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Recent Advances in the Chemistry of Indazoles

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Indazoles are of considerable interest due to the broad variety of their biological activities. This overview summarizes structures of pharmacologically interesting indazoles published during the last decade, as well as syntheses, reactions, and functionalizations. Recent advances in the chemistry of *N*-heterocyclic carbenes of indazole (indazol-3-ylidenes) and indazolium salts are also reported.

1. Introduction

During the last decade, a considerable interest has been paid to the chemistry of indazoles (benzo[*c*]pyrazole, 1,2-benzodiazole). This is undoubtedly due to a broad variety of biological activities of indazole derivatives which inspired the developments of new syntheses and their optimizations, as well as of functionalizations of the indazole ring system. A detailed survey covering the literature to the end of the nineties appeared in *Science of Synthesis*.[1] Other reviews dealing with syntheses,[2–5] and pharmacological properties have been published.[6]

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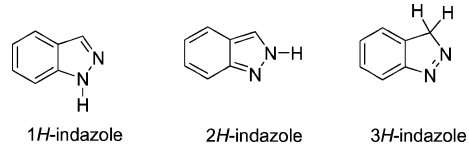
2. Tautomerism and Conformations

Three tautomeric forms of indazole can be discussed, the 1*H*-, 2*H*-, and 3*H*-form (Scheme 1).

Andreas Schmidt was born in 1964 in Wuppertal (Germany). He studied chemistry at the universities of Wuppertal and Bonn, Germany, and received the academic degree Dr. rer. nat. in the group of Professor Heinrich Wamhoff (University of Bonn, 1992). He started then his independent research at the Institute of Organic Chemistry of the University of Greifswald (Germany) and completed his habilitation in 2000. Between 1999 and 2000 he undertook postdoctoral investigations with Professor Albert Padwa at Emory University, Atlanta (Georgia, USA). Since 2000 he is working at the Institute of Organic Chemistry of the Clausthal University of Technology. His research interests include natural product and heterocyclic chemistry, especially heteroaromatic polycations, N-heterocyclic carbenes, and mesomeric betaines.

Ariane Beutler was born in 1978 in Hannover (Germany) and studied chemistry at the Clausthal University of Technology. After studies at the University of Cardiff (UK) working on aza-Diels–Alder reactions, she received her Diploma from the Clausthal University of Technology in 2005. Her thesis was dealing with pseudo-cross-conjugated heterocyclic mesomeric betaines and their conversion into N-heterocyclic carbenes. Due to a malicious disease, Ari had no chance to complete her work. She died in November 2007. We will always remember her professional qualifications, her friendly kindness, her positive attitudes towards life, and her ever present good sense of humor.

Bohdan Snovydovych was born 1980 in Pidhorodyshche (Ukraine). He studied chemistry at the university of Lviv and received his diploma degree in 2002 in the group of Prof. Dr. Mykola Hanushchak. 2002–2005 he was research assistant at the chair of organic chemistry of the University of Lviv and joined the group of Andreas Schmidt at Clausthal University of Technology in 2005. He is currently working on N-heterocyclic carbenes of indazole.

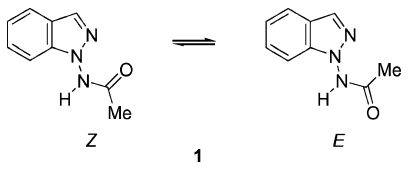


Scheme 1. Tautomers of indazole.

Tautomerisations of indazoles have been thoroughly investigated both from a theoretical and a synthetic view, and a review article summarizing the knowledge appeared in 2000.[7] The tautomeric equilibrium between 1*H*- and 2*H*-indazoles both in the ground state (S_0) and in the excited state (S_1) has been investigated by photophysical and thermochemical techniques, and have also been calculated. According to this study, the 1*H* tautomer is 2.3 kcal mol^{-1} (9.63 kcal/mol) more stable than the 2*H* tautomer, regardless of the ground state or excited state, and this trend is not reversed by solvent effects from water or formic acid. Correspondingly, 1-methylindazole is 3.2 kcal mol^{-1} (13.40 kcal/mol) more stable than 2-methylindazole.[8] The MP2/6-31G* level of theory predicts an energy difference of 3.6 kcal/mol (15.1 kcal/mol), which is characterized also by $\Delta G^0_{298.15}$ = 4.1 kcal/mol (17.2 kcal/mol), when thermal energy correction and entropy effects are taken into account.[9] Calculations on the tautomerism of substituted indazoles lead to similar results in the gas-phase[10] as well as in water.[11] AM1/B3LYP calculations, however, predict also some candidates of substituted and annulated indazoles which are more stable as 2*H*-tautomers.[12]

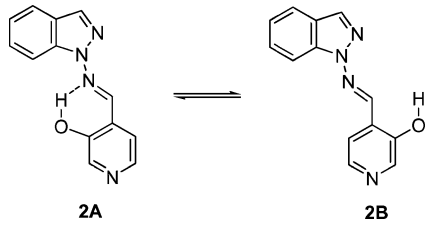
The two tautomeric forms can be identified in solid-state substances by NMR-NQR spectroscopy.[13] In addition, theoretical ^{13}C NMR studies have been carried out,[14] as well as ^{1}H, ^{13}C and ^{15}N NMR studies on indazoles in solution and in the solid state.[15] Only few examples of 3*H*-indazoles are known, which carry alkyl or aryl groups on the five-membered ring.[1] Indazol-3-ones, which can be regarded as 3*H*-indazole derivatives, however, are well-documented.

Some interest has also been focussed on conformers of indazole derivatives. Thus, similar to 1-(formylamino)indazole, 1-(acetylamino)indazole (**1**) exists as an equimolar mixture of *E*- and *Z*-conformers in $CDCl_3$ solution, as evidenced by ^{1}H NMR spectroscopy (Scheme 2).[16]



Scheme 2. Conformers.

NOESY NMR spectroscopy reveals that the imine **2** (Scheme 3) exists in form **A** in $CDCl_3$ and in form **B** with disrupted hydrogen bond in [D_6]DMSO. ^{13}C and ^{15}N-CPMAS NMR studies show that in the solid state no hydrogen bonds exist, so that rotamer **B** is detected.[17]

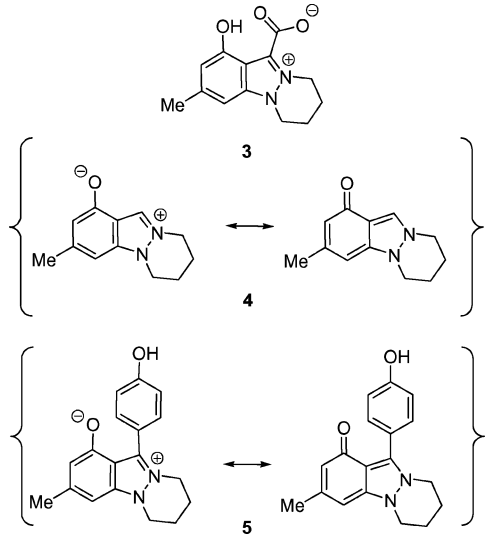


Scheme 3. Conformers and hydrogen bonds.

Two concomitant polymorphs of 3-phenyl-1*H*-indazole were examined by X-ray crystallography and their NMR properties were measured.[18]

3. Indazoles as Natural Products

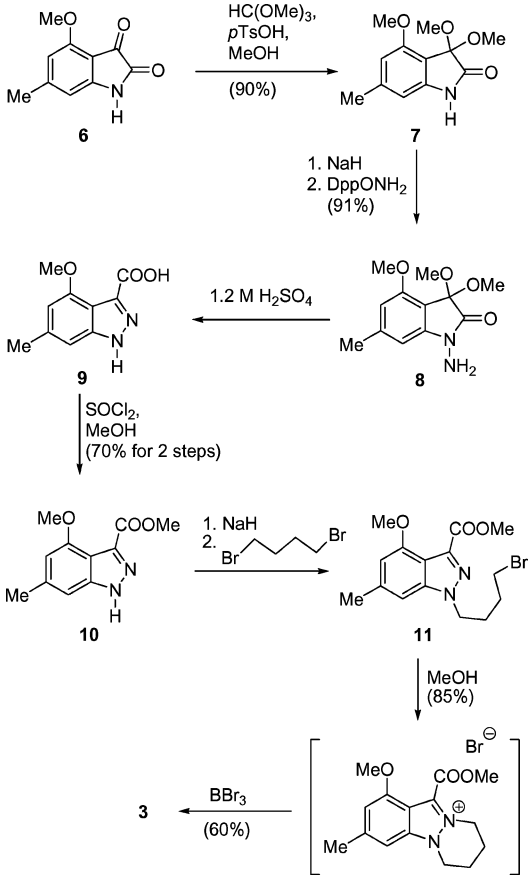
Indazoles are rare in Nature.[19] To date, only three natural products possessing the indazole ring have been isolated: Nigellicine (**3**), Nigeglanine (**4**), and Nigellidine (**5**) (Scheme 4). The alkaloid Nigellicine (**3**), a 6,7,8,9-tetrahydropyridazino[1,2-*a*]indazolium-11-carboxylate, was isolated as yellow crystals from the widely distributed herbaceous plant *Nigella sativa L.* [*Ranunculaceae*; *black cumin* (engl.), *Schwarzkümmel* (name in German)] which is an annual flowering plant, native to southwest Asia.[20] The structure was determined by an X-ray crystal structure analysis. An intramolecular hydrogen bond was found between the carboxylate oxygen atom and the hydroxy group. Nigellicine (**3**) belongs to the class of heterocyclic mesomeric betaines (MB), as it can exclusively be represented by dipolar canonical formulae in which both the positive and negative charge are delocalized in a common π-electron system. More precise, Nigellicine is a pseudo-cross-conjugated heterocyclic mesomeric betaine (PCCMB). The biological, physical, and chemical consequences of the distinct types of conjugation have been surveyed recently.[21] The alkaloid Nigeglanine (**4**) was isolated from extracts of *Nigella gland-*



Scheme 4. The indazole alkaloids Nigellicine, Nigeglanine, and Nigellidine.

ulifera.[22] Nigeglanine (**4**) and Nigellidine (**5**) (*Nigella sativa*)[23] can be represented by zwitterionic as well as by neutral canonical formulae (Scheme 4), thus setting them apart from mesomeric betaines.

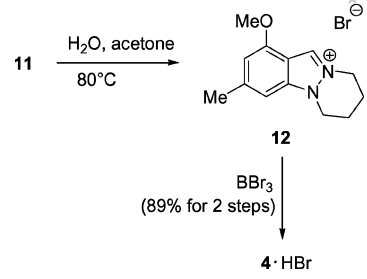
The total synthesis of **3** was accomplished by an isatin–indazole transformation as the key step (Scheme 5).[24] Thus, the dimethyl acetale derivative **7** was aminated via deprotonation with sodium hydride and quenching with *O*-(diphenylphosphanyl)hydroxylamine ($DppONH_2$) to the isatin derivative **8**. Transformation to indazole **9** was accomplished by sulfuric acid. Esterification, alkylation, saponification and demethylation completed this total synthesis.



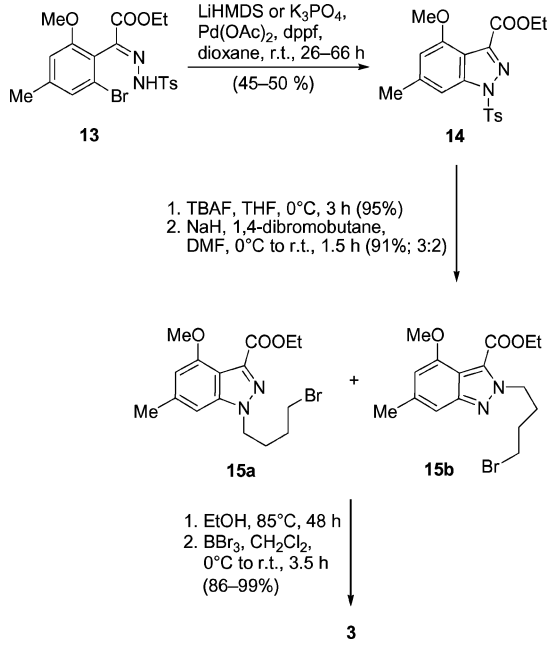
Scheme 5. Total synthesis of Nigellicine.

Treatment of **11** with aqueous acetone resulted in a decarboxylated species, which was directly converted into Nigeglanine hydrobromide **4**·HBr on treatment with BBr_3 (Scheme 6). The authors report that the ^1H, ^{13}C and HMBC NMR spectroscopic data of the hydrobromide of Nigeglanine are in agreement with the natural dihydrate of the alkaloid, but that the UV and IR spectra are different.[24] This is explained by effects of the counterion.

