C3-INDAZOLE FUNCTIONALIZATION: A REVIEW

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Francis Giraud, Fabrice Anizon, Pascale Moreau

Institute of Chemistry of Clermont-Ferrand, Université Clermont Auvergne, CNRS, Clermont Auvergne INP, 63000 Clermont-Ferrand, France

(e-mail: pascale.moreau@uca.fr)

Abstract. *Indazoles are versatile building blocks generating numerous in-depth studies for their synthesis and regioselective functionalization. In this review, we focused on non-patent literature describing efficient synthetic methods (chemical yield≥80%) which allowed the functionalization of non-fused indazoles at the 3-position, and published since 2010.*

Contents

1. Introduction

Syntheses of nitrogen heteroaromatic systems are developed for numerous potential applications, particularly as biologically active compounds. Thus, scaffolds such as pyridinones,[1] pyridoquinazolines,[2] or indazoles (Figure 1) are frequently observed in the structure of biologically active compounds such as protein kinases inhibitors.[3] Therefore, their synthesis, substitution and functionalization have been widely studied. In this review, we report the most efficient and representative examples of substitution/functionalization at the 3-position of non-fused indazole moieties (chemical yields≥80%), published in non-patent literature since 2010.

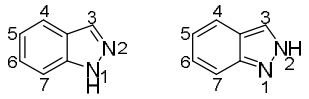


Figure 1. Structure and numbering of 1*H*- and 2*H*-indazoles.

2. Halogenation

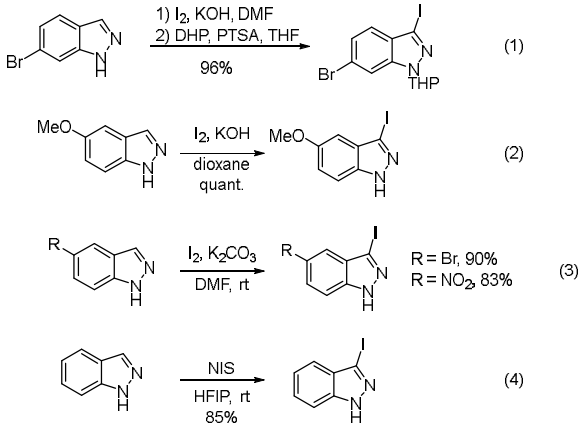
Halogenation reactions are of high interest for further structural modifications using a variety of conditions, such as metalation or metal-catalyzed cross-coupling reactions. Thus, many reports describe various experimental conditions to introduce a halogen atom at indazole C3-position. Most of the reported

halogenations are iodination and bromination with a few examples of chlorination. Concerning fluorination, no example with high chemical yield was found in the non-patent literature.

2.1. Iodination

Few examples of iodination have been reported in patents from *N*-1 protected indazoles by *t*-butoxycarbonyl (Boc), Me or tetrahydropyranyl (THP) groups. However, iodinations are most often performed from non-protected indazoles using I_2 as iodinating agent under basic conditions (potassium hydroxide/sodium hydroxide/potassium carbonate) in DMF or another polar solvent.

3-Iodoindazoles can be obtained in good yields by treating corresponding indazoles with I_2 and KOH in DMF, such as in reaction 1, where 6-bromoindazole was used in the synthesis of VEGFR-2 inhibitors (Scheme 1, reaction 1).[4] 5-Methoxyindazole was also quantitatively iodinated at the 3-position using similar conditions in dioxane (Scheme 1, reaction 2).[5] Another example also reported the use of *N*-methylpyrrolidone (NMP) as a solvent.[6] An alternative to KOH is the use of potassium carbonate. In a structure-activity relationship study (SAR) on 3-vinylindazoles with tropomyosin receptor kinases (Trk) inhibitory potency, 3-iodoindazoles were prepared in good yields from diversely 5-substituted precursors such as 5-bromo or 5-nitroindazole, using I_2 in the presence of K_2CO_3 in DMF (Scheme 1, reaction 3).[7] Similar approaches were used in the synthesis of Axitinib from 6-nitroindazoles,[8] or polo-like kinase 4 inhibitors from indazoles bearing a spirocyclopropane-1′,3′-indolin-2-one moiety at the 6-position.[9] Similarly, 5- and 6-bromo-3-iodoindazoles were also prepared in excellent yields using potassium *tert*-butoxide in THF.[10] *N*-iodosuccinimide (NIS) was also used as an iodinating agent. For example, 5-bromo-3-iodoindazole was prepared using NIS under basic conditions (KOH) in dichloromethane.[11] Hexafluoroisopropanol (HFIP) was found to be an efficient solvent for the preparation of 3-halogenoindazoles in mild conditions (Scheme 1, reaction 4).



Scheme 1. Iodination at the 3-position in the presence of I_2 or NIS as iodinating agents.

