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Catalytic Intermolecular Functionalization of Benzimidazoles

*Jørn H. Hansen and Richard Fjellaksel*

Abstract

This chapter describes contemporary strategies for selective catalytic inter-molecular functionalization of the benzimidazole scaffold. Functionalization at nitrogen and position C-2 is well developed employing copper, palladium, rhodium, nickel, and cobalt catalysis. Direct CH activation is the predominant approach to C-2 functionalization. Nickel-based catalysts can activate C—O bonds in conjunction with C—H activation at benzimidazole which grants access to a very broad range of phenols and enols as convenient functionalization precursors in this chemistry. The remaining carbon positions of benzimidazoles are typically functionalized via a sequential halogenation/coupling strategy to ensure selectivity. A key success factor in enabling these chemistries has been the fine-tuning of catalyst-ligand combinations.

Keywords: benzimidazoles, catalysis, C—H activation, cross-coupling, late-stage functionalization

1. Introduction

Benzimidazoles are tremendously important heterocycles in chemistry. They play a vital part in modern medicinal chemistry due to the importance of the benzimidazole as a pharmacophore in natural products and pharmaceuticals [1]. Benzimidazoles have a central role in contemporary homogeneous catalysis, particularly as ligands in metal catalysis and as a source of *N*-heterocyclic carbenes [2]. Moreover, they are important components of organic materials, e.g., optoelectronic materials [3]. Thus, the generation of a broad range of structurally diverse benzimidazoles is of paramount importance for enabling novel applications and unique properties to emerge.

Substituted benzimidazoles are typically synthesized de novo using a range of methods [1]. This is by far the most common approach, and new methods emerge steadily [4]. However, large libraries of benzimidazoles are needed in medicinal chemistry, catalysis, and materials science in order to discover fine-tuned properties and to optimize these. Thus, de novo synthesis makes for a rather inefficient approach since the benzimidazole scaffold must be constructed for each new analogue needed. A more powerful strategy would be to start with available benzimidazoles and be able to do functionalization with desired groups directly onto the scaffold—so-called late-stage functionalization [5].
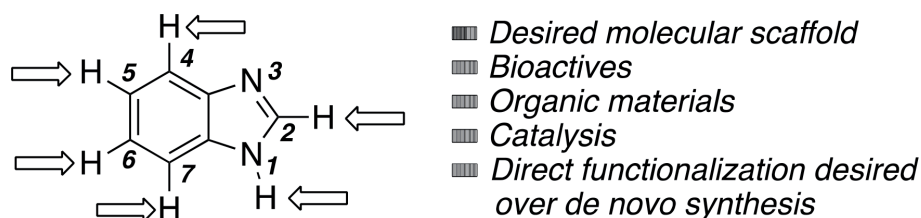
Figure 1.
The benzimidazole scaffold and its functionalization sites.

In this chapter the current catalytic strategies and methods for the intermolecular functionalization of benzimidazoles will be presented. These are surprisingly few, which illustrates the complexity involved when trying to selectively functionalize specific positions in the scaffold (**Figure 1**). The current strategies to solve this problem, and thus greatly streamline the synthesis of substituted benzimidazoles, will be presented herein with selected examples appearing since around 2003. We consider only *catalytic* strategies for *intermolecular* functionalization and aim to provide a good overview of state of the art in late-stage functionalization of benzimidazoles.

2. Catalytic functionalization chemistry

2.1 *N*-functionalization

Functionalization at nitrogen is perhaps the most straightforward. Classical bimolecular substitution can be used to alkylate in the presence of suitable bases. Nucleophilic aromatic substitutions or Ullmann couplings give rise to a number of *N*-arylated heterocycles, albeit with major limitations [1]. In recent years, catalytic methods and more sophisticated reaction conditions facilitate arylation and alkylation of this position with groups unavailable via classical chemistry [6].

A selectivity issue must be mentioned for unsymmetrical benzimidazoles with a free N—H. There is a rapid tautomeric equilibrium in which the proton shuffles between the two nitrogen sites. Thus, a particular tautomer must be "locked" in advance of the functionalization by substitution in order to obtain one distinct isomer.

Shieh and co-workers have reported an effective 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed N-benzylation reaction using dibenzyl carbonate (**2**) in the presence of a stoichiometric amount of the ionic liquid tetraoctyl ammonium bromide (**Figure 2**) [7]. The ionic liquid had a dramatic effect on both the reaction rate and yield, and the model benzylation of benzimidazole (**1**) afforded excellent 95% yield of **3**.

Buchwald et al. have reported one of the most general catalytic systems for efficient and mild *N*-arylations of benzimidazoles **4** (**Figure 3**) [8]. The bidentate ligand **6** in combination with dimethyl sulfoxide (DMSO) as solvent enabled this copper(I)-catalyzed coupling to occur even with unactivated aryl bromides **5** and afford 2-substituted benzimidazoles **7** in 71–98% yields. Notably, the coupling is also efficient with ortho-substituted aryl bromides.

The authors propose a mechanism for this transformation initiated by *N*-coordination of the benzimidazole to a Cu(I)Br-**6** complex followed by deprotonation of the N—H by the base. Subsequent oxidative addition of the aryl bromide to generate a cationic Cu(II) intermediate followed by reductive elimination releases the *N*-arylated benzimidazole **7** and regenerates the active Cu(I) catalyst. The method appears general and is a powerful tool for direct *N*-arylation of benzimidazoles [8].

Bao et al. have reported practical copper-catalyzed methods for *N*-vinylation [9]. In the most practical version, employing copper(I) oxide in the presence of a β-ketoester ligand precursor, they were able to couple electronically diverse *E*-bromostyrenes **8** with benzimidazole **1** to generate *N*-vinylated products **9** in 54–91% yields (**Figure 4**). Notably, the products retained the *E*-stereochemistry in the reaction with excellent >95:5 selectivity.