A palladium-catalyzed reaction is the key step of another total synthesis of Nigellicine (**3**) which was published very recently (Scheme 7). Deprotection of **14**, prepared as shown in Scheme 7, followed by alkylation to a mixture of the 1- and 2-substituted indazoles **15a**,**b** yielded Nigellicine **3** after ring closure, saponification, and demethylation.[25]



Scheme 6. Synthesis of Nigeglanine.

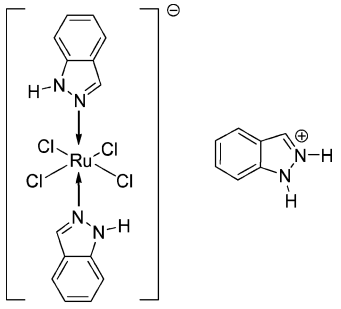


Scheme 7. Palladium-catalyzed total synthesis of Nigellicine.

4. Indazoles as Biologically Active Compounds

The indazole ring system is of great current interest as partial structure of biologically active compounds. Some aspects of pharmacological properties of indazoles have been reviewed in 2005.[6] As the molecular shape and electrostatic distribution play a crucial role in enzyme and receptor recognition and contribute extensively to binding affinity, a study on electroforms of molecules, including indazole, have been presented in order to help drug discovery.[26]

Unsubstituted indazole was used as ligand in metal complexes. Thus, tumor-inhibiting,[27,28] and redox-active antineoplastic ruthenium complexes with indazole have been reported and a correlation between in vitro potency and reduction potential was examined.[29] An example is the water-soluble anionic complex **16** with *trans*-standing indazoles, in which bonding with the metal is achieved via N(2) (Scheme 8).[30]

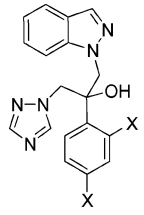


16

Scheme 8. Unsubstituted indazole as ligand.

4.1. Monosubstituted Indazoles

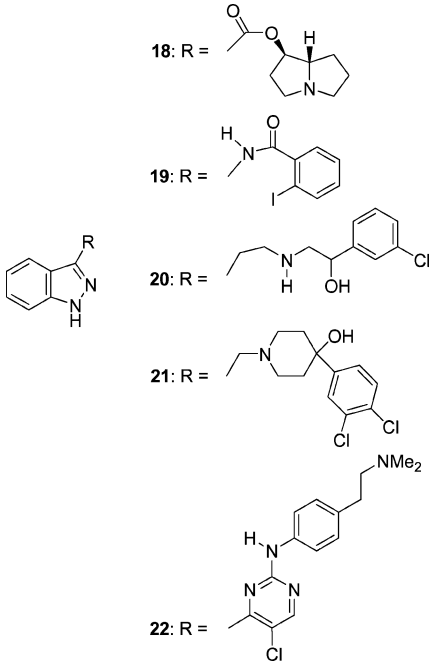
To the best of our knowledge, relatively few examples of N(1)-monosubstituted indazoles were published as biologically interesting compounds during the last decade. As examples, the indazoles **17a**,**b** were screened for antifungal activities as fluconazole analogues (Scheme 9).[31]



17a: X = F
17b: X = Cl

Scheme 9. An N(1)-monosubstituted indazole as biologically interesting compound.

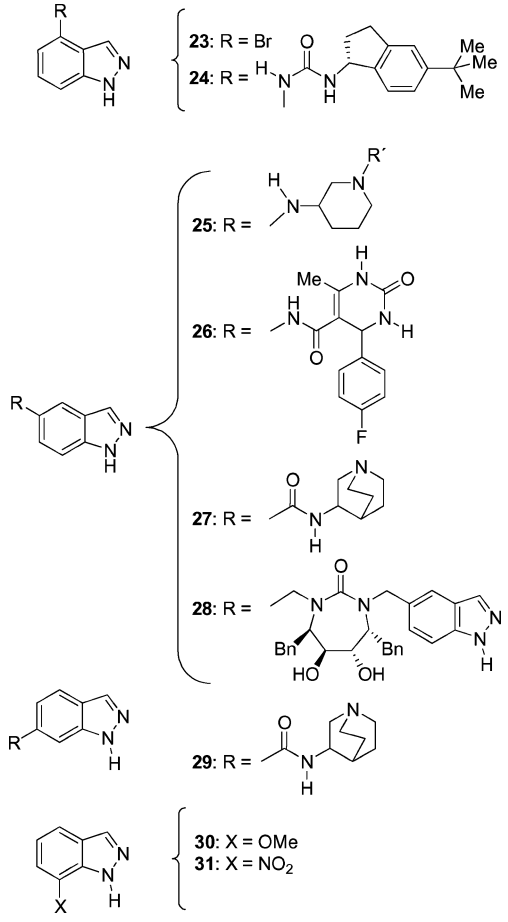
By contrast, several series of C(3)-monosubstituted indazoles were described as biologically interesting compounds (Scheme 10). Thus, **18** was tested as 5-HT_4 receptor agonist.[32] The iodobenzamide derivative **19** shows antifungal activities[33] and derivatives such as **20** were examined in search of β_3-adrenergic receptor agonists as potential drugs for the treatment of type II diabetes.[34] Indazole **21** is interesting as analogue of an dopamine D2 receptor antagonist,[35] while **22** was tested as inhibitor of VEGFR-2 and cyclin dependent kinase 1 (CDK1).[36]



18: R =
19: R =
20: R =
21: R =
22: R =

Scheme 10. C(3)-substituted indazoles.

Introduction of bromine at C(4) provides compound **23** which is almost as potent as the reference compound 7-nitroindazole as inhibitor of neuronal nitric oxide synthase, and 4-nitroindazole also proved to be a potent inhibitor of NOS activity (Scheme 11).[37] ABT-102 **24** has been identified as potent vanilloid receptor (VR1) antagonist and is currently undergoing advanced clinical development for the treatment of chronic pain.[38] 3-Aminopiperidinyl-substituted indazoles **25** with R′ substituents varying from *n*-propyl to 3-methylfuryl represent C(5)-monosubstituted indazoles with potential biological activities as they were tested as Rho kinase inhibitors.[39] More examples are the selective Rho-kinase inhibitor **26**,[40] the A7 nicotinic acetylcholine receptor agonist **27**,[41] and the anti-HIV protease inhibitor **28**.[42] No effect of 5- and 6-nitroindazole nucleosides of D-pinitol as antitumor agents, however, was found.[43] A series of substituted 6-anilinoindazoles as inhibitors of c-Jun *N*-terminal kinase-3 was recently described.[44] The latter mentioned compounds are examples for C(6)-monosubstituted



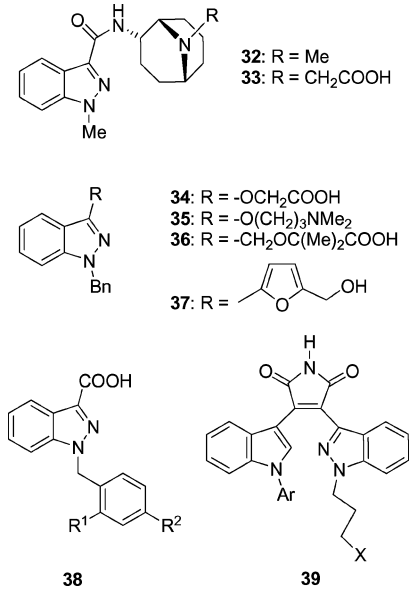
23: R = Br
24: R =
25: R =
26: R =
27: R =
28: R =
29: R =
30: X = OMe
31: X = NO_2

Scheme 11. C(4)-, C(5)-, C(6)-, and C(7)-substituted indazoles.

indazoles of pharmacolocical interest, only few examples of this group are described.[45] Two additional examples are TAS-3–124[46] and **29**.[42] Biologically interesting indazoles substituted at C(7) are represented by **30** and **31**. 7-Methoxyindazole (**30**)[47] as well as 7-nitroindazole (**31**),[48–50] are nitric oxide synthase inhibitors. The latter mentioned (7-NI **31**) and related indazoles were also shown to exhibit antinociceptive and cardiovascular effects.[51] Several substituted indazoles and potential analogues of 7-NI have been reported[45,46] from which 7-methoxyindazole proved to be the most active compound in in vitro enzymatic assays of nNOS activity.[52] *N*-(7-Indazolyl)benzenesulfonamide derivatives were prepared and investigated as cell cycle inhibitors.[53]

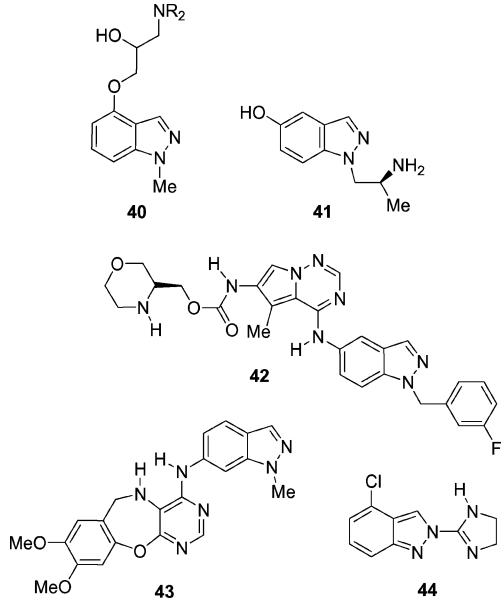
4.2. Disubstituted Indazoles

Numerous examples of N(1)–C(3)-disubstituted indazoles showing pharmacologically interesting properties have been published (Scheme 12). The selective 5-HT_3 receptor antagonist Granisetron (**32**) has been used clinically to prevent nausea and emesis induced by cancer chemotherapeutic agents.[54] Gastrointestinal prokinetic and dopamine D2 receptor antagonists were observed with derivatives such as **33**.[55] A series of N(1)-benzyl-substituted indazoles is represented by **34**–**37**. Bendazac (**34**), a topical anti-inflammatory agent, impedes effects associated with lens opacification and photochemical modes of action have been suggested.[56] Benzydamine (**35**) is a widely applied locally-acting nonsteroidal anti-inflammatory drug with local anaesthetic and analgesic properties. Bindarit (**36**) as well as Bendazac showed a selective inhibition of protein denaturation. The indazole derivative YC-1 (**37**) has been reported as activator of the physiological receptor for nitric oxide, sGC, which is a signalling molecule in the cardiovascular and central nervous system. YC-1 displays also some other biological activities such as inhibition of endothelial cell functions induced by angiogenic factors in vitro and angiogenesis in vivo.[57] It also effects cGMP metabolism by inhibiting the activity of phosphodiesterase isoforms 1–5.[58] The corresponding 2-benzyl isomer showed no activity.[59] Syntheses of YC-1 analogues[60] as well as of structural variations in search for new antithrombotics[61] have been reported. Indazol-3-carboxylic acid derivatives such as **38** compromises non-hormonal and non-steroidal, antispermatogenic agents and found interest in male contraception.[62] It was found that the presence of substituted benzyl groups at N(1) are essential for this specific activity, and so are halogen or methyl groups as R^1. The activity increases when two substituents are present in *o*- and *p*-position ($R^1 = R^2$ = Cl; or R^1 = Me, R^2 = Cl). AF 1311 ($R^1 = R^2$ = H) displays no anti-spermatogenic activity, but is able to reduce protein denaturation. By contrast, in Lonidamine ($R^1 = R^2$ = Cl) this property is decreased. The corresponding indazole-3-carbohydrazide ($R^1 = R^2$ = Cl, AF2364) and 3-acrylic acid ($R^1 = R^2$ = Cl; AF 2785) showed anti-spermatogenic effects.[63] (Indolyl-indazolyl)maleinimides **39** with a broad variety of substituents Ar (vinyl, Ph, 2-thiazolyl, 2-naphthyl, 3-quinolyl etc.) and X (Me_2N, morpholinyl etc.) were tested as inhibitors of protein kinase C-β.[64]



Scheme 12. N(1)–C(3)-disubstituted indazoles.

