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RECENT DEVELOPMENTS IN THE SYNTHESIS OF HETEROCYCLES BY THE APPLICATION OF PALLADIUM-CATALYZED INTRAMOLECULAR HECK REACTION

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Abstract: Palladium-mediated cyclization reaction has been recognized as one of the simplest and useful tool for the regio- as well as stereoselective synthesis of carbo- and heterocyclic compounds. In the multi-step synthesis of natural products Heck reaction is frequently used as one of the most important steps. In this review article, I have summarized recent developments in the construction of heterocyclic rings in various ways under palladium-catalyzed intra-molecular cyclization.

Contents:

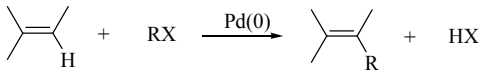
Keywords: Palladium catalyst, fused heterocyclic ring, C-H activation, C-C coupling, annulated heterocycles, domino reaction, Regioselectivity, Stereoselectivity.

1. Introduction:

Heterocyclic moieties are present in natural products[1], pharmaceuticals, organic materials, and numerous functional molecules. Therefore, ongoing interest for developing new versatile and efficient syntheses of heterocycles is expected. Many of the strategies involve the formation of either carbon-carbon or carbon-heteroatom bond from the corresponding acyclic precursors. Several Carbon-Carbon bond forming reaction have been discovered and their application in organic chemistry have been well documented in literature. The most important ones including the Aldol reaction[2,3], Reformatsky reaction,[4] Claisen rearrangement,[5] Friedel-Crafts reaction[6,7], radical reaction[8] and transition metal mediated reactions.[9] A number of synthetic approaches to the heterocyclic ring structure are available in literature, most of which has been compiled in comprehensive reviews to this field.[10] Recently palladium is probably the most versatile and widely used metal for the

synthesis of heterocycles . Palladium has found such wide utility because it affects an extraordinary number of very different reactions, including many carbon-carbon bond-forming reactions, under relatively mild reaction conditions. Furthermore, palladium can usually be used in only catalytic amounts and tolerates a wide variety of functional groups, thus avoiding protection group chemistry.[11] Most palladium-based methodology proceeds stereo- and regioselectively in excellent yields. Palladium catalyzed arylation or vinylation protocols to prepare carbo- and hetero cyclic compounds continue to be wide spread. Palladium-catalyzed processes have proven to be a powerful and useful tool for the synthesis of hetero- and carbo-cyclic compounds. These advantages have attracted unusual growth of organo-palladium chemistry during the last two decades. This has made palladium catalysts an extremely active and reliable reagent for the synthesis of heterocyclic compounds. The palladium-based methodologies have been proven as an efficient tool for the synthesis of highly functionalized furan, indole, thiophene, benzoxazole and thiazole derivatives[12-16] commonly employing $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$ etc. as catalyst.

The palladium-catalyzed coupling of aryl or alkenyl halides or triflates with alkenes to provide more highly substituted alkenes is generally known as the Heck reaction (**Scheme 1**).[17] More than three decades ago, Mozoroki[18] and Heck[17b] independently discovered this methodology of arylation and vinylation of olefins. The reaction is catalyzed by palladium(0) complexes with the tertiary phosphine ligands. The catalyst is either added directly *i.e.* tetrakistriphenylphosphine palladium(0) or more commonly, the catalyst is produced *in situ* by the reductions of the palladium-salts in the presence of a suitable phosphine-ligand. This methodology is attractive from the synthetic point of view due to high chemoselectivity and mild reaction conditions associated with low toxicity and cost of the reagents.[19]



R = aryl, vinyl; X = I, Br, COCl, OTf, etc

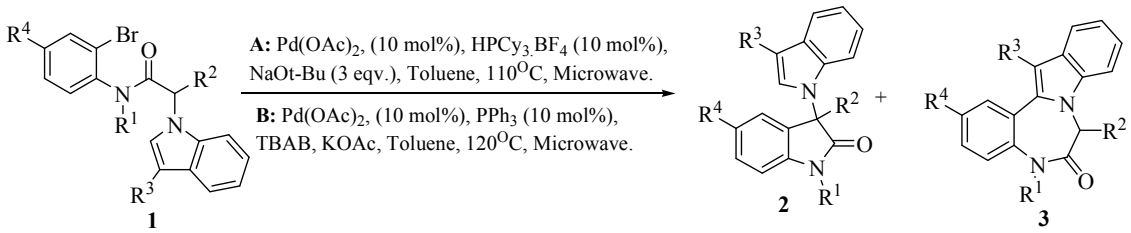
Scheme 1

Though a wealth of books[20] and reviews[21,22] covering particular and limited aspects of organopalladium chemistry and Heck reaction are available still there are many unaccounted reports on this topic. Moreover, during the last two to three years it has been used in the multi-step synthesis of natural products. The main purpose of this review is to show the ongoing importance of palladium-catalyzed cyclization reactions in the field of heterocycle syntheses.

2. Synthesis of Nitrogen Heterocycles:

2. 1. Synthesis of indole alkaloid:

Psychotrimine, an indole alkaloid, isolated in 2004 from the leaves of the plant Psychotria rostrata[23] was synthesized[24] by Marsden *et. al.* by palladium – catalyzed intramolecular arylation of protected α-amino and α-hydroxy acid enolates as the key step. When 2-(N-indolyl)al-kanamides **1** was subjected to palladium catalyzed intramolecular cyclization, the desired products 3- (N-indolyl)oxindole **2** was formed along with a small amount of indolo-fused benzodiazepine **3**. It appears that compound **2** arises from enolate arylation and compound **3** arises from direct C-H arylation. The product ratios were found to depend on the reaction conditions (**Scheme 2**).

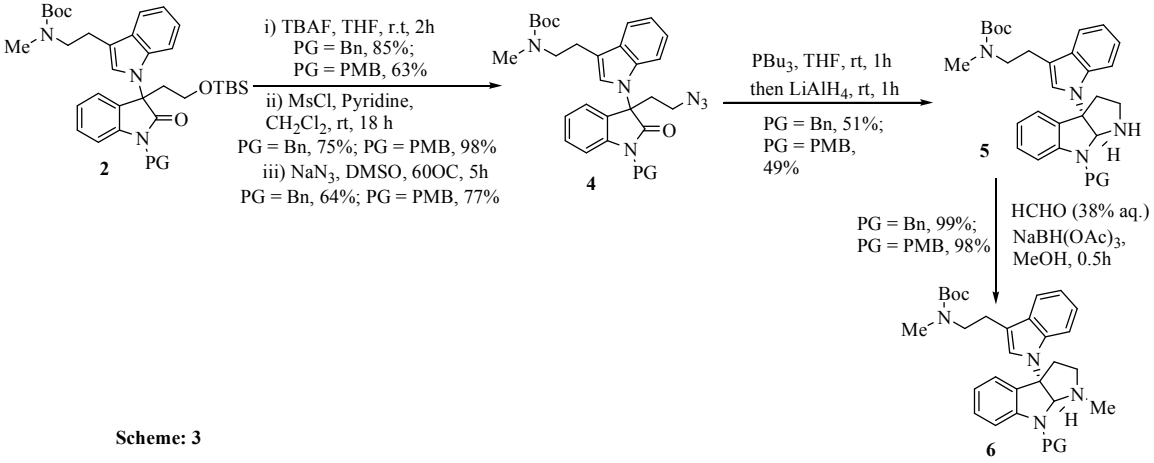


1 **2** **3**

Entry	Substrate	R^1	R^2	R^3	R^4	Conditions	Yield of 2 (%)	Yield of 3 (%)
1	**1a**	Me	Et	H	H	A	65	3
2	**1a**	Me	Et	H	H	B	0	87
3	**1b**	Me	H	H	F	B	0	71
4	**1c**	SEM	Et	H	H	B	0	43
5	**1d**	SEM	H	H	H	B	0	36
6	**1e**	Bn	Et	H	H	A	0	60
7	**1f**	Me	$(CH_2)_2OTBS$	H	H	A	0	57
8	**1g**	Me	$(CH_2)_2OTBS$	$(CH_2)_2NMe(Boc)$	H	A	41	0

Scheme: 2

The indolo-fused benzodiazepine skeleton is found to be bioactive compound and hepatitis C virus inhibitors such as beclabuvir[25]. Use of a weaker base would disfavour the enolate arylation pathway and they found that use of potassium acetate along with tetrabutylammonium bromide led to 87 % yield of the benzodiazepinone.
Then 3- (N-indolyl)oxindole **2** was used for the synthesis of Psychotrimine skeleton **6** by the following way **(Scheme 3)**.



