HETEROCYCLES, Vol. 81, No. 9, 2010, pp.1979 - 2026. © The Japan Institute of Heterocyclic Chemistry
Received, 11th May, 2010, Accepted, 25th June, 2010, Published online, 28th June, 2010
DOI: 10.3987/REV-10-675

RECENT ADVANCES IN THE APPLICATION OF THE HECK REACTION IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

Majid M. Heravi* **and Azadeh Fazeli**

Department of Chemistry, School of Science, Azzahra University, Vanak, Tehran, Iran. E- mail: mmh1331@yahoo.com

Abstract – This brief review represents the synthesis of heterocyclic compounds via application of Heck reaction in recent years.

CONTENTS

1. INTRODUCTION

Heterocyclic compounds are worthy of attention for many reasons, chief among which are their biological activities, which many important drugs having one or more hetero atoms in their cyclic structures. Therefore, organic chemists have been making extensive efforts to produce heterocyclic compounds by

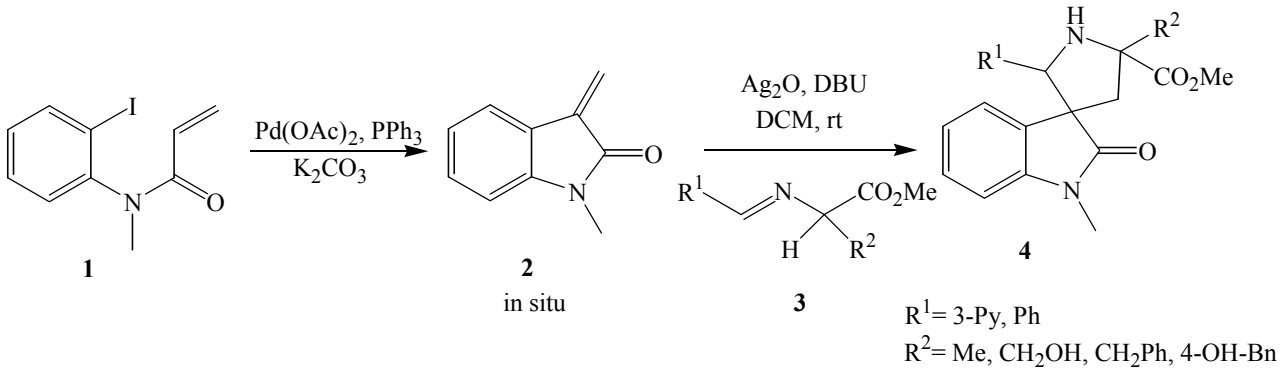
developing new and efficient synthetic transformations. Over the past few decades, palladium-catalyzed coupling reactions have been extensively studied.[1] The impact of the palladium-catalyzed cross-coupling reactions, discovered during the 1970s, has been considerable and continues to be the focus of much organometallic research.[2] Palladium-catalyzed reactions for carbon-carbon bond formation, including Suzuki,[3] Heck,[4] Sonogashira,[1] Tsuji–Trost[5] as well as other reactions, have gained a predominant place in the arsenal of organic chemists. Palladium catalysis usually allows selective reactions with high turnover numbers and turnover frequencies under rather mild conditions. A number of palladium catalysts are commercially available and their reactivity, stability and selectivity can be tuned by ligands (phosphines, carbenes, amines, etc.) and/or additives.[6]

Palladium-catalyzed processes have proven to be a powerful and useful tool for the synthesis of heterocycles. Palladium has found such wide application, since 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 complexity. Most palladium-based methodology proceeds stereo- and regioselectively in excellent yields.[7] The wide utility of palladium in organic synthesis is vivid from the too many number of name reactions where the deep influences of this versatile transition metal enable it in the formation of C-C, C-O, C-N and even C-S bond under relatively mild conditions. The catalytic requirement and excellent tolerance of functional groups avoiding the protection-deprotection chemistry has made possible the use of palladium in the synthesis of small to large ring heterocyclic compounds.[8] Catalytic amount of palladium is required for successful conversion, the catalyzed processes are in fact strongly dependent on other factors e.g. Base, ligand, temperature, additives and solvents.[8] Palladium catalysis has achieved the status of an indispensable tool for both common and state-of-the art organic synthesis. Among basic types of palladium-catalyzed transformation such as, e.g., allylic substitution of cross coupling may seem to be more advanced, none can match Heck chemistry in resourceful versatility, the overwhelming ability to spawn new, hitherto unexpected applications, and resolving challenges.[9] There are many advantages associated with Pd-mediated reactions, particularly ease of scale-up and tolerance to water and/or other functional groups, such as ketones, esters, amides, ethers, or heterocyclic rings, which supply poly functional molecules. The Heck reaction is one of the most important carbon-carbon bond-forming reactions and has been used in a variety of complex natural product syntheses. The interest in the Heck reaction has recently increased significantly. Perhaps the most dramatic progress to date is the development of an enantioselective variant.[10] In the following sections we are trying to cover and update the recent application of Heck reaction in the synthesis of variety of heterocyclic compounds.[10]

2. SYNTHESIS OF AZA HETEROCYCLIC COMPOUNDS

2.1 CYCLIZATION VIA REACTIONS OF ARYL HALIDES

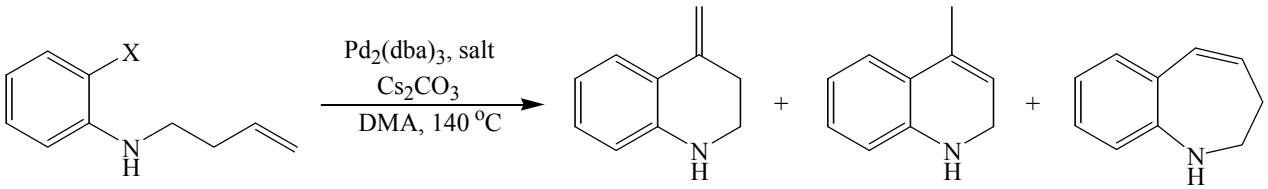
The cascade process utilized a $Pd(OAc)_2$/ PPh_3 precatalyst combination for the intramolecular Heck reaction which affords **2** in situ. The known instability of **2** dictated a search for mild reaction conditions. Using dichloromethane as solvent allowed the reaction to be carried out at room temperature. A subsequent Ag(I) catalyzed imine to azomethine and ylide to cycloaddition cascade led to spiro-oxindoles regiospecifically in good yield with a reaction time of 16–18 h for the total cascade (**Scheme 1**).[11]



1 **2** in situ **3** **4**

Scheme 1

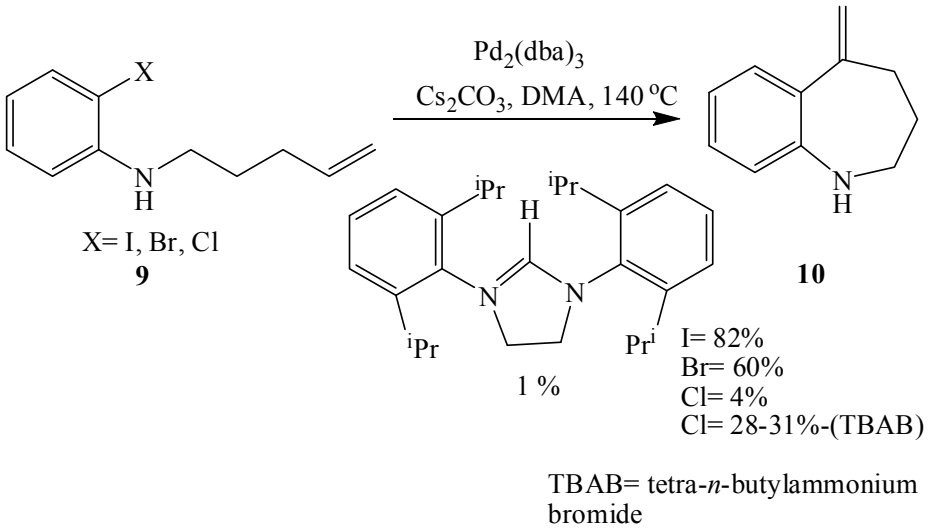
The intramolecular Heck reaction of aromatic amines and ethers using palladium/imidazolium salts was described. The use of tetra-*n*-butylammonium halide salts facilitated the reactivity of aromatic chlorides. An unexpected and novel palladium mediated cyclization was also described leading to the formation of a tricyclic adduct (**Scheme 2, 3, 4**).[12] Further studies on substrate **5** were frustrated by problems of isomer separation; however, Caddick and Kofie have tentatively assigned the product as a mixture of regioisomers **6, 7, 8** (yields, between 20 and 70%) (**Scheme 2**).[12]



5 **6** **7** **8**

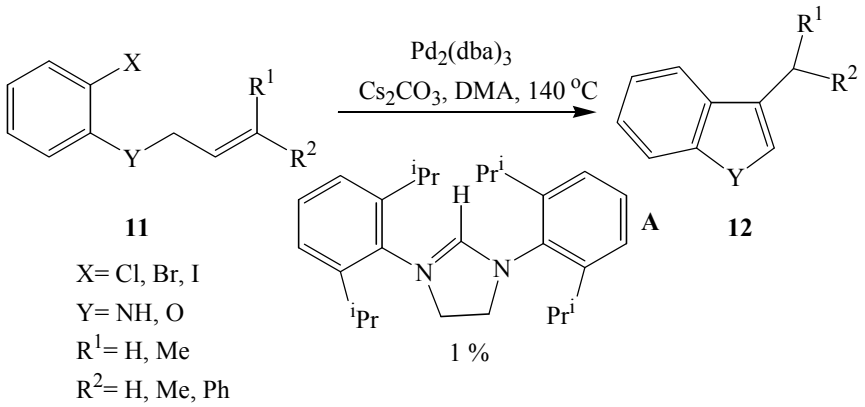
Scheme 2

However, Caddick and Kofie were able to isolate a single product **10** from reaction of substrates **9**. They found that the iodide and bromide **9** proceeded to give the product **10** in good yields (I, 82%, 1 h; Br, 60%, 5 h) but the chloride **9** gave only 4 % of product **10**. However, repetition of the reaction but using tetra-*n*-butylammonium bromide or iodide, had a dramatic effect, improving the yield of **10** from 4% to 28–32% (**Scheme 3**).[12]



Scheme 3

Scheme 4[12] presents the results of studies on intramolecular Heck reactions using Pd_2dba_3 and imidazolium salt **A**.

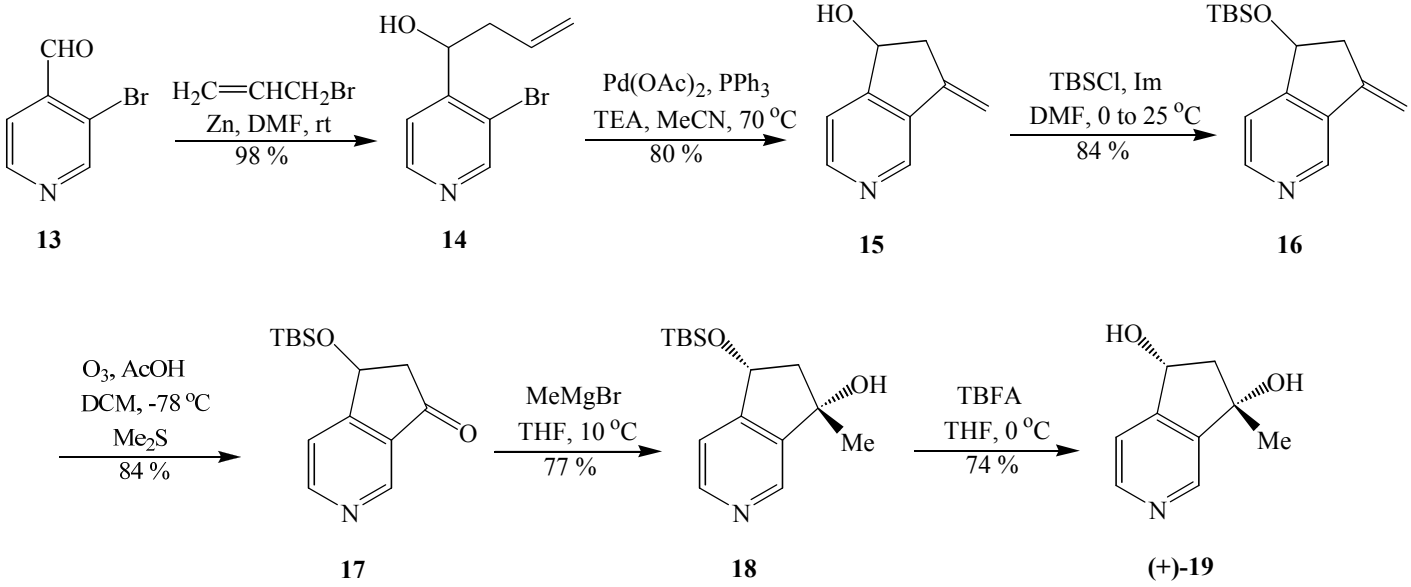


Scheme 4

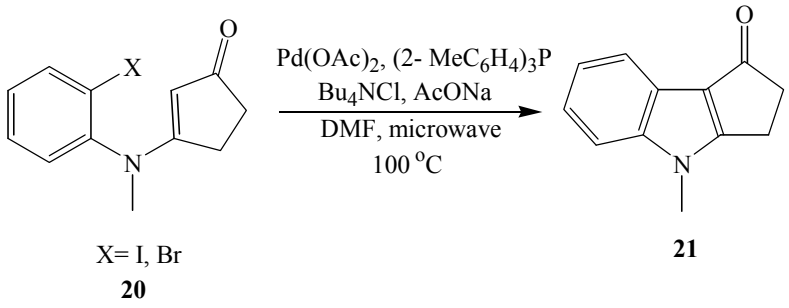
Allylation of aldehyde **13** with allyl bromide and unactivated zinc in DMF for 30 min smoothly afforded in 98% yield homoallylic alcohol **14** as a yellow oil, which set the stage for 5-*exo* cyclization via an intramolecular Heck reaction. Treatment of **14** with $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.1 equiv) and TEA (2 equiv) in MeCN at 70 °C for 3.5 h led to the desired cyclopenta[c]pyridine intermediate **15** in 80% yield (**Scheme 5**).[13]

From *N*-methyl-2-iodoaniline and commercially available cyclopentane-1,3-dione, the condensation product **20** (X= I) was synthesized by heating overnight without any solvent. The key synthetic step was the Pd-catalyzed cyclization of **20** (X= I) to **21** in the presence of $Pd(OAc)_2$ (5 mol%) and tri(*o*-tolyl)phosphine ($(2\text{-}MeC_6H_4)_3P$) in DMF under microwave heating (100 °C, 5 min) to afford, after

column chromatography and recrystallization, 99% of **21**. However, further improvements could be made if it was possible to replace the 2-iodoaniline with the much cheaper 2-bromoaniline as the precursor of **20** (X= Br). Unfortunately, the latter turned out to be less reactive in the cyclization reaction [30% conversion to **21** after 30 min]. However, upon conventional heating at 120 °C overnight, **21** was isolated in 95% yield (**Scheme 6**).[14]



Scheme 5

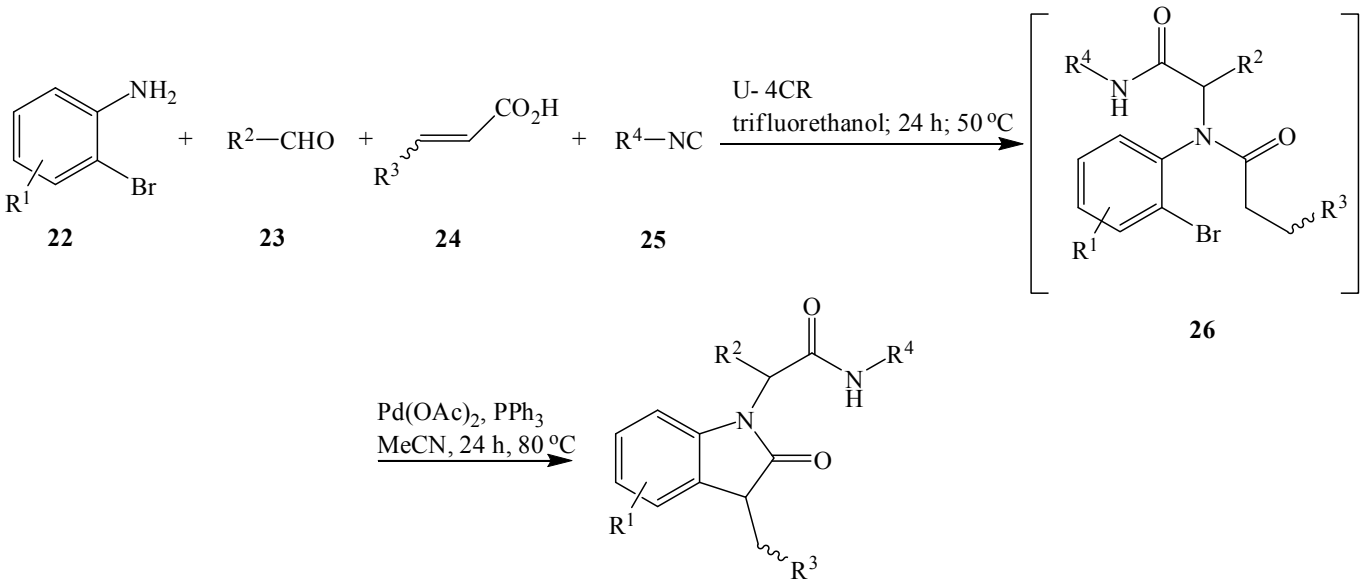


Scheme 6

A novel one-pot-synthesis of highly substituted indol-2-ones using a combination of Ugi and Heck reaction (U-4CRHeck) is described. The synthesized indol-2-ones represent an interesting pharmacological scaffold with four potential points of diversity. Thus, this novel reaction-type is amenable to combinatorial high-throughput screening (**Scheme 7**).[15]

The one-pot synthesis of 2-aryl- and 2-vinylindoles **29** based on a palladium-catalyzed intramolecular

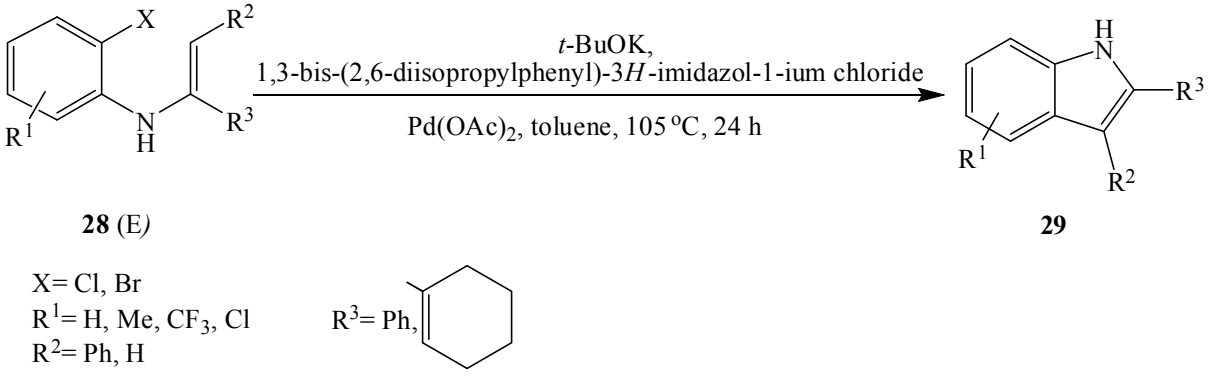
Heck reaction was reported. Intramolecular Heck reactions of the resulting 2-chloroanilino enamines **28** were achieved using an in situ generated palladium complex derived from an *N*-hetercyclic carbine (**Scheme 8**).[16]



22 **23** **24** **25** **26** **27**

R^1= H, NO_2
R^2= H, C_6H_5, *i*Pr
R^3= C_6H_5, Me, *p*- NO_2-C_6H_4, *m*- CF_3-C_6H_4, *m*-*p*-MeO-C_6H_3
R^4= CH_2-CO_2Me, CH_2-C_6H_5, *t*Bu

Scheme 7



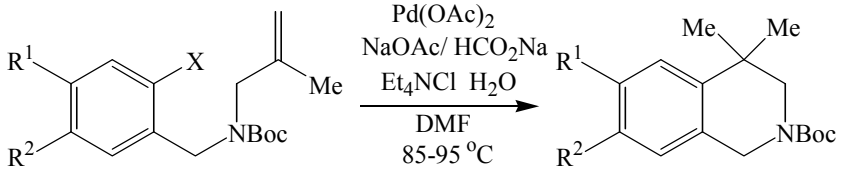
28 (E*)* **29**

X= Cl, Br
R^1= H, Me, CF_3, Cl
R^2= Ph, H
R^3= Ph,

Scheme 8

Synthesis of five and six membered heterocycles, indulines, 2,3-dihydrobenzofurans (**Scheme 10**),[17] chromans, 1,2,3,4-tetrahydroquinolines (**Scheme 11**),[17] and 1,2,3,4- tetrahydroisoquinolines (**Scheme 9**),[17] in 70-99% yield by a ligand-free palladium catalyzed reductive Heck cyclization of phenyl bromides

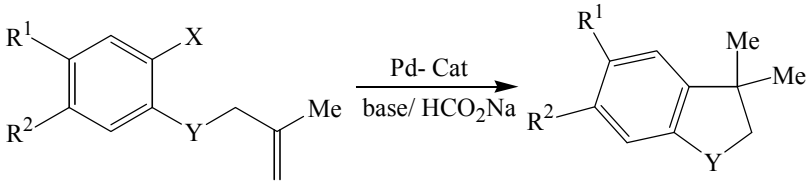
and chlorides, under mild conditions, was reported. Water was found to be essential for these reactions.



