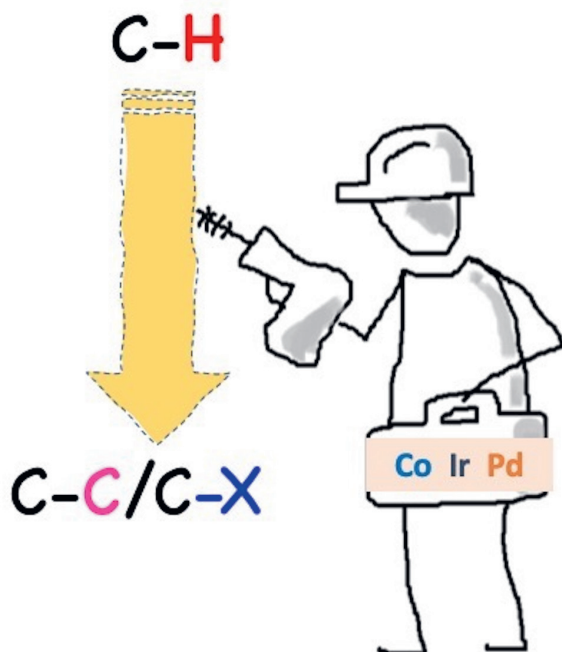


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PRASAD ANASPURE

# NOVEL STRATEGIES FOR C-C/X BOND FORMATION



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## **Novel strategies for C-C/X bond formation**





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FORMATION**

**PRASAD ANASPURE**

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**Novel strategies for C-C/X bond formation**

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## Abstract

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The formation of C-C/X bonds is essential for the manufacture of a broad range of chemicals and materials used in areas critical for maintaining quality of life in modern society, e.g. pharmaceuticals, agrochemicals and polymers, and for aspects of research in organic chemistry. The use of catalysts for facilitating these reactions is highly desirable due to the improvements in energy and atom economies that can potentially be achieved.

The primary objective of the thesis was to explore novel approaches for catalysis of C-C/X bond-forming reactions, both through C-H activation. In paper I, a tunable cobalt catalyzed C-H activation-driven annulation of benzamides with unsymmetrical diynes was developed, where either 3- or 4-substitution of the isoquinolone could be steered by the nature of the diyne used. An unprecedented iridium catalyzed tandem bis-arylsulfonylation of indoles was described (paper II), where an adamantoyl sacrificial directing group plays a key role in the simultaneous direction of arylsulfonylation to the 2- and 4- positions. In paper III, a flow reactor in a lab-on-a-chip device was developed for the Suzuki cross-coupling reaction. Miniaturization provides the opportunity to reduce material consumption. Polyethyleneimine (PEI)-brushes were used for the immobilization of Pd-nanoparticles, and high efficiencies were observed. Collectively, the research underpinning this thesis provides new strategies for C-C and C-X(S) bond formation.

Keywords: annulation, C-H activation, heterocycles, heterogeneous catalysis, homogeneous catalysis, lab-on-a-chip, Suzuki cross-coupling.



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# Populärvetenskaplig sammanfattning

Kemiska reaktioner som leder till bildandet av nya bindningar till kolatomer spelar en avgörande roll för att framställa material (till exempel plaster) och ämnen (till exempel läkemedel och jordbrukskemikalier) som behövs för att upprätthålla och om möjligt förbättra vår levnadsstandard. Dessutom är utvecklingen av nya, och framför allt hållbara, metoder för att snabbt, enkelt och miljövänligt skapa kolbindningar viktig inom organisk kemi och närliggande vetenskapsgrenar. Mot denna bakgrund behandlas två viktiga aspekter i denna avhandling och i båda fallen kan en bredare tillämpning av metoderna ha en positiv inverkan på utveckling och tillverkning av nya material och ämnen av betydelse för samhället.

I **arbete I** och **II** studerades nya sätt att bilda bindningar till kolatomer genom att utnyttja metallerna kobolt och iridium som katalysatorer. En katalysator påskyndar en kemisk reaktion utan att själv förbrukas och gör det möjligt att utföra reaktionen under milda betingelser. I **arbete I** utvecklades en koboltkatalyserad reaktion där man genom att anpassa storleken av ett av startmaterialen kan styra vilken av flera möjliga produkter som bildas. I **arbete II** utvecklades en metod för att i ett steg skapa två nya kol-svavelbindningar till den kemiska strukturen indol, en central byggsten i många biologiskt aktiva ämnen. Här användes iridium som katalysator.

För att minska mängden material och lösningsmedel som går åt vid en kemisk reaktion är miniatyrisering ett alternativ. Detta undersöktes i **arbete III** där Suzuki-reaktionen, ytterligare en metod för bildande av kolbindningar vilken belönades med Nobelpriset i kemi 2010, kunde utföras i en extremt liten flödesreaktor genom att fästa nanopartiklar av katalysatorn palladium på ett guldchip täckt av mikroskopiska plaststrån.

Sammanfattningsvis har avhandlingsarbetet lett till nya verktyg för att på ett mer hållbart sätt skapa bindningar till kolatomer vilket är av stor betydelse vid framställning av material och kemikalier.

# List of Abbreviations

2D NMR	Two-dimensional nuclear magnetic resonance
CMD	Concerted metalation-deprotonation
DCM	Dichloromethane
DME	Dimethyl ether
DMF	<i>N,N</i> -Dimethylformamide
HMBC	Heteronuclear multiple bond correlation
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
mmol	millimoles
PEI	Polyethylenimine
QCM	Quartz crystal microbalance
RAIRS	Reflection absorption infrared spectroscopy
SEM	Scanning electron microscope
TFE	2,2,2-Trifluoroethanol
TON	Turnover number
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction



# List of Publications

This thesis is based upon the following papers, which shall be referred to in the text by their roman numerals:

- I. **Anaspure, P.**; Dhillon, P.; Wiklander, J.G.; Kathiravan, S.; Nicholls, I.A.  
Diyne-steered switchable regioselectivity in cobalt(II)-catalysed C( $sp^2$ )-H activation of amides with unsymmetrical 1,3-diynes  
*Submitted* (2022).
- II. Kathiravan, S.; **Anaspure, P.**; Zhang T.; Nicholls, I.A.  
Tandem iridium-catalyzed decarbonylative C-H activation of indole: Sacrificial electron-rich ketone-assisted bis-arylsulfonylation  
*Organic Letters* (2021) 23, 3331-3336. (DOI: 10.1021/acs.orglett.7b02119)
- III. **Anaspure, P.**; Suriyanarayanan, S.; Nicholls, I.A.  
Palladium nanoparticles immobilized on polyethylenimine-derivatized gold surfaces for catalysis of Suzuki reactions: development and application in a lab-on-a-chip context  
*RSC Advances* (2021) 11, 35161-35164. (DOI: 10.1039/D1RA06851B)

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Additional works outside the scope of this thesis:

Kathiravan, S.; **Anaspure P.**  
Rhodium catalyzed intermolecular C-H/N-H annulation with alkynes through electrochemical anodic oxidation under metal oxidant/additive free conditions  
*Manuscript* (2022)

Chittimalla S.K.; Koodalingam, M.; Gadi, V.K.; **Anaspure, P.**  
 $\alpha$ -Halogenation as a strategy to functionalize cyclohexa-2,4-dienones  
*Synlett* (2017), 28, 475-480. (DOI: 10.1055/s-0036-1588359)

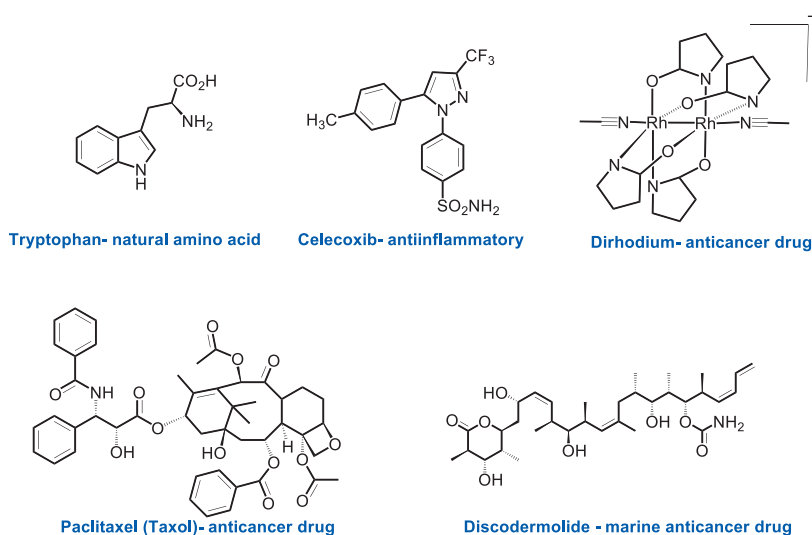
Kudale, A.; **Anaspure, P.**; Goswami, F.; Voss M.E.  
Asymmetric synthesis of 2-substituted cyclic amines  
*Tetrahedron Letters* (2014) 55, 7219-7221. (DOI: 10.1016/j.tetlet.2014.11.022)

# Chapter 1 – Introduction

## 1.1 Making of C–C bonds

### 1.1.1 The importance of the C–C bond

The formation of C-C single bonds is of fundamental importance in synthetic organic chemistry.<sup>1-3</sup> C-C bond forming reactions are not only central in the synthesis of many bioactive compounds but also important in the production of various chemical feedstocks used in pharmaceutical and plastic production.<sup>4,5</sup> Although there is an ever-growing number of methods available for carbon-carbon bond formation,<sup>6-12</sup> more are needed. While several reactions can construct C-C bonds, only a few have proven robust.<sup>13</sup> Furthermore, many organic molecules can contain a diverse range of functional groups making the creation of specific new C-C bonds a challenge and necessitating more high precision methods (Figure 1), and finding environmentally friendly pathways to convert crude carbon sources into useful materials is a real challenge.



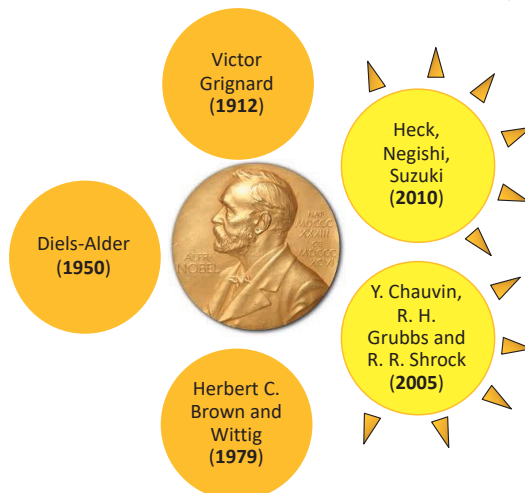
*Figure 1. Common examples of bioactive compounds*

Synthetic organic chemistry deals with many complex molecules that are synthesized from starting materials having specific functional groups. The process of installing or converting these specific functional groups is challenging since it can involve multiple reactions and tedious purification steps. Direct functionalization of C-H bonds could provide a good alternative, due to their omnipresence, and the potential of such strategies to be more environmentally friendly and cost-effective. In this context, the transition-

metal-catalyzed C-H functionalization can offer a green alternative by avoiding multiple steps and the formation of undesired side products during the synthesis, and it has had a significant impact on drug discovery and the pharmaceutical, chemical and material industries.<sup>14-17</sup>

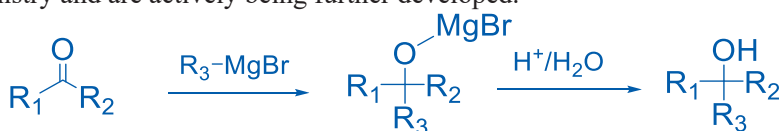
### 1.1.2 Some strategies for C–C bond formation

Over the past century, the importance of carbon-carbon bond construction has driven major advances in organic synthetic methodology, as has been recognized in the award of several Nobel Prizes in Chemistry, Figure 2.



**Figure 2.** Nobel Prizes awarded for catalytic (yellow) and non-catalytic (orange) carbon-carbon bond forming reactions

In 1912, Victor Grignard shared the Nobel Prize in Chemistry for the discovery of the Grignard reagent together with Paul Sabatier for discovering nickel catalyst to hydrogenate organic compounds in the presence of finely disintegrated metals. Today Grignard reagents still find use in synthetic chemistry and are actively being further developed.<sup>18-20</sup>



**Scheme 1.** Grignard reaction

The 1950 Nobel Prize in Chemistry was awarded jointly to Otto Diels and Kurt Alder “for their discovery and development of the diene synthesis”. Diels and Alder demonstrated the first example that shows the cycloaddition reaction between a conjugated diene and an alkene without the use of any external

chemical reagent. The importance of this reaction is reflected in its broad use in industry and synthesis in general.<sup>21-24</sup>



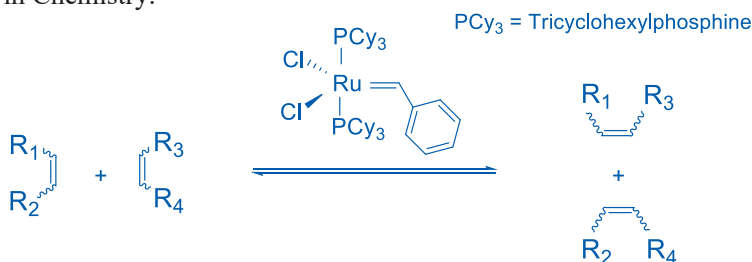
**Scheme 2.** Diels-Alder reaction of 1,3-butadiene and ethene

In 1979 Herbert C. Brown and George Wittig shared jointly the Nobel Prize “for their development of the use of boron- and phosphorous-containing compounds respectively, into important reagent in organic synthesis”. The Wittig reaction occurs between an aldehyde or a ketone and triphenyl phosphorus ylide to form an alkene as the desired product. The reaction is important for the specific introduction of the carbon-carbon double bond, which is extensively used in pharmaceuticals and in the synthesis of complex organic substances.<sup>25-28</sup>



**Scheme 3.** Wittig reaction between a methyl ketone and methylenetriphenylphosphorane

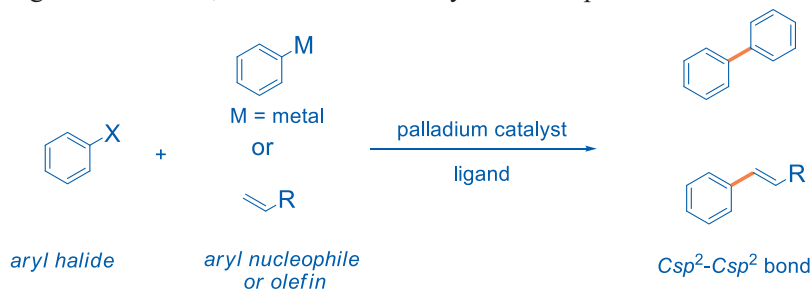
The olefin metathesis reaction is an important tool for rearranging carbon-carbon double bonds catalytically, and therefore sustainably. For this, Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock shared the 2005 Nobel Prize in Chemistry.



**Scheme 4.** Chauvin, Grubbs, and Shrock’s work exemplified using the Ru-catalyzed reaction of two olefins<sup>29</sup>

The 2010 Nobel Prize in Chemistry was awarded jointly to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki. Specifically, this was “for palladium-catalyzed cross couplings in organic synthesis”. The Heck reaction involves reactions of alkenes with aryl or alkenyl halide electrophiles.<sup>30</sup> The Negishi reaction is used with organozinc compounds.<sup>31</sup> The Suzuki-Miyaura cross-coupling,<sup>32</sup> in which aryl electrophiles and aryl boronic acids are joined using transition-metal catalysis, is a powerful tool for the construction of C-C bonds.

