

Laccase-Catalyzed C-C Bond Forming Reactions

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Carbon-carbon bond forming reactions are some of the most powerful tools available to the synthetic organic chemist. The amount of reactions is vast and the conditions under which they are performed vary greatly. One area that has received much research attention over the past few decades is the C-C bond formation involving unactivated aromatic rings. Whilst many of these types of reactions have been successful in creating high yielding products, they are usually carried out using a transition metal catalyst at elevated temperatures in organic solvents.

It is now well appreciated that several well established organic C-C technologies fail to fulfill the 12 principles of green chemistry. However, due to a greater awareness of environmental compatibility and an increased willingness by all involved to aid in benefiting this global challenge, many green chemistry initiatives have been launched, with participation increasing all the time. To this effect, biotechnology and biocatalysis have played a major role in creating a more sustainable industry. The use of microorganisms and their associated enzymes to carry out chemical transformations is both sustainable and environmentally benign compared to many conventional chemical catalysis which can also be rather expensive.

Laccases (benzenediol:oxygen oxidoreductase EC 1.10.3.2) are copper containing enzymes that are found in nature in various species of insects, bacteria, algae, fungi, and plants [1,2]. In their natural environment, laccases are thought to be responsible for both the formation and degradation of lignin (a large macropolymer that is present in the cell wall of woody biomass), thus laccases have been broadly studied in the pulp and paper industry as a green alternative to delignify pulp [3]. The substrates for laccases are mainly phenolic compounds such as catechols and hydroquinones, as well as some aromatic and polyamines. However, the substrate scope of laccases can be expanded via the use of the laccase-mediator system (LMS) (Figure 1). This system employs a small organic molecule to act as a mediator in that it is oxidized by laccase and is then able to go on to oxidize other compounds within the reaction medium that cannot be directly oxidized by laccase.

Laccases are an extremely efficient and environmentally benign biocatalyst as they require O_2 as their only co-substrate and produce water as their only by-product. Because of this, and the fact they are able to oxidize phenolic compounds to produce reactive Quinone intermediates, they have acquired much attention in the field of synthetic organic chemistry for being green catalysts [4,5]. Furthermore, the vast majority of laccase-catalyzed reactions are conducted in an aqueous medium at ambient temperatures and neutral to mild pH.

Historically, laccase-catalyzed reactions involved radical-radical couplings between phenolic monomers to produce dimers, oligomers, and polymers. Over the past 20 years or so, the ability of laccases to create *in situ* generated *ortho*- and *para*-quinones has been harnessed to perform cross-coupling reactions with a variety of nucleophiles (mainly nitrogen based) and the Quinone acting as the electrophile, which has proved to be an efficient method to derive amino acids and peptides [6].

The use of carbon based nucleophiles to perform laccase-catalyzed cross-coupling reactions is a relatively new reaction that provides a green method for C-C bond formation between an aromatic compound (i.e., hydroquinone or catechol) and compounds containing an acidic methylene or methine proton. One of the first reactions of this type was discovered in 2005 when the activated methylene group of heterocyclic 1,3-dicarbonyls were employed as the nucleophiles to attach to substituted catechols for the synthesis of benzofuran ring systems via a domino reaction (Figure 2) [7]. One of the products was found to be an important precursor of the natural product Flemichapparin C.

Since this initial study, several research groups around the world have expanded the scope to include other compounds that contain acidic methylene or methine protons such as a variety of heterocyclic, cyclic, and aliphatic 1,3-dicarbonyls, as well as substituted pyrazolin-5-ones and substituted oxindoles. Some of the products of these reactions have bioactive properties. For example, some of the benzofuran products produced from the domino reaction of cyclic and aliphatic 1,3-dicarbonyls with substituted catechols have showed to possess anticancer activity [8].

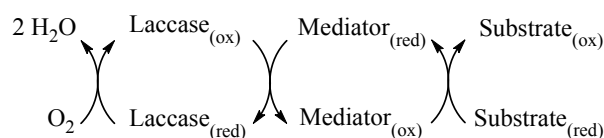


Figure 1: Laccase-mediator system.

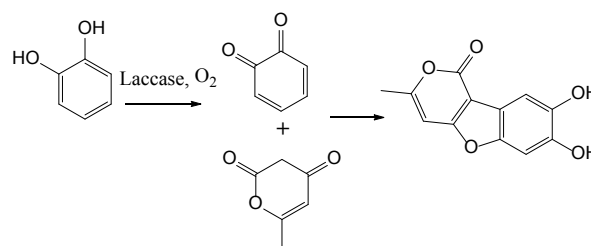


Figure 2: Laccase-catalyzed domino reaction of catechol with a heterocyclic 1,3-dicarbonyl for the synthesis of a substituted benzofuran.

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Received November 15, 2013; Accepted November 16, 2013; Published November 22, 2013

Citation: Cannatelli MD, Ragauskas AJ (2013) Laccase-Catalyzed C-C Bond Forming Reactions. *Organic Chem Curr Res* 2: e125. doi:10.4172/2161-0401.1000e125

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Another C-C bond forming reaction that has been catalyzed by laccases is a Diels-Alder reaction. In this study, the authors employed laccases to react a variety of substituted dienes with catechols and hydroquinones individually to produce 1,2-naphthoquinones and 1,4-naphthoquinones, respectively [9]. The approach involves catechols and hydroquinones that laccase-in-situ oxidizes to the corresponding, the reactive quinone intermediate, which can then go on to react with the diene in a 4+2 cycloaddition.

The field of laccase-catalyzed C-C bond forming reactions is less than a decade old and is thus still in its early days. Research articles are increasingly emerging, with a large majority of the studies published within the past few years. This methodology is certainly a greener and more sustainable means many conventional C-C bond formations involving unactivated aromatic systems compared to conventional methods. Although at the moment these C-C cross-coupling reactions have been limited to compounds containing reactive methylene and methine groups, and the isolated Diels-Alder reaction utilizing a diene, there are many more reactions that remain to be discovered. It will be interesting to witness in the years to come the types of reactions and products that will emerge from using laccases.

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