), $C_6H_3Cl_2$-3,4, 1-Naph; R^2 = Me, Et, Pr^i; R^3 = Ph, C_6H_4X-2 (X = Br, F, NO_2, OMe), C_6H_4X-3 (X = Cl, Br, F, CF_3), C_6H_4X-4 (X = Cl, Br, F, NO_2, Me, OMe), $C_6H_2X_2$ (X = 2,4-Cl_2, 2,5-Cl_2, 3,4-Cl_2, 3,4-$(OMe)_2$), C_6H_3F-2,Y (Y = 4-Br, 5-Br), 2-Fu, 1-Naph, 2-Naph, 1-(2-OMe)Naph

Dehydration and imine hydrolysis gave the pentasubstituted arenes **568** after aerobic oxidation. These two methods starting from a range of enones and enals gave the derived tetra- or penta-functionalized benzoate esters **561** and **568**.

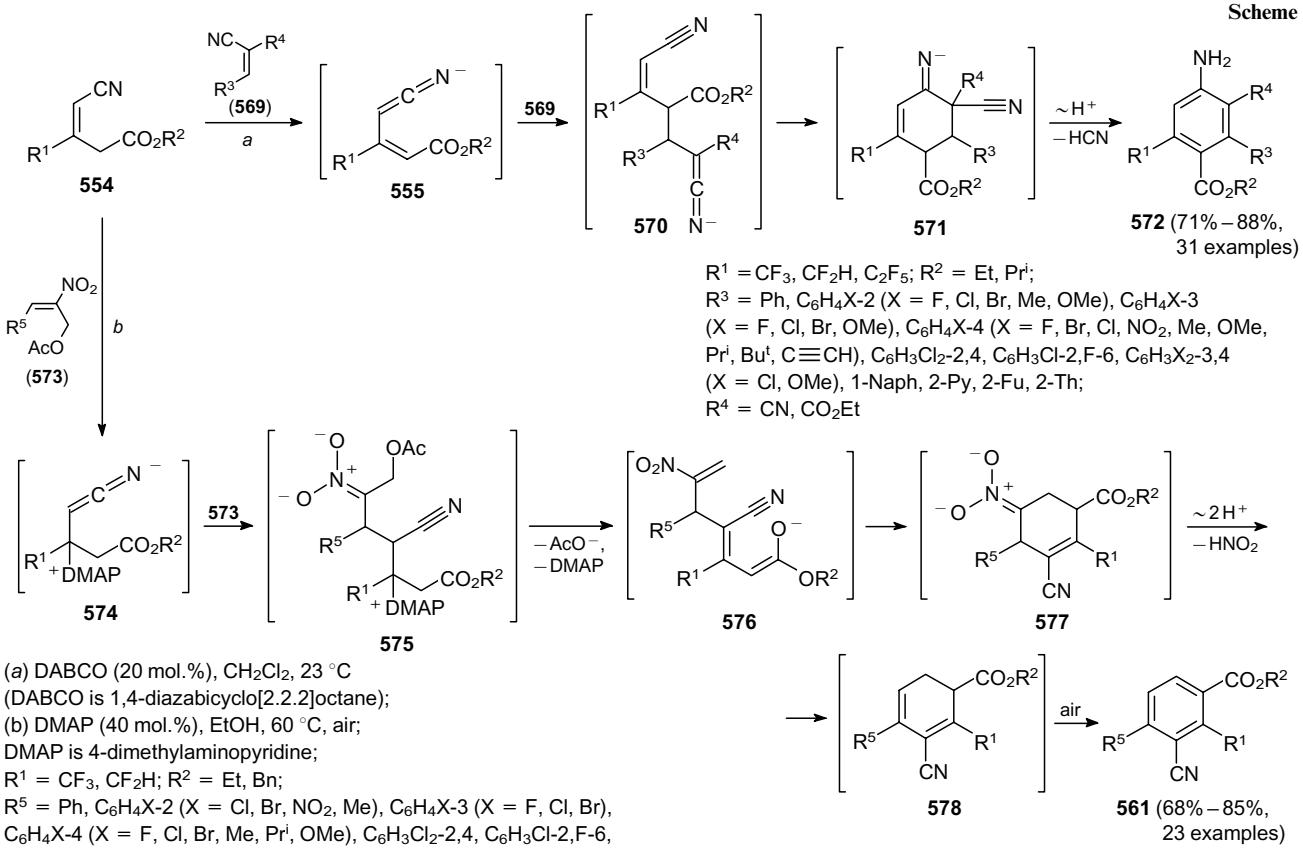
Han and co-workers [132] also reported the synthesis of tetrasubstituted anilines **572** and trisubstituted benzonitriles **561** from acrylonitriles **554** and Michael acceptors **569** and **573** (Scheme 95). The authors suggested that the mechanism involved deprotonation by DABCO and Michael addition to intermediate **570**, which upon ring closure, hydrogen cyanide elimination underwent tautomerization to aniline **572**. Alternatively, using DMAP and Michael acceptor **573**, a Baylis–Hillman type reaction gave intermediate **575**, which underwent elimination of DMAP and acetate. A subsequent Michael addition gave the nitronate **577**, which underwent elimination of nitrous acid followed by aerobic oxidation to give various R_F-substituted benzonitriles in good yields.

5.3. Acid-catalyzed reactions

Similar to Li's approach, Zhai and co-workers [133] retrosynthetically planned their total synthesis of (−)-daphenylline (**285**) to involve an aromatization step applied to a precursor already bearing the ABCD-ring system of the final natural product (Scheme 96). In their approach, however, they utilized a ring expansion process starting with cyclopentanone **579**. After dehydrative cyclization to the furan **580**, the cyclopentane unit was found to undergo a [1,2]-alkyl shift to produce furanyl carbenium ion **581**, which, in turn, underwent aromatization by the elimination of water and proton loss giving the product **582**. In this publication, the results inspired the Zhai group to propose a possible biosynthetic link between the various *Daphniphyllum* alkaloids.

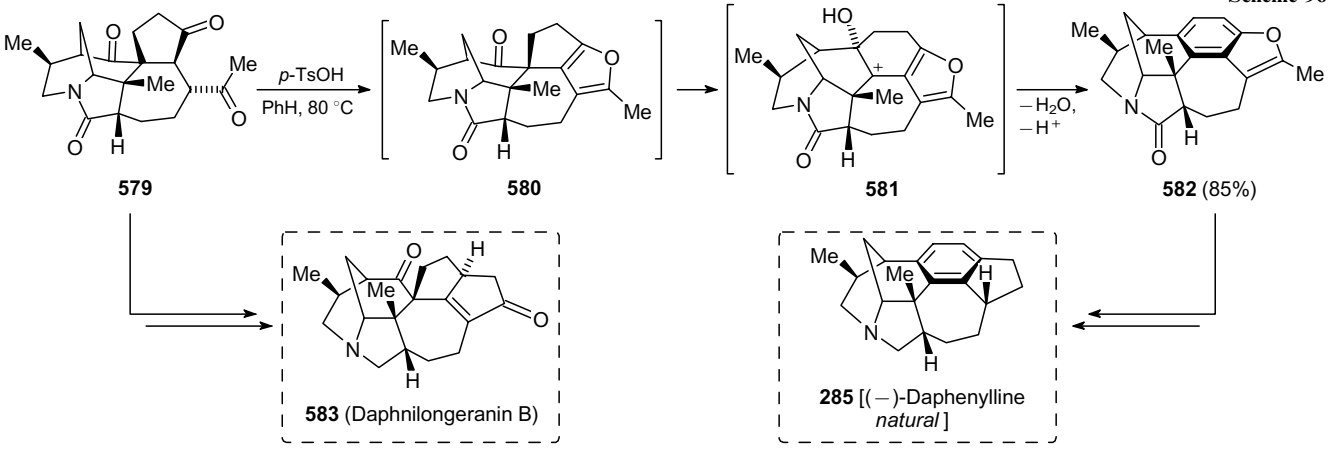
In 2018, Wan and co-workers [134] reported a method to synthesize *m*- and *p*-substituted benzaldehyde derivatives **589** and **591** from enamines **585** and **590** and enals **584** (Scheme 97). An initiatal vinylogous Michael addition of