30 **31** (72-95 %)

X= Br, Cl
R^1= H
R^2= H, F, NO_2
R^1, R^2= -$O(CH_2)_2O$-

Scheme 9

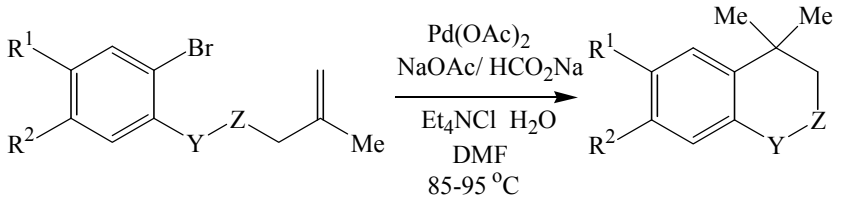


32 **33** (70-99 %)

X= Br, Cl
Y= NAc, NBoc, O, S
R^1= H, R^2= H, NO_2

Conditions **1**: $Pd(OAc)_2$, Cy_2NMe, Et_4NCl, HCO_2Na, DMAc, 100 °C, 2 h
Conditions **2**: $[(t\text{-}Bu)_2P(OH)PdCl_2]_2$, Cs_2CO_3, HCO_2Na, DMAc,100 °C, 4 h

Scheme 10

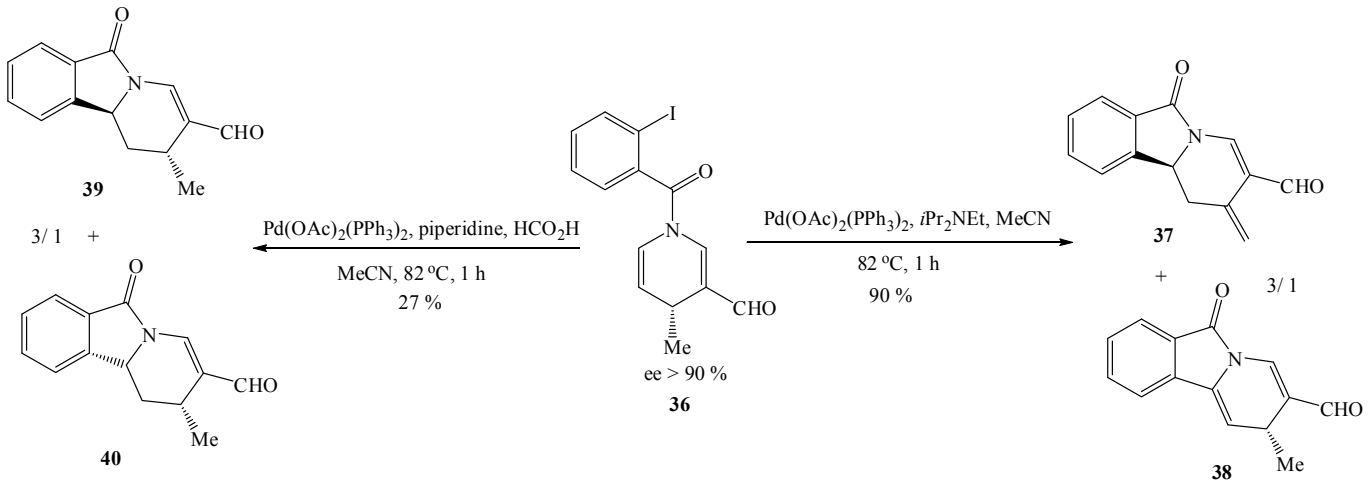


34 **35** (91-97 %)

Y= NHBoc, O, CH_2,
Z= O, CH_2
R^1= H, CN
R^2= H, F
R^1, R^2= -$O(CH_2)_2O$-

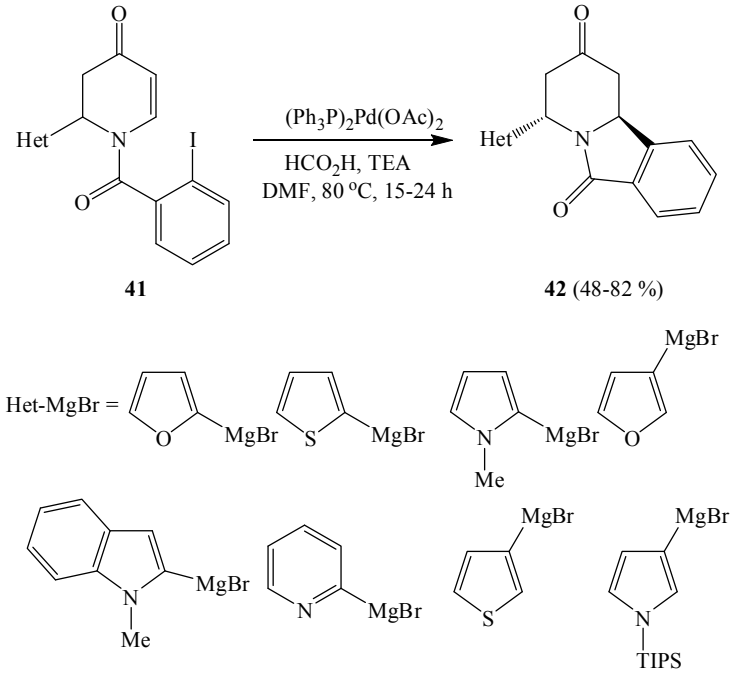
Scheme 11

In the presence of 10% of $Pd(OAc)_2(PPh_3)_2$ and 2 equiv of iPr_2NEt in acetonitrile at 82 °C, **36** yielded to a mixture of two cyclized products (3/1 ratio) in a very good yield. Under the reductive conditions, two aldehydes in a 3/1 ratio were obtained in poor yield. The major one was identical with **39** and the minor one with **40**. Therefore, the stereochemical outcome of the reductive and non reductive cyclizations was not influenced by the presence of the aminal even if a loss of the enantiomeric purity was observe (**Scheme 12**).[18]



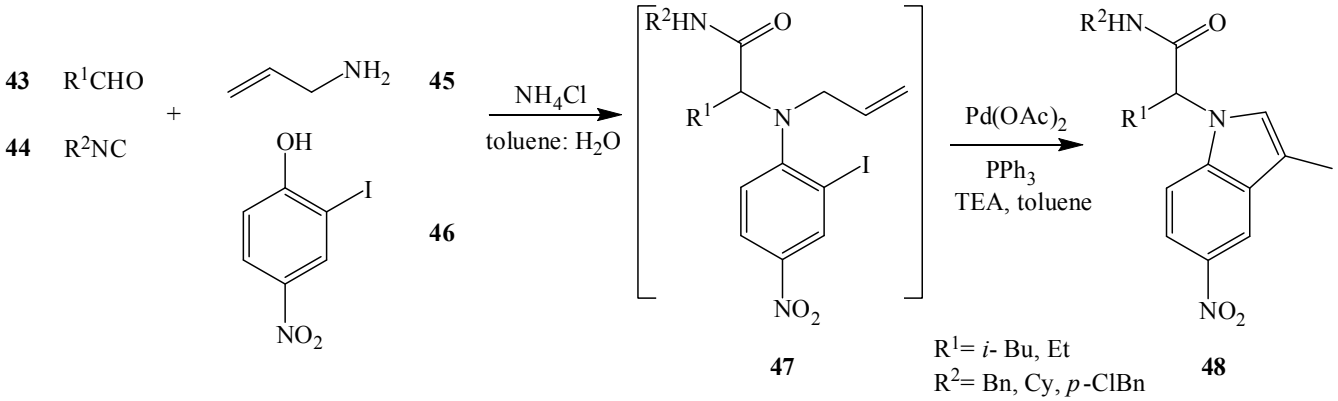
Scheme 12

The various kinds of *N*-acyldihydropyridones **41** were conveniently prepared from heteroaryl Grignald reagents and *N*-acylpyridinium salts. Subsequently, dihydropyridones **41** were converted to **42** by use of an intramolecular Heck cyclization (**Scheme 13**).[19]



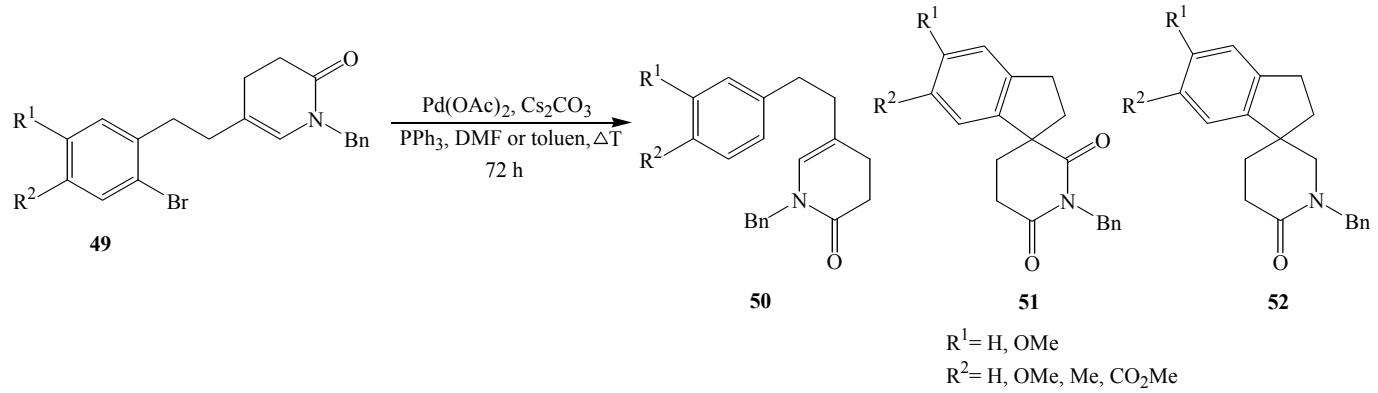
Scheme 13

Ugi-Smiles/Heck coupling/isomerization cascade can be done in a one-pot procedure by destroying the residual isocyanide before the Pd coupling (**Scheme 14**).[20]



Scheme 14

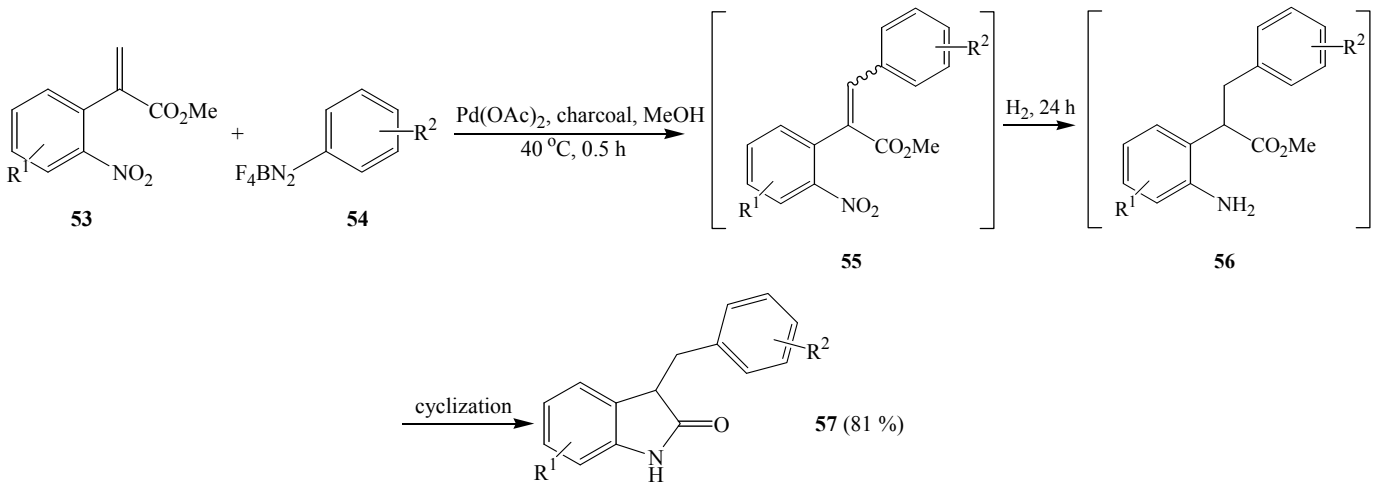
The palladium-mediated transformation of 3,4-dihydro-2(1*H*)-pyridinones **49** featuring a (2-bromophenyl)ethyl substituent in the 5-position produced spirocyclic products, imides **51** and amides **52**. The formation of these products can be explained by insertion of the enamide double bond into the initial aryl-Pd bond followed by oxidation or reduction of the organopalladium intermediate. Alternatively, formation of these spiro compounds might proceed via acyliminium ion intermediates (**Scheme 15**).[21]



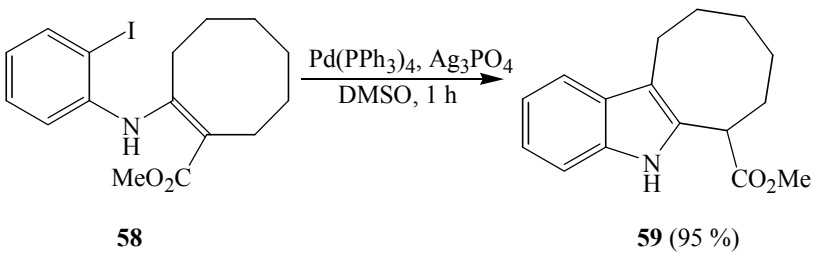
Scheme 15

A tandem sequence involving palladium-catalyzed sequential Heck-reduction-cyclization transformations in mild conditions has been developed for the synthesis of oxindoles. The protocol involved inexpensive reagents and did not require any additives such as bases or ligands (**Scheme 16**).[22]

The best result for cyclization was obtained when **58** was treated with 3 mol% of $Pd(PPh_3)_4$ and 1 equiv of Ag_3PO_4 in DMSO to give **59** (**Scheme 17**).[23]

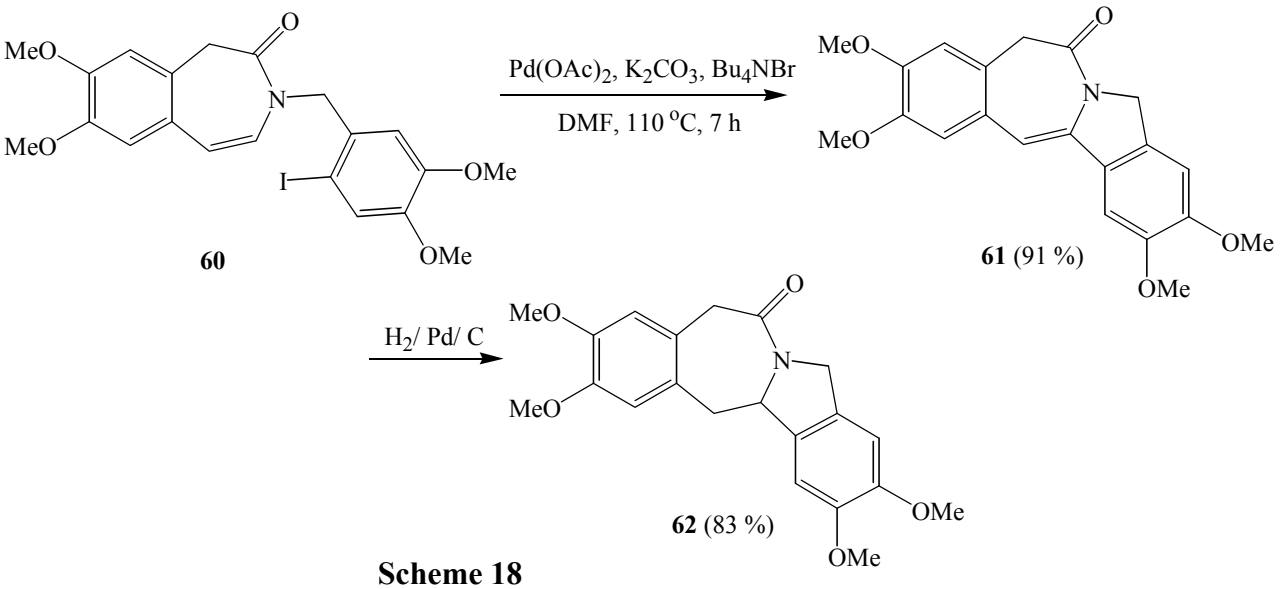


Scheme 16



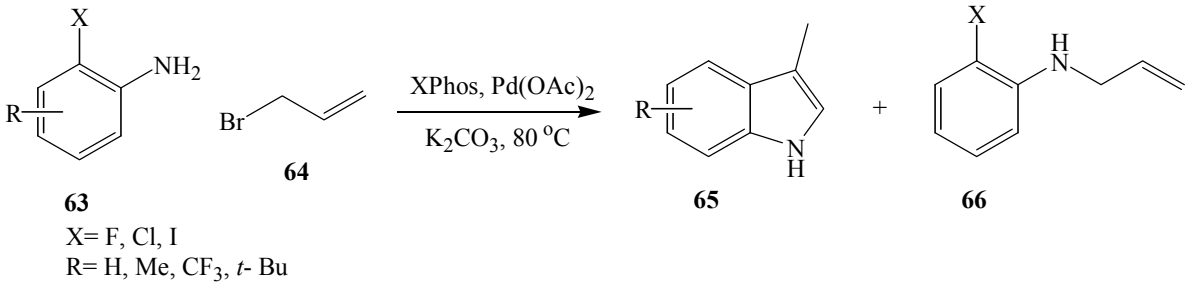
Scheme 17

Treatment of *N*-alkylbenzazepinone **60** with $Pd(OAc)_2$ in DMF containing K_2CO_3 (2 equiv) and $Bu_4N^+Br^-$ (1 equiv) at 110 °C for 2 h provided the desired tetracyclic ring structure of dehydroisoindolinobenzazepinone **61** 91% yield. Subsequent palladium-catalyzed hydrogenation of the dehydroisoindolinobenzazepinone **61** readily furnished the corresponding isoindolinobenzazepinone **62** in 83% yield (**Scheme 18**).[24]



Scheme 18

Weinrich and Beck reported the palladium-catalyzed one-pot *N*-alkylation/Heck cyclization of anilines to substituted indoles employing $Pd(OAc)_2$/XPhos (**Scheme 19**).[25]

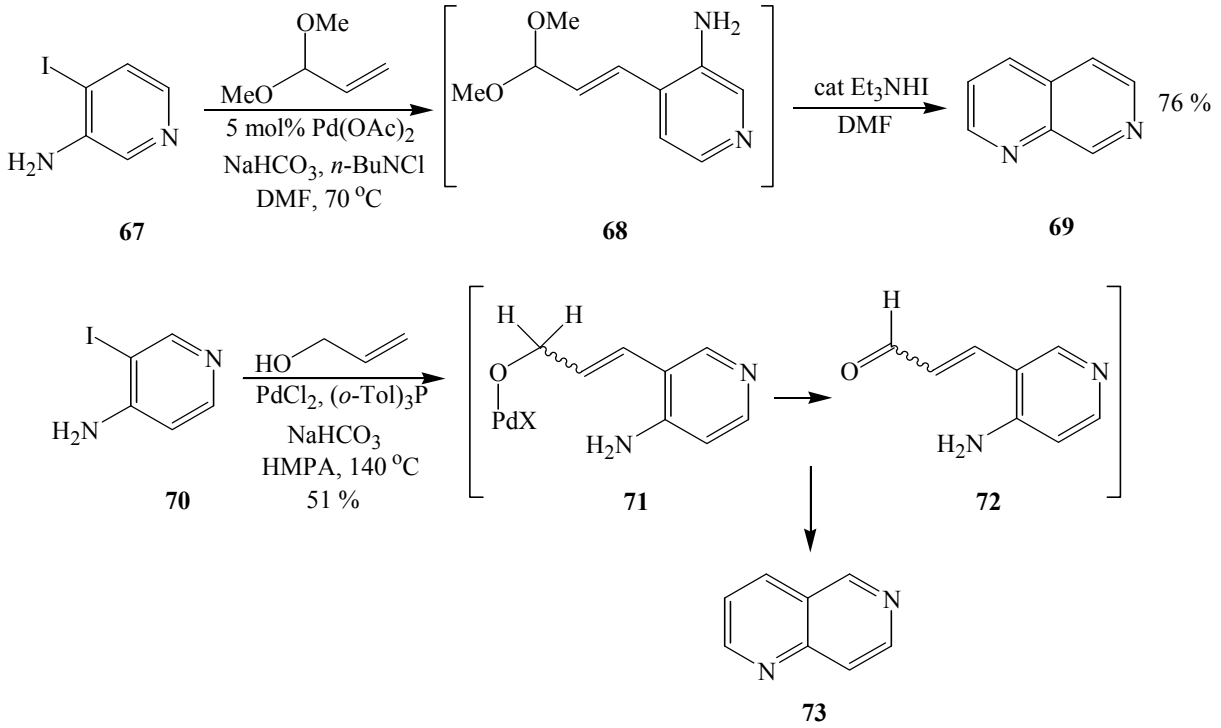


63 **64** **65** **66**

X= F, Cl, I
R= H, Me, CF_3, *t*- Bu

Scheme 19

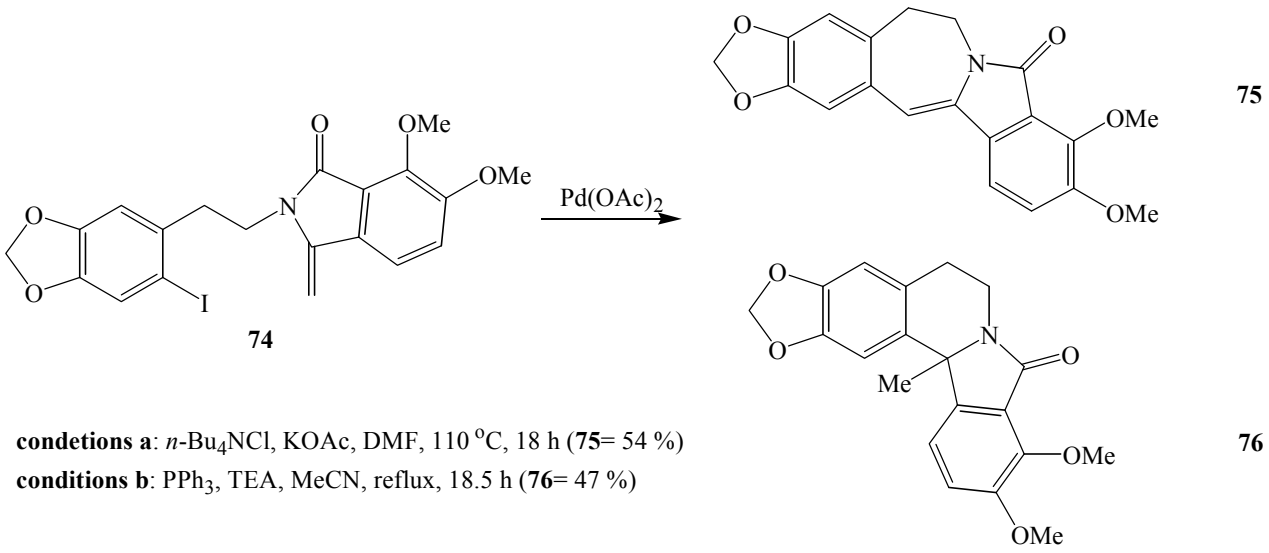
A simple method for the preparation of 1,7-naphthyridine and 1,6-naphthyridine from the corresponding aminopyridine starting materials was presented. Crude **68** was treated with DMF and a catalytic amount of triethylammonium iodide in ethyl ether (generated by mixing TEA and HI) and heated to 70 °C for 16 h to cleanly provide **69** in 76% yield over the two steps. Formation of **73** under these conditions occurred via a multistep sequence involving Heck coupling, palladium-mediated oxidation of the allylic alcohol to the aldehyde, double bond isomerization, cyclization, and dehydration (**Scheme 20**).[26]



67 **68** **69** **70** 51 % **71** **72** **73**

Scheme 20

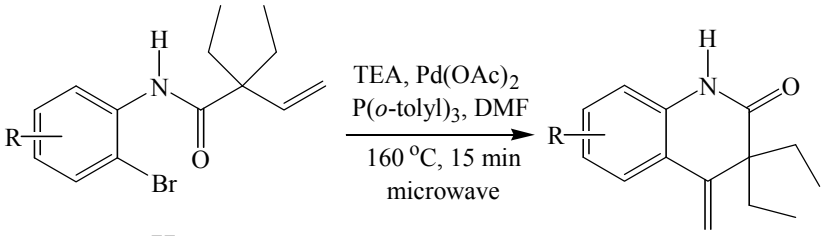
The use of condition **a** and condition **b** in the reaction mixture was found to be critical for the *endo*-type cyclization to provide **75** and **76**. The yields were **75** (54%) and **76** (47%) (**Scheme 21**).[27]



condetions a: *n*-Bu_4NCl, KOAc, DMF, 110 °C, 18 h (**75**= 54 %)
conditions b: PPh_3, TEA, MeCN, reflux, 18.5 h (**76**= 47 %)

Scheme 21

Amides **77**, when irradiated in a microwave vessel using standard Heck conditions [3 equiv TEA, 5 mol% $Pd(OAc)_2$, 10 mol% P(*o*-tolyl)$_3$, DMF], afforded the unexpected 6-*exo*-trig derivatives in 15 minutes. The structures of **78** were confirmed by NMR analyses (**Scheme 22**).[28]



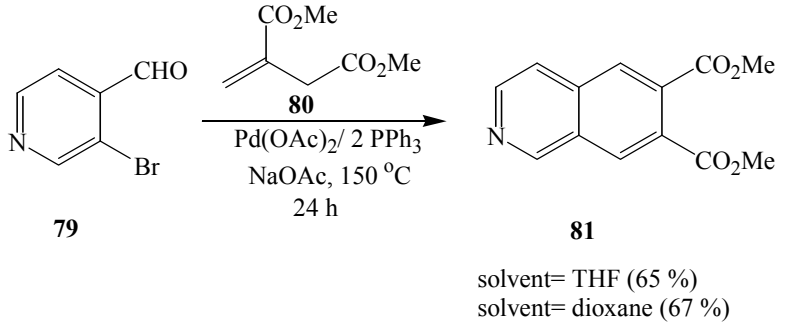
78

R= H **78**= 78 %
R= 4-OMe **78**= 76 %
R= 4-Me **78**= 75 %
R= 4-F **78**= 79 %
R= 4-CF_3 **78**= 77 %
R= 4-OCF_3 **78**= 75 %

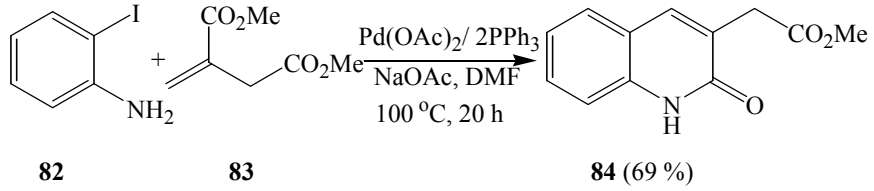
Scheme 22

3-Bromopyridine-4-carbaldehyde **79** was tethered with suitably electron withdrawing group substituted alkenes via Heck coupling followed by aldol reaction in dioxane at 150 °C under a catalytic system of $Pd(OAc)_2/PPh_3$/NaOAc to afford the corresponding isoquinolines in good yields (**Scheme 23**).[29]

