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Tetrahedron
Tetrahedron 64 (2008) 2883–2896
www.elsevier.com/locate/tet

Tetrahedron report number 829

Halovinyl aldehydes: useful tools in organic synthesis

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Received 26 November 2007
Available online 15 December 2007

Contents

Abbreviations: Ac, acetyl; Ar, aryl; Bn, benzyl; Bu, butyl; DCM, dichloromethane; DDQ, dichloro dicyano quinone; TMEDA, tetramethylethylenediamine; DIPEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; ee, enantiomeric excess; Et, ethyl; Me, methyl; Mes, mesyl; Ms, mesityl; Pent, pentyl; Ph, phenyl; PIDA, phenyliodine diacetate; Pr, propyl; py, pyridyl; THF, tetrahydrofuran; TFA, trifluoroacetic acid.

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0040-4020/$ - see front matter
doi:10.1016/j.tet.2007.11.112

1. Introduction

This report presents an overview of the synthesis and use of halovinyl (chloro- and bromovinyl) aldehydes as synthetic tools in organic chemistry. Various groups have reported significant contributions on halovinyl aldehydes and our review aims to give an overview of the latest advances in the chemistry of halovinyl aldehydes, from their preparation to their transformations and applications in organic synthesis.

The present review focuses on the chemistry of halovinyl aldehydes in the last 18 years from 1989 up to mid-2007, because these compounds are still of synthetic interest to organic chemists.

2. Synthesis of chloro- and bromovinyl aldehydes

The Vilsmeier–Haack reagent ($POCl_3$+DMF) has attracted the attention of synthetic organic chemists since its discovery in 1927.[1] One aspect of its importance is that its reaction with a keto methylene group produces β-chloro-acroleins (the mechanism is shown in Fig. 1). Arnold and Zemlicka[2] in 1958 first reported the reaction of $POCl_3$ and DMF with keto methylene compounds.

The bromo analogue of the Vilsmeier reaction was reported by Arnold and Holy,[3] and the mechanism is shown in Figure 2.

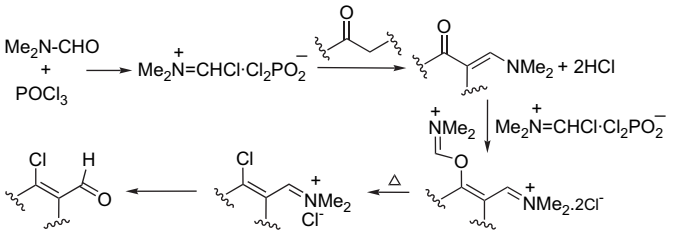


Figure 1.

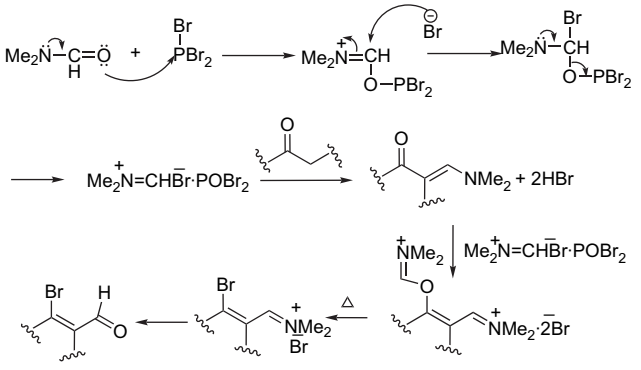


Figure 2.

3. Synthetic utility

Chloroaldehydes are important starting materials for entry into different heterocyclic systems (Fig. 3).[5,6,9–11]

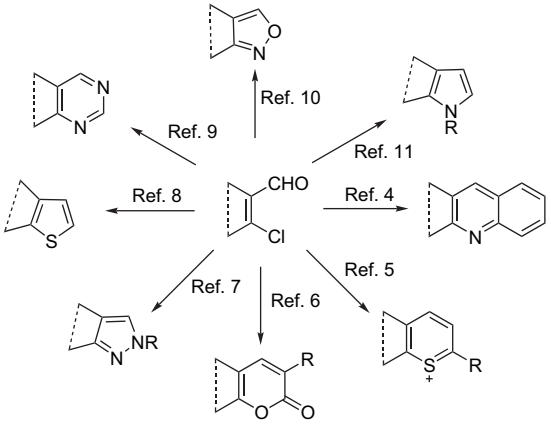
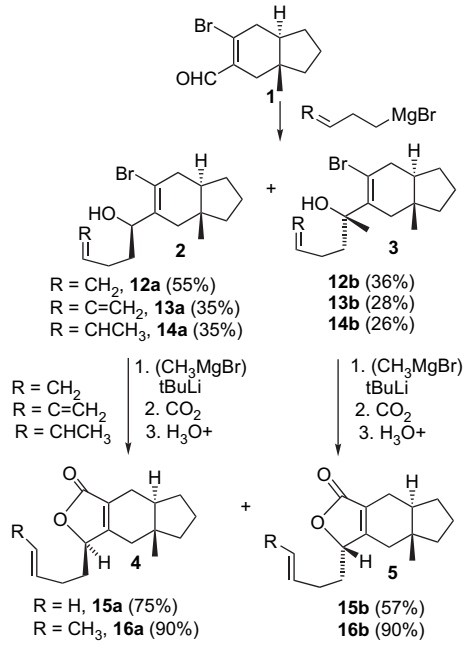


Figure 3.

3.1. Synthesis of hydrindene butenolides

The bromo Vilsmeier reaction of hydrindanone provided a single crystalline bromo aldehyde **1**. Addition of 3-butenyl-, 3,4-pentadienyl-, and (*E*)-4-pentenylmagnesium bromides to this aldehyde afforded mixtures (ratios 1.2–1.5:1) of epimeric bromo alcohols **2** and **3** (Scheme 1). The stereochemistry of the bromo alcohols is assigned by analogy. Metalation of the bromo alcohols with 3.5 equiv of *tert*-butyllithium followed by inverse addition to carbon dioxide in THF at −78 °C and hydrolysis afforded the corresponding alkenyl butenolides **4** and **5**.



Scheme 1. Synthesis of hydrindene butenolides.

Stereoisomeric 4,9a-dimethylhydrodicyclopenta[*a*,*d*]cycloocten-1-ones related to ophiobolins and ceroplastins can be synthesized via annelative ring expansion of hydrindene precursors.[12]

3.2. Synthesis of polycyclic oxa-coumarins

Ray et al.[8] have described the synthesis of polycyclic oxa-coumarins **9**, **13**, and **14** (potential antitumor agents) from chloroaldehyde derivatives **6** and **10** (Schemes 2 and 3). They first converted chloroaldehyde (**6** or **10**) to the methoxy derivative (**7** or **11**) by refluxing with sodium methoxide in methanol. Then methoxyaldehyde (**7** or **11**) on condensation with cyanoacetic ester produced the nitrile derivative (**8** or **12**). They achieved the oxa-coumarin derivatives by heating the nitrile derivatives with pyridine hydrochloride.

They used the chloroaldehydes for the synthesis of naphthopyranoquinolines via regioselective thermal cyclization of enaminoimine hydrochloride derivatives. Ray et al. also reported the synthesis of different quinolines,[13,14] acridines,[15] and polycyclic thiaarenes[16] from different chloroaldehydes.