Scheme 95

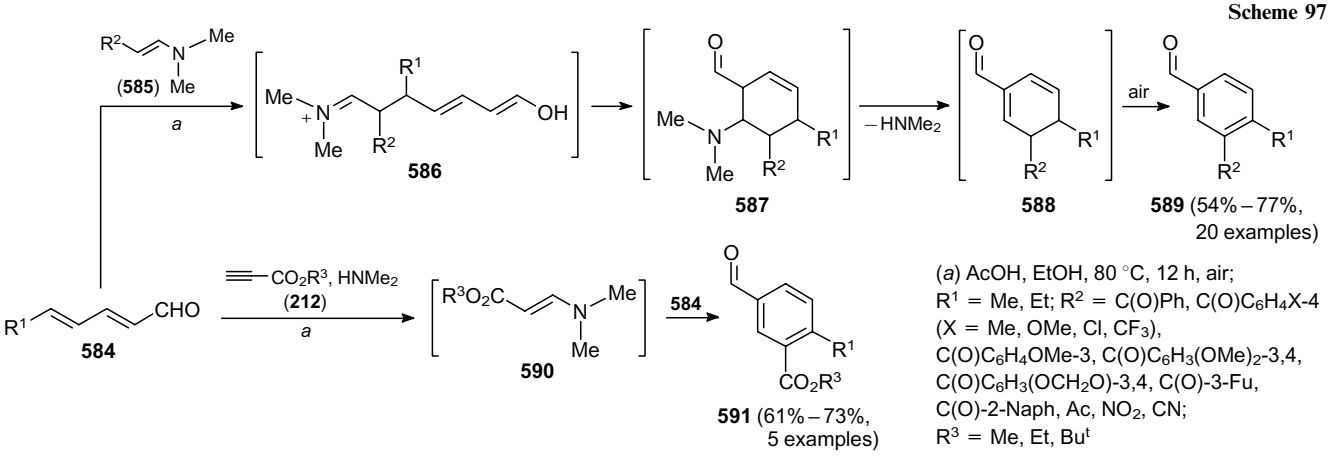


(*a*) DABCO (20 mol.%), CH_2Cl_2, 23 °C
(DABCO is 1,4-diazabicyclo[2.2.2]octane);
(*b*) DMAP (40 mol.%), EtOH, 60 °C, air;
DMAP is 4-dimethylaminopyridine;
R^1 = CF_3, CF_2H; R^2 = Et, Bn;
R^5 = Ph, C_6H_4X-2 (X = Cl, Br, NO_2, Me), C_6H_4X-3 (X = F, Cl, Br), C_6H_4X-4 (X = F, Cl, Br, Me, Pr^i, OMe), $C_6H_3Cl_2$-2,4, C_6H_3Cl-2,F-6, $C_6H_3X_2$-3,4 (X = Cl, OMe), 1-Naph, 2-Fu, 2-Th

Scheme 96



Scheme 97



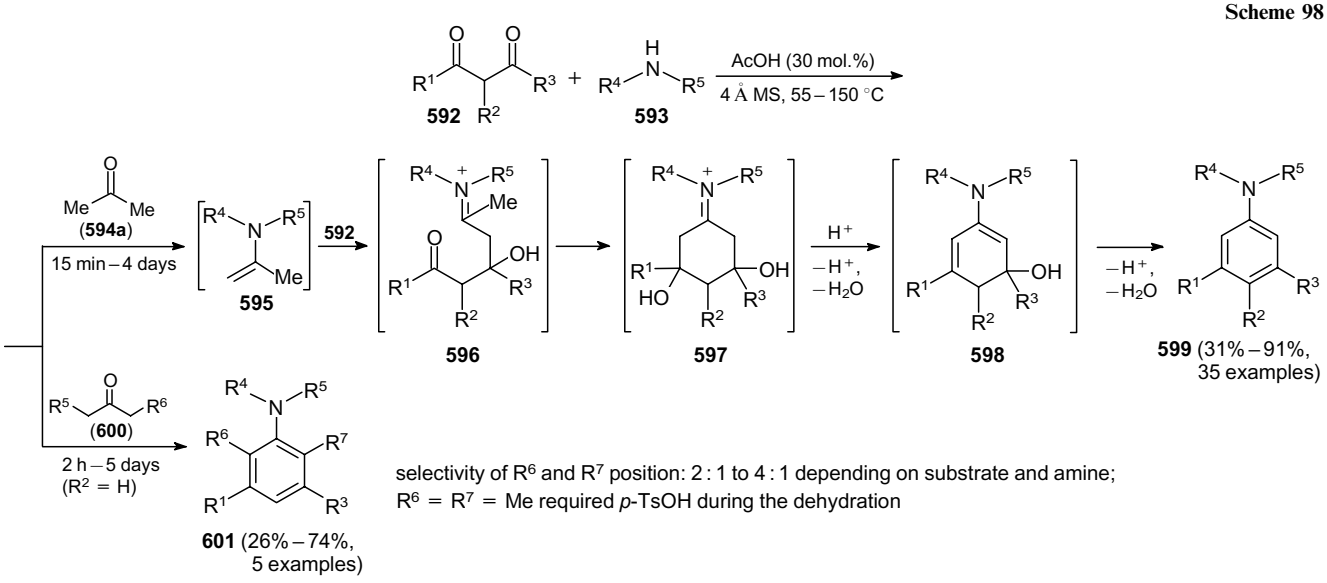
(*a*) AcOH, EtOH, 80 °C, 12 h, air;
R^1 = Me, Et; R^2 = C(O)Ph, $C(O)C_6H_4X$-4 (X = Me, OMe, Cl, CF_3), $C(O)C_6H_4OMe$-3, $C(O)C_6H_3(OMe)_2$-3,4, $C(O)C_6H_3(OCH_2O)$-3,4, C(O)-3-Fu, C(O)-2-Naph, Ac, NO_2, CN;
R^3 = Me, Et, Bu^t

enamine **585** to the protonated enal **584** gave enol **586**, which underwent cyclization to the cyclohexene **587**. Elimination and aerobic oxidation gave the *m*- and *p*-substituted arenes in good yields. In addition, it was shown that the enamines **590** could be formed *in situ* from acetylenes **210** and dimethylamine, which gave the benzoate esters **591** in good yields following a similar reaction pathway.

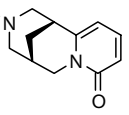
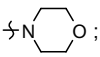
In 2019, Rubin and co-workers [135] published a synthesis of aniline derivatives **599** *via* a three-component coupling of 1,3-diketones **592**, amines **593** and acetone (**594a**) (Scheme 98). The authors suggested that the reaction proceeded by enamine formation and subsequent addition to the 1,3-diketones **592** to give the intermediate **596**. Cyclization gave the cyclohexane **597**, which underwent dehydration to give anilines **599**. A large range of substituents were tolerated under the reaction conditions. Furthermore, penta-substituted anilines **601** could be synthesized with this methodology, albeit requiring longer reaction times and further addition of the dehydrating agent 4-toluenesulfonic acid.

In 2020, Xu and co-workers [136] reported the dimerization of various styryl-epoxides **602** to prepare biaryls **609** under microwave accelerated acid-base conditions (Scheme 99). The authors postulated that an initial Meinwald rearrangement took place to give aldehydes **605** or their corresponding enolates. These intermediates underwent dimerization followed by cyclization with an aldol reaction to hydroxyaldehydes **607**. Dehydration gave diene **608**, which underwent aromatization presumably by loss of toluene possibly in a concerted process. Biaryl benzaldehyde derivatives **609** were obtained in moderate to excellent yields and the reaction tolerated various functional groups on the aryl core. Noteworthy, substituents on the alkene in the *cis*-position were not tolerated and the reaction stopped after formation of the Meinwald rearranged product **605**.

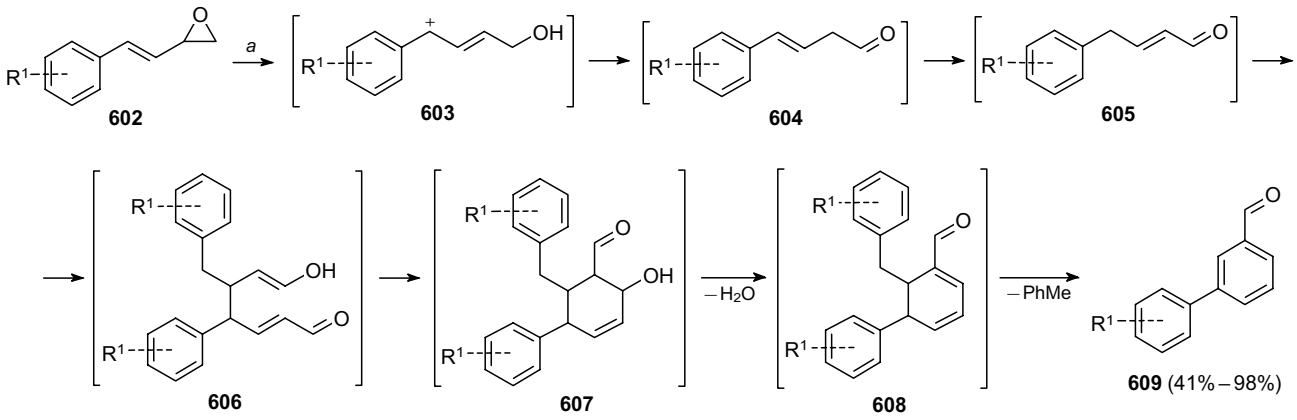
Scheme 98



599: R^1 = Me, Et, Bu^t, Ph, C_6H_4Me-4, styryl, 2-Fu, 2-Th; R^2 = H, Me; R^3 = CO_2Me, C(O)NHPh, C(O)NHC_6H_4Me-4, CF_3; R^4 = H: R^5 = Ph, C_6H_4X (X = 2-OH, 4-Cl, 4-Me, 4-OMe, 4-CF_3, Me_3-2,4,6), 2-Py, Bn, Bu^t, Cy, $(CH_2)_2$OH, CH_2-2-Fu;

