Bidentate ligand promoted palladium-catalyzed C–H olefination of aromatic compounds

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CHAPTER 1

C–H FUNCTIONALIZATION: GENERAL INTRODUCTION
1.1 Direct functionalization of C–H bonds

The direct and selective functionalization of C–H bonds is nowadays an attractive strategy to introduce complexity in organic molecules since no pre-functionalization of the starting materials is required (Scheme 1.1, a).¹ This methodology provides a shortcut as compared to the traditional approach (Scheme 1.1, b), reducing time and cost of the process and waste formation. In addition, new synthetic disconnections can be envisioned using the C–H functionalization approach.²

![Scheme 1.1 C–H Functionalization approach.](image)

For example, biaryl-bridged compound 2, a macrocyclic core of Arylomycin A₂, was synthesized via an intramolecular Suzuki cross-coupling reaction of peptide 1 (Scheme 1.2, a).³ Cyclic compound 2 was obtained in 6.4% overall yield in 14 steps starting from commercially available amino acids. In contrast to the conventional approach, the direct C–H functionalization reaction of peptide 3 shortened the synthetic route for the synthesis of the unprotected biaryl compound 4 from 14 to 8 steps and improved the product yield to 25% (Scheme 1.2, b).²

![Scheme 1.2 Synthetic routes for the synthesis of a precursor of Arylomycin A₂.](image)
The C–H bond is the most common bond in organic molecules and this bond is generally unreactive due to its high pKₐ values (above 35) and dissociation energies (85–110 kcal/mol). Several organo- and photocatalytic methodologies have been reported for the activation of inert C–H bonds. Nevertheless, metal-catalyzed C–H functionalization reactions are by far the most widely used approach.

1.2 Transition metal catalyzed C–H functionalization reactions

Transition metals such as Ru, Rh, Pt, Co, and Pd have been generally employed for the activation of C–H bonds, of which the latest is most extensively studied. Using this approach, a variety of functional groups such as aryl, alkenyl, alkyl, halogens, amines or alcohols has been introduced in C(sp²)– and C(sp³)–H bonds. The general outline for the metal-catalyzed C–H functionalization reaction is depicted in Scheme 1.3. The first step, known as C–H activation, involves the insertion of the transition metal into the C–H bond to form the reactive C–M organometallic species. Eventually, follow up reactions of these metal complexes results in the functionalization of the C–H bond.

![Scheme 1.3 Metal-catalyzed C–H functionalization reaction.](image)

Regarding the mechanism of the C–H activation step, three different pathways have been proposed traditionally:

a) oxidative addition with late transition metals with low oxidation states,
b) σ-bond metathesis with early transition metals that are not prone to undergo oxidative addition and
c) electrophilic metalation with electron deficient late transition metals such as Pd(II) or Pt(II) (Scheme 1.4, a–c).

Besides these pathways, concerted metalation-deprotonation (CMD) or ambiphilic metal-ligand activation (AMLA) has been also reported (Scheme 1.4, d). This mechanism involves the assistance of the C–H bond cleavage via Lewis-basic heteroatom co-ligand with a carboxylate being the most frequently used. The carboxylate abstracts the proton from the R–H bond in a concerted fashion to form a new R–M bond. Few transition states of this transformation have been studied and proposed. In 1997, Martinez proposed that the carboxylate assists abstraction of the proton via a 4-membered transition state TS1. In 2005, Davies and Macgregor suggested that an agostic interaction is sufficient to polarize the C–H bond and allows the acetate to interact with the hydrogen that is going to be transferred (transition state TS2).
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1.3 Selectivity and reactivity in C–H functionalization reactions
Although C–H functionalization is an ideal approach to introduce complexity in organic molecules, two main limitations need to be overcome before this strategy can become a routine synthetic tool for organic chemists. These are 1) the low reactivity of C–H bonds and 2) the low selectivity observed in molecules that contain diverse C–H bonds. To increase the selectivity and/or the reactivity of C–H functionalization reactions, three main strategies have been established: 1) to use the intrinsic reactivity of a specific C–H bond, 2) to use directing groups or templates and 3) to use suitable ligands. In the following sub-sections, we will discuss briefly these approaches focusing on examples of Pd-catalyzed C(sp^2)–H bond functionalization reactions, as these examples are most pertinent to this thesis.