N(1)–C(X)-Substituted indazoles (X ≠ 3) are represented by the structures **40**–**43** (Scheme 13). Indazoles such as **40** exhibit antiarrhythmic, local anaesthetic and analgesic activities,[65] whereas **41** was identified as a periphally acting potent 5-HT2 receptor agonist.[66] BMS-599626 (**42**)[67] is in clinical development as EGFR and HER2 protein tyrosine kinase inhibitor. Structural optimizations have been reported.[68] Compound **43** was reported as inhibitor of epidermal growth factor receptor tyrosine kinase.[69] Syntheses



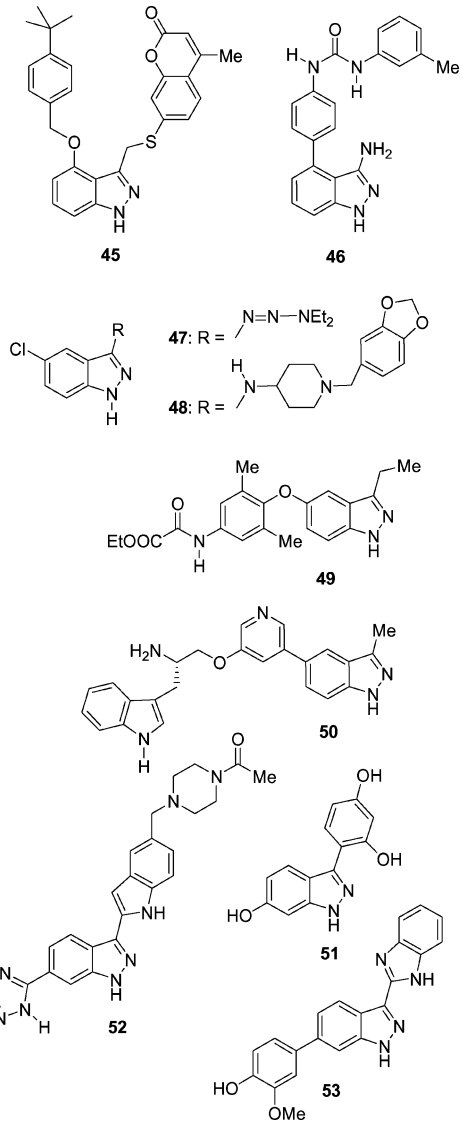
Scheme 13. N(1)–C(X)-disubstituted [X ≠ 3] indazoles **40**–**43** and the N(2)–C(4)-disubstituted indazole **44**.

as well as I_2/α_2-adrenoceptor binding profiles of a series of 2-(4,5-dihydroimidazol-2-yl)indazoles (indazim) such as **44** have been described.[70] These receptors are involved in several diseases such as psychiatric disorders, Parkinson's and Alzheimers's diseases and Huntington's chorea. Compound **44** is a typical N(2)–C(4)-disubstituted indazole.

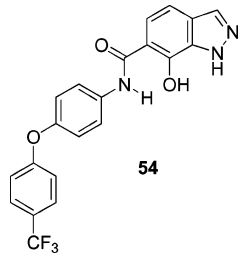
Scheme 14 presents a number of C(3)–C(X)-substituted indazoles (X ≠ 3) which consequently possess an N(1)–H group. Thus, indazole **45** was developed as novel DNA gyrase inhibitor.[71] A structure-based design lead to 3-aminoindazole as hinge-binding template for kinase inhibitors. Incorporation of *N*,*N*′-diarylurea partial structure at C(4) gave a series of receptor tyrosine kinase inhibitors such as ABT-869 (**46**).[72] Triazeno-indazoles such as **47** were prepared for comparison of antiproliferative activities.[73] The derivative in Scheme 14 showed best activity against K562, HL60, L1210, and MCF7 cell lines. The indazoles **48** (active as melanin concentrating hormone receptor-1 antagonist[74]), **49** (thyromimetics[75]), **50** (potent against Akt1[76]) are additional examples. Efforts have been devoted to incorporate functionalities for interactions with amino acid residues in the kinase domain.[77] In this context, an X-ray structure of the complex of 5-nitro-3-phenylindazoles with the 24 kDa fragment of DNA gyrase was described.[71]

4-(Indazolyl)phenols were identified as potent non-steroidal estrogen receptor ligands. Compound **51** was indeed confirmed to have strong inhibition of the NF-κB transcription.[78] Compound **52** was described as Chek1 kinase inhibitor,[79] and modelling predicted the binding mode of key representatives of **53** to the Chk1 ATP-binding site.[80] 3-Benzimidazol-2-yl-1*H*-indazoles were also examined as inhibitors of receptor tyrosine kinases.[81] An indazole with 3,6-disubstitution was tested as 2,3-oxidosqualene cyclase inhibitor.[82]

The C(6)–C(7)-disubstituted indazole **54** proved to be a potent inhibitor of the Qi site of the mitochondrial respiration complex III (Scheme 15).[83]



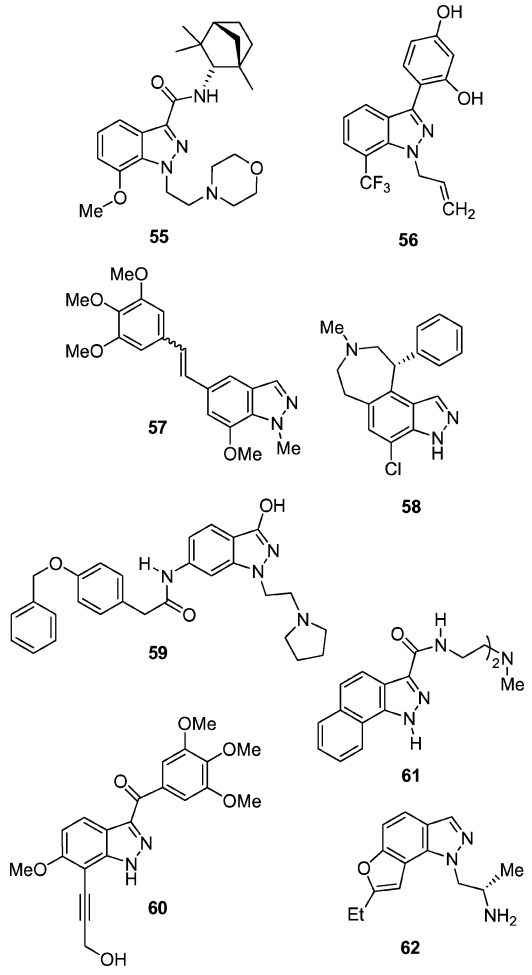
Scheme 14. C(3)–C(X)-disubstituted indazoles (X ≠ 3).



Scheme 15. A C(6)–C(7)-disubstituted indazole.

4.3. Trisubstituted Indazoles

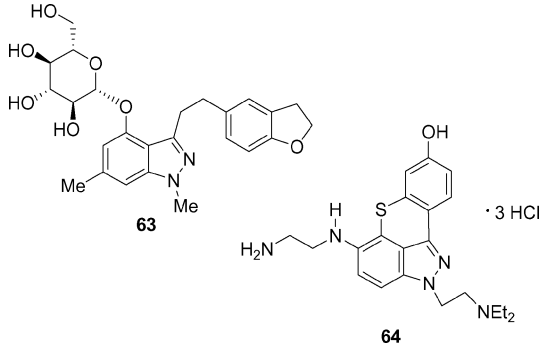
Some trisubstituted indazoles have also been described as biologically active compounds (Scheme 16). Novel Combretastatin analogues endowed with antitumor activity[84] belong to this class of compounds. In addition, a series of indazoles such as **55** was rationally designed and synthesized as cannabinoid ligands (Scheme 16).[85] WAY-169916 (**56**) was described as orally active nonsteroidal ligand with the potential use in the treatment of rheumatoid arthritis without the classical proliferative effects associated with estrogens.[78] The dopamine D1/D5 receptor antagonist **57**, indazole **58** (a phenol bioisosteric analogue of benzazepine derivatives[86]), the orally efficacious melanin-concentrating hormone receptor 1 antagonist **59** (treatment of obesity[87]) and the indazole **60** (binds specifically to the colchicine binding site and inhibits tubulin polymerization in vitro[88]) are examples for active trisubstituted indazoles. In addition, **61** and related systems are potential DNA-intercalators and demonstrated significant antiproliferative activities.[89] The furoindazole YM348 (**62**) was identified as a new and potent 5-HT_{2c} receptor agonist, which is one of the serotonine receptors.[90]



Scheme 16. Biologically active trisubstituted indazoles.

4.4. Tetrasubstituted Indazoles

The N(1)–C(3)–C(4)–C(6)-tetrasubstituted indazole **63** is interesting as sodium glucose co-transporter 2 inhibitor (Scheme 17).[91] A number of benzothiopyrano-indazoles such as **64** demonstrate significant antitumor activities. A promising example is CL-958 which is in clinical evaluation for prostate cancer treatment. In this context, aza-bioisosters of CL-958 were prepared.[92]

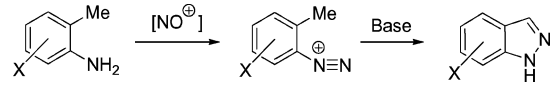


Scheme 17. Tetrasubstituted indazoles.

5. Syntheses of 1*H*-Indazoles

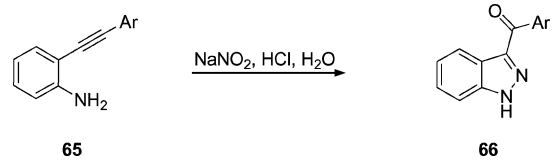
5.1. Reactions from Hydrazines, Hydrazones, Azo, and Diazo Compounds

A general route to indazoles is the intermolecular coupling of diazo groups with *o*-methyl groups (Scheme 18).



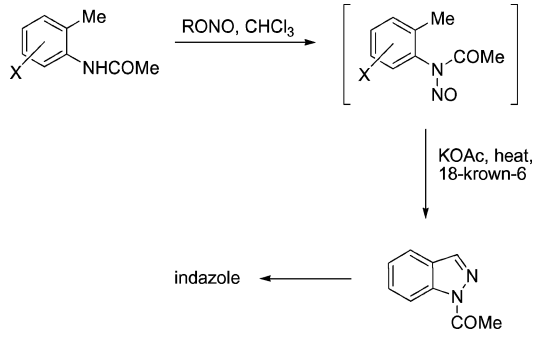
Scheme 18. General routes to indazoles, I.

Some applications of this procedure were described recently.[87,93,94] It was also shown that *o*-alkynylanilines such as **65** can be diazotized to give indazoles **66** (Scheme 19) [88,95] and some studies were presented to elucidate the mechanisms leading to five-membered (pyrazole) or six-membered (pyridazine) partial structures.[96] A similar reaction leading to 1*H*-naphtho[2,3-*g*]indazole-6,11-diones was described before.[97]



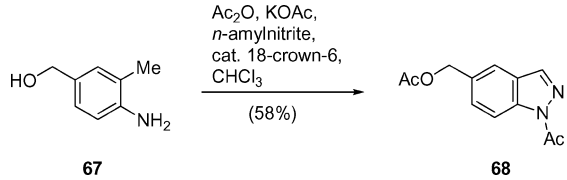
Scheme 19.

Another general route to indazoles is the nitrozation of *N*-acetyl derivatives (Jacobsen modification) (Scheme 20).



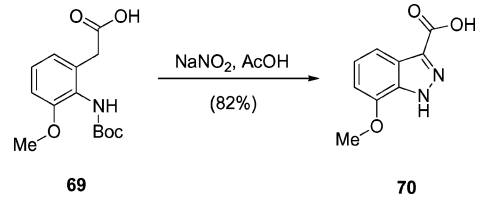
Scheme 20. General routes to indazoles, II.

Thus, acetic anhydride preforms the diacetate of **67**, which yields the indazole **68** on treatment with *n*-amyl nitrite under phase-transfer conditions (Scheme 21).[42]



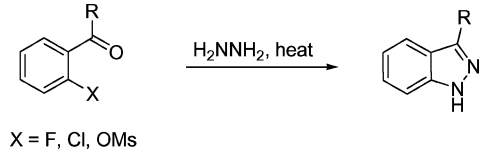
Scheme 21.

A related procedure was described recently. Thus, the NH Boc-protected methoxyaniline **69** cyclized to indazole **70** (Scheme 22).[85]



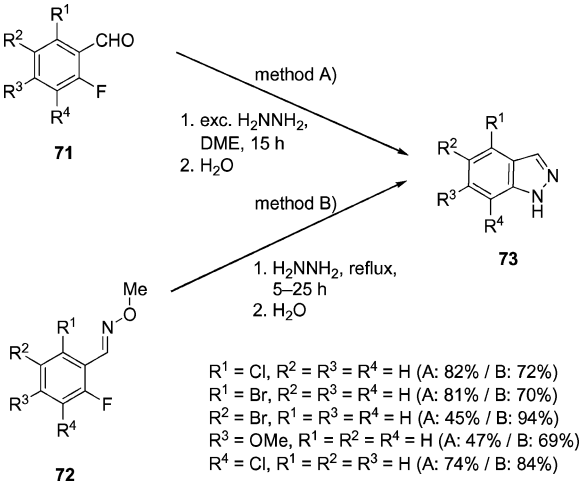
Scheme 22.

The condensation of *o*-substituted benzaldehydes with hydrazine is an alternative common synthetic route for the preparation of indazoles (Scheme 23).