## 2.2 Functionalization at C-2

Catalytic functionalization at position C-2 is by far the most predominant in the literature. This is likely due to the more reactive nature of this particular C—H bond as it is situated between the two electron-withdrawing nitrogen sites. Although palladium, nickel, and rhodium play the major roles in this chemistry, some examples of copper-catalyzed C-2 functionalization exist. For example, copper(II) acetate in the presence of air has been employed for oxidative couplings of benzimidazoles at C-2 [10]. Furthermore, one exciting example of a copper(I) iodide (10 mol%)-catalyzed arylation with iodobenzene at C-2 of *N*-methylbenzimidazole was reported by Daugulis et al. to proceed in 89% yield [11]. Despite these promising results, there are no extensive studies of copper-catalyzed functionalizations at C-2 of benzimidazoles in particular.
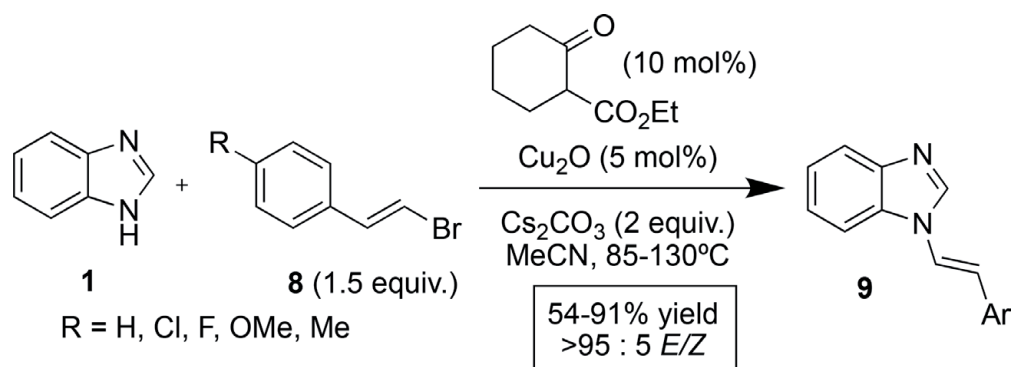
2.2.1 Arylation and vinylation

An early example of palladium-catalyzed C-2 arylation by Bellina and Rossi involves the coupling of aryl iodides **10** with benzimidazole **1** under ligandless and base-free conditions [12]. They employed 5 mol% of palladium(II) acetate and a
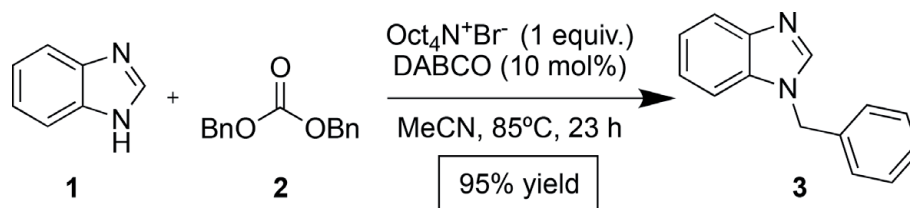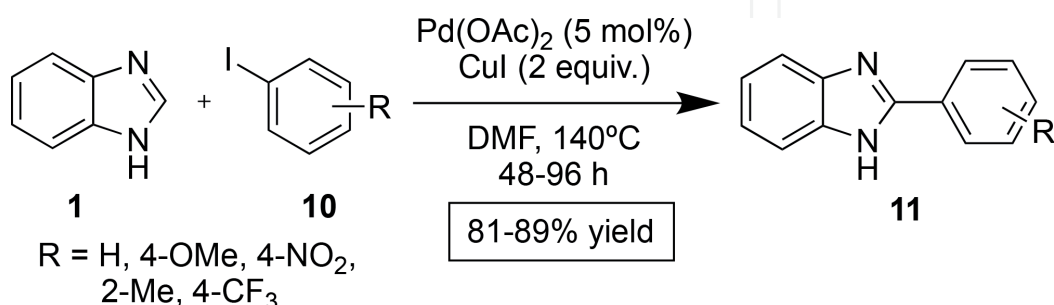

Figure 2.
Selective N-benzylation.
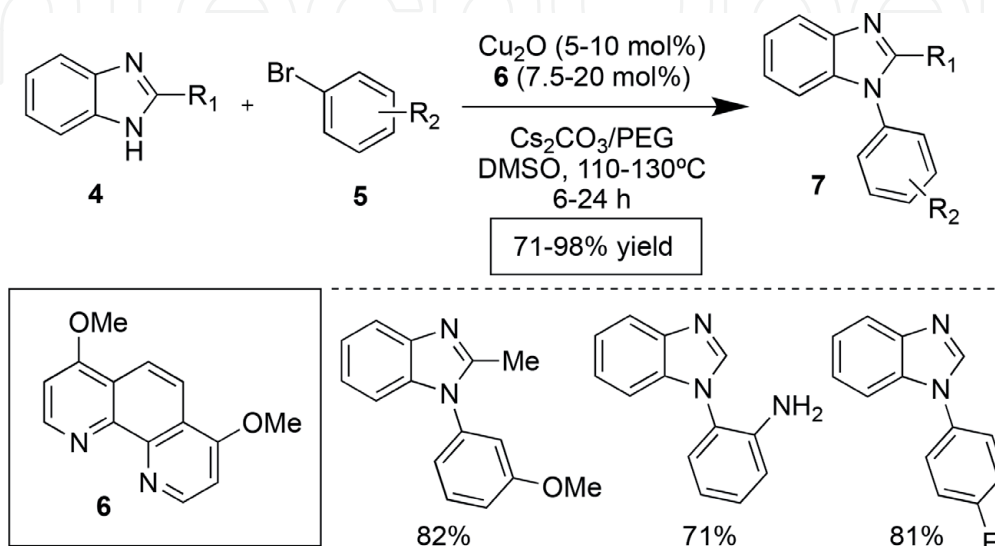
Figure 3.
Cu-catalyzed N-arylation.

Figure 4.
Cu-catalyzed N-vinylation.