It has been shown that 2-iodoaniline **82** undergoes coupling and cyclization with an array of α,β-unsaturated carbonyl compounds **83** in the presence of a palladium catalyst along with a base to afford quinolones **84**. The present reaction is applicable to the synthesis of 2,3- and 2,4-disubstituted quinolines by the variation of the starting α,β-unsaturated ketones (**Scheme 24**).[30]

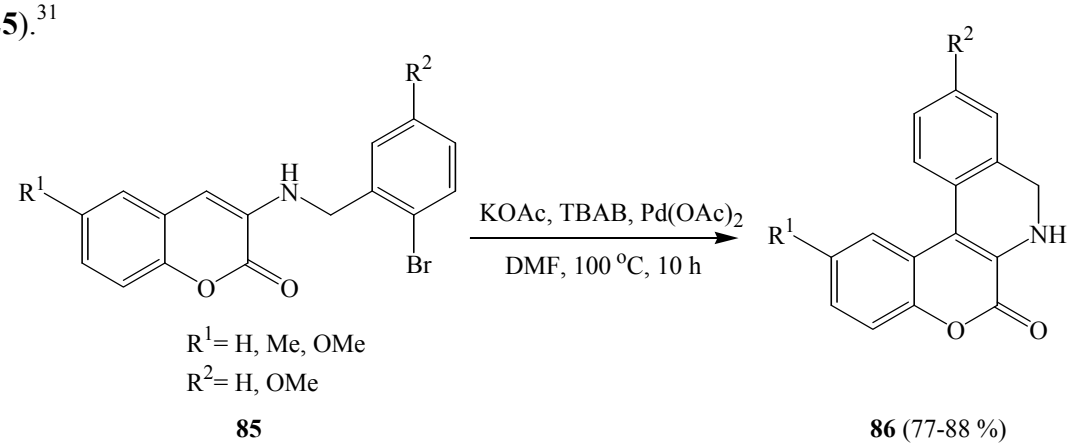


Scheme 23



Scheme 24

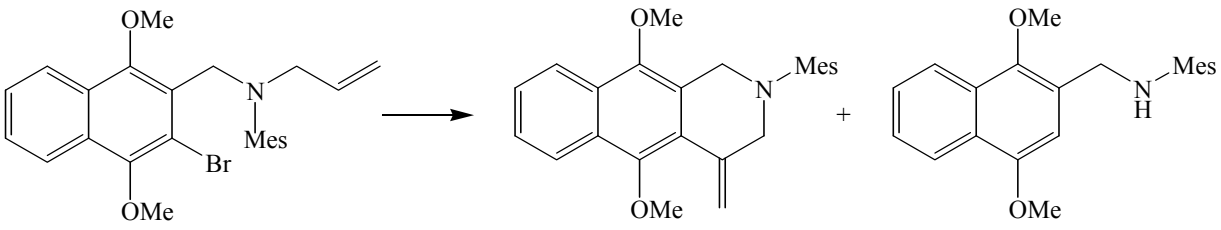
Tetrahydropyrido[2,3-*c*]coumarin derivatives were synthesized by intramolecular radical cyclization and heck coupling. This method allowed the synthesis of the backbone of the santiagonamine alkaloid (**Scheme 25**).[31]



Scheme 25

87 was treated with a catalytic amount of palladium(II) acetate in the presence of (x-phos) and potassium acetate in bis(2-methoxyethyl)ether at 80 °C for 3 days, after which the desired Heck-cyclization product **88** was isolated in 33% yield together with 41% of the deallylated and debrominated naphthalene **89**. In the second reaction, **87** was treated with a catalytic amount of tetrakis(triphenylphosphine) palladium(0) and 4 equiv of sodium acetate in boiling ethanol. After a reaction time of 4 days the desired Heck-reaction product **88** was isolated in 36% yield. Although these two reactions give similar results, the latter reaction conditions were selected to perform the Heck-cyclization of naphthalene **87** since the desired Heck-cyclization product was formed predominantly under these conditions and could easily be purified by

column chromatography (**Scheme 26**).[32]

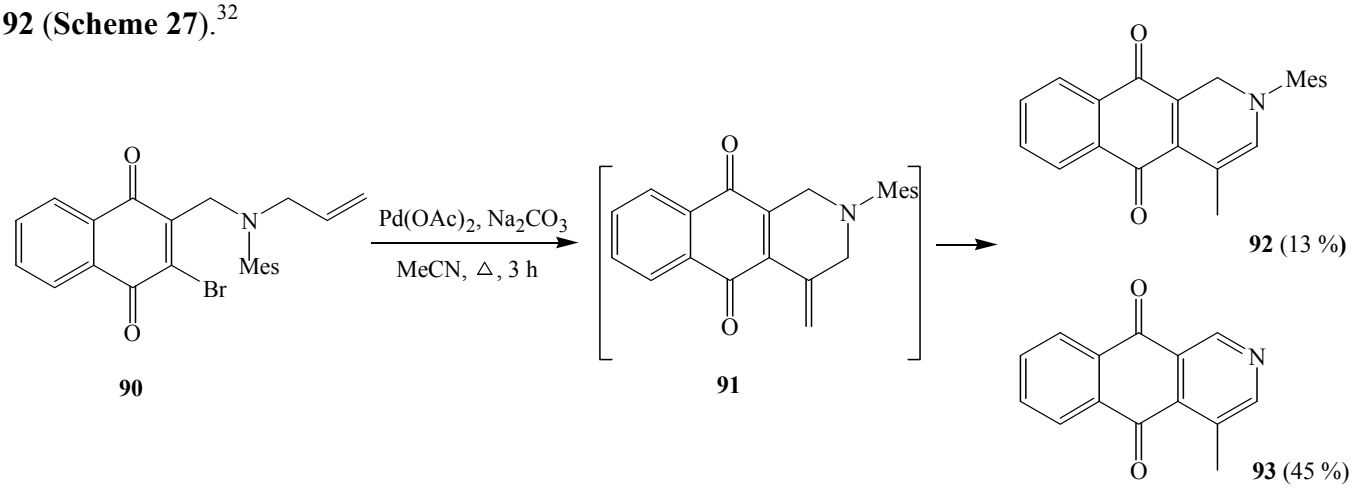


87 **88** **89**

condition **a**: $Pd(Ph_3P)_4$ (5 mol%), 4 equiv. NaOAc, EtOH, △ 4 d
88 (36 %)
condition **b**: $Pd(Ph_3P)_4$ (5 mol%), 1.5 equiv. KOAc, EtOH, 150 °C, 16 h
88 (11 %), **89** (65 %)
condition **c**: 0.1 equiv. $Pd(OAc)_2$, 0.2 equiv. x-phos, 4 equiv. KOAc
A: $Me_2NC(=O)Me$, 80 °C, 16 h **88** (18 %), **89** (54 %)
B: diglyme, 80 °C, 3 d **88** (33 %), **89** (41 %)

Scheme 26

The palladium-mediated intramolecular cyclization of **90** was believed to give rise to the formation of 4-methylene intermediate **91**, which is formed as the Heck cyclization product and is likely to isomerize to the more conjugated and thus, more stable isomer **92**. Indeed, after treatment of the *N*-protected 1,4-naphthoquinone **90** with palladium(II) acetate and an excess of sodium carbonate in boiling acetonitrile for 3 h, none of the 4-methylene intermediate **91** was detected in the reaction mixture. Instead, **93** was obtained as the major reaction product and it was isolated in 45% yield together with 13% of the desired **92** (**Scheme 27**).[32]

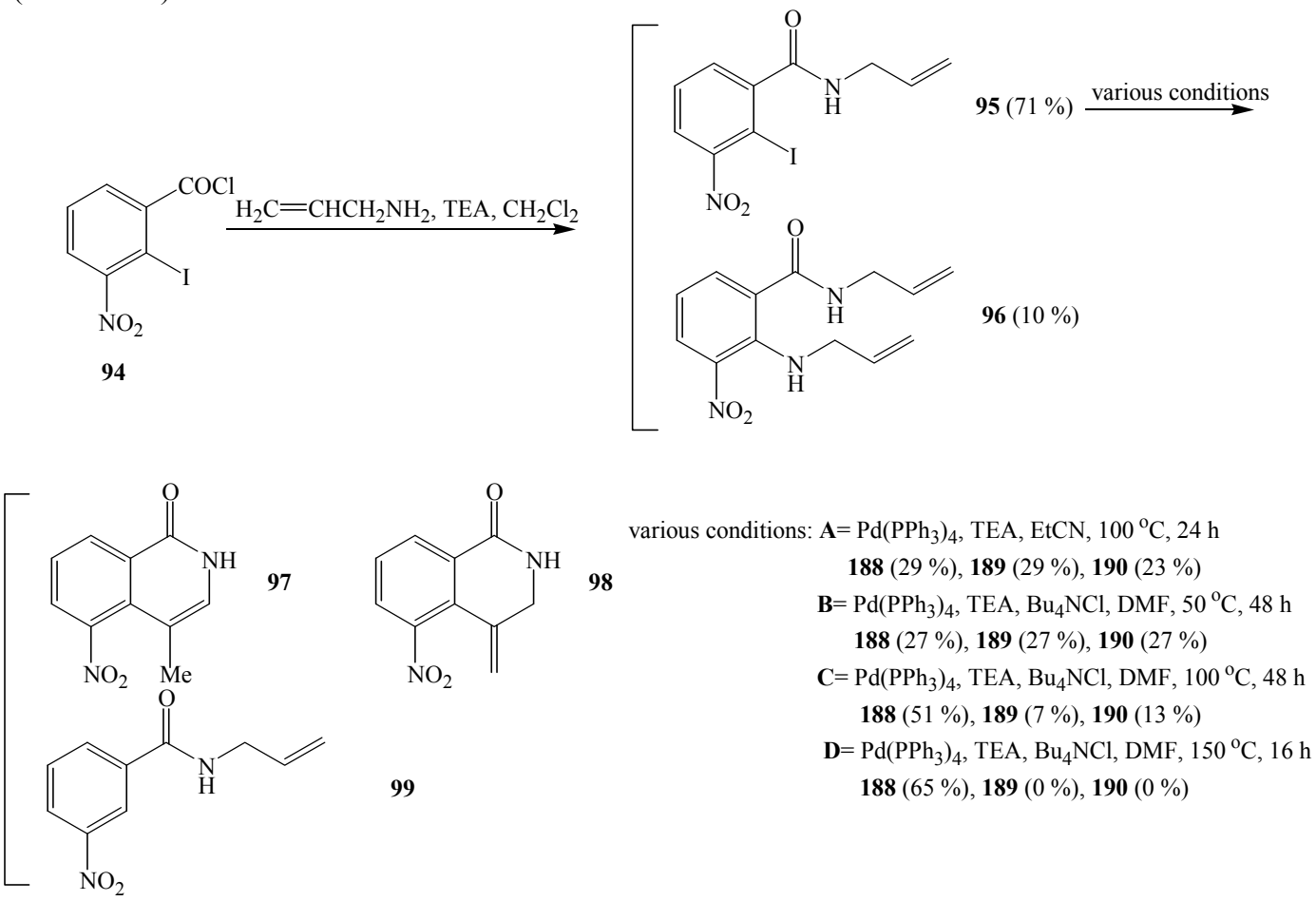


90 **91**

Scheme 27

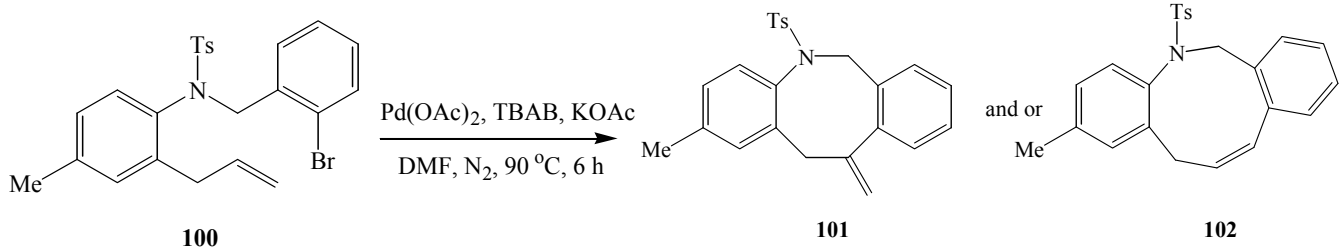
Reaction of **95** with $Pd(PPh_3)_4$ under the conditions used for cyclisation of the tertiary amides (TEA, EtCN, 100 °C) gave the two cyclized products **97** (4-methyl-5-nitroisoquinolin-1-one) and **98** (4-methylene-5-nitro-3,4-dihydroisoquinolin-1-one) in a 1:1 ratio, along with the dehalogenated amide **99**

(**Scheme 28**).[33]



Scheme 28

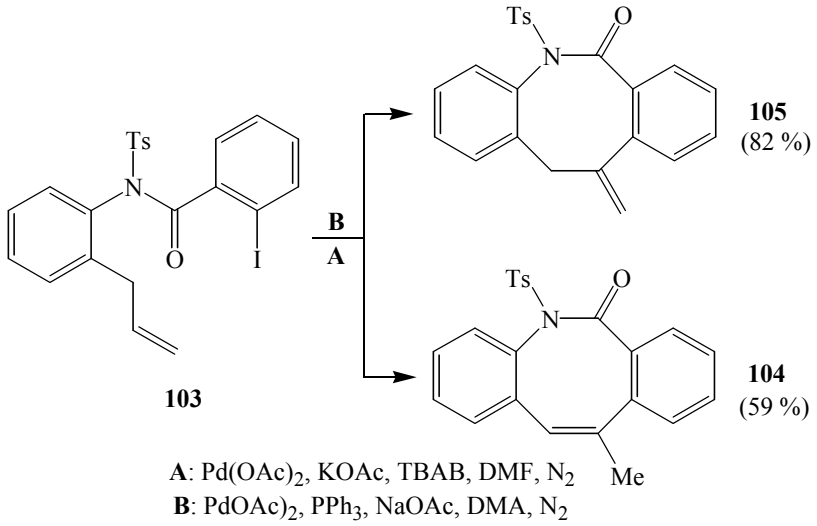
Conducted with substrate **100** by applying the concept of Jeffery's two-phase protocol in the presence of $Pd(OAc)_2$, KOAc and tetrabutylammonium bromide (TBAB) in dry DMF under a nitrogen atmosphere for 6 h. The eight-membered *exo*-Heck product **101** was obtained in 72% yield without any contamination of the *endo*-Heck product **102** (**Scheme 29**).[34]



Scheme 29

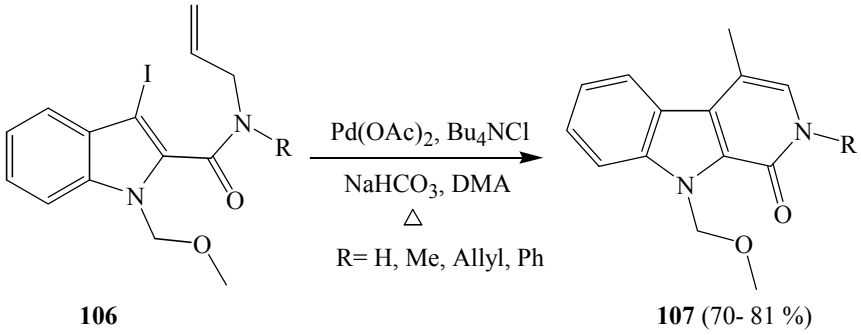
Substrate **103** was allowed to react with phosphine-free Jeffery's two-phase protocol, that is, $Pd(OAc)_2$/KOAc/TBAB/DMF/90 °C/N_2 conditions and pleasingly the cyclized product **104** was obtained in 59% yield. When the reaction was performed with the same substrate **103** using $Pd(OAc)_2$ as catalyst,

NaOAc as base, and Ph_3P as ligand in dry DMA at 90 °C for 3.5 h the corresponding *exo*-Heck product **105** was obtained as the sole product in 82% yield (without TBAB as phase transfer catalyst) (**Scheme 30**).[35]



Scheme 30

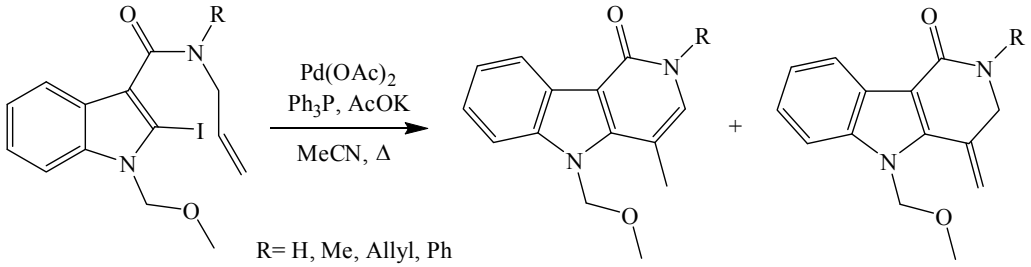
The cyclization reaction to give compounds **107** was performed with a catalyst system containing 10 mol% of palladium(II)acetate, 1.0 equiv of tetrabutylammonium chloride (TBAC) and 2.5 equiv of sodium hydrogen carbonate in dimethylacetamide at 90 °C (**Scheme 31**).[36]



Scheme 31

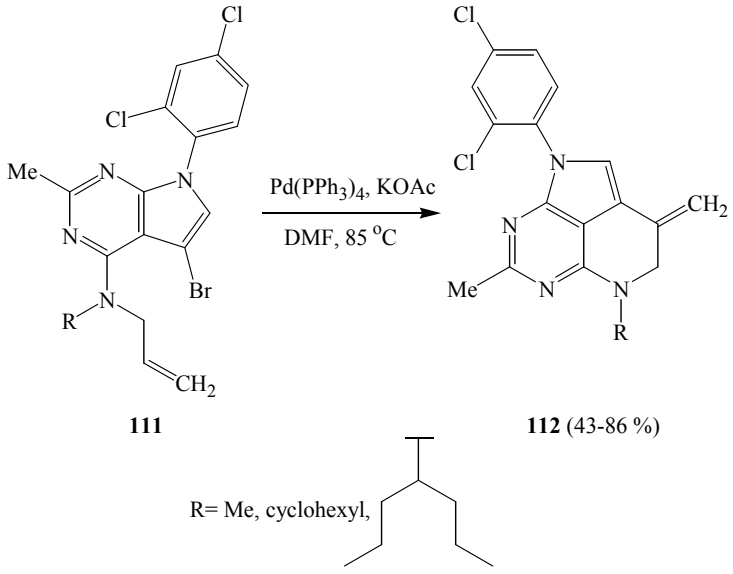
In the case of compounds **108**, better results were obtained using 10 mol% of palladium(II)-acetate, 20 mol% of triphenylphosphine, 3.0 equiv of potassium acetate in acetonitrile at reflux. In these conditions, besides the γ-carbolinones **109**, the isomeric γ-carbolinones with exocyclic double bond, **110** were also obtained (**Scheme 32**).[36]

A synthetic route to pharmaceutically important tricyclic pyrrolopyrimidines was developed. The method employed a palladium-mediated Heck cyclization as the critical step in the construction of the final six membered rings (**Scheme 33**).[37]



108 **109** (26-43 %) **110** (26-56 %)

Scheme 32



111 **112** (43-86 %)

Scheme 33

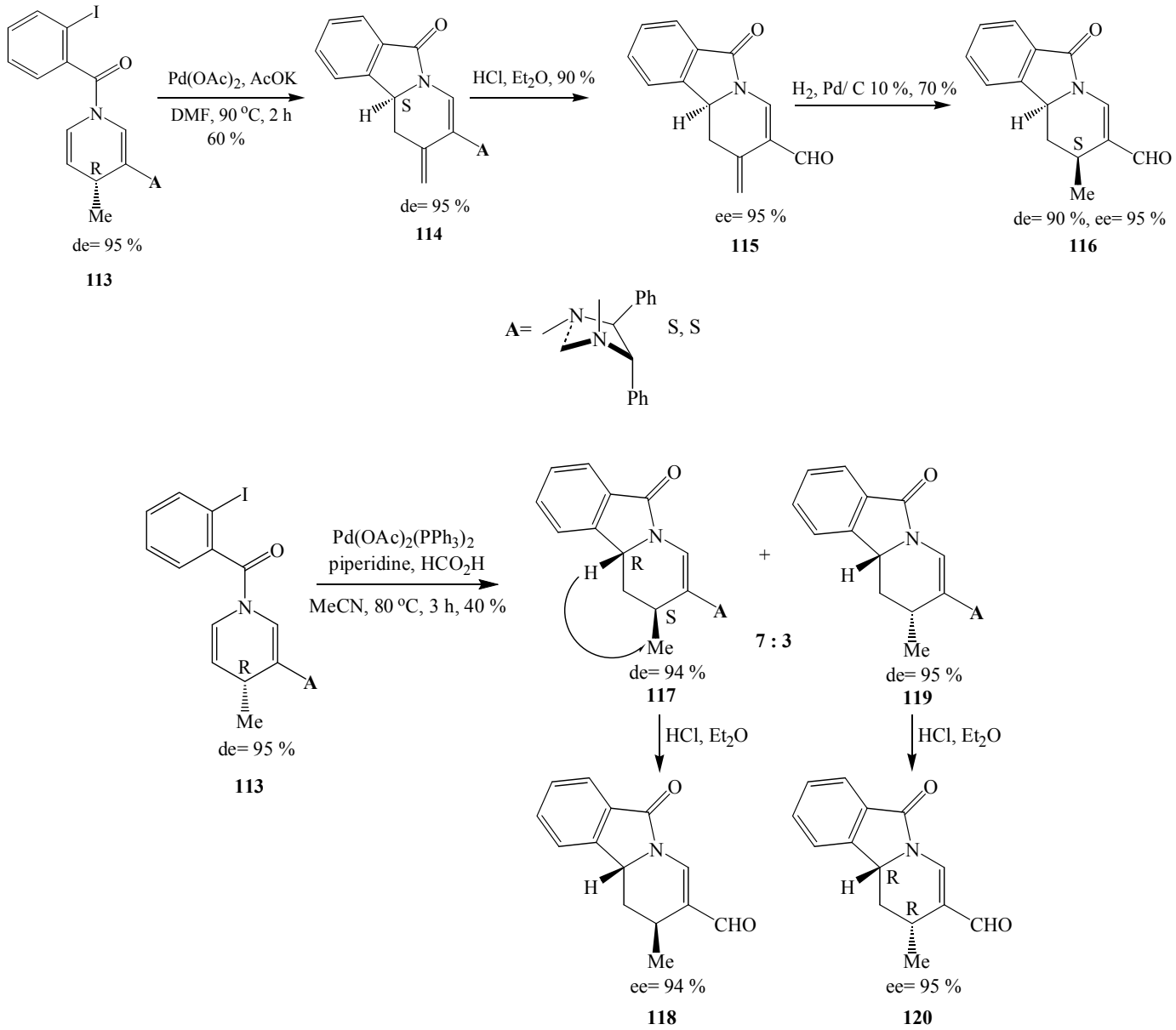
In the presence of a catalytic (5%) amount of $Pd(OAc)_2$, AcOK in DMF (90 °C, 2 h) the dihydropyridine **113** was regioselectively converted into **114.** Therefore, **114** resulted from an *anti* carbopalladation then a *syn* β-elimination and an isomerisation of the double bond. Acidic hydrolysis of the aminal group in **114** afforded the aldehyde **115.** A tandem cyclization–hydride capture performed on **113**, in the presence of 5% of $Pd(OAc)_2(PPh_3)_2$ and piperidinium formate, gave the two diastereomeric products **117** (94% de) and **119** (95% de) in a 7:3 ratio. Aminals **117** and **119** were respectively converted into the aldehydes **118** and **120** by acidic hydrolysis (**Scheme 34**).[38]

Kiely and Guiry described cyclisations of **121** using Pd complexes generated from (*R*)-BINAP **124** and the phosphinamine ligands **125**–**128** (**Scheme 35**).[39]