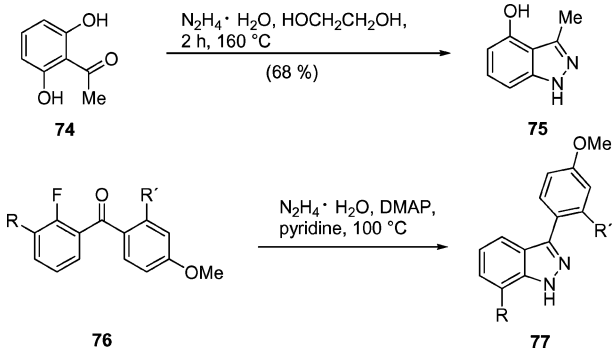
Scheme 23. General routes to indazoles, III.

Efforts have been devoted to new syntheses or optimizations of this traditional method to overcome withdrawings which are due to sometimes fairly harsh reaction conditions. In addition, some methods could not be considered practical for multikilogram preparations. Therefore, an approach starting from *o*-fluorobenzaldehydes **71** and their *O*-methyloximes **72** with hydrazine has been developed (Scheme 24). As *E*-isomers, the methyloximes prevented competitive Wolf–Kishner reductions to fluorotoluenes. The *Z*-isomers gave 3-aminoindazoles via a benzonitrile intermediate.[98] Mechanisms involving two equivalents of hydrazine were discussed.



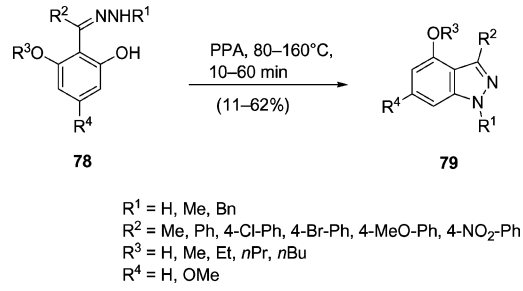
Scheme 24.

At high temperatures, aromatic nucleophilic substitutions of OH,[99] OMs,[100] or halogen[82] groups are observed. A recent example is the reaction of **74** to **75**, presented in Scheme 25.[71] Indazole **77** is a precursor of WAY1–169916 (**56**).[78] Likewise, annullation of an additional pyrazole ring to larger ring systems can be performed.[101]



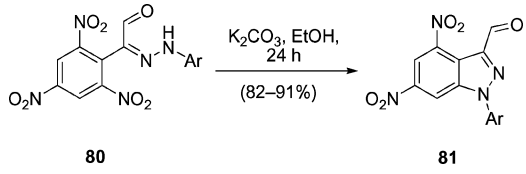
Scheme 25.

The formation of one C–N bond starting from arylhydrazones which are substituted in 2-position with alkyl or acyl groups represents an additional general route for the synthesis of indazoles. A recent application of this type of reaction is the intramolecular cyclisation of hydrazones of substituted acetophenones and benzophenones **78** by polyphosphoric acid (PPA) which resulted in the formation of indazoles **79** (Scheme 26).[102]



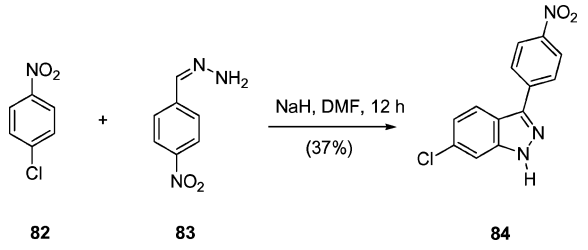
Scheme 26.

Indazoles were also formed from 2-(nitrobenzoyl)hydrazones such as **80**, where the nitro group acts as leaving group.[103,104] Recent examples are given in Scheme 27.



Scheme 27.

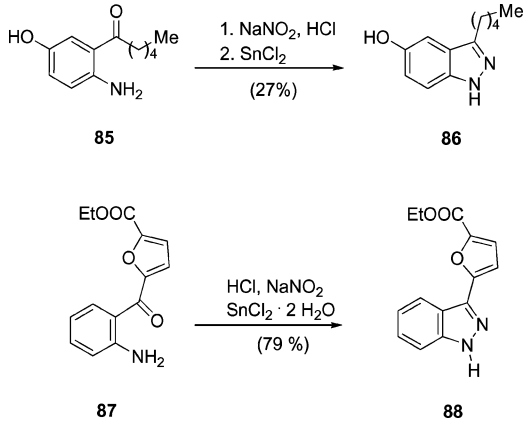
Substituted nitrobenzenes reacted with aromatic hydrazones in the presence of sodium hydride by cyclocondensation to 3-arylindazoles via nucleophilic substitution of the *ortho* hydrogen atom by the hydrazone anion, followed by replacement of the nitro group. On reaction of 4-chloronitrobenzene (**82**), the chloro substituent remained intact to give **84** (Scheme 28).[105]



82 83 84

Scheme 28.

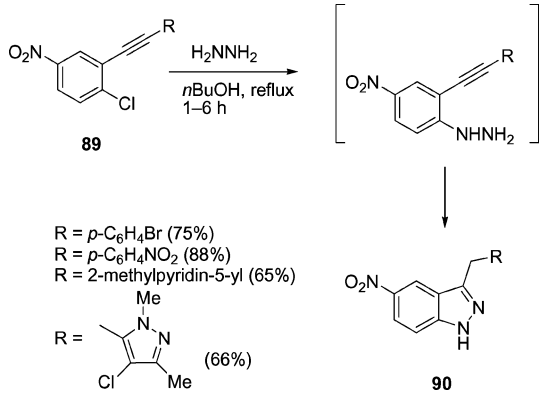
Diazotation can also be employed to prepare 3-alkyl-substituted indazoles starting from keto anilines **85** (Scheme 29); the intermediary diazonium salt is recuced to the hydrazine which then undergoes the ring closure.[75] This intermediate was used to prepare the potential thyromimetic **86**. The YC-1 precursor **88** was prepared starting form **87** in a similar way.[59]



85 86 87 88

Scheme 29.

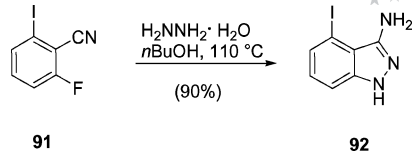
Michael-type additions between hydrazine groups and alkynyl groups, as presented in Scheme 30, can be used to prepare the indazole nucleus.[106] Here, *o*-chloro-alkynylarenes **89** were starting materials to synthesize **90**.



89 90

Scheme 30.

A related procedure is presented in Scheme 31. 2-Fluoro-6-iodobenzonitrile (**91**) reacted with hydrazine monohydrate to indazole **92**.[72]

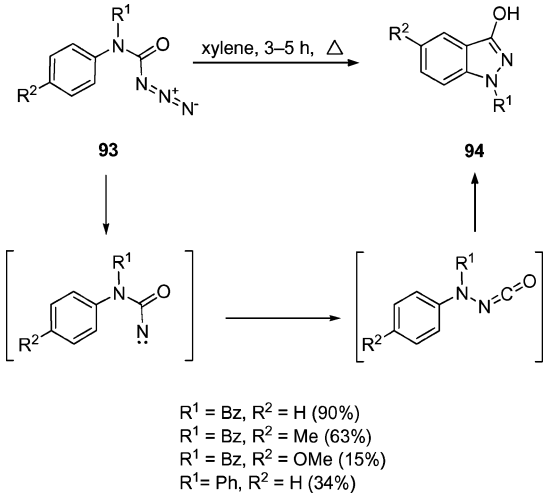


91 92

Scheme 31.

5.2. Rearrangements

In addition to these general approaches and modifications of classical procedures, numerous other strategies for the synthesis of indazoles exist. Thus, it was reported that diphenylcarbamoyl azide **93** underwent a rearrangement to indazole **94**.[107,108] The mechanism is depicted in Scheme 32.

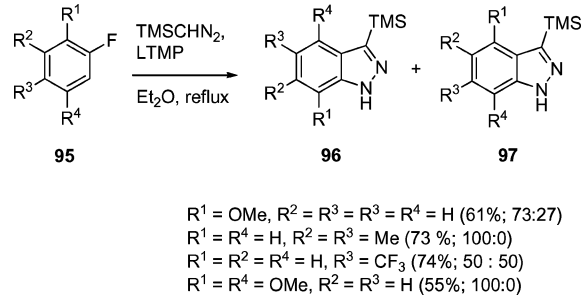


93 94

Scheme 32.

5.3. Cycloadditions

The aryne mechanism was observed on [3+2] cycloaddition starting from fluorobenzenes **95** and trimethylsilyldiazomethane in a basic medium.[109] In some cases, regioisomers **96** and **97** were obtained (Scheme 33).

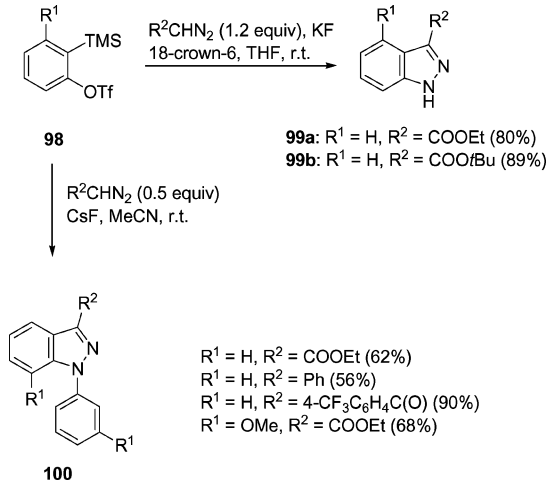


95 96 97

Scheme 33.

Other [3+2] cycloadditions between arynes generated from silylaryl triflates and various diazomethane derivatives were reported. Depending on the reaction conditions, either N(1)-unsubstituted, for instance **99**, or N(1)-aryl-substi-

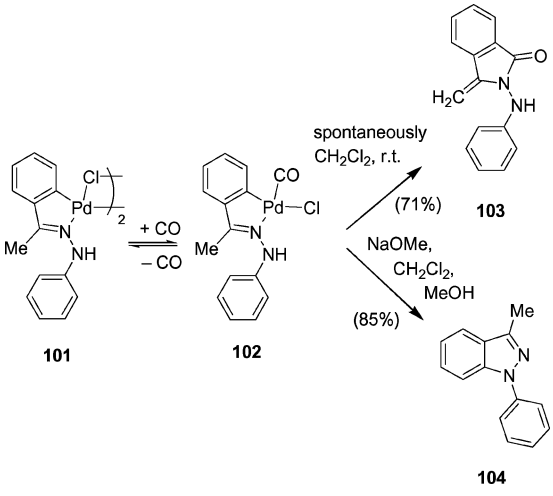
tuted indazoles **100** were formed under very mild conditions (Scheme 34). For the case of R^1 = OMe, a 7-methoxy-substituted indazole was formed. Methyl substitution at C(4) of the starting material yielded a 1:1 mixture of isomeric indazoles, i.e. 5- and 6-methylindazole.[110]



Scheme 34.

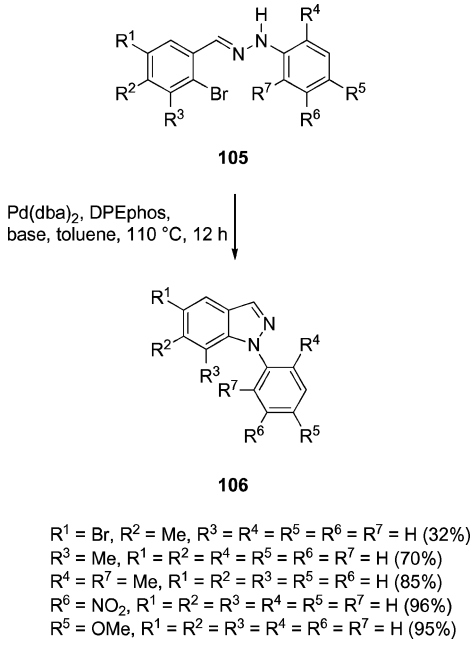
5.4. Metal-Organic Syntheses

Carbonylation of the dimeric *ortho*-palladated arylhydrazone complex **101** yielded a monocarbonyl complex **102** which reacted very slowly to give the isoindolone **103** (Scheme 35). Addition of stoichiometric amounts of sodium methoxide induced a reductive elimination and resulted in the formation of indazole **104**.[111]



Scheme 35.

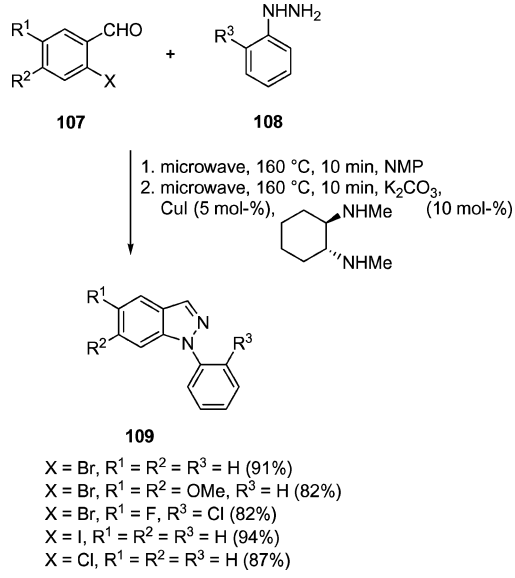
A broad variety of substituted indazoles was prepared starting from 2-bromobenzaldehydes and arylhydrazines by palladium catalysis.[112] Phosphorous-chelating ligands such as 1,1′-bis(diphenylphosphanyl)ferrocene and 1,3-bis(diphenylphosphanyl)propane along with sodium *tert*-butoxide were used. A broad variety of substituted indazoles **106** were prepared via palladium-catalyzed intramolecular amination of aryl halides **105** (Scheme 36).[113,114]



Scheme 36.