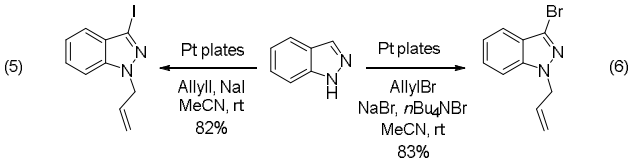
Same conditions using *N*-bromosuccinimide at 0 °C led to 3-bromoindazole in 84% yield.[12] Beside these common methods, an efficient electrochemical preparation of *N*1-allyl-3-iodo- (or 3-bromo) indazoles was developed using Pt plates as both anode and cathode, allyl iodide (or bromide) in the presence of NaI (or NaBr/nBu$_4$NBr) in MeCN (Scheme 2, reactions 5 and 6). A mechanism was proposed by the authors involving a C3-iodination N1-alkylation tandem process.[13]

Finally, magnesiation at the 3-position of N2-THP protected indazoles followed by I_2 trapping led to corresponding 3-iodinated derivatives (Scheme 3, reaction 7).[14]

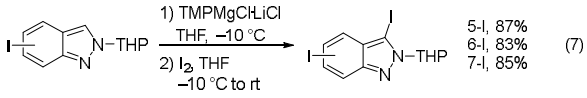
2.2. Bromination

These reactions are less frequently reported than the corresponding iodination. Nevertheless, various experimental conditions allowed the regioselective introduction of a bromine atom at indazole 3-position. In

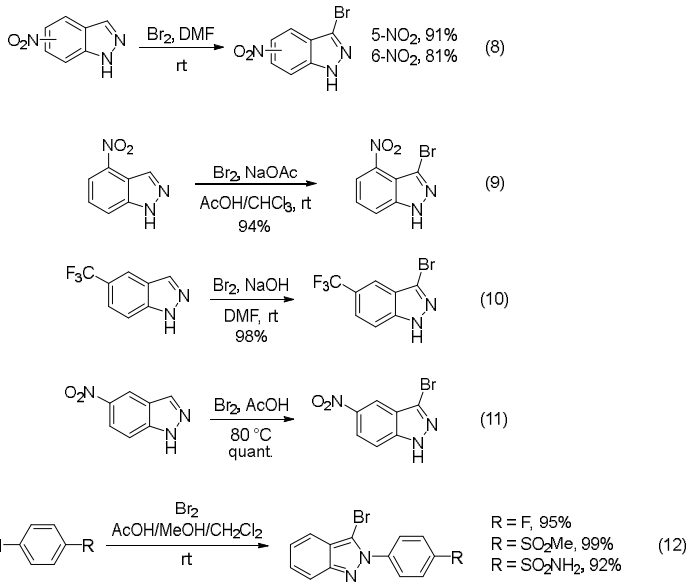
a work focused on the preparation of 3-aminoindazoles by Buchwald-Hartwig coupling from the corresponding halogeno precursors, the use of Br_2 in DMF afforded 5- or 6-nitro-3-bromoindazole in good yields (Scheme 4, reaction 8).[15] In another article, 4-nitroindazole counterpart was brominated using Br_2 in the presence of NaOAc in a 1:1 AcOH/$CHCl_3$ mixture (Scheme 4, reaction 9).[16] Reactions using Br_2 as brominating agent were also described in the presence of sodium hydroxide[17] or in hot acetic acid (Scheme 4, reactions 10 and 11).[18] Finally, from diversely substituted 2-arylindazoles, bromination was performed in the presence of Br_2 in a 2:1:0.1 AcOH/MeOH/CH_2Cl_2 mixture (Scheme 4, reaction 12).[19]



Scheme 2. Electrochemical halogenation at the 3-position of indazole.



Scheme 3. Iodination at the 3-position of N2-protected indazoles.

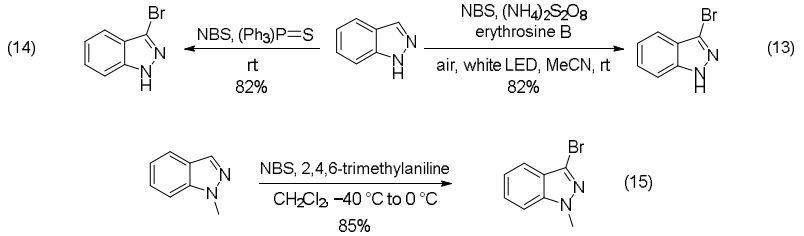


Scheme 4. Bromination at the 3-position in the presence of Br_2 as brominating agent.

N-bromosuccinimide (NBS) in various solvents (*e.g.* MeCN,[20] CH_2Cl_2,[21] $CHCl_3$,[22] MeOH,[23] HFIP[12]) is also widely employed for the regioselective introduction of a bromine atom at the 3-position of the indazole heterocyclic system.