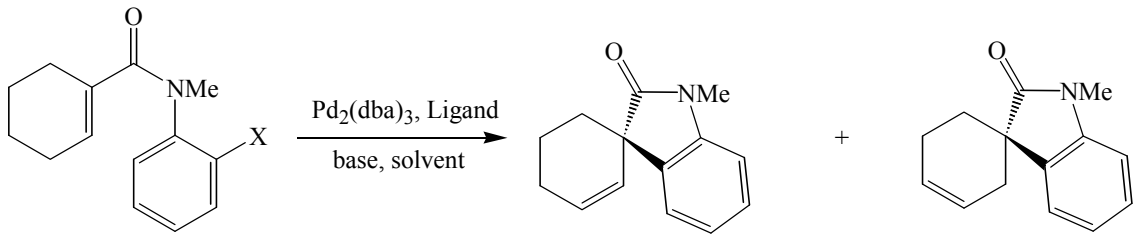
Using $Pd(OAc)_2/PCy_3$ (tricyclohexylphosphine) under standard conditions, the intramolecular Heck cyclization of **129** was found to proceed to completion rapidly. In related intramolecular Heck cyclization

reactions of benzamides, a range of double bond isomers have been reported. In this study, none of the bridgehead double bond isomer was formed, and **131** was observed as the major product, along with trace amounts of **132** and **133** double bond isomers. Investigation of a range of bases at the optimum reaction temperature (140 ^{o}C) showed that DIPEA gave comparable results to those obtained in the presence of $MeNCy_2$ (dicyclohexylmethylamine), however, TEA, K_2CO_3 and 2,6-lutidine gave lower conversion levels (**Scheme 36**).[40]

A novel approach towards the construction of the galanthamine skeleton was demonstrated by the Pd-catalyzed cyclization of *N*-[2-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)ethyl] 2-iodo-4-methoxy-*N*-methyl benzamide, with formation of the benzazepine ring and creation of a quaternary carbon (**Scheme 37**).[41]

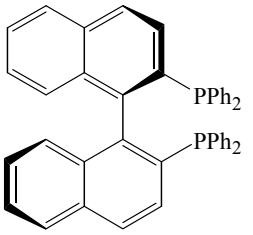


Scheme 34

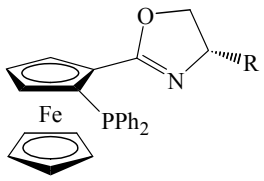


X= I, OTf

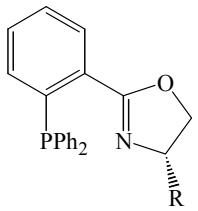
121 **122** **123**



124



125 R= *t*-Bu
126 R= *i*-Pr

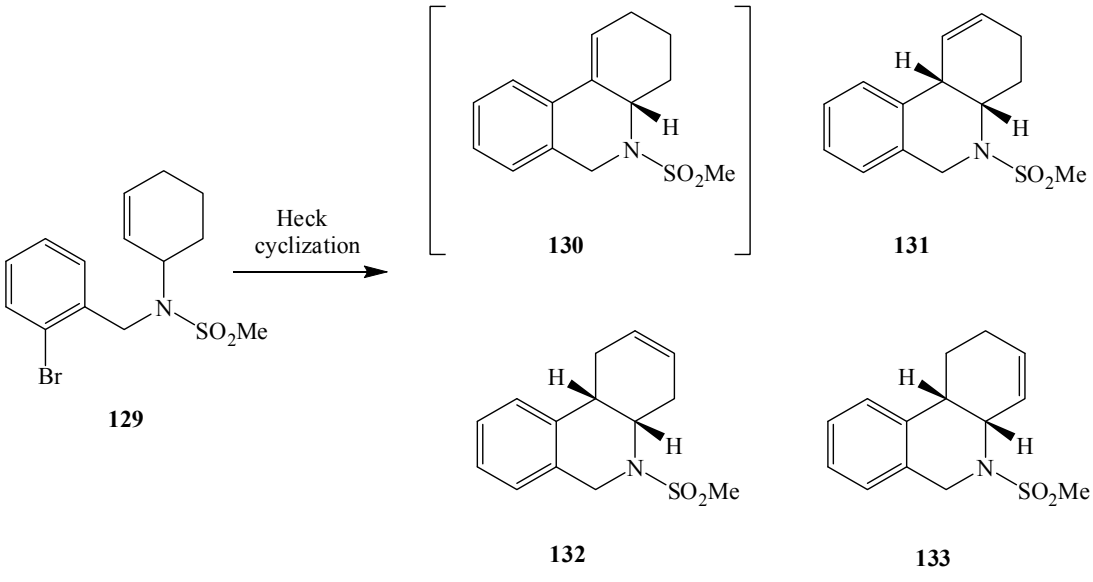


127 R= *t*-Bu
128 R= *i*-Pr

Intramolecular Heck reaction of triflate **121**

Ligand	Solvent	T(°C)	Base	Time(h)	Yield	122/123	ee 122
124	DMA	110	PMP	48	90	25:75	74 (S)
125	DMA	110	PMP	228	36	99:1	65 (R)
125	DMA	110	PS	168	30	99:1	85 (R)
126	DMA	110	PMP	228	13	71:29	37 (R)
127	DMA	110	PMP	228	20	76:24	57 (R)
127	DMA	110	PS	168	20	99:1	71 (R)
128	DMA	110	PMP	228	7	72:28	33 (R)
124	toluene	110	PMP	48	90	75:25	71 (S)
125	toluene	110	PMP	168	70	94:6	51 (R)
125	toluene	80	PMP	168	70	99:1	53 (R)
125	toluene	80	PS	168	15	99:1	82 (R)
126	toluene	110	PMP	168	35	93:7	12 (R)
126	toluene	80	PMP	168	5	90:10	30 (R)
127	toluene	110	PMP	168	20	90:10	19 (R)
125	benzene	80	PMP	168	5	98:2	63 (R)

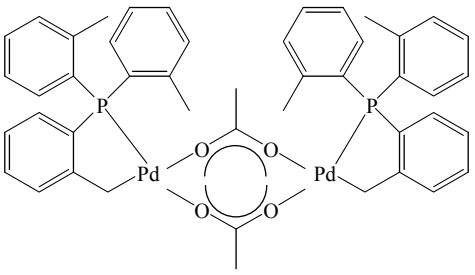
Scheme 35



129 **130** **131** **132** **133**

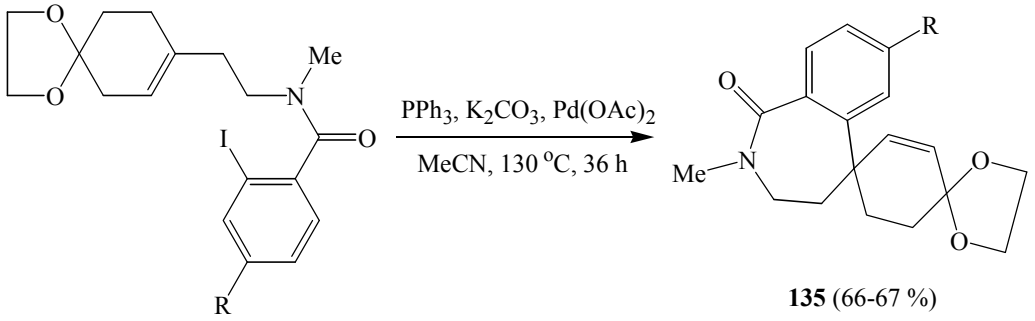
Catalyst screening for the intramolecular Heck cyclization reaction of solfonamide **129**

Entry	Catalyst	Base	T(°C)	t(min)	Solvent	Ratio
1	$Pd(OAc)_2/PCy_3$	$MeNCy_2$	130	70	DMA	77:14:9
2	$Pd(OAc)_2/PCy_3$	$MeNCy_2$	140	60	DMA	96:2:2
3	$Pd(OAc)_2/PCy_3$	$MeNCy_2$	150	30	DMA	95:3:2
4	$Pd(OAc)_2/PCy_3$	Et_3N	140	70	DMA	90:2:8
5	$Pd(OAc)_2/PCy_3$	DIPEA	140	35	DMA	92:5:3
6	$Pd(OAc)_2/PCy_3$	K_2CO_3	140	40	DMA	55:27:18
7	$Pd(OAc)_2/PCy_3$	2,6-Lutidine	140	-	DMA	-
8	$Pd(OAc)_2/PCy_3$	$MeNCy_2$	140	35	DMF	94:5:1
9	$Pd(OAc)_2/PCy_3$	$MeNCy_2$	130	360	DMF	39:38:23
10	Herrmann-Beller(**A**)	$MeNCy_2$	140	180	DMF	44:31:25
11	Herrmann-Beller(**A**)	$MeNCy_2$	150	110	DMF	52:16:32
12	Herrmann-Beller(**A**)	AgF	140	180	DMF	65:23:12
13	Herrmann-Beller(**A**)	Ag_3PO_4	140	120	DMF	67:18:15
14	Herrmann-Beller(**A**)	Ag_2CO_3	140	70	DMF	85:13:2



A= Herrmann-Beller palladacycle

Scheme 36



R= H, OMe

134

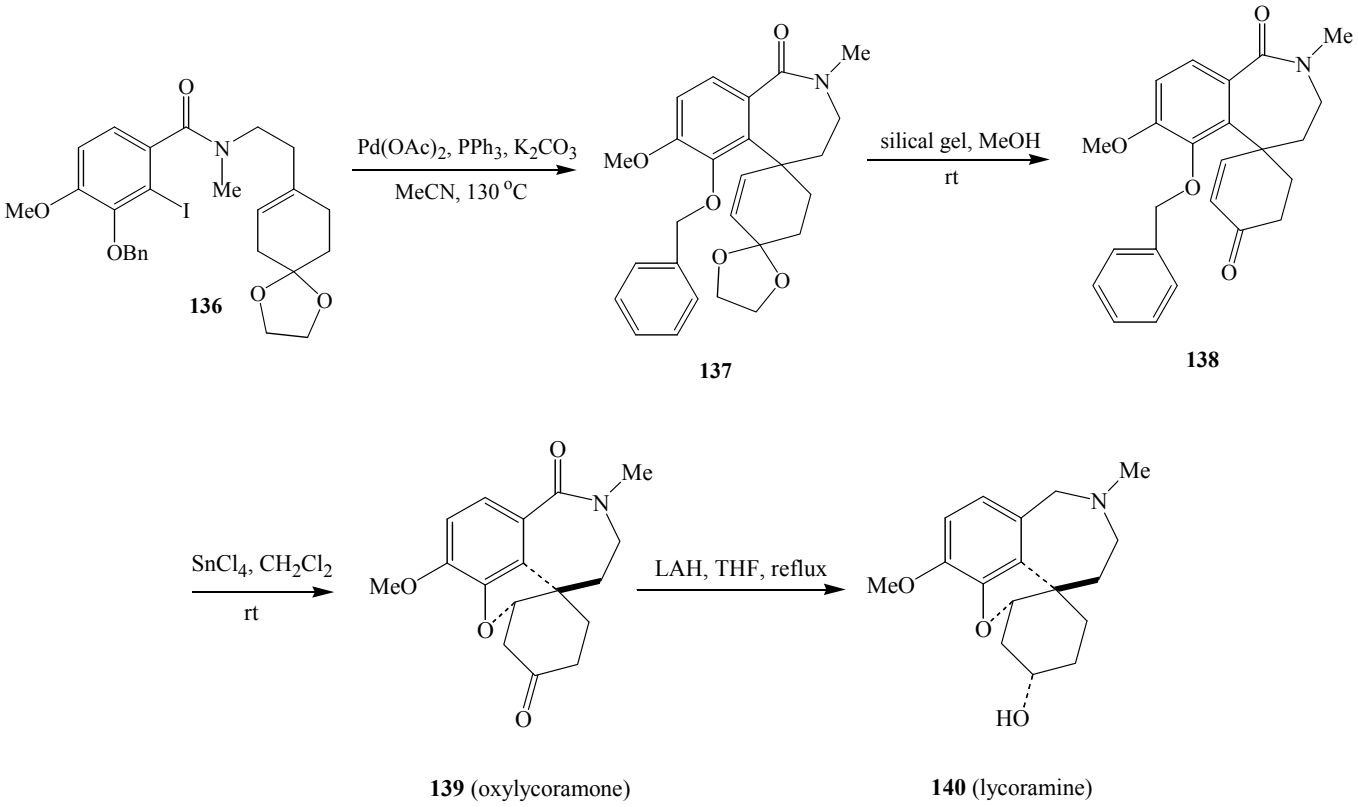
135 (66-67 %)

Scheme 37

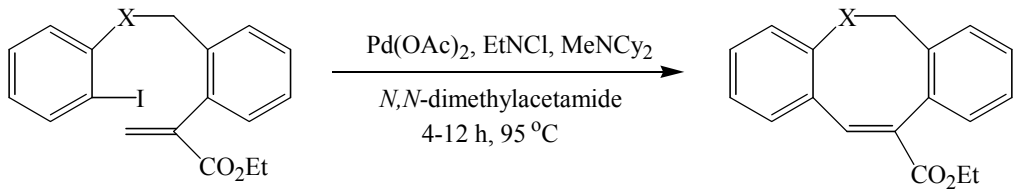
Compound **136** was subjected to Heck reaction condition using $Pd(OAc)_2$, Ph_3P, and K_2CO_3 in MeCN, the desired intramolecular cyclization was achieved to provide dispiro-compound **137**. The ethylene ketal group of **137** was removed easily when put in contact with silical gel in methanol to give ketone **138** in 95% yield. Subsequent removal of the benzyl group in **138** with $SnCl_4$ was accompanied by a spontaneous intramolecular Michael addition to afford tetracyclic oxolycoraminone **139** in 75% yield. Simultaneous reduction of both the ketone and amide groups of **139** with LAH afforded (±)-**140** with excellent diastereoselectivity (de >95%) (**Scheme 38**).[42]

The Heck reaction was carried out in *N,N*-dimethylacetamide using $MeNCy_2$ (dicyclohexylmethylamine) as a base, Et_4NCl as promoter, and $Pd(OAc)_2$ as precatalyst. All reactions gave the 8-*endo* products **142**

exclusively in up to 72% yield. Bromo analogues required longer reaction times (12 h) in contrast to the corresponding iodo compounds (4 h) (**Scheme 39**).[43]



Scheme 38



141

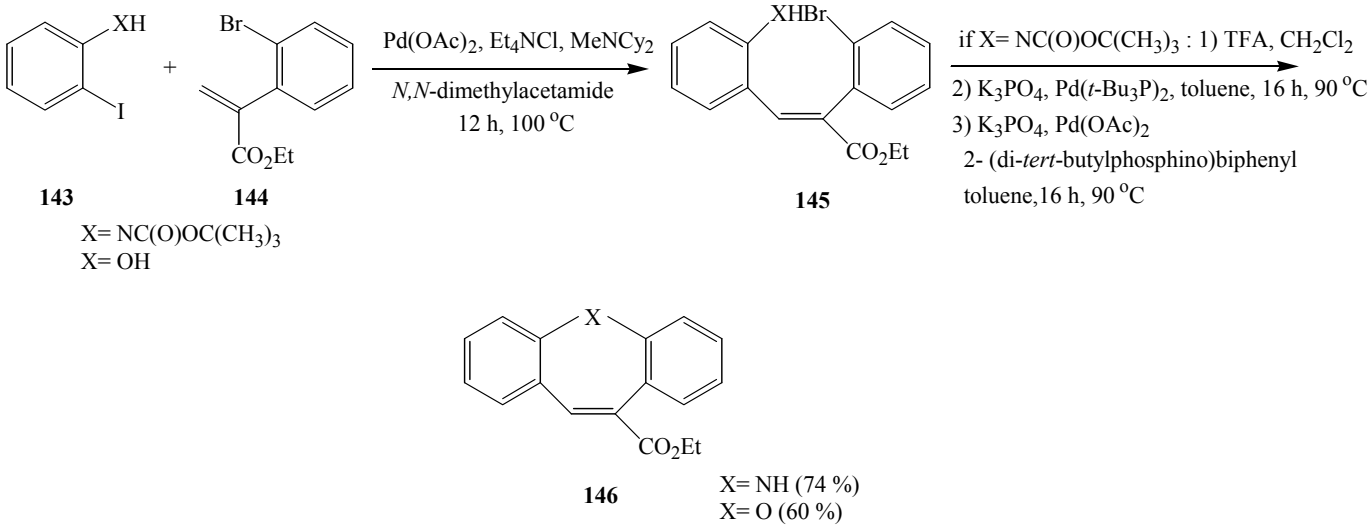
X= NCO_2CF_3
X= O

142

X= NCO_2CF_3 (72 %)
X= O (72 %)

Scheme 39

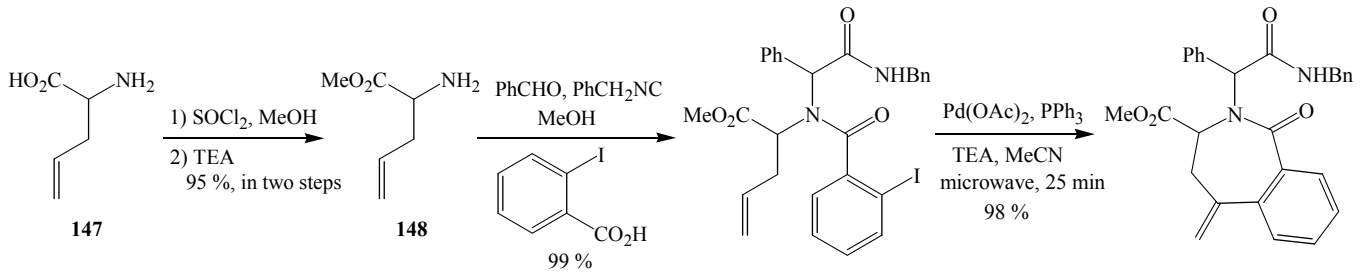
The Heck reaction was carried out first, giving a selective reaction with the aryl iodide in the presence of an aryl bromide **144**. Very good chemoselectivity was observed, giving products **145** exclusively in 82% yield. The carbamate **145** (X= $NC(O)OC(CH_3)_3$) was deprotected using TFA to give the free aniline **145** (X= NH). Compound **145** (X= NH) gave the dibenzo[*b*,*f*]azepine **146** in 74% yield. Phenol **145** (X= OH) was obtained in 82% yield using 2-iodophenol and **144**. The cyclization of **145** (X= OH) using the catalytic conditions developed by Buchwald and coworkers gave **146** (X= O) in 60% yield (**Scheme 40**).[43]



143 **144** **145** **146**

Scheme 40

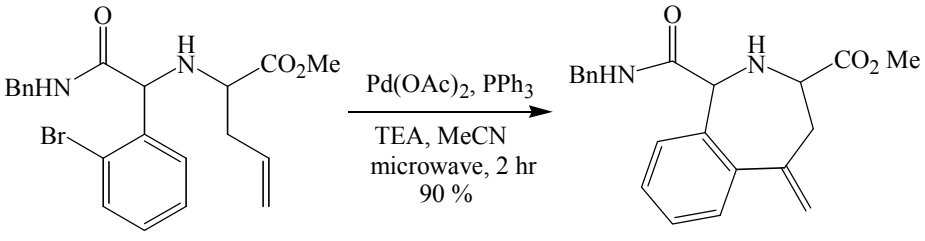
Heck cyclization on the Ugi product **149** proceeded smoothly to produce the seven membered lactam **150** in excellent yield (**Scheme 41**).[44]



147 **148** **149** **150**

Scheme 41

Substrate **151** cleanly underwent microwave-assisted Heck cyclization to generate **152** in 90% yield (**Scheme 42**).[44]

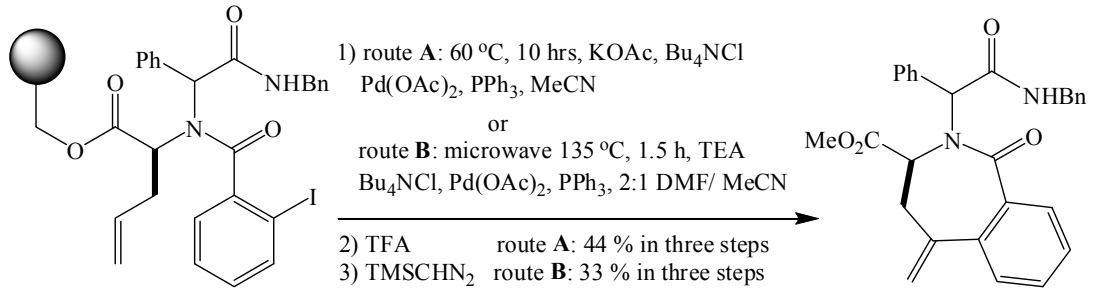


151 **152**

Scheme 42

The resin-bound Ugi adduct **153** was washed with DMF, MeOH, and CH_2Cl_2, and then subjected to two different solid-phase Heck cyclization conditions. The first set of reaction conditions utilized Bu_4NCl,

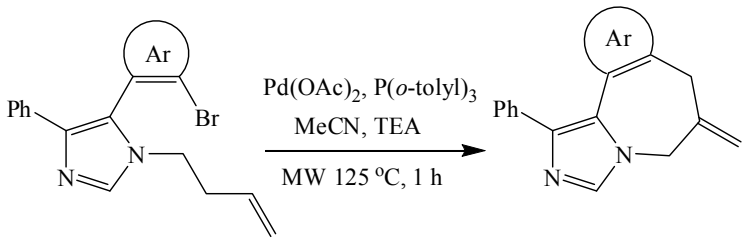
KOAc, Ph_3P, and $Pd(OAc)_2$ in DMF while the second example mimicked their solution phase conditions described above (**149**, **151**) with the sole difference being the addition of Bu_4NCl. Following the Heck reactions, the resin was washed with DMF , DMF/water 1:1, DMF, MeOH, and CH_2Cl_2 . The cyclized adducts were cleaved from the resin (1:1 TFA/CH_2Cl_2) and the resulting acids were methylated utilizing (trimethylsilyl)diazomethane in MeOH, to produce ester **154** with moderate yields (33–44%) (**Scheme 43**).[44]



153 **154**

Scheme 43

Aldehydes containing a vinylogous bromide were condensed with 4-butenamine and then treated with phenylTosMIC and potassium carbonate to give the corresponding imidazoles. The imidazoles were then subjected to the Heck reaction to give the desired imidazo[1,5-*a*]azepines (**Scheme 44**).[45]