3.3. Synthesis of 5,6-dihydrobenz[f]isoquinolines

Gilchrist and Healy have used 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde **15** for the preparation of 1-substituted-3,4-dihydronaphthalene-2-carboxaldehyde *N*,*N*-dimethylhydrazones **16**, **18**, and **20**. Dimethylhydrazones of 1-vinyl-3,4-dihydronaphthalene underwent electrocyclic ring closure followed by loss of dimethylamine to give 5,6-dihydrobenz[*f*]isoquinolines **17**, **19**, and **21** (Scheme 4).[17]

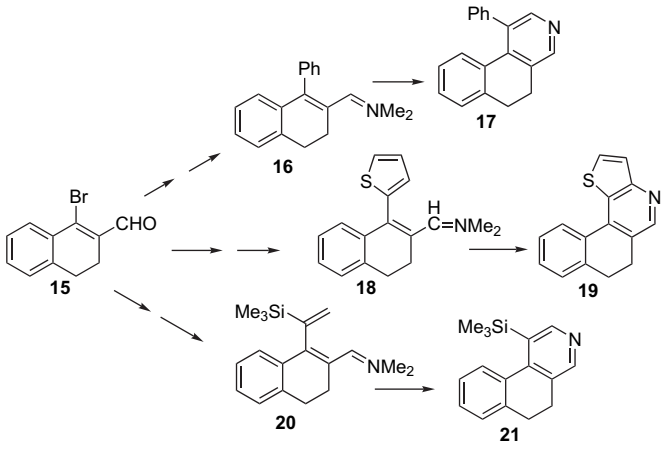
The results established that *N*,*N*-dimethylhydrazones can be used as C=N components in elctrocyclic ring closure reactions of 1-azatrienes. The dimethylhydrazono group has also been shown to allow bromine–lithium exchange at an adjacent carbon atom, and this may be useful in expanding the scope of the reaction.

3.4. Synthesis of non-natural cavity-shaped molecules

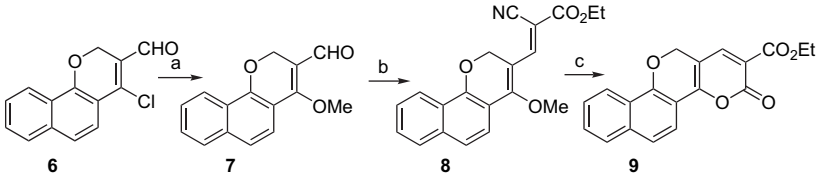
Ray's group has been active in synthesizing non-natural cavity-shaped molecules **27** with selective cavity size and with proper functionality in this region to interact selectively with organic and inorganic substrates, starting from chloroaldehyde **23** of the appropriate ketone **22**[18] (Scheme 5). Here, bis-chloroaldehyde (**23**) on refluxing with 2 equiv of 1-naphthylamine produced Schiff's base **24**. Thermolysis of compound **24** afforded compound **25**. Finally, aromatization of **25** with DDQ/benzene furnished the desired compound **26**, which on direct alkylation by alkyllithiums produced **27**.

3.5. Synthesis of potential dihydrodiol metabolites

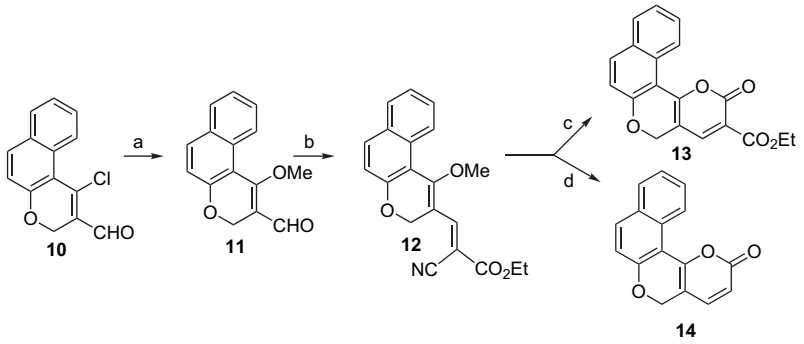
The carcinogenic activities of polycyclic aromatic hydrocarbons are often strongly affected by the substitution of



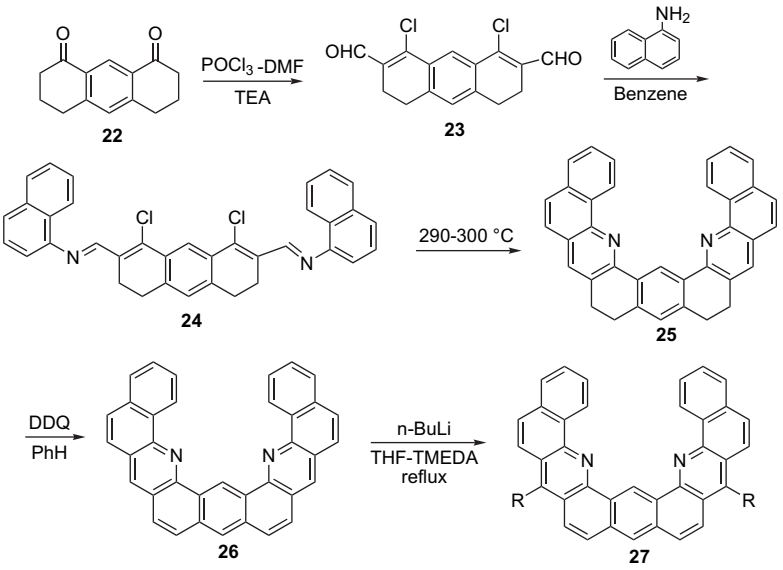
Scheme 4.



Scheme 2.



Scheme 3. Reagents and conditions: (a) NaOMe/MeOH/reflux; (b) $CH_2(CN)CO_2Et$/ethanolic KOH/reflux; (c) PhN·HCl/reflux, 15 min; (d) PhN·HCl/quinoline/reflux.

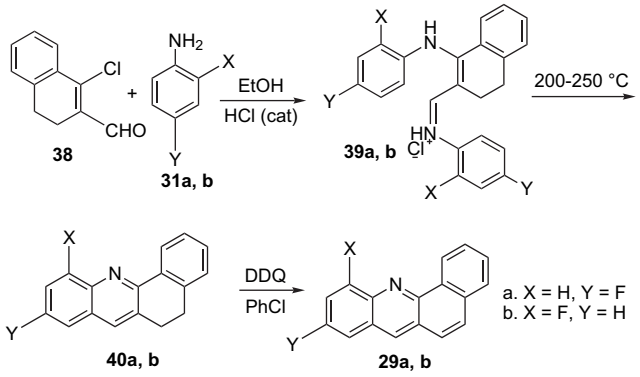


Scheme 5.

