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C-N and N-N bond formation via Reductive Cyclization: Progress in Cadogan /Cadogan-Sundberg Reaction‡

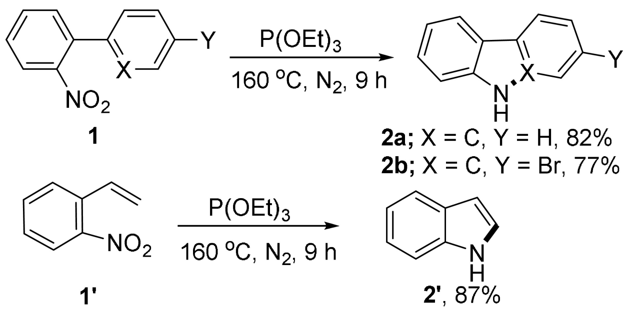
Manpreet Kaur and Raj Kumar*[a]

‡*Dedicated to Professor R. S. Hosmane (Retd.), University of Maryland Baltimore*

Cadogan/Cadogan-Sundberg cyclization reaction has been reported as one of the most efficient routes for the synthesis of a wide variety of *N*-heterocycles from the easily accessible starting materials such as *o*-nitrobiaryls or *o*-nitroarenes, *o*-nitrostyrenes by treating with tetravalent phosphorus compounds (trialkyl or triaryl phosphines or trialkyl phosphites). The reaction has been successfully employed in Carbon-Carbon as well as Carbon-Nitrogen bond formation for the scaffolds like carbazole, indoles, coumarins, and indazoles. To the best of authors' knowledge, the present review is the first compilation of the literature from almost two decades (2000 to present) on Cadogan/Cadogan-Sundberg cyclization reaction, its scope, mechanistic aspects, and limitations.

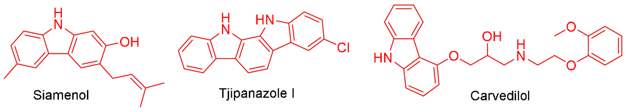
1. Introduction

Nitrogen(*N*)-containing heterocycles[1] exhibit a broad spectrum of applications comprising of pharmacologically active entities,[2] crop protection agents,[3] and building blocks for organic semiconductors.[4] Reductive cyclization of *o*-functionalized nitroarenes has been reported as the most efficient method for the synthesis of *N*-containing heterocycles.[5] Bunyan and Cadogan carried out reductive annulation of 2-nitrobiaryls (**1**) by heating it with $P(OEt)_3$ leading to the formation of carbazoles **2**.[6] Sundberg extended the ring annulation strategy for the synthesis of indole **2'** from *o*-nitrostyrene (**1'**) under Cadogan conditions (Scheme 1).



Scheme 1. Classical Cadogan and Cadogan-Sundberg reactions

This further widened the scope of reaction and led to a series of publications in the field.[7–9] Cadogan reaction conditions have been employed as one of the key steps in the synthesis of drugs (Scheme 2) like siamenol (anti-HIV drug),[2c] tjipanazole I (anti-fungal agent),[2d] and carvedilol (heart failure drug). Besides carbazole and imidazole, reaction finds its scope for the synthesis of indazole, indole, quinoline,[1a] benzimidazole, benzoxazole,[8] and phenothiazines.[9] We report, herein, the first time the progress made in Cadogan/Cadogan-Sundberg cyclization spanning the period from 2000 to present. The review is organized according to the type of heterocycles acquired highlighting the scope of reaction. The mechanistic interventions are briefly discussed at the end of this paper.



Scheme 2. Chemical structures of drugs involving Cadogan reaction as one of the key steps in their synthesis

2. Synthesis of Heterocycles

2.1 Construction of Carbazole Skeleton

The carbazole scaffold (Scheme 3) constitutes many naturally occurring alkaloids of diverse medicinal properties,[10] organic solar cell,[11] electrochemical,[12] and photorefractive liquid crystalline materials[13] in the form of oligomers, dendrimers, and polymers. Numerous methods including palladium catalyzed construction of carbazoles[14] have been reported; how-

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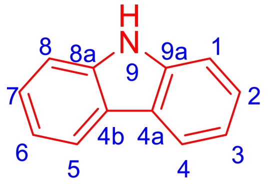
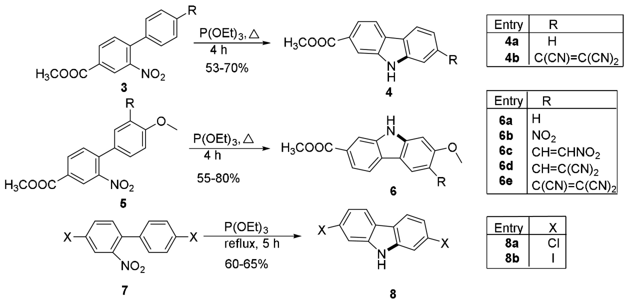
[a] *M. Kaur, Dr. R. Kumar*
Laboratory for Drug Design and Synthesis, Department of Pharmaceutical Sciences and Natural Products, Central University of Punjab, Mansa Road, Bathinda-151001, India
E-mail: raj.khunger@gmail.com
raj.khunger@cup.edu.in



Scheme 3. Chemical structure of carbazole

ever, Cadogan conditions present the best choice for substituted carbazoles.

In 2001, 2,3,7,9-polysubstituted carbazole derivatives were synthesized using Cadogan cyclization.[15] Substrates **3** and **5** were reductively cyclized to yield **4 a-b** and **6 a-e** (Scheme 4).



Entry	R
4a	H
4b	$C(CN)=C(CN)_2$

Entry	R
6a	H
6b	NO_2
6c	$CH=CHNO_2$
6d	$CH=C(CN)_2$
6e	$C(CN)=C(CN)_2$

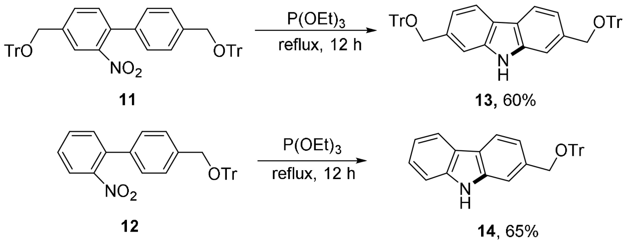
Entry	X
8a	Cl
8b	I

Scheme 4. Synthesis of carbazoles

These compounds were found to have potential in the development of nonlinear optical systems. Similarly, *N*-alkyl-2,7-carbazoles were used to afford conjugated polymers through Cadogan cyclization.[16] The reaction was applied to **7** to get **8 a-b**, which were further polymerized and evaluated for their electrical, electrochemical and optical properties (Scheme 4).