The discoveries made by these three scientists have led to the development of new drugs and materials, and are used in many industrial processes.<sup>33-35</sup>



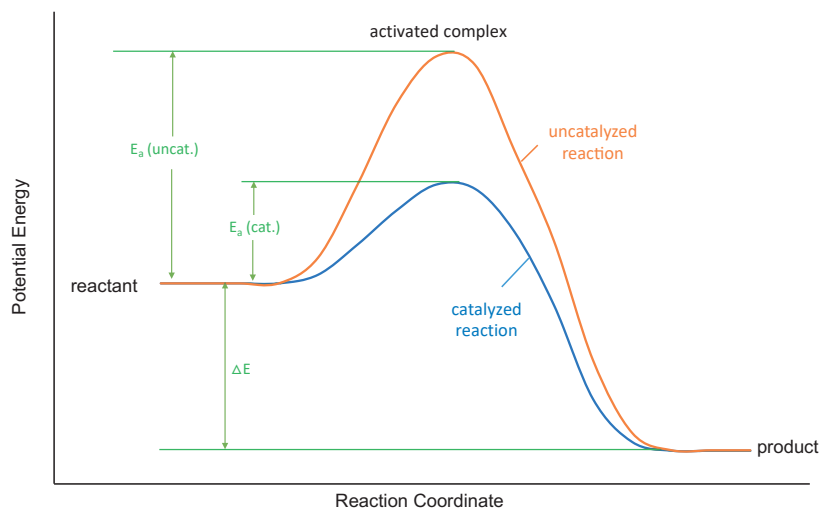
*Scheme 5. Summary of the Heck, Negishi, and Suzuki reactions*

## 1.2 Catalysis

### 1.2.1 Concept

The concept of catalysis was first introduced by the Swedish chemist J. J. Berzelius in 1835.<sup>36</sup> A catalyst is a substance that accelerates the rate of a chemical reaction without being consumed in the process.<sup>37</sup> Catalysis is important for modern chemical processes as it can potentially provide a desired product, using fewer resources and generating less waste.<sup>38</sup> Moreover, from the perspective of the catalyst, it can be described as a cyclic process in which the catalyst participates, is recovered and then returned to its original form at the end of the cycle.

The catalyzed pathway has lower activation energy ( $E_a$ ) due to which the reaction rate of the catalyzed reaction is faster than for the uncatalyzed reaction. However, the difference between the energy of the reactants and products is not affected by the catalyst (Figure 3).<sup>39</sup>



*Figure 3. An energy profile showing the influence of a catalyst*

The demands on the chemical industry have driven the development of catalytic technologies. More than 80% of all products are manufactured using a catalytic process and this percentage is increasing. This highlights the importance of catalysis not only economically but on society in general.<sup>40</sup> Moreover, the demand for new robust and efficient catalysts is important for many technical innovations.<sup>40</sup> In general, reactions can be controlled based on temperature, concentration, pressure, and time. From a sustainability perspective, while raising temperature and pressure will enable stoichiometric reactions to proceed at a reasonable rate, such conditions are less economically viable due to energy demands and in some cases are not suitable due to undesirable side reactions or the thermal stability of compounds. Catalysts offer the possibility of accelerating a reaction at lower temperatures and pressures, with the advantages this can afford.

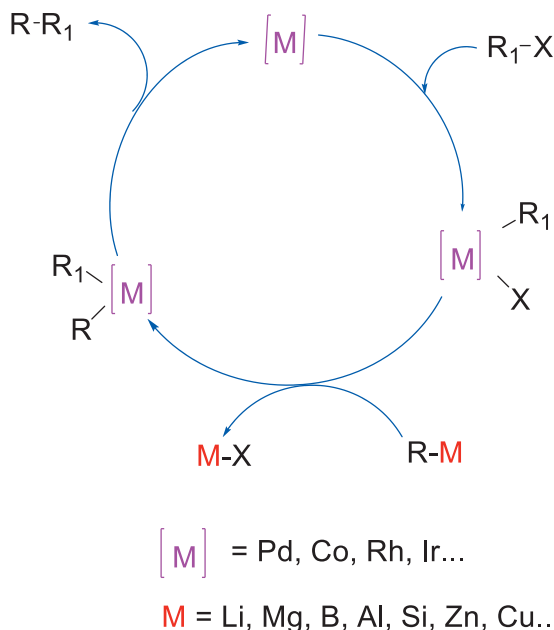
### 1.2.2 Catalysis of C–C bond formation

Methods for the catalysis of carbon-carbon forming reactions are very powerful chemical tools for synthesis. The transition metals provide the basis for a wide range of catalysts for C-C bond formation,<sup>41</sup> as reflected in the recent award of Nobel Prizes in chemistry as presented above (1.1.2.). In addition to these, there are a variety of techniques for carbon-carbon bond formation, examples of which are summarized briefly below.<sup>42-45</sup>

## Cross-coupling reactions

A class, cross-coupling reactions afford carbon-carbon (or carbon-heteroatom) bonds through the combination of an organometallic reagent with an organic electrophile in the presence of a metal catalyst. Many different types of electrophiles and metal complexes have been explored,<sup>46</sup> and this class of reaction is well used in industrial contexts.<sup>46</sup>

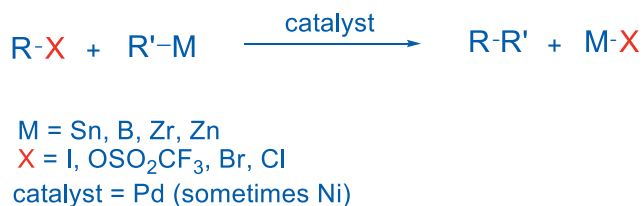
A general catalytic cycle for a cross-coupling reaction is shown in Figure 4.



*Figure 4. General catalytic cycle for cross-coupling reactions*

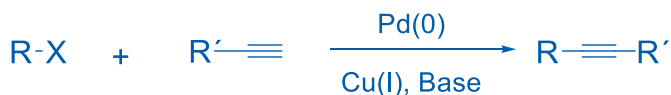
Generally, the reaction proceeds with oxidative addition and transmetalation followed by reductive elimination. The oxidative addition step is frequently considered the rate-determining step in the catalytic cycle. Below, some noteworthy C-C bond-forming cross-coupling reactions are presented

**Stille coupling:** The Stille reaction is a palladium using C-C bond formation which involves the coupling of an organic halide with an organotin compound. The Stille reaction can be considered an alternative to the Suzuki reaction.<sup>47</sup>



*Scheme 6. Stille coupling*

**Sonogashira coupling:** The Sonogashira reaction is the palladium-catalyzed cross-coupling of aryl or vinyl halides with terminal alkynes to generate conjugated enynes and aryl alkynes in presence of a copper(I) co-catalyst, using an amine as a base.<sup>48</sup>



*Scheme 7. Sonogashira coupling*

**Cadiot-Chodkiewicz coupling:** This is a widely used Cu(I)-catalyzed coupling for the synthesis of 1,3-diynes. During this reaction, a terminal-alkyne and a haloalkyne are coupled to afford the 1,3-diyne or di-alkyne.<sup>49</sup>



*Scheme 8. Cadiot-Chodkiewicz coupling*

**Kumada reaction:** This is a cross-coupling reaction analogous to the Grignard reaction, through using an organic halide.<sup>50</sup>



X, X' = Cl, Br, I, OTf

M = catalyst (usually based on Ni or Pd complexes)

*Scheme 9. Kumada coupling*

**Hiyama coupling:** This is another palladium-catalyzed cross-coupling reaction that uses organosilanes with organic halides to form carbon-carbon bonds.<sup>50</sup>



R: aryl, alkenyl or alkynyl

R': aryl, alkynyl, or alkyl

R'': Cl, F, or alkyl

X: Cl, Br, I, or OTf

F<sup>-</sup>: fluoride ion

B: base

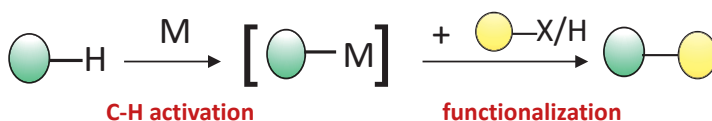
*Scheme 10. Hiyama coupling*



### 1.2.3 Catalysis of C–C bond formation through C–H activation

C-H bonds are ubiquitous in the organic molecular frameworks. Selective catalytic C-H bond cleavage is necessary for achieving shorter synthetic routes and shorter reaction times with less by-product generation.

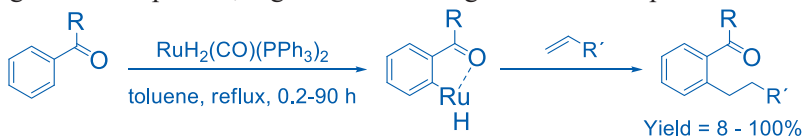
C-H activation and C-H functionalization are two terms that are often used interchangeably in the literature.<sup>51,52</sup> Though, more specifically, direct transformations of C-H bonds into C-[M] bonds is referred to as C-H activation and the term C-H functionalization is used to refer to the overall transformation of a C-H bond into a C-X bond *via* a C-[M] bond (Scheme 11).<sup>53</sup>



*Scheme 11: C-H activation and C-H functionalization*

C-H bond functionalization has undergone explosive growth in recent years, addressing several applications from organometallic chemistry to applications in the synthesis of complex natural products. Metal-catalyzed C-H bond activation followed by C-C bond formation has become a powerful tool for synthesis, *e.g.* for bioactive compounds.<sup>14,16,17,54-56</sup>

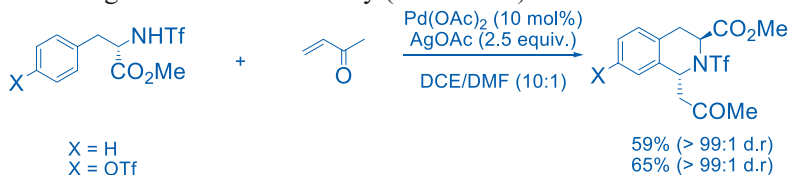
Although there have been many examples of stoichiometric C-H bond cleavage reactions using precious metals over the years, the catalytic versions remained undeveloped until more recently.<sup>57,58</sup> In 1993 Murai *et al.* reported the direct addition of C-H bonds of aromatic ketones to olefins in the presence of the catalytic amount of carbonyl(dihydro)tris(triphenylphosphine)ruthenium(II) [RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub>].<sup>59</sup> Since then, numerous examples of C-H bond activation have been reported. For example (Scheme 12), the ruthenium *ortho*-chelation assisted aromatic C-H bond activation reaction proceeds without the use of halogenated compounds, organic boron or organic metal compounds.<sup>59</sup>



*Scheme 12. Ortho-chelation assisted aromatic C-H bond activation*<sup>59</sup>

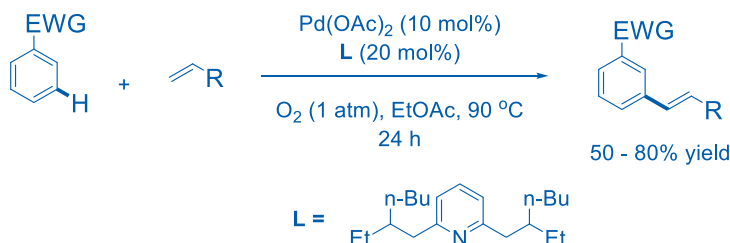
Pd-catalyzed C-H bond functionalization is a powerful technique for use with arenes and alkanes and Pd is the most widely used metal due to its tolerance of different functional groups.<sup>60</sup> In a seminal study, triflamide-directed Pd-catalyzed C-H activation and alkenylation were described by Yu *et al.* where 50-65% monoalkenylated products were obtained using a wide range of substrates. When tandem C-H alkenylation and the aza-Michael reaction were

performed using vinyl ketones, tetrahydroisoquinolines were obtained in good yield with higher diastereoselectivity (Scheme 13).<sup>60</sup>



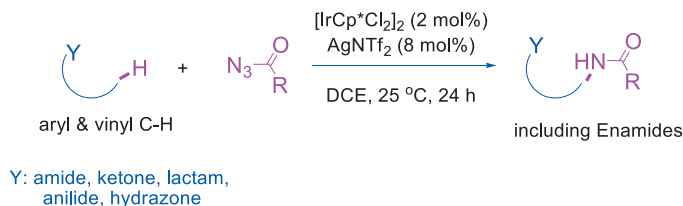
**Scheme 13.** Pd-catalyzed triflamide-directed C-H activation and alkenylation reaction<sup>60</sup>

Another noteworthy contribution by Yu *et al.* was the Pd-catalyzed olefination of arenes containing strongly electron-withdrawing groups (EWG) using 2,6-dialkylpyridines as ligands (Scheme 14).<sup>61</sup> This work opened the door for the next step towards the reaction of electron-poor arenes. This reaction offered the major desired product which was used as a valuable precursor in medicinal chemistry.



**Scheme 14.** Pd-catalyzed olefination of EWG containing arenes<sup>61</sup>

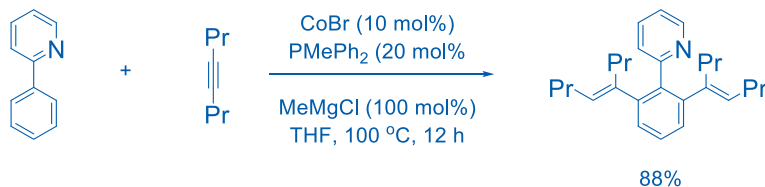
Chang *et al.* described iridium-catalyzed direct C-H amidation of arenes and alkenes using acyl azides. This novel approach utilized acyl azides as the nitrogen donor of an acyl amino group (Scheme 15).<sup>62</sup>



**Scheme 15.** Ir-catalyzed C-H amidation of arenes/alkenes<sup>62</sup>

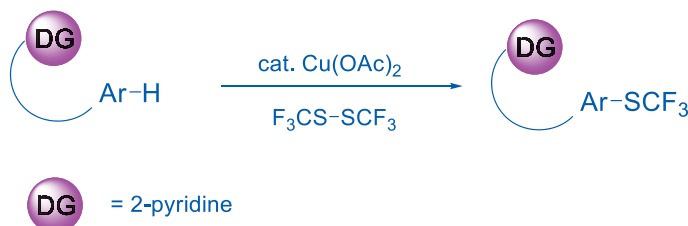
Cobalt, a highly abundant transition metal, has also widely been used for chelation-assisted functionalization of C-H bonds. In 1995, Murahashi described the *ortho*-carbonylation of azobenzene using  $\text{Co}_2(\text{CO})_8$ . The reaction proceeds via cobalt-mediated cyclometalation followed by CO insertion.<sup>63,64</sup> In 1994 Kisch reported the first example of cobalt-catalyzed hydroarylation of alkynes.<sup>65</sup> Yoshikai *et al.* have shown effective hydroarylation of alkynes with various C-H bonds using cobalt catalyst, ligand, stoichiometric reductant, and

in some cases additives. More recently, in 2014 Yoshikai *et al.* successfully afforded a 2-fold-syn-alkynylated product with a variety of alkynes by employing CoBr, PMePh<sub>2</sub> (as a ligand), and MeMgCl (as reductant) (Scheme 16).<sup>55</sup> Apart from seminal work by Yoshikai,<sup>66</sup> other groups such as Nishimura,<sup>67,68</sup> and Ackermann<sup>69</sup> have also made an impressive contribution to this field.