NR^4R^5 =  ; **601**: R^2 = H: R^1 = Ph, 2-Th; R^3 = CO_2Me, CF_3; R^4 = H; R^5 = Bn; NR^4R^5 =  ;
R^6 = H: R^7 = Me, Pr^i; R^6 = R^7 = Me

Scheme 99



(*a*) NEt_3, p-TsOH·H_2O, mesitylene, MW, 200 °C, 1 h; R^1 = H, 2-X (X = Cl, F, OMe), 3-X (X = Cl, CF_3), 4-X (X = Cl, F, CF_3, Me), 2,3-$(Cl)_2$

5.4. Base-catalyzed reactions

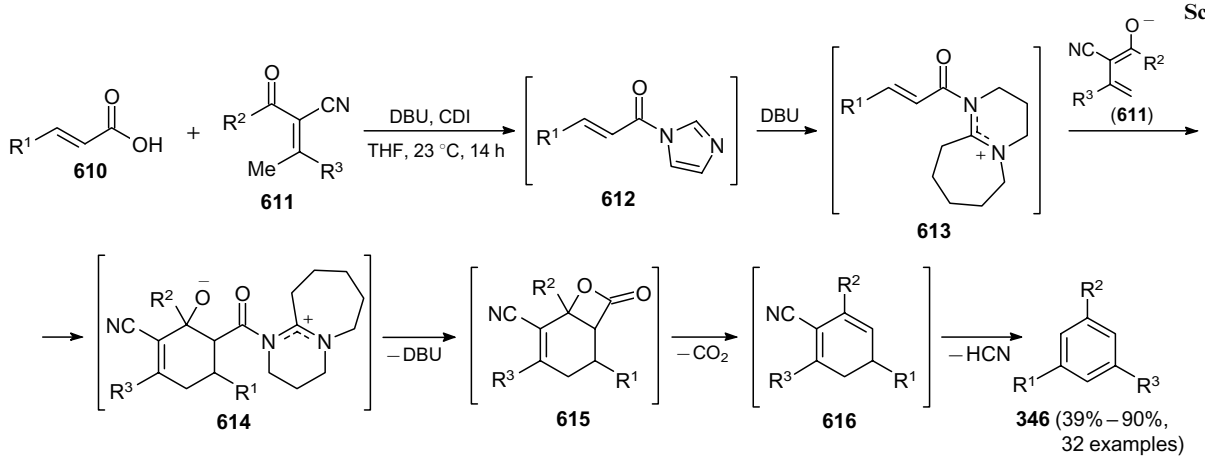
Recently, Ye and co-workers [137] reported a DBU mediated synthesis of tri-substituted arenes **346** from readily available α,β-unsaturated carboxylic acids **610** and α-cyano-enones **611** (Scheme 100). This method was applied for the synthesis of thirty two biaryls **346** in moderate to good yields. Mechanistically, the authors suggested that DBU had a dual role both as base as well as nucleophilic catalyst through a CDI activated acyl transfer of the α,β-unsaturated carboxylic acids to DBU **613**. In their control-experiment without DBU, the reaction only formed traces of the product **346** even from the carboxylic acid CDI adducts. The acylated DBU intermediate **613** was found to react with the cyano-enone **611** (or its derived enolate) to produce the cyclohexenes **614**, which upon β-lactone **615** formation, decarboxylation **616** and cyanide elimination underwent aromatization to produce the product arenes **346**.

Thorimbert and co-workers [138] showed that reaction of methyl coumalate **79** with trifluoromethyl-1,3-diketones **617** gave the corresponding trifluoromethylated arenes **622** (Scheme 101). Various aliphatic and aromatic substituents on the starting diketone were tolerated. Mechanistically, the authors suggested that the reaction proceeded by Michael-addition of the enolate derived from **617** followed by ring opening to the linear dienoate **619**. Subsequent ring closure and loss of carbon dioxide and hydroxide in a Grob-type fragmentation gave the arene **622** in good yields. With this study the authors developed a potentially sustainable transformation of a renewable precursor into trifluoromethyl-functionalized arenes in a simple manner.

In 2018, Shi and co-workers [139] published a base promoted synthesis of heavily substituted benzonitriles **629** from diketo compounds **392** and α-cyanoenones **623** (Scheme 102). This method was applied for the preparation of biaryl compounds including hexa-substituted arenes **629** in moderate yields. Mechanistically, the synthesis involved a Michael addition of the enolate derived from cyano enones **623** with enones **392**, followed by a tautomerization and aldol ring closure. Subsequent (*C* to *O*) acyl transfer and E_1cB elimination of benzoic acid gave cyclohexadienes **628**. Aerobic oxidation produced arenes **629** in fair to good yields.

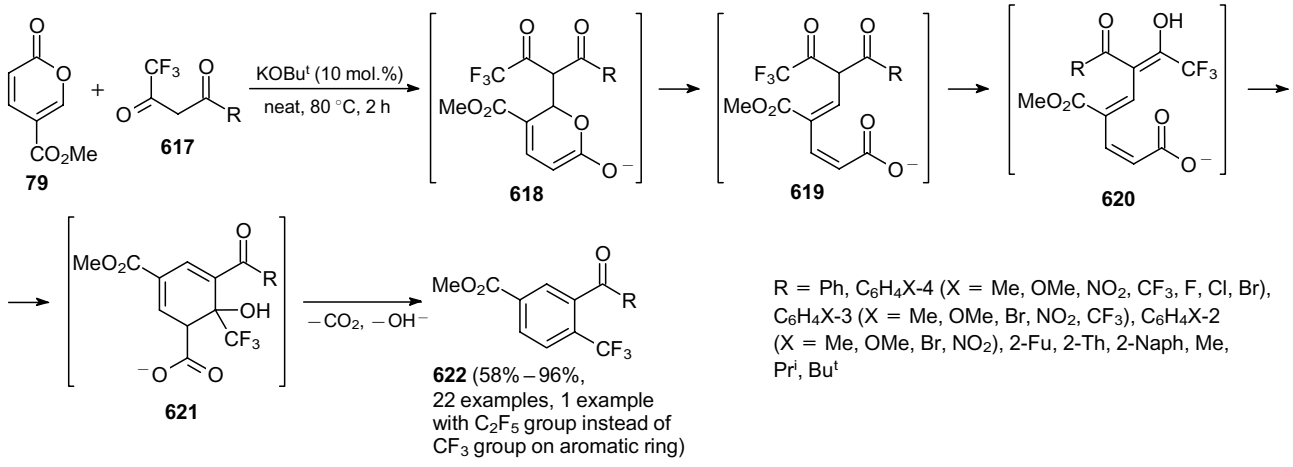
Recently, Qiu and co-workers [140] reported the total synthesis of (−)-daphenylline (**285**) including a key Robinson annulation and aromatization sequence to build up the ABCE ring system (Scheme 103). Diketone **630**, prepared from the corresponding ketone using the Stork-Ganem reagent $MeCOC(=CH_2)SiMe_3$, was converted into the aromatic compound **633** in good yield through a base mediated aldol-condensation, dehydration and oxidative aromatization in air.

Scheme 100



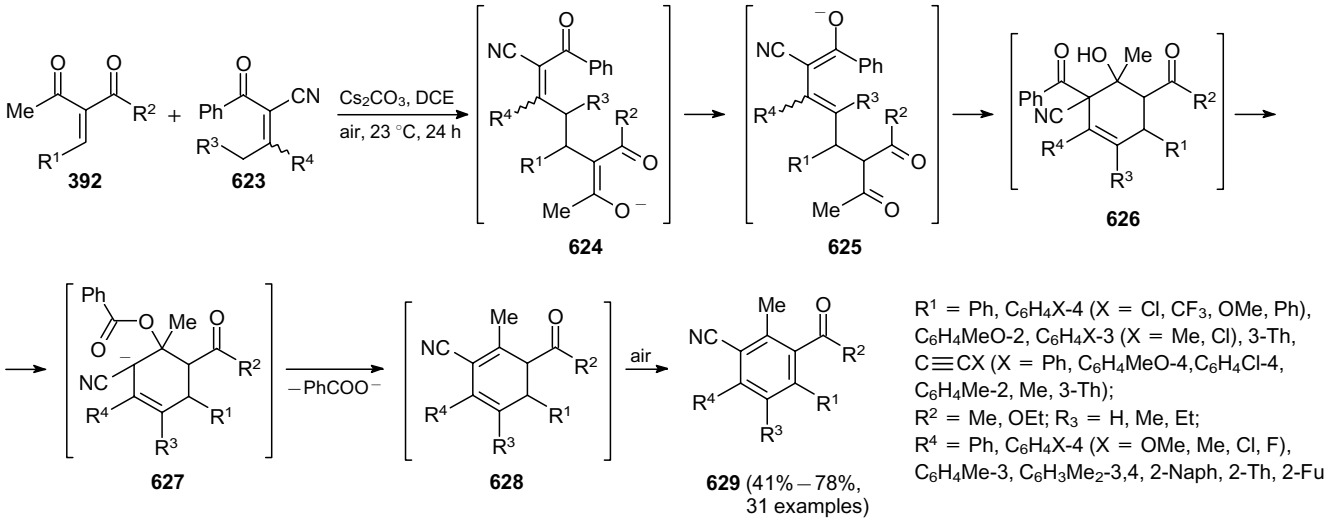
R^1 = Ph, C_6H_4X-4 (X = OMe, Me, Cl, Br, Ac), C_6H_4X-3, C_6H_4X-2 (X = Me, Br), $C_6H_3Cl_2$-2,6, $C_6H_3Cl_2$-3,4, 2-Fu, 3-Py, CO_2Et;
R^2 = Ph, C_6H_4X-4 (X = OMe, F), 2-Th, Me; R^3 = Ph, C_6H_4X-4 (X = OMe, Me, Cl, Br, NO_2), C_6H_4X-3, C_6H_4X-2 (X = Me, Cl), 2-Th, 2-Naph, Pr^n, Bu^i; CDI is 1,1′-carbonyldiimidazole