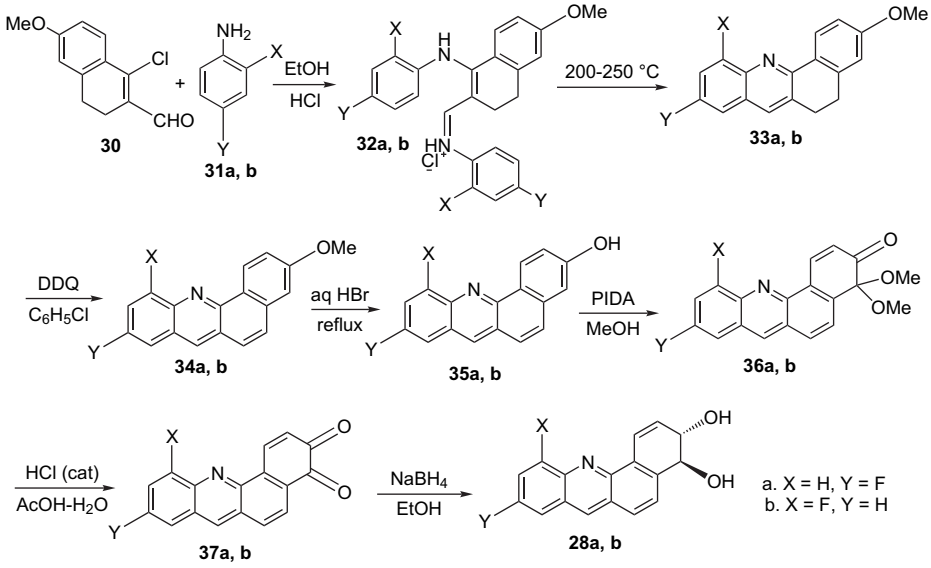
fluorine in appropriate molecular sites.[19] The presence of fluorine at a suitable position can alter the conformation of two hydroxy groups to affect the mutagenic activity of *trans* diol epoxide derivatives.[20] Ray's group has undertaken the synthesis of two potential dihydrodiol metabolites of two isomeric fluorobenz[*c*]acridines **28a**,**b** (Scheme 6), as well as their parent fluoroazaarenes **29a**,**b** (Scheme 7).

Ray et al. reported[21] the first synthesis of the hitherto unknown *trans* 9-fluoro-3,4-dihydroxy-3,4-dihydro-benz[*c*]acridine **28a** and 11-fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine **28b**, as oxidative metabolites of 9- and 11-fluorobenzacridine derivatives in six high-yielding steps, starting from 1-chloro-6-methoxy-3,4-dihydronaphth-2-aldehyde **30**.

Here, treatment of chloroaldehyde **30** with 2.5 equiv of fluoroanilines **31a**,**b** afforded arylenaminoimine hydrochlorides **32a**,**b**. Thermal cyclization of **32a**,**b** at 200–250 °C furnished



Scheme 7.



Scheme 6.

dihydrobenz[*c*]acridine derivatives **33a**,**b**. Aromatization produced **34a**,**b** and subsequent demethylation of **34a**,**b** generated compounds **35a**,**b**. Oxidation of **35a**,**b** with PIDA resulted in the formation of *o*-quinone monoketals **36a**,**b**, which on hydrolysis with aq HCl in AcOH gave *o*-quinones **37a**,**b**. Stereoselective reduction of this quinones with excess of sodium borohydride afforded **28a**,**b**.

In their studies, they found that *trans* dihydrodiols (**28a** and **28b**) of the respective fluorobenz[*c*]acridines showed no decrease in mutagenicity, compared to their parent fluoroazaarenes **29a** and **29b**, respectively. From the chloroaldehyde **38**, **29a**,**b** was prepared through **39a**,**b** and **40a**,**b** as per Scheme 7. In addition, the presence of a fluorine atom in the non-interactive position of the dihydrodiols (**28a** and **28b**) does not reduce their mutagenicity, compared to the analogous dihydrodiol of the unsubstituted benz[*c*]acridine.

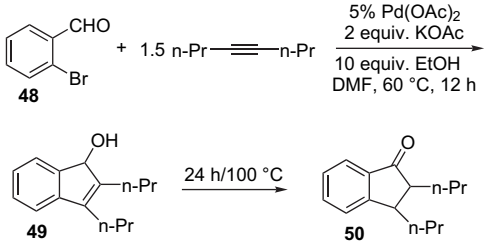
3.6. Synthesis of substituted nicotine derivatives

Kanomata and Nakata[22] have investigated the reactivity and synthetic utility of various 2-(phosphoranylideneamino)acrylaldehydes, formyl-substituted (vinylimino)phosphoranes, as precursors for more generally substituted nicotine derivatives. They described the preparation of several alkyl- and phenyl-substituted 2-(phosphoranylideneamino)acraldehydes **44** from the formyl-substituted azirines **43** (Scheme 8) and their reactions with acetylinic esters as unique synthetic approaches to 2-mono- and 2,5-disubstituted nicotinate derivatives **45**–**47** (Scheme 9). Here, formyl-substituted azirines were obtained from the corresponding chlorovinyl aldehyde **42** starting from appropriate ketone **41**.

The novel pyridine formation reaction of 2-(phosphoranylideneamino)acrylaldehydes **44** with acetylinic esters provides a convenient method for the syntheses of 2-mono- and 2,5-disubstituted nicotinate derivatives.

3.7. Synthesis of indanones

Gevorgyan et al.[23] showed that *o*-bromobenzaldehyde **48**, in the presence of a palladium catalyst, smoothly underwent consecutive intermolecular carbopalladation with an internal alkyne and then intramolecular nucleophilic vinylpalladation of the aldehyde function to produce the indenol derivative **49** in high yield. Further heating under more elevated temperatures caused complete isomerization to the corresponding indanone **50** in 68% yield (Scheme 10).



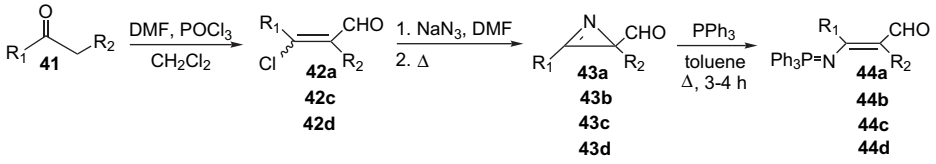
Scheme 10.

3.8. Synthesis of macrocyclic ligands

Ray's group[24] achieved the first synthesis of 18-membered macrocyclic ligands based on a dibenz[*c*,*h*]acridine framework **58** (Scheme 11), from a β-chlorovinyl aldehyde derivative **52** of 7-bromo-1-tetralone **51**, having a binding capability with urea. Here, chlorovinylimine **53** was obtained from chlorovinyl aldehyde **52** on refluxing with 7-bromo-1-naphthylamine. The thermal cyclization of chlorovinylimine produced dihydrobenz[*c*,*h*]acridine derivative **54**. Dehydrogenation of **54** with DDQ generated 2,12-dibromodibenz[*c*,*h*]-acridine **55**. The dibromo derivative was converted to dialdehyde **56** by *n*-BuLi and DMF. This was condensed with diethyltriamine to generate the macrocyclic compound **57**. Finally, compound **57** on reduction with $NaBH_4$ afforded **58**, which has correct functionalities to bind the urea molecule.