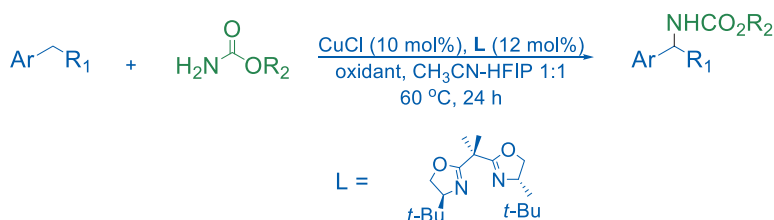
**Scheme 16.** Hydroarylation of alkynes with 2-arylpyridine and ortho C-H functionalization reactions<sup>55</sup>

Over the past years, copper salts have found wide use as catalysts of C-H activation reactions.<sup>70-74</sup> As early as 1995, Fujiwara *et al.* reported an aminomethylation of gaseous alkanes through C-H bond activation.<sup>75</sup> Very recently Daugulis *et al.* reported sulfenylation of benzamide  $\beta$ -C-H bonds and benzylamine derivative  $\gamma$ -C-H bonds promoted by copper (II) catalyst (Scheme 17).<sup>76</sup>



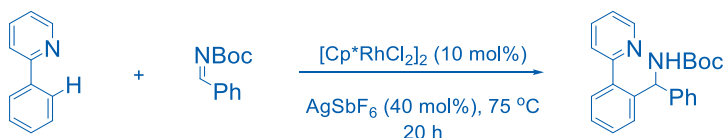
**Scheme 17.** Copper promoted arylsulfenylation of  $sp^2$  C-H bonds<sup>76</sup>

Very recently Landais *et al.* developed a Cu-catalyzed C-H amination of benzylic carbamates that leads to C-N bond-formation using Cu(I)/diamine ligand and NFSI ((PhSO<sub>2</sub>)<sub>2</sub>NF or FTEDA-PF<sub>6</sub> as oxidant (Scheme 18).<sup>77</sup>



**Scheme 18.** Copper-catalyzed C-H amination of benzylic carbamates leads to C-N bond formation<sup>77</sup>

In 1973, the Nobel Prize in Chemistry was awarded jointly to Geoffrey Wilkinson and E. O. Fischer for pioneering work in organometallic chemistry.<sup>78</sup> Work on complexes containing phosphorus-based ligands led to the discovery of  $[\text{RhCl}(\text{PPh}_3)_3]$ , commonly known as Wilkinson's catalyst.<sup>78,79</sup> Rhodium is one of the most widely used catalysts for C-C bond forming reactions *via* C-H activation because it tolerates functional groups under a wide variety of synthesis conditions. Since then, many Rh-catalyzed methods for heteroatom-directed C-H bond functionalization have been reported.<sup>80,81</sup> As an illustration of the state-of-the-art, Ellman *et al.* presented the first rhodium-catalyzed arylation of imines *via* C-H bond functionalization that provides a novel method for C-C bond formation (Scheme 19).<sup>82</sup>



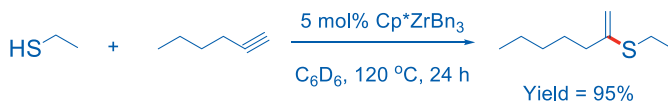
**Scheme 19.** First Rh-catalyzed arylation of imine *via* C-H bond functionalization

Another interesting element is manganese (Mn), which in some cases can provide sustainable catalysis due to its specific reactivity, low price, low toxicity, and availability.<sup>83</sup> The first example Mn-catalyzed allene hydroarylation and cascade cyclization was documented by Rueping.<sup>84</sup> Very recently, White *et al.* explored a Mn-catalyzed regioselective and chemoselective oxidative  $\text{C}(\text{sp}^3)$ -H methylation method which may find application in drug and natural product synthesis.<sup>85</sup>

### 1.2.4 Formation of C-S bonds

While C-C bonds are a major focus for C-H activations, C-X bonds, where X is a heteroatom, are also of significant importance.<sup>14,86,87</sup> Of importance for this thesis is the construction of C-S bonds, which play an important role in the synthesis of natural products, biologically active compounds, functional materials, nano-materials and in pharmaceuticals. In this context, the recent development of efficient direct C-H functionalization to yield C-S bond *via* decarboxylative reactions is important.<sup>86</sup>

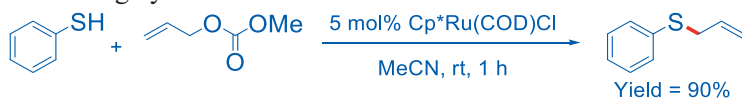
There are several ways by which generation of a carbon-sulfur bond can be achieved using transition metal catalysis, such as addition reactions involving nucleophilic sulfur reagents and electrophiles with carbon-carbon double bonds, triple bonds, or epoxides. Weiss *et al.* disclosed an organozirconium-catalyzed hydrothiolation of terminal alkynes, following Markovnikov's rule to afford vinyl sulfides with excellent yield (Scheme 20).<sup>88</sup>



**Scheme 20.** Organozirconium-catalyzed hydrothiolation of terminal alkyne

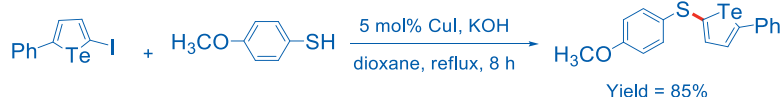
Another noteworthy strategy for making a C-S bond is a substitution reaction in which nucleophilic or electrophilic sulfur is involved.<sup>89</sup>

In 1999 Mitsudo *et al.* first investigated the Ru-catalyzed allylation of thiols to construct the corresponding sulfides (Scheme 21). In this reaction, thiol acts as a nucleophile that reacts with allyl methyl carbonate to provide the desired product with high yield.<sup>90</sup>



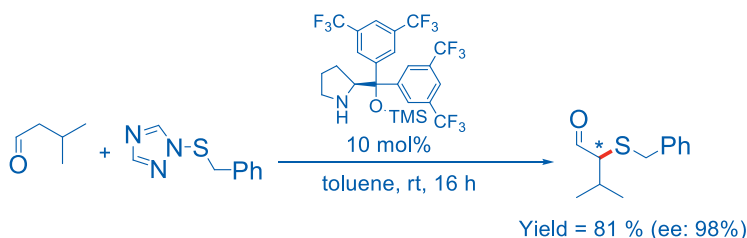
**Scheme 21.** Ru-catalyzed allylation of thiol to form allylic sulfides

Another important method employed for C-S bond formation is a metal-catalyzed cross-coupling reaction. For example, Zeni *et al.* described a Cu-catalyzed thiol cross-coupling reaction (Scheme 22). 2-iodo-5-phenyltellurophene reacted with 4-methoxybenzenethiol without any ligand in presence of CuI as a catalyst afford the corresponding product in excellent yield.<sup>91</sup>



**Scheme 22.** Cu-catalyzed thiol cross-coupling reaction

Sulfenylation is a reaction in which an electrophilic sulfur reagent reacts with a nucleophile to give the corresponding sulfide. Marigo *et al.* disclosed enantioselective  $\alpha$ -sulfenylation of aldehydes in presence of catalytic L-prolinol derivative in excellent yields as well as high enantioselectivities (Scheme 23).<sup>92</sup>



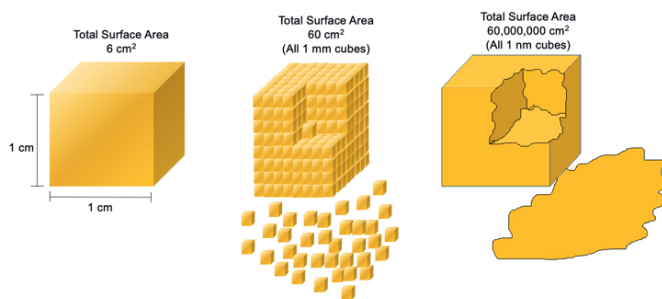
**Scheme 23.** Enantioselective  $\alpha$ -sulfenylation of aldehydes

## 1.3 Nano-structured materials

Nanostructured materials and nanotechnology are broad and interdisciplinary areas of research and development that have expanded explosively over the last decades. The high impact of this sector is reflected in number of products on the market.<sup>93,94</sup> Nanostructured materials can be defined as having dimensions in the range of 1 to 100 nm.<sup>95</sup> Nanostructured materials, such as nanoparticles,

nanowires, nanotubes, and thin films, provide a particularly useful platform in the field of catalysis and also for the successful development of wide-ranging therapeutic and diagnostic applications in biomedical science.<sup>96</sup>

In comparison with bulk materials, nanomaterials exhibit different physicochemical properties due to their high surface-to-volume ratios (Figure 5).<sup>94,97,98</sup> The high surface-to-volume ratios in nanostructures can enhance their reactivity, and catalytic activities.<sup>99,100</sup>



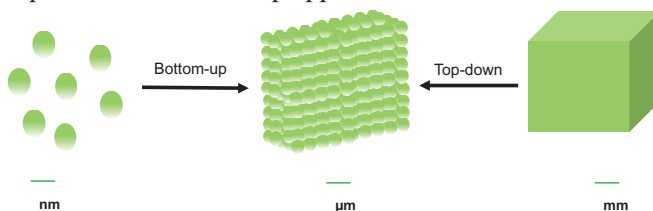
**Figure 5:** Illustration demonstrating the effect of the increased surface area provided by nanostructured materials.

### 1.3.1 Synthesis of nanomaterials

Different methodologies are available for the fabrication or synthesis of nanomaterials,<sup>101-104</sup> some of which are discussed below.

**The top-down approach** is used to fabricate nano-scale entities starting from larger entities (Figure 6).<sup>105</sup> It generally relies on physical processes – the combination of chemical, electrical or thermal processes. Top-down methods include crushing or high-energy milling, ion implantation, and lithography vapor deposition.<sup>105-107</sup> From an industrial point of view these types of approaches can be readily applied due to their relatively low cost, however, the main challenges are the broad particle size distribution or lack of scalability.

In contrast to top-down, **bottom-up** techniques start from smaller building blocks and assemble them to achieve a nanostructured material (Figure 6).<sup>102</sup> Examples of bottom-up methods include sol-gel, precipitation, electrical deposition, atomic layer deposition, and anodization.<sup>101</sup> Various researchers have also developed novel technologies to fabricate nanomaterials by combining top-down and bottom-up approaches.<sup>108-110</sup>



**Figure 6:** Bottom-up and top-down strategies to produce multifunctional nanomaterials

Due to their unique properties as well as their applications in different research fields, nanomaterials have attracted the attention in many fields of research.<sup>101,111,112</sup> In the last decades, nanomaterials have been used for many fascinating applications in the fields of catalysis,<sup>113-115</sup> sensors,<sup>116,117</sup> electronics,<sup>118</sup> drug delivery,<sup>119</sup> industrial lithography,<sup>120</sup> quantum devices,<sup>121</sup> and optical and biological devices.<sup>122</sup>

### 1.3.2 Nano-structured materials in catalysis

Recent years have witnessed tremendous growth in the field of catalysis using nanostructured materials due to sustainability demands. Catalysis allows chemical reactions to be performed under mild conditions, lower temperature and pressure, thereby saving energy, and even producing minimal waste when used for exploring alternative chemical feedstocks, and opening the door for new synthetic routes.

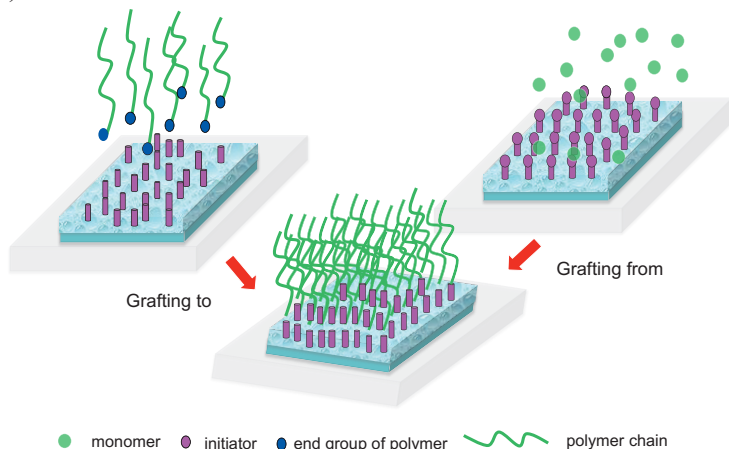
Catalysis can be divided into two main categories: homogeneous catalysis, where catalyst and reactants are in the same phase and heterogeneous catalysis is where catalyst and reactants are in different phases. Well-known chemical compounds such as mineral acids, and metal-ligand complexes are examples of highly efficient homogeneous catalysts. Heterogeneous catalysts, such as metal oxides, zeolites, and supported metals have also found wide applications in chemistry.<sup>123,124</sup> Heterogeneous catalysts can be easily separated from a reaction mixture, and are useful in flow-based reaction systems.<sup>125</sup> However, in a heterogeneously catalyzed reaction the amount of adsorbed catalyst can be a limiting aspect. Incorporating homogeneous catalysts into heterogeneous catalyst formats has led to the development of efficient immobilized molecular catalysts.<sup>126-131</sup>

### 1.3.3 Catalyst Immobilization

Catalysts are attached to solid supports either covalently, or by physisorption. Generally, covalent attachment<sup>132</sup> is preferred due to offering better stability, thus enhancing reusability and recyclability.<sup>133</sup> In addition, immobilization of catalyst on a surface or support enables applications in lab-on-a-chip or flow reactor contexts.<sup>134,135</sup> The types of solid supports, used are many, and range from include inorganic (e.g. zeolites, silica) to organic (polymers) substrates.<sup>128,136</sup> Polymer brushes can be used to efficiently immobilize some catalysts and can provide improvements in catalytic activity.<sup>137,138</sup>

Polymer brushes refer to structures where polymer chains are terminally tethered to a surface at a high density.<sup>139</sup> Polymer brushes generally demonstrate tolerance of high temperatures and extreme pH.<sup>139</sup> There are two main strategies

for generating polymer brushes namely “grafting to” and “grafting from” (Figure 7).<sup>140,141</sup>



**Figure 7:** Schematic illustration describing the “grafting-to” and “grafting-from” approaches

Polymers can be directly grafted onto a surface by a process called the “grafting-to” method *via* an ‘anchoring’ group. “Grafting to” is based on the chemical attachment of preformed polymer chains onto a substrate bearing functional groups suitable for coupling. The “grafting from” method uses surface-initiated polymerization where polymer chains grow from initiators anchored at the surface of the substrate. This method can be used to prepare polymer-supported catalysts with high grafting density. Although the preparation, characterization, processing techniques, and thermal, mechanic and electric properties of organic polymers have been extensively studied, only a limited number of examples of their applications in catalysis could be found in the literature,<sup>142-145</sup> indicating more efforts are needed to develop the organic polymer-supported catalysts.



## 1.4 Objectives of this thesis

With the importance of C-C and C-X forming reactions for society, and catalysis and miniaturization as approaches to developing more sustainable chemical processes, as a backdrop, the primary aim of this thesis was to explore novel strategies for the catalysis of reactions leading to C-C and C-X(S) reactions.

To achieve this objective, two aspects were targeted for investigation:

1. Exploring new types of catalytic C-C/(X)S bond-forming reactions that could provide access to more highly functionalized structures. This aspect is addressed in **Paper I** and **Paper II**.
2. Examining new materials for use in catalysis of C-C bond forming reactions in lab-on-a-chip formats. This aspect is addressed in **Paper III**.

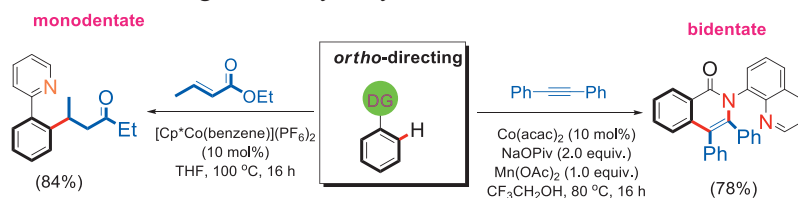
# Chapter 2 – Cobalt and Iridium catalysed C-C/C-S bond formation (Paper I and II)

## 2.1 Cobalt(II)-catalyzed C(sp<sup>2</sup>)-H activation of amides derived from 8-aminoquinoline

Cobalt (Co) is the most widely used first-row transition metal for C-H activation reactions.<sup>146-148</sup> This is due to a combination of its reactivity and its low cost, low toxicity and high abundance.<sup>69,149-152</sup> Numerous elegant works on Co-catalyzed C-H activation have been explored by researchers, highlighting the development of this research area.<sup>147,153-157</sup>

Recently, the potential of using 8-aminoquinoline as a chelating group in C-H activation reactions has been presented in several publications.<sup>155,158,159</sup>

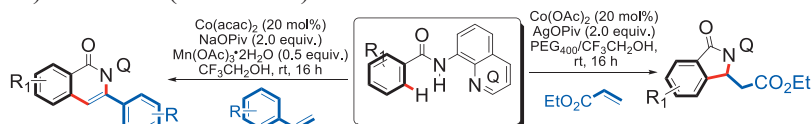
Matsunaga/Kanai and Daugulis independently demonstrated the unique catalytic activity of a Co-based catalytic systems (Scheme 24).<sup>160,161</sup> The former group explored the high valent Cp\*Co(III) complex to promote 2-arylpyridine coupling without the use of any additional reagents. Daugulis in 2014, developed a Co(II)-catalyzed functional group tolerant method using 8-aminoquinoline as a powerful bidentate directing group by synthesizing isoquinolones in good yield. After the successful development of these bidentate-directing Co-catalyzed C-H activation reactions, many other reactions were examined using this catalytic system.