In addition, efficient bromination of indazoles using NBS were reported under different reaction conditions. Thus, a visible-light photoredox process with erythrosine as a photocatalyst in the presence of NBS, O_2 and ammonium persulfate,[24] or a phosphine sulfide-catalyzed electrophilic bromination,[25] led to 3-bromoindazole in 82% yield (Scheme 5, reactions 13 and 14). *N*-Methylindazole was brominated in good yield at the 3-position from NBS and 2,4,6-trimethylaniline, *via* generated *N*-bromoarylamine as a highly

reactive catalytic electrophilic halogen source (Scheme 5, reaction 15).[26] However, bromination of *N*-methylindazole using the same conditions led to 3-bromination product in low yield. Efficient bromination of 6-bromoindazole using mechanochemical activation in the presence of NBS, NaOH, silica and stainless-steel balls was also reported.[27]



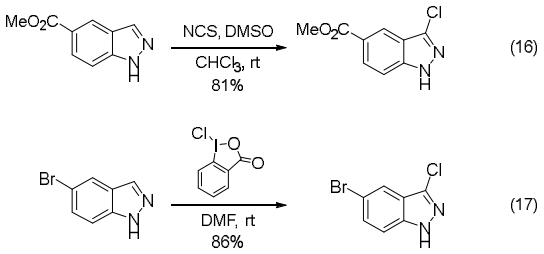
Scheme 5. Bromination at the 3-position in the presence of NBS in various conditions.

In other reaction conditions, mild and efficient indazole bromination using *N*-chloro-*N*-fluorobenzenesulfonamide (CFBSA)/KBr system afforded 3-brominated analog in 98% yield.[28] 3-Bromoindazole was also synthesized in 97% yield using tribromoisocyanuric acid in EtOH at room temperature.[29]

Finally, as already mentioned in the iodination section, the introduction of a bromine atom at the 3-position together with N1-allylation was also reported using an electrochemical approach (Scheme 2, reaction 6).[13]

2.3. Chlorination

N-chlorosuccinimide (NCS) is a chlorinating agent which was used in solvents such as MeCN.[30] A DMSO-catalyzed reaction using NCS allowed the chlorination of 5-methoxycarbonylindazole at the 3-position (Scheme 6, reaction 16). The same reaction carried out without DMSO yielded the same product in only 23% yield. Mechanistic studies led to a mechanism proposal.[31] Similarly to the reaction mentioned in the bromination section going through an *N*-haloarylamine (Scheme 5, reaction 15), indazole chlorination can be performed with NCS in the presence of 2,4,6-trimethylaniline.[26] Finally, 5-bromoindazole led to the corresponding 3-chloro derivative in good yield after electrophilic chlorination using 1-chloro-1,2-benziodoxol-3-one, an hypervalent iodine reagent (Scheme 6, reaction 17).[32]

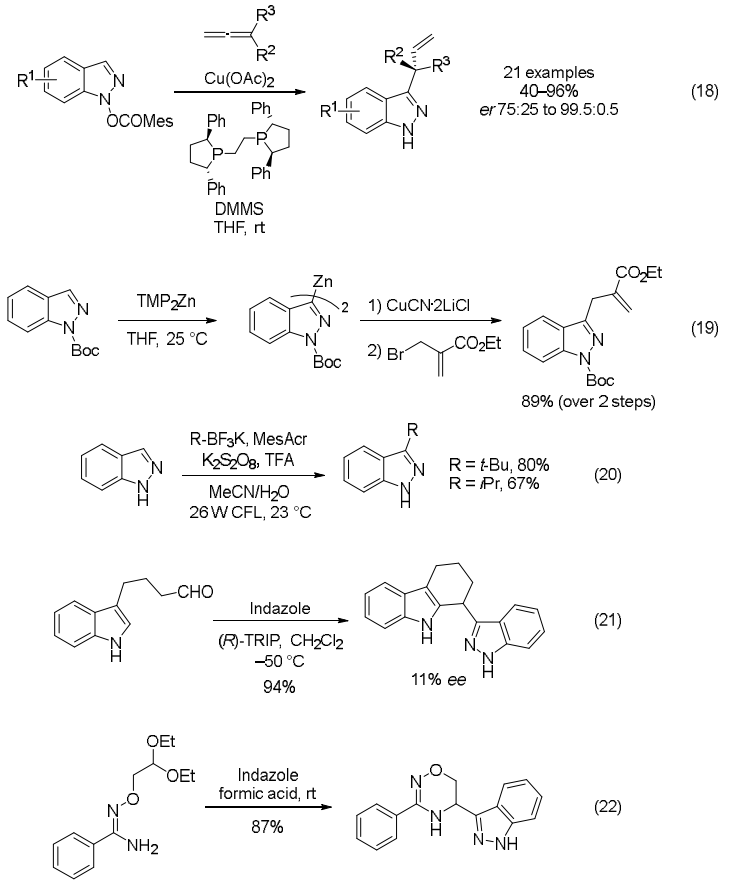


Scheme 6. Chlorination at the indazole 3-position using various conditions.