Scheme 101

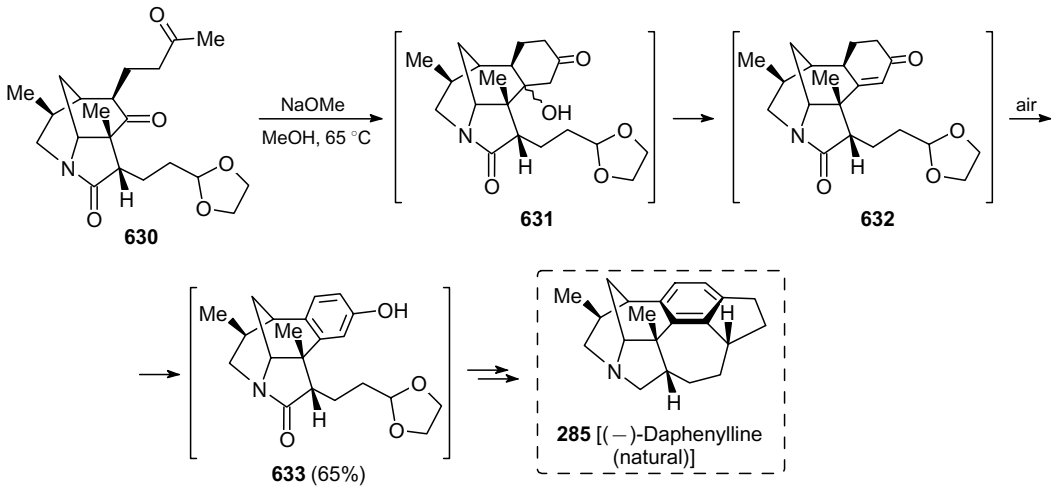


R = Ph, C_6H_4X-4 (X = Me, OMe, NO_2, CF_3, F, Cl, Br), C_6H_4X-3 (X = Me, OMe, Br, NO_2, CF_3), C_6H_4X-2 (X = Me, OMe, Br, NO_2), 2-Fu, 2-Th, 2-Naph, Me, Pr^i, Bu^t

Scheme 102



Scheme 103

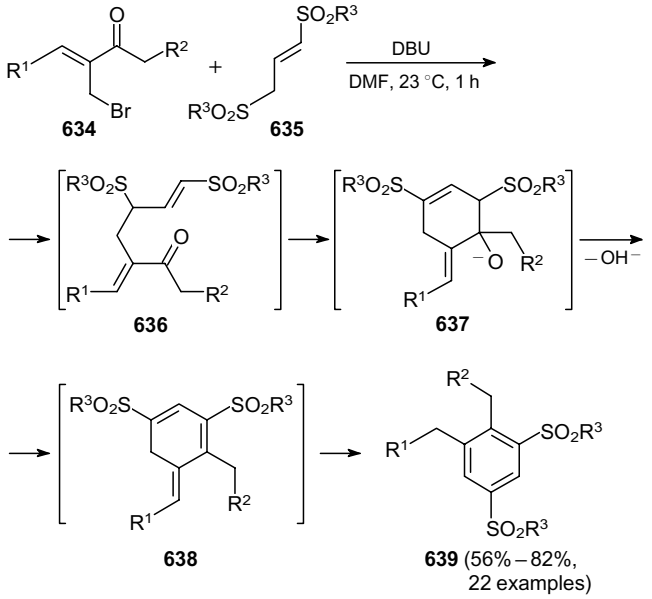


Yadav *et al.*[141] reported a formal [3 + 3] benzannulation between bromo-enones **634** and α,β-unsaturated sulfones **635** (Scheme 104). Both of these precursors were readily synthesized from commercially available starting materials through simple functional group interconversions. Subsequent DBU-mediated coupling readily gave tetrasubstituted arenes **639** under mild reaction conditions.

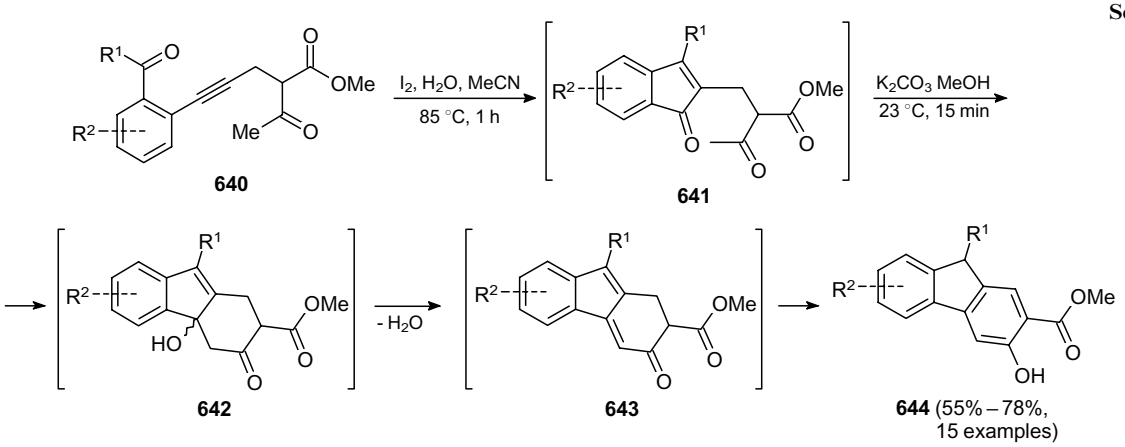
The group of Tummatorn[142] reported the sequential transformation of alkynyl-aryl ketones **640** to provide indenones **641**, which were subsequently aromatized to provide 3-hydroxyfluorenes **644** (Scheme 105). This procedure was also used to synthesize 4-azafluorenes by employing ammonium acetate in methanol in the cyclization process (*via* the corresponding enamine of **641**) and aromatization step.

Baidya and co-workers[143] reported the base-mediated coupling of alkylidene malonitriles **645** with cyclopentene-1,3-diones **532** to produce penta- and hexasubstituted 4-amino-1*H*-indene-1,3(2*H*)-diones **648** (Scheme 106). The authors suggested that this reaction proceeded *via* a vinylogous Michael-addition and subsequent cyclization by addition to the nitrile group, followed by oxidative aromatization. The reaction showed a broad functional group tolerance for aliphatic, aromatic and bulky steroid substituents.

Scheme 104

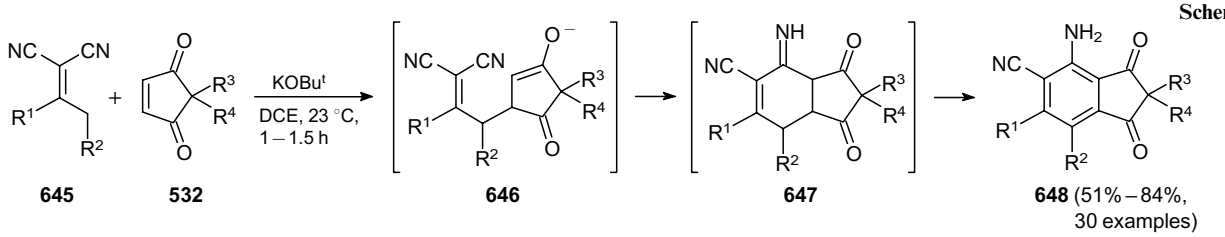


Scheme 105

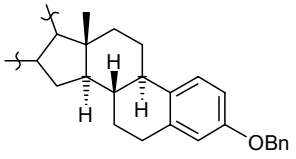


R^1 = Ph, C_6H_4X-4 (X = Me, Cl, F, OMe), C_6H_4X-3 (X = F, OMe), $C_6H_2(MeO)_3$-2,4,5, N(Ns)-3-indolyl; R^2 = 6-F, 7-F, 8-F, 6-Cl, 7-BrO, Me-7