As depicted in Scheme 7, similar reactions were applied in the total synthesis of Nigellicine, starting from 2-bromoacetophenone (4-methylphenyl)sulfonylhydrazones using $Pd(OAc)_2$, dppf, $CsCO_3$ in dioxane.[25]

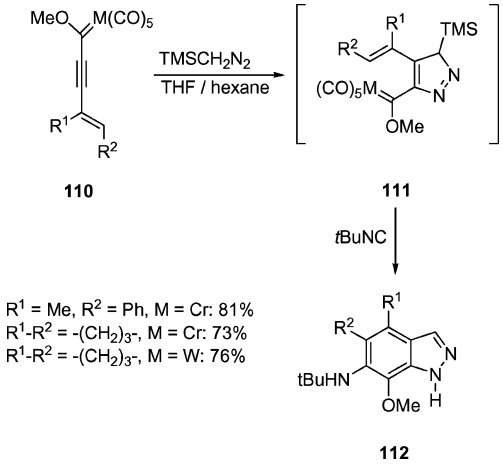
Iodo-, bromo- and chloro-substituted benzaldehydes **107** react with hydrazines **108** under microwave conditions in the presence of CuI and a ligand to give indazoles **109** (Scheme 37).[115]



Scheme 37.

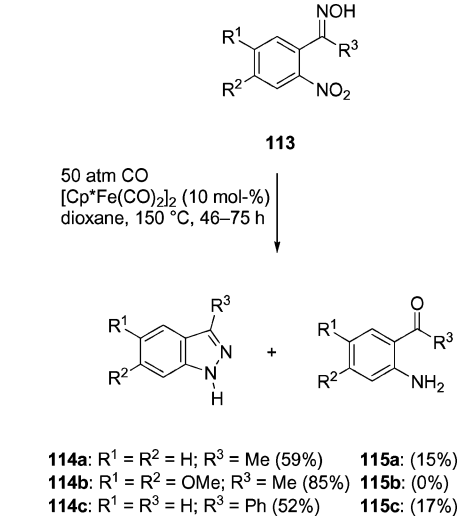
Trimethylsilyl diazomethane was used as dipole for the preparation of 1,3,5-metallahexatrienes **111** from the chromium or tungsten alkynyl complexes **110** which were sub-

jected to a tandem isocyanide insertion–electrocyclization, as shown in Scheme 38. Addition of two equivalents of *tert*-butyl isocyanide resulted in the formation of indazoles **112** as single regioisomers.[116]



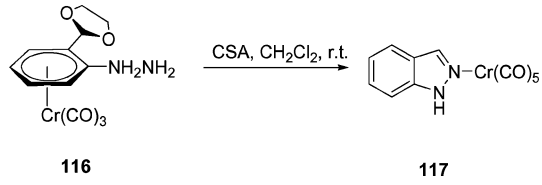
Scheme 38.

It was reported that 2-nitroacetophenone oximes **113** react with the dimer of dicarbonyl(pentamethylcyclopentadienyl)iron(II) in dioxane under CO to yield indazoles **114** and 2-aminoacetophenones **115**. The mechanism is not yet known (Scheme 39).[117]



Scheme 39.

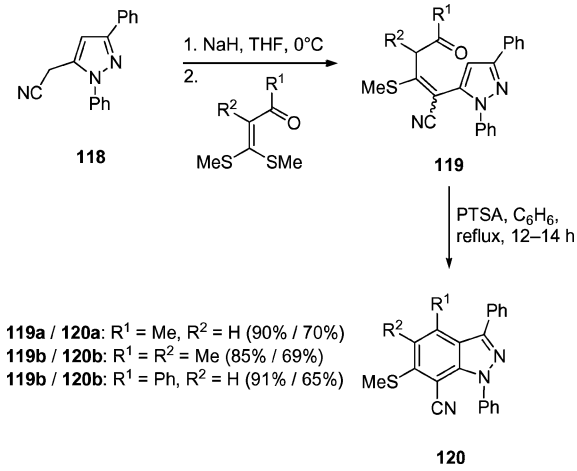
Tricarbonyl[η^6-2-(2′-phenylhydrazine)-1,3-dioxolane]chromium **116** can be converted into the indazole complex **117** by treatment with *rac*-camphorsulfonic acid (Scheme 40). A solution of this complex in diethyl ether was exposed to air and sunlight to give indazole.[118]



Scheme 40.

5.5. Syntheses Starting from Pyrazoles

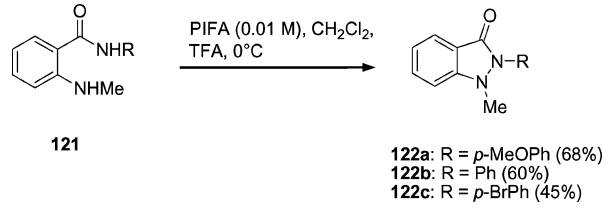
A two-step [3+2] annulation of 1,3-diphenyl-5-cyanomethylpyrazole **118** with α-oxoketenes dithioacetals afforded functionalized indazoles **120** with high regioselectivity (Scheme 41).[119]



Scheme 41.

5.6. Oxidative N–N Coupling Reactions

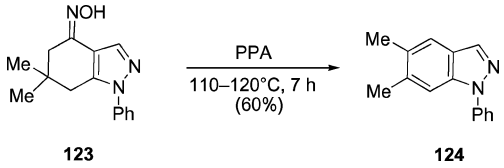
Most syntheses of indazoles involve the formation of the pyrazole moiety. A suitable method is the oxidation of anthranilic acid amides **121** with iodine reagents such as the hypervalent iodine reagent phenyliodine(III) bis(trifluoroacetate) (PIFA) to 1,2-disubstituted indazolones **122**.[120] The key cyclization step embraces the PIFA-mediated formation of an *N*-acylnitrenium intermediate (Scheme 42).



Scheme 42.

5.7. By Carbocycle Aromatization

Aromatization of 4-hydroxyimino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydroindazole (**123**) to **124** was accomplished by heating in PPA. The proposed mechanism proceeds via the formation of an iminium cation, followed by subsequent hydride and methyl migration, and final oxidation to indazole **124** (Scheme 43).[121]

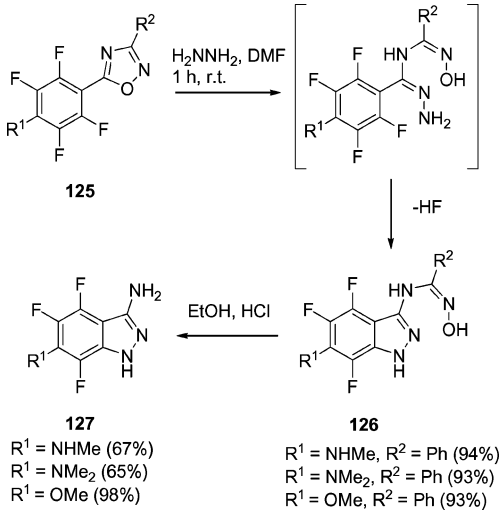


123 124

Scheme 43.

5.8. By Nucleophilic Ring Transformation

A series of fluorinated indazoles **126** and **127** (Scheme 44) was synthesized by an ANRORC-type rearrangement of 5-tetrafluorophenyl-1,2,4-oxadiazoles **125** with hydrazine.[122]



125

127
R^1 = NHMe (67%)
R^1 = NMe_2 (65%)
R^1 = OMe (98%)

126
R^1 = NHMe, R^2 = Ph (94%)
R^1 = NMe_2, R^2 = Ph (93%)
R^1 = OMe, R^2 = Ph (93%)

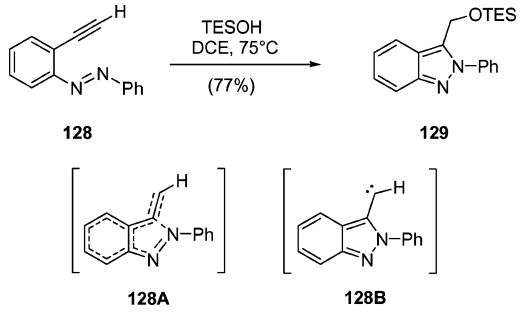
Scheme 44.

6. Syntheses of 2*H*-Indazoles

6.1. By Coarctate Reactions

Coarctate[123] cyclizations are defined by the presence of a coarctate atom where two bonds are being broken and two are being made and that bond breaking and making do not occur in a cyclic array, thus setting them apart from pericyclic reactions. By definition, pericyclic reactions exhibit a cyclic transition state of delocalized electrons. Bond making and breaking occur simulaneously in a cyclic array. In pseudopericyclic reactions, the cyclic delocalization of electrons in the transition state is interruppted because the orbitals involved in the delocalized system are orthogonal at these points. They do not follow the Woodward–Hoffmann rules. Analogous disconnections in coarctate reactions are termed pseudocoarctate.

A coarctate mechanism formed 2-phenylisoindazoles **129** from (2-ethynylphenyl)phenyldiazenes **128** (Scheme 45); the intermediary carbene **128B** was formed under neutral conditions via transition state **128A** at moderate temperatures.[124] The free carbene could also be trapped as a [2+1] cycloadduct with 2,3-dimethyl-2-butene.

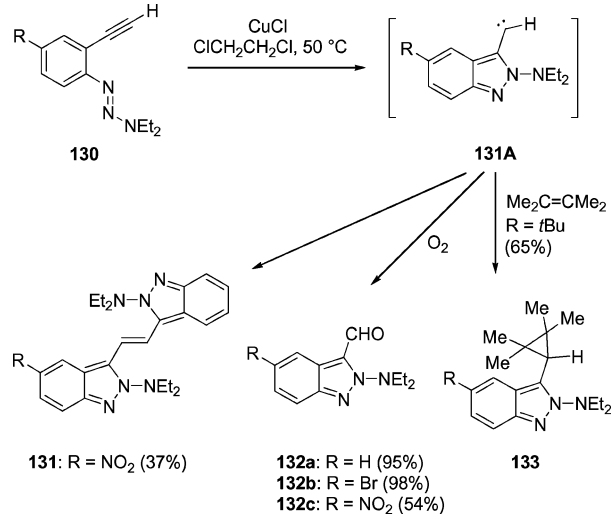


128 129

128A 128B

Scheme 45.

The behaviour of (2-ethynylphenyl)triazenes on heating is dependent on the temperature. Either mixtures of isoindazole aldehydes such as **132** or cinnolines are formed (Scheme 46). Higher temperatures (1,2-dichlorobenzene, 200 °C) result in the exclusive formation of cinnolines.[125] Evidence for the carbene **131A** was found on heating the starting material in the presence of copper salts which results in aldehydes **132** (Scheme 46); nitro substitution leads to **131** as by-product, and the presence of 2,3-dimethyl-2-butene results in the formation of the cyclopropane **133**.[126] Some additional examples have been described.[127] Experimental as well as theoretical results suggest reversible formation of the carbene which can regenerate the starting material to give cinnolines at higher temperatures. Formation of the five-membered ring, however, was explained by a coarctate-type mechanism. Mechanistic aspects of this cyclization both under thermal and copper-catalyzed conditions were calculated. A pseudocoarcate mechanism was found for the formation of the isoindazoles; the thermal cyclization proceeded via a pericyclic pathway and zwitterionic intermediates to cinnolines.[128]



130 131A

131: R = NO_2 (37%)

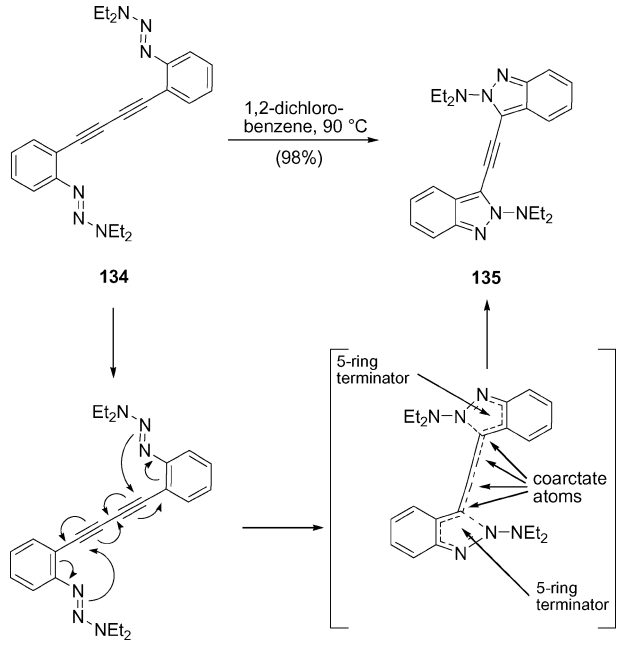
132a: R = H (95%)
132b: R = Br (98%)
132c: R = NO_2 (54%)

133

Scheme 46.