155 **156**

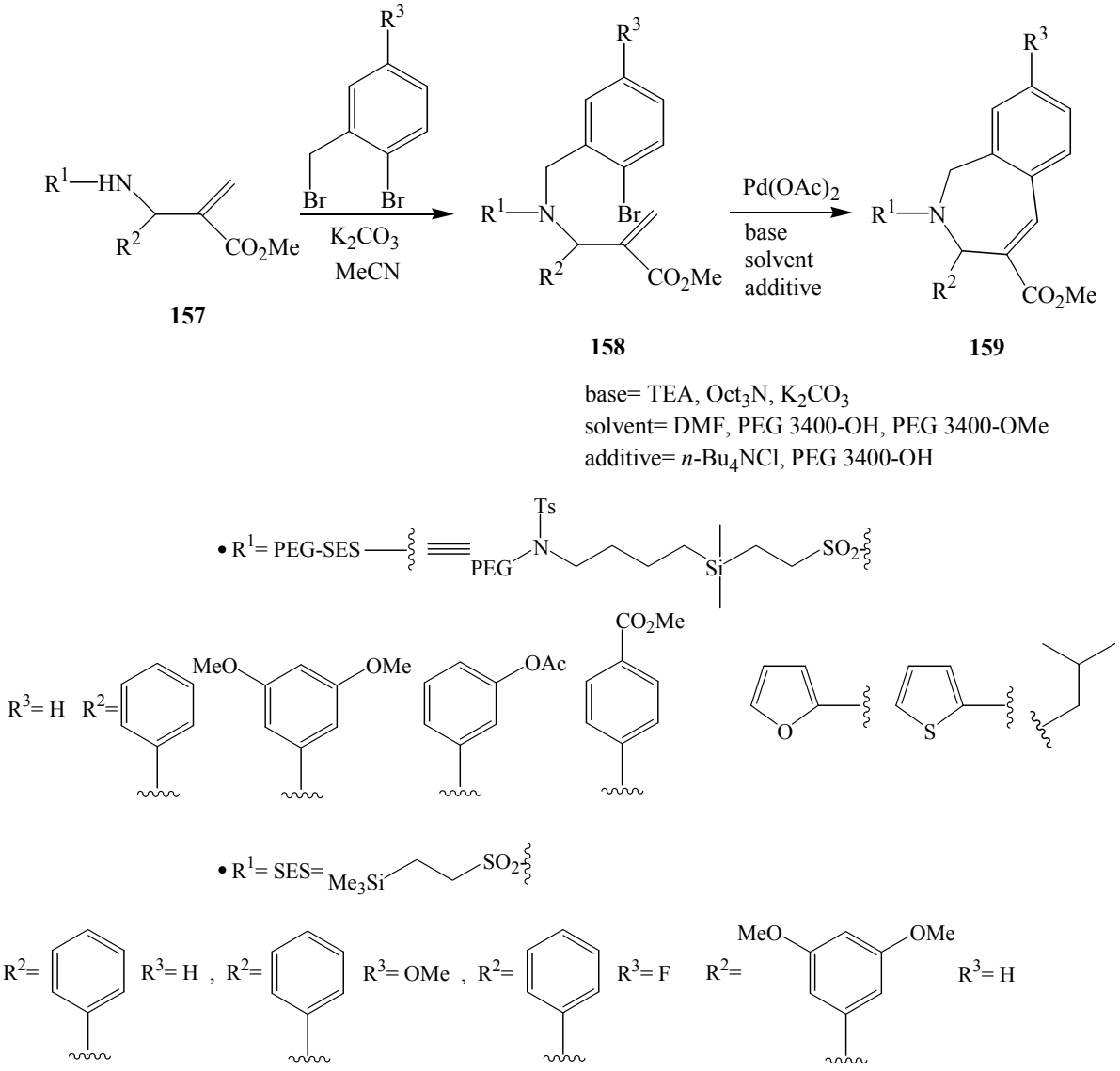
Scheme 44

Compounds **158**, obtained by alkylation of **157** with 2-bromobenzyl bromide, were subjected to different Heck reaction conditions using $Pd(OAc)_2$ as catalyst in the presence of a base in DMF. **158** were fully converted to the cyclized benzazepines **159** using either K_2CO_3 or Oct_3N as a base. The reaction was very selective since only **159** were obtained among the different products, which could be formed during the reaction. Since the reaction products **159** were isolated by precipitation in Et_2O and filtration, the use of lipophilic Oct_3N was preferred because it was readily eliminated during this operation (**Scheme 45**).[46]

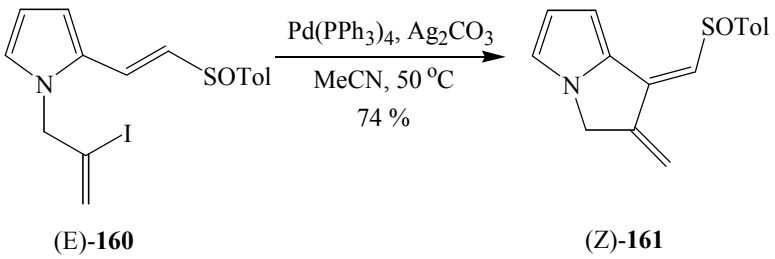
2. 2 CYCLIZATION VIA REACTIONS OF VINYL HALIDES

The Heck reaction of (*E*)-**160** occurred under somewhat harsher conditions: $Pd(PPh_3)_4$ (20 mol%), Ag_2CO_3 (2 equiv) in acetonitrile at 50 °C for 5 h, furnishing after chromatographic purification the diene

(*Z*)-**161** in 44% yield (74% based on converted product) along with 40% of starting (*E*)-**160** (**Scheme 46**).[47]



Scheme 45

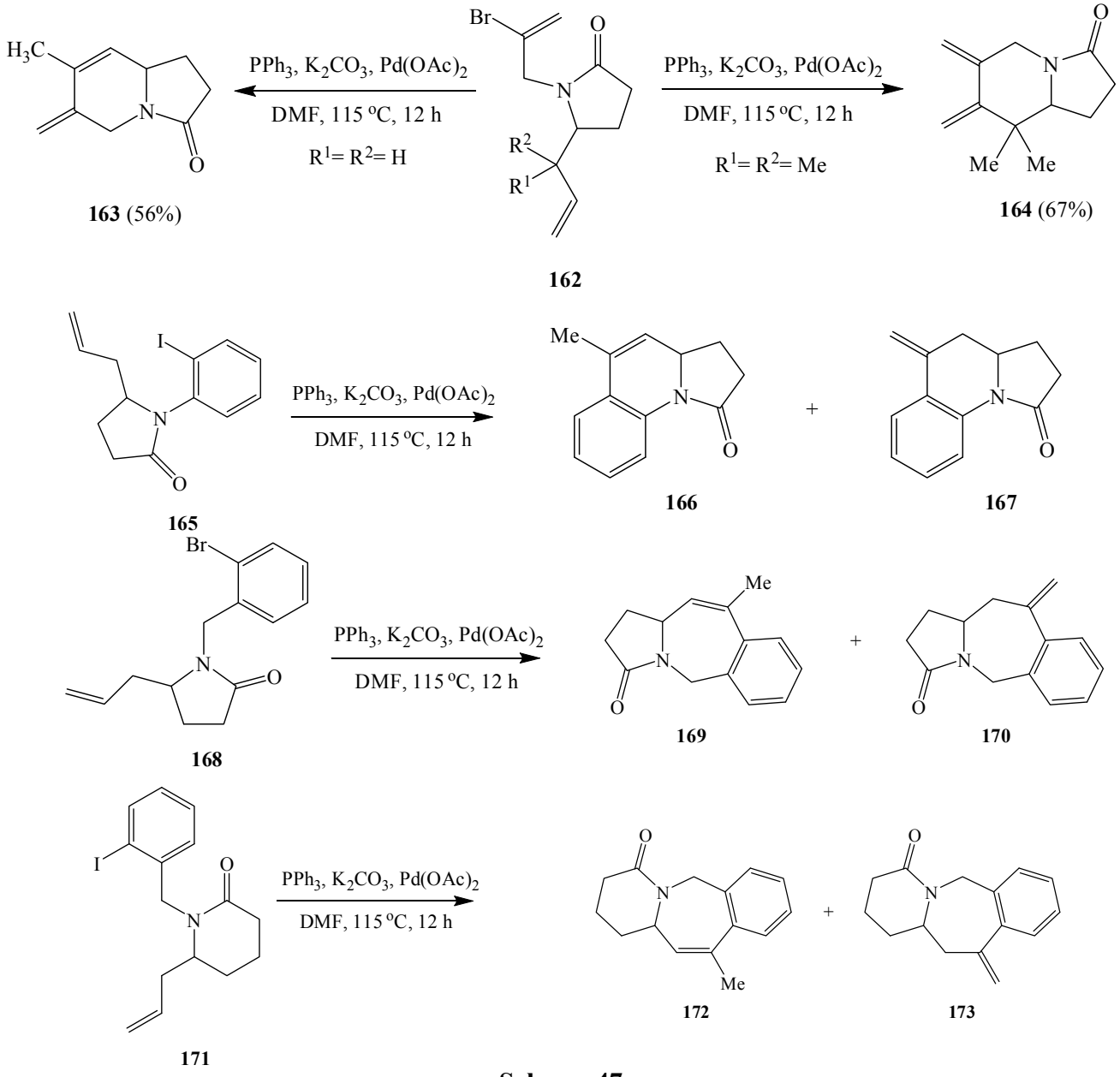


(E)-**160** (Z)-**161**

Scheme 46

The intramolecular heck cyclization of *N*-allyl-, -aryl- or –benzyl-5-allyl-2-pyrrolidinones and *N*-allyl-, -aryl-, or –benzyl-6-allyl-2-piperidinones, prepared through allyltrimethylsilan addition to the

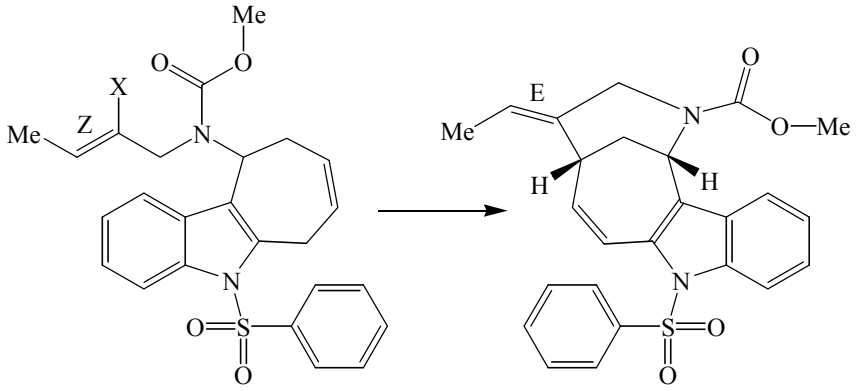
corresponding cyclic *N*-acyliminium ions, afforded indolizidinones, quinolizinones and benzoazepinones in moderate to good yields (56-90%) (**Scheme 47**).[48]



Scheme 47

An efficient approach to the bridged framework of the indole alkaloid ervitsine , featuring a ring-closing metathesis reaction from a 2,3-disubstituted indole followed by a vinyl halide Heck cyclization upon the resulting cycloheptane ring, was described (**Scheme 48**).[49]

The precursors **176** on reaction with $Pd(OAc)_2$ (10 mol%), PPh_3 (0.25 equiv) and Cs_2CO_3 (1.2 equiv) in DMF at 90–100 °C yielded the fused tetrahydropyridine derivatives **177** in good to excellent yields via 6-*exo*-trig cyclization (**Scheme 49**).[50]

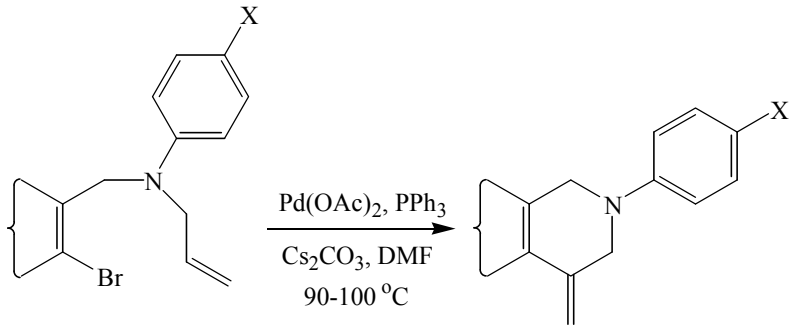


174 **175**

X= Br **Conditions**: PPh_3, K_2CO_3, proton sponge, $Pd(OAc)_2$, toluene, 4 h, △, 30 %

X= I **Conditions**: TEA, K_3PO_4, phenol, $Pd(PPh_3)_4$, toluene, 12 h, △ , 65 %

Scheme 48



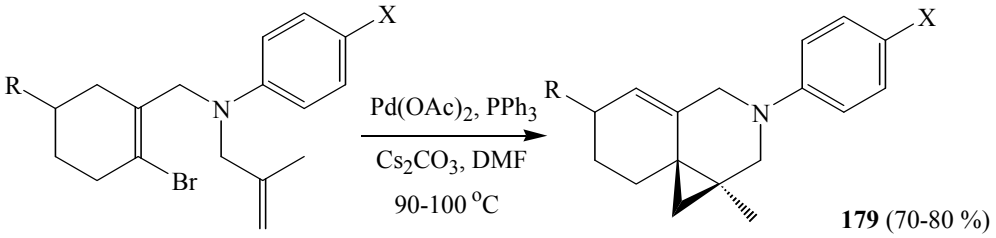
176

X= Cl, Me

177 (80-90 %)

Scheme 49

But when *N*-methallylated derivatives **178** were subjected to the Heck reaction under the same reaction conditions (**Scheme 49**)[50] they gave cyclopropa[*d*]fused isoquinoline derivatives **179** (**Scheme 50**).[50]



178

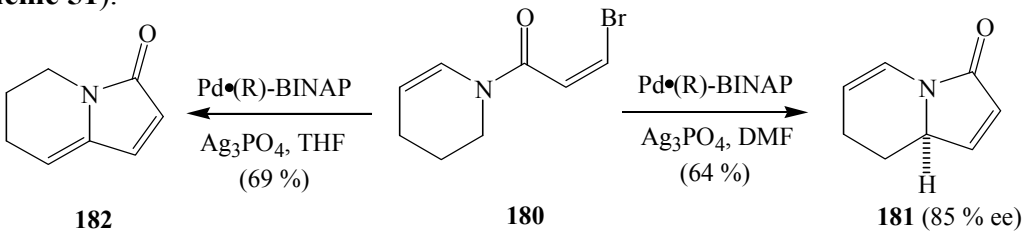
R= H, Me

X= F, Cl

179 (70-80 %)

Scheme 50

Asymmetric intramolecular Heck cyclization of enamide **180** using Ag_3PO_4 as a halide scavenger in combination with Pd·(*R*)-BINAP complex in DMF at room temperature provided **181** in 85% enantiomeric excess, while reactions conducted in tetrahydrofuran gave dieneamide **182** as the major product (**Scheme 51**).[51]

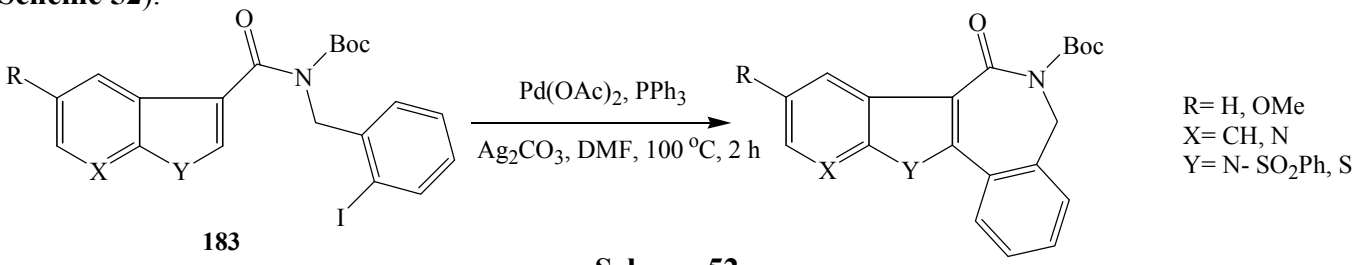


182 **180** **181** (85 % ee)

Scheme 51

2. 3 CYCLIZATION VIA FUNCTIONALIZATION OF AROMATIC C-H BONDS

The Heck reaction was effective in the presence of a $Pd(OAc)_2/PPh_3$ catalytic system and silver carbonate as base. The reaction was performed in excellent yield with 0.1 equiv of palladium catalyst in 2 h (**Scheme 52**).[52]

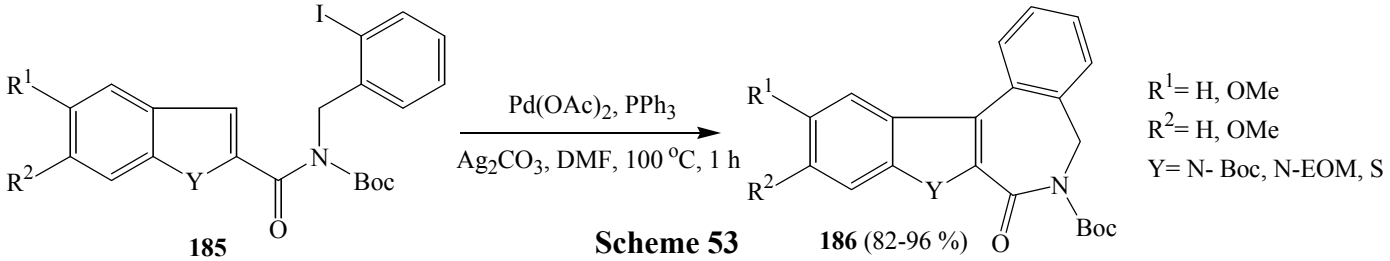


183

Scheme 52

184 (86-100 %)

Protected indole **185** was submitted to the Heck coupling reaction and afforded the desired product **186** in an excellent yield. The cyclization occurred with only 0.05 equiv of $Pd(OAc)_2$ in 1 h (**Scheme 53**).[52]



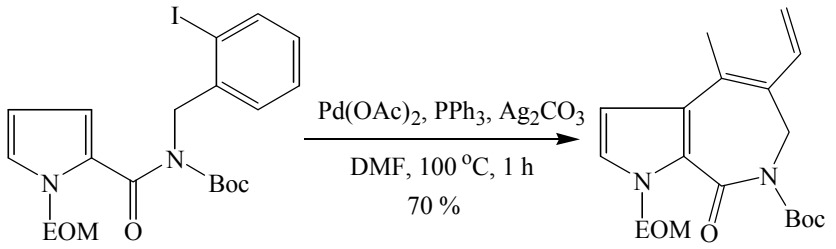
185

Scheme 53

186 (82-96 %)

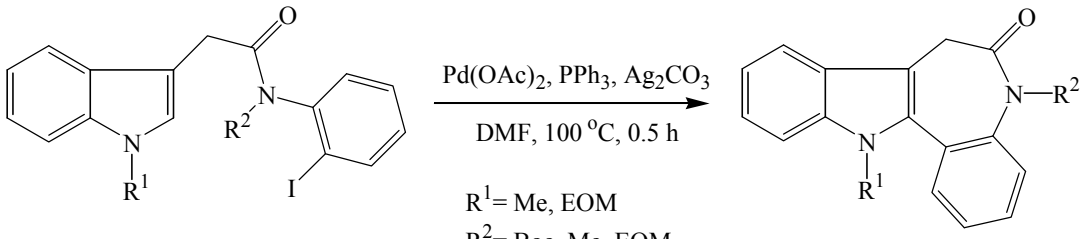
The cyclization of **187** (0.05 equiv of $Pd(OAc)_2$) afforded **188** in 59% yield and was then improved up to 70% when 0.1 equiv of $Pd(OAc)_2$ was used (**Scheme 54**).[52]

N-electron withdrawing protecting groups such as Boc or SO_2Ph prevented cyclization. However, *N*-Me and *N*-EOM compounds **189** (R^1= Me, R^2= Me) and **189** (R^1= EOM, R^2= EOM) allowed the intramolecular cyclization with excellent yield (89-92%) (**Scheme 55**).[52]



187 **188**

Scheme 54

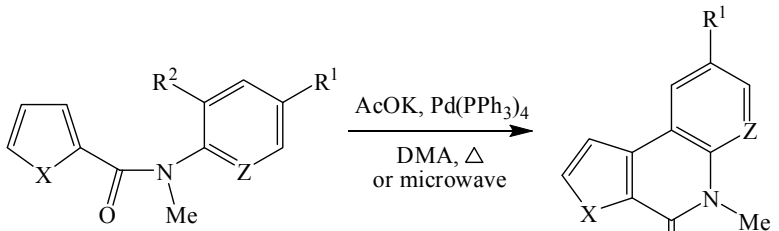


189

190 (89-92 %)

Scheme 55

Beccalli and coworkers reported the synthesis of tricyclic fused quinolone and naphthyridone derivatives, by an intramolecular Heck cyclization. They also reported the use of microwave irradiation to obtain, in some cases, better yields of cyclized products (**Scheme 56, 57**).[53]

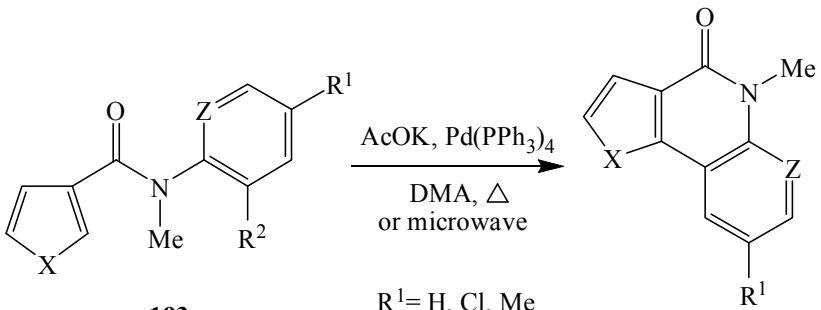


191

X= NMe, S
Z= CH, N
R^1= H, Cl, Me
R^2= I, Br

192 (49-92%)

Scheme 56



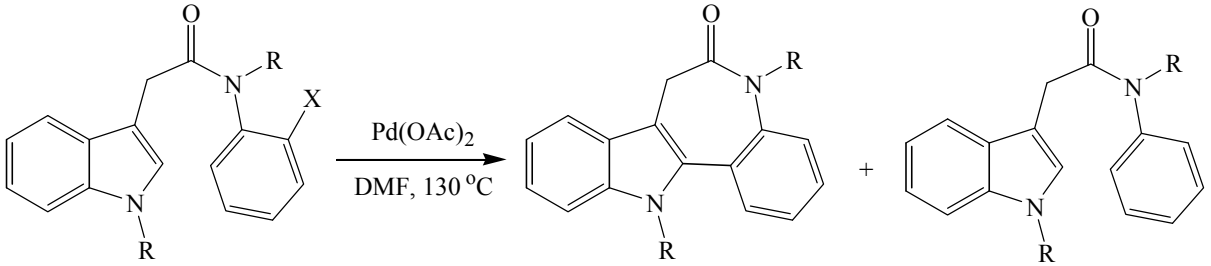
193

R^1= H, Cl, Me
R^2= I, Br
Z= CH, N
X= O, S

194 (36-96%)

Scheme 57

The short total synthesis of paullone **198** and dimethyl paullone **199** via a novel palladium-catalyzed intramolecular coupling using the *o*-bromo- and *o*-iodo anilides of indoles (**195** and **196**) and *N*-methyl indole **197** was described (**Scheme 58**).[54]



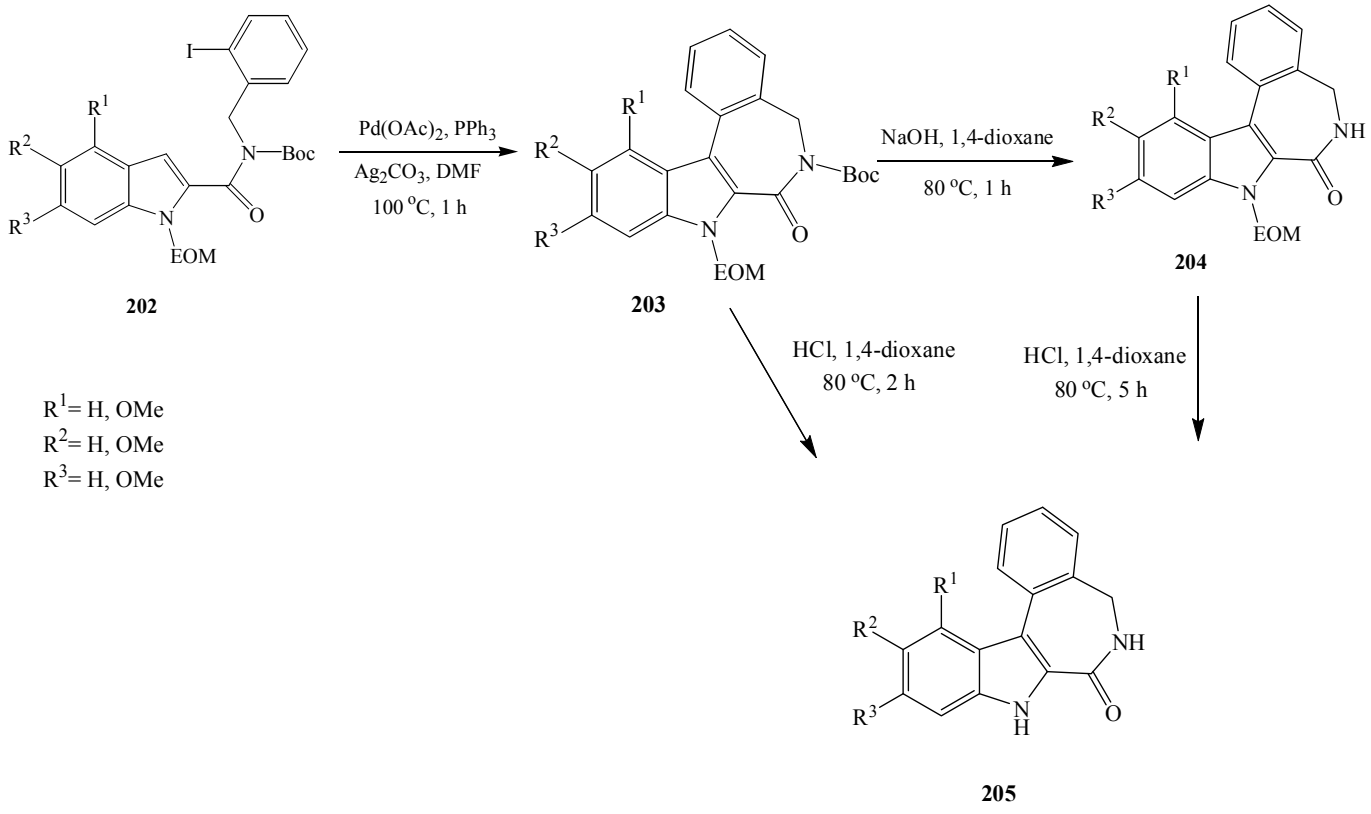
195 R= H, X= Br (condition: MgO)
196 R= H, X= I (condition: MgO)
197 R= Me, X= Br (condition: Cs_2CO_3)