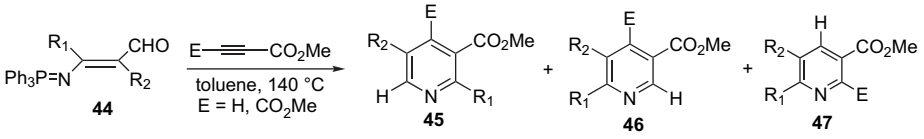
3.9. Synthesis of vic-diols

Shimizu et al.[25] described the pinacol reaction of β-halogenated α,β-unsaturated aldehydes **59** promoted by

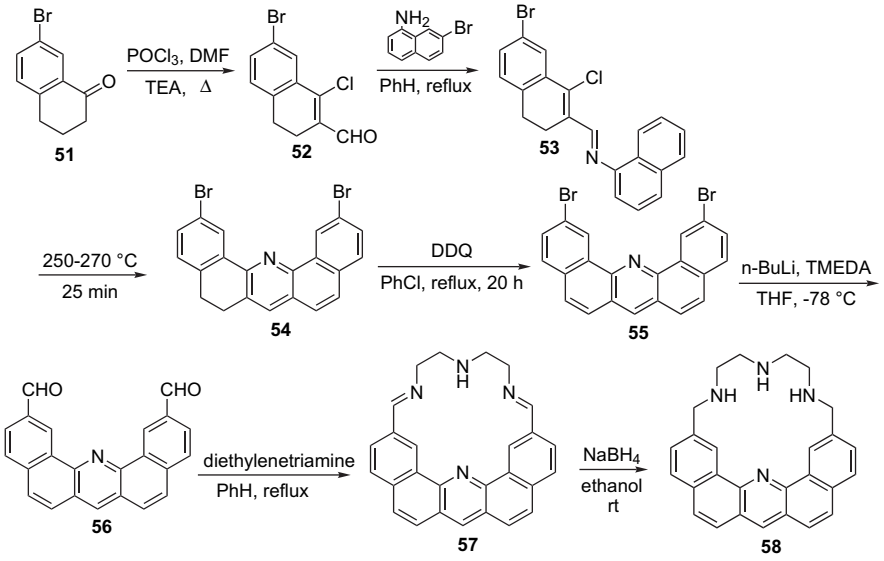


a: R_1 = Ph, R_2 = Me; b: R_1 = Ph, R_2 = H; c: R_1 = n-Pr, R_2 = Et; d: R_1 = n-Bu, R_2 = n-Pr

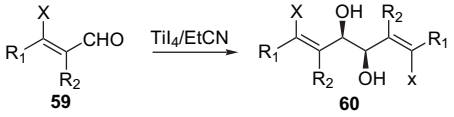
Scheme 8.



Scheme 9.



Scheme 11.



Scheme 12.

titanium tetraiodide to give the coupling products **60** in good yields with high dl-selectivity (Scheme 12). Subsequent reduction with H_2/Pd–C gave the saturated *vic*-diols in good yields. A Heck coupling reaction enabled the displacement of the halogens with vinyl groups without the loss of stereochemical integrities. Results are tabulated in Table 1.

These 1,2-diols can be utilized as synthons for the synthesis of biologically important compounds such as HIV protease inhibitors and natural products.

Table 1
Pinacol coupling reaction of α,β-unsaturated aldehyde

Entry	R_1	R_2	R_3	Temp (°C)	Time (h)	Yield (%)[a]	dl/*meso*[b]
1: **a**	Ph	H	H	From −78 to −20	2.5	83	>99:1
2: **b**	Ph	H	Cl	From −78 to −70	0.5	87	>99:1
3: **c**	Ph	H	Br	From −78 to −50	1.5	85	>99:1
4: **d**	Ph	H	I	From −78 to −20	4.0	88	>99:1
5: **e**	Ph	Br	H	From −78 to 0	6.5	68	>99:1
6: **f**	*n*-Pr	H	H	From −78 to −10	3.5	16	>99:1
7: **g**	*n*-Pr	H	Br	From −78 to −20	2.5	82	>99:1
8: **h**	*n*-Pr	H	I	From −78 to 0	5.0	72	>99:1
9: **I**	*t*-Bu	H	H	From −78 to rt	20	0	0
10: **j**	*t*-Bu	H	Cl	From −78 to rt	10	57	93:7
11: **k**	$-(CH_2)_4-$	H		From −78 to rt	24	0	0
12: **l**	$-(CH_2)_4-$	Cl		From −78 to rt	22.5	32	97:3

[a] Isolated yield.
[b] Determined by ^{1}H NMR.

3.10. Synthesis of receptors for the recognition of dicarboxylic acids

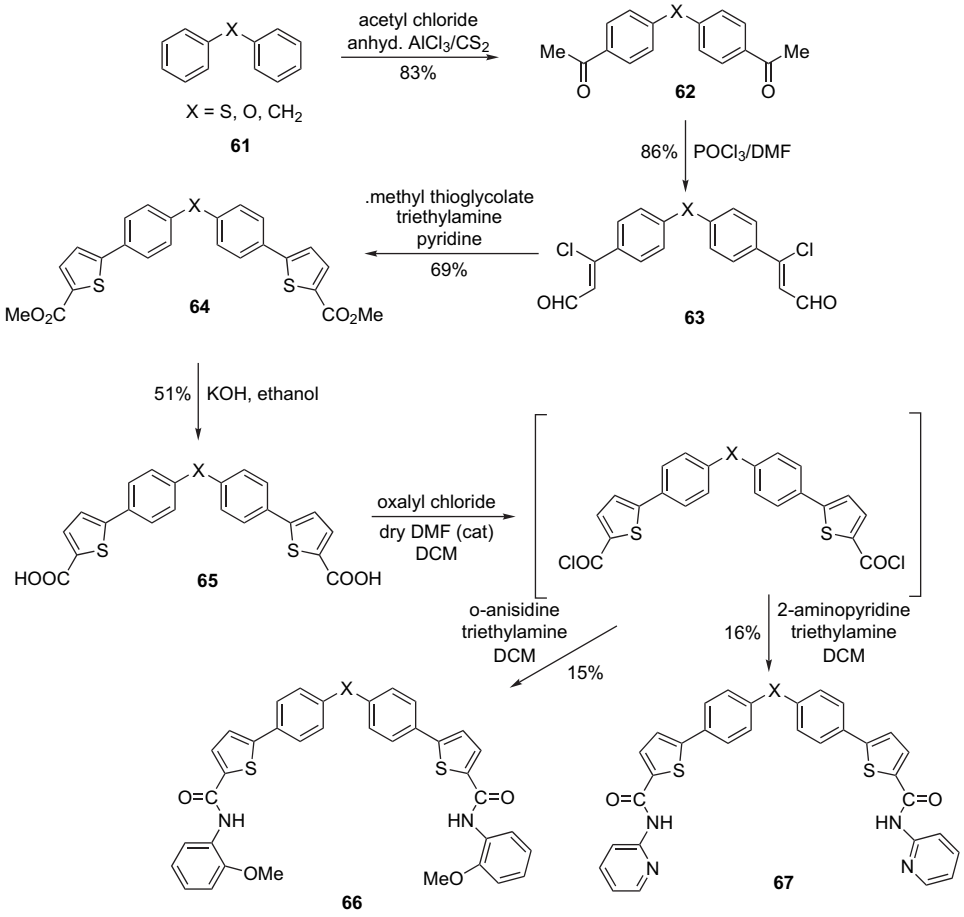
Studies of supramolecular systems designed as receptors with the capability to bind carboxylic acids have recently received much attention. The host–guest complexation studies of the carboxylic acids and their derivatives with suitable receptors have become the central focus of the molecular recognition studies to mimic the biochemical processes.

Ray et al.[26,27] have designed and executed a number of forceps-type receptors **66** and **67** containing oxygen, sulfur, and carbon at the pivot, and an amide functionality at the end (Scheme 13) to selectively bind appropriately sized dicarboxylic acids. They reported the selective recognition of different dicarboxylic acids through multipoint hydrogen bonds.

