Beyond C2 & C3: Transition-Metal Catalyzed C-H Functionalization of Indole

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ABSTRACT: The indole scaffold will continue to play a vital part in the future of drug discovery and agrochemical development. Due to this the necessity for elegant techniques to enable the selective C-H functionalization is vast. Early developments have led to primarily C2 and C3 functionalization due to the inherent reactivity of the pyrrole ring. Despite this, elegant methods have been developed to enable selective C-H functionalization on the benzen moiety at C4, C5, C6 & C7. This review focuses on the contributions made in benzenoid C-H functionalization of indoles and other related heteroaromatics such as carbazoles.

The indole heteroaromatic and has become one of the most widely studied organic templates over the past century.[1] This is due to their wide prevalence in the natural world and biologically active structures (Figure 1a).[2] The indole alkaloid motif itself is a bacterial intercellular signal molecule, and is also present in the natural amino acid tryptophan, the neurotransmitter serotonin, the plant growth hormone auxin, a number of marketed drugs sumatriptan (migraine), indomethacin (anti-inflammatory) and ondansetron (nausea) and bioactive hallucinogens such as dimethyltryptamine and LSD. From the review "Rings in Drugs" by Taylor, it is reported that the indole ring is present in 24 current marketed pharmaceuticals, where it lies as the 4th most prevalent heteroaromatic.[3]

The biological relevance of the indole scaffold has pushed it through to the forefront of synthetic developments. Classical syntheses such as the Fischer,[4] Bartoli,[5] and Larock[6] have become universally used, amongst a multitude of other synthetic protocols.[7] The indole scaffold has also been a key substrate in the development of C-H functionalization methodologies for its synthesis and modification (Figure 1b).[8] Whilst these methods effectively grant access to the bicyclic system, they require the requisite functionality of the indole ring to be pre-installed on the organic reagents.

Transition metal-catalyzed C-H functionalization has emerged as a powerful tool for the late stage modification of biologically relevant structures such as indoles.[9] The synthetic toolbox has expanded to utilize a variety of metal catalysts using multiple different techniques to install a huge selection C-C and C-X bonds.[10] Effective C-H activation is achieved either via a reactive metal centre or through chelation assistance to a directing group.[11]

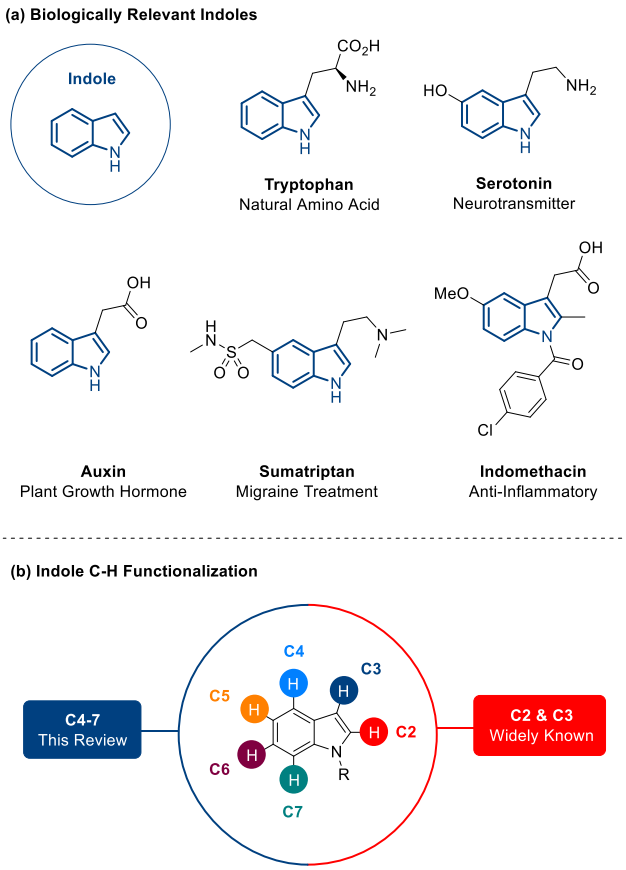


Figure 1: (a) Biologically Relevant Motifs Containing the Indole Heteroaromatic (b) Site Selective Indole C-H Functionalization

The indole scaffold has been widely used in both direct and directed C-H functionalization at C2 and C3, as covered in depth in an excel-

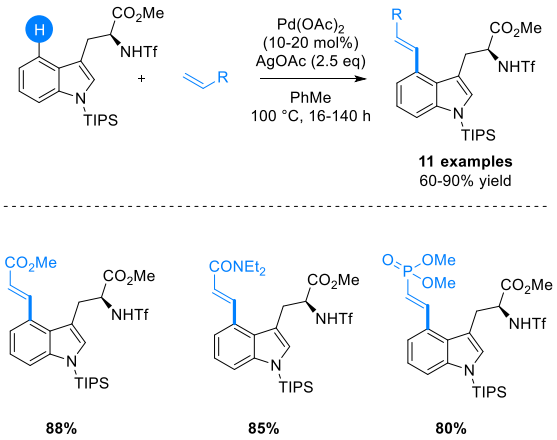
lent review by Sandtorv.[12] There have also been a few elegant examples of systems that allow a reaction condition dependent switch between C2 and C3 functionalization.[12c-d,13]

Due to the inherent reactivity of the pyrrole-type ring, the development of methodologies to enable site selective C-H functionalization on the benzenoid ring has remained a great challenge in catalysis.[14] Despite this there have been a variety of elegant methods developed that will be discussed in detail herein, where this review will focus on accessing reactivity in less activated positions, at C4, C5, C6 & C7. These will be herein colour coded as in Figure 1b. The benzenoid C-H functionalization of related heteroaromatics such as carbazoles and benzothiophenes will also be discussed when relevant.