198 R= H, 24 h (70 %)
199 R= Me, 30 h (86 %)

200 R= H
201 R= Me

Scheme 58

The intramolecular ring closure of **202** was performed in the presence of $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.1 equiv), and silver carbonate (2 equiv) in DMF at 100 °C for 1 h to give **203** in excellent yield Sequential deprotection of **203** was achieved by removal of the *N*-Boc group (1N NaOH and 1,4-dioxane) and then the *N*-EOM group (1N HCl and 1,4-dioxane) to afford, respectively, **204** and **205** in good yield (**Scheme 59**).[55]



202

203

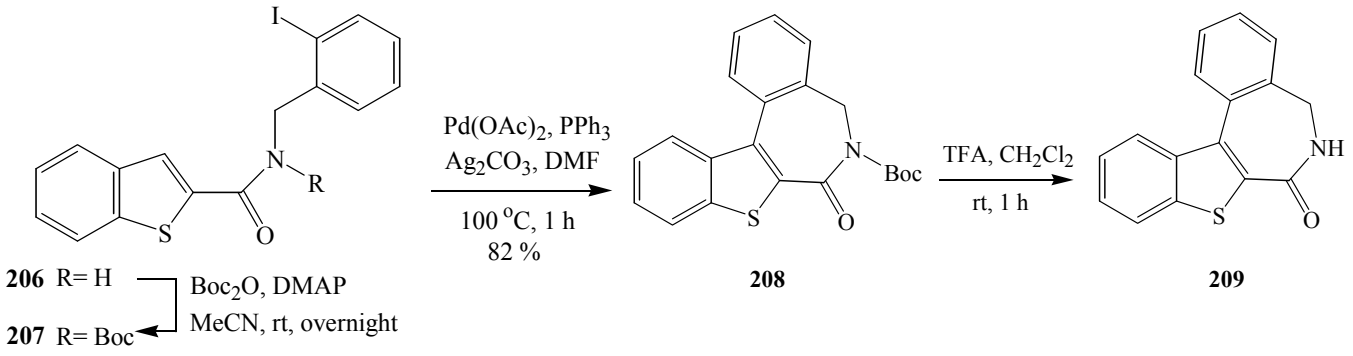
204

205

R^1= H, OMe
R^2= H, OMe
R^3= H, OMe

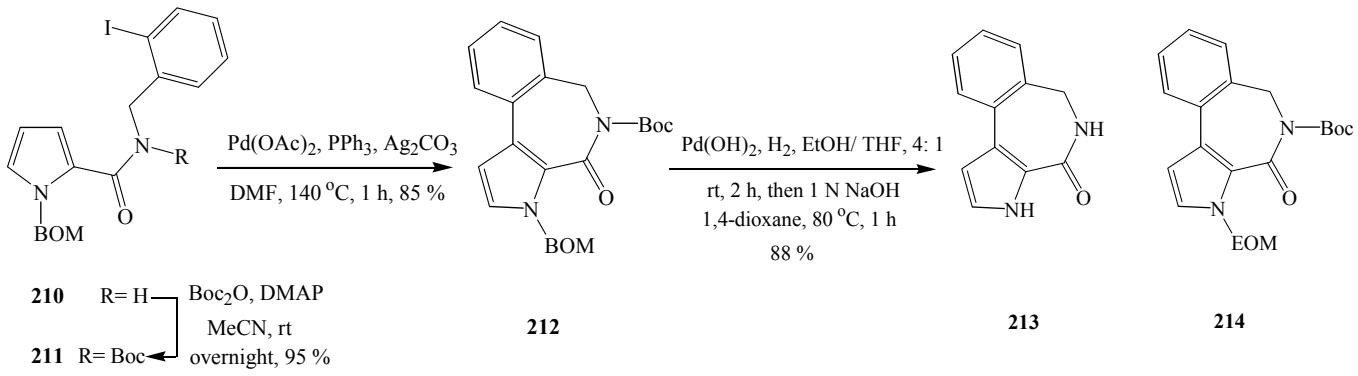
Scheme 59

Heck cyclization procedure was applied on **207** to afford **208** in 82% yield. Removal of the Boc group of **208** was effective by treatment with a solution of trifluoroacetic acid in dichloromethane at room temperature to give **209** in 88% yield (**Scheme 60**).[55]



Scheme 60

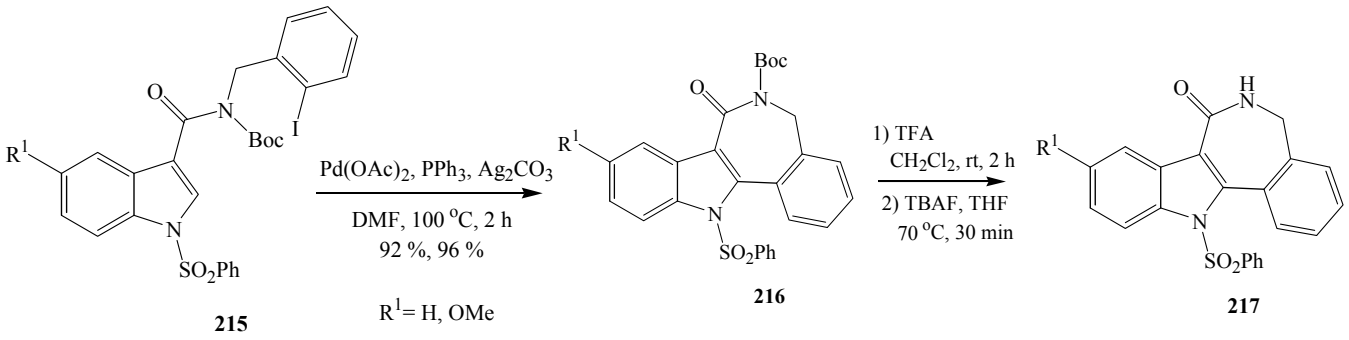
The ring closure of **210** and **211** were carried out when 0.1 equiv of $Pd(OAc)_2$, PPh_3 and Ag_2CO_3 in dimethylformamide were used and the cyclization was performed at 140 °C (**Scheme 61**).[55]



Scheme 61

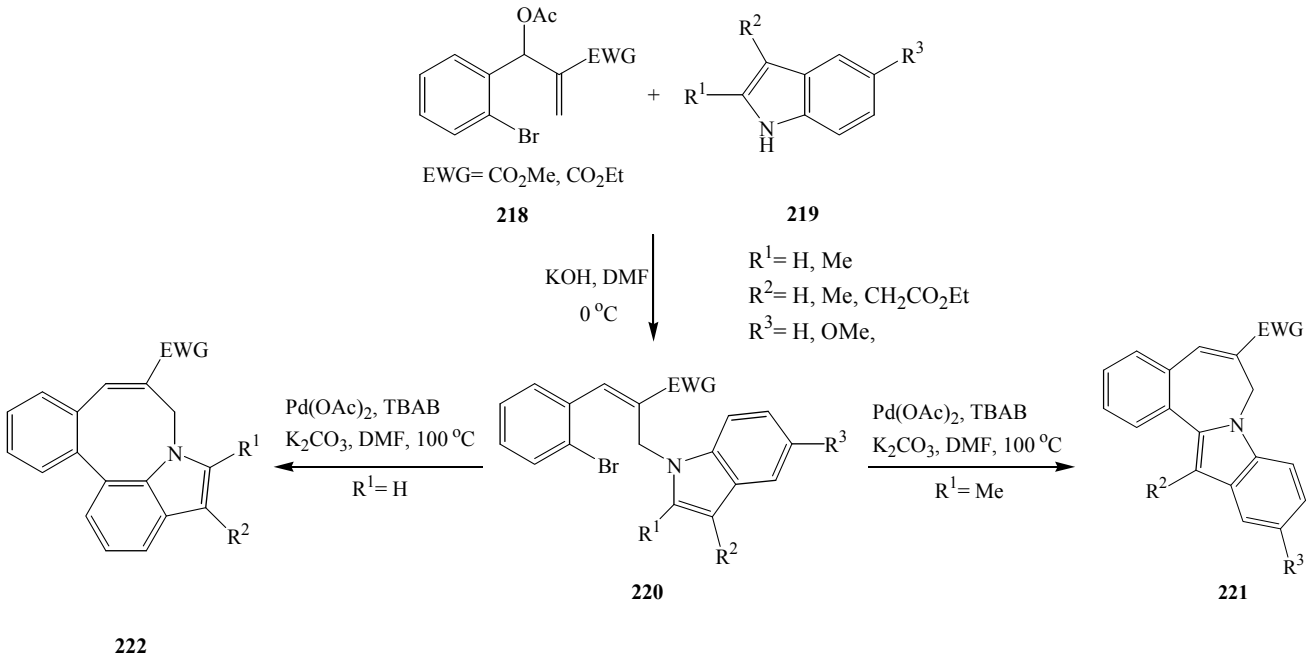
The cyclization reaction of **215** was performed in the presence of 0.1 equiv of palladium catalyst at 100 °C for 2 h to afford **216** in 92–96% yield. A two-step deprotection sequence was developed to reach compounds **217**. Removal of the *N*-Boc group was first carried out by treatment of **216** with trifluoroacetic acid in dichloromethane at room temperature followed by the second deprotection in the presence of TBAF in refluxing THF. The derivatives **217** were obtained in 40–43% yield (two-step yield) (**Scheme 62**).[55]

Lee and coworkers synthesized novel tetracyclic fused indole derivatives via the intramolecular Heck reaction of indole-containing Baylis–Hillman adducts in good to moderate yields (**Scheme 63**).[56]



215 **216** **217**

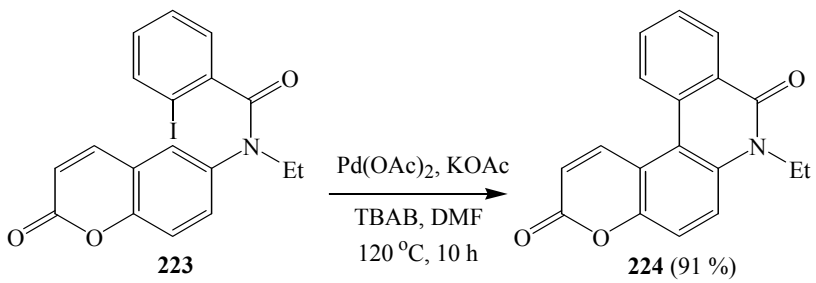
Scheme 62



218 **219** **220** **221** **222**

Scheme 63

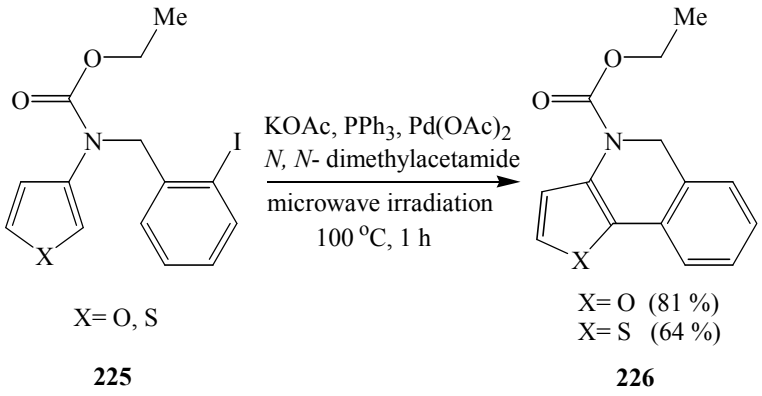
A new synthetic protocol has been developed for the arylation of secondary and *N*-alkylated amide Heck precursors by the implementation of the palladium-catalyzed intramolecular Heck reaction strategies (**Scheme 64**).[57]



223 **224** (91 %)

Scheme 64

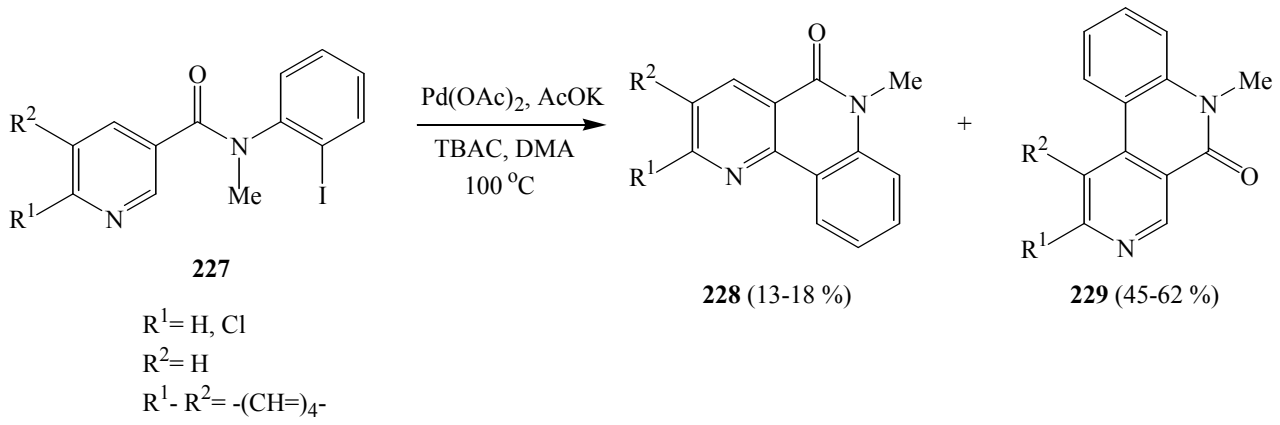
Nitrogenated heteropolycyclic systems were obtained by intramolecular palladium-catalyzed coupling reactions promoted by microwave irradiation (**Scheme 65**).[58]



225 **226**

Scheme 65

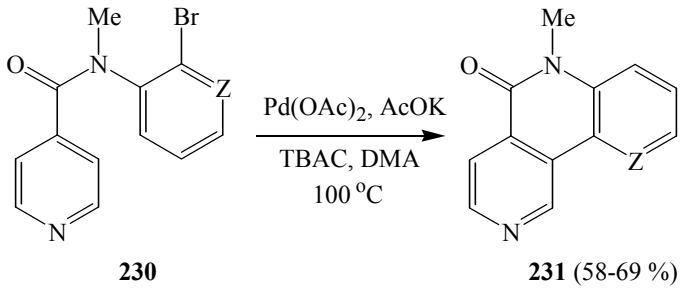
The intramolecular process, obtained using $Pd(OAc)_2$ as precatalyst, AcOK as base, TBAC as additive and DMA as solvent, afforded two regioisomers **228** and **229** arising from the cyclization on position 2 or 4 of the pyridyl ring, in 1:3 ratio in favour of the para position. Similarly tricyclic systems **231** was obtained when **230** were treated with $Pd(OAc)_2$, AcOH, TBAC and DMA at 100 °C (**Scheme 66**).[59]



227

R^1= H, Cl
R^2= H
R^1- R^2= -(CH=)$_4$-

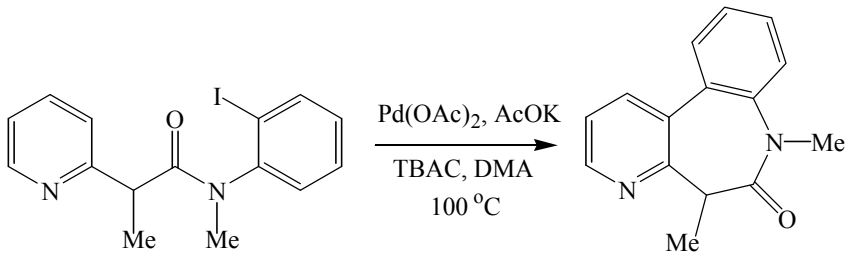
228 (13-18 %) **229** (45-62 %)



230 **231** (58-69 %)

Scheme 66

The tertiary amide **232** was then treated according to the reported conditions, to give the cyclized product **233** in good yield (**Scheme 67**).[59]



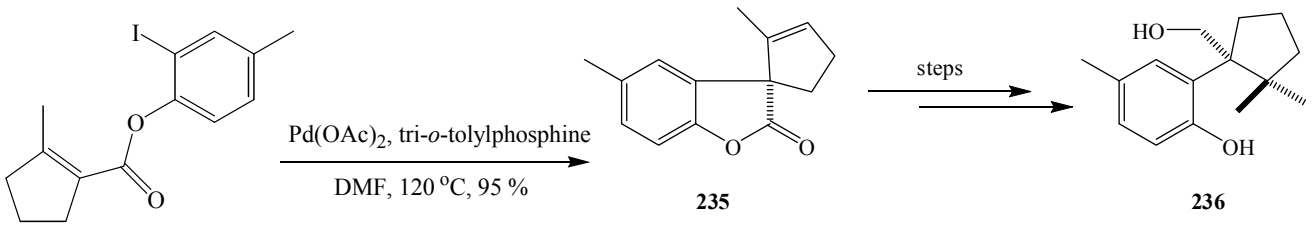
232 **233** (90 %)

Scheme 67

3. SYNTHESIS OF OXYGEN- BEARING HETEROCYCLIC COMPOUNDS

3. 1 CYCLIZATION VIA REATIONS OF ARYL HALIDES

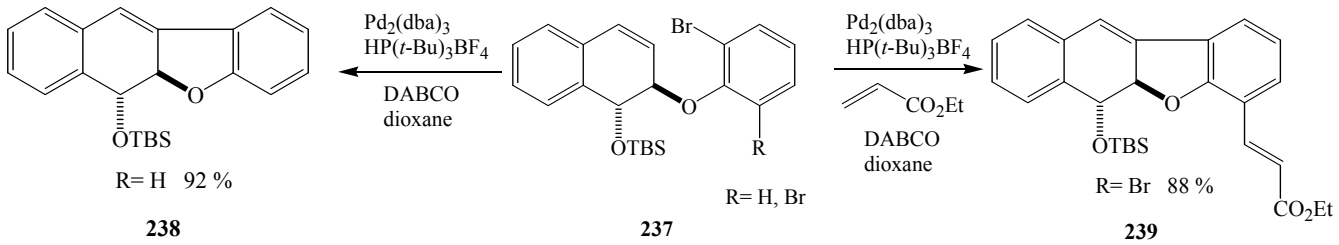
The ester **234** was subjected to Heck reaction under standard conditions (10 mol% $Pd(OAc)_2$, 20 mol% (*o*-tol)$_3$P and *n*-Bu_3N in DMF). The cyclization reaction was smoothly preceded in a 5-*exo*-trig manner to give rise to a spiro-lactone **235** in 95% yields. Finally, in the next stages, 1,13-dihydroxyherbertene **236** was obtained in 100% yield (**Scheme 68**).[60]



234 **235** **236**

Scheme 68

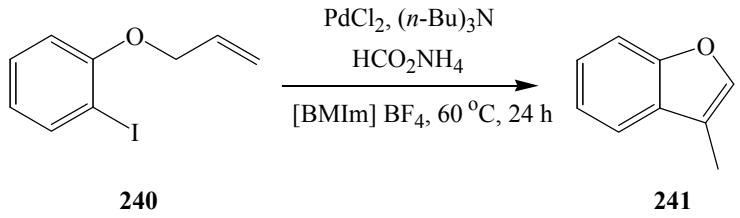
The catalytic combination of $Pd_2(dba)_3$/HP(t-Bu)$_3$.BF_4 and DABCO gave an unusual intramolecular Heck reaction with dihydronaphthalene substrates, yielding formal *anti*-hydride elimination products in good to excellent yields under mild conditions. For dibromo substrates, multiple Heck reactions was possible when an external acceptor was added to afford more highly functionalized products (**Scheme 69**).[61]



238 **237** **239**

Scheme 69

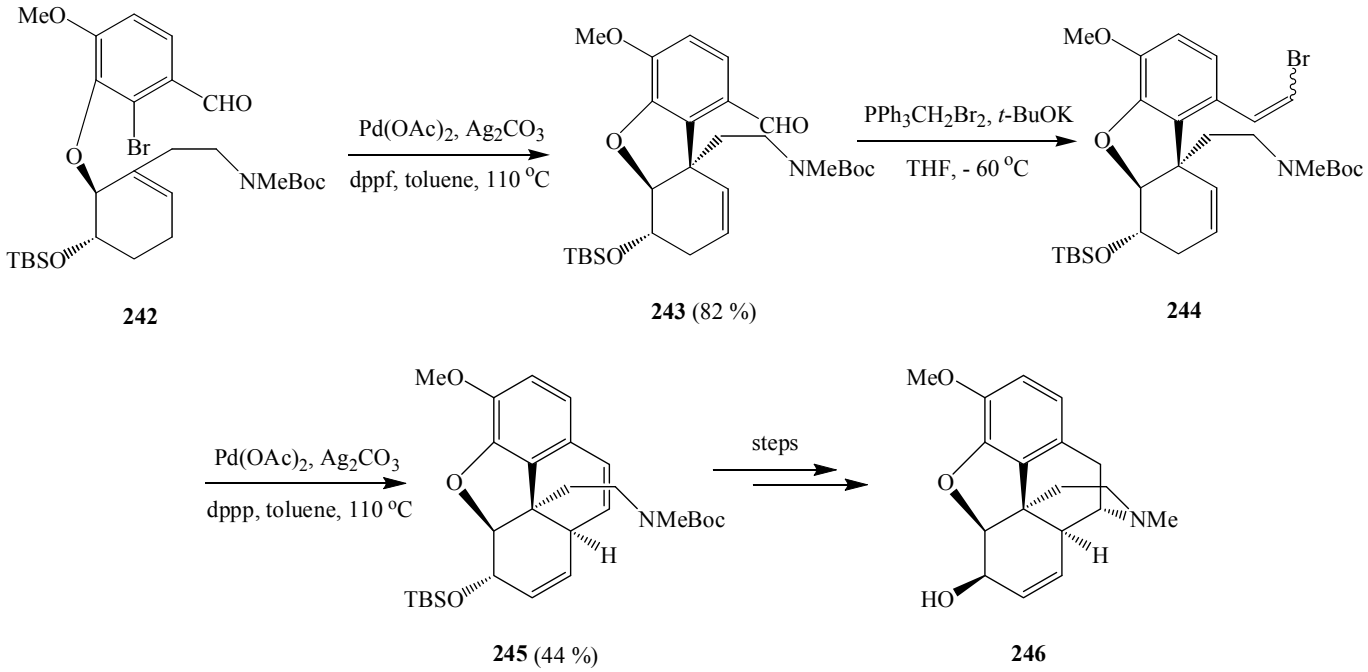
When *ortho*-iodobenzyl allyl ether was treated with 5 mol% $PdCl_2$, 1.5 equiv $(n\text{-}Bu)_3N$ and 1 equiv HCO_2NH_4 at 60 °C for 24 h, it disappeared completely and the product **241** was obtained in 71% isolated yields (**Scheme 70**).[62]



240 **241**

Scheme 70

An enzymatically generated diene diol was utilized as homochiral starting material in the total synthesis of (+)-codeine featuring a Mitsunobu inversion and two intramolecular Heck cyclizations. The first Heck cyclization was mediated by $Pd(OAc)_2$ and provided aldehyde **243** in 82% yield, which was converted to vinyl bromide **244** by a Wittig reaction. The second Heck cyclization, performed according to Trost's conditions, gave a low yield (44%) of the complete phenanthrene skeleton in **245** (**Scheme 71**).[63]