Under Cadogan conditions, dinitro substituted carbazole **9** was used to provide symmetric compound **10** (Scheme 5).[17] Further, optical and electrochemical properties of **10** were demonstrated and the studies revealed neutral semiconducting form of **10** to be stable in air. Deoxygenation under Cadogan conditions provided a simple entry to 2,7-carbazolenevinylene-based conjugated oligomers and polymers.[18] 4,4′-Bis(methyltrityloxy)-2-nitrobiphenyl **11** and 4-(methyltrityloxy)-2-nitrobiphenyl **12** were reductively cyclo-condensed to afford 2,7-bis(methyltrityloxy)carbazole **13** and 2-(methyltrityloxy)carbazole **14,** respectively (Scheme 6).

Scheme 5. Synthesis of diindolocarbazole



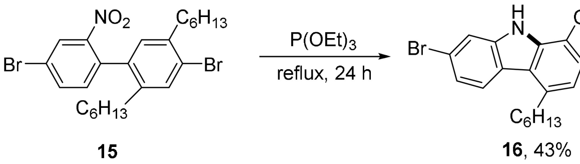
Scheme 6. Synthesis of substituted methyltrityloxy carbazoles

Yaqin Fu reported two approaches to synthesize high molecular weight soluble conjugated carbazole polymers using Cadogan and palladium-catalyzed Suzuki polycondensation conditions.[19] 2,7-dibromo-1,4-dihexylcarbazole **16** monomer unit was prepared by heating a mixture of 4-bromo-2-nitro-2′,5′-di-n-hexyl-4′-bromobiphenyl **15** and $P(OEt)_3$, under N_2 atmosphere (Scheme 7).

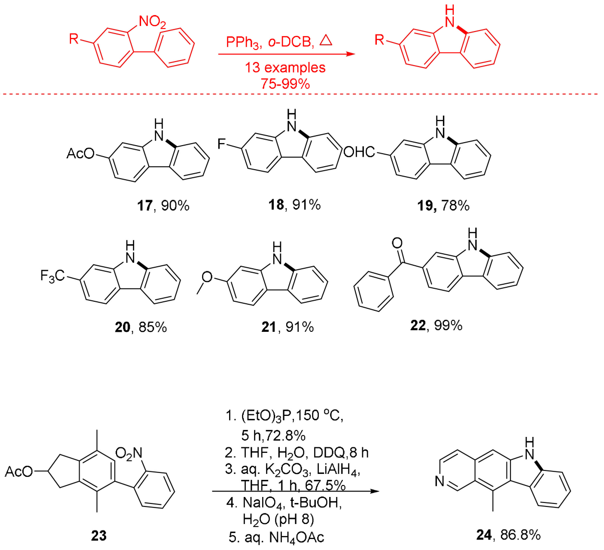
Several *o*-nitrophenyls were synthesized *via* Suzuki-Miyaura cross-coupling and were subjected to reductive Cadogan cyclization under reflux in o-DCB in the presence of PPh_3 to afford compounds **17–22** (Scheme 8).[20]

Manpreet Kaur *earned her M.Sc. degree in Chemical Sciences (specialization in Medicinal Chemistry) at Central University of Punjab, Bathinda. She is pursuing her Ph.D. in the area of Cadogan cyclization and metal complexation at Central University of Punjab, Bathinda, under the supervision of Dr. Raj Kumar.*

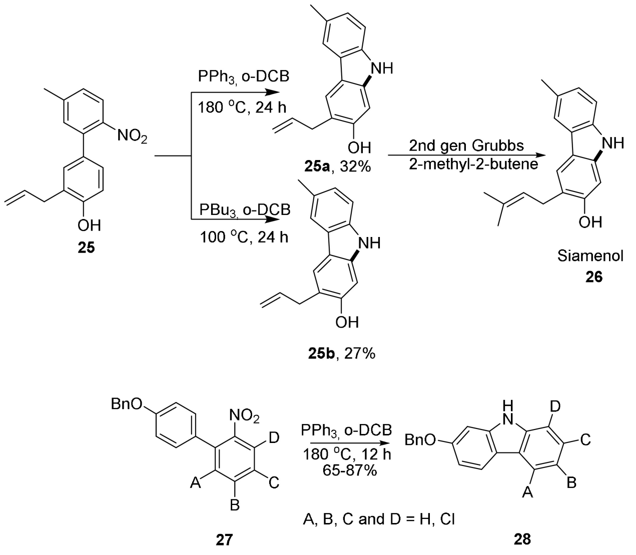
Raj Kumar *is an Associate Professor of Organic Medicinal Chemistry at the Central University of Punjab, Bathinda, India. He obtained his Ph.D. in Medicinal Chemistry (2007) from NIPER, Mohali, India and completed his postdoctoral fellowship (2007-2008) at the University of Maryland Baltimore County (UMBC), Maryland where he co-invented a fused heterocycle RK-33 (Raj Kumar-33) molecule for the treatment of Lung Cancer. His research interests focus on the design and synthesis of novel fused heterocycles of biological importance.*



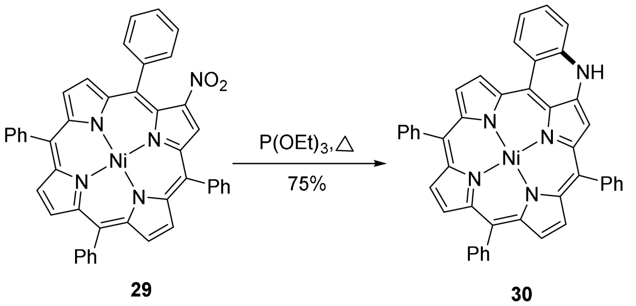
Scheme 7. Synthesis of 2,7-dibromo-1,4-dihexylcarbazole



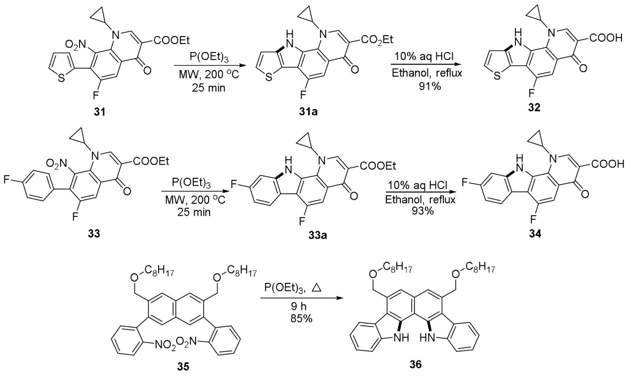
Scheme 8. Synthesis of carbazole analogs