Thus Friedel–Crafts acylation of **61** produced diketone **62**. Diketone **62** on treatment with $POCl_3$/DMF afforded 4,4′-bis-(1-chloro-2-formylethenyl)-phenylmethane **63**. Bis-chloroaldehyde on condensation with methyl thioglycolate/Et_3N in pyridine followed by ring closure with 50% KOH solution produced the bis-thiophene-5-carboxylic ester derivative **64**. Subsequent hydrolysis with aq ethanolic KOH afforded bis-carboxylic acid **65**. Reaction of this bis-acid with oxalyl chloride formed the bis-acid chloride derivative, which on treatment with 2-aminopyridine resulted in the formation of the receptor **67**. The reaction of the bis-acid chloride with *o*-anisidine under identical condition furnished another receptor **66**.

3.11. Synthesis of aromatics

Cho's group[28] showed that β-bromovinyl aldehydes **69**, obtained from ketone **68**, undergo an aromatization with various suitably electron-withdrawing group-substituted alkenes in the presence of a palladium catalyst and a base via domino Heck and aldol processes (Scheme 14). This reaction will operate as

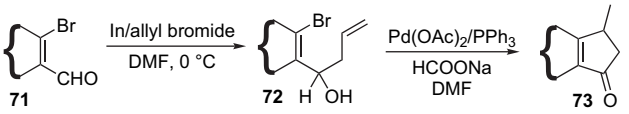


Scheme 13. Synthesis of ditopic receptors.

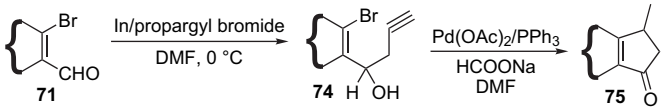
a useful procedure for the synthesis of aromatics **70** from ketones.

3.12. Synthesis of cyclopentanone-containing fused rings

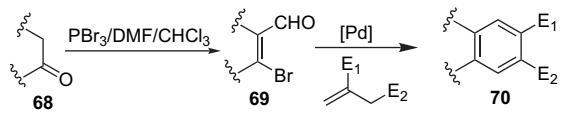
Ray's group[29,30] has outlined a palladium-catalyzed cycloisomerization toward the synthesis of fused carbocycles **73** and **75** (Schemes 15 and 16) starting from bromovinyl aldehyde **71**. The developed methodology serves as an effective transition metal-catalyzed protocol for the cyclization of unactivated alkenes **72** and alkynes **74** to functionalized ketones via a tandem process. Cyclopentanone-containing 5,5-, 6,5-, 7,5-, and 8,5-fused rings were prepared by using this methodology.

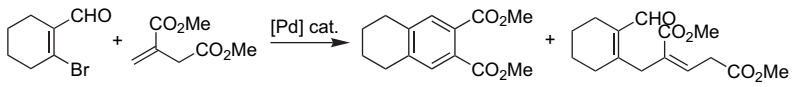


Scheme 15.



Scheme 16.

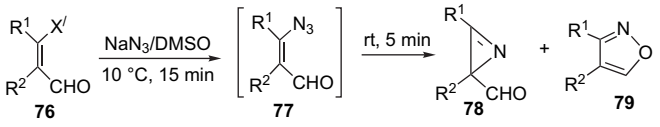




Scheme 14.

3.13. Synthesis of azirines and isooxazoles

Ray and Brahma[31] have also developed a simple and useful method for the synthesis of azirines containing an aldehyde functionality, from open-chain bromo/chloroaldehydes at room temperature. In this synthesis, the acyclic bromo/chloroaldehydes **76** were reacted with sodium azide in DMSO at 10 °C to give the corresponding non-isolable 3-azidoaldehydes **77**, which at room temperature, underwent spontaneous denitrogenation and ring closure to 2-formyl-azirines **78** as the major products via the corresponding vinyl nitrenes (Scheme 17).



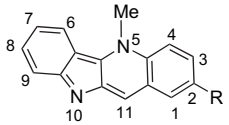
Scheme 17.

Bis-bromo/chloroaldehydes **80** also underwent this reaction in an analogous fashion, i.e., giving mainly 2*H*-azirines **82** with minor amounts of isooxazoles **83** (Scheme 18) via non-isolable bis-azidoaldehyde intermediate **81**. On the other hand, the fused-system azidoaldehydes **85**, obtained from **84**, on thermolysis resulted in only the isooxazoles **86** (Scheme 19). Here, they isolated azidoaldehyde intermediate[4] **85**.

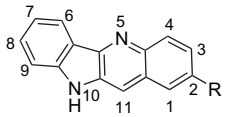
3.14. Synthesis of various 2-substituted cryptolepines

Cryptolepine **87a** is an important indoloquinoline alkaloid found in *Cryptolepis sanguinolenta*, a shrub used in traditional medicine for the treatment of malaria as well as a number of other diseases in Central and West Africa.

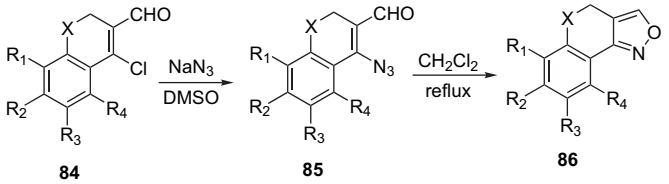
In order to develop a general method for the synthesis of various 2-substituted cryptolepines, Ray et al.[32] undertook



87a (R = H), **87b** (R = Me)
87c (R = Br), **87d** (R = I)



88a (R = H), **88b** (R = Me)
88c (R = Br), **88d** (R = I)



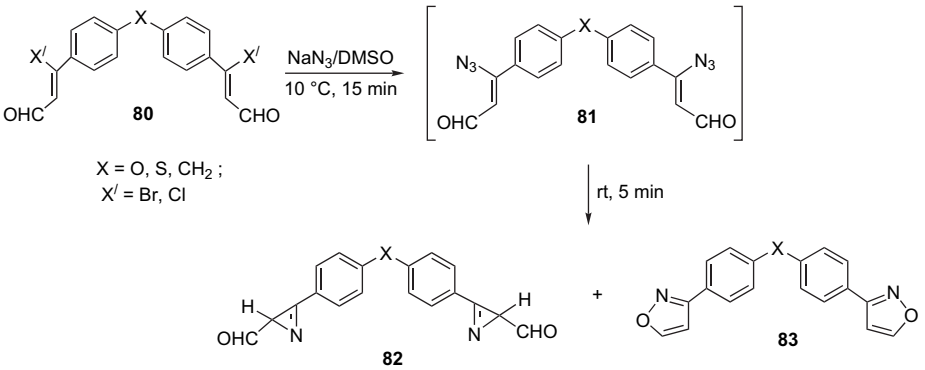
Scheme 19.

the preparation of 2-substituted quindolines **88** starting from the chloroaldehyde of 2-nitroacetophenone **89** (Scheme 20). When 2-nitroacetophenone was treated with $POCl_3$ in DMF, it underwent a Vilsmeier–Haack reaction to produce β-chlorocinnamaldehyde **90**, with the nitro group remaining intact. Chloroaldehyde upon reaction with 2.2 equiv of aniline in 2 N ethanolic HCl at 0 °C produced the corresponding enaminoimine hydrochloride **91** in very good yield. Thermal cyclization of this compound at 200–300 °C produced 2-(2-nitrophenyl)quindoline **92** (R=H) as a major isolable product. The desired quinoline **93** (R=H) was synthesized by heating 2-(2-nitrophenyl)quindoline with triethyl phosphate at 160 °C. Ray et al. also synthesized various 2-substituted quinolines **93** following this procedure.