3. Alkylation

As presented below, many different synthetic approaches can afford 3-alkylated indazoles. As a first example, diversely substituted 3-allyl-1*H*-indazoles were prepared with good enantioselectivity and regioselectivity from 1*H*-indazoles, substituted at the 1 position by a mesitylcarbonyloxy group, and allenes. This method used an umpolung CuH-catalyzed strategy in the presence of a chiral phosphine ligand and dimethoxymethylsilane (DMMS). A density functional theory (DFT) study explained the reactivity difference between indazole and indole electrophiles (Scheme 7, reaction 18).[33] In another strategy, regioselective zincation at the 3-position of N1-Boc indazole using TMP_2Zn

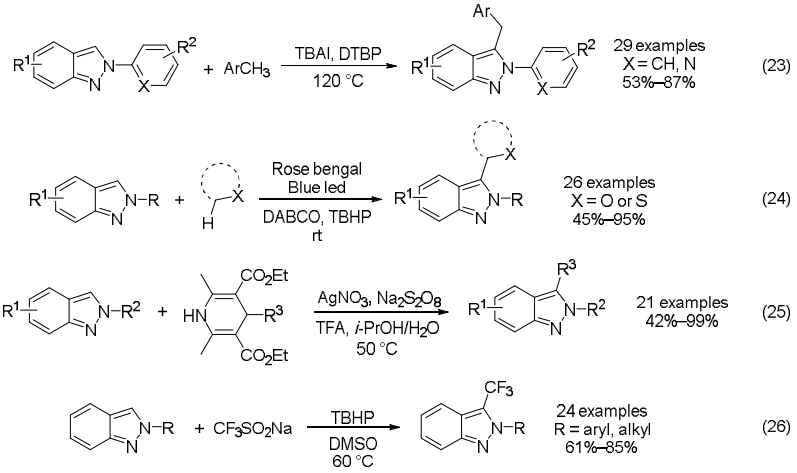
(bis(2,2,6,6-tetramethylpiperidinyl)zinc), transmetalation with CuCN·2LiCl and reaction with ethyl 2-(bromomethyl)acrylate led to the allyl derivative in 89% yield (Scheme 7, reaction 19).[34] The same metalation strategy was used for subsequent acylation or Negishi coupling (see below in the corresponding sections). 3-Alkylindazoles were also prepared *via* photoredox Minisci chemistry using alkyltrifluoroborates, a mild oxidant (potassium persulfate) and an organic photocatalyst (MesAcr, mesityl acridinium) under visible light irradiation using a compact fluorescent lamp (CFL) (Scheme 7, reaction 20).[35] In a paper focused on enantioselective domino Friedel-Crafts-type synthesis of tetrahydrocarbazoles, a single example of tetrahydrocarbazole substituted at the 1 position by a 1*H*-indazol-3-yl moiety was reported from a 4-indolylbutanal using 1*H*-indazole as nucleophile in the presence of (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((*R*)-TRIP) (Scheme 7, reaction 21).[36] The product was obtained with 94% yield, however with low enantioselectivity. Similarly, nucleophilic addition of indazole to the iminium intermediate generated *in situ* from *N*'-(2,2-diethoxyethoxy)benzimidamide in formic acid led to the corresponding 3-phenyl-5,6-dihydro-4*H*-[1,2,4]oxadiazine bearing an indazol-3-yl moiety at the 5-position (Scheme 7, reaction 22).[37]



Scheme 7. C3-Alkylation of 1*H*-indazoles.

Alkylation of 2*H*-indazole derivatives has also been reported through different methods. For instance, direct Bu_4NI-catalyzed oxidative cross dehydrogenative coupling between indazoles and methylated arenes