1.3.1 Substrate control
Selective functionalization of C–H bonds can be achieved in substrates where one C–H bond is more favorable than the others for steric- and/or electronic reasons. In general, substrates in this category are electron rich heteroarenes such as pyrrole, indole, thiophene or furan. For example, Pd-catalyzed C–H functionalization of pyrrole and indole occurred selectively at the C-2 and C-3 positions, respectively, which are the most electron rich positions (Scheme 1.5, a). On the other hand, site selectivity can be regulated by steric hindrance. For example, C–H arylation of 2-cyclohexyl-5-methyl N-methylpyrrole occurred preferentially at the ortho position with respect to the methyl group to avoid the steric clash with the cyclohexyl
substituent (Scheme 1.5, b).\textsuperscript{20} In contrast, when the cyclohexyl substituent was replaced by an ethyl group, the selectivity dropped from 29:1 to 2:1.

\begin{scheme}
\begin{align*}
\text{a)} & \quad \text{IMesPd(OAc)}_2 (6 \text{ mol}\%)
\quad [\text{Ph}_2 \text{]BF}_4 (1 \text{ equiv}) \\
& \quad \text{AcOH, 25 °C, 15 h} \\
& \quad \text{Ph} \\
& \quad 69\% \\
\text{b)} & \quad \text{Pd(OAc)}_2 (10 \text{ mol}\%)
\quad [\text{Ph}_2 \text{]BF}_4 (1 \text{ equiv}) \\
& \quad \text{KOAc (2 equiv)} \\
& \quad \text{O}_2 \text{ balloon, DMF} \\
& \quad 150 \text{ °C, 24 h} \\
& \quad \text{Ph} \\
& \quad 73\%
\end{align*}
\end{scheme}

Scheme 1.5 Selectivity regulated by the substrate for a) electronic or b) steric reasons.

This strategy is an efficient and useful pathway to obtain the desired product with excellent selectivities. However, this approach can be used only for certain types of substrates. In addition, only the most activated C–H bond can be functionalized.

1.3.2 Directing groups and templates control

The selectivity and reactivity of C–H functionalization reactions can be boosted by using directing groups (DGs) or coordinating ligands attached to the substrate.\textsuperscript{11a,11b,21} The DG chelates to the metal and places the catalyst in proximity to a specific C–H bond in the molecule (Scheme 1.6). In addition, the association of the substrate with the metal complex converts the intermolecular process into a pseudo-intramolecular one. Therefore, both the reactivity and selectivity of the reaction are enhanced.

\begin{scheme}
\begin{align*}
\text{[M]} & \rightarrow \text{H} \\
\text{DG} & \rightarrow \text{H} \\
\text{C-H cleavage} & \rightarrow \text{DG}
\end{align*}
\end{scheme}

Scheme 1.6 Activation mode of directing groups.

In the field of metal-catalyzed C–H functionalization, major efforts have been devoted to the discovery of DGs. As a result, a wide number of DGs based on nitrogen, oxygen or sulfur has been successfully developed for C–H functionalization reactions (Figure 1.1).\textsuperscript{11a,11b,21-22} DGs can be mainly categorized in three types: 1) native DGs, which are common functional groups
present in organic molecules, 2) DGs that cannot be removed from the substrate and 3) removable and transient DGs.

![Figure 1.1 Examples of DGs for C–H functionalization reactions.]

As mentioned above, native DGs are common functional groups that are part of the target molecule. The synthesis of several natural products has been accomplished via C–H functionalization using native directing groups. For example, the synthesis of hexamethyl lithospermate, a derivative of (+)-lithospermic acid, was obtained in excellent yield via intermolecular C–H olefination using carboxylic acid as DG (Scheme 1.7). Although the use of this type of DGs is a powerful method for the selective functionalization of C–H bonds, this approach is limited to certain substrates and generally, these native directing groups are not capable to activate efficiently, for example, C(sp$^3$)–H bonds.

![Scheme 1.7 Carboxylic acid directed ortho C–H olefination.]

Non-removable DGs are functional groups which are difficult to manipulate after the C–H functionalization reaction. For example, pyridine was widely used as DG when C–H functionalization started to bloom. Using pyridine as the DG, a broad number of functionalities was introduced at the ortho position of the arene (Scheme 1.8). Unfortunately, after the C–H functionalization step, the pyridine DG cannot be easily removed and therefore the applicability of this approach is limited.

![Scheme 1.8 Pyridine directed ortho C–H functionalization of arenes.]

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To expand the applicability of C–H functionalization in organic synthesis, many efforts have been dedicated to develop removable or traceless DGs that can be easily modified or removed after the functionalization step.\textsuperscript{21e,26} For example, pyridinediisopropylsilyl (PyrDipSi) DG promoted ortho C–H pivaloxylation in good yields (Scheme 1.9).\textsuperscript{26a} After the functionalization step, removal of the DG or the introduction of other functionalities (I, Bpin) was performed under mild conditions.