Figure 5.
Early Pd-catalyzed C-2 arylation under ligandless conditions.

superstoichiometric amount of copper(I) iodide in dimethylformamide (DMF) at high temperatures to afford 2-arylbenzimidazoles **11** in high purities and 81–89% yields. This demonstrated for the first time the possibility of using base-sensitive, unprotected N—H containing heterocycles without prior protection in this chemistry. A major drawback of the ligandless approach is relatively long reaction times (>48 hrs) at elevated temperatures in addition to the large amounts of copper(I) salt needed [12] (**Figure 5**).

The contemporary power of palladium-catalyzed coupling chemistry lies in ligand design [13]. The size and nature of the ligand play a crucial role in determining the possible pathways, selectivity, and kinetics, and, as such, optimization of ligand structure to suit the needs of the desired coupling reaction is key to modern catalytic reaction design. The number of ligands with vast spread in electronic and steric properties for palladium catalysis available today is large and expanding rapidly. This area lies at the forefront of modern catalysis research in organic chemistry [14].

A major step forward from the ligandless C-2 arylation reported above is the C—H arylation of *N*-substituted benzimidazoles **12** and aryl/heteroaryl chlorides **13** in the presence of the well-defined *N*-heterocyclic carbene-imidazole catalyst **14** (**Figure 6**). The reaction afforded moderate to good yields (56–97%) of a variety of C-2-arylated benzimidazoles **15** [15].

The first Ni-catalyzed C—H arylation and vinylation at C-2 of benzimidazoles were reported by Itami et al. in 2015 [16]. A major advance in the chemistry was the use of carbamate derivatives of phenols (**16**) or enols (**17**) as the source of aryl and vinyl groups, respectively (**Figure 7**). The catalytic system consists of nickel(II) triflate with potassium phosphate as base and bis-phosphine ligands; the latter are crucial. The use of a tertiary alcohol (AmylOH) as solvent was also crucial for this chemistry. 1,2-Bis(dicyclohexylphosphino)ethane (dcype) was the optimal ligand for the arylation chemistry and afforded C-2-arylated benzimidazoles **15** in 53–95%
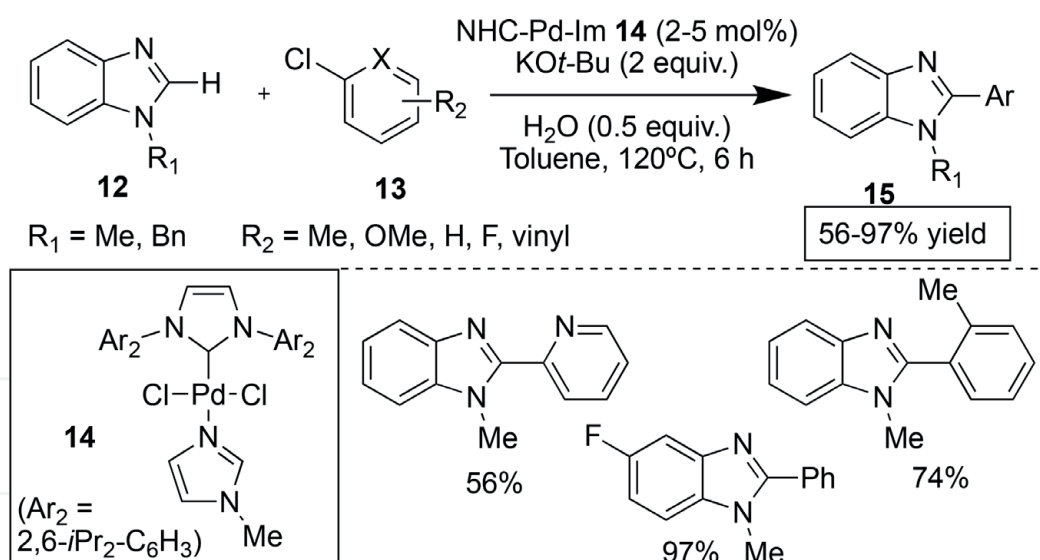
Figure 6.
Pd-catalyzed C-2 arylation with aryl chlorides.
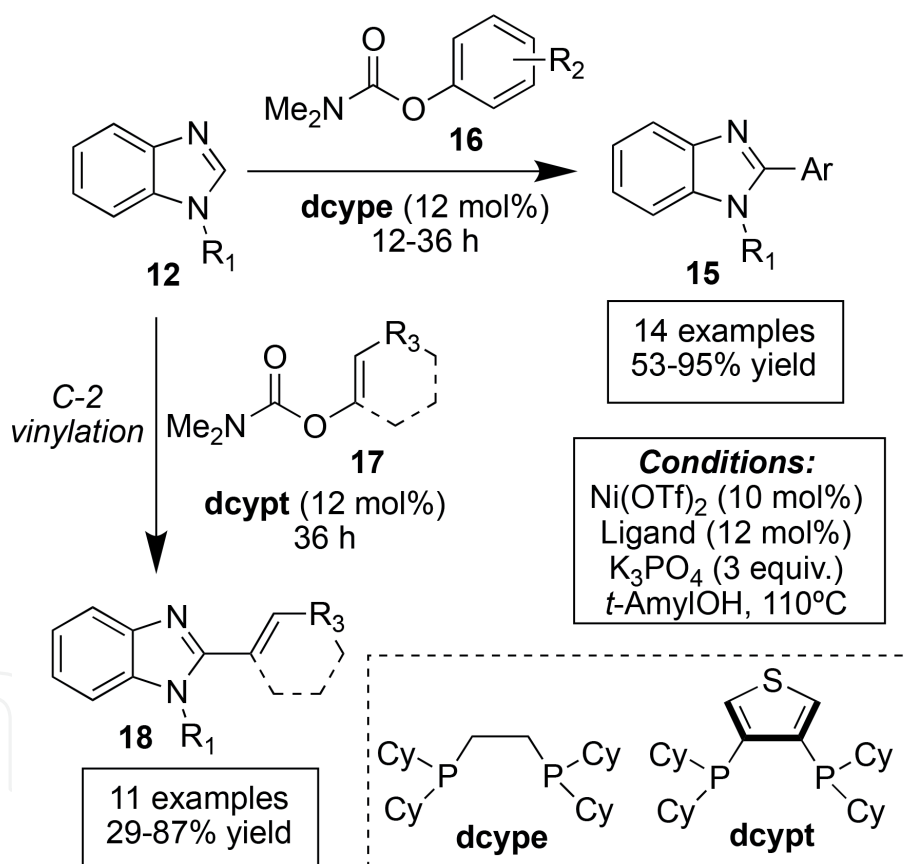
Figure 7.
Ni-catalyzed arylation and vinylation by domino C—H/C—O activation.