Scheme 9. Synthesis of Siamenol and chlorinated carbazoles



Scheme 10. Synthesis of nickel enaminoporphyrin



Scheme 11. Synthesis of fluoroquinolones and carbazolo[1,2-*a*]carbazole

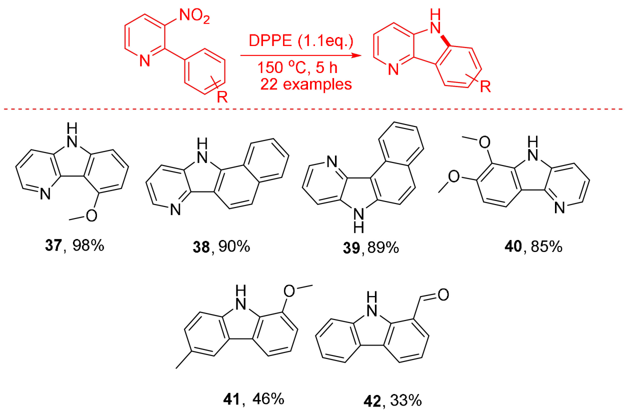
The scope and functional-group tolerance of new reaction conditions like nature of solvent and temperature dependence were also elucidated well. However, the reason for the less or no yield with substrates such as hydroxyl and carboxylic acid functional groups remained unknown. A series of tetracyclic pyridocarbazole alkaloids were synthesized and their biological evaluation revealed ellipticine (**24**) [$IC_{50} = 1.6\ \mu M$] as the most potent anti-tumor agent.[21] Naffziger prepared a series of chlorinated carbazoles **28** involving Diels-Alder reaction followed by Suzuki coupling and Cadogan cyclization. The reaction conditions were utilized for the total synthesis of siamenol (**26**, anti-HIV agent; $EC_{50} = 2.6\ \mu g/mL$) (Scheme 9).[2c]

Cadogan cyclization with $P(OEt)_3$ was used for the synthesis of nickel enaminoporphyrin (Ni-2)[22] (**30**) from nickel 2-nitro-*meso*-tetraphenylporphyrin (Ni-1) (**29**) (Scheme 10) which was further used for the synthesis of a π-extended metalloporphyrin Ni-3.[23]

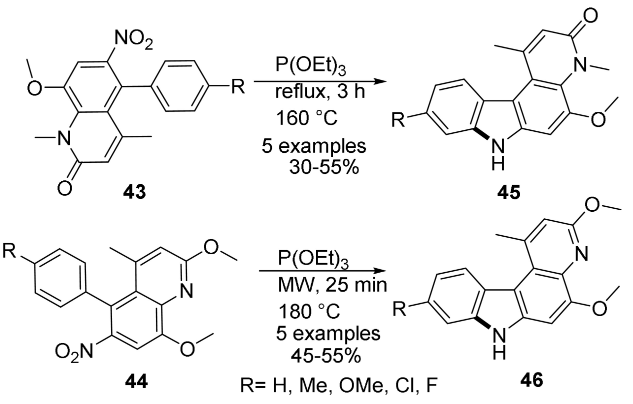
Microwave irradiations are reported to accelerate the rate of reaction by several folds in comparison to conventional heating and results in higher yield.[24] Since, Cadogan reaction involves heating at high temperature for several hours. Thus, microwave heating could be effective in producing high yields in shorter time. In 2010, Trawneh and team utilized microwave assisted Cadogan cyclization to synthesize a variety of tetracyclic fluoroquinolones[25] (Scheme 11) and their evaluations for *in-vitro* antimicrobial and anti-proliferative activity showed **32** as the most active antibacterial agent and **34** as the most active anticancer agent against MCF-7 cell lines with IC_{50} of $0.8\ \mu M$ (having greater potency than ellipticine $IC_{50} = 1.6\ \mu M$).

In the same year, Curie *et al.* designed carbazolo[1,2-*a*] carbazole **36** as π-extended *N*-fused heteroacenes and evaluated its optical and electrochemical properties (Scheme 11).[26]

Usually P(OEt)$_3$ and PPh$_3$ are employed as reductants. Peng and colleagues synthesized a series of δ-carbolines/carbazoles from 3-nitro-2-phenylpyridines/2-nitrobiphenyl derivatives using 1,2-Bis(diphenylphosphino)ethane (DPPE) as a reducing agent for Cadogan cyclization under solvent-free conditions.[27] Twenty-two compounds were prepared using 1.1 equiv. DPPE at 150 °C for 5 h, among which 4 compounds **37–40** had more than 80% yields. DPPE is shown to be more effective, eco-friendly, high yielding with short reaction time as compared to P(OEt)$_3$ and PPh$_3$. Compound **42,** intermediate of carvedilol and glycozolicine **41** were obtained in moderate yields using Cadogan annulation (Scheme 12).

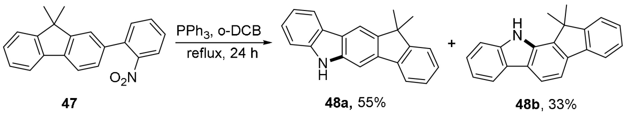


Scheme 12. Synthesis of various carbazole derivatives



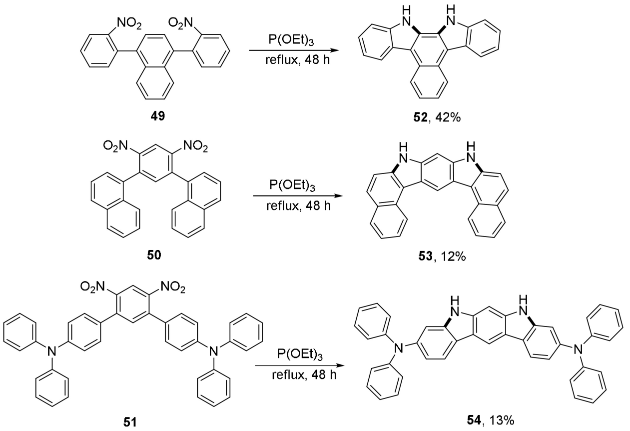
Scheme 13. Synthesis of tetracyclic fused linear or angular carbazoles

In 2012, Sanchez and researchers designed tetracyclic fused linear or angular carbazoles from 6-nitroquinolines **43** and **44** using Cadogan cyclization with P(OEt)$_3$ under reflux and microwave irradiation to give **45** and **46**, respectively with yields 30–60% (Scheme 13).[28] Jung *et al.* prepared aza-indenofluorene derivatives **48 a-b** under Cadogan conditions and reported their photoluminescent properties which were found to be a green light emitting materials for Organic Light-Emitting Diodes or fluorescence pigment dye (Scheme 14).[29]



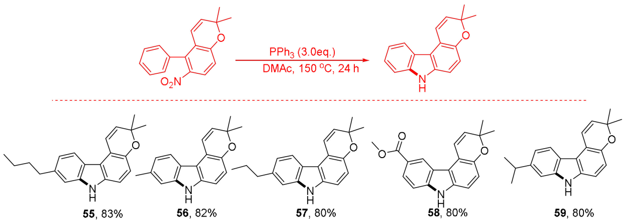
Scheme 14. Synthesis of aza-indenofluorene derivatives

Gong *et al.* synthesized indolocarbazoles **52–54** from **49–51** under Cadogan conditions (Scheme 15).[30] Compounds obtained were further proposed for the synthesis of novel functional soft materials, exhibiting unique photophysical, optoelectronic properties and as a fluorescent sensor for detecting vapors of explosives.