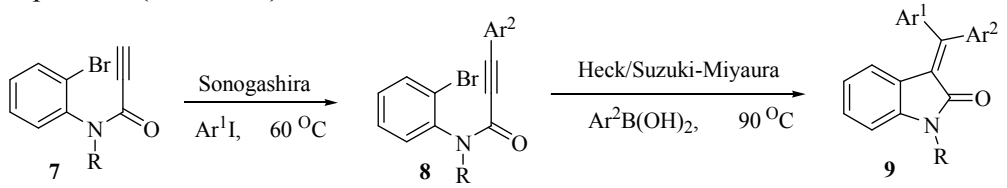
Scheme: 3

2. 2. Synthesis of 3-(diarylmethylene)oxindole:

Seo *et. al.* have developed[26, 27] a rapid and efficient multicomponent tandem reaction for the synthesis of 3-(diarylmethylene)oxindole **9**, which possess biological activities such as antidiabetic[28] and anticancer properties[29]. They combined three palladium-catalyzed reactions (Sonogashira, Heck and Sujuki-Miyaura reactions) to produce 3-(diarylmethylene)oxindole from simple propiolamides, aryl iodides and arylboronic acids.

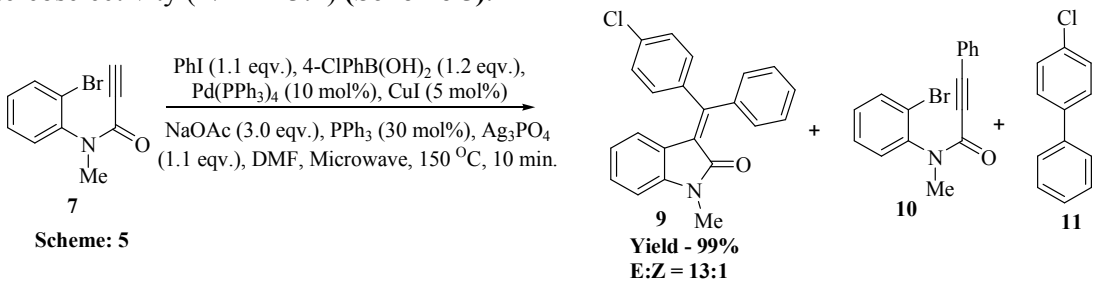
First in 2013 they reported[26] an efficient one pot synthetic method of 3-(diarylmethylene)oxindole **9** by combining a Sonogashira reaction of the electron deficient

propiolamide **7** and a Heck and Sujuki-Miyaura domino reactions of the Sonogashira adduct **8**. To achieve one pot synthesis first Sonogashira coupling was performed at 60^{O}C to form the adduct **8**, then arylboronic acid was added at elevated temperature (90^{O}C temp.) to form the compound **9 (Scheme 4)**.



Scheme: 4

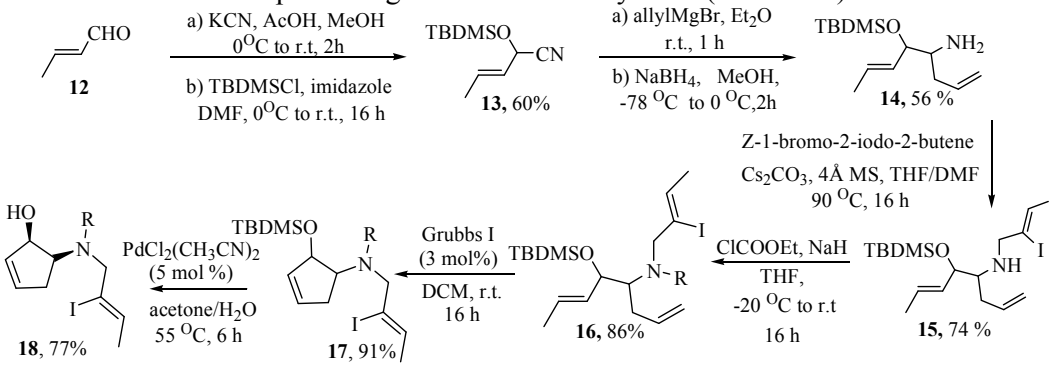
Recently they reported[27] the previous one-pot two operation into a three component tandem reaction under microwave assisted condition. For this first they added three substrate (propiolamide **7,** phenyl iodide and 4-chlorophenylboronic acid) to the reaction mixture and the resulting mixture was exposed to one-pot reaction condition with sequential temperature and time control. At first stage reaction was run for 1.5 h at 60 ^{O}C followed by 90 ^{O}C for 24 h. Under this conditions, the desired product 3-(diarylmethylene)oxindole **9** was formed in good yield along with a small amount of biphenyl **11** (**Scheme 5**). The E/Z stereoselectivity of olefin was moderate (E/Z = 2:1). They optimized the reaction by sequential changing temperature, ligand, additive etc. and found that best results were obtained under microwave irradiation at 150^{O}C for 10 min. this condition afforded **9** in high yield (99%) with high stereoselectivity (E/Z = 13:1) **(Scheme 5)**.



Scheme: 5

2. 3. Synthesis of bicyclic core structure of corialstonidine:

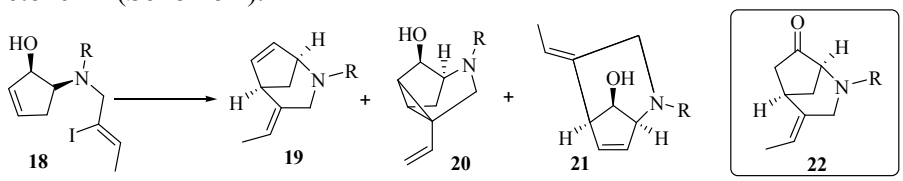
Savic *et. al*. reported[30] the synthesis of bicyclic core structure of corialstonidine **22** by the application of intramolecular Heck reaction. For this study they prepared the cyclisation precursor **18** in several steps starting form crotonaldehyde **12** (**Scheme 6**).



Scheme: 6 , Synthesis of cyclisation precursor **18**

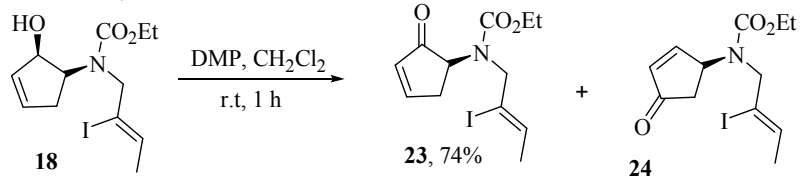
When the intramolecular Heck reaction was performed under standard conditions or alternative conditions [**18** (0.28 mmol), $Pd(OAc)_2$ (0.028 mmol), PPh_3 (0.056 mmol), toluene (29 mL), 110^{o}C, 16 h, using base: Et_3N (0.56 mmol or Ag_2CO_3 (0.84 mmol); or Et_3N (1.68 mmol), K_3PO_4 (0.84 mmol), PhOH (0.056 mmol)], the reaction afforded a separable mixture

of three products (**19–21**) in a combined yield of 71%, without any trace amount of desired bicyclic ketone **22** (**Scheme 7**).