yield. This catalytic system could also facilitate arylations with aryl chlorides (**13**) in 64–86% yield. The potential synthetic power of this arylation approach was demonstrated by performing a functionalization of the nonsteroidal anti-inflammatory drug indomethacin with *N*-methylbenzimidazole at the chlorine site (26% yield). A different ligand, 1,2-bis(dicyclohexylphosphino)thiophene (dcypt), was employed as the optimal to achieve efficient C-2 vinylations with enol derivatives (**17**) to afford 2-vinylbenzimidazoles **18** in 29–87% yields [16].

The proposed mechanism for the nickel(II)-catalyzed approach involves reduction to a nickel(0) species by action of the bisphosphines or benzimidazole

to initiate a Ni(0)–Ni(II) catalytic cycle [16]. Oxidative addition of the carbamate aryl C—O bond onto the activated Ni(0)-bisphosphine complex followed by C—H nickelation assisted by departure of the corresponding carbamic acid generates a key intermediate for reductive elimination of the product and regeneration of the active Ni(0) species [16].

The ability of nickel to undergo C—O activation enables the use of a range of practical and available substrates for functionalization. Wang and co-workers have recently disclosed C-2 arylations of benzimidazoles using methoxyarenes as functionalization agents in the presence of Grignard reagents [17]. Thus, the reaction system effects tandem C—O/C—H activation with subsequent coupling. The Grignard reagent was critical in order to minimize nonproductive couplings. A major demonstration of the applicability of this method is the reaction between steroidal hormone β-estradiol methoxy derivative **19** and *N*-methylbenzimidazole which afforded the C-2 steroid-functionalized benzimidazole **20** in very good 74% yield (**Figure 8**). The selectivity of aromatic methoxy group activation is striking, as the aliphatic methoxy group is left intact. The unusual dicarbene ligand carbodicarbene (CDC) was crucial for this reactivity and also demonstrates the importance of benzimidazoles as components of ligands for transition metal catalysis [17].

C-2 vinylation with alkynes as functionalization reagents has been reported, and these reactions occur under mild conditions with nickel or cobalt complexes in the presence of phosphine ligands. In a nickel-catalyzed process reported by Nakao et al., *N*-methylbenzimidazole reacts with internal alkynes to afford the C-2 vinylated products in 80–92% yields [18]. The cobalt-catalyzed vinylation of *N*-pyrimidylbenzimidazole **21** with alkyne **22** affords vinylation product **23** in 82% yield (**Figure 9**) in the presence of the phosphine ligand 2-[2-(diphenylphosphanyl) ethyl]pyridine (pyphos) and an equivalent of a Grignard reagent in tetrahydrofuran (THF) at ambient temperatures [19]. The *N*-pyrimidyl group is required for directing the chemistry to the C-2 site but can be easily removed from the scaffold after functionalization.
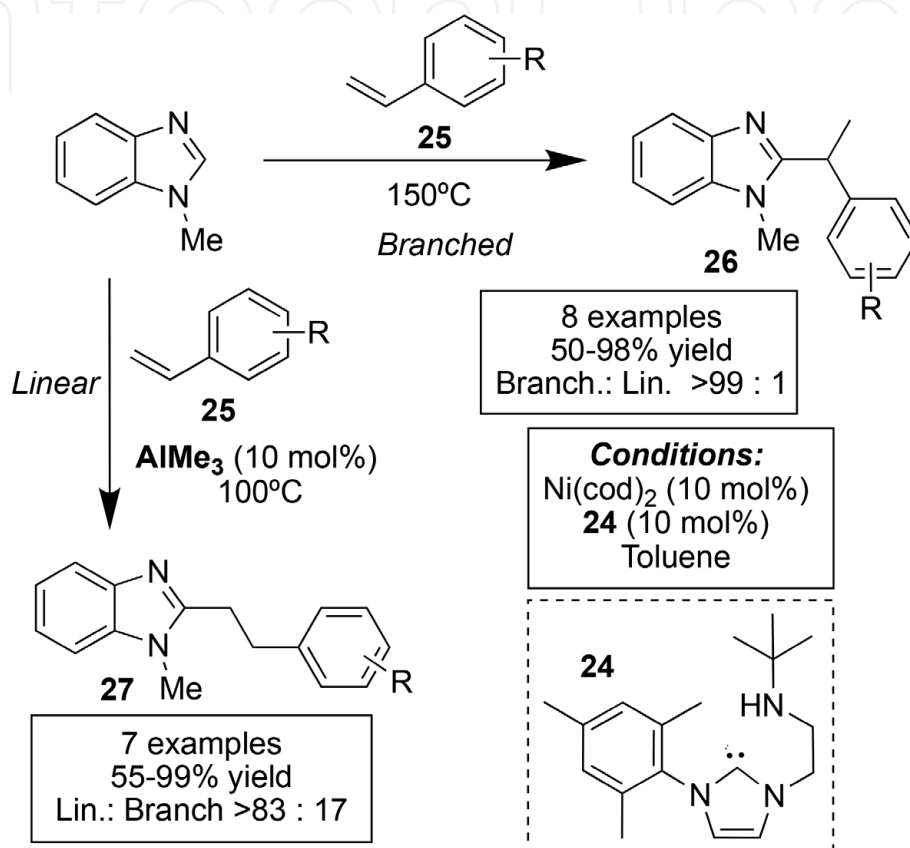
2.2.2 Alkylation