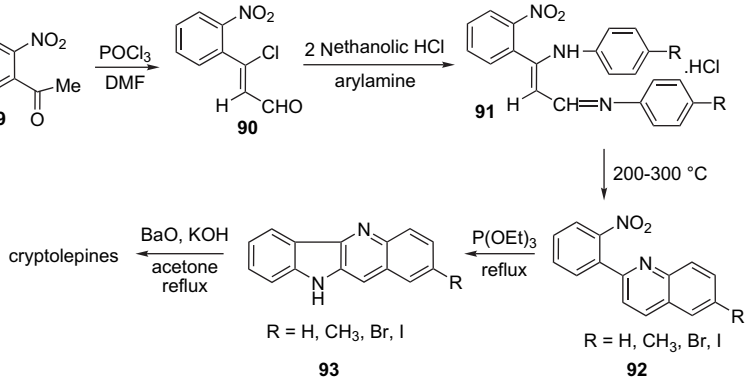
3.15. Synthesis of substituted benzene by homo/hetero-coupling of halovinyl aldehydes

Different substituted benzene derivatives can be obtained from homo- and hetero-coupling of bromovinyl aldehydes followed by McMurry coupling.

Ray et al.[33] have developed a convenient synthetic approach to substituted benzene derivatives by modified Ullmann cross-coupling of bromovinyl aldehydes followed by intramolecular McMurry coupling. Thus, when keto methylene compounds **94** were treated with PBr_3 in DMF, bromovinyl aldehydes **95** were produced, which, upon treatment with an equivalent of Cu powder and 10 mol % of $Pd(PPh_3)_4$ in anhydrous DMSO with heating at 110 °C, afforded the



Scheme 18.

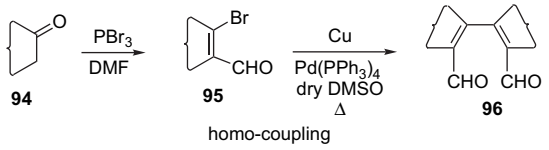


Scheme 20.

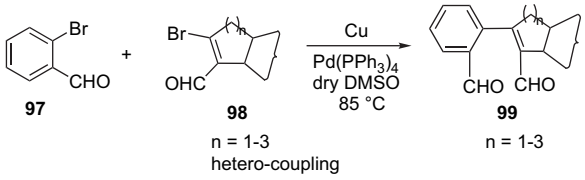
homo-bis-aldehydes **96** (Scheme 21) by a modified Ullmann reaction.[7]

When two different bromovinyl aldehydes **97** and **98** were reacted, only the cross-coupled bis-aldehydes **99** were isolated under similar conditions to the homo-coupling reaction at 85 °C (Scheme 22). Raising the temperature from 85 to 110 °C led to a mixture of homo- and hetero-coupled bis-aldehydes. Thus, these workers had determined the optimum temperature for preparing the cross-coupled products.

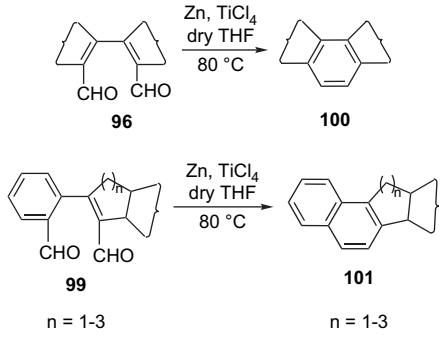
These bis-aldehydes **96** and **99** upon treatment with $TiCl_4$ and Zn dust underwent intramolecular McMurry coupling to generate the substituted benzenes **100** and **101** (Scheme 23).



Scheme 21.



Scheme 22.

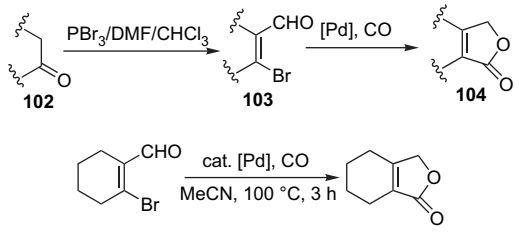


Scheme 23.

Ray et al. have therefore developed a convenient methodology for the synthesis of various substituted benzenes starting from keto methylene compounds. Their method provides short reaction times and good yields.

3.16. Synthesis of lactones

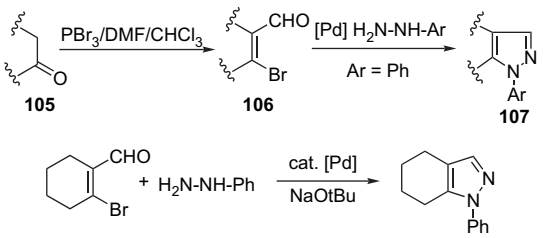
Cho's group[34] demonstrated that β-bromovinyl aldehydes **103**, obtained from the corresponding ketone **102**, undergo an unusual carbonylative cyclization under carbon monoxide pressure in the presence of a palladium catalyst and a base to afford the corresponding lactones **104** in high yield (Scheme 24).



Scheme 24.

3.17. Synthesis of substituted pyrazoles

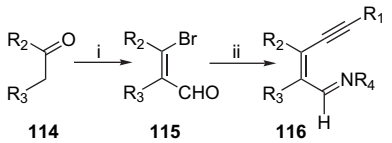
Cho and Patel[35] have described that cyclic and acyclic β-bromovinyl aldehydes **106**, derived from appropriate ketone **105**, are cyclized with an array of arylhydrazines in toluene at 125 °C in the presence of a palladium catalyst and a phosphorus chelating ligand together with NaO^{t}Bu to give 1-aryl-1*H*-pyrazoles **107** in moderate-to-good yield via an intrinsic C–N bond formation (Scheme 1). The present reaction is a new route for the synthesis of pyrazoles from ketones (Scheme 25).



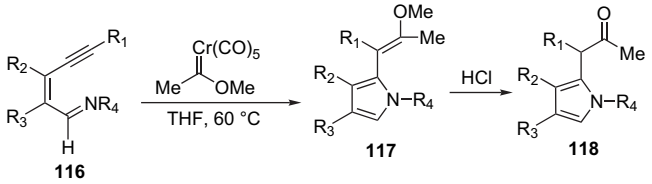
Scheme 25.

3.18. Synthesis of 1,2-disubstituted arylnaphthalenes

de Koning et al.[36] have developed a methodology for the synthesis of 1,2-disubstituted arylnaphthalenes from α-tetralones. In this synthesis, α-tetralones such as **108** were initially converted into 1-bromo-dihydronaphthalene-2-carbaldehydes and 1-bromo-naphthalene-2-carbaldehydes **109a**,**b**. These precursors were then subjected to Suzuki coupling reactions to afford 1,2-disubstituted aryldihydronaphthalenes and 1,2-disubstituted arylnaphthalenes **110a**,**b**, respectively. Reduction with sodium borohydride afforded alcohols **111a**,**b**. It was converted to acetate derivatives **112a**,**b** by treating with Ac_2O in pyridine. The former products were oxidized with DDQ to give 1,2-disubstituted arylnaphthalenes **113** (Scheme 26).