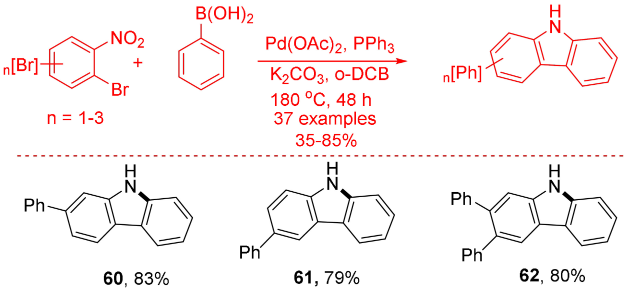
Scheme 15. Synthesis of indolocarbazoles

Anti-cancer pyrano[2, 3-c]carbazoles **55–59** (Scheme 16) were obtained by heating 2,2-dimethyl-2H-chromenes with PPh$_3$ under Cadogan conditions.[31] The compounds exhibited anticancer activity which were further supported by molecular docking studies.[32] In 2016, Goo and Woo synthesized a series of aryl-substituted carbazoles *via* tandem double or triple C–C and C–N bond formation using one pot Suzuki coupling and

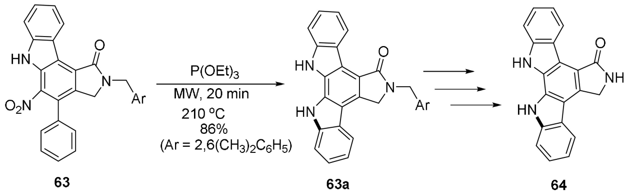


Scheme 16. Synthesis of pyrano[2, 3-*c*] carbazoles

Cadogan cyclization.[33] Polybromonitrobenzenes and arylboronic acids were treated with palladium acetate catalyst, PPh_3, K_2CO_3 and *o*-DCB to obtain compounds with moderate to excellent yields. Compounds **60–62** are shown as representative compounds having good yield (Scheme 17). In the same year, bioactive indolocarbazole[34] K-252c (staurosporinone, **64**) was synthesized from **63** using Cadogan cyclization as one of the key steps (Scheme 18).

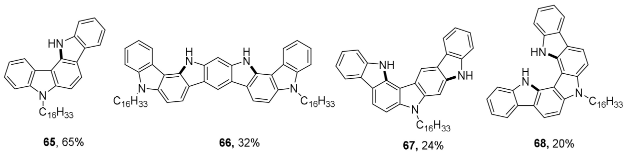


Scheme 17. Phosphite-mediated one pot synthesis of carbazole derivatives



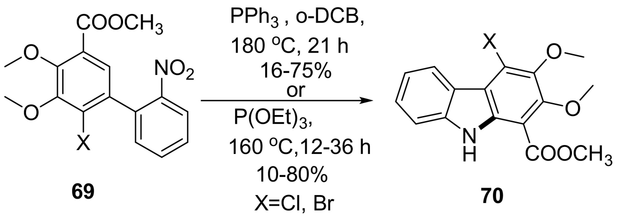
Scheme 18. Synthesis of Staurosporinone

Ran Lu *et al.* synthesized four compounds **65–68** having π-extended *N*-fused heteroacenes under Cadogan conditions using $P(OEt)_3$ as deoxygenating reagent (Scheme 19).[35] Organic field-effect transistor applications of compounds **65–68** were also studied.

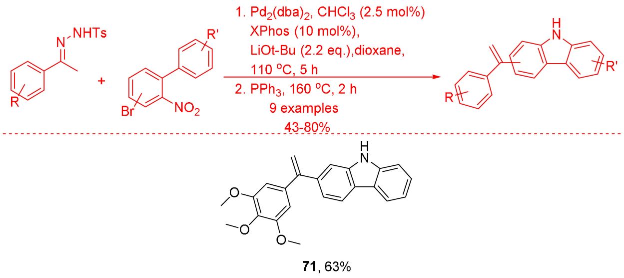


Scheme 19. Synthesis of N-fused heteroacenes

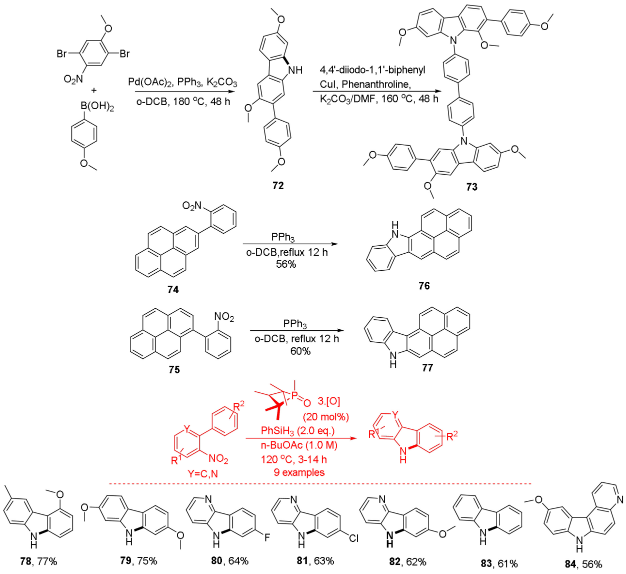
Sravanthi and team synthesized carbazoles **70** *via* Grob fragmentation of norbornyl α-diketones and Cadogan cyclization with PPh_3 or $P(OEt)_3$ in o-DCB at 180 °C (Scheme 20).[36] However, the better yields (upto 80%) were obtained with $P(OEt)_3$. A variety of (1-arylvinyl) carbazoles were obtained from *N*-tosylhydrazones and 2-nitro-haloarenes using PPh_3 as reducing agent in dioxane for cyclization. The carbazoles were evaluated for anti-proliferative activity and the results showed **71** to be the most potent anti-proliferative agent with $IC_{50} = 2.3$ nM[37] against colon cancer cell lines (Scheme 21). In 2017, an aryl-substituted carbazole-based solvatochromic bluish fluorophore **73** was synthesized *via* one pot Suzuki cross-coupling and Cadogan cyclization (Scheme 22). In the same year, two