**Scheme 24.** Co-catalyzed C-H activation using a monodentate and bidentate directing group as developed by Matsunaga/Kanai<sup>160</sup> and Daugulis<sup>161</sup>

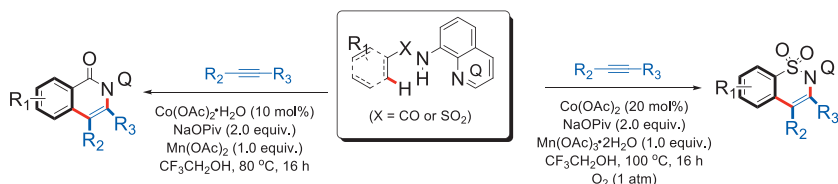
Daugulis in 2014, developed a Co-catalyzed C(sp<sup>2</sup>)-H bond functionalization using the 8-aminoquinoline moiety for the transformation of benzoic amides at room temperature using Mn(OAc)<sub>3</sub> as an oxidant, affording products in high yields (Scheme 25).<sup>162</sup> Later, Ackermann used the 8-aminoquinoline auxiliary for efficient Co-catalyzed oxidative C-H functionalization of electron-deficient

alkene using a mixture of polyethylene glycol (PEG 400) and trifluoroethanol (TFE) as solvent (Scheme 25).<sup>163</sup>



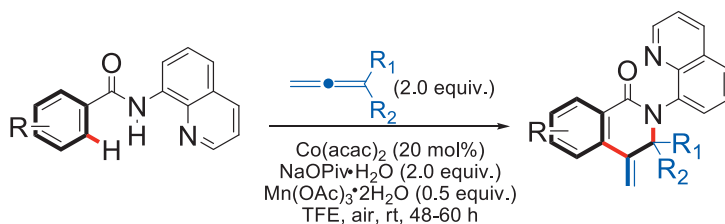
**Scheme 25.** Synthesis of isoquinolones<sup>162</sup> and isoindolinone<sup>163</sup> through Co-catalyzed C-H functionalization of amides with alkenes

Co-catalyzed aminoquinoline-directed C-H alkyne annulation was reported by Daugulis in 2014. In this work, he explored the alkyne annulation reaction using  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  as the catalyst,  $\text{Mn}(\text{OAc})_2$  as oxidant, and TFE as the solvent (Scheme 26).<sup>161</sup> Inspired by his work, Sundararaju *et al.* reported Co-catalyzed C-H/N-H annulation of aryl sulfonamide with terminal and internal alkynes using  $\text{O}_2$  as terminal oxidant and  $\text{Mn}(\text{III})$  as a co-catalyst (Scheme 26).<sup>164</sup>



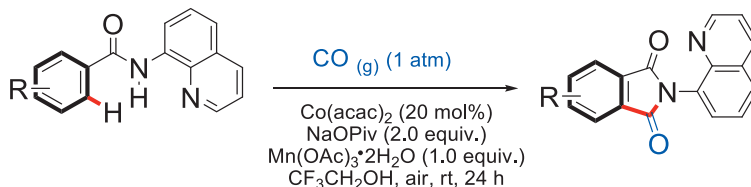
**Scheme 26.** Co-catalyzed C-H functionalization with alkynes as developed by Daugulis<sup>161</sup> and Sundararaju<sup>164</sup>

Recently, allenes have emerged as versatile coupling partners for Co-catalyzed C-H functionalization. A novel Co-catalyzed intermolecular heterocyclization reaction of arylamides with allenes was reported by Maiti in 2016 (Scheme 27).<sup>165</sup>



**Scheme 27.** Co-catalyzed C-H functionalization with allenes<sup>165</sup>

Carbon monoxide (CO) is widely exploited in transition metal catalysis for a wide range of applications in the construction of new C-C bonds as well as organic carbonyl compounds.<sup>166</sup> Daugulis in 2014, established a room temperature aerobic oxidative carbonylation of aminoquinoline benzamides using CO and Co(acac)<sub>2</sub> as a catalyst and Mn(OAc)<sub>3</sub> as the co-catalyst (Scheme 28).<sup>167</sup>

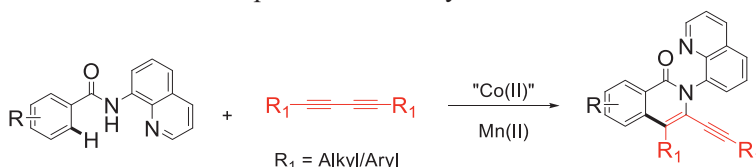


**Scheme 28.** Co-catalyzed C-H functionalization with carbon monoxide CO<sub>(g)</sub><sup>167</sup>

The recent introduction and growing number of examples of cobalt catalyzed C-C bond-forming reactions using aminoquinoline benzamides motivated our interest to explore this area.

## 2.2 Diyne-steered switchable regioselectivity in cobalt(II)-catalyzed C(sp<sup>2</sup>)-H activation of amides with unsymmetrical 1,3-diynes (Paper I)

The starting point for paper I was a paper published by our group in 2017 describing a robust and regioselective Co(II)-catalyzed C-H activation reaction between amides and symmetrical diynes (Scheme 29).<sup>168</sup> While the use of symmetrical diynes in this reaction offers two potential regioisomeric products, a dominant regioisomer was obtained, that with the residual alkyne present as a substituent in the 3-position of the isoquinolone. The possibility of using unsymmetrical diynes was a natural next step, despite the increased number of potential products (regioisomers) it could lead to. This led to the question, “what regiochemical outcomes are preferred and why?”.



**Scheme 29.** Aminoquinoline-directed C-H activation of benzamides using symmetrical 1,3-diynes as presented by Kathiravan et al.<sup>168</sup>

Determining which factors, steric and/or electronic, that influence the regiochemical outcome of these annulation reactions when using unsymmetrical 1,3-diynes, could potentially provide access to different isoquinolone substitution patterns (Figure 8).

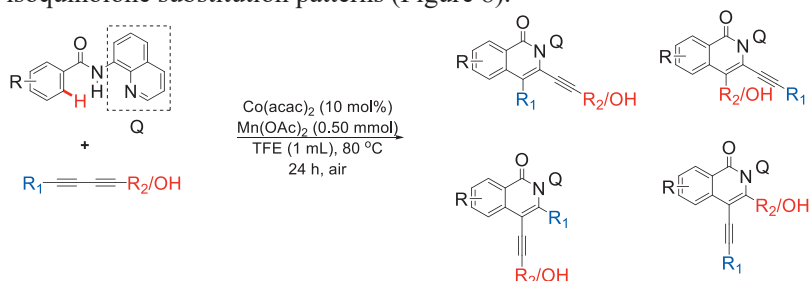
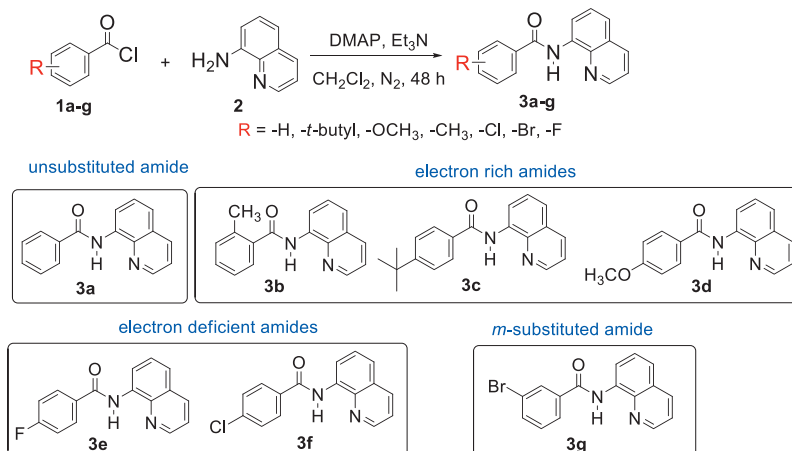


Figure 8. C-H activation reactions with unsymmetrical 1,3-diynes

## 2.2.1 Synthesis of benzamides

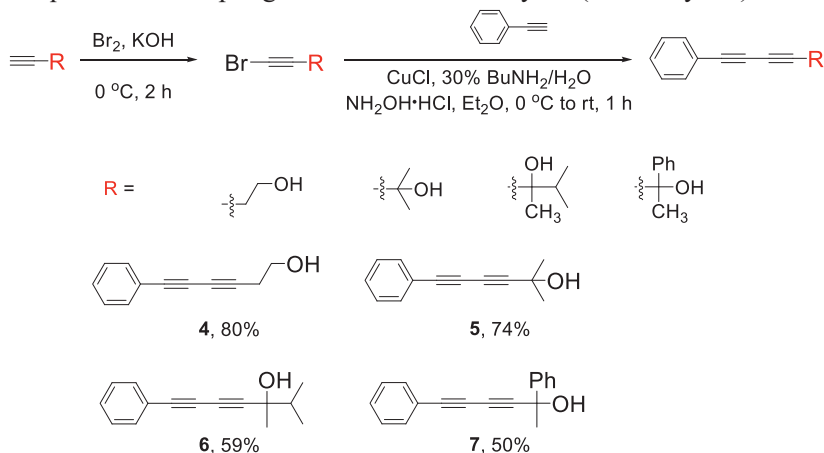
Benzamides (**1a-g**) bearing different substituents (Scheme 30) were tested for C-H activation/annulations. The amides were prepared following a standard reaction of the benzoic acid chloride with 8-aminoquinoline under nitrogen, in presence of *N,N*-dimethyl-4-aminopyridine (DMAP) and triethylamine ( $\text{Et}_3\text{N}$ ) in anhydrous  $\text{CH}_2\text{Cl}_2$ . After the workup and purification by flash column chromatography, the corresponding *N*-(quinolin-8-yl)benzamides were obtained in 85-95% yields.



Scheme 30. Synthesis of benzamides

## 2.2.2 Synthesis of unsymmetrical 1,3-diynes

Synthesis of the unsymmetrical diynes used in this study was achieved in two steps using a modification of the Cadiot-Chodkiewicz coupling reaction<sup>169</sup> (Scheme 31), where initial bromination (>95% yield) of a terminal alkyne and a subsequent cross-coupling affords the desired diynes (50-80% yield).



*Scheme 31. Synthesis of unsymmetrical 1,3-diynes used in this study*

## 2.2.3 C-H activation reactions

The C-H activation annulation reaction used was based upon that previously reported by our group.<sup>168</sup> Reaction of benzamides (**3a-g**) using 10 mol% of cobalt(II)acetylacetonate, 0.50 mmol of manganese(II)acetate as the external oxidant, 0.50 mmol of sodium trimethylacetate hydrate as base and 2,2,2-trifluoroethanol (TFE) as solvent. The reaction was carried out under air, at 80 °C for 24 h. In each case, the major regioisomer was isolated and purified by flash column chromatography or preparative thin layer chromatography, and characterized using 2D NMR, IR, HRMS and, where possible XRD.

## 2.2.4 HPLC-based yield determination

As the reaction resulted in complex mixtures due to the presence of minor isomers with similar chromatographic properties, an HPLC-based assay was proposed as a tool to directly determine the yield of the major isomer *in situ*, to avoid misinterpretation of reaction outcomes due to losses during purification. Pure samples of each of the major regioisomeric products were used to construct calibration curves (Figure 9), which were used to determine reaction yields from aliquots taken from reaction mixtures, and to confirm purity (Figure 10).

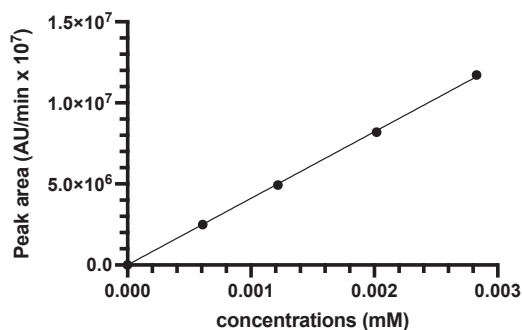


Figure 9. A typical calibration curve, in this case for **8d** (error bars are smaller than symbol size)

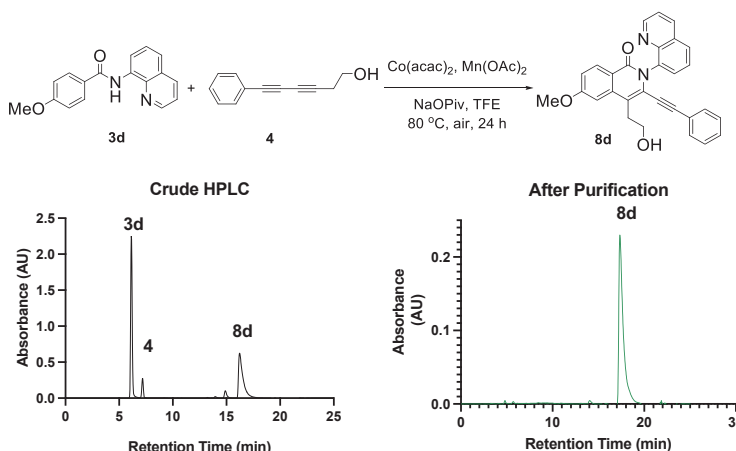


Figure 10. HPLC of **8d** before and after purification

### 2.2.5 Structure determination using XRD and 2D NMR

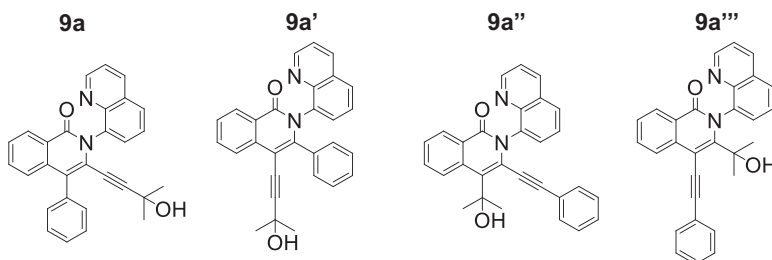
Determining the structure of the reaction products was achieved by 2D NMR and where possible XRD. There are two possible ways to identify the exact structure of the molecule including the identification of regioisomers.

**X-ray diffraction (XRD):** This is a powerful non-destructive technique widely used for the characterization of crystalline material. It provides information on structure, preferred crystal orientations, phases, and other crystal parameters. The limitations of this technique are the need for obtaining a substance in a homogeneous crystalline form, and the influence of crystal packing forces on conformations.<sup>170,171</sup>

**Two-dimensional nuclear magnetic resonance (2D NMR):** This is a highly effective technique for determining the structure of an unknown molecule. A range of 2D NMR techniques have been developed over the years, *e.g.* HMBC,

COSY, HSQC, NOESY, and ROESY.<sup>172</sup> HMBC (heteronuclear multiple bond correlation)<sup>173</sup> was used in this work for structure determination.

Below is an example of the HMBC spectrum (Figure 11) of the C-H activation product obtained from the reaction between benzamide **3a** and diyne **5**. There are four possible regioisomers, **9a**, **9a'**, **9a''**, and **9a'''**:



**9a** and **9a'** will have HMBC correlations between methyl protons and alkyne carbons whereas **9a''** and **9a'''** will have HMBC correlations between aromatic protons and alkyne carbons. The HMBC spectrum below confirms **9a** or **9a'** and rules out **9a''** and **9a'''**.

The HMBC pattern (Figure 11) also reveals the orientation of alkyne insertion. **9a** can be distinguished from **9a'** by the HMBC correlation between the *ortho*-protons (26, 30) on the phenyl ring and the carbon to which it is attached (8 or 9). In this case, the HMBC spectrum confirms structure **9a**.