Scheme 106



R^1 = Ph, C_6H_4X-4 (X = Me, OMe, Cl, Br, OAll, $CH_2C{\equiv}CH$, styryl), C_6H_4Cl-3, 2-Naph, 2-Th, 1-Ad, Fc; Fc is ferrocenyl; cyclic R^1CCHR^2 = 4-chromanidene, 4-thiochromanidene, 1,2,3,4-tetrahydro-1-naphthalidene, 1-indenylidene, *O*-benzyl-17-deoxyestron-17-ylidene, (2-methyl-2-benzyl)-3-oxocyclopentylidene; R^2 = H, Me; R^3 = Me; R^4 = Bn, $CH_2C_6H_4X$-2 (X = Me, Br, NO_2), $CH_2C_6H_4Me$-3, $CH_2C_6H_4Me$-4, All, CH_2-1-Naph,



Sosnovskikh and co-workers[144] showed that enaminodiones **649** were dimerized by condensation using lithium hydride and tetraethoxysilane to produce trisubstituted phenolic diketones **653** (Scheme 107). The authors postulated that these reactions proceeded *via* a double-Michael addition to intermediates **651** with subsequent, highly selective retro-Claisen reaction to yield benzophenones after aromatization. This method enabled the authors to rapidly synthesize different phenols **653** from simple precursors in three steps.

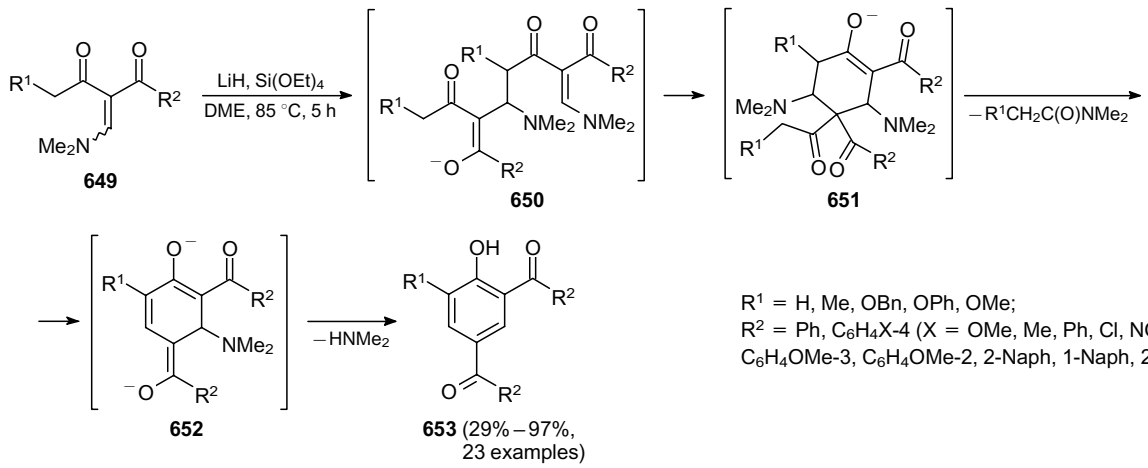
Pratap and co-workers[145] reported the synthesis of tetrahydroquinolines **659** from 2-pyrone derivatives **654** or **661** as C(4) building blocks and Boc-protected 3-piperidone **655** as a C(2) building block (Scheme 108). This method, following trifluoroacetic acid Boc-deprotection, gave tetrahydroquinolines **660** from easily accessible precursors in good yields. The authors proposed that Michael addition of the enolate derived from **655** with 2-pyrone **654**, followed by ring opening and ring closure to cyclohexadienes **658** and a Grob-type fragmentation with concomitant aromatization gave arenes **659**. Trifluoroacetic acid mediated Boc deprotection completed the synthesis of tetrahydroquinolines **660**.

In 2019, Kano and co-workers[146] reported the synthesis of benzophenones **666** *via* base mediated annulation of imino-dienes **662** as C5 building blocks and substituted acetophenones **594** (Scheme 109). The authors proposed reaction mechanism involved Mannich-type additions of the enolates derived from ketones **594** with imines **662** followed by piperidine elimination to give the trienones **664**. Cyclization of these gave cyclohexadiene **665**. These intermediates underwent aromatization by elimination of a second equivalent of piperidine to give benzophenones **666** in fair to excellent yields. The reaction was extended to 4,4′-diacetyl-biphenyl, 1,3,5-triacetylbenzene and 4,4′,4″-triacetyl-triphenylamine derivatives of **594**.

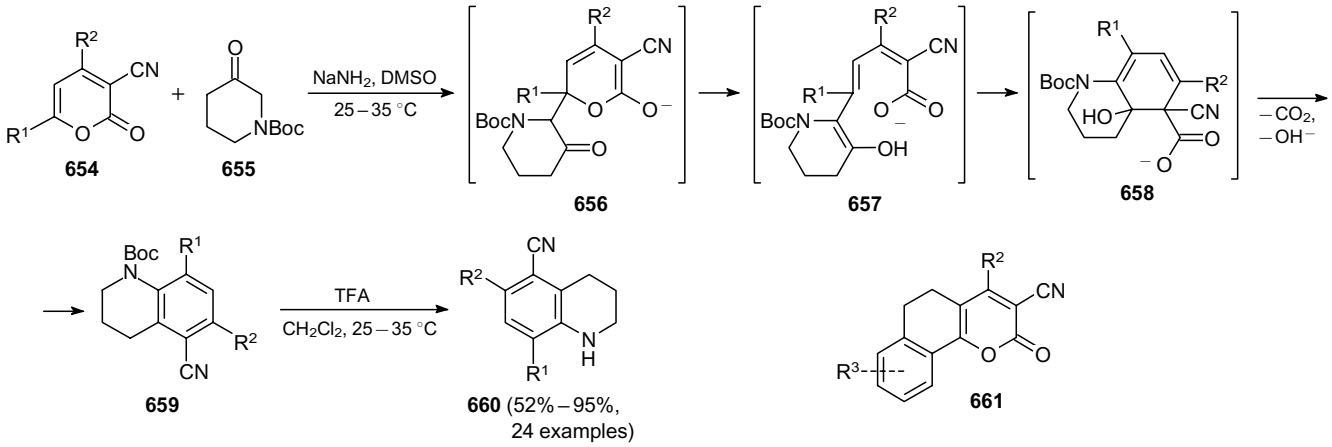
In 2019, Wang and Kraus[147] reported the total synthesis of (±)-dihydro eurotiumide B (**675**), which employed a cascade sequence to build up the arene and lactone ring (Scheme 110). These authors showed that this reaction also worked with other epoxides as well as methyl sorbate, which lacked the epoxide functionality. They proposed that butanolide **667** underwent alkylation *via* the corresponding enolate with subsequent selective Michael addition onto the α,β-unsaturated ester **668**. A subsequent aldol reaction gave the tetrahedral intermediate **670**, which underwent fragmentation to the diketone **671** by thiophenolate elimination. Aromatization by tautomerization gave intermediate **672**. Opening of the styryl epoxide by participation of the electron rich arene gave enolates **673**, which readily underwent aromatization by the diastereoselective addition of thiophenolate. Substitution of the thio ether by sodium methoxide gave dihydro-eurotiumide B (**675**) in 41% yield.

Yu and Kraus,[148] in further studies on pyrone Diels–Alder chemistry, reported that electron-poor dienophiles including dihydroxy-*p*-quinones **676** do not undergo Diels–Alder reactions to provide arenes. However, addition of a