Scheme 20. Synthesis of carbazole scaffold



Scheme 21. Carbazole synthesis from N-tosylhydrazones and 2-nitrobromoarenes

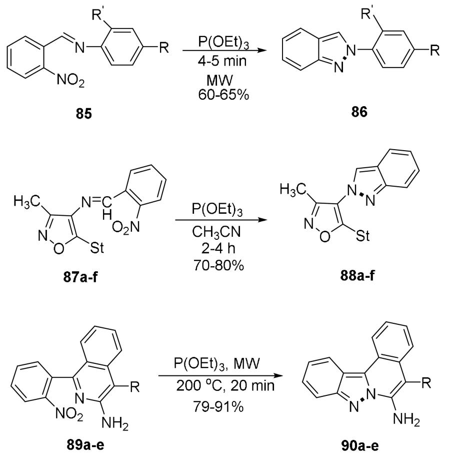


Scheme 22. Cadogan-Sundberg cyclization: carbazole

regioisomeric phenalenocarbazoles[38] **76,77** were constituted from 2′-nitrophenylpyrene isomers (**74,75**) by heating with PPh_3 in o-DCB under reflux for 12 hours (Scheme 22). Generally, stochiometric or excess amount of PPh_3 or $P(OEt)_3$ are employed for Cadogan reaction. Recently, Nykaza and researchers first time introduced catalytic amount of hexamethylphosphetane P-oxide for intramolecular C−N bond formation to design carbazole scaffolds **78–84** (Scheme 22) from o-nitrobiaryl derivatives in the presence of a hydrosilane terminal reductant. In situ nuclear magnetic resonance reaction monitoring studies were used to support a mechanism consisting catalytic $P^{III}/P^{V}{=}O$ cycling for preparation of carbazole motifs.[39]

2.2. Synthesis of Indazole Nucleus

Indazole moiety plays an important role in the drug discovery as it possesses diverse medicinal applications such as antifungal, antibacterial, kinase inhibitors.[40] Cadogan cyclization is found to be an easy and convenient approach to access indazole moiety.[41] Varughese *et al.* carried out microwave assisted one pot Cadogan cyclization to obtain compounds **86 a-e** from **85 a-e** using $P(OEt)_3$ as reducing agent (Scheme 23).[41a] Similarly a variety of isoxazolylindazoles **88 a-f** was prepared from isoxazole Schiff bases **87 a-f** by heating in acetonitrile with an excess of $P(OEt)_3$ (Scheme 23).[41b] Likewise, a series of fluorescent indazolo[3,2-*a*] isoquinolin-6-amines **90 a-e** (Scheme 23) was synthesized from compounds **89 a-e** under microwave assisted Cadogan cyclization using $P(OEt)_3$.[41c]



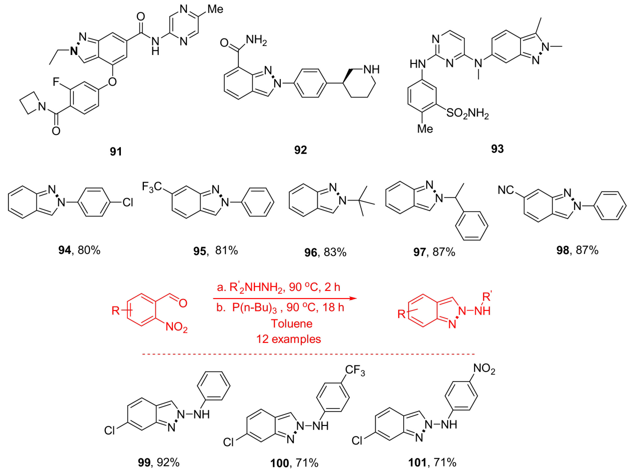
Entry	R	R'
86a	H	H
86b	OCH_3	H
86c	H	OCH_3
86d	OEt	H
86e	CH_3	H

Entry	Ar
88a	C_6H_5
88b	$4\text{-}CH_3C_6H_4$
88c	$4\text{-}OCH_3C_6H_4$
88d	$4\text{-}ClC_6H_4$
88e	$2\text{-}ClC_6H_4$
88f	$2\text{-}CH_3C_6H_4$
St = CH=CH-Ar	

Entry	R
90a	H
90b	CH_3
90c	Et
90d	Bn
90e	COOEt

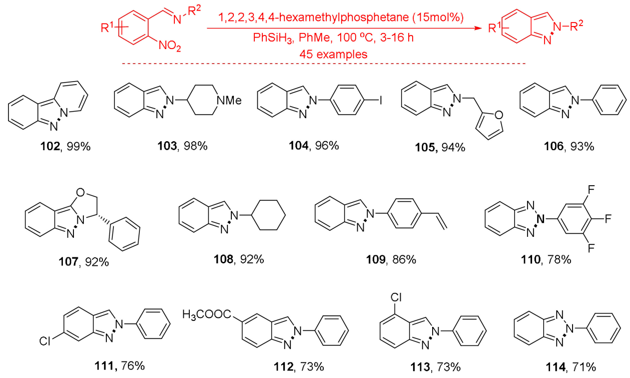
Scheme 23. Phosphite-mediated synthesis of various indazole derivatives

In 2014, Nathan E. Genung *et al.* synthesized a series of 2*H*-indazoles **94–98** using one-pot Cadogan reductive cyclization with tri-n-butylphosphine to generate 'drug-like' moieties similar to Pfizer (**91**), MK-4827 (**92**) and Pazopanib-GSK (**93**) (Scheme 24).[42] Schoene and researchers performed one-pot reaction for the synthesis of *N*-substituted-2*H*-indazol-2-amine to get compounds **99–101**.[43] For optimizing reaction conditions, various organophosphorus reagents comprising of $P(OEt)_3$, PPh_3, $P(n\text{-}Bu)_3$, $P(n\text{-}Pr)_3$ and $P(Cy)_3$ were used. $P(n\text{-}Bu)_3$ afforded the desired products in good yield (70-92%) (Scheme 24) with clean conversion of starting material upon heating reaction mixture under microwave irradiation (100 °C, 30 min) as compared to other organophosphorus reagents. The reaction conditions were shown to be highly suitable for cyclization of hydrazines substituted with electron withdrawing groups.