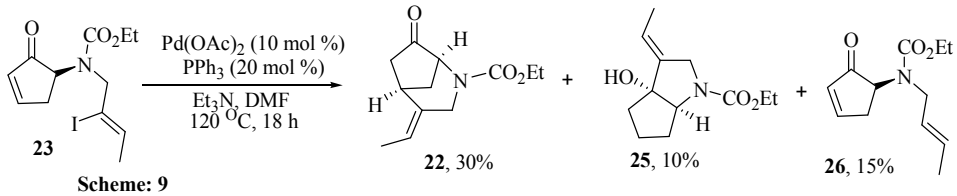


Scheme: 7

Then they opted an alternative route and perform the intramolecular reductive Heck reaction on conjugated ketone **23**, which was prepared by the oxidation of alcohol **18** with Dess–Martin periodinane (**Scheme 8**). Finally reductive Heck reaction was performed using $Pd(OAc)_2$ (10 mol %) as catalyst; PPh_3 (20 mol %) as ligand; Et_3N as base in DMF at 120 ^oC for 18 h the desired ketone **22** was isolated in 30% yield along with two byproducts **25** (10%) and **26** (15%) (**Scheme 9**).



Scheme: 8

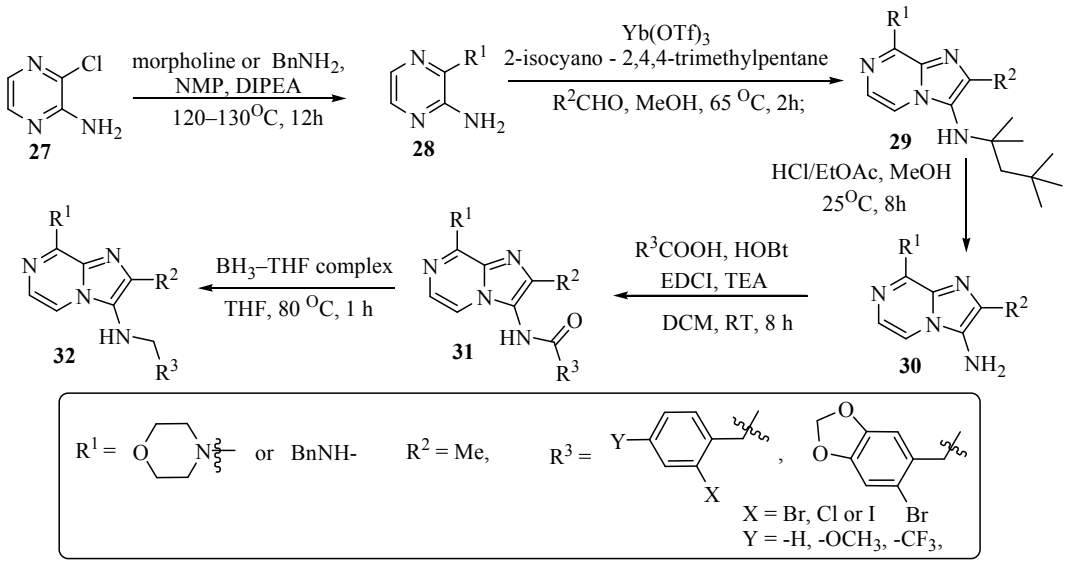


Scheme: 9

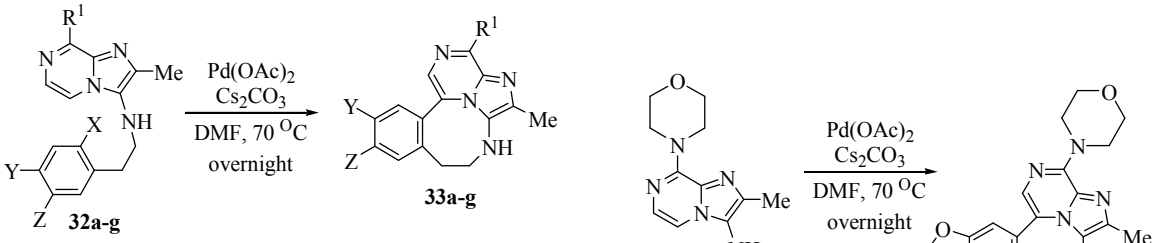
2. 4. Synthesis of diazocine derivative:

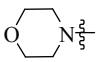
(Z)-4,5-dihydro-3H-[1,3]diazocine system have been synthesized[31] by a Pd-catalyzed cyclization C-H arylation of multi-substituted 8-aminoimidazo[1,2-a]pyrazines **32**. The cyclization precursor for this investigation was prepared via modified Groebke–Blackburn–Bienaymé multicomponent reaction (MCR)[32], starting form pyrazine with the following sequence of reaction (**Scheme 10**).

The cyclization reaction then performed and best result obtained by using $Pd(OAc)_2$ as catalyst, Cs_2CO_3 as base, DMF as solvent at 70^OC for overnight. This optimization was performed by sequential changing the catalyst, base and solvent and they found that a large excess of DMF is one of the key factor for the cyclization. With bromobenzene side chains gave diazocine products with 22–57% yields. The iodo-derivative did not show better cyclization yield, and the chloro-analogue failed to give cyclization. The results are summarize in **scheme 11**.



Scheme: 10



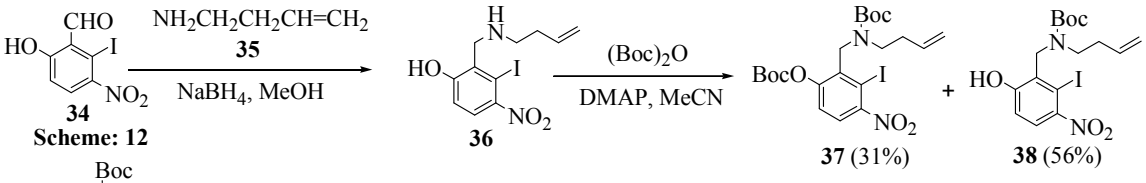
Entry	R^1	X	Y	Z	Yield (%)
1, 32a		Br	H	H	**33a**, 46
2, 32b		I	H	H	**33b**, 30
3, 32c		Br	CF_3	H	**33c**, 32
4, 32d		Br	H	F	**33d**, 57
5, 32e	BnNH-	Br	H	H	**33e**, 27
6, 32f		Br	F	H	**33f,** 22
7, 32g		Br	H	OCH_3	**33g**, 25

Scheme: 11

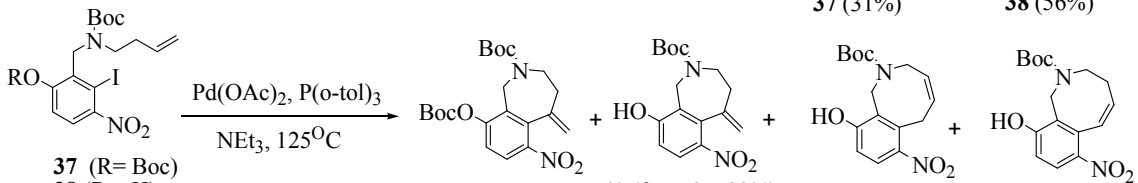
2. 5. Synthesis of cimitrypazepine and fargesine:

Total syntheses of naturally occurring azepino[5,4,3-cd]indoles (**43, 44)** , tricyclic alkaloids cimitrypazepine **45** and fargesine **47** has been reported[33] by Soderberg *et. al*. using intramolecular Heck reaction and palladium catalyzed reductive N - heterocyclization as the key steps. The starting materials **37, 38** for the Heck reaction has been synthesized by reductive amination of **34** using 4-amino-1-butene **35** to form compound **36**, followed by hydroxy and amino group protection to give a mixture of compound **37** (di-protected compound) and **38** (only N-protected compound) (**Scheme 12**).

When intramolecular Heck reactions were performed on both **37** and **38** four different products were obtained. Two 2-benzazepines, the N-Boc protected compound **39** and the di-O, N-Boc protected compound **40**, were obtained as the major products, along with a minor amounts of two 2-benzazocines (**41** and **42**) differing in the position of the unsaturation in the eight-membered ring were also obtained. The compounds **41** and **42** had lost the O-Boc group during the reaction (**Scheme 13**).