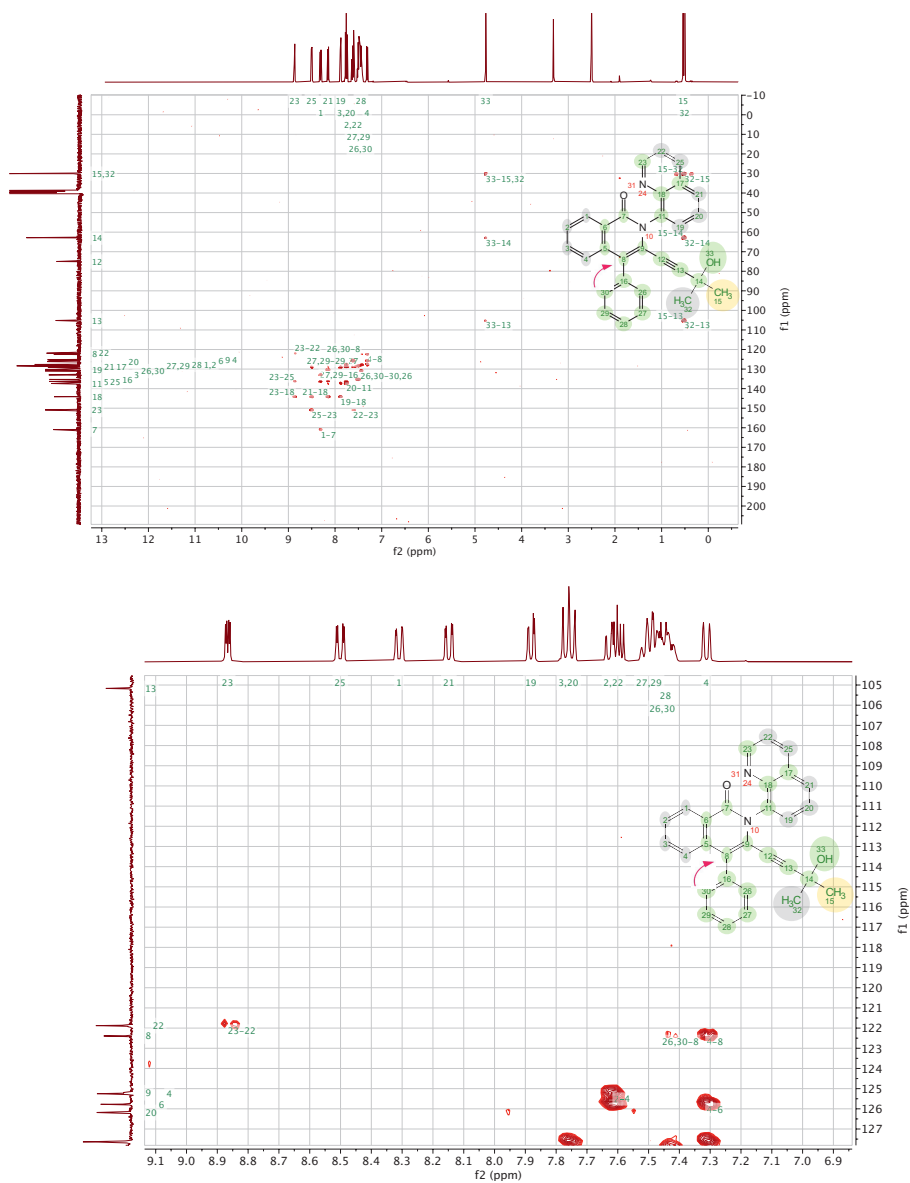
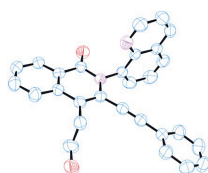


Figure 11. HMBC spectra of **9a**

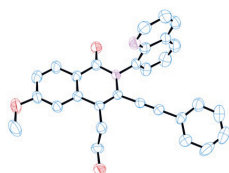
## 2.2.6 Scope of C-H activation

Table 1. Substrate scope with 1,3-diyne **3**

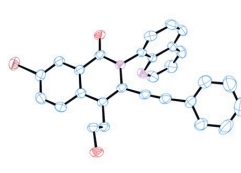
Entry	Amides (R)	Products ( <i>in-situ</i> yield)
1	H, <b>3a</b>	<b>8a</b> , 24±1.15
2	2-Me, <b>3b</b>	<b>8b</b> , 28±1.53
3	4- <i>t</i> Bu, <b>3c</b>	<b>8c</b> , 21±3.46
4	4-OMe, <b>3d</b>	<b>8d</b> , 54±2.52
5	4-F, <b>3e</b>	<b>8e</b> , 35±2.65
6	4-Cl, <b>3f</b>	<b>8f</b> , 31±2.00
7	<i>m</i> -Br, <b>3g</b>	<b>8g</b> , 7±2.08



ORTEP of **8a**  
CCDC - 2041992



ORTEP of **8d**  
CCDC - 2041960



ORTEP of **8g**  
CCDC - 2041961

Tables 1 and 2 summarize the HPLC assay-based *in situ* yields of the major regioisomers isolated from the C-H activation reaction between the various benzamides (**3a-g**) and the unsymmetrical 1,3-diynes (**4-7**).

Initially, we tested C-H activation reactions of a series of amides (**3a-3g**) with diyne **4** (Table 1) which exhibit less steric bulk than the symmetrical diyne used in our earlier work.<sup>168</sup> Interestingly, we observed the same preferred geometry for alkyne insertion when forming the annulated product as that previously described.<sup>168</sup> The reactions tolerated a range of benzamides. The highest yield was observed with the benzamides with strongly electron donating *para*-methoxy substituent (**8d**). A low yield was obtained when *meta*-bromo benzamide (**3g**). A low yield is argued to be due to the possibilities of obtaining 8 regioisomers as well as the steric effect provided by the bromo-substituent.

**Table 2.** Substrate scope with 1,3-diyne **3-5**

Entry	Amides (R)	1,3-Diynes	Products ( <i>in-situ</i> yield)
1	H, <b>3a</b>	<b>5</b>	<b>9a</b> , 40±1.73
2	2-Me, <b>3b</b>	<b>5</b>	<b>9b</b> , 43±1.53
3	4- <i>t</i> Bu, <b>3c</b>	<b>5</b>	<b>9c</b> , 47±2.00
4	4-OMe, <b>3d</b>	<b>5</b>	<b>9d</b> , 56±2.52
5	4-F, <b>3e</b>	<b>5</b>	<b>9e</b> , 22±4.36
6	4-Cl, <b>3f</b>	<b>5</b>	<b>9f</b> , 21±1.00
7	<i>m</i> -Br, <b>3g</b>	<b>5</b>	<b>9g</b> , 18±2.08
8	H, <b>3a</b>	<b>6</b>	<b>10a</b> , 32±4.51
9	H, <b>3a</b>	<b>7</b>	<b>11a</b> , 29±4.04

ORTEP of **9a**  
CCDC - 2041954

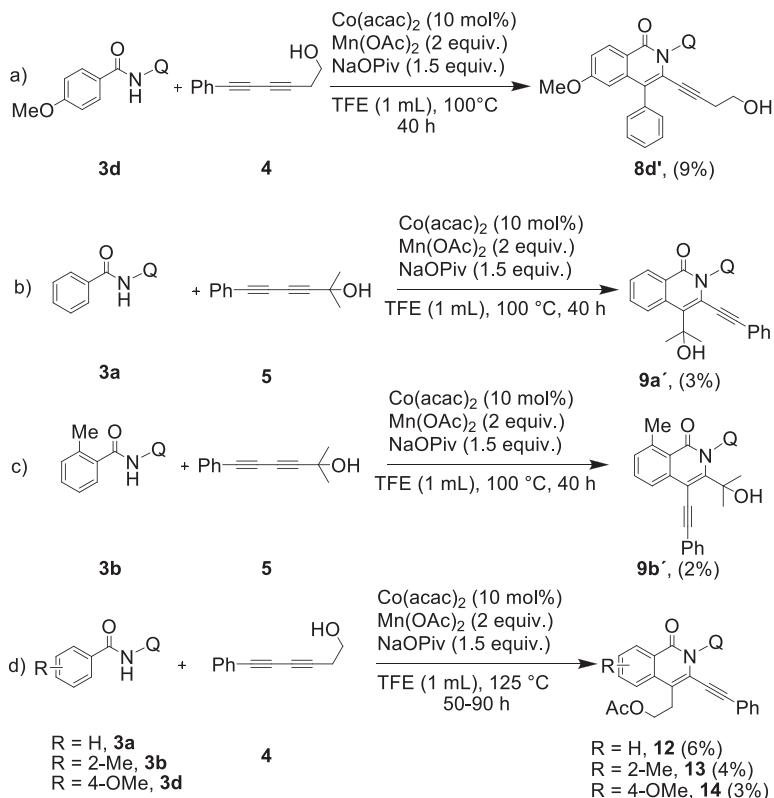
ORTEP of **9d**  
CCDC - 2042374

ORTEP of **9f**  
CCDC - 2041962

The scope of the C-H annulation reactions between benzamides (**3a-g**) and diyne **5**, that has a greater degree of steric bulk around the hydroxyl moiety (Table 2) was then explored.

Here it was found that the yields of the unsubstituted and the electron-rich amides were remarkably higher than those obtained with simpler diyne **4**. Again, we observed the alkynyl substituent of all the major isomers to be found *ortho* to the isoquinolone nitrogen. Surprisingly, however, was the regioselectivity of the annulation with respect to placement of the hydroxyl-containing substituent, which was reversed relative to that obtained using **4**.<sup>168</sup> Similarities were observed in relation to the highest yield for the strong electron-donating *para*-methoxy substituents (**3d**) and lower yields when using the *meta*-bromo substituent containing benzamide (**3g**).

Next, we explored the scope of C-H annulation reactions between **3a** and the even more sterically substituted diynes **6** and **7** and the preferred regiochemistry reflected that found when using diyne **5**, though with lower yields, which were attributed to the additional steric bulk of the hydroxyl containing substituent of the diyne.



*Scheme 32. Isolation of some minor regioisomers and acetylated byproducts*

When we have carried out some reactions at higher temperatures and longer reaction times (Scheme 32), the regiochemistry of the major isomers and their yields remained unchanged. The minor isomers were obtained with the levels that allowed isolation, and structure confirmation by 2D-NMR (Scheme 32, **8d'**, **9a'** and **9b'**). In some cases, the acetylated by-product was isolated using the least sterically hindered diyne **4** (Scheme 32, **12-14**).

## 2.2.7 Proposed mechanism for C-H activation

Initially, Mn(II) is oxidized to Mn(III) by atmospheric oxygen. Mn(III) then oxidizes Co(II) to Co(III). The aminoquinoline moiety of structure **A** acts as a bidentate directing group to activate the *ortho* carbon atom on the substrate. The activated carbon atom forms a coordinate bond with the Co(III) species to yield complex **B** through the concerted metalation deprotonation (CMD) process. Complex **B** is followed by the formation of complex **C** in which a particular orientation of the unsymmetrical diyne is preferred based on its intrinsic stereoelectronic properties and the electronic property of complex **C** to give a regioselective complex **D** (**D1/D2/D3/D4**). Complex **D** undergoes reductive elimination at Co(III) which regenerates the initial oxidation state of Co to complete the cycle.

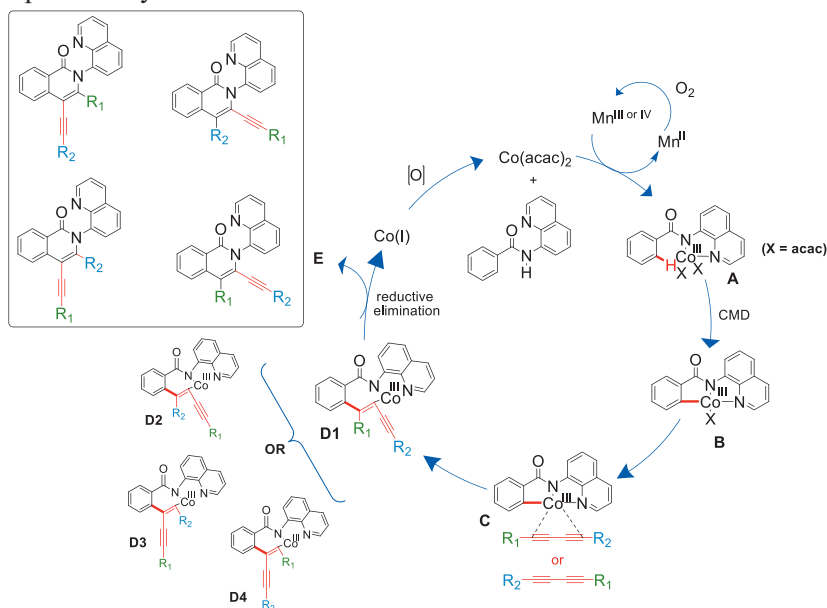


Figure 12. Proposed catalytic cycle for C-H activation with unsymmetrical 1,3-diyne

## 2.2.8 Conclusion

In this paper, we have established a highly regioselective Co-catalyzed C-H activation with unsymmetrical 1,3-diyne to furnish the corresponding alkynylated heterocycles in moderate yields. Substituents on the 1,3-diyne have a high impact on the regiochemical outcome of this reaction furnishing 3- or 4-hydroxyalkyl substituted heterocycles. For the efficient synthesis of isoquinolinone-derived molecules or bioactive agents, the orientation of insertion and its subsequent location could play a crucial role.

## 2.3 Transition metal-catalyzed C-H activation of indoles (Paper II)

The indole moiety can be found in many important classes of bioactive chemicals, ranging from amino acids and neurotransmitters, plant growth hormones, migraine treatment and to anti-inflammatory drugs (Figure 13).<sup>174</sup>

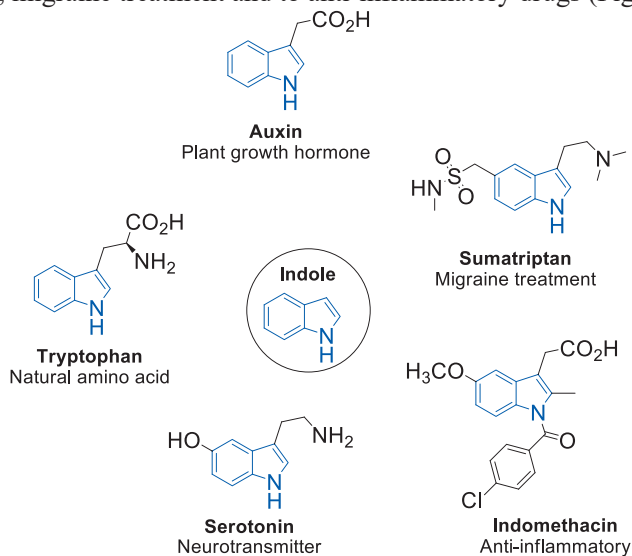
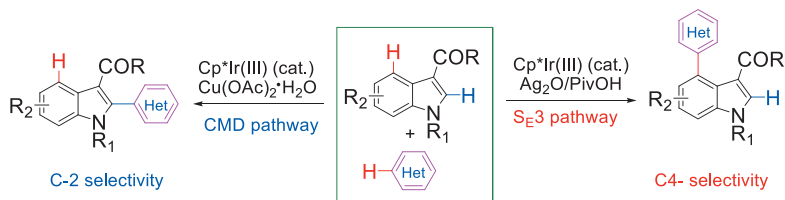


Figure 13. Examples of biologically relevant indoles

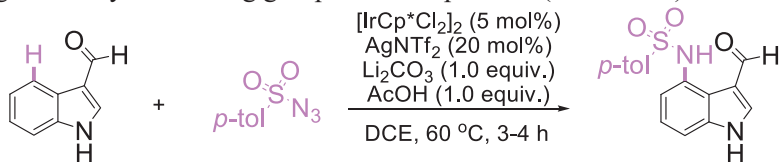
Accordingly, great effort has been devoted to the transition metal-catalyzed C-H functionalization of indoles. Historically, focus has been on functionalization at the C2 and C3 positions of the pyrrole ring<sup>175,176</sup> and more recently C4-C7 of the benzene ring.<sup>177</sup> Recently, You *et al.* disclosed an iridium-catalyzed C2/C4 regioselective heteroarylation of indole with pivaloyl group at the C3 position. (Scheme 33)<sup>178</sup>



Scheme 33. Regioselective C4-H and C2-H heteroarylation of indoles with heteroarenes<sup>178</sup>

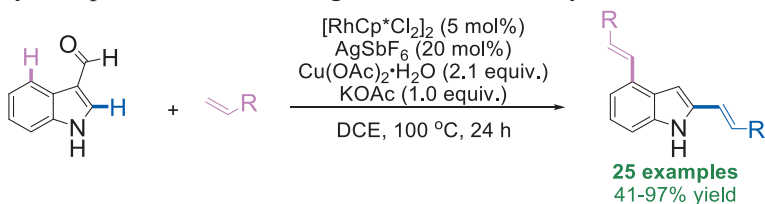
The C2-heteroarylation proceeds *via* a CMD pathway while the C4-heteroarylation of indole proceeds *via* a trimolecular electrophilic substitution ( $S_E^3$ ) pathway.<sup>178</sup>

C4-selective amidation of indoles was presented by Prabhu *et al.* in 2017 using an aldehyde directing group at the C4 position (Scheme 34).<sup>179</sup>



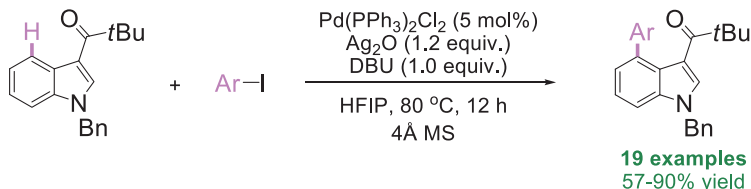
**Scheme 34.** Ir-catalyzed C4 sulfonamidation of indole derivatives<sup>179</sup>

Dialkenylation at C4 and C2 positions followed by in situ decarboxylation was reported by Zhang *et al.* using rhodium catalysis (Scheme 35). The obtained dialkenylated product further undergoes in-situ decarboxylation.<sup>180</sup>



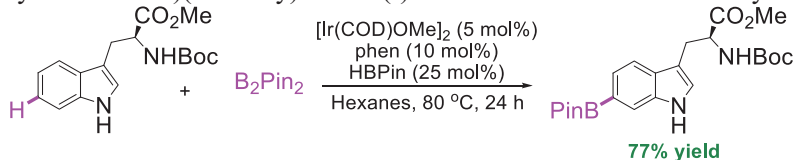
**Scheme 35.** Rh-catalyzed C4 and C2 di-alkenylation and in situ decarboxylation<sup>180</sup>

By utilizing carboxylic acid group strategy, Shi *et al.* in 2017 enable the palladium-catalyzed C4-selective C-H arylation of indole derivatives (Scheme 36).<sup>181</sup>



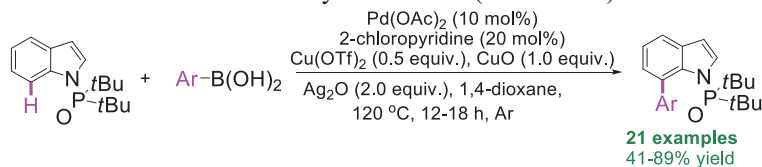
**Scheme 36.** Pd-catalyzed C4-arylation of indole derivatives<sup>181</sup>

In 2015, Baran *et al.* reported iridium-catalyzed C-H borylation of tryptophan derivatives during the synthesis of veruculogen and fumitremorgin A (Scheme 37).<sup>182</sup> During this reaction a bulky ligand (1,5-cyclooctadiene)(methoxy)iridium(I) dimer controlled the selectivity.