Scheme 24. Cadogan-Sundberg cyclization: indazole

Recently, chemoselective catalytic Cadogan ring annulation of 2*H*-indazoles, 2*H*-benzotriazoles, and related fused heterocyclic systems **102–114** was reported using hexamethylphosphetane and hydrosilane terminal reductants (Scheme 25).[44]



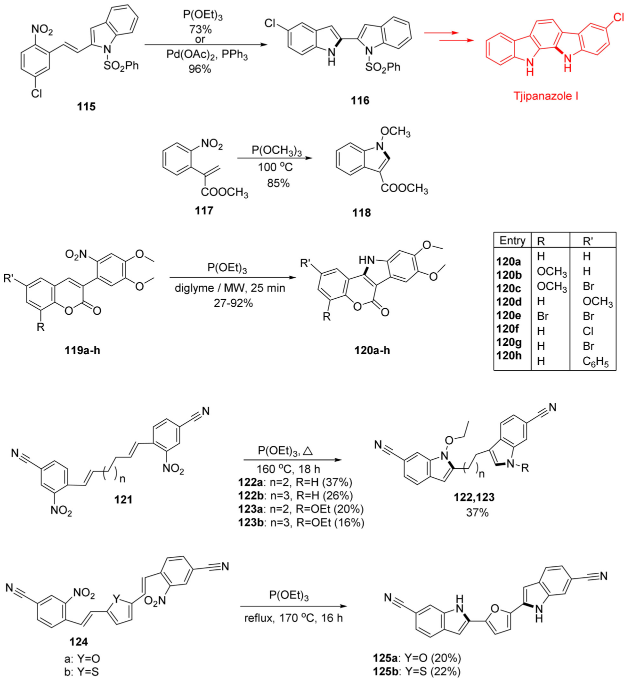
Scheme 25. Catalytic indazole synthesis

2.3. Formation of Indole Moiety

Indole ring system is the most ubiquitous heterocycle[40c] found in natural alkaloids[45] and synthetic drug molecules.[46] Indole scaffold can be designed by methods[47] like Fisher indole synthesis,[48] Leimgruber-Batcho indole synthesis.[49] Cadogan –

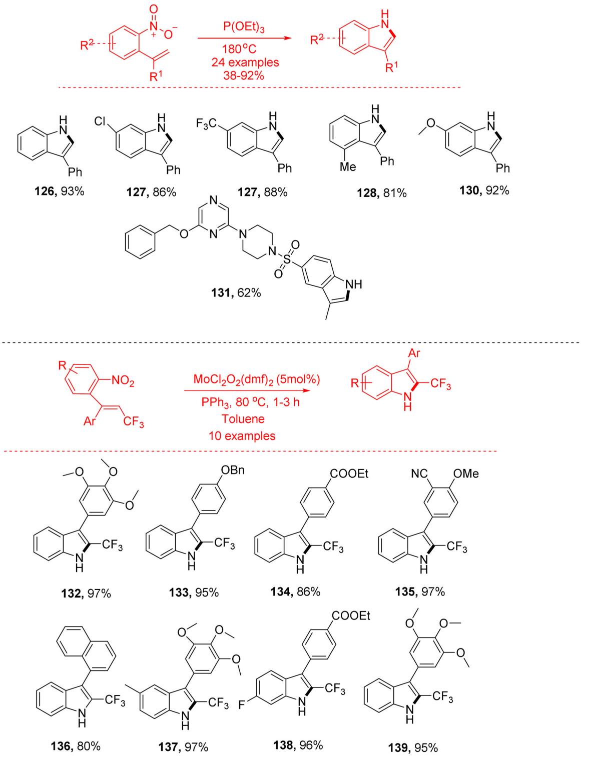
Sundberg deoxygenation or cyclization of *o*-nitrostyrene has been reported to be another attractive method for indole synthesis.

Kuethe synthesized various indolo carbazole aglycons and glycosides for the total synthesis of Tjipanazoles B, D, E, and I.[2d] The synthesis of tjipanazole I[50] involved the preparation of biindole **116** from *trans*-nitrostyrene **115** (Scheme 26). Further, by heating **116** with N, N-dimethylacetaldehyde diethyl acetal in acetic acid, Tjipanazole I (anti-fungal agent) was synthesized. Bing Li introduced two new syntheses of Wasabi phytoalexin methyl-1-methoxyindole-3-carboxylate **118** using reductive cyclization with stannous chloride and Cadogan–Sundberg deoxygenation[51] (Scheme 26) from common substrate **117**. Here, modified Cadogan–Sundberg deoxygenation was carried out using trimethylphosphite to give **118** with 85% yield. Irgashev and co-workers synthesized indolo[3,2-*c*] coumarins **120 a-h** from 3-(2-nitroaryl)-substituted coumarins **119 a-h** by using both PPh_3 and $P(OEt)_3$ (Scheme 26).[52] $P(OEt)_3$ gave better yield than PPh_3. Cadogan-Sundberg Cyclization reaction was performed for the synthesis of bisamidine analogs **122 a-b, 123 a-b**, and furan or thiophene linked MBX 1066 analogs **125 a-b** by using $P(OEt)_3$ under reflux (Scheme 26).[53] The compounds were shown to be potent inhibitors of bacterial DNA replication.



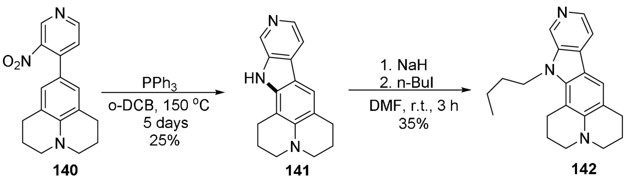
Entry	R	R'
120a	H	H
120b	OCH_3	H
120c	OCH_3	Br
120d	H	OCH_3
120e	Br	Br
120f	H	Cl
120g	H	Br
120h	H	C_6H_5