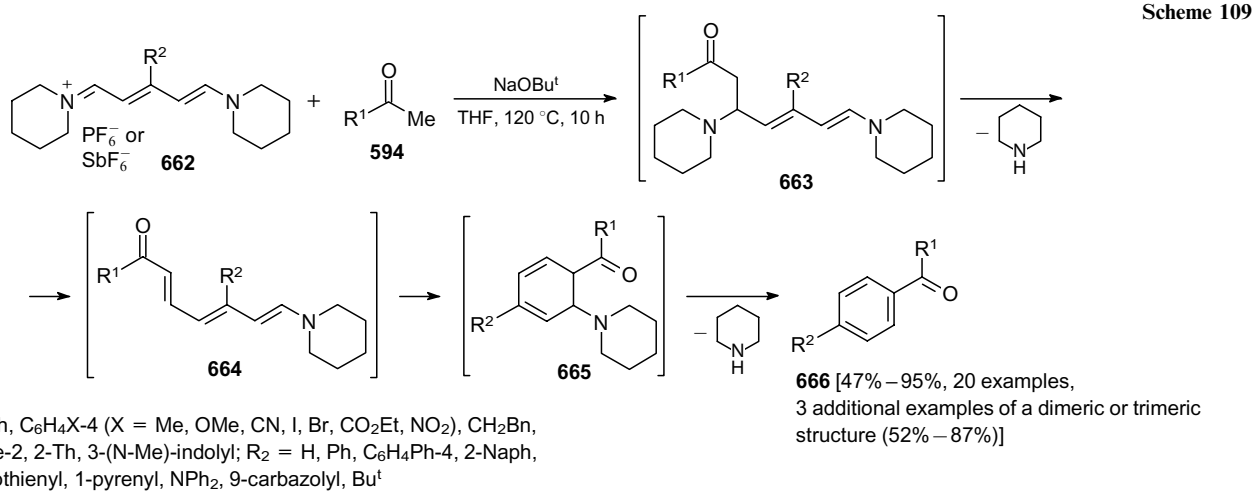
Scheme 107



Scheme 108



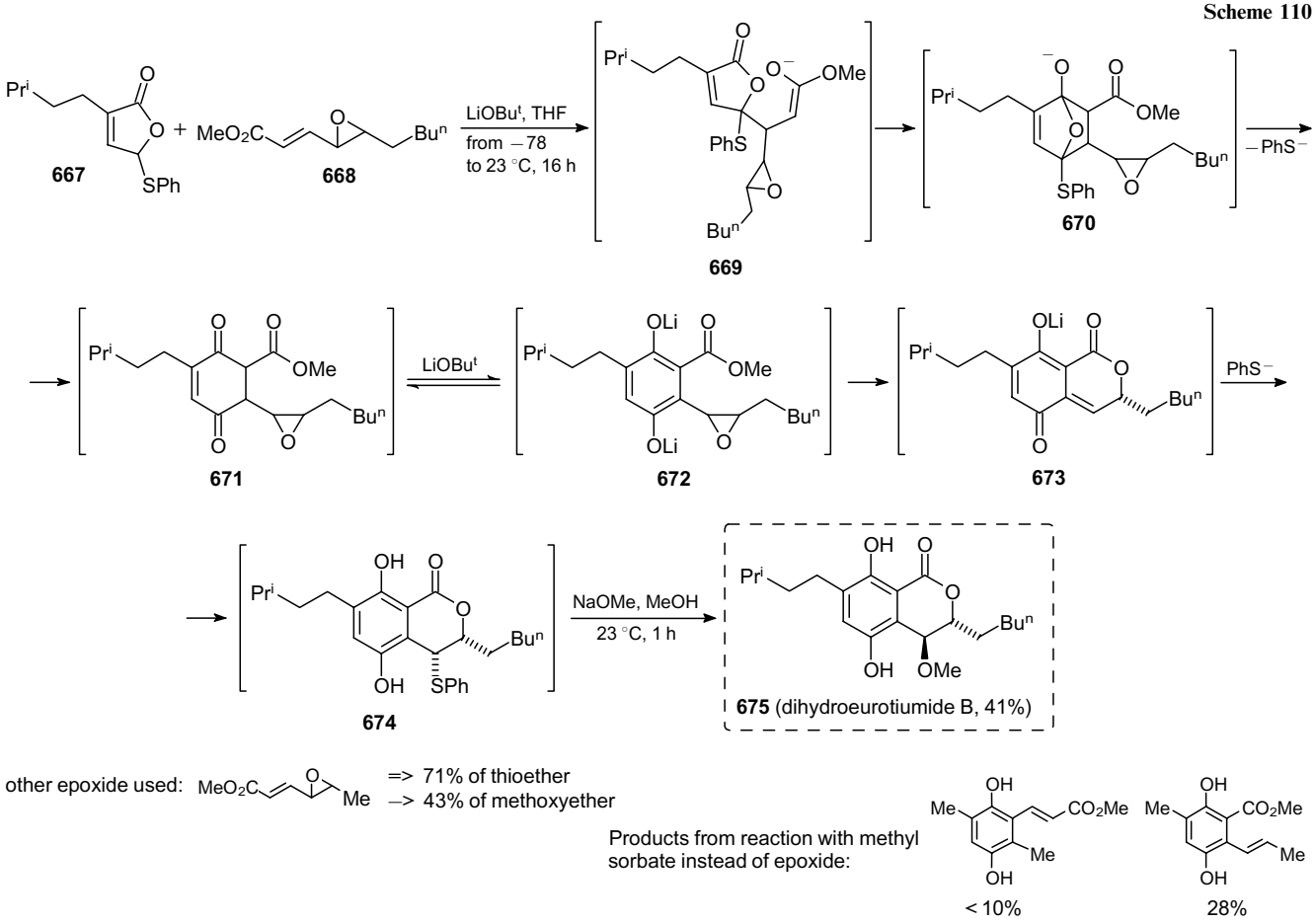
Scheme 109



base such as triethylamine mediated the formal Diels – Alder reaction of 2-pyrones **131** with hydroxyquinones **676** and **681** (Scheme 111). The authors suggested that these reactions involved base mediated enolate formation of the hydroxyquinones and subsequent Michael addition to give adducts **677** thereby allowing the aldol reaction to give intermediate **678**. Subsequent decarboxylation and loss of water gave the arenes **680** in fair to excellent yields. In the case of dihydroxybenzoquinone **676** ($R^3 = H$), a double addition was observed giving rise to anthraquinones **683**. Of particular note, acetylene substituents in the R^2 position underwent oxidation to the corresponding ketones during the progress of this reaction, presumably after the elimination of water.

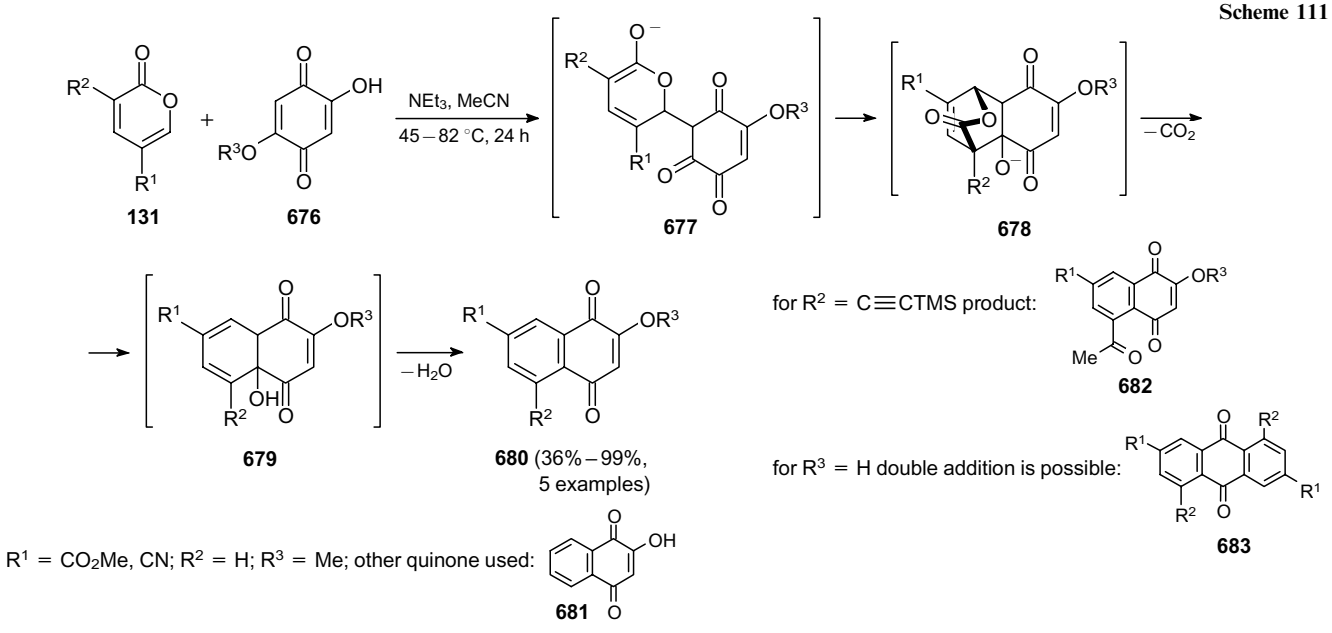
In 2020, Xu and co-workers [149] reported the synthesis of hydronaphthofurans **685** *via* rhodium catalyzed coupling of