Scheme 27. Reagents and conditions: (i) PBr_3/DMF/$CHCl_3$; (ii) R_1CCH/$(PPh_3)_2PdCl_2$/CuI/Et_3N/THF.



Scheme 28.

3.19. Synthesis of alkenylpyrrole derivatives

Herndon and Zhang[37] have described that alkenylpyrrole derivatives can be prepared from the coupling of enyne-imines with Fischer carbene complexes. Here, enyne-imines **116** were synthesized from the corresponding bromoaldehydes **115** (Scheme 27), which were prepared from **114**.

A variety of imines **116** were treated with a chromium carbene complex to produce the alkenylpyrrole derivatives **117** (Scheme 28). The initially formed enol ether-pyrrole derivatives **117** were unstable with respect to air oxidation and were hydrolyzed to the corresponding ketones **118** for characterization purposes. Results are shown in Table 2.

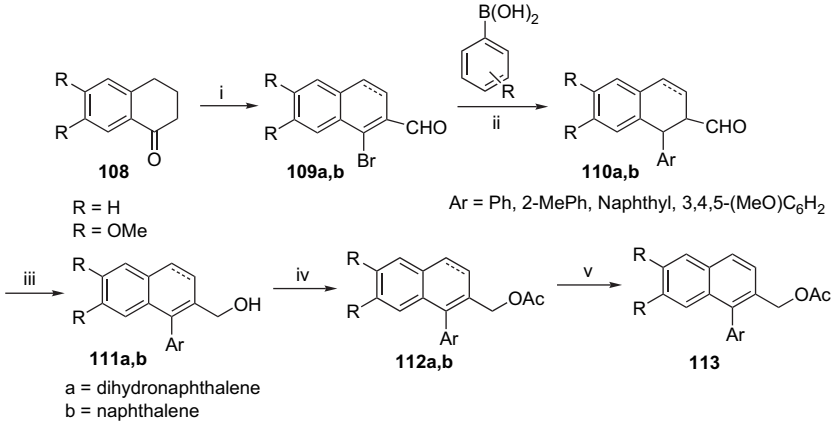
Table 2
Synthesis of pyrroles **118** through coupling of enyne-imines with Fischer carbene complexes

Entry	R_1	R_2	R_3	R_4	Yield **118** (%)
A	Bu	Ph	H	NMe_2	62
B	Bu	Ph	H	Ts	37
C	Bu	Ph	H	Ms	35
D	Bu	Ph	H	CH_2Ph	9
E	Bu	Bu	H	NMe_2	64
F	H	Bu	H	NMe_2	59
G	Bu	H	H	NMe_2	70
H	Bu	H	Et	NMe_2	74
I	Bu	H	Allyl	NMe_2	64
J	Bu	$-(CH_2)_4-$		NMe_2	36
K	Bu	$-(CH_2)_3-$		NMe_2	25

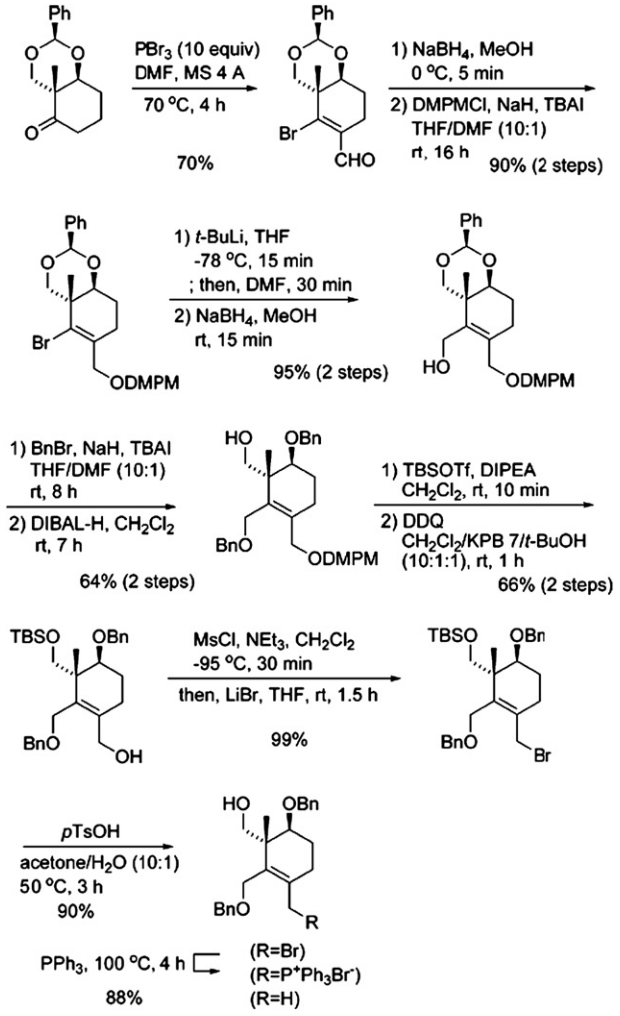
3.20. Stereoselective synthesis of taxol C-ring

Nakada et al. have achieved the highly stereoselective construction of the C3 stereogenic center of the taxol C-ring.[38] The trans isomer at the C3–C8 position of the taxol C-ring, which is required for the total synthesis of taxol, as well as its cis isomer, was successfully synthesized by the diastereoselective S_N2' reduction of allylic phosphonium salts. The reaction commenced with the bromoaldehyde obtained from the enantiopure ketol (Scheme 29).

This is the first diastereoselective S_N2' reduction of an allylic phosphonium salt, which constructs a stereogenic tertiary carbon center with high selectivity. This protocol would be applicable for other cyclic systems as well as for acyclic systems to generate a new stereogenic center.



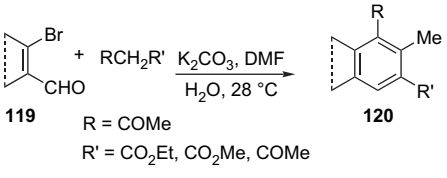
Scheme 26. Reagents and conditions: (i) DMF, PBr_3, CH_2Cl_2, reflux, R=H, 70%; R=OMe, 63%; (ii) cat. $Pd(PPh_3)_4$, aq Na_2CO_3, boronic acid, DME/EtOH, reflux; (iii) $NaBH_4$, EtOH, rt; (iv) Ac_2O, pyridine, reflux; (v) DDQ, CH_2Cl_2, reflux.



Scheme 29.

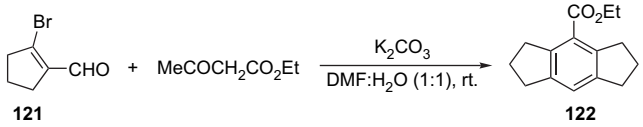
3.21. Synthetic approach toward substituted benzene derivatives

Ray and Ray[39] developed a simple, convenient, one-pot synthetic approach toward the substituted benzene derivatives **120** using base catalyzed condensation of β-bromovinyl aldehydes **119** with β-ketoesters followed by water-mediated cyclization and aromatization (Scheme 30).



Scheme 30.

They performed the reaction in various solvents and found varying percentages of yields. During their trial for the establishment of this methodology, they obtained an interesting result by varying the solvent system. When 2-bromo-cyclopent-1-encarbaldehyde **121** was treated with ethyl acetoacetate and potassium carbonate in a solvent system containing DMF and water (1:1), compound **122** was unexpectedly obtained in 52% yield (Scheme 31).



Scheme 31.