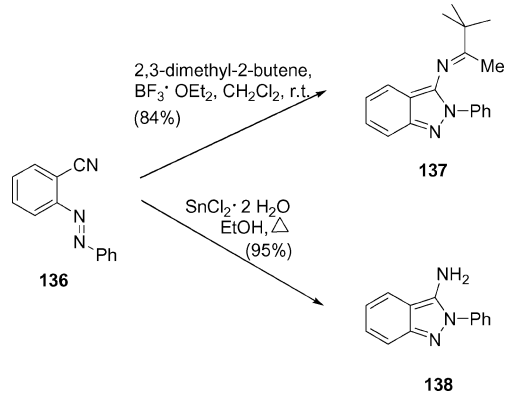
Triazene cyclisation starting from **134** in 1,2-dichlorobenzene or in a variety of low-boiling solvents yields **135** (Scheme 47).[129] DFT calculations, in agreement with experimental observations, indicate that the reactions occur via a short-lived carbene intermediate, are concerted via an

asymmetrical transition state, or are even synchronous, with as many as 16 bonds that are made or broken simultaneously.



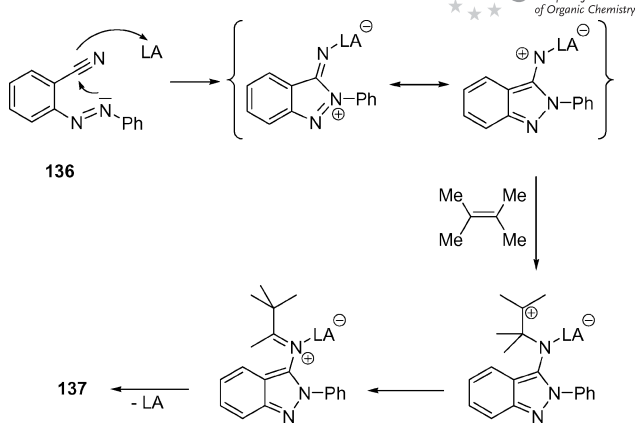
Scheme 47.

Coarctate cyclization of the ene-ene-yne moiety of 2-(phenylazo)benzonitrile derivatives **136**, promoted by Lewis acids (LA), results also in the formation of isoindazoles[130] (Scheme 48). Depending on the reaction conditions, imines **137** or amines **138** are formed, and functional groups such as halogen, nitrile, ester, nitro, and methoxy are tolerated. The proposed mechanism for this procedure is displayed in Scheme 49.



Scheme 48.

Efficient syntheses of 3-alkoxy-2*H*-indazoles by one-step heterocyclisation of *o*-nitrobenzylamines were described.[131,132] They represent an additional elegant approach to 2*H*-indazole derivatives.

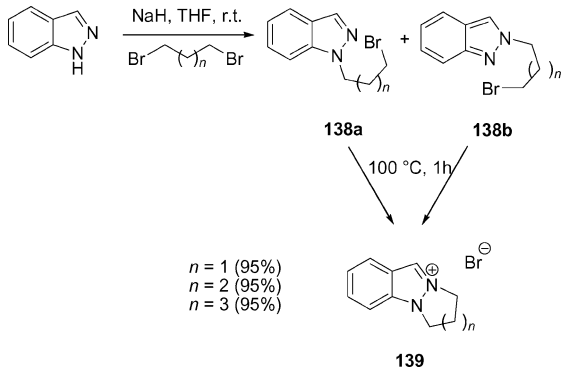


Scheme 49.

7. Reactions of Indazoles

7.1. Alkylations and Arylations of N(1) and N(2)

Indazoles are alkylated or acylated at N(1), N(2), or at both positions depending on the reaction conditions.[61,133–137] For example, indazole reacts with dihalo alkanes to afford *N*-alkylation products **138a** and **139b** which cyclized thermally into the indazolium salt **139**[138] (Scheme 50). This procedure resembles the syntheses of the alkaloids **3** and **4** (cf. Schemes 5 and 7).



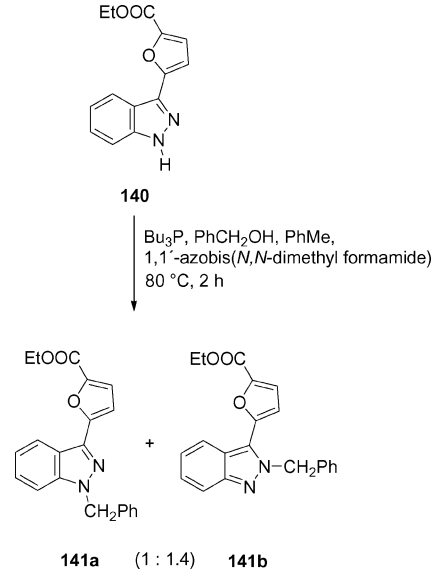
Scheme 50.

A Mitsunobu reaction was applied to prepare the YC-1 precursors **141a**,**b** from **140** (Scheme 51). Again, mixtures of regioisomers are obtained.[59]

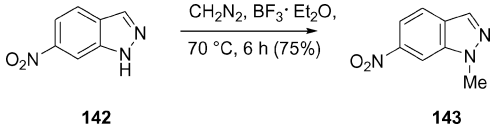
It was reported that methylation of 6-nitro-1*H*-indazole **142** with diazomethane in the presence of BF_3 resulted in the formation of the N(1)-methylated product **143** (Scheme 52).[139]

Copper(I) iodide induces the reaction of indazole with (*S*)-1-(3-bromophenyl)ethylamine under microwave irradiation conditions to yield **144** (Scheme 53).[140] Some other examples have been described elsewhere.[141]

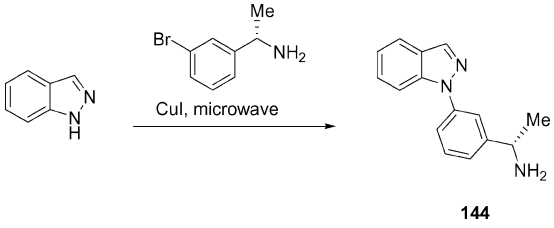
Alternatively, aryl- and hetarylboronic acid derivatives can be employed for copper-catalyzed reactions to N(1)-arylated indazoles such as **145** (Scheme 54).[142,143] Depending on the reaction conditions, arylations of N(1), C(3), or both positions can be achieved.[144]



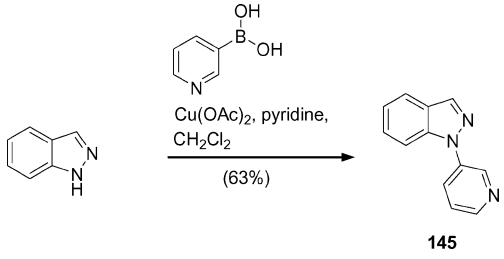
Scheme 51.



Scheme 52.

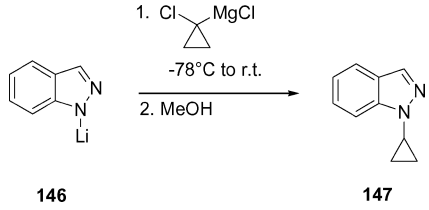


Scheme 53.



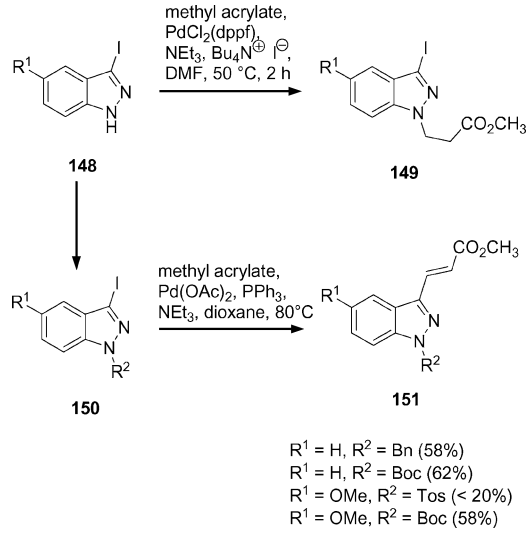
Scheme 54.

Reaction of 1-lithioindazole **146** with cyclopropylmagnesium derivatives yields indazoles **147** which are cyclopropanylated at N(1) (Scheme 55).[145]



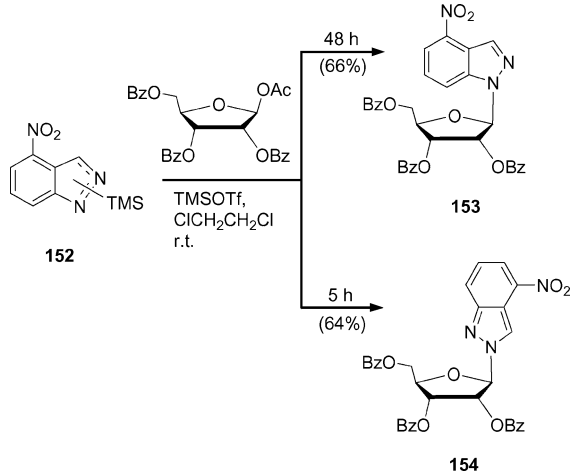
Scheme 55.

When a Pd-catalyzed cross-coupling of 3-iodoindazoles **148** with methyl acrylate was attempted, Michael adducts **149** are formed. *N*-Protected indazoles, however, result in the desired cross-coupled products **151** (Scheme 56).[146]



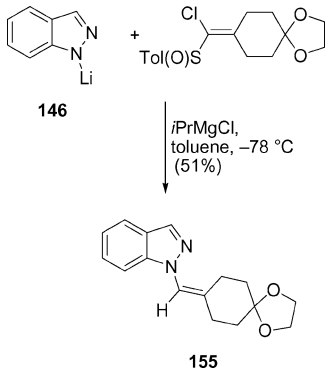
Scheme 56.

A regioselective synthesis of indazole N^1- and N^2-(β-D-ribonucleosides) was described.[147] The N(1)-substituted derivative **153** is formed under thermodynamic control of the silyl Hilbert–Johnson glycosylation reaction, whereas kinetic control affords the N(2) substituted product **154** (Scheme 57).



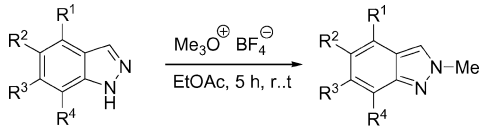
Scheme 57.

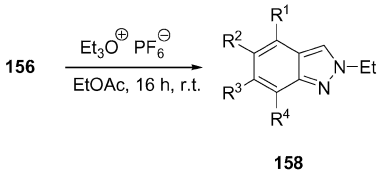
In addition, an interesting method for the alkenylation of indazole was described (Scheme 58).[148] Thus, treatment of magnesium alkylidene carbenoids, generated from 1-chlorovinyl *p*-tolyl sulfoxides with a Grignard reagent, react with *N*-lithioindazole **146** to give **155**.



Scheme 58.

Syntheses of 2-methyl- and 2-ethyl-2*H*-indazoles were reported which overcome problems concerning the regioselectivity of this reaction.[139] Thus, treatment of the indazoles **156** with trimethyloxonium tetrafluoroborate yields the N(2)-methylated species **157**. Triethyl hexafluorophosphate gives the corresponding N(2)-ethyl derivatives **158** in high yields (Scheme 59).

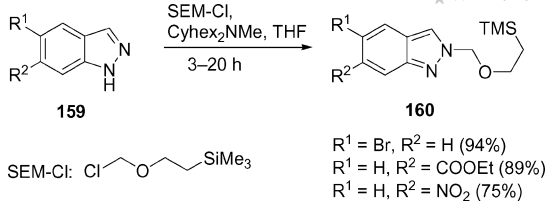




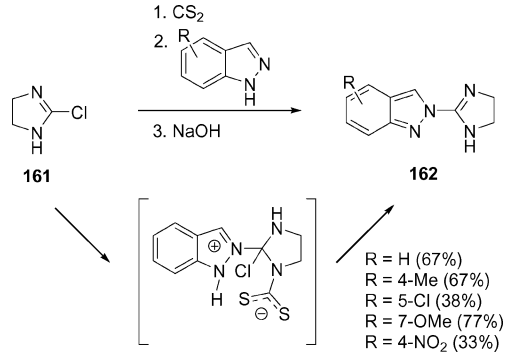
Scheme 59.