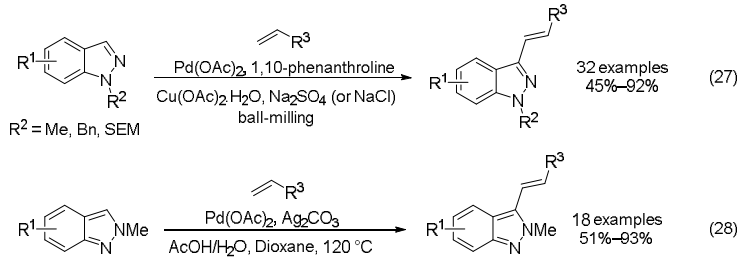
produced compounds substituted at the 3-position. The reaction was promoted by *tert*-butylperoxybenzoate (DTBP) and generated benzyl free-radical species (Scheme 8, reaction 23).[38] Regioselective C3-substitution of 2*H*-indazoles was also achieved in the presence of bengal rose as photoredox catalyst and *t*-butylhydroperoxide (TBHP) as an oxidant, *via* a visible-light-promoted cross-dehydrogenative coupling between 2*H*-indazoles and cyclic (thio)ethers (Scheme 8, reaction 24).[39]A series of 2*H*-indazoles diversely alkylated at the 3-position were also prepared *via* a direct radical alkylation using dihydropyridine derivatives (DHP) as radical sources in the presence of a Ag(I)/$Na_2S_2O_8$ system (Scheme 8, reaction 25).[40] Finally, 3-trifluoromethylation involving radical intermediates formed in the presence of sodium trifluoromethanesulfinate and TBHP was reported with acceptable to good yields (Scheme 8, reaction 26).[41] Using sodium trifluoromethanesulfinate, regioselective photoredox-catalyzed reaction under visible light irradiation in the presence of methylene blue and PIDA also led to 3-trifluoromethylation of 2*H*-indazoles.[42]



Scheme 8. C3-Alkylation of 2*H*-indazoles.

4. Alkenylation

Only few examples of C3-alkenylation were reported with chemical yields ≥ 80%. One consisted in a mechanochemical approach allowing the direct alkenylation of N1-protected 1*H*-indazoles through palladium-catalyzed cross-coupling with acrylates or phosphonates (Scheme 9, reaction 27).[43] Guillaumet's group also reported oxidative alkenylation of N1- or N2-protected indazoles in solution (Scheme 9, reaction 28).[44]

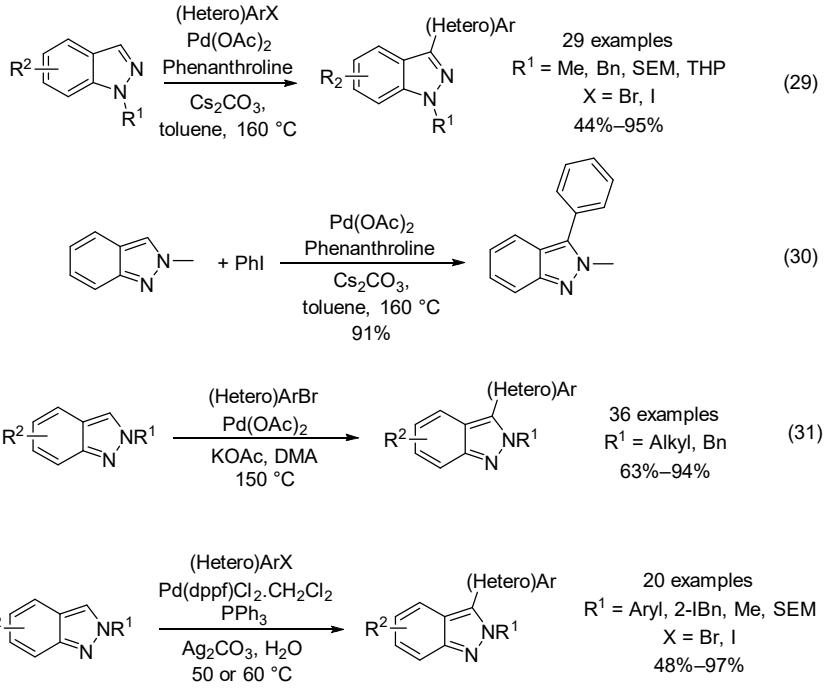


Scheme 9. Alkenylation at the 3-position of 1*H*- or 2*H*-indazoles.

5. (Hetero)arylation

Development of indazole 3-(hetero)arylations was more often reported. Such direct (hetero)arylation at C3-position of N-substituted 1*H*- or 2*H*-indazoles was described using a Pd/phenanthroline catalytic system