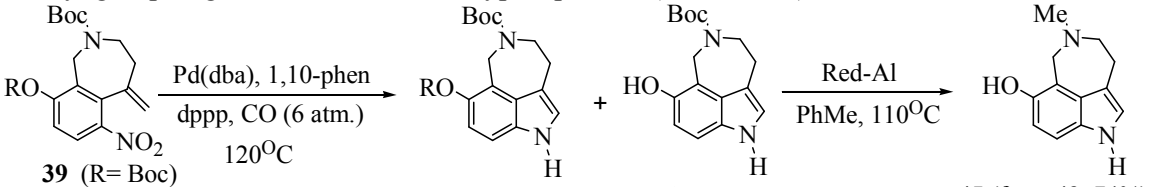


Scheme: 12



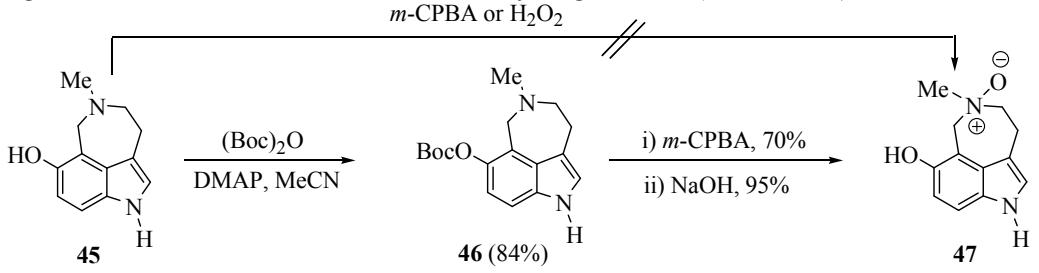
Scheme: 13

Reductive N-heterocyclization of compound **39** or **40** using a bis(dibenzylideneacetone)palladium-1,3-bis(diphenylphosphino) propane-1,10-phenanthroline catalyst system in the presence of carbon monoxide (pCO = 6 atm at 120^{O}C) in N,N-dimethylformamide, afforded the di-N,O-protected azepino[5,4,3-cd]indole **43** along with N-protected analog **44** in 79% total yield. Finally, the compound **43** or **44** upon treatment with sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al) in toluene at refluxing condition, the O-Boc group was removed and the N-Boc group was reduced to a methyl group to give the alkaloid cimitrypazepine **45** (**Scheme 14**).



Scheme: 14

Finally they reported the synthesis of fargesine **47** by oxidation of the azepine–nitrogen of cimitrypazepine **45** using *m*-chloroperbenzoic acid (*m*-CPBA) after Boc protecting the hydroxyl group followed by deprotection by sodium hydroxide. Direct oxidation of **45** using *m*-CPBA in dichloromethane or hydrogen peroxide–ammonium hydrogen carbonate in water did not furnish any fargesine **47** (**Scheme 15**).[33]

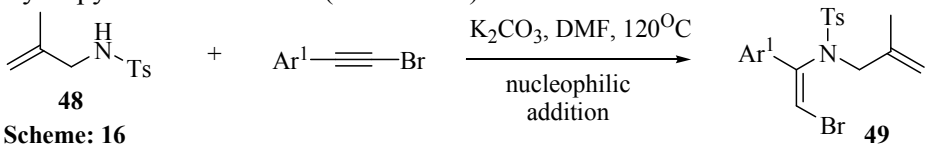


Scheme: 15

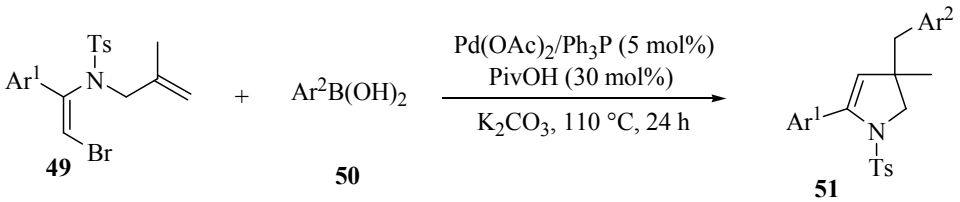
2. 6. Synthesis of 2,3-dihydropyrrole derivative:

The 2,3-dihydropyrrole framework **51** is widely found in natural products,[34] synthetic building blocks,[35] materials,[36] antiproliferative agents,[37] and kinesin spindle protein inhibitors[38] was synthesized[39] by the nucleophilic addition of sulfonamides to alkynyl bromides, followed by a palladium-catalyzed tandem Heck and Suzuki carbon–carbon cross-coupling reaction. The starting material *N*-[(*Z*)-2-Bromo-1-phenylvinyl]-4-methyl-*N*-(2-

methylprop-2-en-1-yl)benzenesulfonamide **49** for this investigation was prepared by addition of 4-methyl-*N*-(2-methylprop-2-en-1-yl)benzenesulfonamide **48** to (bromoethynyl)benzene,[40] in presence of base K_2CO_3, DMF, 120°C (**Scheme 16**). Then reaction of *N*-[(*Z*)-2-Bromo -1 -phenylvinyl]-4-methyl-*N*-(2-methylprop-2-en-1-yl)benzenesulfonamide **49** and (4-methoxyphenyl)boronic acid **50** on the palladium-catalyzed tandem intramolecular Heck/intermolecular Suzuki cross-coupling reaction produce the desired 2,3-dihydropyrrole derivative **51**. The optimization condition for this reaction was found to be mixture of palladium (II) acetate (5 mol%) as catalyst, triphenylphosphine (5 mol%), and potassium carbonate (2 equiv) as base with pivalic acid (30 mol%) as the additive in *N*,*N*-dimethylacetamide at 110 °C for 24 hours and the desired 2,3-dihydropyrrole **51** was obtained in high yield. With the optimized conditions they reported the synthesis of a variety of 2, 3-dihydropyrroles derivatives (**Scheme 17**).



Scheme: 16

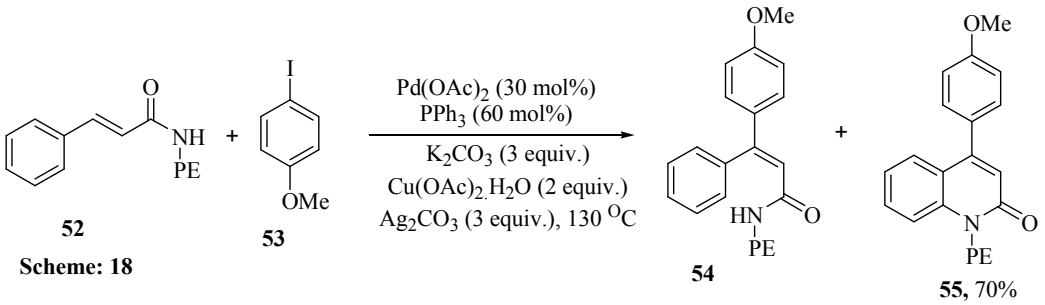


Entry	Bromoalkene	Arylboronic acid	Product	Yieldb (%)
1	**49a**, Ar^1 = Ph	**50a**, Ar^2 = Ph	**51aa**	60
2	**49a**, Ar^1 = Ph	**50b**, Ar^2 = 4-$MeOC_6H_4$	**51ab**	66
3	**49a**, Ar^1 = Ph	**50c**, Ar^2 = 4-ClC_6H_4	**51ac**	52
4	**49a**, Ar^1 = Ph	**50f,** Ar^2 = 2-thienyl	**51af**	57
5	**49b**, Ar^1 = 4-$MeOC_6H_4$	**50d**, Ar^2 = 3-FC_6H_4	**51bd**	62
6	**49b**, Ar^1 = 4-$MeOC_6H_4$	**50e**, Ar^2 = 4-MeC_6H_4	**51be**	54
7	**49b**, Ar^1 = 4-$MeOC_6H_4$	**50a**, Ar^2 = Ph	**51ba**	62
8	**49b**, Ar^1 = 4-$MeOC_6H_4$	**50c**, Ar^2 = 4-ClC_6H_4	**51bc**	55
9	**49c**, Ar^1 = 4-MeC_6H_4	**50a**, Ar^2 = Ph	**51ca**	59