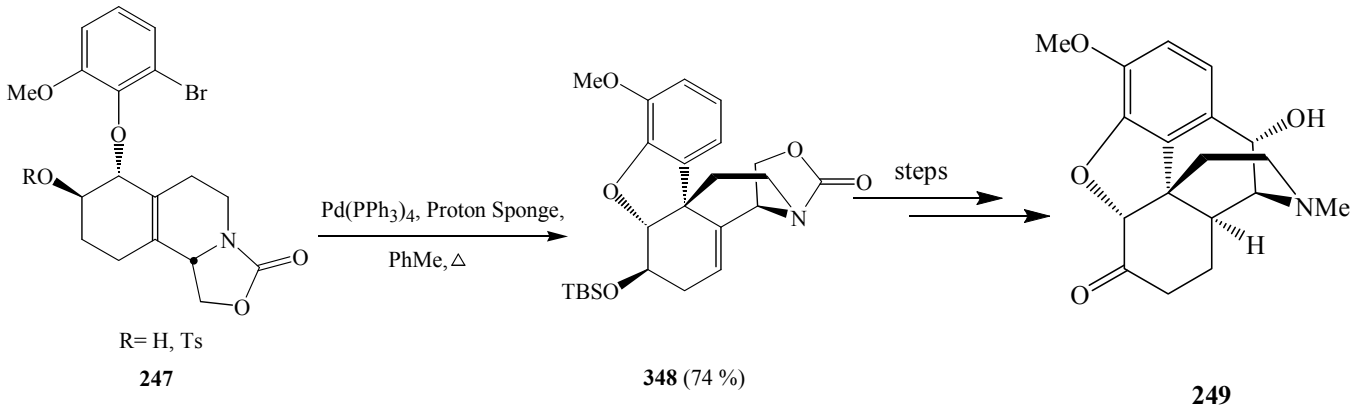


242 **243** (82 %) **244**

245 (44 %) **246**

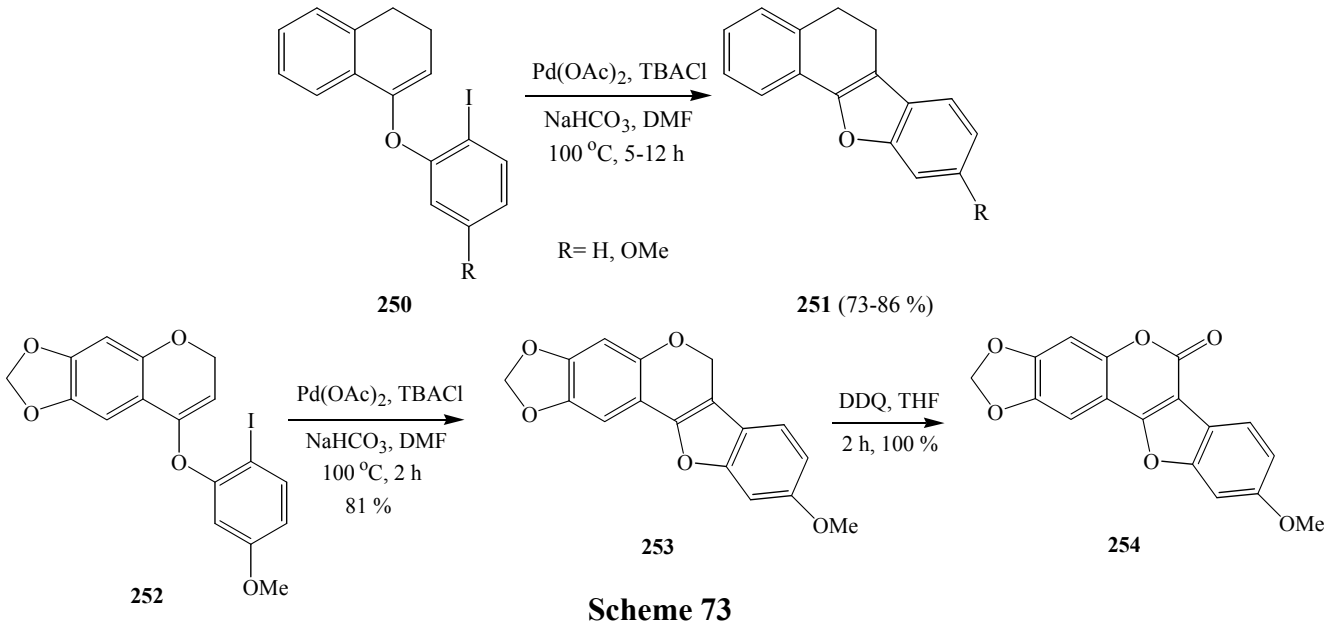
Scheme 71

Enzymatic dihydroxylation of β-bromoethylbenzene provided a homochiral diene diol that served as starting material for the synthesis of the complete morphinan skeleton via an intramolecular Heck cyclization. Protection of the C-6 hydroxyl as the silyl ether **247** (R= TBS) provided the key intermediate for the Heck reaction leading to the pentacyclic carbamate **248** in 74% yield (**Scheme 72**).[64]



Scheme 72

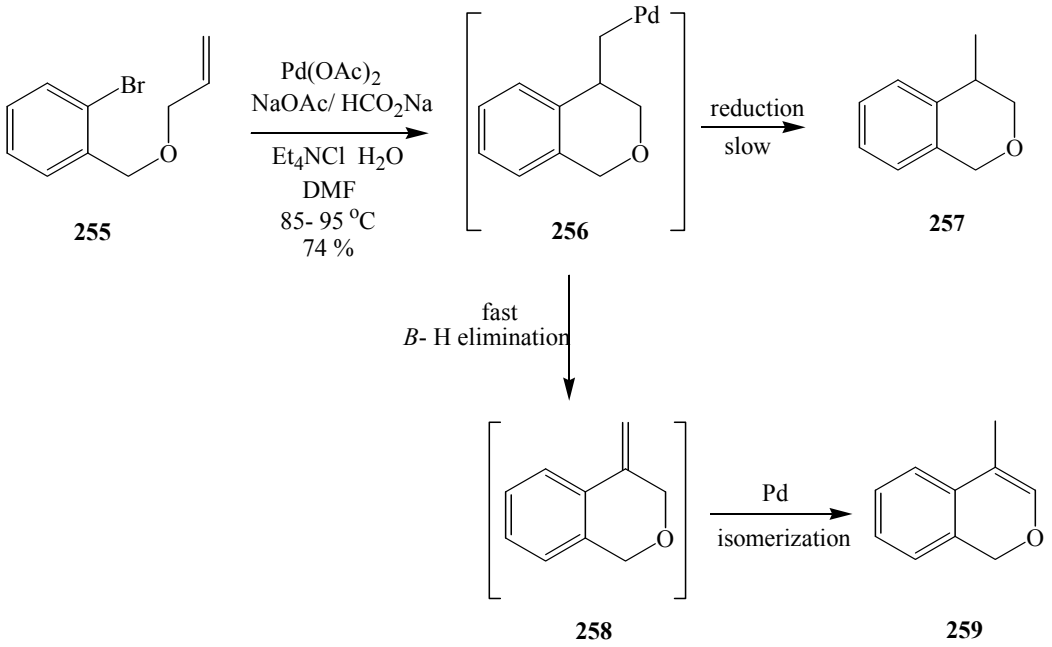
These olefins **250** cyclized to the corresponding 5-desoxipterocarpens **251** (R=H, OMe) in the presence of 5 mol% of $Pd(OAc)_2$ and Pterocarpen **253** was obtained from **252** through an intramolecular Heck reaction in the presence of 5 mol% of $Pd(OAc)_2$. Finally, coumestan **254** was prepared in quantitative yield by oxidation of **253** with DDQ in THF (**Scheme 73**).[65]



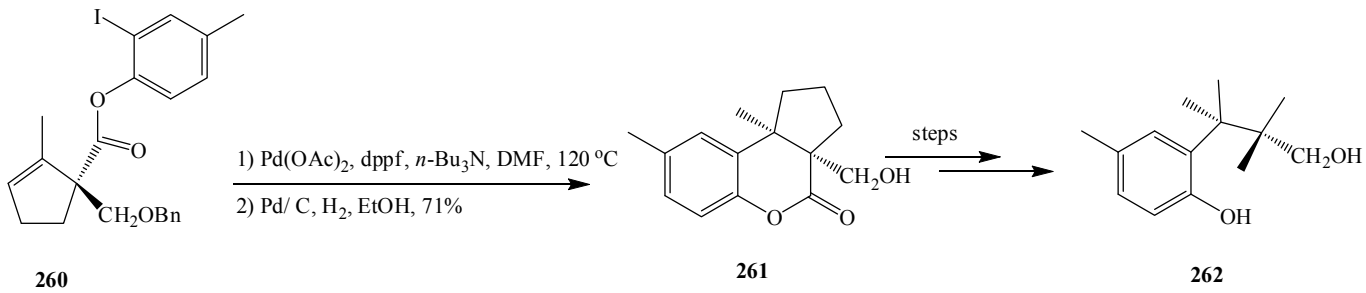
Scheme 73

Synthesis of **257** and **259**, in 74% yield by a ligand-free palladium catalyzed reductive Heck cyclization of phenyl bromides, under mild conditions, was reported. Water was found to be essential for this reaction (**Scheme 74**).[17]

Intramolecular Heck reaction of **260**, followed by hydrogenation, smoothly proceeded to afford the lactone **261** in 71% yields. Finally, in the next stages, 1,15-dihydroxyherbetene **262** was obtained in 83% yield (**Scheme 75**).[60]



Scheme 74



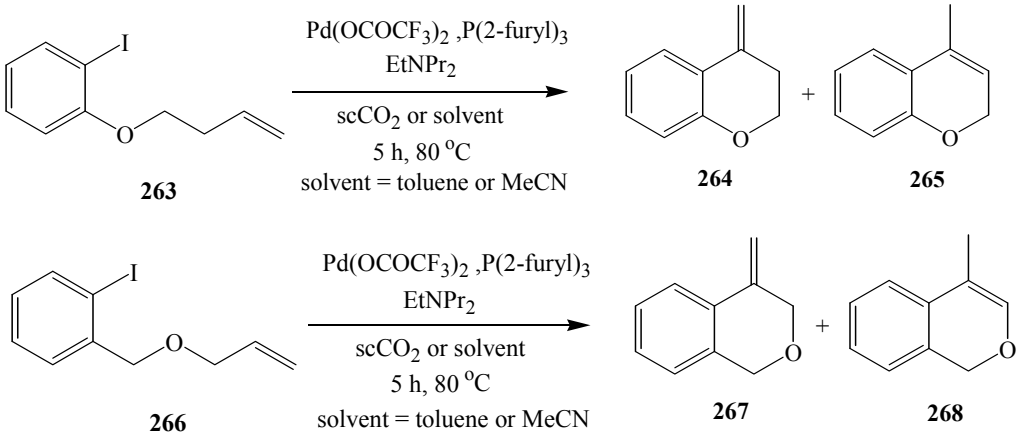
Scheme 75

The modified reagent system [$Pd(OCOCF_3)_2$/$P(2\text{-furyl})_3$/EtN^iPr_2] gave enhanced conversions compared with standard conditions [$Pd(OAc)_2$/PPh_3/NEt_3] for intramolecular Heck cyclizations, and when used in supercritical carbon dioxide ($scCO_2$) results in the suppression of double bond isomerisation to minimal levels, which is otherwise a serious competing side reaction in conventional solvents (**Scheme 76**).[66]

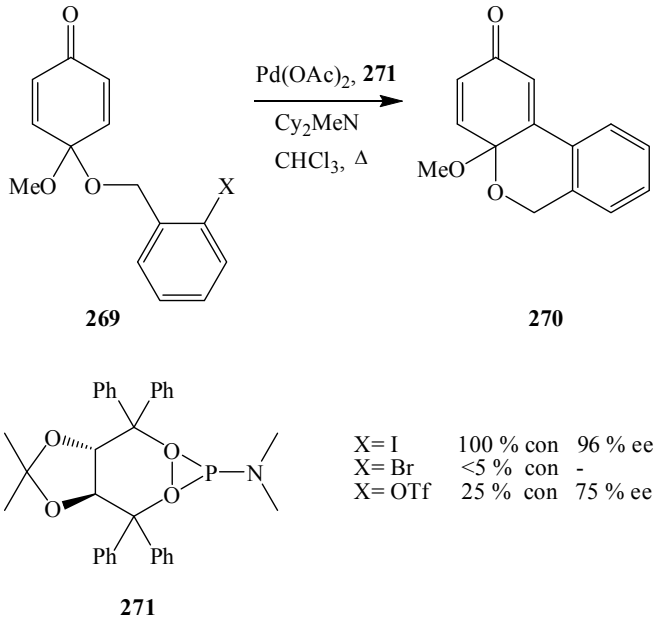
An *in situ* formed catalyst of $Pd(OAc)_2$ and ligand **271** (10 mol%, Pd : L ratio = 1 : 2) was utilized and the reaction was performed in $CHCl_3$, using 3 equiv of Cy_2MeN as a base. The reaction mixture was heated to 80 °C for 48 h under an inert atmosphere (**Scheme 77**).[67]

Compound **272** was reacted under standard Heck condition to give a mixture of three isomeric 5-nitro-1-benzopyrans (**273-274-275**) in an 18:4:1 ratio. Reductive *N*-heteroannulation of **273** using 10 mol% palladium diacetate ($Pd(OAc)_2$), 20 mol% 1,3-bis(diphenylphosphino)propane (dppp) in DMF at 120 °C

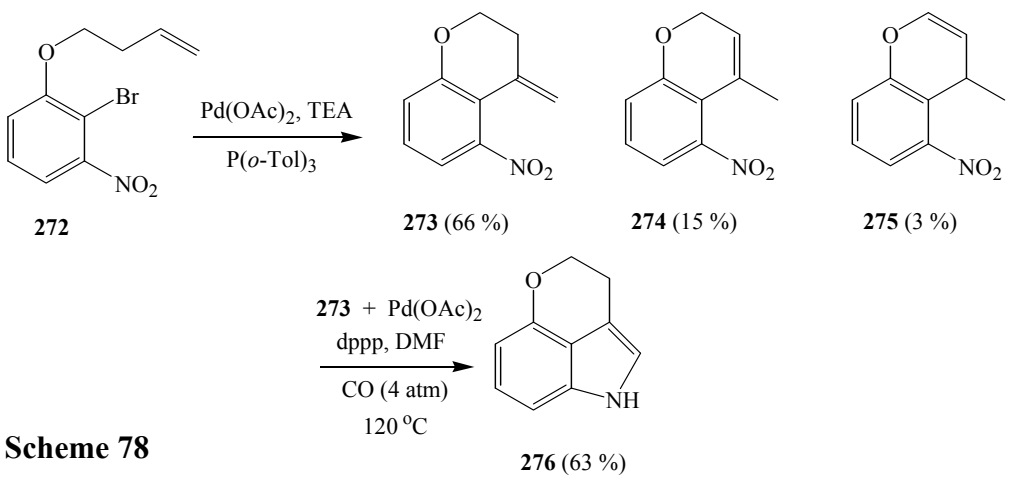
and 4 atm of carbon monoxide gave an acceptable 63% yield of the fused indole **276** after 70 h (**Scheme 78**).[68]



Scheme 76

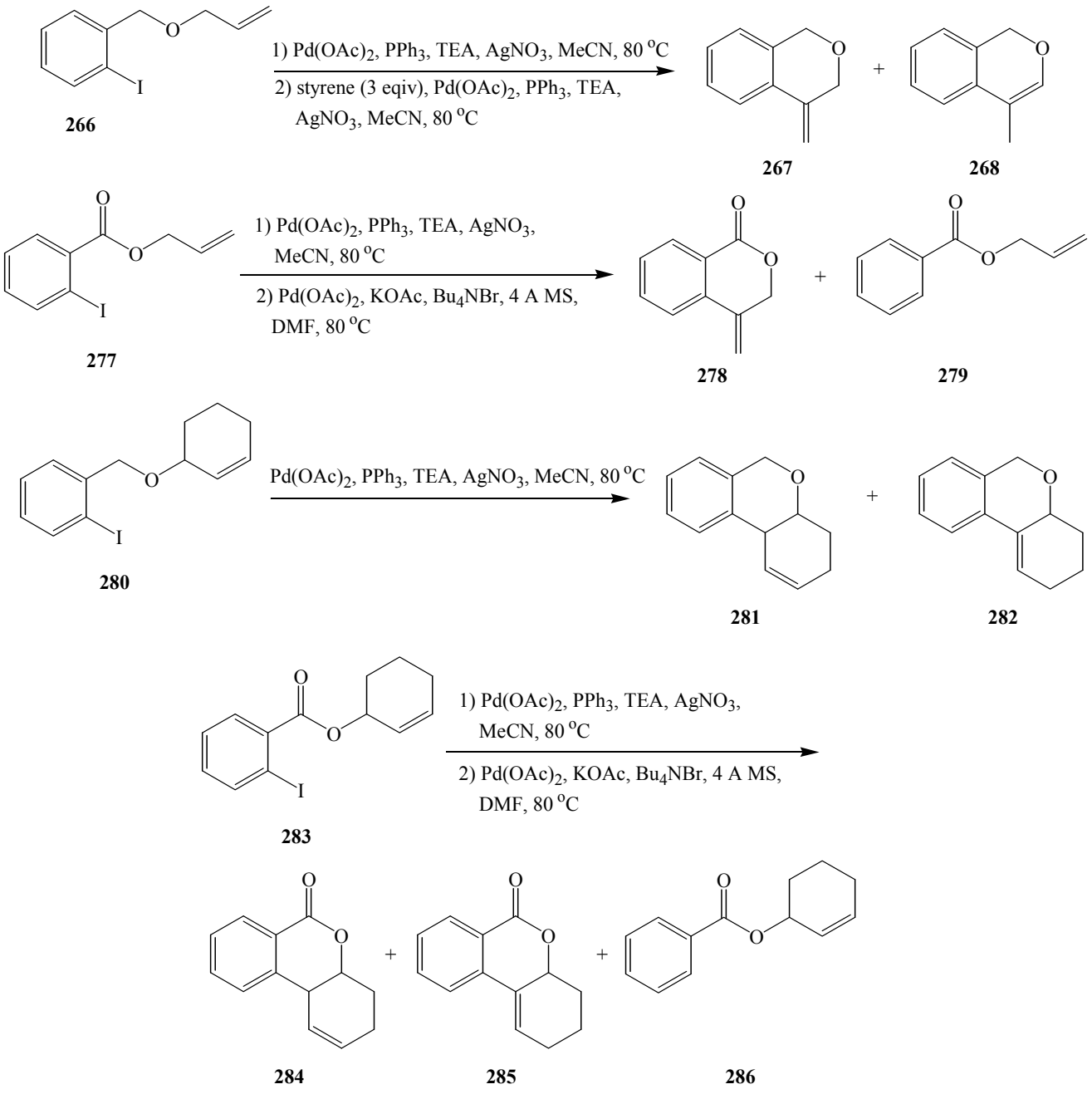


Scheme 77



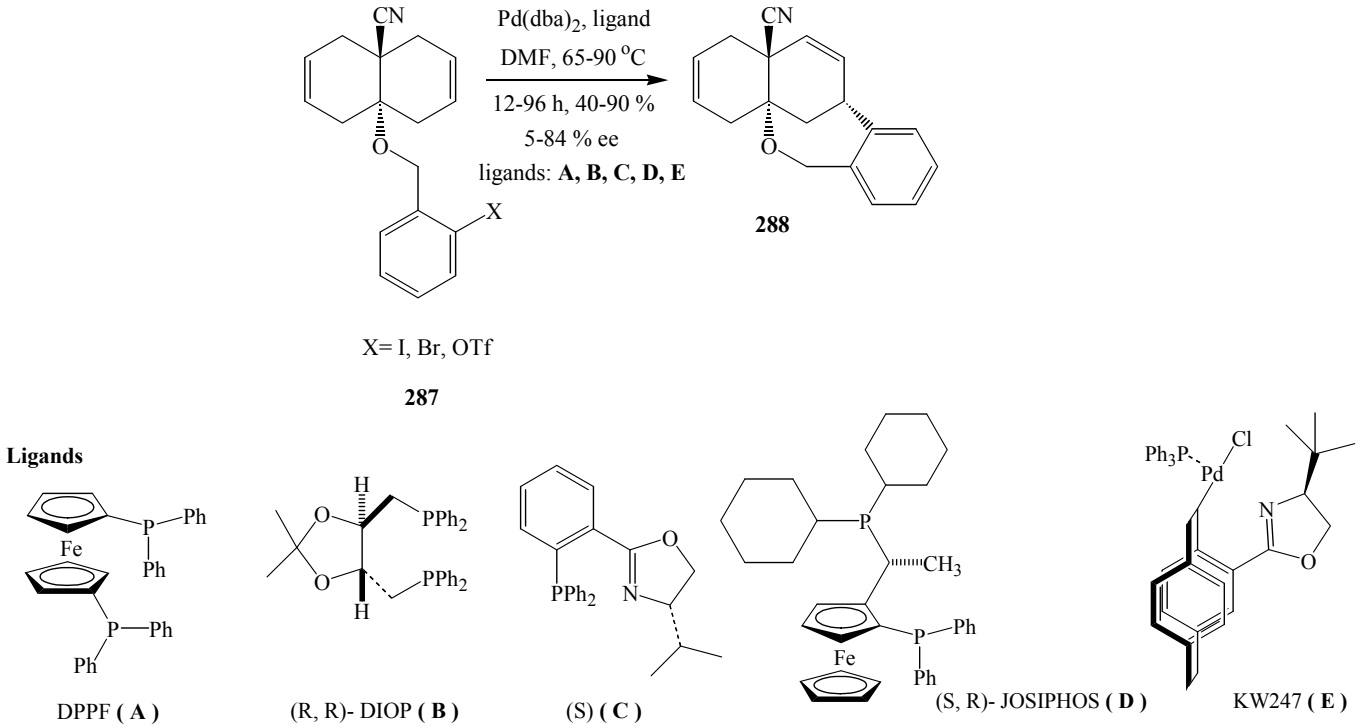
Scheme 78

Allyl 2-iodobenzyl ether **266**, allyl 2-iodobenzoate **277**, cyclohexenyl 2-iodobenzyl ether **280**, and cyclohexenyl 2-iodobenzoate **283** were subjected to Heck conditions [$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), TEA (2 equiv), $AgNO_3$ (1 equiv), MeCN, 80 ^oC], and the products were isolated by flash chromatography. For ether-tethered aryl iodides **266** and **280**, cyclization gave high yields of products **267+269** and **281+282**. Ester-tethered aryl iodides **277** and **283** gave only unreacted starting material and deiodinated, uncyclized products **279** and **286**. Ester-tethered cyclization products **278** and **284+285** were produced in trace amounts. Oxidation of cyclic ethers **281+282** with PCC provided cyclic esters **284+285** in good yield (59%) (**Scheme 79**).[69]



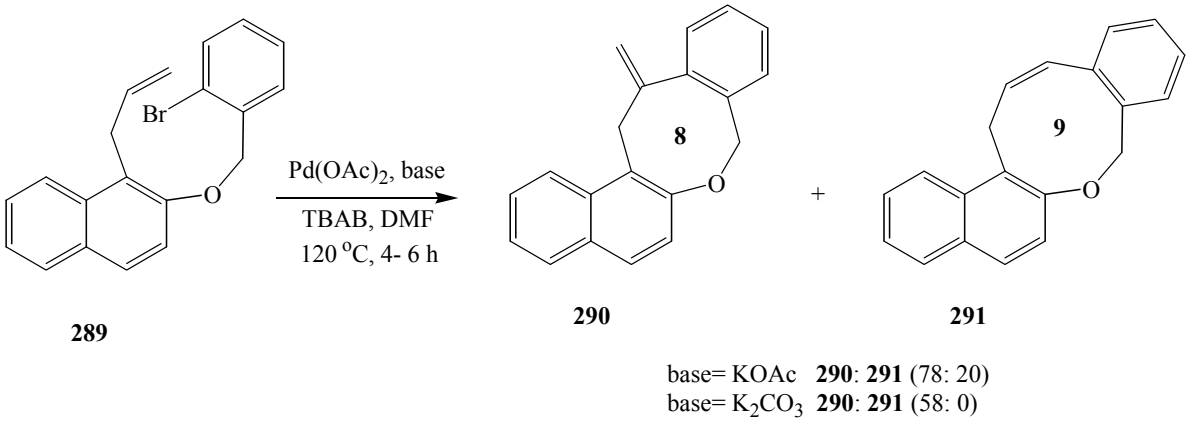
Scheme 79

Heck reaction with iodide **287** (X=I), bromide **287** (X=Br) and triflate **287** (X=OTf) under various conditions led to the formation of **288** with different results. The usual ligands for asymmetric Heck reactions, BINAP or the oxazoline **C**, led to very low enantioselection or no conversion at all. The conversion rates could be increased by the addition of silver carbonate, but this had almost no positive effect on the enantiomeric excess. Other ligands ((R)-PHANEPHOS, (S, S)ET-BPE, ligand **E**) were either inactive or produced tricycles with low stereoinduction. The use of the JOSIPHOS ligand **D**, employed primarily in hydrogenation reactions, gave a remarkably high enantiomeric excess. Recrystallisation of this product gave a virtually enantiopure material. Additionally, the use of bromide **287** (X=Br) gave almost the same enantiomeric excess but with lesser yield than the use of **287** (X=I). However, in this case, the conversion of starting material was complete. The reaction gave rise to the hydrogenated product **287** (X=H), which in the case of the iodide was only observed with an addition of silver carbonate. The change from a bromide to a triflate or non-aflate leaving group had almost no effect on the stereoinduction of the product, although the yields were relatively lower (**Scheme 80**).[70]