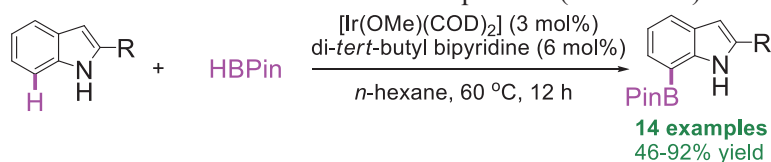
**Scheme 37.** Ir-catalyzed ligand controlled C6 C-H borylation<sup>182</sup>

Shi *et al.* explored Pd-catalyzed C-H arylation using 2-chloro pyridine as the ligand to enable selective C-H arylation at C7 (Scheme 38).<sup>183</sup>



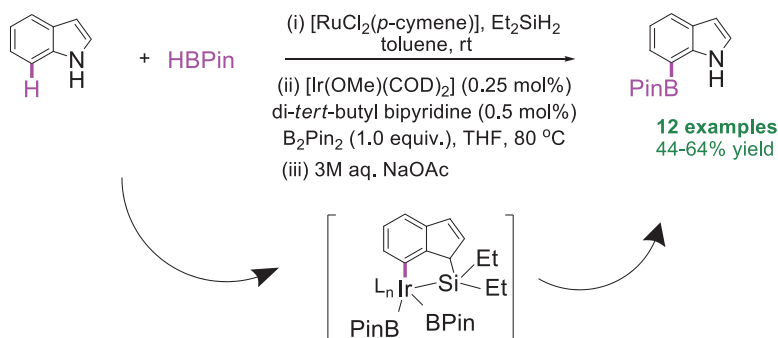
**Scheme 38.** Pd-catalyzed C7 arylation of indoles<sup>183</sup>

C7 functionalized indoles have been explored by multiple groups that performed alkenylation,<sup>184,185</sup> alkylation,<sup>186</sup> arylation,<sup>187,188</sup> amidation,<sup>189</sup> acylation,<sup>190</sup> and cyanation<sup>191</sup> reactions using a variety of catalytic metal systems. Smith *et al.* successfully used an Ir-catalyzed system for C-H borylation of C2-substituted indole at the C7 position (Scheme 39).<sup>192</sup>



**Scheme 39.** Ir-catalyzed C-H borylation of 2-substituted indoles at C7<sup>192</sup>

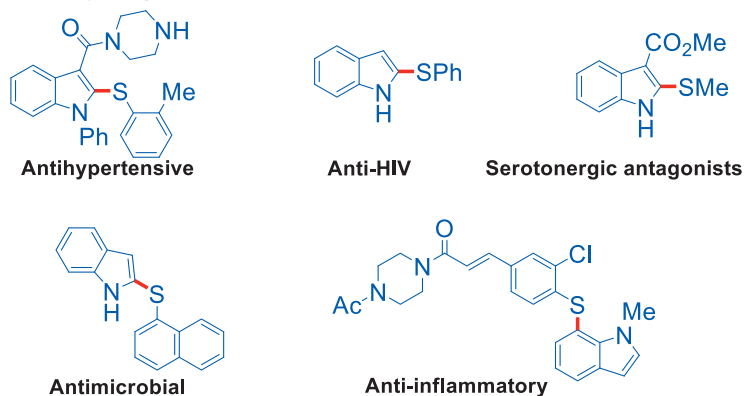
Hartwig *et al.* reported one of the most important examples of C7 C-H functionalization of free indole.<sup>193</sup> He explored the use of a bulky silyl directing group to direct cycloiridation at C7 (Scheme 40). This incredibly selective method is also applicable to various substituted indoles, tetrahydroquinolines, and carbazoles.



**Scheme 40.** Ir-catalyzed silyl-directed C-H borylation of indoles at C7<sup>193</sup>

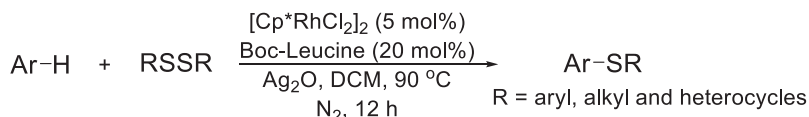


Thioethers often show different biological activities and have important applications in the pharmaceutical industry.<sup>194</sup> Thioethers are important structural units in natural products,<sup>195</sup> and organic functional materials.<sup>196</sup> Several C7 and C2 thioether-linked indoles display unique biological properties such as antihypertensive, anti-HIV, serotonergic antagonists, antimicrobial, and anti-inflammatory (Figure 14).



**Figure 14.** Examples of bioactive thioether-linked indoles

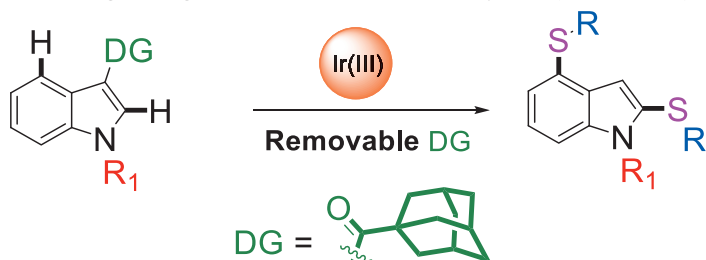
Ligand promoted Rh(III)-catalyzed *ortho*-C-H thiolation using amide directing group was reported by Yu *et al.* (Scheme 41).<sup>197</sup> This was the first example of Rh(III)-catalyzed aryl thiolation reactions through weakly coordinating directing amide groups.



**Scheme 41.** Transition metal-catalyzed C-H thiolation

## 2.4 Tandem Ir-catalyzed decarbonylative C-H activation of indole

Paper II reports an iridium(III)-catalyzed decarbonylative direct arylsulfenylation of indole at C2/C4 C-H bonds. We identified a removable directing group, adamantoyl group, that could facilitate double C-S bond formation through the generation of dual metallacycles (Scheme 42).



*Scheme 42. Iridium-catalyzed C-H activation of indole*

### 2.4.1 Optimization studies

Initially, to explore the possibility of arylsulfenylation of **15a**, with the reactivity of pentamethylcyclopentadienyl iridium dichloride dimer [IrCp\*Cl<sub>2</sub>]<sub>2</sub>, we performed C-H activation reaction of substrate **15a** with disulfide **16a**, using [IrCp\*Cl<sub>2</sub>]<sub>2</sub> as the catalyst, AgNTf<sub>2</sub> as the silver additive, silver carbonate as a terminal oxidant, anhydrous 1,2-dichloroethane (DCE) as solvent at 120 °C for 22 h (Table 3). The bis-aryl sulfenylated C-H activation product **17a** was obtained in 68% isolated yield without any observed formation of monosubstituted indole products. Initially, pivalic acid (PivOH) was tested as the additive, and product was isolated in 17% yield (Table 3, entry 1). By changing the additive from pivalic acid to 1-adamantanecarboxylic acid, product formation increased to 35% (Table 2, entry 2). Product formation was reduced after switching oxidant from silver carbonate (Ag<sub>2</sub>CO<sub>3</sub>) to silver oxide (Ag<sub>2</sub>O) or silver acetate (AgOAc) (Table 3, entries 3 and 4), while the use of AgF gave no desired product (Table 3, entry 5). Interestingly it is observed that when Ag<sub>2</sub>CO<sub>3</sub> is replaced by Cu(OAc)<sub>2</sub> product is obtained with a reduced yield. This implies that acetate ion is not required for the coordination of the metal center (Table 3, entry 6). Changing the solvent from DCE to dichloromethane (DCM) also resulted in a lower yield (Table 3, entry 7). No reaction was observed when the reaction was performed under air (Table 3, entry 8). 35% yield was obtained when the reaction was performed at a lower temperature (60 °C) (Table 1, entry 9), and at room temperature, no reaction was observed (Table 3, entry 10).

**Table 3.** Optimization of reaction conditions and control experiments<sup>a</sup>

entry	deviation from above	yield <sup>b</sup> (%)
1	PivOH	17
2	1-AdCOOH	35
3	Ag <sub>2</sub> O	15
4	AgOAc	28
5	AgF	NR
6	Cu(OAc) <sub>2</sub>	55
7	DCM as solvent	16
8	Under air	NR
9	at 60 °C	35
10	at room temperature	NR
11	[RuCl <sub>2</sub> ( <i>p</i> -cymene) <sub>2</sub> ] <sub>2</sub>	NR
12	[RhCp*Cl <sub>2</sub> ] <sub>2</sub>	50

<sup>a</sup>Reaction conditions: **15a-15d** (0.17 mmol), **16a** (0.25 mmol), [IrCp\*Cl<sub>2</sub>]<sub>2</sub> (5 mol%), AgNTf<sub>2</sub> (30 mol%), Ag<sub>2</sub>CO<sub>3</sub> (2.0 equiv.), 1,2 DCE (2 mL), 120 °C, 22 h. <sup>b</sup>Isolated yield; NR = no reaction.

Two additional catalysts were screened, specifically, [RuCl<sub>2</sub>(*p*-cymene)<sub>2</sub>]<sub>2</sub> and pentamethylcyclopentadienyl rhodium dichloride dimer ([RhCp\*Cl<sub>2</sub>]<sub>2</sub>) but neither afforded the product in better yield (Table 3, entry **11** and **12**).

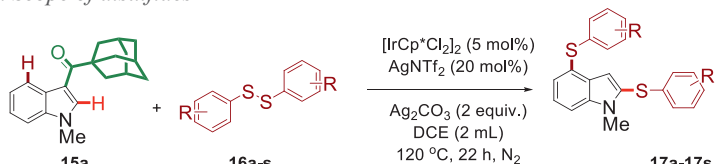
We explored the scopes of the directing ketones on the reaction with optimized conditions for iridium(III)-catalyzed C-H activation. The more electron-rich adamantoyl derivatives gave the product in the highest yield (68%). The importance of having an electron-rich ketone for generating the proposed five- and six-membered metallacycles is reflected in the low yields from acetyl and pivaloyl groups that gave the expected products in 6 and 25% yields respectively.

Surprisingly, the formyl group was also well-tolerated and delivered the aryl sulfonylated product in a 33% yield.

## 2.4.2 Scope of disulfides

After having established these reaction conditions, we tested the effect of disulfide substituents on the reaction with model substrate **15a** (Table 4).

Table 4. Scope of disulfides

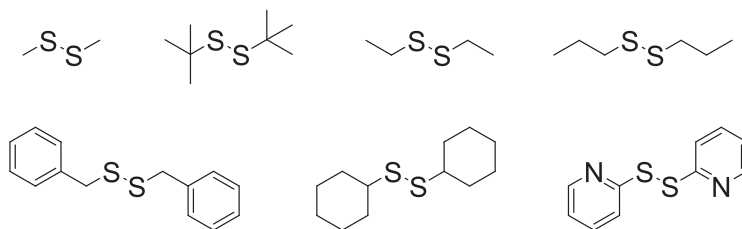


Entry	Disulfide (R)	Product (%) <sup>a</sup>
1	H, <b>16a</b>	<b>17a</b> , 68
2	2-Me, <b>16b</b>	<b>17b</b> , 34
3	3-Me, <b>16c</b>	<b>17c</b> , 50
4	4-Me, <b>16d</b>	<b>17d</b> , 55
5	<i>ortho</i> -Cl, <b>16e</b>	<b>17e</b> , 42
6	<i>para</i> -Cl, <b>16f</b>	<b>17f</b> , 38
7	<i>ortho</i> -Br, <b>16g</b>	<b>17g</b> , 40
8	<i>meta</i> -Br, <b>16h</b>	<b>17h</b> , 51
9	<i>para</i> -Br, <b>16i</b>	<b>17i</b> , 70
10	<i>ortho</i> -F, <b>16j</b>	<b>17h</b> , 68
11	<i>meta</i> -F, <b>16k</b>	<b>17k</b> , 53
12	<i>para</i> -F, <b>16l</b>	<b>17l</b> , 64
13	4-CF <sub>3</sub> , <b>16m</b>	<b>17m</b> , 43
14	4- <i>tert</i> -Butyl, <b>16n</b>	<b>17n</b> , 37
15	3,5-dimethyl, <b>16o</b>	<b>17o</b> , 60
16	3,5-difluoro, <b>16p</b>	<b>17p</b> , 48
17	3,5-dichloro, <b>16q</b>	<b>17q</b> , 60
18	2,4-dichloro, <b>16r</b>	<b>17r</b> , 56
19	3,5-di-trifluoromethyl, <b>16s</b>	<b>17s</b> , 60

<sup>a</sup> Isolated yield

A broad tolerance was observed with both electron-donating and withdrawing groups were well tolerated (Table 4). It was observed that halogenated disulfides (Cl, Br, and F) were well tolerated irrespective of their position (*ortho*, *meta*, or *para*) and all gave products in moderate to good yields (entries 5-12). The reaction progressed well with trifluoromethyl, and *tert*-butyl substituted disulfides (entries, 13-14). Moreover, even sterically crowded disubstituted disulfides provided the desired products in moderate yields

(entries 15-19). Figure 15 summarizes various aliphatic disulfides as well as 2-pyridine disulfide that were tested but failed to produce the desired products.



**Figure 15.** Unsuccessful disulfides

### 2.4.3 Scope of indoles

We then proceeded to explore the reaction tolerance to an indole substitution (Table 6). Indoles bearing Cl, Br, I, F, and CN, were all well-tolerated as was a COOMe at the C5 position (Table 6, entries 1-6). Interestingly, good yields were observed for C6 substituted indoles bearing either electron-donating or electron-withdrawing groups (Table 6, entries 7-9). C7 substituted methyl-indole was also found compatible (Table 6, entry 10).

Table 6. Scope of indoles

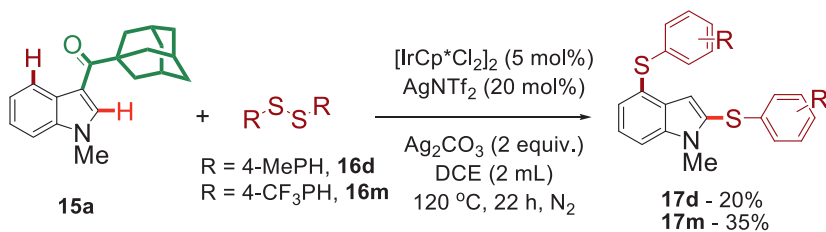
Entry	Indole (R)	Product (%) <sup>a</sup>
1	5-Cl, <b>15b</b>	<b>17b</b> , 50
2	5-Br, <b>15c</b>	<b>17c</b> , 54
3	5-I, <b>15d</b>	<b>17d</b> , 60
4	5-F, <b>15e</b>	<b>17e</b> , 76
5	5-CN, <b>15f</b>	<b>17f</b> , 25
6	5-CO <sub>2</sub> Me, <b>15g</b>	<b>17g</b> , 49
7	6-Cl, <b>15h</b>	<b>17h</b> , 70
8	6-Br, <b>15i</b>	<b>17i</b> , 71
9	6-Ome, <b>15j</b>	<b>17j</b> , 70
10	7-Me, <b>15k</b>	<b>17k</b> , 32

<sup>a</sup> Isolated yield

## 2.4.4 Mechanistic studies

To determine the mechanism underlying this reaction, a series of control experiments were devised.