Scheme: 17

2. 7. Synthesis of 4-aryl-2-quinolinone:

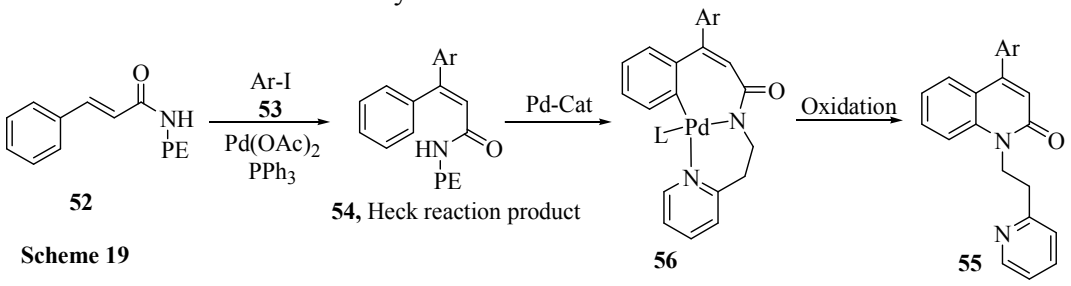
2-Quinolinones are one of the most important heterocyclic compounds because of their anticancer,[41] antimicrobial,[42] antivirus[43] and as oxytocin antagonist[44] activities. Further, many natural products contain 4-aryl-2-quinolinone unit **55**.[45] A convenient approach[46] for the synthesis of 4-aryl-2-quinolinone bearing several substituent on both rings involves a Pd(II)-catalyzed cascade Heck/intramolecular C(sp^2)-H amidation reaction. The reaction of N- (2-(pyridin-2-yl)ethyl)cinnamamide **52** and 1-iodo-4-methoxybenzene **53** was carried out under optimal conditions for the reaction to give the product **55** up to 70% yield. The optimal reaction condition was: $Pd(OAc)_2$ (30 mol%) as catalyst, PPh_3 (60 mol%) as ligand, K_2CO_3 (3 equiv.) as base, $Cu(OAc)_2.H_2O$ (2 equiv.) and Ag_2CO_3 (3 equiv.) as oxidants, toluene as solvent at 130^{O}C (**Scheme 18**). It was found that oxidants had a significant role on the yields of the reaction.



52 **53** **54** **55,** 70%

Scheme: 18

Possible mechanism for the reaction is presented in **Scheme 19**. Initially, Heck reaction takes place between cinnamamides **52** and aryl iodides **53**. Then, C(sp2)-H is activated via the intermediate **56** occurs, and intermediate **56** then undergoes an intramolecular oxidation cyclization to give the final product 4-aryl-2-quinolinone **55**. They introduce 2-(pyridin-2-yl)ethanamine group as orientation group of C(sp2)-H activation to promote intramolecular oxidation cyclization.



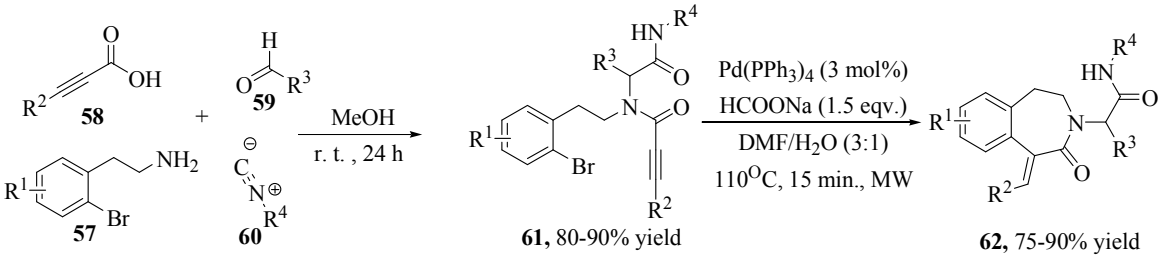
52 **54,** Heck reaction product **56** **55**

Scheme 19

2. 8. Synthesis of 3-benzazepine framework:

Peshkov *et. al*. recently reported[47] the synthesis of 3-benzazepine framework **62** by two step sequence involving Ugi reaction followed by reductive Heck cyclization. Ugi reaction of 3-substituted propiolic acids **58** and 2- bromophenethylamines **57** with various aldehydes **59** and isocyanides **60** produce propargylamide precursors **61** in 80-90% yield. Treatment of propargylamide precursors **61** with $Pd(PPh_3)_4$ (3 mol%) and HCOONa (1.5 eqv.) in DMF/H_2O (3:1) at about 110^{O}C for 15 min. under microwave irradiation produce 3-benzazepines **62** in good to high yield (**Scheme: 20**).

They also reported that ketone as carbonyl component gave only 35% yield of Ugi product even at elevated reaction temperature of 70^{O}C for 72 h. But Heck cyclization afford good yield (56%) of 3-benzazepine **62**. Further, they also reported that, 2-bromophenethylamine give better yield than the iodo-analog in the Ugi-step, but the 2-iodophenethylamine-derived propargylamide is somewhat better substrate than 2-bromophenethylamine-derived propargylamide in the reductive Heck ring-closure.



58 **59** **57** **60** **61,** 80-90% yield **62,** 75-90% yield

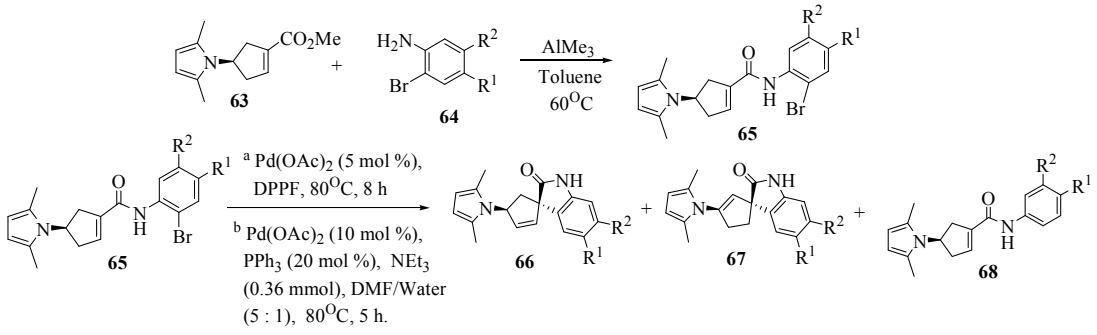
R^1 = H; 4,5-$(OMe)_2$ R^2 = Me, Et, Hexyl, Phenyl

R^3 = Pr, Phenyl, ^{i}Bu R^4 = Bn, ^{t}Bu, 2-Naphthyl

Scheme: 20

2. 9. Synthesis of cyclopentene-spirooxindole derivative:

Many natural products, contain spirooxiindoles[48,49] and are important synthetic targets due to their biological activity, applications for pharmaceutical lead discovery[50] and medicinal chemistry projects. Recently, Savmarker and Larhed *et. al*.[51] reported a highly diastereoselective synthesis of cyclopentene-spirooxindole derivative by the intramolecular Heck-Mizoroki reaction using aryl bromides as precursors. The precursors **65** for this investigation were prepared by the reaction between 2-bromoanilines **64** and the pyrrole-protected esters **63** using stoichiometric amounts of $AlMe_3$. When the ring-closing Heck−Mizoroki reaction was performed under various reaction conditions using $Pd(OAc)_2$ as catalyst and in presence of various phosphine ligand [triphenylphosphine, tri(otolyl)phosphine, tri-tert-butylphosphine tetrafluoroborate, Xphos (2-bicyclohexylphosphino–2', 4', 6' -triisopropylbiphenyl), JohnPhos (2-(di-tert butylphosphino)biphenyl)] to form the desired product **66** along with double-bond-migrated side products **67**. However the ligand DPPF [1,1′ -bis(diphenylphosphino)ferrocene)] were found to strongly suppress the double-bond-migrated product and produce only the normal product and the optimum condition was found to be $Pd(OAc)_2$ as catalyst (5 mol %) in presence of ligand DPPF at $80^{O}C$ for 8 h. They reported that presence of water produce some dehalogenated product **68 (Scheme 21)**.