FUNCTIONALIZATION AT C4

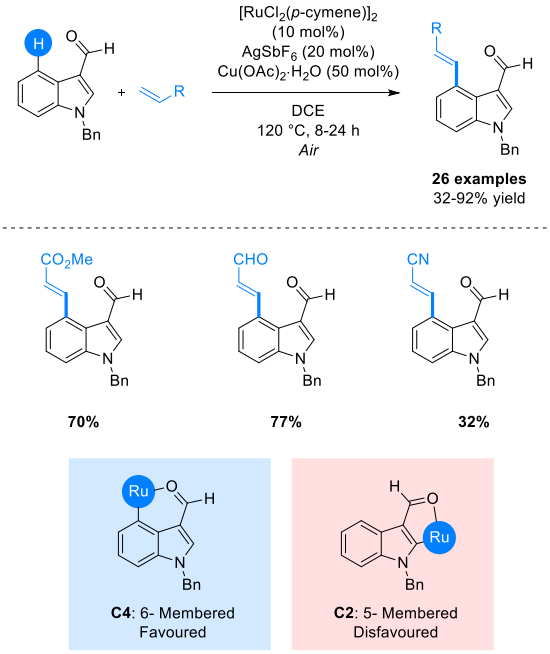
The C4 position of an indole has been accessed almost exclusively through blocking the C3 position. This would then deem the C4 position the next most electron rich carbon centre on the indole structure. Jia and co-workers reported the direct C4 alkenylation of tryptophan derivatives employing palladium catalysis (Scheme 1). This reaction methodology gave complete selectivity for C4 however relatively high catalyst loadings and long reaction times were needed for more challenging substrates.[15]

Scheme 1. Direct Palladium-Catalyzed C4 Alkenylation of Tryptophan Derivatives



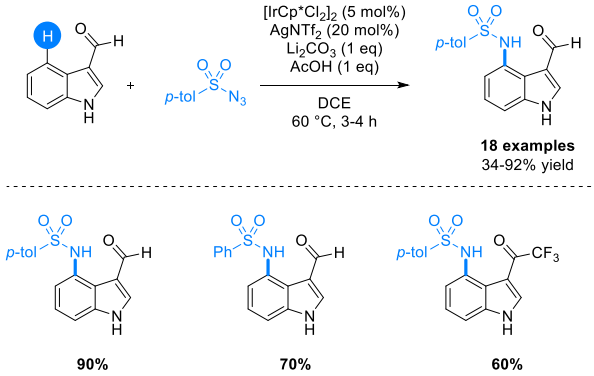
Following on from this seminal example of C4 functionalization, Prabhu and co-workers reported the complementary ruthenium-catalyzed alkenylation. This was proposed to take place by the furnishing of C3 with an aldehyde directing group. It was shown that this directing group favoured forming a 6-membered transition state at C4 over a five membered metalacycle at C2 (Scheme 2). This alkenylation reaction was shown to be tolerant of a wide range of alkene coupling partners including acrylates, acrylonitrile, styrenes, and vinyl ketones.[16]

Scheme 2. Ruthenium-Catalyzed C4 Selective C-H Alkenylation of Indole-3-carboxaldehydes



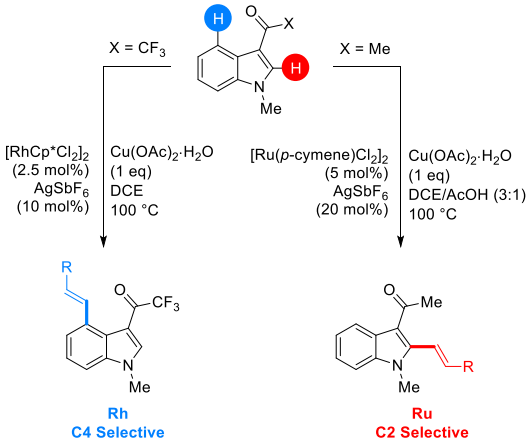
In 2017, Prabhu reported the use of a C3-aldehyde directing group in selective C4 amidation of free indoles. This reinforces the concept that the aldehyde directing group preferentially assist in C4 metalation (Scheme 3). This methodology permitted access to C4-substituted sulfonamides which were shown to be deprotected to give the corresponding aminoindole.[17]

Scheme 3. Iridium-Catalyzed C4-Sulfonamidation of Indole Derivatives.



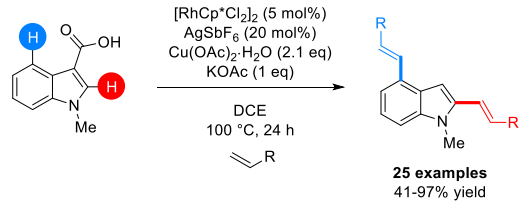
Prabhu and co-workers succeeded this with further insight into C4 vs C2 selectivity by developing complementary ketone directing groups at C3 where the methyl derivative selectively facilitated C-H functionalization at C2 under ruthenium catalysis, where the trifluoromethyl derivative exclusively gave C4 selectivity under complementary rhodium catalysis (Scheme 4). This along with the above investigation allowed the elucidation that stronger directing groups (COMe) carry out directed C-H insertion, giving C2 selectivity, and weaker directing groups (CHO, $COCF_3$) assist in the stabilisation of direct electrophilic metalation.[18]

Scheme 4. Directing Group/Metal Dependent C4 vs C2 C-H Functionalisation of 3-acylindole Derivatives