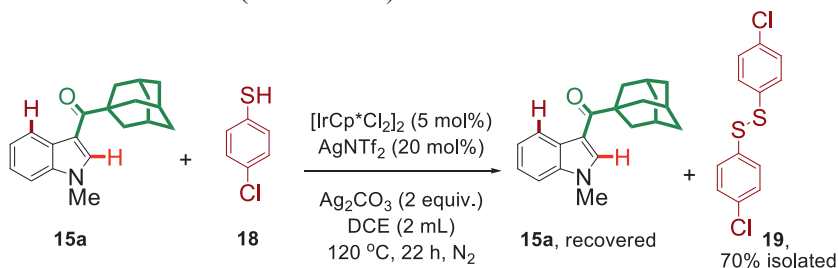
During the intermolecular competition experiment, electron-deficient substituted disulfide **16m** was found to be dominant over electron-rich substituted disulfide **16d** in terms of higher reactivity. Also, we did not observe the cross-sulfonylation which implies that the reaction does not proceed *via* the concerted metalation deprotonation (CMD) pathway (Scheme 43a).



Scheme 43a. Intermolecular competition experiment

Reaction with thiol **18** under these oxidative conditions resulted in disulfide **19** as the only product, along with the unreacted starting material **15a**, further

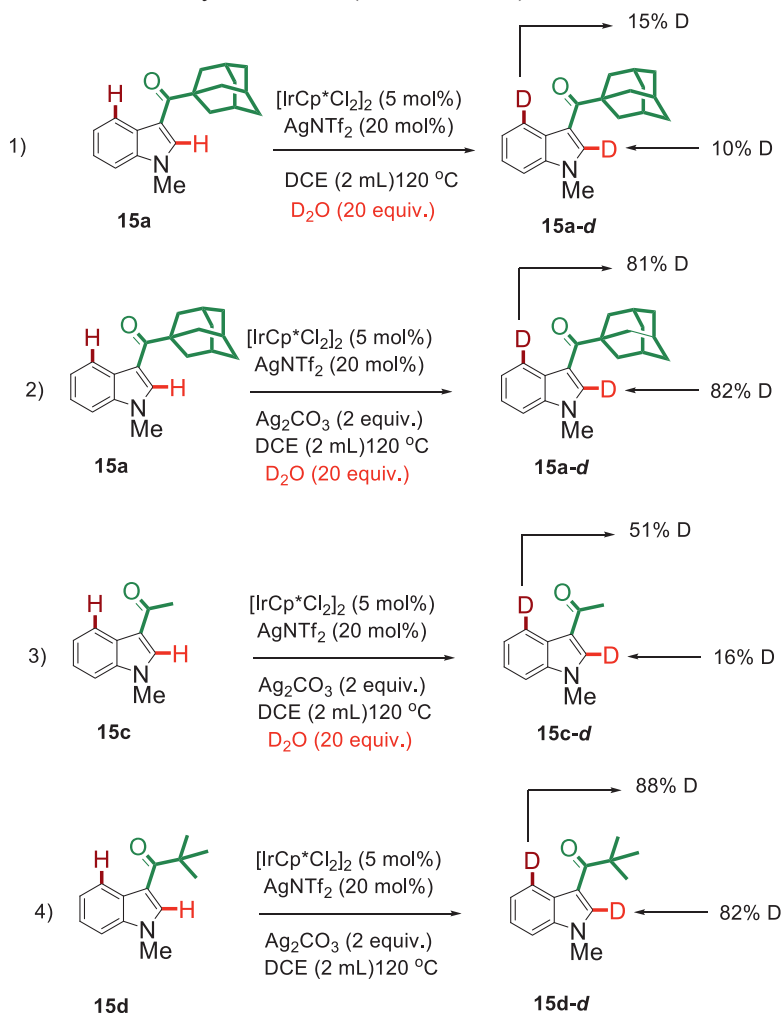
suggesting that disulfides were oxidatively added to the metal center during the C-H activation reaction (Scheme 43b).



*Scheme 43b.* Reaction of **15a** with thiol

Next, reactions were performed using deuterated solvents (Scheme 43c). 10% deuteration was observed at C2 and 15% deuteration was observed at C4 in absence of silver carbonate. This shows the dual personality of silver carbonate which works not only as a promoter but also as an oxidant (Scheme 43c-2). Remarkably, when we examined the reaction in the presence of  $\text{Ag}_2\text{CO}_3$ , we observed 82% of D/H exchange at C4/C2 positions. This pointed to the fact that there was an efficient formation of five and six-membered iridacycles (Scheme 43c-2). Moreover, this further highlights the role of silver carbonate in the mechanism for initiation of cyclometalation using a second silver additive in stoichiometric amount. The D/H exchange effect of electron-deficient ketone *N*-methyl-3-acetyl indole was higher at C4 (51%) than at C2 (16%). This further proved that the acetyl directing group especially forms a more stable six-membered iridacycle (Scheme 43c-3). We also tested the pivaloyl indole

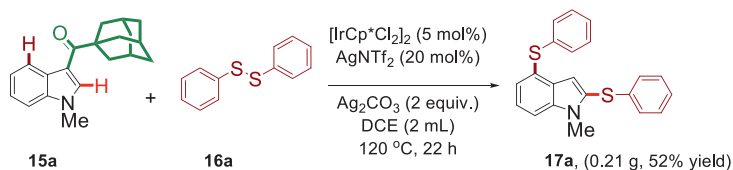
derivative and observed C4/C2 D/H exchange comparable to that of the more electron-rich adamantyl derivative (Scheme 43c-4).



**Scheme 43c.** Reactions with deuterated solvents

To demonstrate the robustness of this iridium(III) catalysis, we carried out the reaction on a gram-scale (1 mmol) and observed no substantial loss of catalytic activity, and obtained the product in moderate yield (52%) (Scheme 43d).

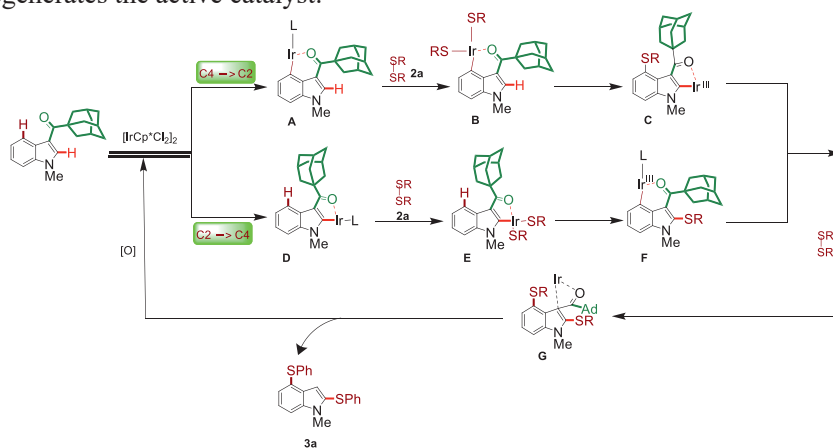




*Scheme 43d. Reaction at 1 mmol scale*

## 2.4.5 Proposed mechanism

Based on the results from the control experiments and in combination with reported literature,<sup>198</sup> we proposed that the mechanism proceeds through a tandem pathway (Scheme 44). Firstly, the catalyst coordinates with either C4 or C2 C-H bond and electron-rich ketone to form either the corresponding six-membered **A** or five-membered **D** metallacycle, respectively. **A** or **D** upon oxidative addition with disulfide **2a** affords complex **B** or **E**, that further undergoes reductive elimination, producing complex **C** or **F**. After the reaction via both the pathways, iridacycle **G** is formed followed by carbonyl group dislocation. Finally, reductive elimination delivers product **3a**, and reoxidation regenerates the active catalyst.



*Scheme 44. Proposed mechanism*

## 2.4.6 Conclusion

In this paper, we have developed an Ir(III)-catalyzed first tandem decarbonylative arylsulfenylation of indoles at C2/C4 positions. The formation of five and six-membered iridacycles is facilitated by the electron-rich adamantyl ketone directing group. Here we have introduced a new sacrificial electron-rich adamantoyl-directing group that facilitates the indole C-H bisfunctionalization with a traceless *in situ* removal.

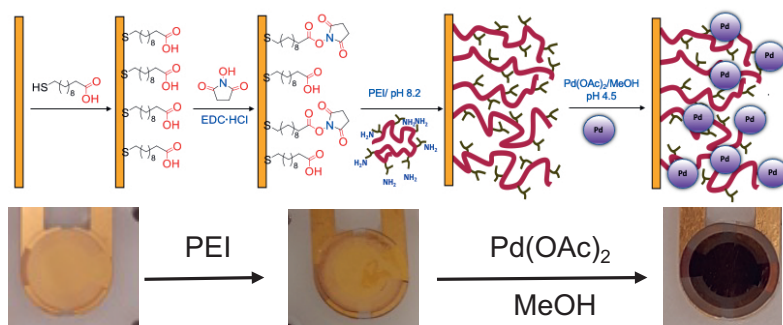
# Chapter 3 – Development of novel immobilized catalysts for Suzuki-coupling reactions for possible lab-on-a-chip-based synthesis applications (Paper III)

## 3.1 Catalytic surface fabrication

An immobilized catalyst can be defined as a metal or enzyme in a defined region of space on a solid support.<sup>128</sup> The catalyst must retain its catalytic activity after immobilization. Immobilized transition metal catalysts demonstrating a higher degrees of selectivity and activity have been used for many industrial processes.<sup>199</sup> Recently, our group demonstrated the immobilization of hyperbranched polyethyleneimine (PEI) for use as antifouling surfaces on a metallic surface.<sup>200</sup> This type of material has features in therapeutic applications such as bio-mineralization as well as nanostructure formation.<sup>201,202</sup> PEI is a cationic polymer having a high density of primary, secondary, and tertiary amino groups in the ratio of 1:2:1 and is capable of coordination with transition metals to form nanostructures.<sup>203,204</sup>

In paper III, we established the use of the PEI surface-supported nanoparticles as a support for catalysis of the Suzuki reaction and the possibility of using these Pd-nanoparticle immobilized PEI-derivatized gold surfaces for performing Suzuki reactions in a microfluidic device.

Gold sputtered quartz surfaces (Au/quartz) were first functionalized with 11-mercaptoundecanoic acid and then activated with *N*-hydroxy succinimide and (1-ethyl-3-dimethylaminopropyl)carbodiimide before derivatization with PEI (Scheme 45).

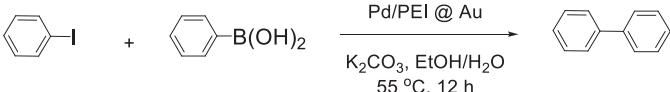


*Scheme 45. Palladium immobilization on polyethyleneimine coated Au/quartz surfaces*

By varying incubation times and Pd(OAc)<sub>2</sub> concentrations optimization of the Pd nanoparticle synthesis procedure was optimized (Table 7). The amount of Pd deposited on the PEI-coated Au/quartz resonators was determined by a quartz crystal microbalance (QCM).

It is important to note that errors in the calculation of the turnover numbers (TON) were identified during the writing of the thesis. The correct numbers are presented in the tables here in the introduction to the thesis. The original version is presented in the attached appended paper. Although the absolute numbers differ, the same trends are observed and the conclusions drawn are the same. An errata has been submitted to the publisher.

**Table 7.** Suzuki reactions of iodobenzene and phenylboronic acid in the presence of catalytic Pd immobilized PEI coated Au/quartz surface with varying incubation times



Amount of Pd, µg	Amount of Pd, /cm <sup>2</sup>	Pd loading from Pd(OAc) <sub>2</sub>	Yield	TON
1.6	3.13	1 mg/mL for 2 h	67%	4.4 x 10 <sup>4</sup>
2.5	4.90		80%	3.4 x 10 <sup>4</sup>
2.5	4.90		74%	3.1 x 10 <sup>4</sup>
7.8	15.29	1 mg/mL for 5 h	74%	1.0 x 10 <sup>4</sup>
6.1	11.96		80%	1.3 x 10 <sup>4</sup>
5.5	10.78		80%	1.5 x 10 <sup>4</sup>
0.4	0.78	0.5 mg/mL for 30 min	60%	15.9 x 10 <sup>4</sup>
1.1	2.15		70%	6.7 x 10 <sup>4</sup>
0.74	1.45	0.5 mg/mL for 1 h	54%	7.7 x 10 <sup>4</sup>
0.45	0.88		54%	12.7 x 10 <sup>4</sup>
1.31	2.56		54%	4.3 x 10 <sup>4</sup>
0.54	1.05	0.5 mg/mL for 2 h	74%	14.5 x 10 <sup>4</sup>
0.62	1.21		67%	11.5 x 10 <sup>4</sup>
2.2	4.31	0.5 mg/mL for 5 h	93%	4.5 x 10 <sup>4</sup>
1.8	3.52		90%	5.3 x 10 <sup>4</sup>
2.0	3.92		90%	4.8 x 10 <sup>4</sup>

## 3.2 Surface characterization

### 3.2.1 Energy dispersive X-ray (EDX)

The presence of Pd in the PEI film was confirmed with the energy dispersive X-ray (EDX) spectrum with the distinct band at 2.8 keV (Figure 16).

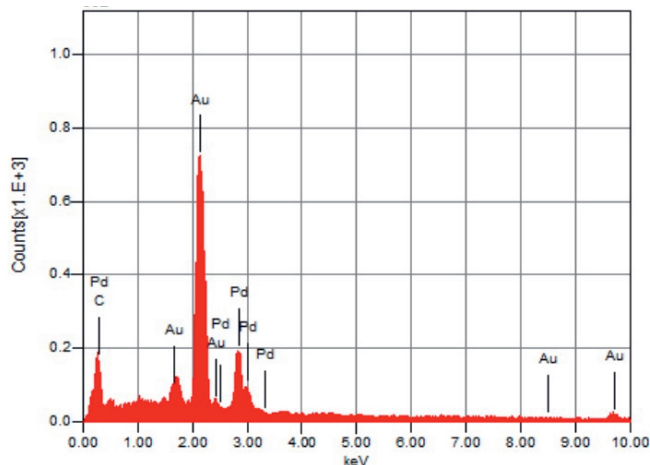


Figure 16. Energy dispersive X-ray (EDX) analysis

### 3.2.2 X-ray photoelectron spectroscopy (XPS)

XPS spectra of Pd-bound PEI surfaces revealed the presence of anticipated proleptic elements ( $C_{1s}$ ,  $N_{1s}$ ,  $O_{1s}$ ,  $Pd_{3d}$ , and  $Au_{4f}$ ) (Figure 18 A). Deconvoluted peaks clearly differentiated the amine N of PEI (399.8 eV) from that of amide N ( $-N-C=O-$ , 400.8 eV) (Figure 17 C).<sup>205,206</sup>

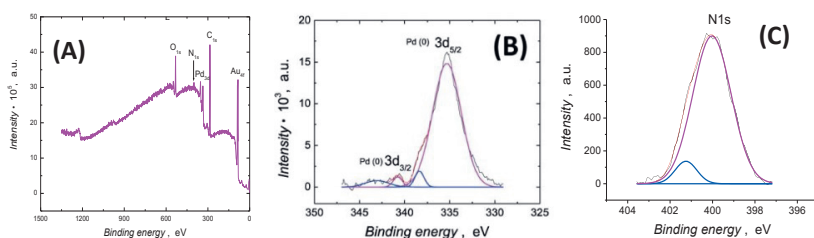
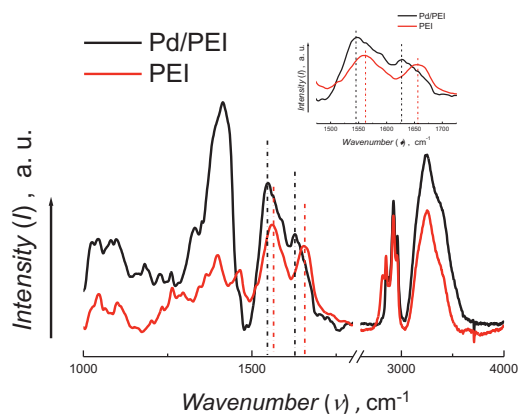


Figure 17. (A) X-ray photoelectron spectra (XPS) of the Pd nanoparticles immobilized PEI coated Au/quartz surface. (B) XPS- Survey spectra of the Pd nanoparticle immobilized on PEI coated Au/quartz surface (C) Deconvoluted XPS bands of  $N_{1s}$  for the amine groups in PEI

Bands around 335 and 340 eV in the survey spectra correspond to the  $3d_{5/2}$  and  $3d_{3/2}$  states of the surface-bound Pd.<sup>207</sup> The deconvoluted bands at 335.3 and 338.2 confirmed the presence of Pd(0) and Pd(II) respectively (Figure 18 B). Significantly, peak integration showed the immobilized Pd to be predominantly in the Pd(0) state, with less than 5% present as Pd(II).<sup>207</sup>

### 3.2.3 Reflection absorption IR spectroscopy (RAIRS)

RAIR spectra confirmed the presence of PEI on the gold surface based on the discernible vibrational bands of the -N-H, -CH- and -CN- bending modes of the adsorbed PEI film (Figure 18)

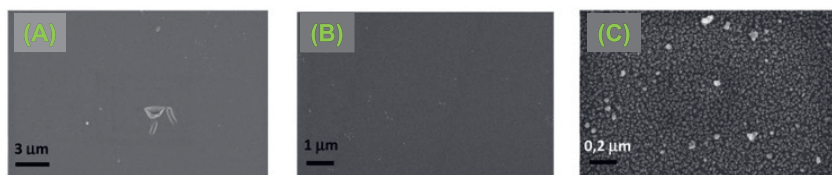


**Figure 18.** RAIR spectra of PEI coated Au/quartz surface before and after Pd immobilization

Subtle differences can be found in the RAIR spectra of PEI before and after Pd immobilization. The band corresponding to the -N-H bending mode has been significantly red-shifted highlighting the interaction of the Pd particles with the amine moieties of the PEI film (Figure 19, inset). This result in conjunction with the XPS data revealed the evidence for the reduction of Pd(II) to Pd(0) as well as its incorporation as nanoparticles into the PEI brush layer.