Scheme 26. Synthesis of Indole skeleton

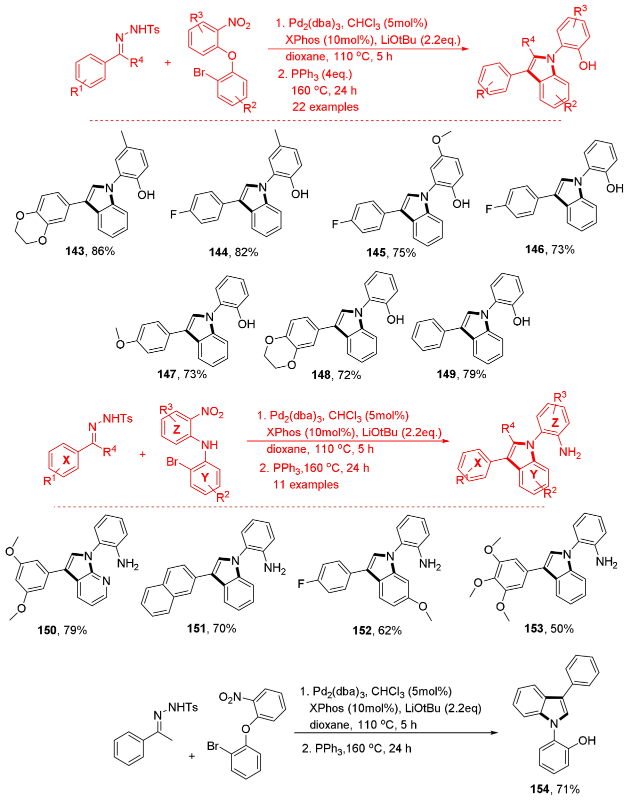


Scheme 27. Cadogan-Sundberg cyclization: indole

A series of aza-heterocycles **126–131** were prepared by treating *o*-nitro-vinylarene[54] with $P(OMe)_3$, $P(OEt)_3$, or $P(n\text{-}Bu)_3$ under conventional heating or microwave irradiation at 180 °C (Scheme 27).[55] Yamamoto *et al.* synthesized 3-Aryl-2-(trifluoromethyl) indoles *via* copper-catalyzed hydroarylation and molybdenum-catalyzed Cadogan cyclization in high yields.[56] A series of cyclized compounds **132–139** (Scheme 27) was prepared from earlier synthesized hydroxylated precursors in presence of $MoCl_2O_2(dmf)_2$ and PPh_3, heating in toluene at 80 °C for 1–3 hour. This modified Cadogan cyclization was found to be more beneficial as the reaction conditions used were well tolerated by both electron-donating, and the electron-withdrawing substituent, and reactive ester and cyano groups. Enoki and co-workers designed a pyrido[3,4-*b*]indole dye **142** using Cadogan cyclization as one of the key steps (Scheme 28).[57] On the basis of optical and electrochemical measurements, it was found to act as calorimetric and fluorescent sensor for Brønsted and Lewis acids. Bzeih and researchers designed one pot reaction of *N*-tosylhydrazones and bromonitrobenzene derivatives to develop *N*-phenylindolylphenols and *N*- phenylindolylanilines (Scheme 29). It included Pd-catalyzed carbene coupling reaction, followed Cadogan reductive cyclization using PPh_3 for synthesis of **143–154**



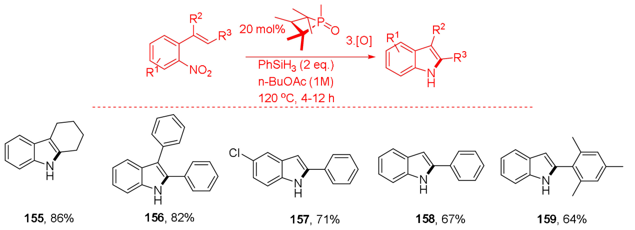
Scheme 28. Synthesis of pyrido[3,4-*b*] indole dye



Scheme 29. Cadogan cyclization strategy for the synthesis of indole derivatives

(Scheme 29). The novel compounds synthesized were evaluated for cytotoxic activity against human colon cancer cell lines and **153** was found to have highest cytotoxic activity ($IC_{50} = 8$ nM).[58]

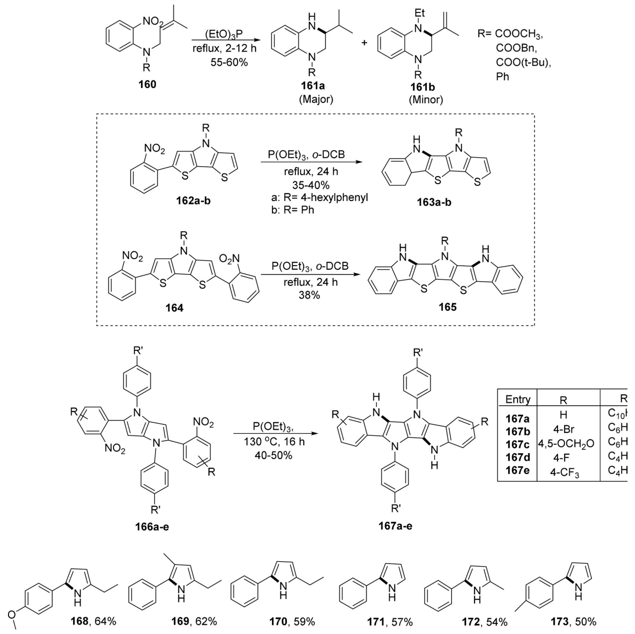
Nykaza and co-workers designed indole derivatives **155–159** from *o*-nitrostyrene derivatives using hexamethylphosphetane P-oxide as catalyst in the presence of a hydrosilane terminal reductant (Scheme 30).[39]



Scheme 30. Cadogan reaction utilising catalytic amount of catalyst for indole synthesis

2.4. Construction of Other Heterocycles

This class includes preparation of benzoxazine, pyrrole, indolothienopyrrole scaffolds by using Cadogan cyclization. Substituted 3,4-dihydro-2*H*-1,4-benzoxazine **161 a-b** were obtained by treating ω-nitroalkene **160** with $P(OEt)_3$ (Scheme 31).[9a] In 2009, Balaji *et al.* synthesized unsymmetric indolodithienopyrrole and extended diindolodithienopyrrole using Cadogan annulation.[59] Compounds **163 a-b** and **165 a** were synthesized by treating compound **162 a-b** and **164 a** with an excess of $P(OEt)_3$ in o-DCB (Scheme 31). In 2015, ladder type fluorophores **167 a-e** consisting of diindolo[2,3-*b*:2′,3′-f]pyrrolo[3,2-*b*]pyrrole moieties were prepared from **166 a-e** and explored for their optical properties (Scheme 31).[60] Using Cadogan cyclization conditions along with Mo catalyst, bis(acetylacetonato) dioxomolybdenum (VI) (5 mol%) substituted pyrroles **168–173** (Scheme 31) were prepared from nitrodienes.[61]



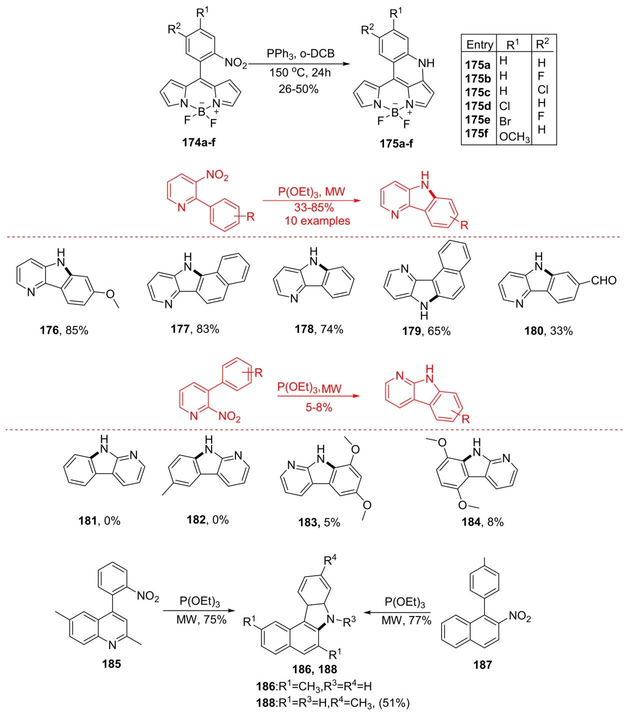
Scheme 31. Cadogan cyclization for the synthesis of various heterocycles