Scheme 110

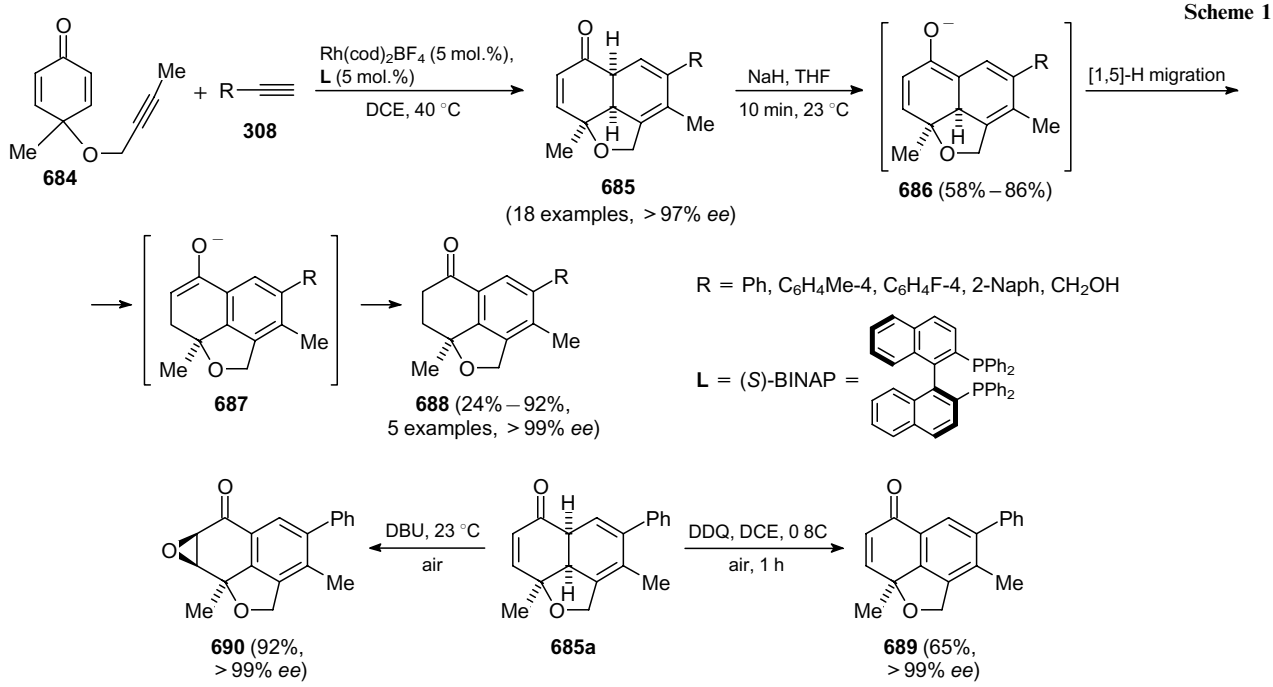


1,6-enynes **684** with acetylenes **308** (Scheme 112). When (*S*)-BINAP was used as a ligand in the [2+2+2] cycloaddition reaction, enones **685** were formed with excellent enantioselectivities (>97% *ee*). Upon addition of sodium hydride, the derived enolate **686** underwent an oxy-accelerated [1,5]-hydride shift with concomitant aromatization to give arenes **688** in good yields with no reduction in enantiomeric excesses (>99% *ee*). In one case, the authors showed the reaction could be carried out as a one-pot process in good yield (62%) and enantioselectivity (99% *ee*). Other standard aromatization procedures, such as with DDQ, gave enone **689**. Furthermore, aerobic oxidation in the presence of DBU gave arene epoxide **690** in excellent yield and enantioselectivity. In this case, oxidation of diene **685a** with oxygen gave rise to hydrogen peroxide, which subsequently underwent reaction with the enone moiety *via* a stereospecific Scheffer–Weitz epoxidation to give epoxide **690**.

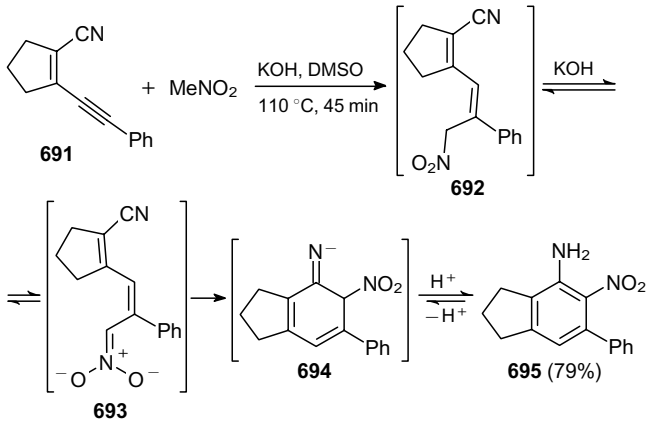
Scheme 111



Scheme 112



Scheme 113



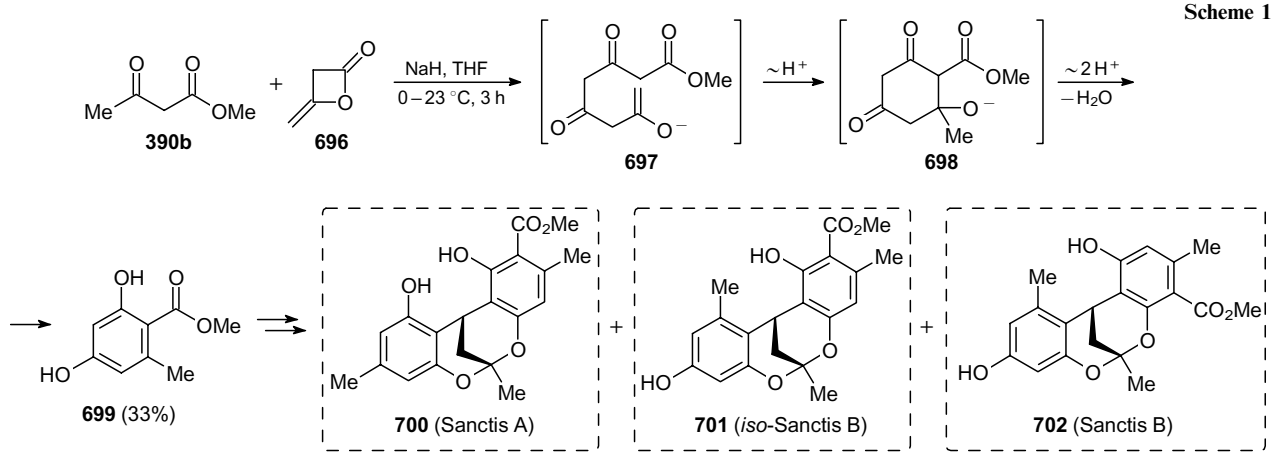
Verma and co-workers[150] reported the synthesis of indane **695** *via* an aza-Henry reaction between nitrile **691** and nitromethane (Scheme 113). Reaction of the nitronate from nitromethane with nitrile **691** and tautomerization and cyclization gave cyclohexadiene imine **694**, which underwent aromatization to give the nitro-indane **695**. We consider the mechanism involves these intermediates through nitronate addition to the acetylene and protonation by water to **692**, followed by deprotonation to form nitronate **693** and cyclization to **694** and not *via* a vinyl carbanion as suggested by the authors. In addition, the authors reported 37 additional examples for the synthesis of naphthalene derivatives, which is outside of the scope of this review.

Recently, Tan and co-workers[151] reported a biomimetic total synthesis of the natural products sanctis A (**700**), isosanctis B (**701**) and sanctis B (**702**) using a classical orsellinate synthesis (Scheme 114).[152] 1,3-Keto-ester **390b** was allowed to react under basic conditions with diketene **696** to provide the triketo-ester **697**, which readily underwent cyclization and aromatization to give resorcylate **699**. This intermediate was converted into the three natural products **700** – **702**.

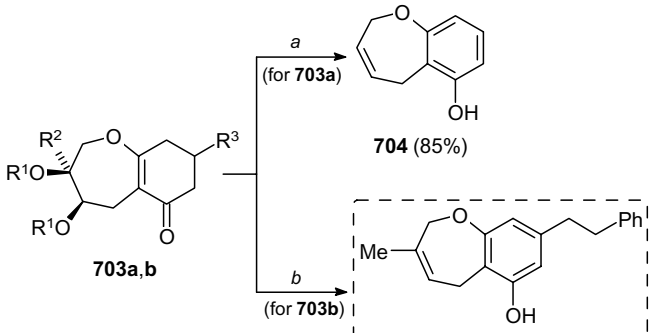
5.5. Other oxidation reactions

Zhang *et al.*[153] reported a one-pot procedure for the syntheses of 5,7,8,9-tetrahydrobenzo[*b*]oxepin-6(2*H*)-one, which on dihydroxylation using osmium tetraoxide and NMO in aqueous acetone and double methanesulfonylation

Scheme 114

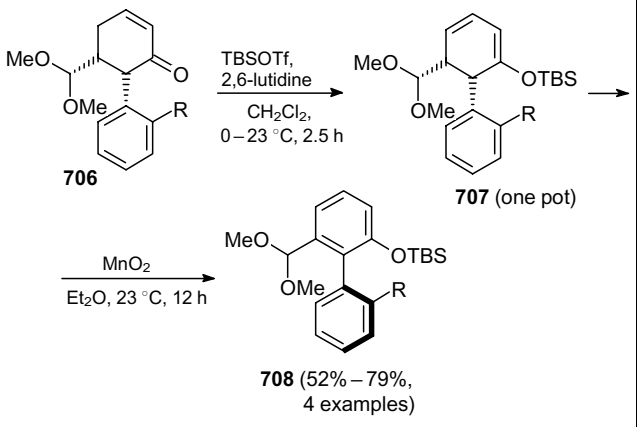


Scheme 115



(a) TBAF, DMSO, 1 h;
(*b*) 1) Ms_2O, PyH, 23 °C, o/n,
2) TBAF, DMSO, 0–23 °C, 1 h;
703: R^1 = Ms, R^2 = R^3 = H (**a**),
R^1 = H, R^2 = Me, R^3 = $(CH_2)_2Ph$ (**b**)