In addition, the SEM-protecting group can regioselectively be introduced into the 2-position (→**160**) and can then be used to direct lithiations at C(3) (Scheme 60).[149]

Catalyzed by carbon disulfide, indazoles react with 2-chloroimidazoline **161** to give the N(2)-substituted indazoles **162**.[70] (cf. indazim **44**, Scheme 13). The proposed mechanism[150] is depicted in Scheme 61.

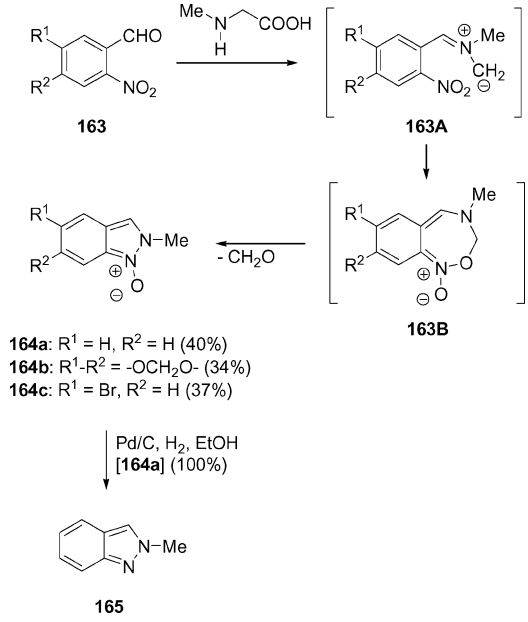


Scheme 60.



Scheme 61.

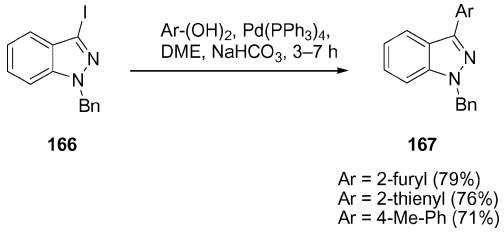
2-Methylindazole *N*-oxides were prepared via 1,7-electrocyclization of azomethine ylides. Decarboxylative condensation of *o*-nitrobenzaldehydes **163** and sarcosine followed by 1,7-electrocyclization presumably results in the formation of an unstable benz-1,2,6-oxadiazepine intermediate **163B** which undergoes ring contraction (Scheme 62). Final extrusion of formaldehyde gives the indazole *N*-oxides **164** and 5-aryl-3-methyloxazolidines as by-products.[151] Compound **164a** gives 2-methylindazole **165** on reduction.



Scheme 62.

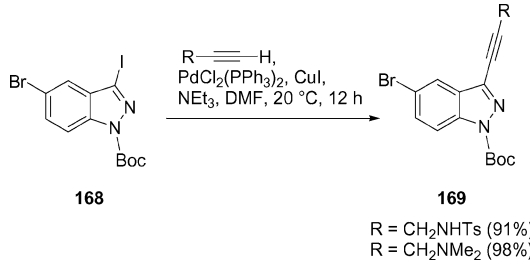
7.2. Functionalizations of C(3)

In view of the large number of biologically active indazoles substituted at C(3), functionalizations of this position are of great current interest. In this context, Heck[152] as well as Suzuki-type cross-couplings of 3-iodoindazoles have been described. As example for the latter mentioned procedure, **166** reacts with aryl- and hetarylboronic acids to give 3-arylated indazoles **167** (Scheme 63).[153]



Scheme 63.

Sonogashira reactions for acetylenizations of C(3) of the starting material **168** were also described. The reaction products **169** undergo an additional Sonogashira coupling to afford bis-acetylene-substituted indazoles (Scheme 64).[154,155]



Scheme 64.

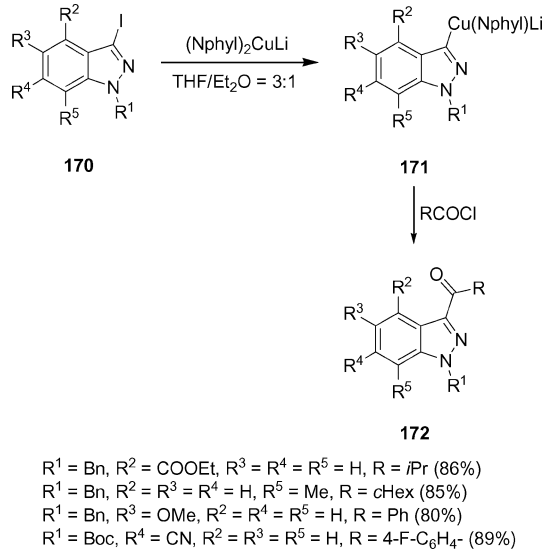
Polyfunctional 3-acylindazoles **172** can be prepared from copper derivatives **171** of 3-iodoindazoles **170** (Scheme 65).[156]

Stille couplings of **173** with **174** were performed to prepare compounds **175**, which are analogues of YC-1 (**37**, see chapter 4.2, Scheme 66).[60]

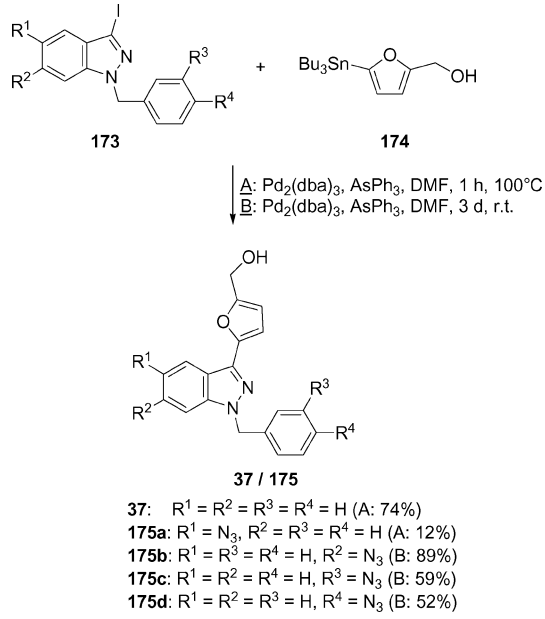
As already mentioned (cf. Scheme 60), the SEM protecting group at N(2) can direct regioselective C-3-lithiations of **176**, and the resulting nucleophile can react with a number of electrophiles. The SEM group of **177** can be removed with TBAF or hydrochloric acid in ethanol.[149] Examples are presented in Scheme 67.

Functionalizations of C(3) in 2-methylindazoles **165** can also be achieved by lithiation followed by reaction with a variety of electrophiles to **178** (Scheme 68).[157] On the other hand, site-selective carbonylations at C(7) were observed in $Ru_3(CO)_{12}$-catalyzed reactions of 2-methylindazol with 3,3-dimethylbut-3-ene to **179**.[158]

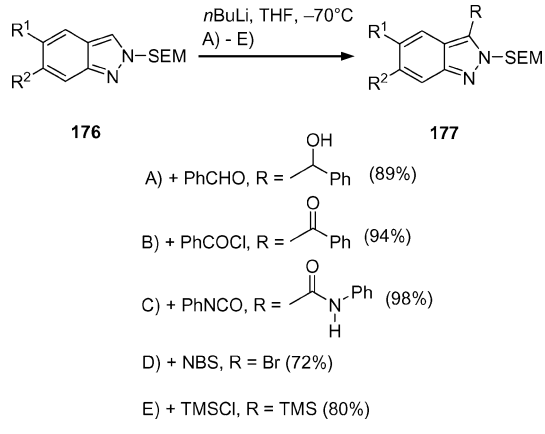
Conversion of the nitro group into an amino group by tin(II)chloride in ethanol surprisingly resulted in the formation of the C(4)-substituted indazoles **181** (Scheme 69). The 3-iodoindazoles **180** were treated successfully with different alcohols to introduce alkoxy groups in position 4.[159]



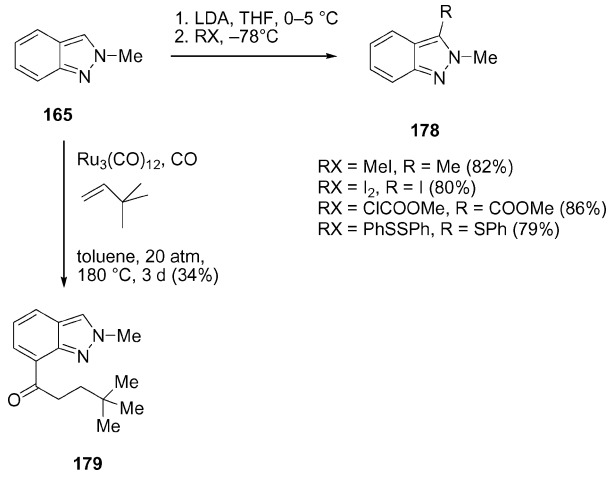
Scheme 65.



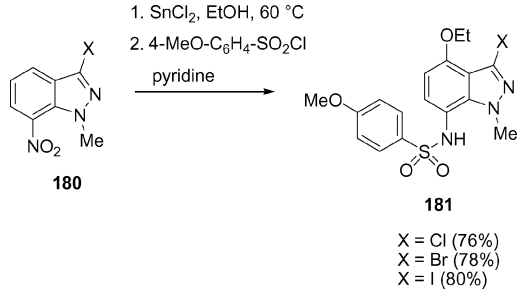
Scheme 66.



Scheme 67.

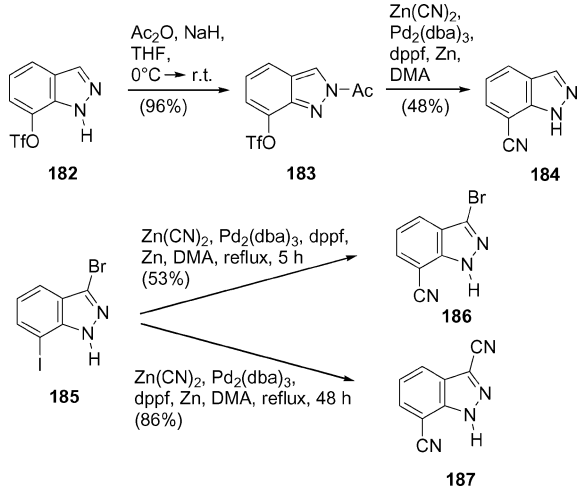


Scheme 68.



Scheme 69. Surprising functionalization of C(4).

A Palladium-mediated cyanation of 7-OTf-substituted indazoles **183** to afford **184** was reported (Scheme 70). In the course of the cyanation of **185**, the amount of zinc cyanide added and the reaction time determined the formation of 7-cyano or 3,7-dicyanoindazoles **186** and **187**, respectively.[160]



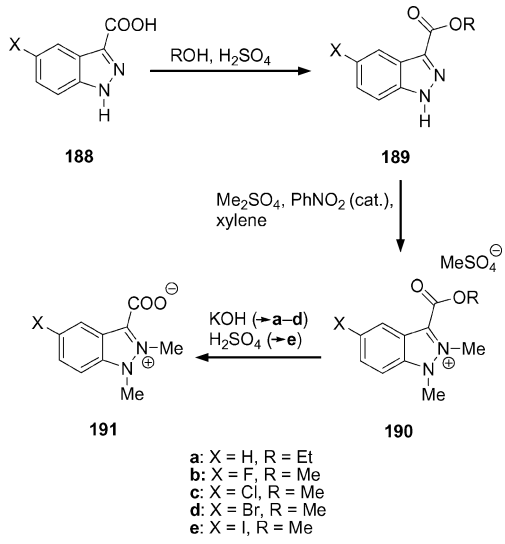
Scheme 70.

As mentioned before, an additional method for arylations at C(3) uses boronic acids.[144]

8. *N*-Heterocyclic Carbenes of Indazole

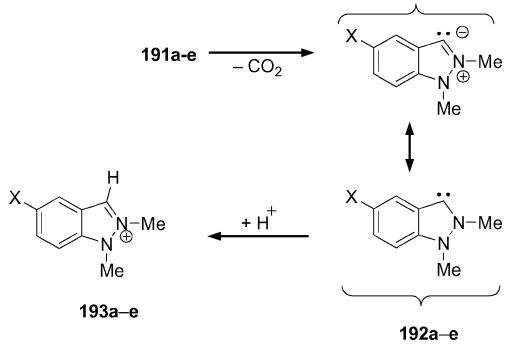
8.1. Trapping Reactions

N-Heterocyclic carbenes of indazole are accessible by extrusion of heterocumulenes from pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB). Indazolium-3-carboxylates are examples for those systems (Scheme 71). They were prepared starting from the indazole-3-carboxylic acids **188** which were first converted into the esters **189**, then methylated to indazolium salts **190** with dimethyl sulfate in the presence of catalytic amounts of nitrobenzene, and finally saponified.[161,162]



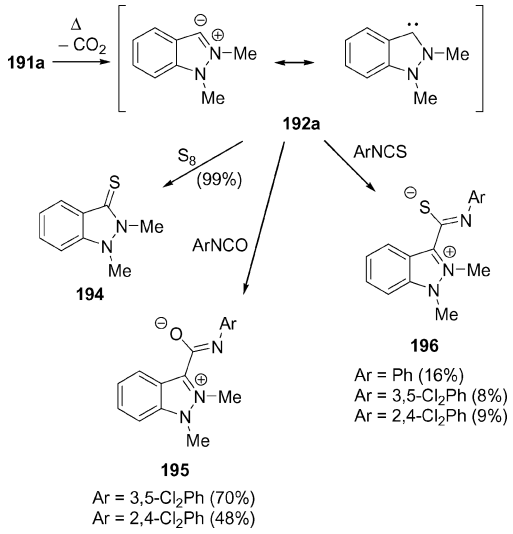
Scheme 71. Synthesis of pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB) of indazole.