In 2017, Hua Lu and researchers designed a series of boron dipyrromethene (BODIPY) dyes **175 a-f** by reductive cyclization using PPh_3 in o-DCB (Scheme 32).[62]

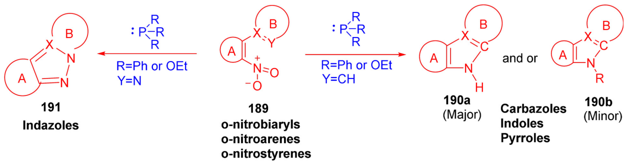
In 2018, β-carbolines **176–180** and δ-carbolines **186**, **188** from aryl-nitropyridines were synthesized under microwave-assisted Cadogan cyclization conditions using triethyl phosphite. An attempt was also made for the synthesis of α-carbolines **181–184** from α-nitro-biarylpyridines (Scheme 32), but the substrate was found to be inappropriate. However, naphthonitriles were obtained as main products along with small amount of dimethoxy-α-carbolines due to greater electron density and supposed to form via nitrene pathway.[63]

3. Mechanism of Cadogan/Cadogan-Sundberg reaction

Cadogan reaction could lead to two pathways depending upon the reagents and substrates used as shown in Scheme 33. Cadogan cyclization of **189** results in the formation of **190 a**

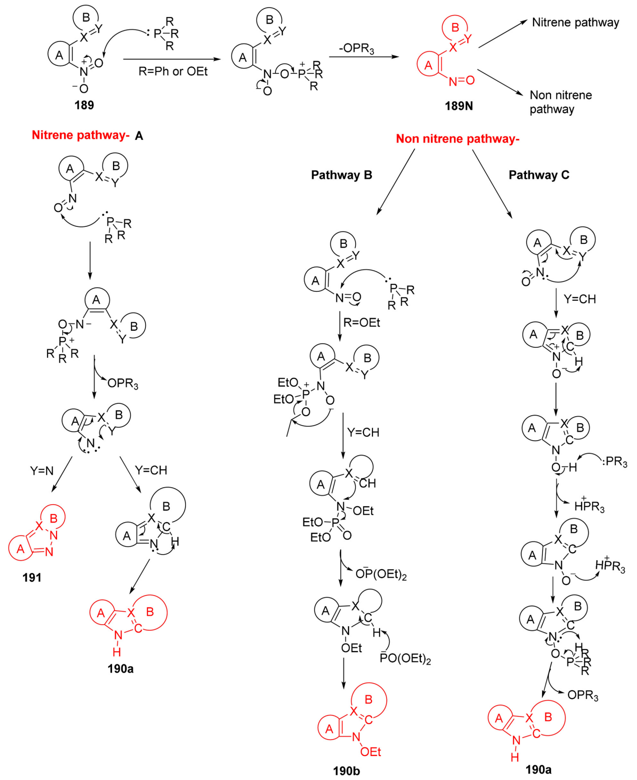


Scheme 32. Synthesis of BODIPY dyes and substituted carbolines



Scheme 33. Generalized Cadogan/Cadogan-Sundberg reaction

(major) and **190 b** (minor) when Y=CH. However, when Y=N; **191** is formed (Scheme 33). The formation of products involve the nucleophilic attack of a lone pair of PR_3 on the oxygen atom of the nitro of **189** followed by removal of PR_3O and resulted in the formation of nitroso intermediate (**189 N**).[7,64] **189 N** may undergo change *via* any of the three pathways involving nitrene (**A**) or non-nitrene (**B** or **C**) (Scheme 34). Pathway **A** involves deoxygenation of nitroso intermediate by PR_3 followed by removal of PR_3O and formation of nitrene intermediate. The nitrene intermediate further undergoes ring closure followed by intramolecular [1,5] H-shift to gain aromaticity resulting in the formation of **190 a** when Y=CH or **191** when Y=N. Pathway **B** involves the nucleophilic attack of PR_3 on nitrogen atom of nitroso intermediate followed by abstraction of ethyl group by oxygen atom of nitroso group. Further, it undergoes a concerted mechanism and intramolecular [1,5] H-shift resulting in the formation of **190 b** (R= OEt). Majgier *et al.* evidenced through O^{18} labelling that oxygen atom in **190 b** comes from nitro group and does not belong to $P(OEt)_3$.[64] Pathway **C** involves the intramolecular attack of a lone pair of the nitrogen atom of nitroso intermediate followed



Scheme 34. Mechanism of Cadogan/Cadogan-Sundberg reaction

by proton abstraction by oxygen atom and removal of PR_3O results in the formation of **190 a** (Y=CH).

4. Conclusion

Cadogan reaction has been successfully applied in the synthesis of functioning azaheterocycles, including carbazole, indazole, indole, and pyrrole which possess numerous properties such as drug candidates, light emitting diodes, semiconductors, fluorescence dyes or sensors and π-extended metalloporphyrin. The natural occurrence of similar molecules has also prompted researchers to synthesize them either using Cadogan or its modification Cadogan-Sundberg cyclization. Cadogan annulation provides an easy and inexpensive approach; however, it utilizes stochiometric or excess amount of deoxygenative reagents ($P(OEt)_3$, $P(OMe)_3$, $P(nBu)_3$, PPh_3 or 1,2- DPPE). Among these, DPPE provides better results and is environmentally benign. The reaction involving use of catalytic amount of such reagent remains to be developed, although the first successful attempt using catalytic amount of hexamethylphosphetane P-oxide has been made recently.[39] Substrates with a wide range of functional groups like aldehydes, ketones, halogens, nitriles, and amides are well tolerated under Cadogan condition. Noteworthy, substrates having carboxylic acids and phenolic moieties did not yield Cadogan products. Until now there are no reports on intermolecular Cadogan cyclization; thus, there is a wide scope to develop heterocycles of diverse nature and of novel use. We believe this review will be helpful to the scientific community to develop and optimize more Cadogan reaction conditions in the synthesis of natural, as well as synthetic bioactive compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cadogan/Cadogan-Sundberg reaction · Carbazole · Indazole · Reductive cyclization · Trialkylphosphite

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