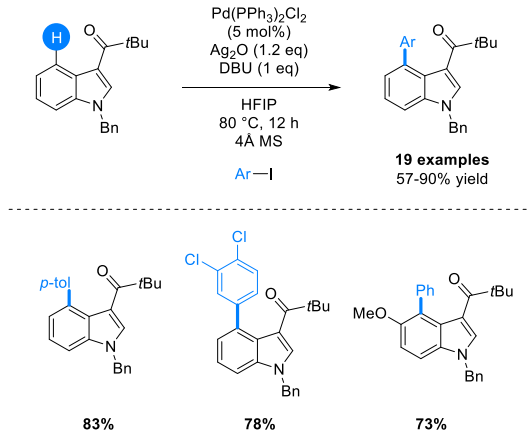
This work has been expanded upon by Zhang and co-workers where a carboxylic acid directing groups enables double C2 and C4 alkenylation using rhodium catalysis. This di-alkenylated product then undergoes an *in-situ* decarboxylation to afford a free C3 position (Scheme 5).[19]

Scheme 5. Rhodium-Catalyzed C4 and C2 Di-alkenylation and *in situ* Decarboxylation



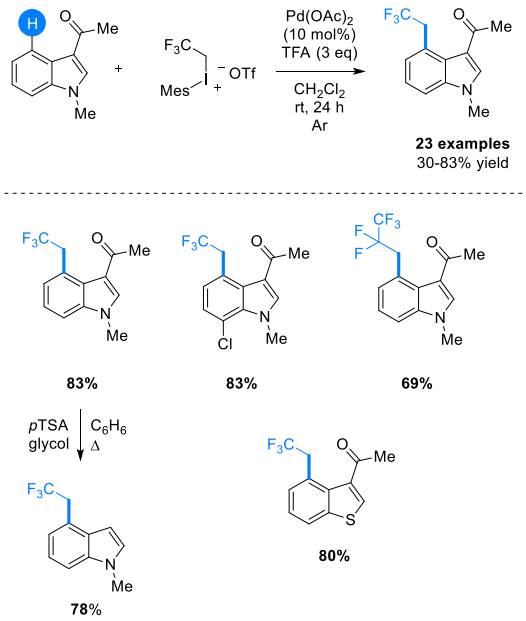
In 2017, Shi and co-workers have utilized this directing group strategy to enable the palladium catalyzed C4 selective C-H arylation of indole derivatives. Here the bulky pivaloyl directing group preferentially cyclopalladates at C4 and subsequent oxidative addition of the aryl iodide and reductive elimination gives the C4-arylated indole (Scheme 6). The pivalate directing group can also be readily cleaved to the proton using glycolic acid.[20]

Scheme 6. Palladium Catalyzed C4 Arylation of Indole Derivatives.



The same group also published the C4 alkylation of indoles in 2017, using hypervalent fluoroalkyl iodine reagents as coupling partners. Here, complementary to Prabhu's work,[18] they employed acetyl assistance to afford the relevant palladacycle to give the C4-substituted product (Scheme 7). The methodology was shown to be incredibly functional group tolerant, including boronate esters and benzothiophene. The directing group was again shown to be readily cleaved.[21]

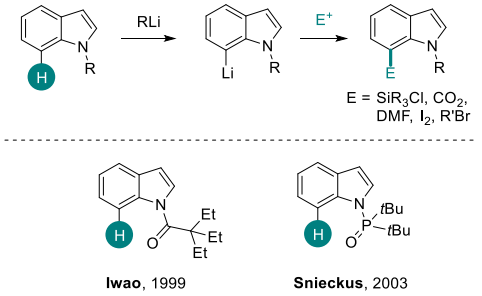
Scheme 7. Palladium-Catalyzed C4 Alkylation of Indole Derivatives



FUNCTIONALIZATION AT C7

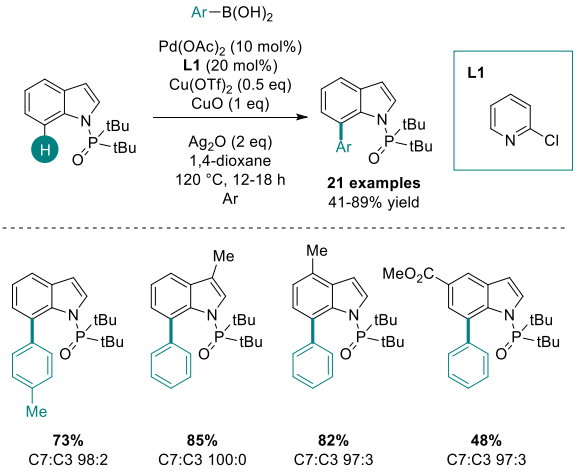
The first report to access the C7 position came from Iwao and co-workers in 1999. Here they employed a specialized sterically demanding directing group to facilitate directed *ortho*-lithiation at the C7 position. they then showed they could quench this organolithium species with a variety of electrophiles including silanes, CO_2, DMF and alkyl groups (Scheme 8). Despite preferential selectivity for C7, C2 by-products were still observed in yields up to 13%.[22] This work was improved on in 2003 by Snieckus and co-workers. Here they detailed the use of a phosphonate directing group which was proposed to enact regioselectivity in a similar manner to above, however here the directing group was completely selective for C7.[23]

Scheme 8. C7 C-H Functionalisation of Indoles *via* Directed *ortho*-Lithiation



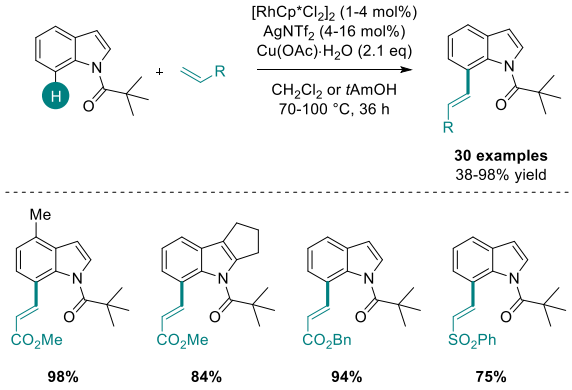
Shi and co-workers have recently devised a manner in which to apply Snieckus' directing group to transition metal catalysed C-H functionalization rather than directed *ortho*-lithiation. Here they use a pyridine ligand to enable palladium-catalyzed selective C-H arylation at C7 (Scheme 9). In this methodology competing direct C3 arylation was the main by-product observed although consistently in low quantities (with exception).[24]