In the area of catalytic C-2 alkylations, rhodium(I) and nickel(0) complexes play a major role. Rhodium(I)-catalyzed *linear* C-2 alkylation was reported first by Bergman and Ellman [20]. In 2012, Shih et al. reported alkylations with full
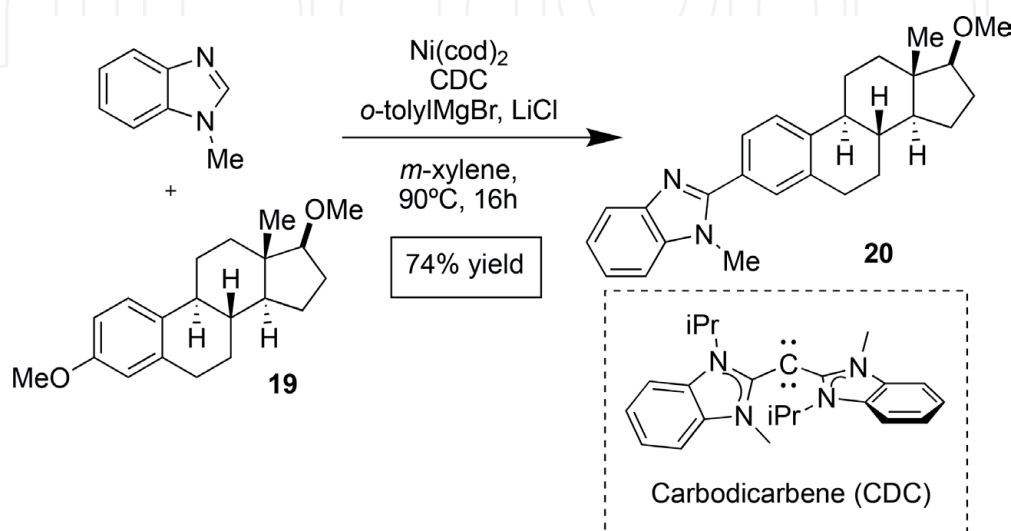
Figure 8.
Complex Ni-catalyzed C-2 arylation with estradiol dimethyl ether.
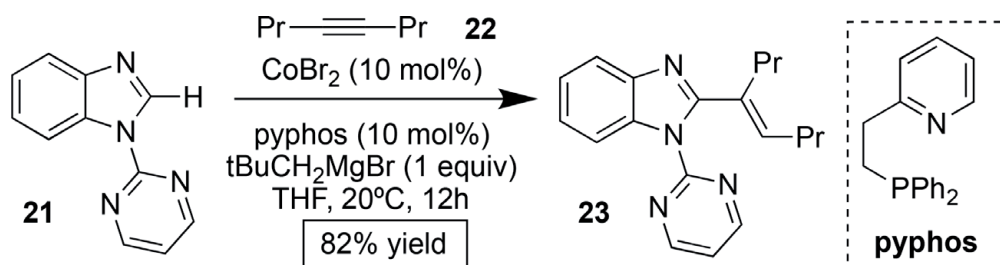
Figure 9.
A Co-catalyzed C-2 vinylation with alkynes.

Figure 10.
AlMe$_3$ as a chemical switch for branched vs. linear alkylations at C-2.

control of linear versus branched selectivity using AlMe$_3$ as a chemical switch
(**Figure 10**) [21]. In the presence of 10 mol% of Ni(cod)$_2$ (cod = cyclooctadiene)
and the bidentate *N*-heterocyclic carbene (NHC) ligand **24** in toluene, the reaction
between *N*-methylbenzimidazole and substituted styrenes **25** afforded exclusively
branched alkylation products **26** in 50–98% yields. The addition of 10 mol% of
AlMe$_3$ completely switched the selectivity toward linear alkylation products **27**
in 55–99% yields. The branched product is electronically favored, but the linear
product arises in the presence of AlMe$_3$ because the benzimidazole nitrogen at
position 3 will generate a Lewis acid/base adduct causing a steric switch in the
preferred binding orientation of the styrene during the catalytic cycle. Thus, the
linear product is formed predominantly [21].

Obtaining branched selectivity in C-2 alkylations has been one of the major
challenges in this chemistry, and the above example is the only report appearing
before 2017 demonstrating this. As is often the case, fine-tuned selectivity control
can be a matter of discovering fine-tuned ligand properties. Thus, Tran and Ellman
recently reported a rhodium(I)-catalyzed C-2 alkylation of benzimidazoles **28**
using acrylic systems **29** in the presence of the bidentate phosphine ligand dAr^{F}pe

yielding exclusively branched alkylation products **30** in 12–96% yields (**Figure 11**) [22]. The use of ethyl methacrylate afforded products with a quaternary carbon at the C-2 site. The amide group can easily be converted to an aldehyde, thus making these products useful building blocks in medicinal chemistry.