![Scheme 1.9 PyrDipSi directed ortho C–H pivaloxylation of arenes.](image)

Recently, new types of DGs, namely transients DGs, have been developed.\textsuperscript{27} The concept of a transient DG relies on the reversible binding of an organocatalyst, containing a Lewis base, with the substrate/product generating an effective DG. For example, ortho C–H arylation of benzaldehyde was performed using 2-aminoisobutyric acid as transient DG (Scheme 1.10).\textsuperscript{27c} 2-Aminoisobutyric acid reacted reversibly with the aldehyde forming an imine derivative that acts as DG (Scheme 1.10, intermediate). Importantly, using this methodology, catalytic amounts of the traceless DG can be employed. This synthetic approach is still in its infancy but will, in time, play a more prominent role in the C–H functionalization field.

![Scheme 1.10 Transient DG promoted ortho C–H arylation of arenes.](image)
Finally, templates have been developed to achieve C–H functionalization reactions at the remote positions. This approach requires three main components comprising a linker, an organic chain and an end-on DG to coordinate with a transition metal catalyst. Common linkers are carbonyl, silyl and sulfonyl while the most common end-on DG is a nitrile. For example, Maiti and co-workers reported the meta C–H functionalization of arenes using a nitrile based template with a sulfonyl linker (Scheme 1.11). The reaction provided meta olefinated products in good yield. Afterwards, the template was removed by hydrolysis under basic conditions.

Scheme 1.11 Nitrile template assisted meta C–H olefination.

Although these templates showed promising results in terms of reactivity and site selectivity, the synthesis of the template required several synthetic steps. In addition, both the introduction and removal of the template are necessary.

1.3.3 Ligand control
An attractive alternative to the use of DGs to improve both reactivity and selectivity of C–H functionalization reactions is by using suitable ligands. Ligands coordinate to the metal center, modifying the catalyst and therefore the activation energy of the reaction. By tuning the steric and electronic properties of the ligands, the selectivity of the reaction can be tailored. In addition, ligands can enhance the solubility of the metal catalyst in organic solvents and extend catalyst lifetimes by preventing or slowing down the degradation pathways of the catalysts.

A wide number of ligands has been developed in different fields of metal catalysis such as cross coupling or metathesis. In contrast, the use of ligands in C–H activation is still scarce. In the particular in the case of Pd-catalyzed C–H functionalization of arenes, only a few classes of ligands such as mono-protected amino acids (MPAA), phosphines and pyridine derivatives have been found capable of promoting C–H functionalization reactions. In general, these ligands are specific for certain type of substrates. Catalytic systems using a MPAA as the ligand are in general suitable for starting materials that contain DGs. The DG controls the site selectivity while the MPAA enhances the reactivity and in some cases the site selectivity. For example, substrates bearing an ether or carboxylic acid as the DG underwent selective C–H olefination in the presence of MPAA (Scheme 1.12) (see Schemes 1.7 and 1.11 for other examples). In these examples, the MPAA is crucial to obtain the olefinated products in high yields. In addition, using carboxylic acid as DG, the MPAA also enhanced the site-selectivity of the reaction.
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Scheme 1.1 Pd/MPAA ligand promoted ortho C–H olefination of arenes using a) ether and b) carboxylic acid DGs.

Phosphine ligands are used in C–H functionalization reactions where at least one of the starting materials is an organohalide. These reactions proceed via a Pd(0)/Pd(II) manifold. For example, the intramolecular C–H arylation reaction of an aryl bromide was efficiently performed under basic conditions using a Pd/phosphine ligand catalyst (Scheme 1.13) (see Schemes 1.16 and 1.17 for other examples).

Scheme 1.12 Pd/MPAA ligand promoted ortho C–H olefination of arenes using a) ether and b) carboxylic acid DGs.

Pyridine-based ligands are at present the most versatile type of ligands for Pd-catalyzed C–H functionalization reactions, for which both directed and non-directed arenes may act as suitable substrates. For example, C–H olefination of 2-phenylacetamide derivatives was achieved efficiently using a pyridine-type ligand. Interestingly, the reaction without ligand did not provide any of the desired product (Scheme 1.14).
As mentioned previously, pyridine ligands were also used to promote C–H functionalization reactions of non-directed arenes. For example, Sanford and co-workers reported the beneficial effect in the reactivity and site-selectivity of the C–H acetoxylation reaction of simple arenes using pyridine as the ligand (Scheme 1.15).42d

These examples showed that ligands have an enormous effect on the reactivity and selectivity of C–H functionalization reactions. Using ligands, a broader substrate scope and efficiency in C–H functionalization reactions of directed and undirected substrates can be realized.