Scheme 80

When the intramolecular Heck reaction was carried out with **289** in the presence of 10 mol% of $Pd(OAc)_2$ as a catalyst and KOAc (2.75 equiv) as a base and tetrabutylammonium bromide as a promoter in DMF at 120 °C for 4–6 h, the 8-*exo* cyclized product **290** was obtained as the major product in 78 % yield, along with the 9-*endo* cyclized **291** as a minor product in 20% yield (**Scheme 81**).[71]

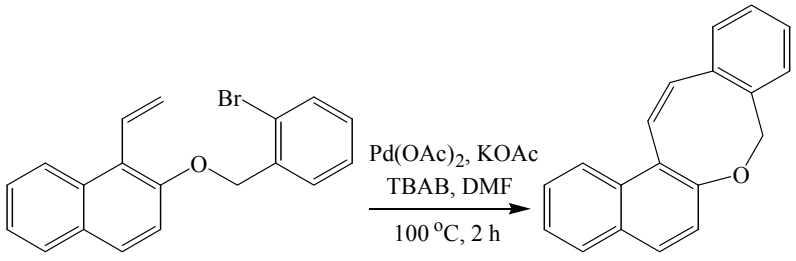


289 **290** **291**

base= KOAc **290**: **291** (78: 20)
base= K_2CO_3 **290**: **291** (58: 0)

Scheme 81

When the intramolecular Heck reaction was performed with precursor **292** in the presence of $Pd(OAc)_2$ as a catalyst, KOAc as a base, and tetrabutylammonium bromide (TBAB) as an additive in dry DMF as solvent for 2 h under a nitrogen atmosphere, the eight-membered naphthoxocine compound **293** was obtained in excellent yield (86%) (**Scheme 82**).[72]



292 **293** (86 %)

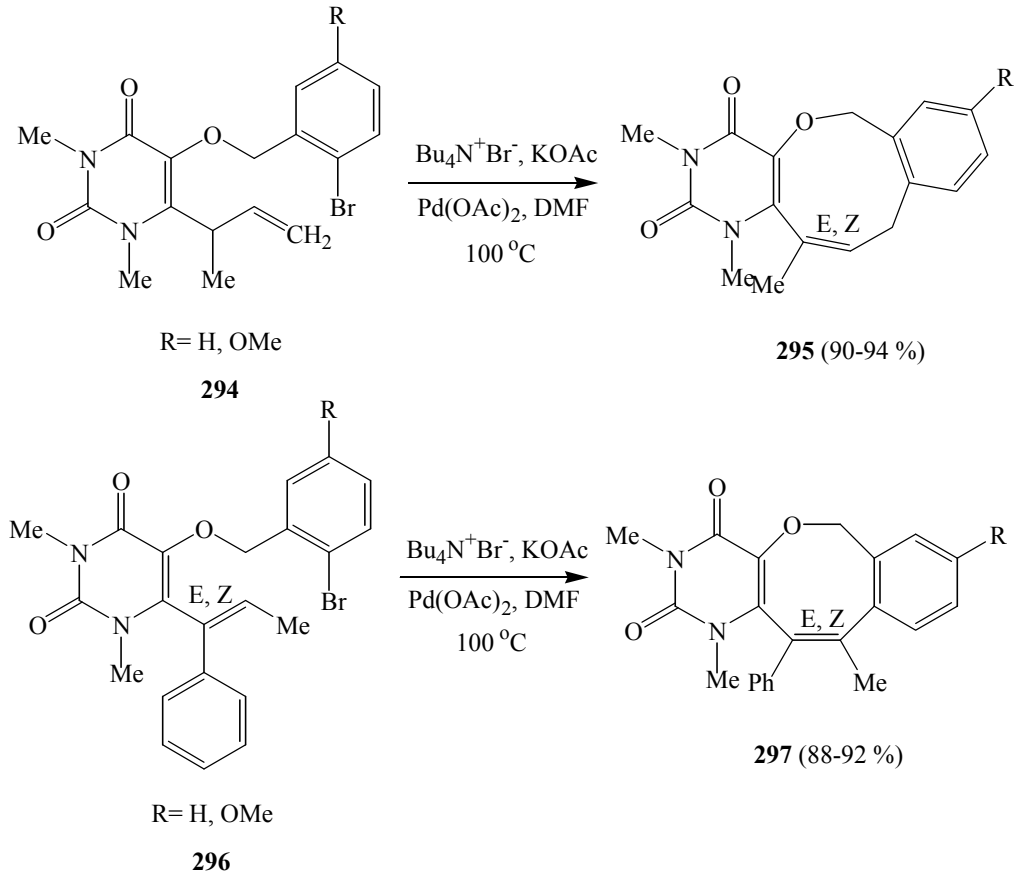
Scheme 82

Syntheses of nine-membered oxa-heterocyclic compounds by the application of the intramolecular Heck reaction have been difficult to develop. Herein, Majumdarand and Chattopadhyay, described the synthesis of this class of compounds through the 9-*endo-trig* cyclization and 8-*endo-trig* cyclization, respectively a rare mode of cyclization in the literature (**Scheme 83**).[73]

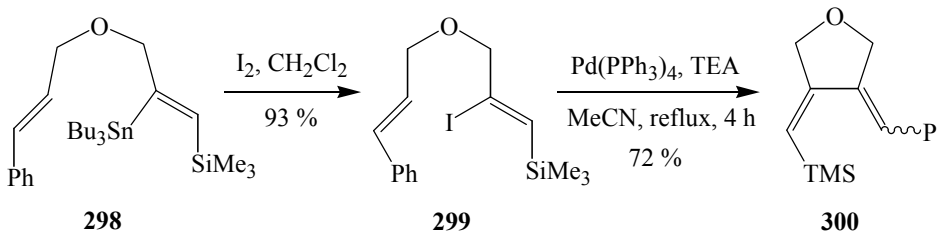
3. 2 CYCLIZATION VIA REACTIONS OF VINYL HALIDES

The vinyl iodide **299** was prepared starting from propargyl bromide and *trans*-cinnamyl alcohol in three steps and was subjected to intramolecular Heck reactions to give the product as a mixture of two isomers in a ratio of 9:1, with the (*Z,E*)-product **300** predominating (**Scheme 84**).[74]

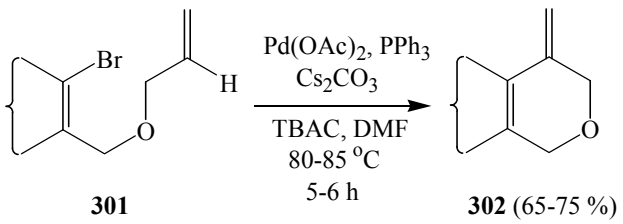
The intramolecular Heck reaction was performed with *O*-allylated **301** in the presence of $Pd(OAc)_2$, PPh_3, Cs_2CO_3 and TBAC (tetrabutylammonium chloride) in DMF at 80-85 °C to afford pyran derivatives **302** (**Scheme 85**).[75]



Scheme 83

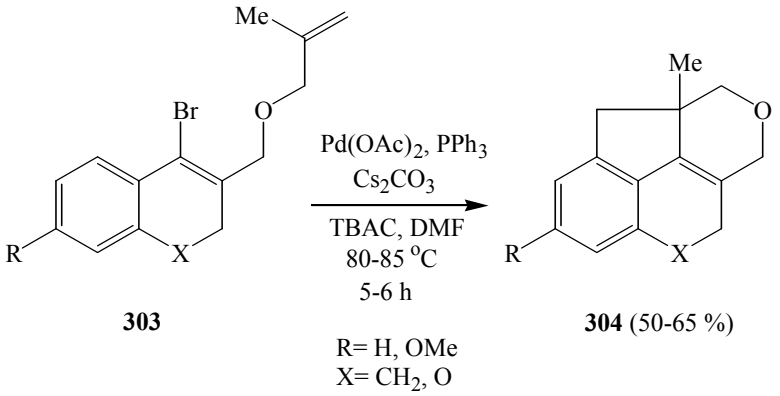


Scheme 84



Scheme 85

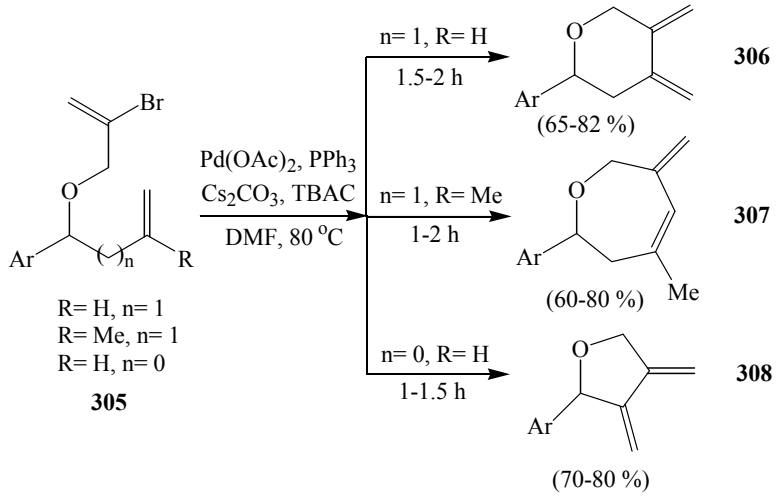
O-Methallylated compounds **303** and aromatized compounds were subjected to intramolecular Heck reaction under the same conditions ($Pd(OAc)_2$, PPh_3, Cs_2CO_3 and TBAC (tetrabutylammonium chloride) in DMF at 80-85 °C) to afford pyrans **304** (**Scheme 86**).[75]



303 **304** (50-65 %)

Scheme 86

An efficient and convenient method for the synthesis of 2-aryl substituted tetrahydropyran, tetrahydrofuran, and oxepine derivatives via palladium catalyzed intramolecular Heck reaction was developed (**Scheme 87**).[76]

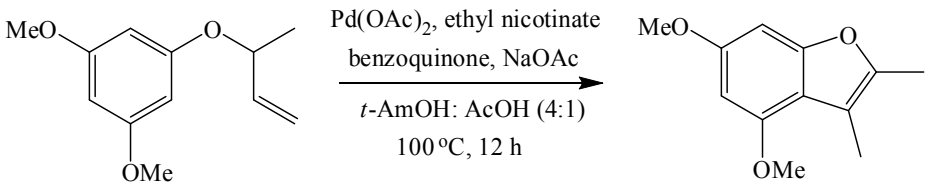


305 **306** **307** **308**

Scheme 87

3. 3 CYCLIZATION VIA FUNCTIONALIZATION OF AROMATIC C-H BONDS

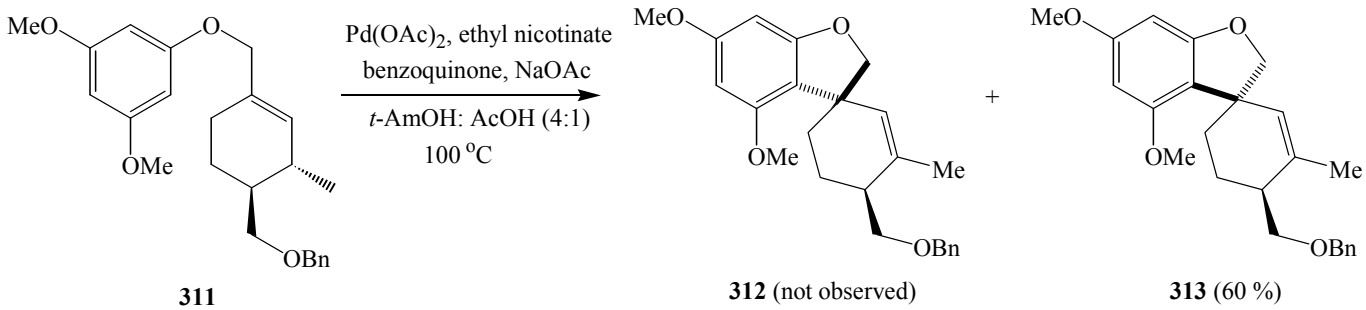
It was found that a 1:2 ratio of Pd:ethyl nicotinate was ideal and that inclusion of a substoichiometric amount of NaOAc (20 mol%) provided increased yields. Finally, increasing the temperature to 100 °C led to optimal results, providing benzofuran **310** in 77% yield after 12 h (**Scheme 88**).[77]



309 **310** (77 %)

Scheme 88

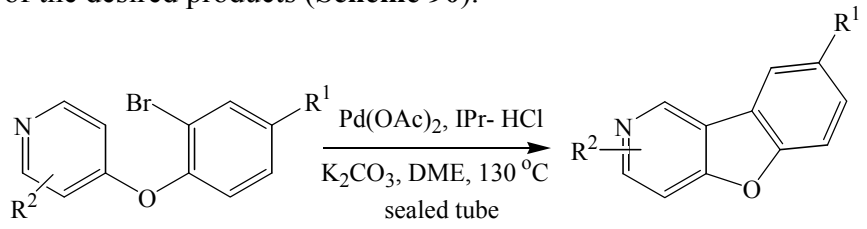
Under standard reaction conditions ($Pd(OAc)_2$ 10 mol%, ethyl nicotinate 20 mol%, benzoquinone 1 equiv, NaOAc 20 mol%, *t*-AmOH: AcOH 4: 1, 100 °C), ether **311** cyclized to produce a diastereomerically pure product in 60% yield, which was determined to be dihydrobenzofuran **313** by ^1H NMR NOE experiments (**Scheme 89**).[77]



311 **312** (not observed) **313** (60 %)

Scheme 89

2-bromophenoxy pyridines were treated with $Pd(OAc)_2$ to afford functionalized benzo[4,5]furo-[3,2-*c*]pyridine **315**. Under optimized conditions, both electron-deficient and electron-donating substrates gave good yields of the desired products (**Scheme 90**).[78]



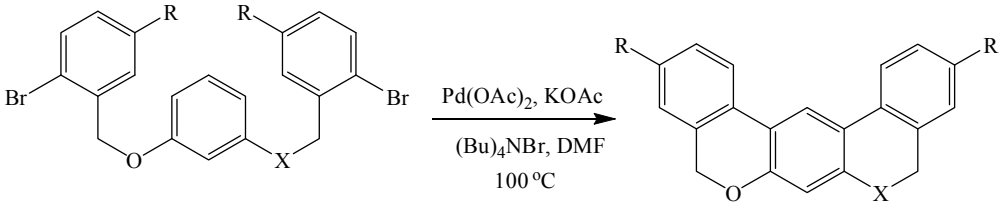
314 **315** (5-95 %)

R^1= H, CO_2Et, NO_2, OMe, Cl, F
R^2= H, NO_2, CONHMe

ligand= IPr-HCl= 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride

Scheme 90

Precursor **316**, when subjected to intramolecular Heck reaction in the presence of 10 mol% of $Pd(OAc)_2$ as catalyst KOAc as base and tetrabutylammonium bromide as promoter in DMF at about 100 °C, afforded linearly fused bis-cyclized product **317** (**Scheme 91**).[79]



R= H, OMe
X= O, NH

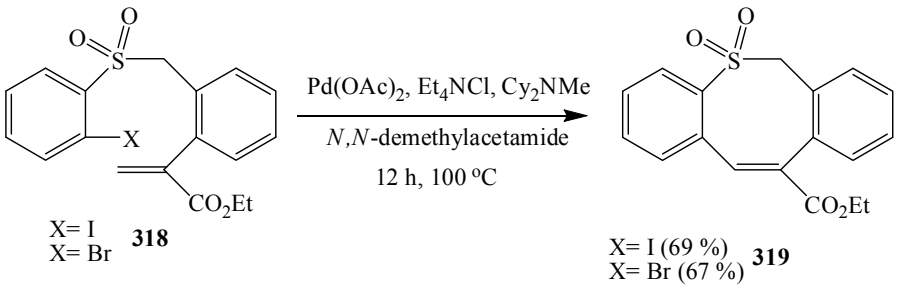
316

317 (75-80%)

Scheme 91

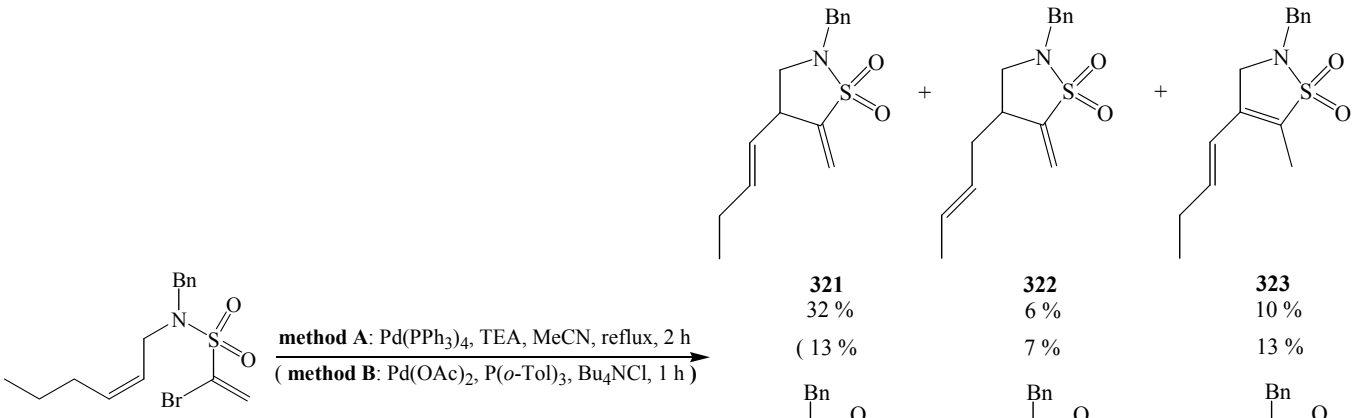
4. SYNTHESIS OF HETEROCYCLIC COMPOUNDS CONTAININ SULFUR, SULFUR AND NITROGEN, SULFUR AND OXYGEN

Both the iodo and bromo derivatives **318** afforded cyclic products in good yield when exposed to the Heck reaction conditions (67% and 69%), giving a novel cyclic sulfone **319** (**Scheme 92**).[43]



Scheme 92

For Heck cyclizations of the α-bromovinylsulfonamides Merten and his coworkers chose two established catalytic systems. Besides standard conditions **A**, they also applied conditions **B**, which have recently been utilized for the synthesis of lactams via a tandem Heck-allylic substitution reaction. However, next to formation of the expected α-methylene-γ-sultams, double bond migration by readdition of the palladium hydride species and occasionally also a complementary regioselectivity of carbopalladation (6-*endo* instead of 5-*exo*) was noticed under both conditions. Since these undesired features were especially pronounced for substrate **320**, Merten and his cowokers investigated the effect of silver and thallium additives on the Heck cyclization of this bromovinylsulfonamide (**Scheme 93**).[80]

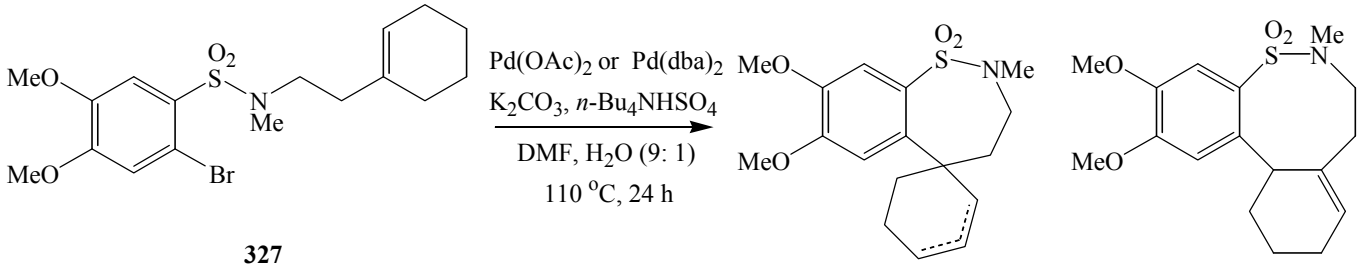


Effect of silver and thallium salts on the Heck cyclization of **320**

Additive	t [h]	Sultams	
Ag_3PO_4	29	**321** (58 %)	**322** (10 %)
Ag_2CO_3	48	**321** (58 %)	
Tl_2CO_3	14	**321** (58 %)	**323** (5 %)
TlOAc	2.5	**321** (58 %)	

Scheme 93

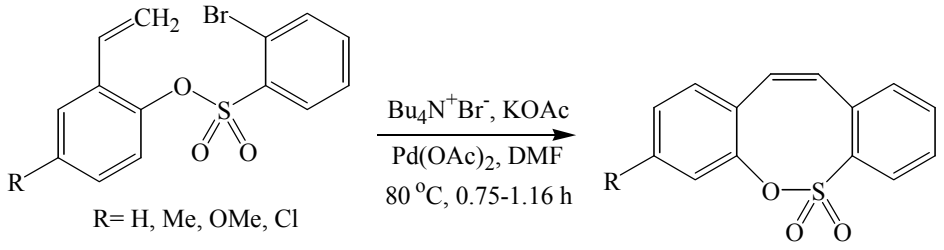
Substrate **327** was subjected to standard Heck conditions in the hope that a regioselective cyclisation would occur. In the event, using catalytic amounts of either $Pd(OAc)_2$ or $Pd(dba)_2$, starting material **327** was completely consumed (**Scheme 94**).[81]



327 **328** **329**

Scheme 94

Syntheses of hitherto unreported heterocycles, such as oxathiocine derivatives, in excellent yields, and a doubly cyclized oxathiocine derivative, through a intramolecular Heck reaction via an unusual 8-*endo-trig* cyclization, were reported (**Scheme 95**).[82]



330 **331** (79-91 %)

Scheme 95

5. CONCLUSION

In this review, we have presented numerous very useful processes for the synthesis of heterocycles, via intramolecular Heck cyclization, reported in recent years. The reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups. Most palladium-based methodologies proceed stereo- and regioselectively in excellent yields.

6. ACKNOWLEDGEMENTS

The authors are thankful to Alzahra university Research Council for partial financial support.

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Majid. M. Heravi was born in 1952 in Mashhad, Iran. He received his BSc degree from the National University of Iran in 1975 and his MSc and Ph.D degrees from Salford University, England in 1977 and 1980. He completed his doctoral thesis under supervision of the late Jim Clarck in Salford University. He started his career as a research fellow in Daroupakksh (a pharmaceutical company) in 1981 Tehran, Iran and joined as an assistant professor to Ferdowsi University of Mashhad. Iran. In 1999 he moved to Azzahra University Tehran, Iran as professor of chemistry where he is still working in. He has previously been a visiting professor at UC Riverside, California, USA and Hamburg University, Hamburg, Germany. His research interests focus on heterocyclic chemistry, catalysis and organic methodology.

Azadeh Fazeli was born in 1980 in Tehran, Iran. She received her B.Sc. degree from Islamic Azad University, Tehran, Iran in 2002 and her M.Sc. degree from K. N. Toosi University, Tehran, Iran, in 2006. She admitted as a Ph.D student at Azzahra University Tehran, Iran in 2008. She is presently continuing her studies in a course leading to Ph.D degree in organic chemistry.