### 3.2.3 Scanning electron microscopy (SEM)

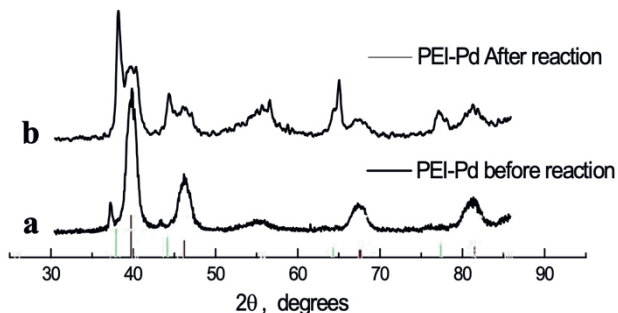
SEM images showed uniform long-range coating of the palladium nanoparticles on the PEI immobilized surface (Figure 19).



**Figure 19.** SEM images of (A) gold surface, (B) polyethyleneimine (PEI) film, and (C) PEI-supported Pd particles fabricated on Au/quartz surfaces

### 3.2.5 Powder X-ray diffraction

Powder diffraction measurements were used to evaluate the crystallinity of the Pd-coated PEI surface which showed peaks characteristic peaks for Pd(111), Pd(200), and Pd(220) with Miller indices of 40, 47.2, and 68.3° (JCPDS No. 98-004-7386), respectively, which again confirmed the presence of Pd nanoparticles in the (0) oxidation state (Figure 20, **curve a**).



*Figure 20. Powder X-ray diffraction pattern of Pd immobilized PEI coated Au/quartz surfaces before (curve a) and after (curve b) catalyzing Suzuki reaction*

## 3.3 Suzuki reaction

The story of C-C bond formation is incomplete without the Suzuki-coupling reaction as explained in section 1.1.2. It has many applications, as discussed below.

### 3.3.1 Applications of Suzuki reactions

The Suzuki reaction is versatile due to its mild reaction conditions, readily available organoboranes, low toxicity of starting materials, and tolerance towards diverse functional groups.<sup>208</sup> These properties have attracted researchers to explore its application in areas ranging from natural product synthesis to the development of polymeric materials to the synthesis of agrochemicals and pharmaceuticals.<sup>209</sup> It is arguably the most effective method used for the construction of biaryls in organic synthesis. Usually, the Suzuki reaction is carried out using a homogeneous catalyst, which can often provide excellent yields, selectivities, and all in a one-pot synthesis. A supported Pd catalyst which can act as a heterogeneous catalyst has greater advantages as discussed in section 1.3.4.

### 3.3.2 Scope of Suzuki reactions

We explored various Suzuki reactions using a series of phenylboronic acids and substituted aryl halides using these surfaces (Table 8). Corresponding control reactions were performed in the absence of PEI and/or PEI (using an unmodified Au/quartz surface), though in these cases none of the desired biphenyl product was formed.

**Table 8.** Suzuki cross-coupling reactions of aryl halides with arylboronic acids using PEI/Pd as catalyst<sup>a</sup>

Entry	R <sub>1</sub>	X	R <sub>2</sub>	Amount of Pd, $\mu$ g	Yield	TON
1	H	I	H	3.2	93%	$3.1 \times 10^4$
2	H	Br	H	2.8	95%	$3.4 \times 10^4$
3	H	I	2-CH <sub>3</sub>	3.9	82%	$2.2 \times 10^4$
4	H	I	3-OCH <sub>3</sub>	4.0	57%	$1.5 \times 10^4$
5	H	I	4-OCH <sub>3</sub>	3.7	84%	$2.4 \times 10^4$
6	H	I	2-CN	3.99	15%	$0.4 \times 10^4$
7	H	I	4-CN	3.6	95%	$2.8 \times 10^4$
8	4-CH <sub>3</sub>	Br	H	6.2	88%	$1.5 \times 10^4$
9	4-OCH <sub>3</sub>	Br	H	8.4	95%	$1.2 \times 10^4$
10	H	I	3-NH <sub>2</sub>	3.5	n.r.	-
11	H	Cl	H	1.0	94%	$10.0 \times 10^4$
12	4-OCH <sub>3</sub>	Cl	H	1.62	80%	$5.3 \times 10^4$
13	4-COCH <sub>3</sub>	Cl	H	1.5	n.r.	-

<sup>a</sup>General procedure: 1.0 mmol of aryl halide (in 1 mL of EtOH), 1.2 mmol of arylboronic acid (in 1 mL of H<sub>2</sub>O), 2.0 mmol of K<sub>2</sub>CO<sub>3</sub> (in 1 mL of H<sub>2</sub>O). Turn over number TON = mol product/mol Pd. n.r. = no reaction.

Reactions of aryl halides with a series of arylboronic acids offered the corresponding desired products in good to excellent yield (Table 7, entries **1-9**, **11-12**), except for the 2-cyano substituted phenyl boronic acid, where low yield could be due to an electronic effect, in addition to the steric crowding caused by the interaction between the cyano group with Pd/PEI (Table 7, entry **6**). No reactions were observed when iodobenzene and 4-acetyl chlorobenzene were treated with 3-amino boronic acid and phenylboronic acid respectively (Table 7, entries **10** and **13**).

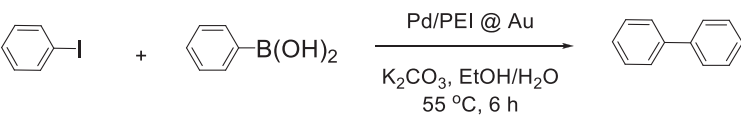
### 3.3.3 Catalyst poisoning test

To check whether catalyst poisoning was an issue, we performed a PPh<sub>3</sub> poisoning test by using 5 equivalents of PPh<sub>3</sub> combined with 1 equivalent of the catalyst and stirring for 15 min before the addition of iodobenzene (1.0 mmol, 204 mg) in 1 mL of ethanol and phenylboronic acid (1.2 mmol, 146 mg) in 1 mL of water, K<sub>2</sub>CO<sub>3</sub> (2.0 mmol, 276 mg) in 1 mL of water at 55 °C. After 12 hours, the biphenyl product obtained in 93% yield. This negligible effect on Pd catalyst poisoning confirms that the catalytic Pd exists predominantly in the (0) oxidation state.<sup>210</sup>

### 3.3.4 Suzuki reactions using shorter reaction times

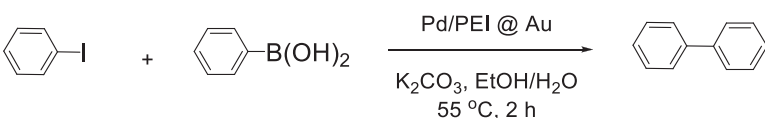
Further optimization was carried out by performing the Suzuki reaction with shorter reaction times (6 h and 2 h), providing the desired product in acceptable yields (84% and 78%) respectively (Table 9 and 10).

**Table 9.** Suzuki cross-coupling reactions of iodobenzene and phenylboronic acid in presence of catalytic Pd immobilized PEI coated Au/quartz surface for 6 h



Amount of Pd, µg	Pd loading from Pd(OAc) <sub>2</sub>	Yield	TON
0.4	0.5 mg/mL	83%	22.1 x 10 <sup>4</sup>
0.7	0.5 mg/mL	84%	12.7 x 10 <sup>4</sup>

**Table 10.** Suzuki cross-coupling reactions of iodobenzene and phenylboronic acid in presence of catalytic Pd immobilized PEI coated Au/quartz surface for 2 h



Amount of Pd, µg	Pd loading from Pd(OAc) <sub>2</sub>	Yield	TON
0.65	0.5 mg/mL	78%	12.7 x 10 <sup>4</sup>

### 3.3.5 Reusability/recyclability of PEI/Pd surface

To assess the stability of this surface and the potential for their reuse, the surfaces were removed from the reaction mixtures and the amount of residual Pd was determined by QCM after the use of the surfaces in a series of reactions (Table 11) with ≈1.5% loss per cycle over four cycles.<sup>3</sup>



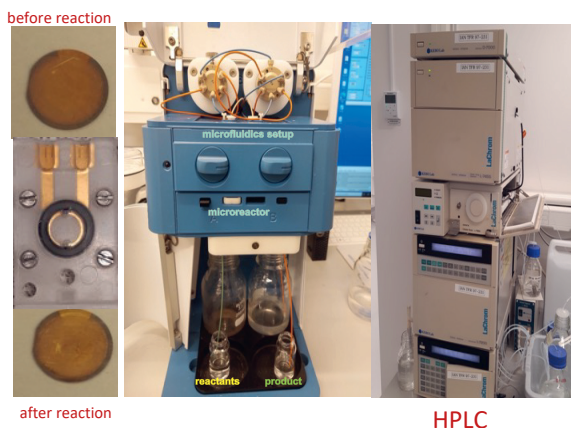
**Table 11.** Reusability/recyclability of PEI/Pd surface

Entry	Run	Conc. of Pd, $\mu\text{g}$	Yield	TON
1	1 <sup>st</sup>	$\pm 2.3$	93%	$4.4 \times 10^4$
2	2 <sup>nd</sup>	$\pm 2.22$	89%	$4.3 \times 10^4$
3	3 <sup>rd</sup>	$\pm 2.22$	85%	$4.0 \times 10^4$
4	4 <sup>th</sup>	$\pm 2.15$	80%	$3.9 \times 10^4$

The long-term stability of the catalyst surfaces was examined by storing freshly prepared surfaces in water under inert conditions (Milli-Q grade water, 18.2 M $\Omega$ , purged with UHP grade N<sub>2</sub>) for three months, after which, use led to the desired product being obtained in 93% yield.

### 3.3.6 Use of surface in lab-on-a-chip-context

We explored the use of the catalyst surface in a lab-on-a-chip format by placing it in a QCM instrument fitted with a microfluidic liquid delivery system, and performing a Suzuki reaction using iodobenzene and phenylboronic acid under the flow injection analysis conditions (Figure 21). The reactants [1.0 mmol of iodobenzene (in 2 mL of EtOH), 1.2 mmol of phenylboronic acid (in 2 mL of H<sub>2</sub>O), 2.0 mmol of K<sub>2</sub>CO<sub>3</sub> (in 2 mL of H<sub>2</sub>O)] were introduced into the 2  $\mu\text{L}$  volume microreactor using the instrument peristaltic pump while maintaining the temperature of the reaction at 40 °C for 6 h at the flow rate of 10  $\mu\text{L}/\text{min}$ . The HPLC of the crude filtrate product is consistent with the purified biphenyl. The formation of biphenyl was further confirmed by <sup>1</sup>H and <sup>13</sup>C NMR.



**Figure 21.** Suzuki coupling reaction on PEI/Pd surface in lab-on-a-chip context

Importantly, the Pd/PEI surfaces presented here have significantly lower Pd loadings (<0.001 mol%) as compared with other reported heterogeneous catalysts<sup>202</sup> for the Suzuki reaction (Table 12). This highlights the role of the PEI matrix in facilitating the mass transfer of substrates and for avoiding aggregation of the Pd.

**Table 12.** Comparison of other reported catalytic systems on Suzuki reaction of halobenzenes with phenylboronic acid

Catalysts <sup>a</sup>	Size (nm)	Time(h)	Temp (°C)	Solvent	Yield (%)
Au-G <sup>211</sup>	2-3	4	100	H <sub>2</sub> O	85
Fe <sub>3</sub> O <sub>4</sub> -Bpy-Pd(OAc) <sub>2</sub> <sup>212</sup>	6-20	6	80	Toluene	>99
Pd/NiFe <sub>2</sub> O <sub>4</sub> <sup>213</sup>	100-300	5	90	DMF:H <sub>2</sub> O (5:2)	97
Pd/G <sup>214</sup>	7-9	10	~80	H <sub>2</sub> O:EtOH (1:1)	>99
Pd/GO <sup>214</sup>	12-18	10	~80	H <sub>2</sub> O:EtOH (1:1)	>99
Pd-SBA-15 <sup>215</sup>	1.5	30 min	100	H <sub>2</sub> O:EtOH (3:2)	21
Fe <sub>3</sub> O <sub>4</sub> -Pd <sup>(0)</sup> <sup>216</sup>	8-10	24	50	DMF	54
Ru/Al <sub>2</sub> O <sub>3</sub> <sup>217</sup>	2-3	12	60	DME:H <sub>2</sub> O (1:1)	96
LDH-Pd <sup>(0)</sup> <sup>218</sup>	4-6	10	100	1,4-dioxane:H <sub>2</sub> O (5:1)	93
Diatomite-Pd <sup>(0)</sup> <sup>219</sup>	20-100	20 min	110	DME:H <sub>2</sub> O (1:1)	95
Organostannoxane-Pd <sup>(0)</sup> <sup>220</sup>	4.3	4	110	Toluene	95
Pd/SiO <sub>2</sub> <sup>221</sup>	>100	12	100	CH <sub>3</sub> CN:H <sub>2</sub> O (3:1)	>90
<b>PEI/Pd</b>	<b>20-100</b>	<b>12</b>	<b>55</b>	<b>H<sub>2</sub>O:EtOH (1:1)</b>	<b>95</b>

<sup>a</sup> References.

### 3.3.7 Conclusion

The catalytic efficiency and stability of the gold surface-bound hyperbranched polyethyleneimine (PEI) film were studied for lab-on-a-chip-based synthesis applications. A miniaturized microfluidic setup for the Suzuki coupling reaction has been developed using this thin film and a quartz crystal microbalance (QCM) instrument. Excellent catalytic efficiency (TON up to 15.9 x 10<sup>4</sup>), as well as the stability of this thin film format, highlights the scope of this technique and its potential for use in microfluidic devices to study synthetic applications.

## Chapter 4 – Conclusions & future outlook

Society's dependence on C-C and C-X forming reactions for delivering materials, *e.g.* polymers, and substances, *e.g.* pharmaceuticals and agrochemicals, necessary for maintaining and where possible improving quality of life, is significant. With this overarching perspective, the development of new sustainable methods for the efficient construction of C-C and C-X bonds is an important goal for organic chemistry and related disciplines.

Within the framework of this thesis two key aspects have been explored:

Firstly, the development of new methodologies for the efficient construction of C-C and C-X(S) bonds. This was investigated in **paper I** and **paper II**. These studies have resulted in novel methods for predetermining 3/4-substitution of isoquinolone and for the tandem bis-thioarylation of indoles, respectively. In both cases, the broader application of the methodologies may have a positive impact on the development and manufacture of new materials and substances critical for society. In both cases, aside from exploring the broader scope of the reactions studied, further work on application development is warranted. In the case of **paper II**, even methods for the recovery and recycling of iridium used in this reaction are of interest.

Secondly, the use of nanotechnology-inspired approaches to the presentation of catalysts for potentially enhancing catalysis and providing the opportunity to reduce material consumption are of significant interest. In **paper III**, a flow reactor in lab-on-a-chip device for the Suzuki reaction, a significant reaction in a wide range of synthetic applications, was developed and used in a proof-of-concept study. The significant enhancements of catalytic efficiency provided by the miniaturized flow-cell device warrant further investigation of this concept, and the use of PEI-brushes as a more general approach to the immobilization of transition metal catalysts.

Collectively, the research underlying this thesis provides new strategies for C-C and C-X(S) bond formation, and opens for the use of these developments as new strategies for organic synthesis and applications thereof.

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