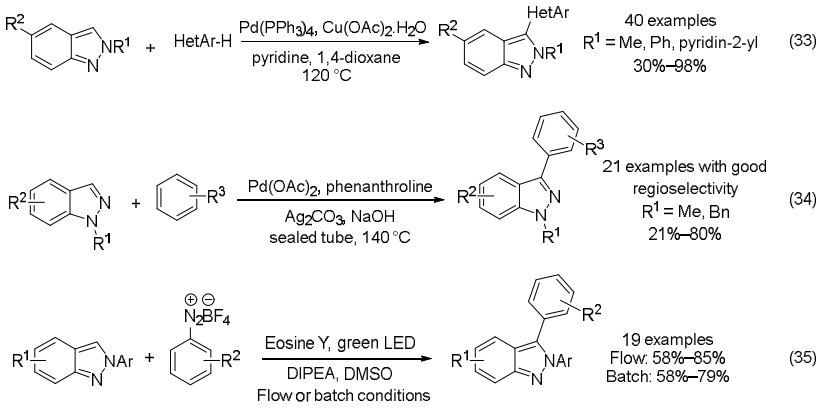
in good yields (Scheme 10, reactions 29 and 30).[45] Similarly, palladium-catalyzed C3-(hetero)arylation of *N*2-benzyl or akyl-2*H*-indazoles was described in the presence of potassium acetate in DMA (Scheme 10, reaction 31).[46] Palladium and copper-catalyzed C-H arylations with iodoarenes were also reported with lower yields using $PdCl_2$/phenanthroline/Ag_2CO_3/K_3PO_4 as catalytic system for 1*H*- and 2*H*-indazoles or CuI/phenanthroline/LiO*t*-Bu for 2*H*-indazoles.[47] On water conditions were also developed to access diversely substituted C3-arylated indazoles by direct palladium-catalyzed arylation of 2*H*-indazoles (Scheme 10, reaction 32).[48] Recently, a similar approach using $Pd(OAc)_2$/PPh_3/Ag_2CO_3 catalytic system was reported.[49]



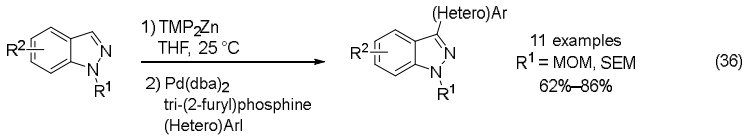
Scheme 10. (Hetero)arylation at the 3-position of 1*H*- or 2*H*-indazoles.

In a work aiming at identifying new photostable near-infrared probes, various donor-acceptor-type biheteroaryl fluorophores were prepared *via* palladium-catalyzed oxidative cross-coupling of electron-deficient 2*H*-indazoles with electron-rich heteroarenes (Scheme 11, reaction 33).[50] Such palladium-catalyzed oxidative arylation with arenes was also recently reported from 1*H*-indazole leading to C3-arylated derivatives (Scheme 11, reaction 34).[51] Another approach was a metal-free photocatalytic C3-arylation of 2*H*-indazoles using aryldiazonium salts, Eosin Y and green LED irradiation (Scheme 11, reaction 35).[52] The reaction was described by continuous flow or batch synthesis and a plausible reaction mechanism was proposed. The same group published similar reaction using an Eosin Y catalyst immobilized on a capillary reactor tube.[53] C3-Arylation of 2*H*-indazoles using mild visible-light-mediated photocatalyst-free conditions (pyridine, blue LEDs, DMSO, 23 °C) in the presence of aryldiazoniums was also reported.[54]

As previously mentioned in the alkylation section, C3 substitution of indazoles *via* regioselective C3-zincation of N1-protected indazoles using TMP_2Zn followed by Negishi coupling led to various (hetero)arylindazoles (Scheme 12 reaction 36).[34] Similar metalation strategy from 2-SEM protected 2*H*-indazole using *n*-BuLi, transmetalation with $ZnCl_2$ and Negishi coupling was also reported recently.[55,56]



Scheme 11. (Hetero)arylation at the 3-position of 1*H* or 2*H*-indazoles.



Scheme 12. (Hetero)arylation at the 3-position of 1*H* or 2*H*-indazoles.

6. Acylation

Together with allylation and arylation described above (reactions 19 and 36), the Knochel group reported 3-acylation reactions using similar metalation conditions with TMP_2Zn. Thus, reaction of 1*H*- or 2*H*-protected (Boc, MOM, SEM) indazoles with various acyl chlorides led to the corresponding C3-acylated products *via* regioselective C3-zincation, subsequent transmetalation with CuCN·2LiCl and reaction with acyl chlorides.[34,57]

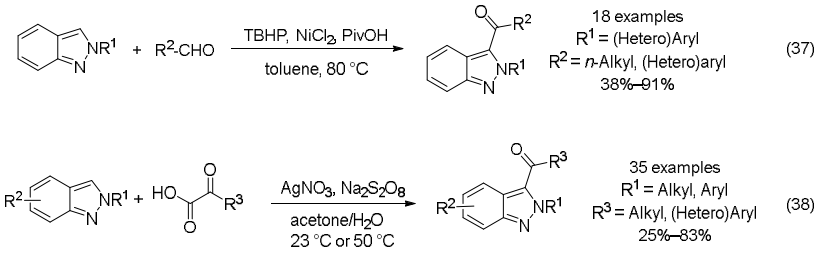
Ni-catalyzed C3-acylation of 2*H*-indazoles was reported using aldehydes as acylating reagents. This reaction was performed in the presence of TBHP as free-radical initiator and pivalic acid as an additive (Scheme 13, reaction 37).[58] 3-Acyl-2*H*-indazoles were also prepared in modest to good chemical yields by direct radical addition using Ag-catalyzed decarboxylative coupling of α-keto acids (Scheme 13, reaction 38).[59] Recent acylation reaction of 2*H*-indazoles with acyl-DHP in the presence of a $Ag(I)/Na_2S_2O_8$ system used similar conditions as those reported for alkylation with alkyl-DHP (Scheme 8, reaction 25). Corresponding 3-acylindazoles were obtained in acceptable to good yields (15 examples, 40% to 92% yields).[40]