On heating, carbon dioxide is extruded from the mesomeric betaines **191** to yield indazol-3-ylidenes **192** which can be detected by electrospray ionization mass spectrometry. In protic solvents, these carbenes add a proton to the indazolium salts **193** (Scheme 72).



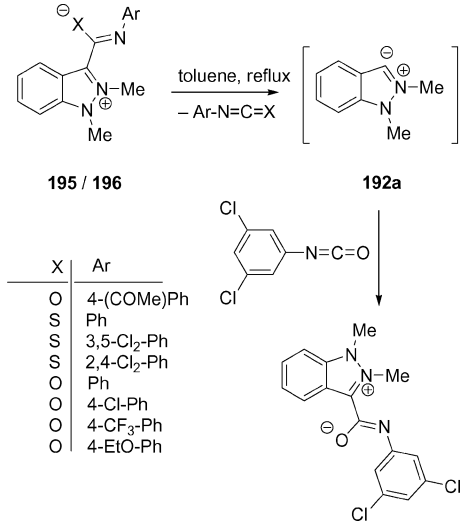
Scheme 72. Formation of indazol-3-ylidenes by decarboxylation of PCCMBs.

A number of trapping reactions of the *N*-heterocyclic carbenes **192** has been described (Scheme 73). Thus, heating **191a** in toluene with sulfur gives the thione **194**, isocyanates lead to indazolium-3-amidates **195**, and thioisocyanates yield indazolium-3-thioamidates **196**.[163]



Scheme 73. Trapping reactions of NHC **192a**.

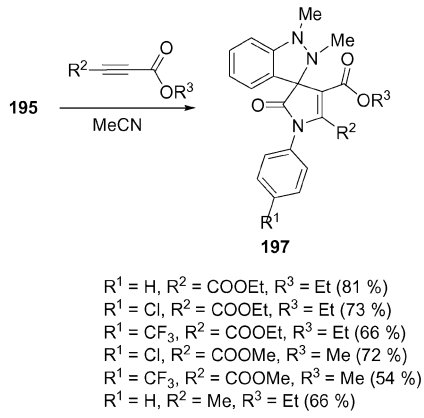
The mesomeric betaines **195** and **196** are new representatives of pseudo-cross-conjugated systems and are also able to extrude their heterocumulene partial structures to give indazol-3-ylidene **192** which can be trapped again by other reagents (Scheme 74). Thus, certain isocyanates or thioisocyanates in **195** and **196** can be exchanged to others. Exchange reactions to 3,5-dichlorophenylamidate are shown in Scheme 74.[163]



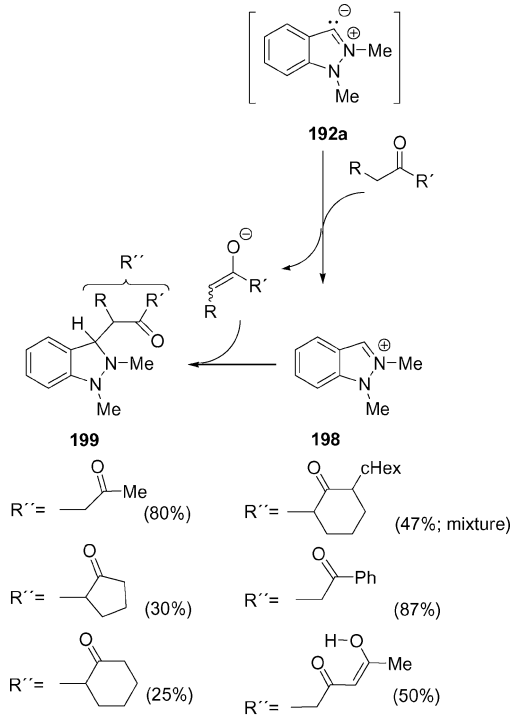
Scheme 74. Heterocumulene exchange reactions via NHC **192a**.

1,3-Dipolar cycloadditions were performed starting from **195** and acetylenes to give the new spiro ring system **197** (Scheme 75).[164]

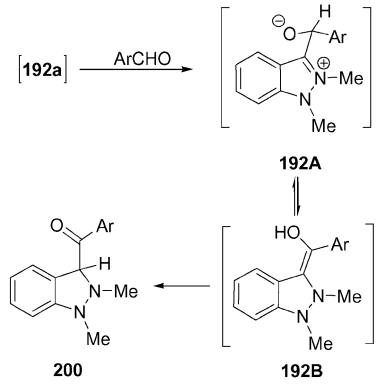
Decarboxylation of the mesomeric betaine **191a** to the *N*-heterocyclic carbene **192a** in the presence of ketones yields stable 1:1 adducts **199** (Scheme 76). A mechanism was suggested, in which the NHC deprotonates the α-position of the ketone which in turn adds to the iminium bond of the resulting indazolium salt **198**.[165]



Scheme 75. Cycloadditions to spiro-indazoles.



Scheme 76. Formation of 1:1 adducts from NHC **192a** and ketones.

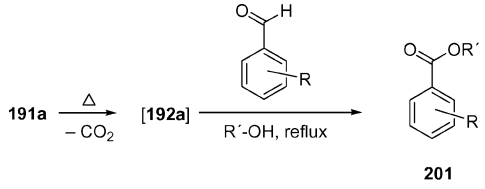


Scheme 77. Compound **200**, a tautomer to the Breslow intermediate **192B**.

Only few examples for nucleophilic attacks of the *N*-heterocyclic carbene **192a** on aromatic aldehydes (cf. **A**) have been detected to date. 2-Methylbenzaldehyde give the tautomer **200** of the Breslow intermediate **192B** in low yield (Scheme 77).[165]

8.2. Redox Reactions

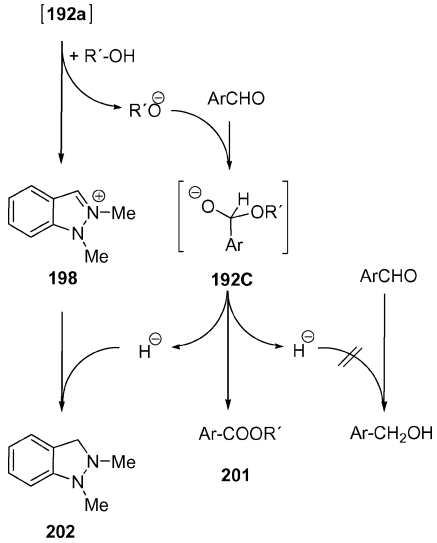
Redox esterifications of aldehydes to the benzoates **201** were found on generation of NHC **192** in the presence of aromatic aldehydes and alcohols (Scheme 78).[165]



201	R	R´	
a	H	Et	(49%)
b	4-Et	Et	(51%)
c	4-OMe	Et	(69%)
d	2,4-Cl_2	Et	(22%)
e	2-Me	Et	(33%)
f	4-NMe_2	Et	(80%)
g	4-NMe_2	nPr	(93%)
h	4-NMe_2	nBu	(47%)
i	4-NMe_2	iPr	(49%)

Scheme 78.

The following mechanism was proposed: the in-situ-formed alcoholate attacks the aldehyde to give adduct **192C**, the latter reduces the indazolium salt **198** to give indazoline **202** with formation of benzoates **201** (Scheme 79). No Cannizzaro reaction with formation of benzyl alcoholes was observed, because the indazolium salt **198** is able to reoxidize these alcohols to the corresponding aldehydes. Indazoline **202** can on the other hand be reoxidized to indazolium salt **198**. This mechanism is supported by DFT calculations and model reactions.[165]

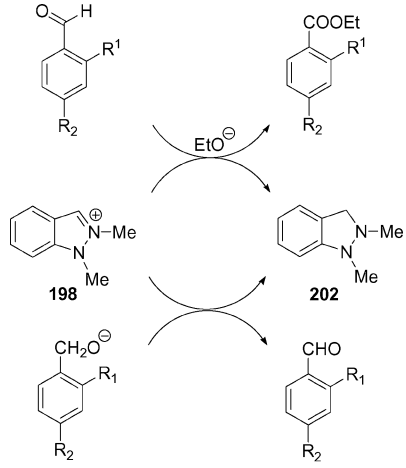


Scheme 79.

9. Indazolium Salts

The calculated Gibbs' free energies for protonation (ΔG^0) of 1*H*-indazole at N(2) and 2*H*-indazole at N(1) are 209.5 and 214.6 kcal/mol according to calculations. The corresponding values for the deprotonations were calculated to be 339.8 and 334.7 kcal/mol, respectively.[166]

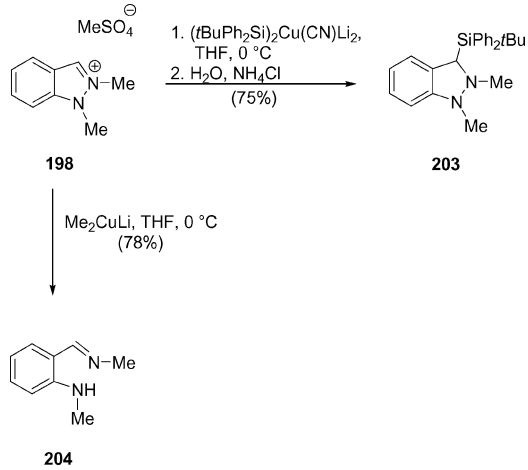
In accordance with the mechanisms proposed in Scheme 79, indazolium salt **198** proved to be able to oxidize benzaldehydes in the presence of ethanolate, and to reduce benzyl alcoholates to aldehydes (Scheme 80).[165]



R^1	R^2	yield
H	Et	71%
H	OMe	54%
Me	H	75%
H	Et	17%
H	OMe	66%
Me	H	26%

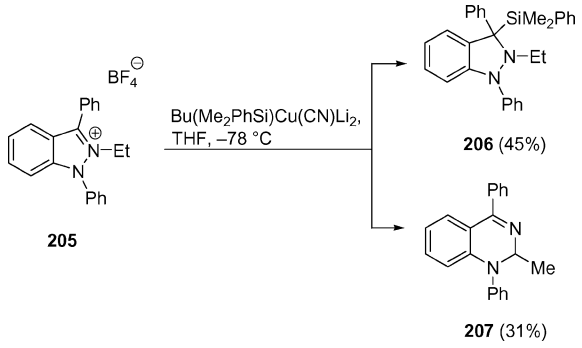
Scheme 80.

Lithium bis(silyl)cuprates react with indazolium salt **198** to give 3-silylindazolines such as **203** (Scheme 81). Variation of the cuprate results in reductive ring opening leading to benzo-β-enaminoimines such as **204**, or mixtures of both.[167]



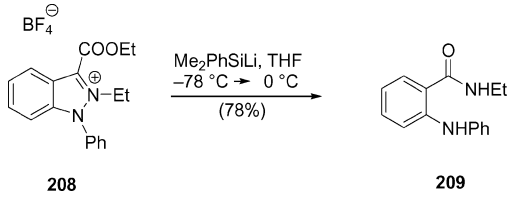
Scheme 81.

3-Phenylindazolium salt **205** yields a mixture of indazoline **206** and dihydroquinazoline **207** on treatment with lithium butyl(dimethylphenylsilyl)cuprate (Scheme 82). The formation of the latter mentioned ring system was explained by deprotonation of the ethyl group, ring opening to a diazatriene, and electrocyclic ring closure.[167]



Scheme 82.

3-(Ethoxycarbonyl)indazolium salt **208** undergoes ring-opening reaction to give **209** on treatment with silyllithium reagents (Scheme 83).[168]



Scheme 83.

Conclusions

Indazole chemistry is of growing interest and numerous exciting aspects of this heterocyclic ring system have been discovered during the last decade.

Acknowledgments

The Deutsche Forschungsgemeinschaft (DFG) is gratefully acknowledged for financial support of some projects dealing with indazole chemistry.

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