Scheme 9. Palladium-Catalyzed C7 Arylation of Indoles



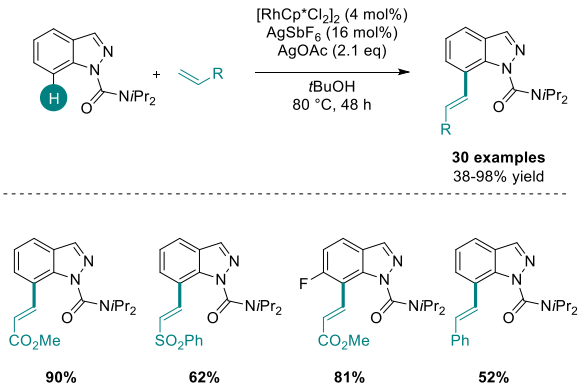
Ma and co-workers have also applied to the use of a sterically demanding directing group at N1 to afford C7 selectivity. Here the pivaloyl (CO*t*Bu) group acts as a weakly coordinating directing group for rhodium catalysis allowing C-H alkenylation (Scheme 10). The reaction methodology was shown to be widespread with 30 examples and yields up to 98%. Despite this the catalysis was not tolerant of C6 substitution and occasional competing C2 alkenylation was also observed in substantial quantities.[25]

Scheme 10. Piv Directed C7 Selective Rhodium-Catalyzed C-H Alkenylation of Indoles



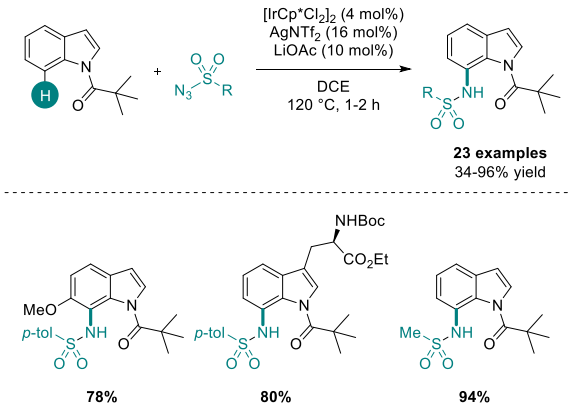
Pan and co-workers have also described the C7-selective rhodium catalyzed C-H alkenylation of indazole derivatives. Here a urea directing group is employed in the reaction methodology (Scheme 11). The catalysis was also shown to be amenable to both electron poor (acrylate) and electron rich (styrene) coupling partners.[26]

Scheme 11. Rhodium-Catalyzed C7-Selective C-H Alkenylation of Indole Derivatives



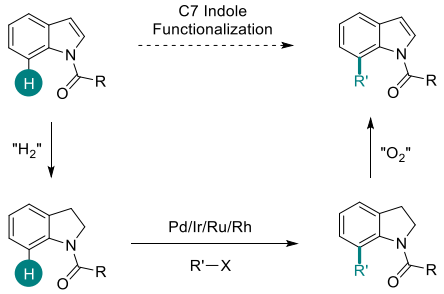
Shortly after the work from Ma, Antonchick applied the pivaloyl directing group to the C7 selective C-H sulfonamidation on indoles, this time employing iridium catalysis (Scheme 12). This methodology was shown to be applicable to aryl, heteroaryl and alkyl sulfonylazides and to be tolerant of C6 functionalization. Indole structures synthesized in this report were also shown to inhibit HeLa cell proliferation. This manifests the biological relevance of indole derivatives.[27]

Scheme 12. Piv Directed Iridium Catalyzed C-H Sulfonamidation of Indoles



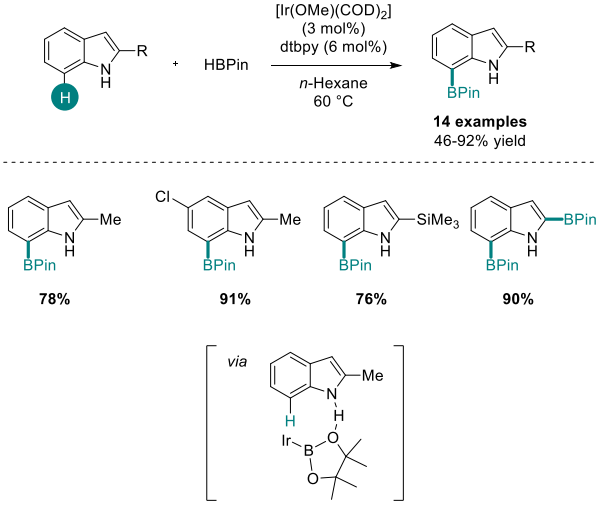
C7 functionalized indoles have been shown by multiple groups to be accessed *via* the indoline intermediate (Scheme 13). Here reduction of indoles, followed be directed C-H functionalisation and subsequent re-oxidation to the indole structure gave the desired product (Scheme 13). The C7 functionalization of indolines has been widely explored and has been applied to alkenylation,[28] alkylation,[29] arylation,[30] amidation,[31] acylation,[32] cyanation,[33] and chalcogenation[34] reactions using a variety of metal systems.