7. Formylation

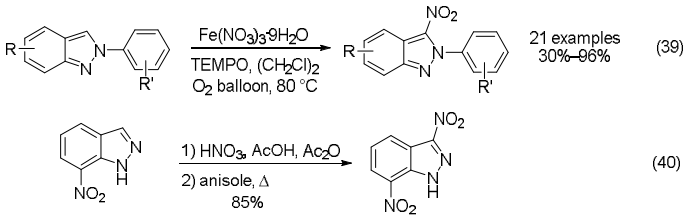
Very few examples of 3-formylation were described for indazoles. However, Vilsmeier-Haack reaction using $POCl_3$/DMF was performed on 5-nitro-1*H*-indazole, leading to the corresponding 3-formyl analogue in 92% yield.[60]

8. Nitration

Only few examples of indazole nitration reactions have been reported since 2010 in the non-patent literature. Radical C3-nitration of 2*H*-indazoles has been achieved using $Fe(NO_3)_3$ in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) and oxygen as oxidants (Scheme 14, reaction 39). A plausible mechanism established on control experiments and quantum chemical calculations was proposed.[61] The synthesis of 3,7-dinitro-1*H*-indazole from corresponding 7-nitroindazole was described by Claramunt *et al.*[62] using a procedure previously reported by Habraken group after a thermal rearrangement of a 2,7-dinitroindazole intermediate (Scheme 14, reaction 40).[63]



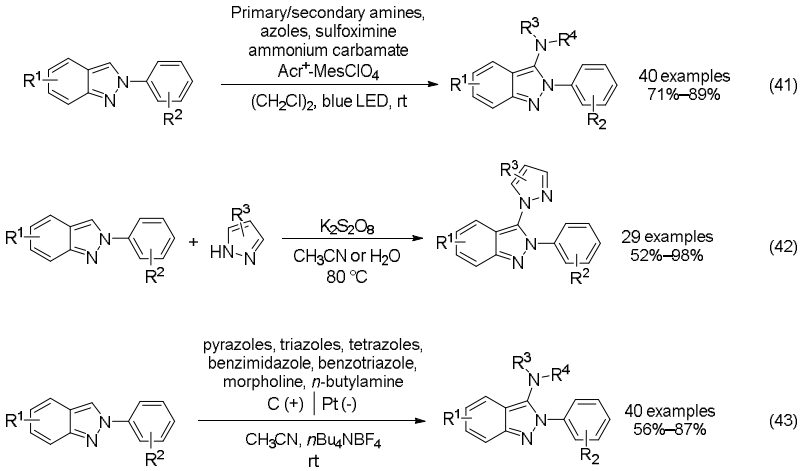
Scheme 13. Acylation at the 3-position of 2*H*-indazoles.



Scheme 14. Nitration at the 3-position of 1*H*- and 2*H*-indazoles.

9. Amination

A few examples of 1*H*-indazoles amination were found. However, none of them led to corresponding 3-aminated-1*H*-indazole with yields higher than 80%.[64-66] For 2*H*-indazoles, a versatile C3 amination method involved organophotoredox-catalyzed oxidative coupling in the presence of 9-mesityl-10-methylacridinium ion (Acr^+-$MesClO_4$) under blue LED irradiation (Scheme 15, reaction 41).[67] In another method, metal-free 2*H*-indazoles C3 amination using mainly pyrazole(s) as coupling partner(s) was performed via a radical process using potassium persulfate (Scheme 15, reaction 42).[68] Finally, an electrochemical C3-amination of 2*H*-indazoles was recently described (Scheme 15, reaction 43).[69]



Scheme 15. Amination at the 3-position of 1*H*- and 2*H*-indazoles.

