

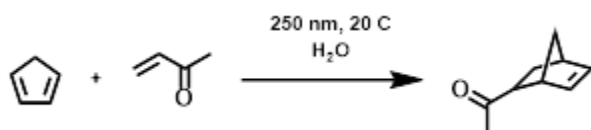
# GREEN CHEMISTRY: CATALYZED C-C BOND FORMATION UNDER AQUEOUS CONDITIONS

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## INTRODUCTION

Compared to common organic solvents, water is an abundant, non-toxic, and cheap alternative. However, limitations such as the deactivation of transition metal catalysts and the insolubility of organic molecules in aqueous media pose significant challenges. In 1980, Breslow and coworkers reported the first example of an organic reaction that demonstrated water can increase its activity and selectivity.<sup>1</sup> They observed a 700-fold rate acceleration and a higher endo preference for the Diels-Alder reaction between cyclopentadiene and butenone in water compared to that in isooctane due to hydrophobic interactions, the



*Scheme 1. Diels-alder reaction.*

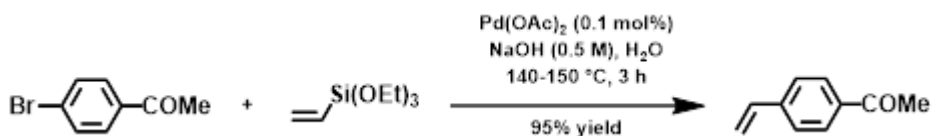
idea that nonpolar substrates associate in water to decrease the hydrocarbon-water surface area (Scheme 1).

Since then, water's unique properties have been utilized to achieve many interesting C-C bond formations in aqueous media.<sup>2,3</sup> Replacing organic solvents with water has also led to significant progress in green chemistry, the design of products and processes to reduce or eliminate the use and generation of toxic chemicals.<sup>4</sup>

## OUTLINE

There are three strategies to achieve catalyzed C-C bond formation in aqueous media: (1) single-layer, (2) interfacial chemistry, (3) and phase transfer catalysis. Single-layer implies that all the reactants and the catalyst are in the same phase, either the water layer, the organic layer, or a solution of two miscible liquids. Water's many roles in organic reactions, such as solvent, Bronsted acid, and nucleophile, have been observed to lead to changes in rates of reaction and stereoselectivities. For example, in 1994, Kobayashi and coworkers reported a Mukaiyama aldol reaction catalyzed by lanthanide triflates in aqueous media with high yields and *syn* preference.<sup>5</sup> More recently, computational studies by Morokuma and coworkers supported two key roles for water.<sup>6</sup> In aqueous conditions, the rate and yield increase because water favors the forward reaction by serving as a proton source for proton transfer and a nucleophile for trimethyl silyl dissociation. The *syn* product becomes entropically favorable

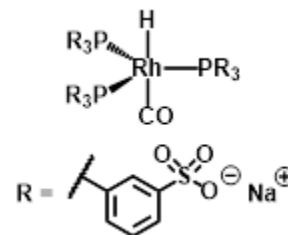
because hydrogen bonding within the *anti*-transition state lowers its flexibility. Further, organic reactions in water may



*Scheme 2. Pd-catalyzed cross-coupling reaction in aqueous media.*

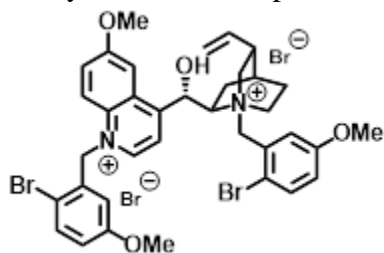
proceed through mechanisms that differ from those reported in organic solvents. For example, the Pd-catalyzed cross-coupling of aryl halides and alkoxy vinyl silanes in THF occurs through a Hiyama coupling but the same reaction in water occurs through a Heck reaction followed by transmetalation or syn-desilylation (Scheme 2).<sup>7</sup>

Interfacial chemistry, also known as biphasic homogeneous catalysis, addresses some limitations of single-layer chemistry: the insolubility of organic molecules in aqueous media and the ability to recover and recycle the catalyst. In this method, the reactants are dissolved in the organic layer, the catalyst is dissolved in the aqueous layer, and the reaction takes place at the interface of the two phases. Cationic and anionic ligands have been designed to form water-soluble complexes with metals, which allows the catalyst to be recovered simply by decanting the organic layer containing the hydrophobic products, collecting the water layer, and reintroducing the aqueous solution of catalyst to fresh reactants. The most common and significant application of biphasic homogeneous catalysis is the Rh-catalyzed hydroformylation of simple olefins in industry (Scheme 3).<sup>8</sup>



**Scheme 3.** Ionic ligands form water-soluble [Rh] complex for hydroformylation.

In phase transfer catalysis, the catalyst transports one reactant from the aqueous layer to the organic layer for the reaction to proceed. Phase transfer catalysts were first reported by Starks and coworkers in 1971.<sup>9</sup> No substitution reaction between an alkyl halide and an aqueous solution of NaCN was observed under reflux after two days. Upon addition of a phosphonium salt or an ammonium salt as a phase transfer catalyst, the reaction proceeded at mild conditions. More recently, the development of chiral phosphonium



**Scheme 4.** Phase transfer catalyst.

salts and ammonium salts has been used to tackle the challenging task of setting tertiary stereogenic centers during C-C bond formation. This method was recently used to synthesize a key intermediate for the drug ubrogepant, in which a phase transfer catalyst closes the ring and sets the stereochemistry of a spiro compound (Scheme 4).<sup>10</sup>

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