Scheme 13. C7 Functionalisation of Indolines to Access Indoles



The above methodology functions *via* nullifying the reactivity of the C2 position towards directed metalation. This has also been used successfully by Smith and co-workers by using C2-substituted indoles in a C7 selective C-H borylation reaction (Scheme 14). Here the N-H is proposed to act as the directing group by coordinating the boronate ligand to enable site selective C-H iridation.[35] Interestingly the same group have also reported the selected protodeboronation of polyborylated indole derivatives using catalytic $Bi(OAc)_3$.[36]

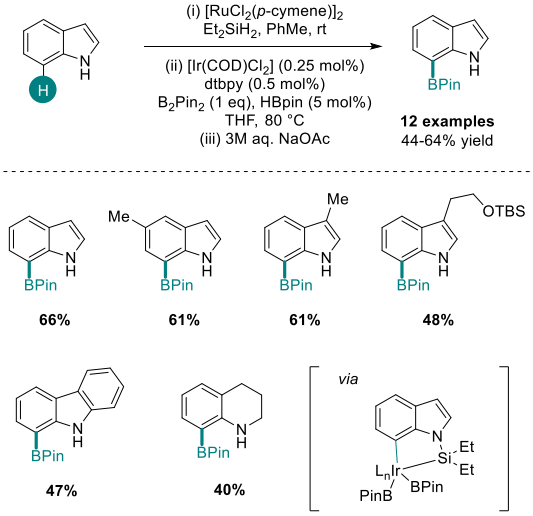
Scheme 14. C7 Iridium Catalysed C-H Borylation of 2-Substituted Indoles



Movassaghi and co-workers expanded on this methodology by using Smith's reaction conditions on C2 free substrates, allowing C2 and C7 diborylation followed by a C2 selective acid promoted deborylation, affording solely the C7 borylated structure.[37] This methodology has also been applied under forcing conditions to afford the C2/5/7 triborylated indole.[38]

One of the most important examples of C7 C-H functionalisation of free indole came from the Hartwig group in 2010. They reported the iridium-catalysed C-H borylation on free indole with no other tricks to give the C7 functionalized product. Here they used a transient bulky silyl directing group to direct cycloiridation at C7 (Scheme 15). This methodology was shown to be incredibly selective and applicable to various substituted indoles as well as carbazoles and tetrahydroquinolines.[39]

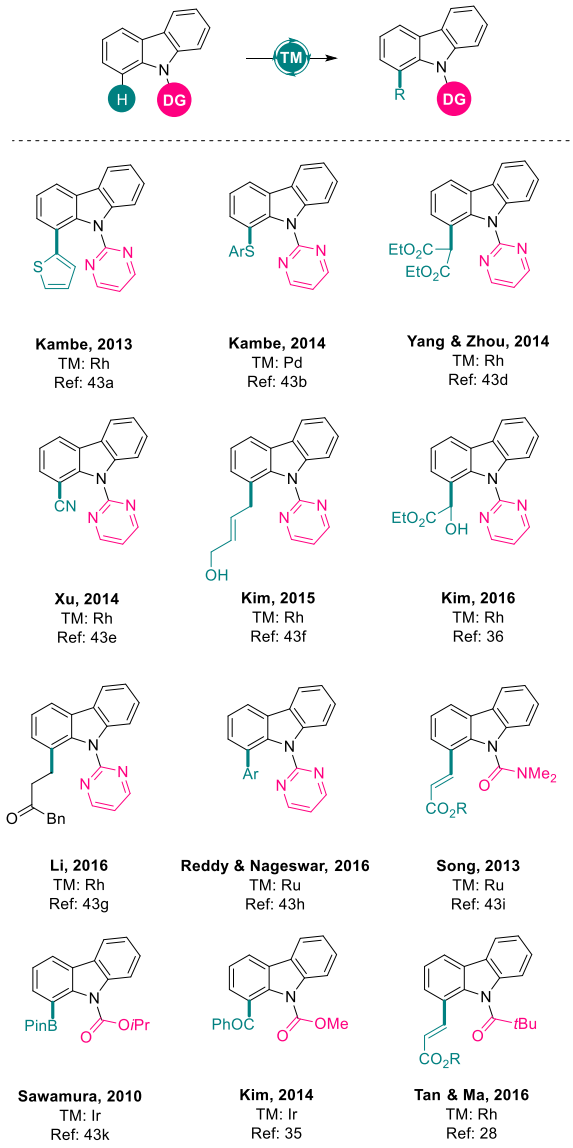
Scheme 15. Iridium-Catalysed Silyl-Directed C-H Borylation at C7



The C1-selective C-H functionalization of Carbazoles has also been explored *via* the furnishing of the NH with a directing group. A summary of the transformations, transition metal used and references is displayed in Scheme 16. This selectivity has been achieved

in a wide number of systems as there is no competing direct selectivity observed at C2/C3 such as in indole.[40]

Scheme 16. Transition-Metal Catalyzed C-H Functionalization of Carbazole Derivatives

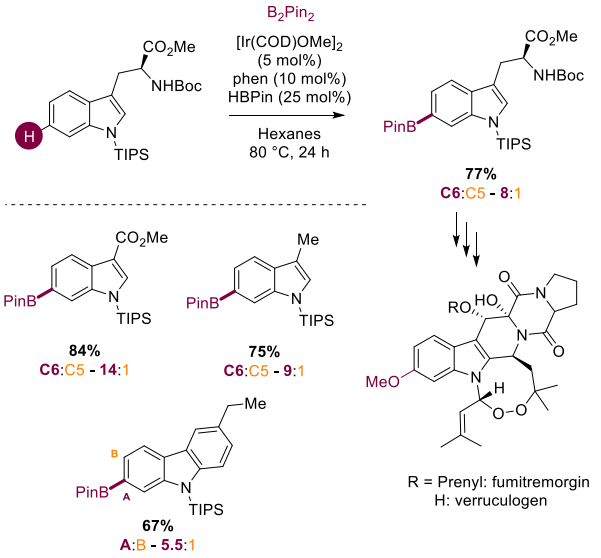


FUNCTIONALIZATION AT C6

It has been demonstrated that the use of carefully tailored directing groups or reaction systems allow functionalization at C7. Unfortunately, the C6 position lies even more remote from a directing group therefore other strategies have been employed to access this regioselectivity. These strategies have been more sparingly observed and more closely mimic those used for remote *meta*-functionalization.