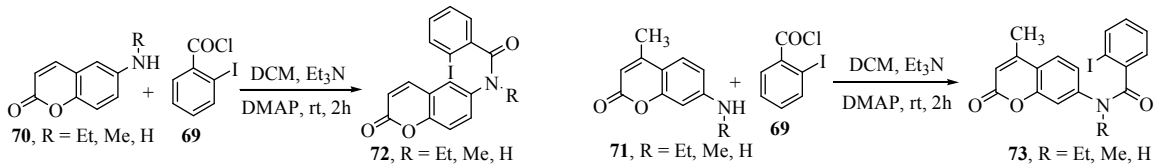
Entry	R^1	R^2	63 (%)	Yield (%) [a]	66 :67 : 68[a]	Yield (%) [b]	66 : 67 : 68[b]
1	H	H	82	76	98 : 2 : 0	74	96 : 2 : 2
2	OCH_3	H	84	81	99 : 1 : 0	74	96 : 2 : 2
3	CH_3	H	82	79	99 : 1 : 0	76	96 : 2 : 2
4	F	H	78	80	99 : 1 : 0	75	95 : 4 : 1
5	Cl	H	78	82	99 : 1 : 0	78	97 : 1 : 2
6	CF_3	H	77	77	99 : 1 : 0	72	95 : 4 : 1
7	CN	H	80	80	98 : 2 : 0	72	93 : 5 : 2
8	H	CH_3	80	77	99 : 1 : 0	77	96 : 2 : 2
9	H	OCH_3	73	80	93 : 7 : 0	75	82 : 8 : 10
10	H	CF_3	77	78	96 : 4 : 0	70	87 : 12 : 1
11	H	COOH	56	70	99 : 1 : 0	70	97 : 1 : 2

Scheme: 21

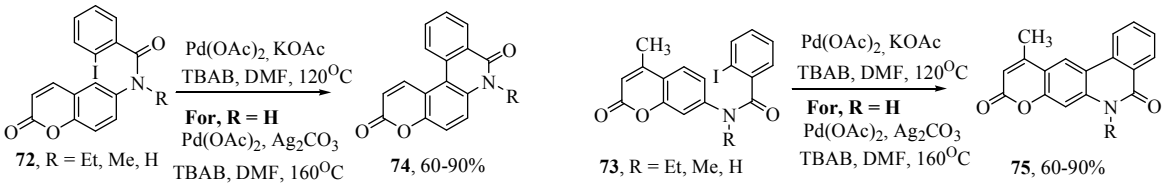
2. 10. Arylation of Secondary and Tertiary amide:

We developed[52] a synthetic protocol for the arylation of secondary and N-alkylated amide Heck precursors by the implementation of the Pd-catalyzed intramolecular Heck reaction strategies. The synthesis of the amide starting materials **72** and **73** for this investigation were synthesized by the reaction of acid chloride **69** (prepared from the 2-iodo benzoic acid with the oxalyl chloride in dichloromethane solution in the presence of a catalytic amount of DMF) with **70** and/or **71** in DCM and triethylamine in the presence of a catalytic amount of DMAP at rt for 2h (**Scheme 22**). When the Heck reaction was performed with **72** and **73** as

amide precursor in the presence of $Pd(OAc)_2$ as the catalyst and anhydrous potassium acetate as a base, tetrabutylammonium bromide (TBAB) as additive in dry DMF under a nitrogen atmosphere for 10 h, the cyclized amide product piperidin-2-one derivatives **74** and **75** was obtained in 60-90% yield (**Scheme 23**).



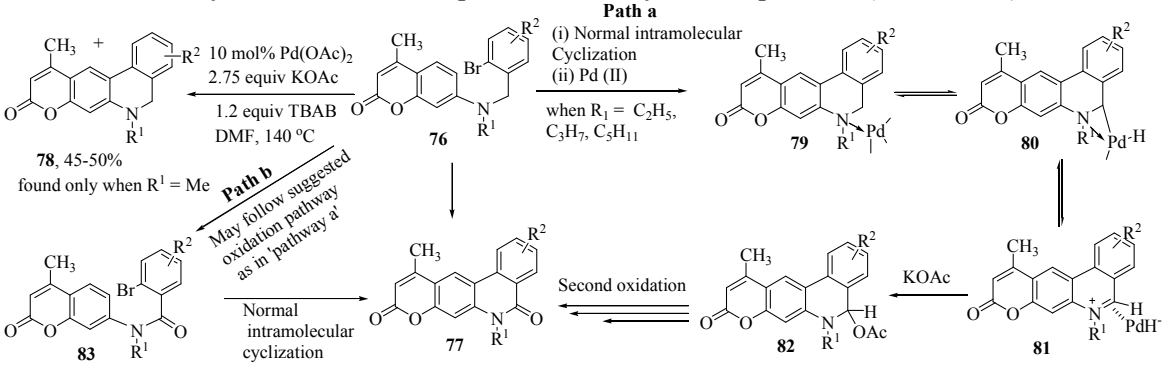
Scheme: 22



Scheme: 23

2. 11. Synthesis of pyridocoumarin derivative by unusual oxidation:

Recently, we have developed a new synthetic protocol[53] through the implementation of the palladium-mediated benzylic C-H activation followed by tethered intramolecular arylation strategy to give linearly fused and unusually oxidized pyridocoumarin derivatives. When 7-[(*N*-alkyl)(2-bromobenzyl)amino]-4-methylcoumarins **76** were subjected to typical Heck type reaction protocol using $Pd(OAc)_2$ as catalyst, KOAc as base, TBAB as additive in DMF at 140°C, in most of the cases [when, R^1 = -C_2H_5, C_3H_7, C_5H_{11}], the benzylic methylene was oxidized to carbonyl group in the expected biaryl coupling product **77**. The substrates only with Me as *N*-protecting group [when, R^1 = -CH_3], gave usual unoxidised products **78** in 45-50 % yields. The unusual reaction is supposed to preceed by the initial coordination of the nitrogen lone pair to Pd (0) followed by a metal insertion into the adjacent carbon-hydrogen bond to form **80**[54] which remain in a rapid equilibrium with the iminium ion **81**.[55] The intermediate **82** may be formed from **81** by the reaction of KOAc in the reaction medium. A second oxidation followed by hydrolysis produced the final oxidized product **77**. Alternatively, in a second pathway first oxidation to produce 83 followed by the normal intramolecular arylation to afford the products **77** may also be possible (**Scheme 24**).



Scheme 24

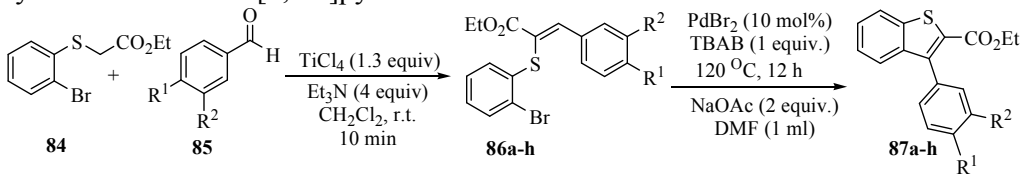
The presence of an electron withdrawing group (-$COCH_3$) on the nitrogen and with unsubstituted nitrogen prohibits the reaction leaving almost all the starting materials unchanged. The reaction only occurs with electron-donating groups (except methyl) on nitrogen. This may be due to; electron donating groups on nitrogen accelerate initial coordination of the nitrogen lone pair to Pd (0).