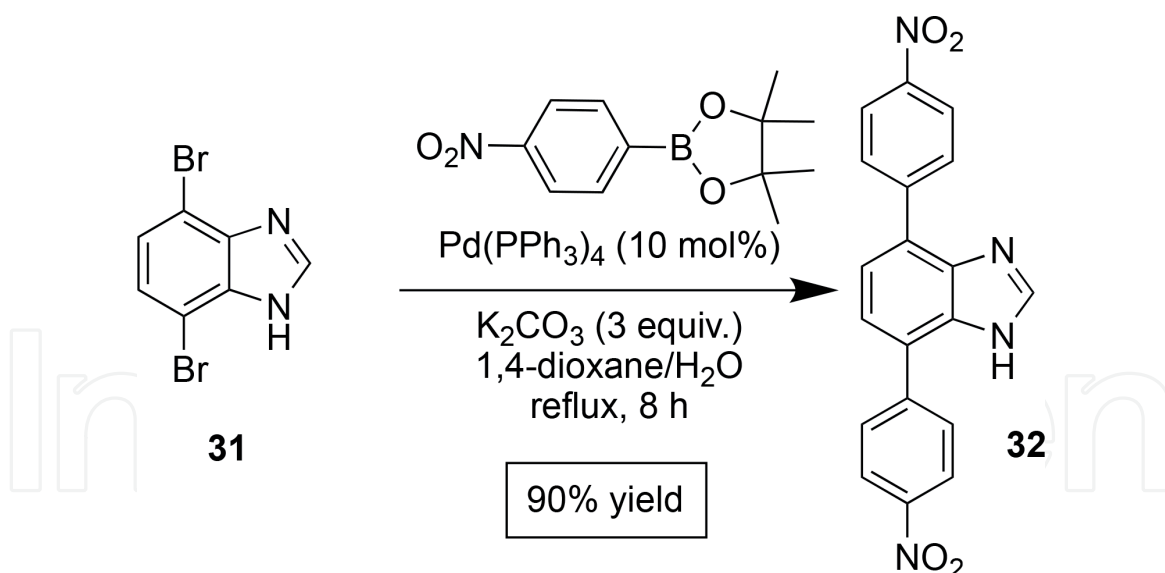## 2.3 Functionalization at C-4/C-7

Catalytic functionalizations at positions 1–3 are rather common in benzimidazoles. The activated nature of these positions makes direct functionalization chemistry feasible with a variety of catalytic systems as surveyed in Sections 2.1 and 2.2. Selective catalytic functionalization at positions 4–7 is significantly more challenging since these positions are less activated and also less chemically distinguishable from each other. Benzimidazoles that are pre-functionalized with some reactive functional group (mostly halogens), generated by de novo synthesis, are commonly used to achieve selectivity in these cases.

In order to obtain a key monomer for the construction of crystalline covalent organic frameworks (COFs), Xu et al. reported the double functionalization of 4,7-dibromobenzimidazole **31** using a Suzuki-Miyaura approach (**Figure 12**) [23]. Under rather standard cross-coupling conditions with 10 mol% of palladium(0) tetrakistriphenylphosphine and two equivalents of pinacol boronic ester **32**, double functionalization was achieved in 90% yield [23]. This is an example of the utility of benzimidazole functionalization in materials chemistry.

A great example of the utility of benzimidazole functionalization at C-4/C-7 in medicinal chemistry was reported by Auberson et al. in 2015 [24]. The 4-bromo-6-carbomethoxybenzimidazole **33** was treated with bisboronic ester **34** under catalytic action of Pd(dppf)Cl$_2$ (dppf = 1,1′-ferrocenediyl-bis(diphenylphosphine)), which afforded 92% yield of the boronic acid **35** (**Figure 13**). **35** was next employed as a coupling partner in a Suzuki-Miyaura coupling with heterocyclic bromide **36** to afford the complex product **37** in 77% yield [24]. This demonstrates an interesting strategy in which an accessible bromobenzimidazole can be transformed into a
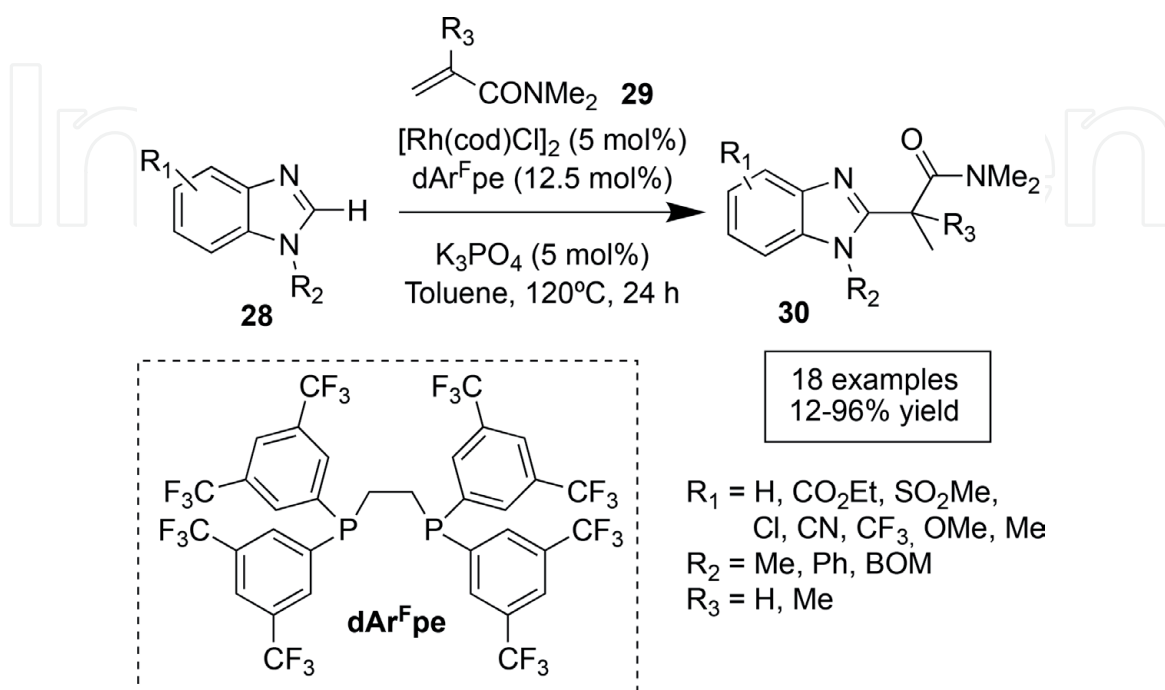
Figure 11.
Rh(I)-catalyzed branched alkylation at C-2.