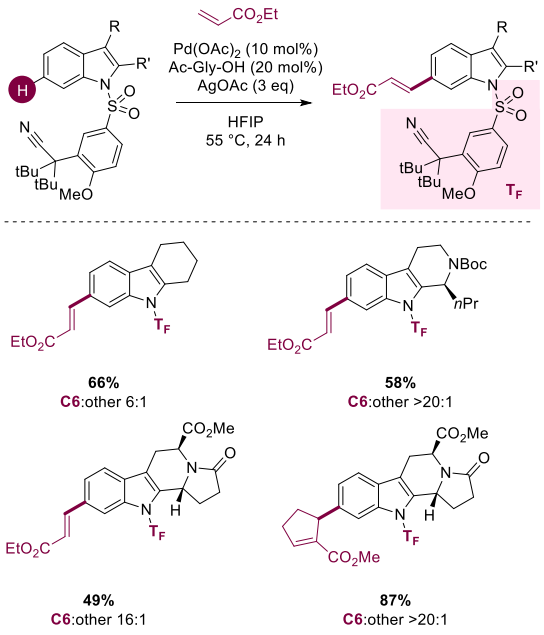
The first to be discussed is the work by Baran and co-workers in 2015. They reported the remote C6 selective C-H borylation of tryptophan derivatives utilizing iridium chemistry. This selectivity was controlled by a bulky ligand to access the less hindered C-H bonds and selectivity issues were observed between C6 and C5 C-H borylation (Scheme 17). This was developed as the key step in the total synthesis of Verruculogen and Fumitremorgin natural products.[41]

Scheme 17. Iridium-Catalysed Ligand-Controlled C6 C-H Borylation



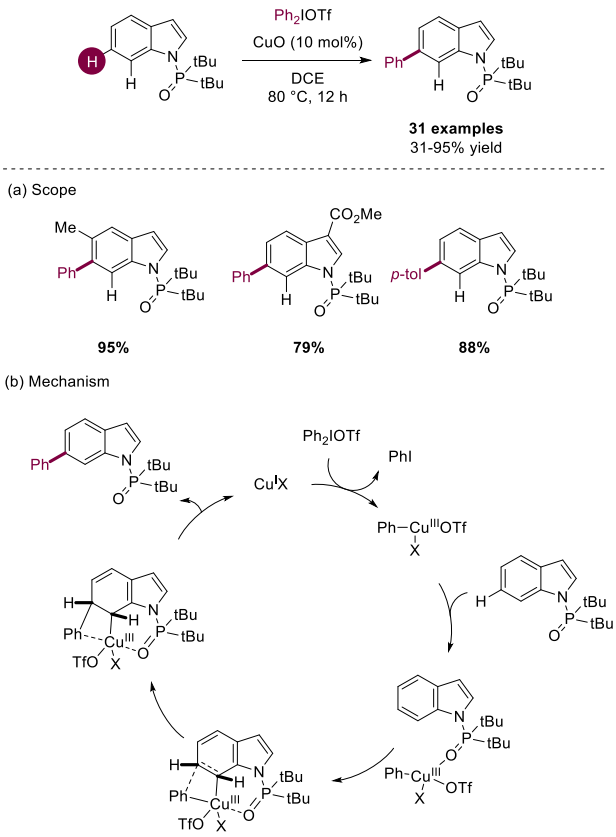
Yu and co-workers have pioneered the developments in remote functionalization *via* the use of a meticulously designed templated directing group.[42] From this, they have developed the remote C6 olefination, arylation and acetoxylation of indolines. Among the scope of this reaction there were two indole motifs which were functionalised in a C-H alkenylation reaction in good selectivity at C6 (Scheme 18). In both examples C2 and C3 are already functionalised. The template has been shown to be removable on the indole structures albeit under forcing conditions.[43]

Scheme 18. Template Controlled Palladium-Catalysed C-H Alkenylation of Indole Derivatives



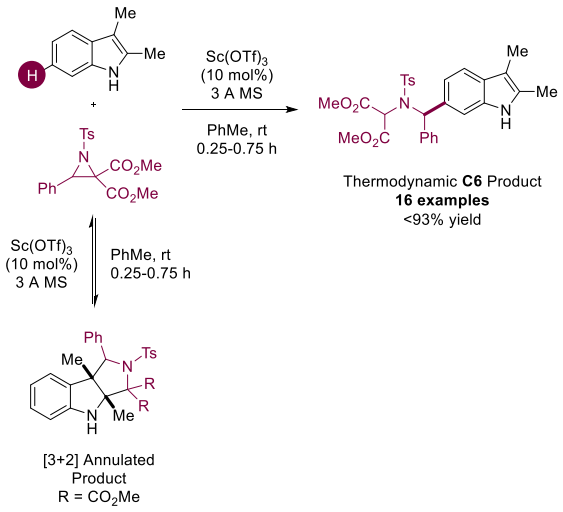
Shi and co-workers now applied established *meta*-selective C-H functionalization techniques to this *N*-phosphonate substituted indole. They successfully developed Gaunt's copper-catalyzed *meta*-arylation technique on this structure to afford C6 functionalized material in absolute selectivity, a feature which the previous two techniques have not provided (Scheme 19).[14h] A very wide scope with varying indole and coupling partner functionality was shown to be amenable to the reaction conditions. The reported mechanism entails coordination of a copper(III) species to the phosphonate directing group which on steric grounds preferentially positions itself towards the C7 proton. Here Cu-Ph across the double bond, followed by rearomatization gives the C6-arylated indole. The group also reported the C6-alkenylation using the corresponding hypervalent iodine salt.[44]