3. Synthesis of Sulphur Heterocycles:

3. 1. Synthesis of Benzo[*b*]thiophenes:

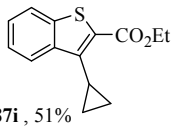
Benzo[*b*]thiophenes[56] are found to be biologically important heterocyclic compounds, are synthesized[57] by Gong *et. al.* by the implementation of intramolecular Mizoroki–Heck reaction of 2-thiosubstituted acrylates **86**, which in turn prepared by the Aldol condensation using titanium tetrachloride. Aldol condensation of ethyl (2-bromophenyl)thioacetate **84** with different aldehydes **85** using $TiCl_4$ with triethylamine in dichloromethane produce the Heck precursor acrylate **86a** in a good yield (80%) within 10 min. Then intramolecular Heck reaction was performed under Jeffery conditions[58] and optimized condition was found to be palladium(II) bromide as catalyst, sodium acetate as base, DMF as solvent and TBAB (tetrabutylammonium bromide) as additive at 120 °C for 12 h to produce the desired 3-Substituted Benzo[*b*]thiophene- 2-carboxylates **87** in reasonable good yield (**Scheme 25**).

They reported that cyclization proceeded well when acrylates **86** contain an electron-donating or electron-withdrawing group on the phenyl ring to afford **87a**–**h**. Furthermore, acrylates having alkyl groups under the conditions gave the corresponding benzo[*b*]thiophenes **87i** and **87j** except for ethyl (2-arylthio)crotonate **87k**. Unfortunately, acrylates involving heterocycles gave poor yields **(87l)** or no products **(87m)**. Attempts to synthesize the thieno[2,3-*b*]pyridine failed.

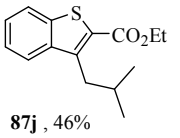


84 **85** **86a-h** **87a-h**

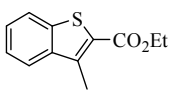
Entry	R_1	R_2	Yield of 71 (%)	Yield of 72 (%)
a	H	H	80	75
b	CF_3	H	88	53
c	CN	H	76	58
d	NO_2	H	81	53
e	H	F	86	62
f	H	Cl	85	70
g	CO_2Me	H	88	73
h	OMe	H	85	56



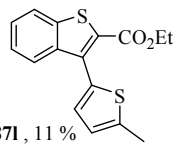
87i , 51%



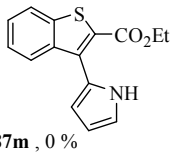
87j , 46%



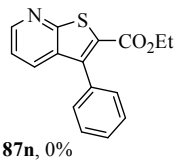
87k , 0 %



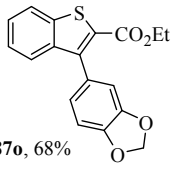
87l , 11 %



87m , 0 %



87n, 0%



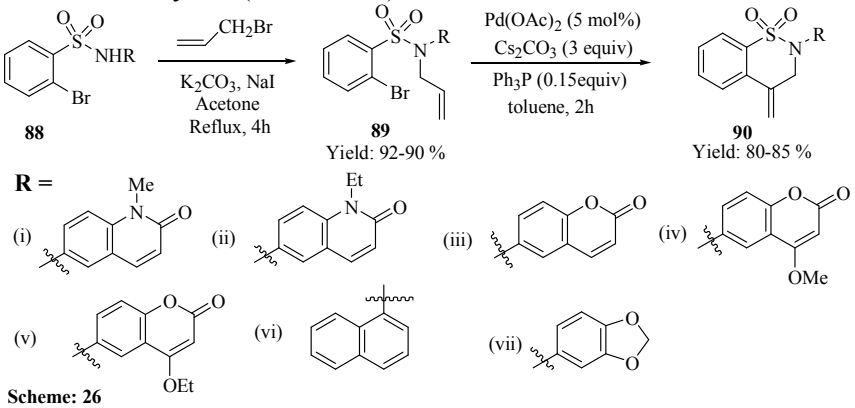
87o, 68%

Scheme: 25

3. 2. Synthesis of Sultams:

Sultams have been widely used in agricultural, medicinal fields and pharmaceutical due to their diverse and enormous biological activities.[59] Recently Debnath *et. al*. reported[60] an efficient method for the synthesis benzosultams via Pd-catalyzed intramolecular Heck cyclization. The starting materials **89** for the intramolecular Heck cyclization were prepared by the allylation of compounds **88** with allyl bromide, in presence of base K_2CO_3, and a

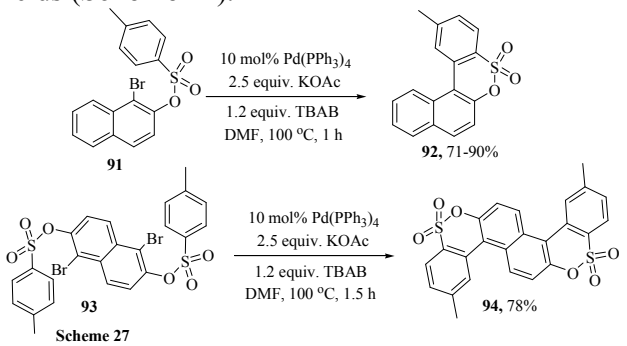
catalytic amount of NaI in refluxing acetone for 4 hours. When intramolecular Heck reaction was performed under optimized reaction conditions using $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (3 equiv), Ph_3P (0.15equiv) in toluene at refluxing condition for 2 hours compound sultams **90** was obtained in excellent yield (**Scheme 26**).



Scheme: 26

3. 3. Synthesis of Sultones:

Recently, synthesis of polycyclic sultones[61] has developed by Majumdar *et. al*. *via* ligand-free Pd-catalyzed intramolecular Heck coupling reaction. When the intramolecular Heck coupling reaction was carried out on the substrate **91** using the Jeffery's two phase protocol[58] at 100°C for 1 h under nitrogen atmosphere, the starting materials underwent total decomposition. But under the catalytic systems using $Pd(PPh_3)_4$ as catalyst, KOAc as base, TBAB as additive, in DMF, at 100 °C the substituted aromatic sultones **92** and **94** were obtained in 71-90% yields (**Scheme 27**).[62]