10. Borylation

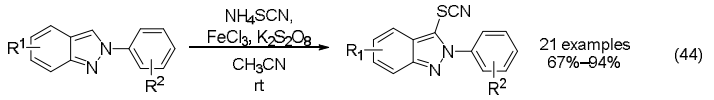
C3 borylation of indazoles is a chemical transformation allowing the preparation of useful intermediates for further coupling such as Suzuki-Miyaura reactions. A regioselective iridium catalyzed

borylation of 1-methyl-1*H*-indazole was achieved in the presence of $[Ir(OMe)(COD)]_2$/di-*tert*-butyl bipyridine (dtbpy), bis(pinacolato)diboron (B_2Pin_2) in TBME with a modest 50% yield.[70] However, a one-pot procedure borylation/Suzuki-Miyaura coupling showed interesting results. Similar procedure was reported for diversely *N*-protected 1*H*- and 2*H*-indazoles with full conversion.[71]

11. Sulfenylation

As mentioned above for iodination (Scheme 3, reaction 7), magnesiation at the 3-position of N2-THP protected indazoles is possible by using TMPMgCl·LiCl in THF. Similarly, subsequent trapping with Me_2S_2 led to corresponding 7-iodo-3-methylsulfanyl-2-THP-2*H*-indazole in 87% yield.[14]

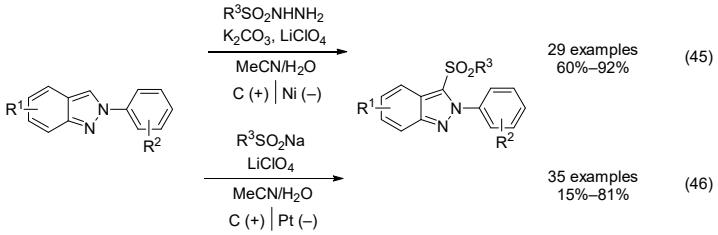
Potassium persulfate-mediated C3 thiocyanation using ammonium thiocyanate under iron-catalysis was successfully applied to diversely substituted 2*H*-indazoles (Scheme 16, reaction 44). The putative mechanism involved a radical pathway. Interestingly, similar conditions in the presence of KSeCN instead of NH_4SCN allowed C3 selenocyanation of 2*H*-indazoles.[72]



Scheme 16. Thiocyanation at the 3-position of 2*H*-indazoles.

12. Sulfonylation

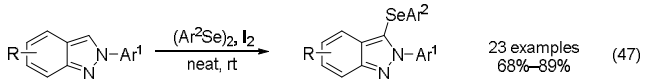
Electrochemical sulfonylation of diversely substituted 2*H*-indazoles was recently reported using sulfonyl hydrazides (Scheme 17, reaction 45)[73] or sodium sulfinates (Scheme 17, reaction 46)[74] as sulfonyl donors.



Scheme 17. Sulfonylation at the 3-position of 2*H*-indazoles.

13. Selenylation

1*H*-indazole was regioselectively selenylated at the 3-position using iodine-catalyzed process in the presence of various diaryl diselenides and I_2/DMSO as oxidant system (3 examples, 79%-85% yields). In the proposed mechanism, an electrophilic species was formed between diphenyl diselenide and I_2.[75] More recently, similar approach in the absence of DMSO was reported for C3-selenylation of 2*H*-indazoles (Scheme 18, reaction 47).[76]



Scheme 18. Selenylation at the 3-position of 2*H*-indazoles.

3-Phenylselenyl-1*H*-indazole was also prepared *via* a radical pathway in 81% yield by reacting indazole and diphenyl diselenide in the presence of bis(trifluoroacetoxy)iodo)benzene (PIFA) as a promoter in dichloromethane.[77] The same selenylated indazole was also prepared in 81% yield using rose Bengal, diphenyl diselenide and blue LED irradiation.[78]

Finally, as mentioned above in the sulfenylation section (see Scheme 16, reaction 44), 2*H*-indazoles were selenylated at the C3-position using potassium persulfate and potassium selenocyanate under iron-catalysis.[72]

14. Conclusions

Due to the growing interest on indazole-containing compounds in medicinal chemistry or for the photophysical properties of organic materials, numerous projects have been dedicated to set up new methodologies allowing regioselective functionalization of this heteroaromatic moiety. This review focused on the regioselective 3-position functionalization of 1*H*- or 2*H*-indazoles and mentioned numerous works devoted to the introduction of various substituents at this position. Halogenation reactions, especially those introducing Br or I atoms are useful steps for further metal-catalyzed cross coupling reactions. For the same purpose, a few direct 3-borylations have been reported. Alkylation and reactions leading to Csp2 coupling (alkenylation, (hetero)arylation, acylation) have also been extensively studied. However, despite the intense efforts made in this area, some specific functionalization such as fluorination, formylation, alkoxycarbonylation, cyanation, borylation or azidation were only rarely reported, with poor to modest yields. In addition, 3-functionalizations involving N1- or N2-protected indazoles, *i.e.* bearing easily cleavable nitrogen-substituents, are reported in some cases, but are not widespread. Altogether, if current methods offer many solutions for the organic chemist, improvements and complementary procedures are still needed.

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