Scheme 19. Copper Catalyzed C6 Selective C-H Arylation of Indoles



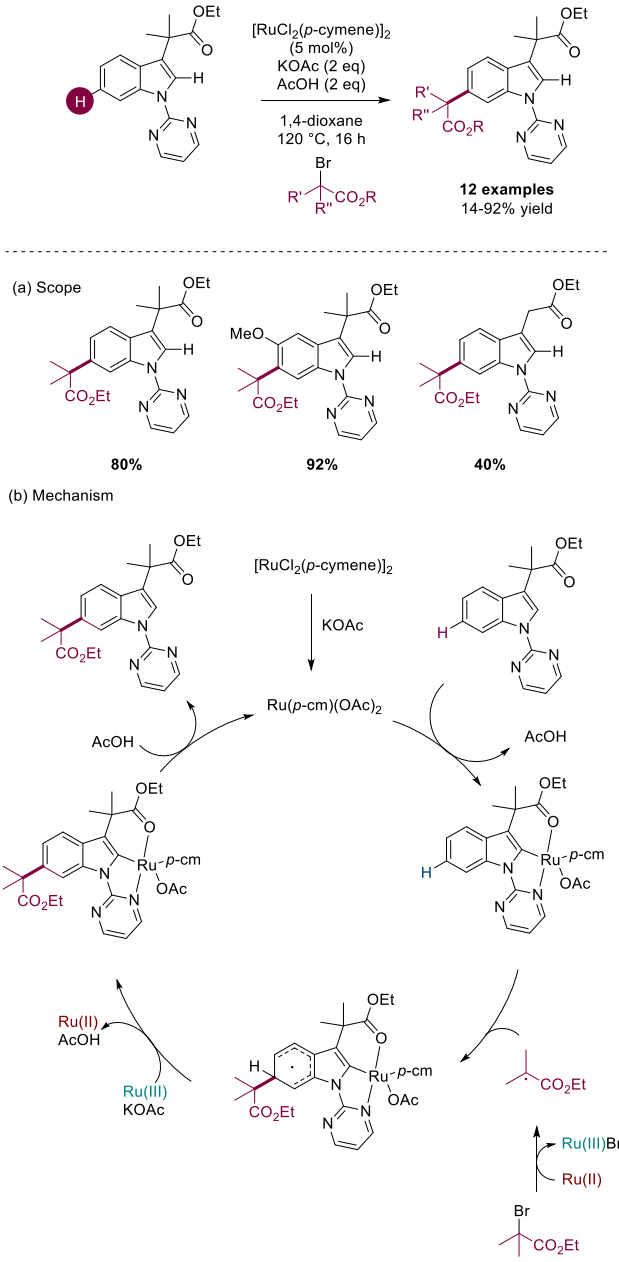
In 2014 You and Zheng developed the catalytic C6 functionalization C2/C3-disubstituted indoles using scandium triflate as catalyst. The reaction showed the indoles reacting with an aziridine in ring opening chemistry to afford C6 alkylated indoles after a reversible [3+2] annulation at the C2/C3 bridge (Scheme 20). DFT calculations elucidated a reversible annulation process that allowed the formation of the more thermodynamically stable C6 alkylated product. Again, with some of the above methods issues with C5 selectivity were also observed.[45]

Scheme 20. Scandium Triflate Catalysed C6 Alkylation of Indoles



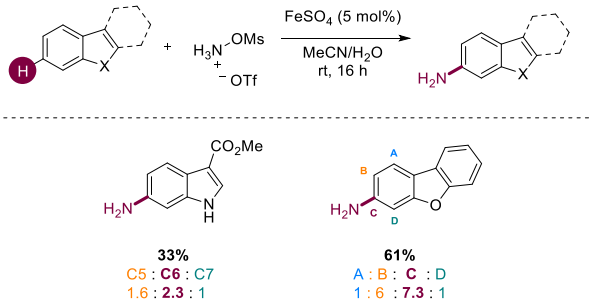
Ruthenium-catalyzed σ-activation has become a more widely used technique for the *meta*-functionalization of arenes.[14j-k,46] Here a strong metalacycle enables radical functionalization *para*-to the cyclometalation. This concept was applied to the indole structure by Frost and co-workers in 2017 (Scheme 21). This methodology used a strongly coordinating directing group at N1 and a weakly coordinating directing group at C3 to enable remote C6 selectivity. The reported mechanism shows a C-H activation at C2 with interaction from both N1 (strong) and C3 (weak) directing groups. Redox radical generation from a ruthenium centre then enables remote radical addition to the most electronically activated benzenoid position. Computational Fukui indices were shown to validate the shift in electron density in the proposed cyclometalation at C2 to the remote C6 position.[47]

Scheme 21. Remote C6 Selective C-H Alkylation of Indole Derivatives *via* σ-Activation



In 2016, Morandi reported the iron-catalyzed C-H amination of arenes. Here they employ the protonated hydroxylamine as a new amination reagent and iron sulphate as catalyst. Electronic bias and sterics were shown to affect the regioselectivity of functionalization in non-biased substrates. In the case of indoles (Scheme 22) the major C-H aminated product observed was with functionalization taking place at the C6. The methodology was also applied to dibenzofurans where a higher yield was observed although the selectivity issues remained.[48]

Scheme 22. Iron Catalyzed C-H Amination of Indole and Dibenzofuran

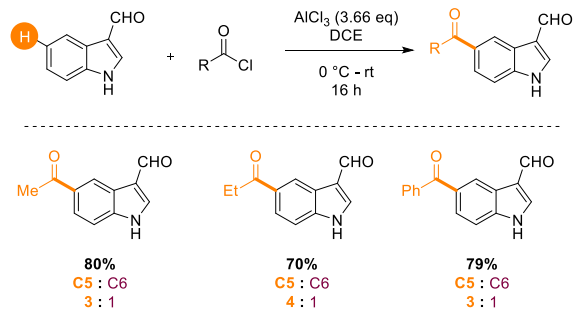


FUNCTIONALIZATION AT C5

The most sparingly observed selectivity in direct indole functionalization has been accessing chemistry at C5. Despite selectivity issues in some methods discussed above between C6 and C5 there have been incredibly limited reports showing conditions that preferentially go for the C5 position.