Figure 12.
Double Suzuki-Miyaura coupling to generate COF monomer.
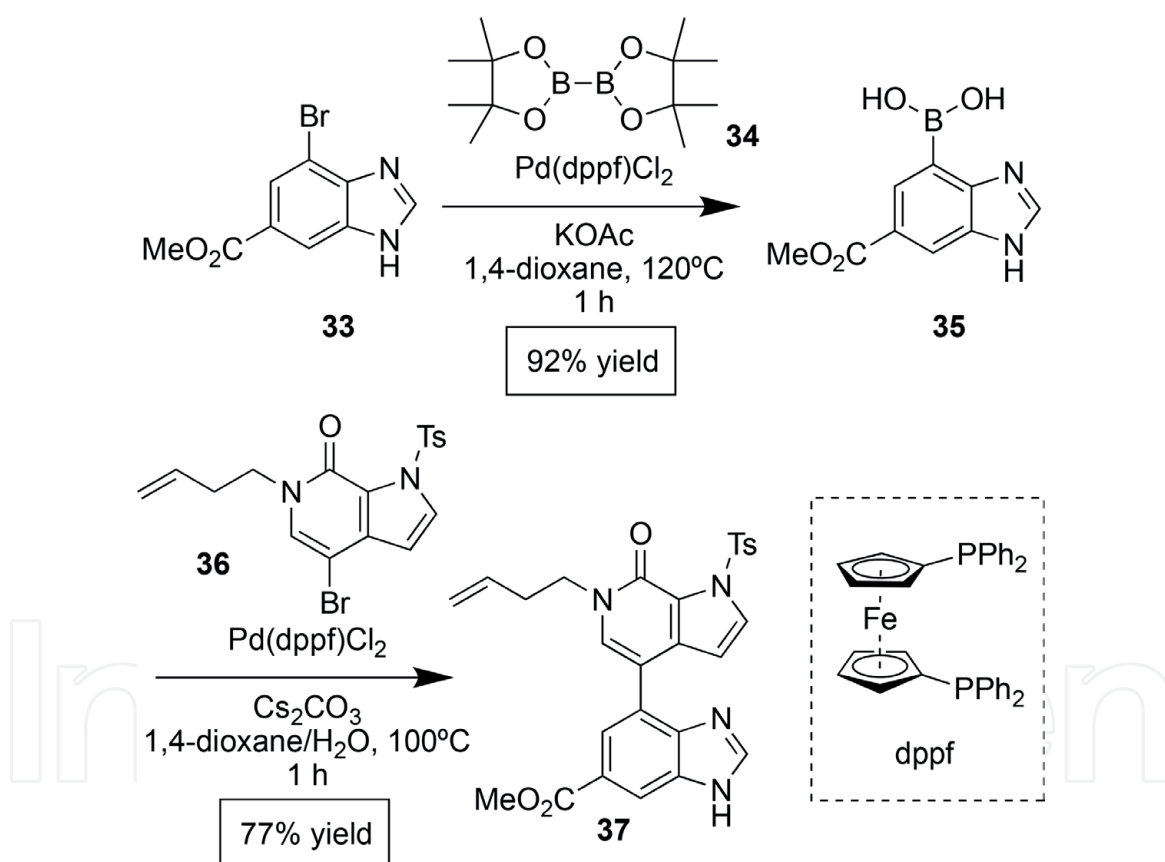
Figure 13.
Complex C-4 functionalization via borylation-cross-coupling sequence.

boronic acid for cross-coupling chemistry. Thus, it is overall a cross-coupling of two aryl bromides, really harnessing the full power of palladium catalysis.

Another powerful cross-coupling transformation of aryl halides is the Buchwald-Hartwig amination. The selective formation of C—N bonds clearly has numerous applications in medicinal chemistry. De la Fuente et al. have reported Buchwald-Hartwig functionalization with *N-tert*-butoxycarbonyl (Boc)-protected piperazine at position 4 of 4-chlorobenzimidazole **38** in the presence of Pd_2dba_3 and a phosphine ligand $P(tBu)_3$ (**Figure 14**) [25]. The [2-(trimethylsilyl)ethoxy] methyl acetal (SEM) protecting group at nitrogen was installed indiscriminately at

the two nitrogen sites, so the starting material was effectively a 1:1 mixture of the 4- and 7-chlorobenzimidazole. However, the desired isomer was the 4-piperazinyl-benzimidazole **39** which could be isolated in a very good 43–49% yield (50% is theoretical maximum yield of one isomer) [25].
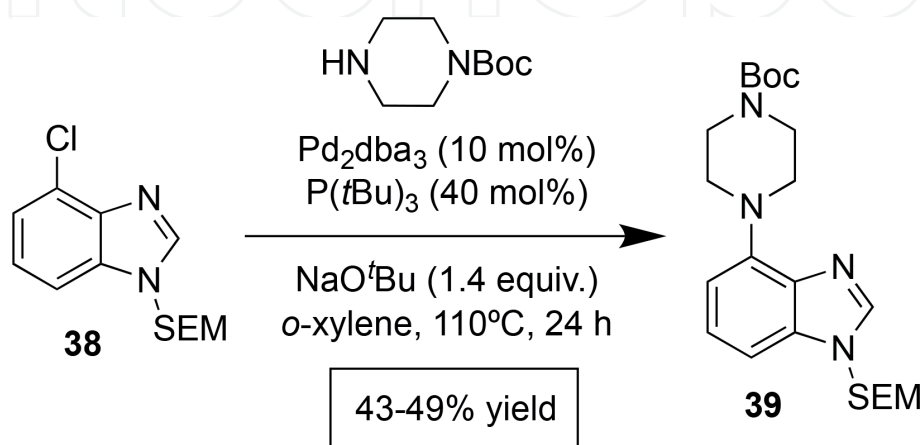
2.4 Functionalization at C-5 and C-6

Although most reported halogenated benzimidazoles are generated by de novo synthesis, in which the halogen is pre-functionalized on the starting materials used for assembling the benzimidazole scaffold, some examples exist of selective catalytic halogenations directly onto benzimidazole.