3.22. Synthesis of cuparenone

A large number of multistep methods have been developed for the synthesis of cuparenone, herbetenone, etc., where the synthetic approaches are lengthy and hazardous. In this context, Ray's group[40] highlighted the formation of a *gem*-dimethylcyclopentenone moiety from 1-bromo-5-methyl-1-aryl-hexa-1,5-dien-3-ols **123** obtained from the corresponding bromoaldehydes using palladium-catalyzed Heck reaction conditions.

They utilized the method in obtaining two different products **124** and **125** from a common starting material by varying the reaction conditions (Scheme 32).

The retrosynthetic pathway for the formation of the compounds is as follows (Scheme 33).

When the precursors were subjected to Heck reaction conditions in the presence of bases other than sodium formate, *gem*-dimethylcyclopentenone derivatives were obtained (Scheme 34). The reaction was then attempted by changing the base, solvent, and catalyst to optimize the reaction conditions.

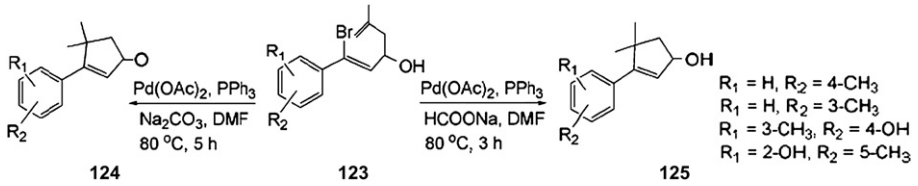
This methodology has the potential to be of great benefit in the convergent synthesis of a number of natural product moieties.

3.23. Synthesis of various quinolines

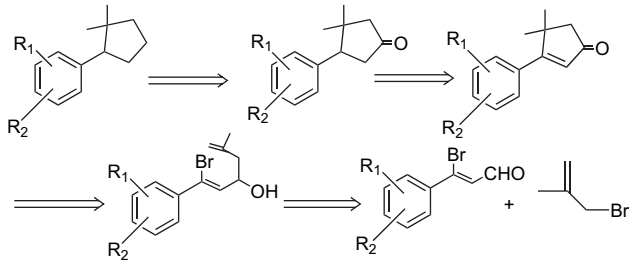
Recently, Ray's group has developed two short, distinct, and complementary methods for the synthesis of various 3,4-annulated and 4-substituted quinolines from β-bromo-α,β-unsaturated aldehydes (**127**) and either 1-bromo-2-nitrobenzene (**128**, X=Br) or 2-bromoacetanilide.

These involved subjecting certain enolizable (and often cyclic) ketones **126** to a Vilsmeier–Haack haloformylation reaction and then engaging the resulting β-bromo-α,β-unsaturated aldehydes **127** in a Pd(0)-mediated Ullmann cross-coupling reaction with 1-bromo- or 1-iodo-2-nitrobenzene **128** to generate the corresponding β-(*o*-nitrophenyl)-α,β-unsaturated aldehydes **129**. Subjection of this last type of compound to reductive cyclization using dihydrogen in the presence of 10% Pd on C or a large excess of $TiCl_3$ then gave the target quinolines **130** (Scheme 35).[41]

New protocols for the reductive cyclization of compounds of the general form **129** have been identified and these should



Scheme 32.

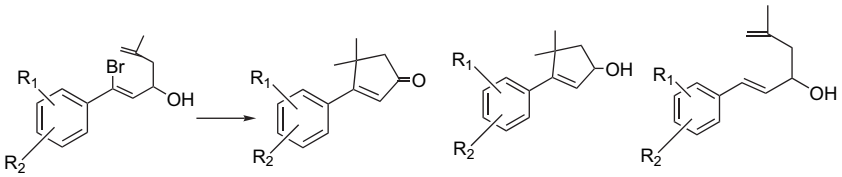


Scheme 33.

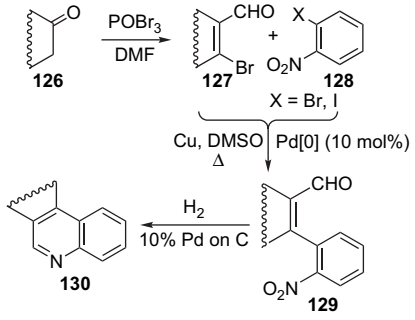
prove broadly applicable to the preparation of quinolines bearing a range of different functional groups.

3.24. Synthesis of polycyclic quinolines

Recently, Ray and Some[42] have reported a simple, two-step procedure for the facile synthesis of polycyclic quinolines **135**, which involves selective Pd-catalyzed arylamination of β-bromovinyl aldehydes **131** by substituted aromatic amines **132** followed by acid-catalyzed cyclization with trifluoroacetic



Scheme 34.

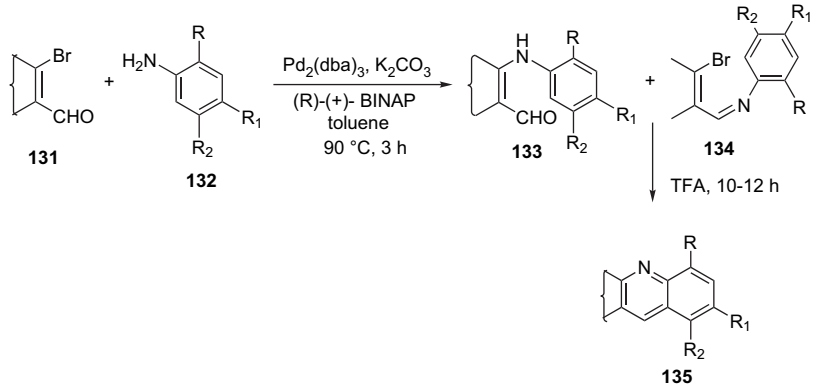


Scheme 35.

acid (Scheme 36). Compounds **133** and **134** were formed as intermediates. Thus two-step methodology for the synthesis of various polycyclic quinolines required short reaction times and gave improved yields of products (Scheme 36). Results for the formation of **133** and **134** are shown in Table 3.

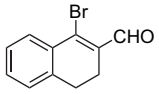
4. Conclusions

In conclusion, it is clear that halovinyl aldehydes have already found a unique position in organic chemistry in view



Scheme 36.

Table 3
Reaction of **131** with various substituted anilines



136

Entry	R	R_1	R_2	Yield (% of **133**)	Yield (% of **134**)
1	H	OMe	H	80	18
2	Me	H	Me	50	30
3	OMe	H	H	70	18
4	Me	H	H	45	24
5	OMe	H	OMe	95	0
6	OH	H	H	14	5
7	H	OH	H	20	8
8	NO_2	H	H	10	2

Bromovinyl aldehyde **136** (1 mmol), amine (1 mmol), $Pd_2(dba)_3$ (3 mol %), K_2CO_3 (1.4 mmol), and (*R*)-(+)-BINAP (4 mol %) at 90 °C for 3–4 h under an argon atmosphere.

of their use in synthesizing organic compounds of different types. Ever since the discovery of the halovinyl aldehydes, the chemical world has witnessed a remarkable progress in their use as synthetic tools for various organic syntheses. Many new methodologies are continuously developing in this field and our laboratory is contributing to those. New and interesting achievements in halovinyl aldehyde chemistry can be expected in the near future.

Acknowledgements

We thank the DRDO, the DST, the CSIR (New Delhi), and the Indian Institute of Technology for financial assistance.

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