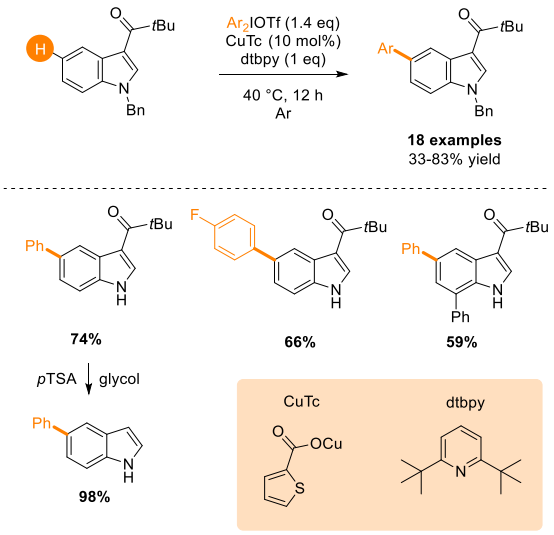
There have been reports of non-catalyzed Friedel-Crafts type acylation of the free indole structure using $AlCl_3$ as a Lewis acid by Demopoulos. This was shown to lead to a mixture of C5 and C6 substituted indoles with ratios of generally ~3:1 in favour of C5 (Scheme 23).[49] The product was also shown to undergo heterogeneous palladium catalysed deformylation to give the solely C5 substituted product mixtures.

Scheme 23. Aluminium trichloride mediated C5 acylation of indole derivatives



The sole example of selective transition-metal catalyzed direct C5 functionalization of the indole benzenoid ring came out from the Shi lab in 2017. Here they used a combination of the pivaloyl directing group at C3 (which directs to C4) and the remote copper catalysed process (which enabled C6 functionalization) to permit access to the C5 C-H bond (Scheme 24). The reaction pathway was proposed to follow the same mechanism as their work with the C6 arylation. As with the above methodology, the functionality at C3 (in this case the directing group) can be removed to give solely the C5 substituted indole. In this case the directing group is removed cleanly using *p*TSA in glycol.[20] This report also completed Shi's clean sweep of benzenoid indole functionalization having developed methods to access C4,5,6 & 7.

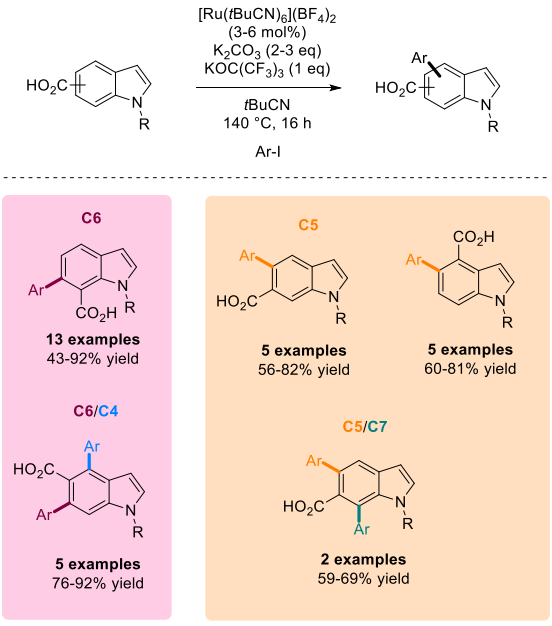
Scheme 24. Copper-Catalyzed C5 Arylation of Indole Derivatives



A clear majority of the examples that have been discussed above utilise a directing group on the pyrrole-type ring to enable positional selective catalysis on the benzenoid ring. However, there have been examples where a directing group on the benzene ring enables indole functionalization without reactivity at C2 or C3. The position of these directing groups enables a wide breadth of potential products.

In 2017, Larrosa and co-workers reported the regioselective C-H functionalization of indole-carboxylic acids. When using indole-7-carboxylic acids, C6 arylation was the only product observed (Scheme 25).[50]

Scheme 25. Ruthenium-Catalyzed C-H arylation of indole derivatives.



When using indole-5-carboxylic acid the C6/C4 disubstituted structure was observed on using heightened catalyst loading. When using indole-6-carboxylic acid or 4-carboxy derivative C5 arylation was observed. On increasing the catalyst loading using certain substrates

the C5/C7 difunctionalized motif is also observed. This showed that depending on the functionality present on the benzenoid ring, any regiochemistry could be accessed using their ruthenium catalysis.[50]

Pedro and co-workers have also reported the organocatalyzed enantioselective Friedel-Crafts aminoalkylation of indoles on the carbocyclic ring directed by a hydroxy group already present on the benzenoid moiety of the indole heteroaromatic.[51]

CONCLUSION

The indole scaffold has become one of the most widely studied organic structure due to its prevalence throughout the natural product, pharmaceutical and agrochemical worlds. The ability to access site selective C-H functionalization on the benzenoid ring has remained a challenge due to the inherent reactivity of C2 and C3. In spite of this, elegant methods have come to the forefront of modern transition-metal catalysis. This review has covered the techniques to access the C4, C5, C6 and C7 positions of the benzenoid ring utilizing a vast number of remote functionalization techniques and selective directing group chemistry. The development of site selective C-H functionalization will continue to be an integral part to synthetic development in the derivation of biologically relevant structures and these early methods set the stage for a full-frontal assault on everyday synthesis.

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