A practical and selective monobromination at C-5 has been reported by Das et al. in which sulfonic-acid functionalized silica acts as a heterogeneous acid catalyst system [26]. With only 13 wt% catalyst in the presence of an equivalent of N-bromosuccinimide (NBS), 77% yield of 5-bromobenzimidazole **40** was observed (**Figure 15**). Although the catalyst system is heterogeneous, its reactive Brønsted acidic sites are highly mobile on the catalyst surface and therefore achieve efficiency similar to that of homogeneous catalysts. Moreover, the catalyst could be recycled up to three times without loss of activity. The above study is interesting, particularly since no C-2 bromination was observed [26]. An early study by Smith et al. also used NBS as a brominating agent, but in the presence of pure silica gel acting as the heterogeneous catalyst, which yielded C-2 bromination only (67% yield), unless this position was occupied. They predominantly achieved C-2/C-5 dibromination when using two equivalents of NBS (60% yield) [27].

Cui et al. report a strategy for iodination at C-6 of **41** involving a pre-installed C-6 bromo substituent (**Figure 16**) [28]. By using a Pd(0)-catalyzed stannylation reaction, the C-6 tributyltin-substituted benzimidazole **42** can be generated albeit in low yields (14–29%). These products can further undergo oxidative iodination in the presence of molecular iodine in low to moderate yields (27–47% yields). The method was applied to radioiodination at C-6 with 125-I derived from [^{125}I]NaI under oxidative conditions and afforded 43% radiochemical yield of the desired labeled product [28].

The strategy of bromination/Pd-catalyzed coupling has been employed for installment of various groups at positions C-5/C-6 in benzimidazoles. However, many are described only in the patent literature which often presents little information about conditions and chemical yields. Notably, this strategy has been employed for regioselective cyanation and carboxylation [29], alkylation (Negishi coupling)

Figure 14.
Buchwald-Hartwig amination functionalization at C-4.
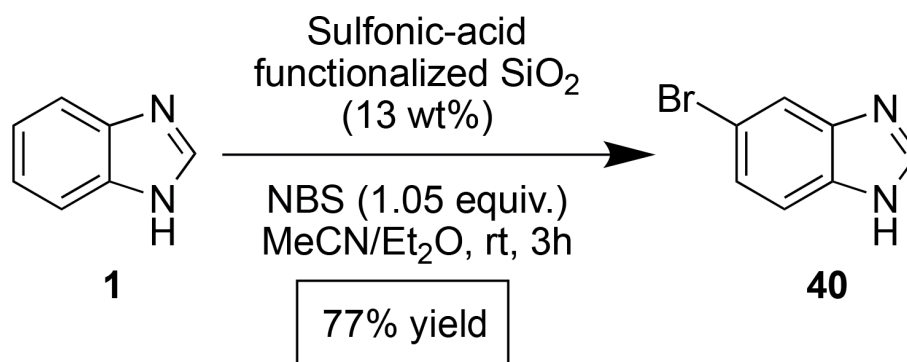
Figure 15.
Heterogeneously catalyzed C-5 bromination by functionalized silica.
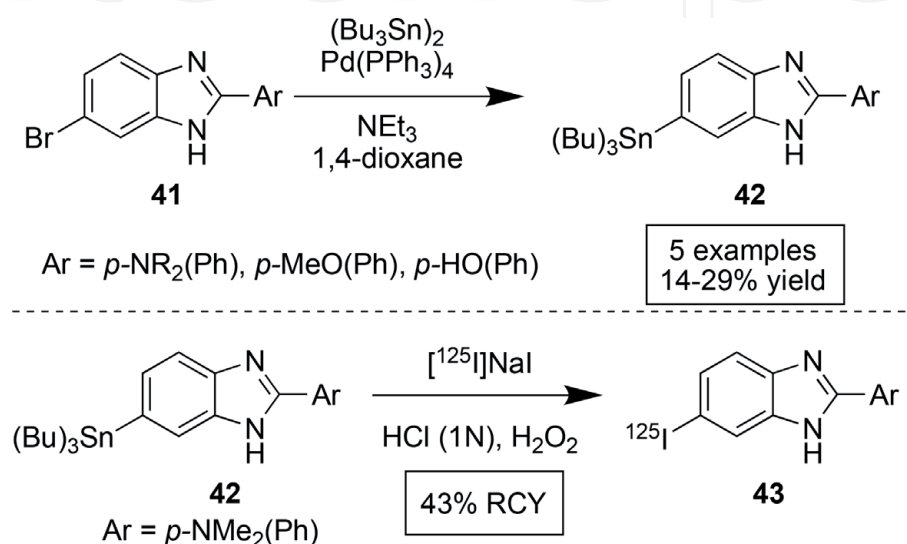
Figure 16.
Pd-catalyzed stannylation and subsequent radioiodination at C-5/C-6.

[30], alkynylation (Hiyama coupling) [31], and heteroarylation (Suzuki-Miyaura coupling) [32], thus demonstrating that a variety of combinations of halogens and cross-coupling chemistries are possible for synthesis of diverse benzimidazoles.

3. Conclusions

The need for new benzimidazoles with unique appendages and well-defined regioselectivity is undeniable from the viewpoints of medicinal and materials chemistry. The numerous applications, some of which are described herein, warrant further studies into the synthesis of novel analogues. This chapter has described the role of state-of-the-art catalytic chemistry in intermolecular functionalization of de novo assembled benzimidazole scaffolds. Particularly well developed are functionalizations at nitrogen and at position C-2 in the scaffold. *N*-Arylation and vinylations are effectively mediated by copper catalysts, whereas C-2 functionalization can be affected by a wider spectrum of palladium, rhodium, nickel, and cobalt catalysts involving direct C—H activation chemistry. A key success factor in enabling these chemistries has been the fine-tuning of ligand properties in the various catalytic systems. Functionalization of positions C-4 through C-7 is more challenging as these are less activated and less chemically distinguishable, so the use of pre-functionalization by de novo installment of halogens followed by contemporary cross-coupling chemistries is the most successful strategy to date. Even more

powerful methods are anticipated to emerge in this area to make these positions also available for selective late-stage functionalization through direct C—H activation.

Acknowledgements

Conflict of interest

The authors declare no conflicts of interest.

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