1.4 Base-assisted C–H functionalization reactions
It has been reported that the use of stoichiometric or catalytic amounts of bases such as carboxylates can enhance the reactivity of C–H functionalization reactions.13a,14-15 The role of carboxylates has been investigated by experimental and computational studies.13a,14-15 The results suggested that these bases facilitate C–H bond cleavage, which is generally the rate-determining step, via a CMD mechanism (see Scheme 1.4). The carboxylate interacts with the proton that is going to be transferred, debilitating the C–H bond and therefore promoting the C–H bond cleavage.

For example, Echavarren and co-workers reported an intramolecular C–H arylation using Pd(OAc)2, a phosphine ligand and a base (Scheme 1.16).15d,15e They found out that the use of K2CO3 was crucial for the reaction favoring the cyclization with the most electron-deficient aromatic ring.
### Scheme 1.16 Base-assisted intramolecular C–H arylation.

Three different transition states using DFT calculations were proposed. The intra- and intermolecular carbonate assisted proton abstraction via a CMD mechanism were energetically more favorable than the non-assisted transition state (Figure 1.2). Between the intra- and intermolecular transition states, the energy difference was small and the favorable pathway depended on the substituent on the ring being activated.

![Scheme 1.16](image)

**Figure 1.2** Proposed transition states for the C–H bond cleavage.

The same year, Lafrance and Fagnou proved the key role of the carboxylate co-catalyst on the C–H arylation of benzene (Scheme 1.17). The conversion of this reaction dramatically increased from less than 5% to full conversion when 30 mol% of PivOH was added.

![Scheme 1.17](image)

**Scheme 1.17** Carboxylate assisted intermolecular C–H arylation.
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Figure 1.3 Proposed transition state of pivalate anion assisted C–H bond cleavage.

1.5 Purpose and outline of the thesis
As mentioned above, an attractive alternative to the use of DGs is to use suitable ligands capable of improving the reactivity and selectivity of metal-catalyzed C–H functionalization reactions. This thesis deals with the design and synthesis of new classes of bidentate ligands for Pd-catalyzed C–H functionalization reactions of non-directed arenes. We postulate that bidentate ligands, containing both heteroatom and carboxylic acid functionalities, will be capable of promoting C–H bond activation via a hydrogen bonding interaction (Figure 1.4).

We hypothesize that the carboxylate of the ligand will interact with the hydrogen being transferred accelerating the C–H bond cleavage, which is, in general, the rate-determining step of the reaction. In addition, we expect that the bidentate ligand will stabilize the catalyst, extending the catalyst lifetime.

Chapter 2 describes a general protocol for the synthesis of bidentate ligands based on phosphorus and carboxylic acid functionalities (α-substituted phosphinoacetic acids; P,O-ligands) using simple esters and diphenylchlorophosphine-borane as starting materials. The synthesis of a palladium complex bearing two P,O-ligands is also described.

Chapter 3 deals with the synthesis of bidentate ligands based on sulfur and carboxylic acid functionalities (S,O-ligands). The application of the S,O-ligand in Pd-catalyzed C–H olefination of non-directed arenes with activated alkenes is described. This chapter also includes the C–H olefination of complex molecules.

In Chapter 4, the application of the new catalyst based on Pd(OAc)$_2$ and S,O-ligand in the C–H olefination of non-directed arenes with different allylic substrates is described. This chapter also contains the application of the new methodology in complex molecules.

Chapter 5 deals with the development of the first general para-selective C–H olefination of aniline derivatives using the Pd/S,O-ligand catalyst. The reaction proceeds under mild reaction conditions with a broad range of anilines, including mono-, di- and trisubstituted anilines bearing both electron donating and withdrawing groups.
In Chapter 6, the mechanism of the Pd/S,O-ligand-catalyzed C–H olefination of arenes is investigated. The isolation, characterization and reactivity of several Pd complexes are described. Kinetic studies are performed to elucidate the role of the S,O-ligand in the reaction. All the results are consistent with a base-assisted internal electrophilic substitution (BIES) mechanism.

1.6 References


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For selected examples of C–H functionalization reactions using nitrogen-based heterocycles as DGs, see:

(a) Leow, D.; Li, G.; Mei, T. 