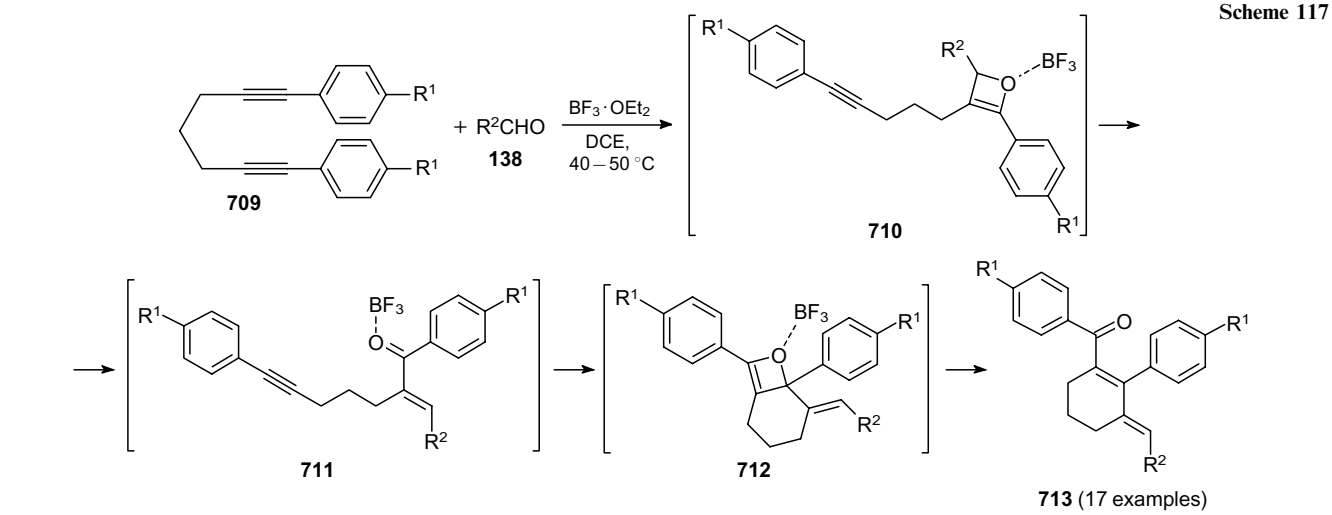
Scheme 116

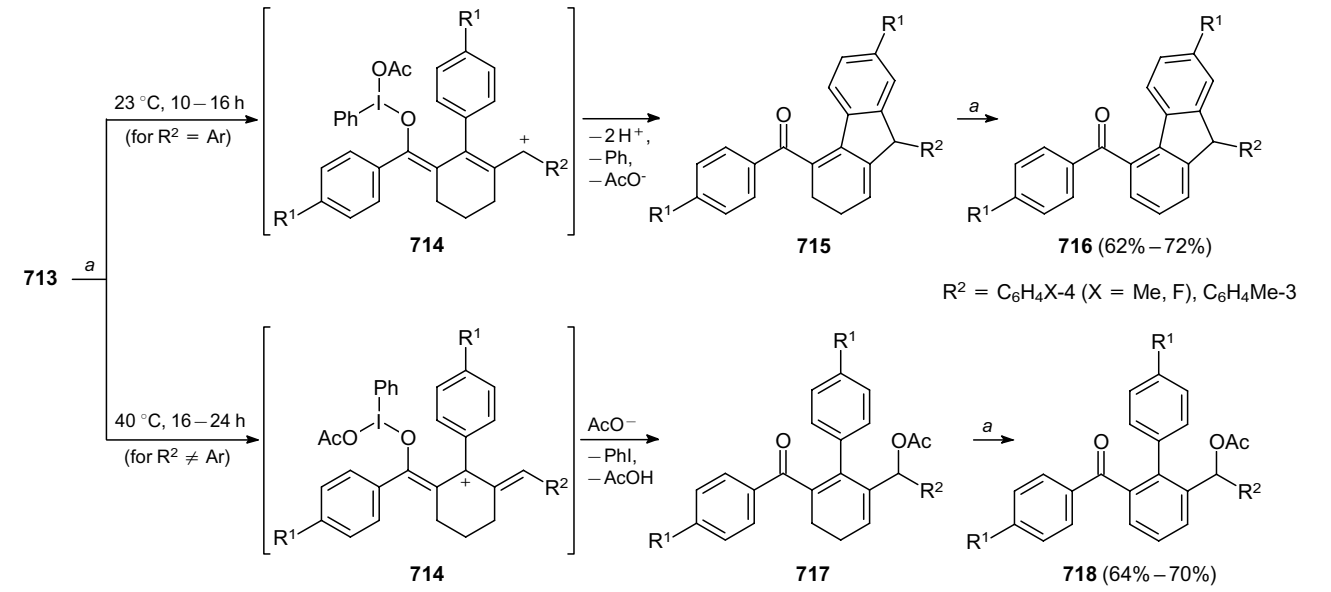


R = Br (96% *ee*), I (98% *ee*), Me (98% *ee*)

using methanesulfonyl chloride in pyridine was converted into the dimesylate **703a**. Subsequent aromatization was carried out by reaction with tetra-n-butylammonium fluoride (TBAF) to produce the 2,5-dihydrobenzoxepine **704** (Scheme 115). Additionally starting from compound **703b**,

Scheme 117





R2 = C6H4X-4 (X = Me, F), C6H4Me-3

(*a*) $In(OTf)_3$, $PhI(OAc)_2$; R^1 = OMe, OEt, OBn; R^2 = Cy, cyclo-C_5H_9, Bu^i

this reaction was successfully applied for the synthesis of radulanin A (**705**), a phenol with phytotoxic activity.

Ishida and co-workers [154] have recently reported the synthesis of atropisomerically enriched biaryls **708** *via* manganese dioxide mediated aromatization of cyclohexanones **707**, which were readily prepared through an organocatalytic enantioselective (99% *ee*) Michael – Henry reaction (Scheme 116). A one-pot silyl-enol ether **707** formation followed by manganese dioxide oxidation gave the three biaryls **708** in high atroposelectivities (96 – 98% *ee*) as well as the 1-naphthyl-analogue (56%, 95% *ee*).

Lastly, Yanada and co-workers [155] reported the synthesis of benzophenones **716** and **718** from 1,6-diynes **709** and aliphatic and aromatic aldehydes **138** under Lewis acidic conditions (Scheme 117). The authors suggested that the mechanism of reaction involved a carbonyl – acetylene metathesis and was applied to 17 different benzophenones **713**. Subsequently, in a one-pot procedure, these compounds were converted into indanes **716** and benzyl acetates **718** the ratio of which depended on the R^2 substituent. When R^2 was aromatic, upon addition of the oxidant iodobenzene diacetate and indium(III) trifluoromethanesulfonate, the stabilized allylic, benzylic carbenium ion **714** underwent Friedel – Crafts alkylation to give cyclohexadiene **715**. Further oxidation with iodobenzene diacetate gave indanes **716** in good yields. Alternatively, when R^2 was aliphatic, the same reaction promoted the formation of the allylic, benzylic carbenium ion **714**, which was trapped with acetate, and loss of a proton to produce cyclohexadiene **717**. Further addition of the oxidant iodobenzene diacetate gave benzyl acetate derivatives **718** in good yields.

6. Conclusion

Inspired in part by nature's methods for the biosynthesis of aromatic compounds, chemists have devised procedures for the synthesis of variously substituted benzenes, phenols, anilines, and other aromatic and heteroaromatic compounds from both cyclic and non-cyclic precursors. The underlying synthetic pathways are robust and well understood processes and depend on Diels – Alder, electrocyclic, pericyclic, cross-coupling, RCM, cyclo-isomerization, aldol or Michael addition reactions. The resulting aromatic compounds have diverse applications from medicinal chemistry to materials. Recent applications are in drug discovery and the total syntheses of meroterpenoids, polyketides and *Daphniphyllum* alkaloids with both early and late-stage incorporation of the aromatic units. Furthermore, the use of stereodefined catalysts to generate precursors for aromatization, has proven very valuable for the enantio- and diastereoselective synthesis of biaryl atropisomer systems, stereodefined ligands and compounds relevant to the elaboration of molecular machines. It is, therefore, reasonable to expect future developments in this important area of synthetic organic chemistry, given the extensive use of aromatic compounds in pharmaceuticals, agrochemicals, organic electronics and other materials.

We greatly appreciate the GlaxoSmithKline endowment (to A.G.M.B.) and extend our thanks to Dr. Alfred (AH) and Dr. Isabel Bader for their support. We thank Ms. Virginia Manch, Ms. Elfie Cavalli and Ms. Jiaxu Han for proofreading this review article.

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