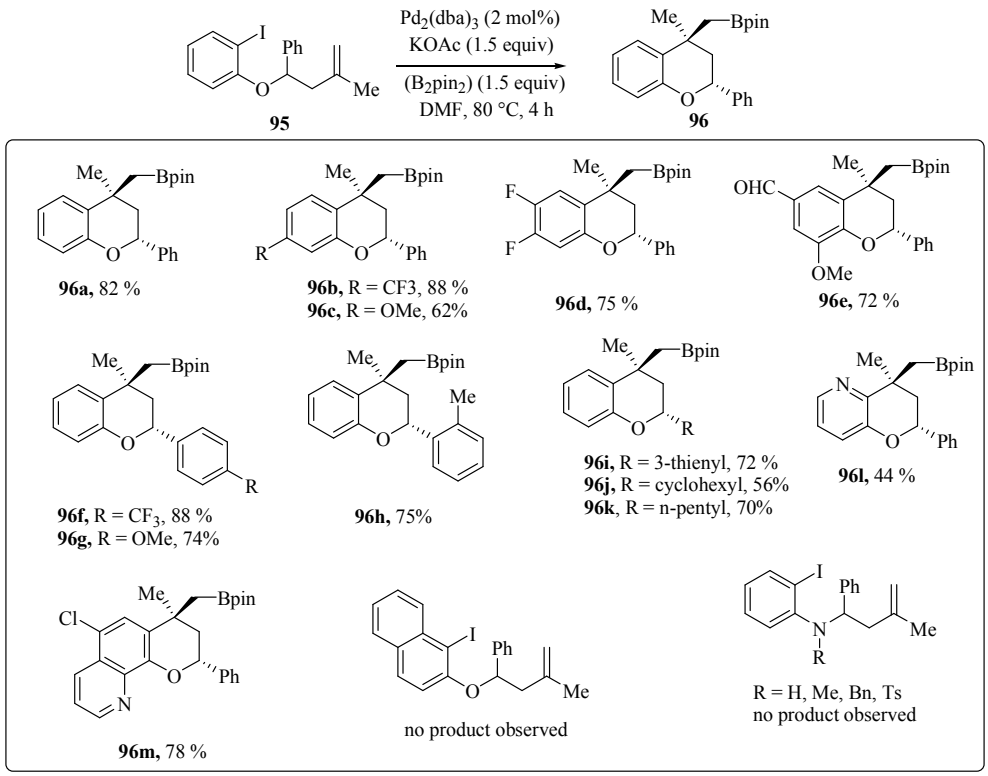
Scheme 27

4. Synthesis of Oxygen Heterocycles:

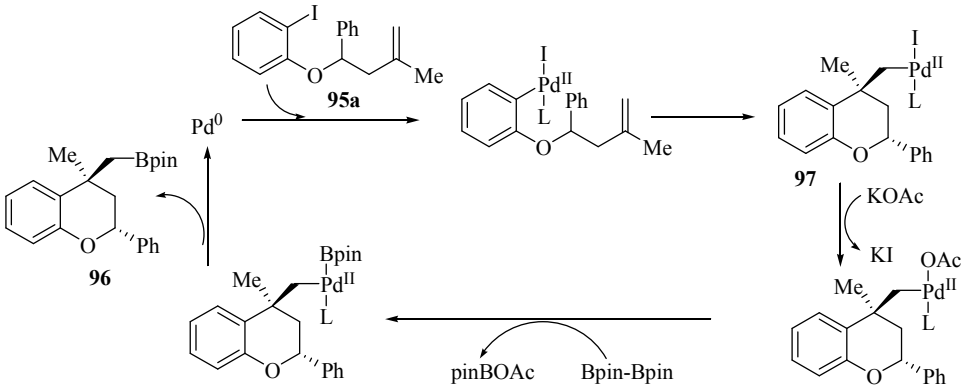
4.1. Synthesis of alkylboronate containing chroman:

Recently Yoon *et. al.* reported[63] a diastereoselective palladium-catalyzed domino Heck/arylborylation of aryl iodides to form an alkylboronate containing a chroman. When the aryl iodide **95** was treated with $Pd_2(dba)_3$ (2 mol%), KOAc (1.5 equiv), and bis(pinacolato)diboron (B_2pin_2) (1.5 equiv) in DMF at 80 °C for 4 hours (optimal conditions) the desired alkylboronate **96** was produced in 82% yield and >20:1 dr. With the optimized conditions they synthesize a number of compounds **96a**–**m** and each compounds produced are exclusively the *trans*-diastereomer (>20:1 dr). Electron-rich aryl iodide **95c** and trifluoromethyl-bearing aryl iodide **95b** cyclized in good yield with prolonged reaction time. Multisubstituted aryl iodides **95d** and **95e** produced the desired products **96d** and **96e** in excellent yield with higher catalyst loading. A thienyl group was also tolerated and afforded the final product **96i** in 73% yield (**Scheme 28**).

They also propose a plausible mechanism for both the Pd-catalyzed domino Heck cascade reactions and Miyaura borylation (**Scheme 29**).



Scheme: 28

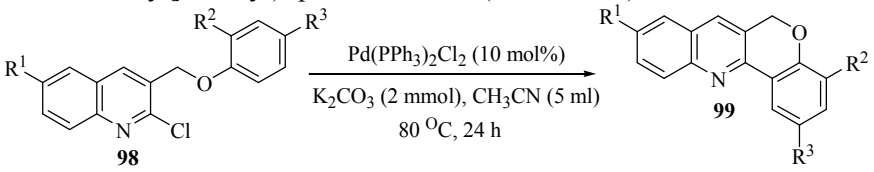


Scheme: 29, Postulated mechanism of diastereoselective Pd-catalyzed domino Heck/arylborylation

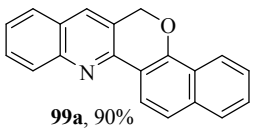
4. 2. Synthesis of 6H-chromeno [4, 3-*b*] quinoline derivatives:

Recently Shiri *et. al*. reported[64] the synthesis of 6H-chromeno [4, 3-*b*] quinoline derivatives **99** by the application of intramolecular Heck reaction. The starting materials[65] 2-chloro-3-(phenoxymethyl) quinolines **98** on treatment with $Pd(PPh_3)_2Cl_2$ (10 mol%) as catalyst, K_2CO_3 as the base under refluxing condition in CH_3CN for 24 h afforded the desired heterocyclic compound 6H-chromeno [4, 3-*b*] quinoline **99** in 70-90% yield (**Scheme 30**). The optimization condition was obtained by sequential change in catalyst, solvent, base. They also reported that both electron-withdrawing and electrondonating groups on the both sides of ether may be effective in this cyclization reaction.

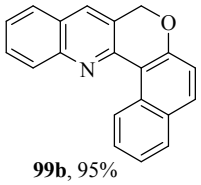
Further they also reported[64] the synthesis of five cycle indolo quinolines **101a** and **101b** starting from 3-[(1Hindol- 1-yl) methyl]-2-chloroquinoline **100a** and 2-chloro-3-[(5- chloro-1H-indol-1-yl] methyl) quinoline **100b** (**Scheme 31**).



Product	R^1	R^2	R^3	Yield (%)
99c	H	H	H	83
99d	H	H	Cl	88
99e	H	H	F	90
99f	H	H	CN	95
99g	H	H	CMe_3	70
99h	H	Me	H	80
99i	Br	H	H	77
99j	Cl	H	CN	80
99k	Me	H	CN	95
99l	Me	H	F	92

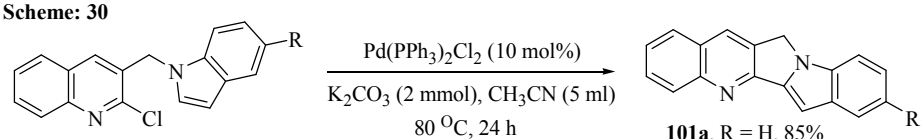


99a, 90%



99b, 95%

Scheme: 30



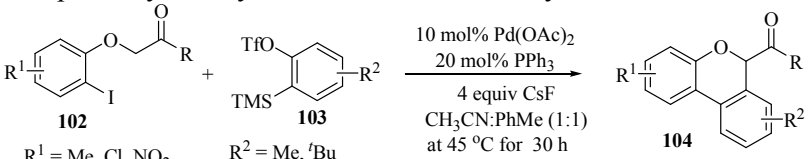
100a, R = H
100b, R = Cl

101a, R = H, 85%
101b, R = Cl, 92%

Scheme: 31

4. 3. Synthesis of 6*H*-benzo[*c*]chromenes:

A mild method for the synthesis of 6*H*-benzo[*c*]chromenes, **104** have developed[66] by Liang and Li, by palladium-catalyzed annulations of 2-(2-iodophenoxy)-1-arylethanones and 1-(2-iodophenoxy)propan-2-one **103** with arynes **103**. This new route utilized $Pd(OAc)_2$ as catalyst, PPh_3 as additive and CsF in a mixed solvent of CH_3CN and PhMe and this allowed the formation of two carbon-carbon bonds in one-pot through an sp3-carbon functionalization process (**Scheme 32**). In some cases two regioisomers were obtained in nearly same ratios. Many substituents, either electron-withdrawing or electron-donating groups, on the 2-iodophenoxy moiety were tolerated uniformly.



R^1 = Me, Cl, NO_2

R^2 = Me, ^{t}Bu

R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4
4-ClC_6H_4

Scheme 32

5. Conclusion:

In this review, I have summarized numerous useful methodologies for the synthesis of nitrogen, sulphur and oxygen heterocycles, which involve palladium-catalyzed cyclizations

or annulations. Most of the reactions proceed under very mild reaction conditions and tolerate a wide variety of functional groups. By this methodology, different heterocycle-fused ring compounds are synthesized which are either themselves biologicallay important or can be converted into natural product moieties *via* synthetic manipulation. This is still an emerging area. I hope this article will attract the synthetic organic community to develop many new synthetic methodologies for the synthesis of application-oriented complex and new heterocyclic compounds.

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