

# THE ELECTRON AS AN EFFECTIVE CATALYST FOR RADICAL REACTIONS

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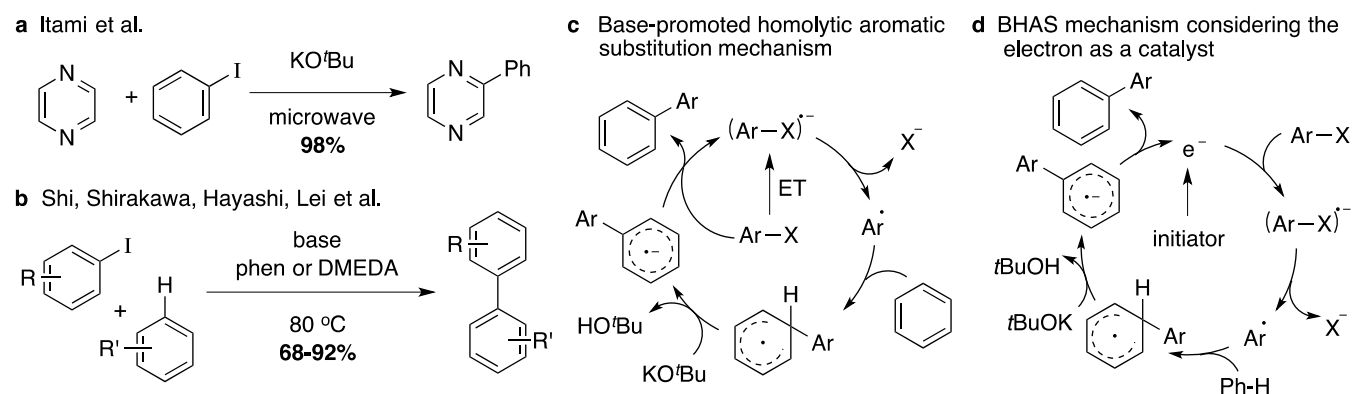
November 12<sup>th</sup>, 2015

## INTRODUCTION

Of the two, elementary charged particles, the proton is well recognized as an effective catalyst. One of the first reactions taught in organic chemistry is acid-catalyzed Fischer esterification. On the other hand, the electron is not typically recognized as a catalyst. The catalytic process which involves *addition* or *removal* of an electron is now called redox catalysis because reactive intermediates operate in different oxidation states in a redox-neutral transformation.<sup>1</sup> Historically, however, redox catalysis of radical chain reactions was called “electron transfer catalysis.”<sup>2</sup> Specifically, a radical chain reaction involving a radical anion as a result of *addition* of electron to the substrate can be viewed as electron catalysis<sup>3</sup> with the unimolecular radical nucleophilic substitution ( $S_{RN}1$ ) reaction<sup>4</sup> from being the classic example. Recently, reports of a new class of electron-catalyzed reaction, base-promoted homolytic aromatic substitution (BHAS), have rejuvenated interest in electron catalysis and have opened new opportunities in radical chemistry.<sup>1,3</sup>

## RECENT EXAMPLES OF ELECTRON CATALYSIS

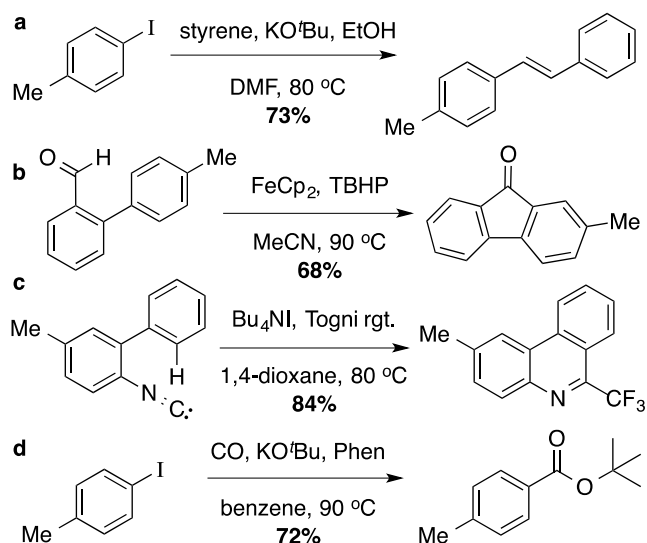
In 2008 Itami first reported the arylation of pyrazine with iodobenzene using KO*t*-Bu under microwave irradiation at 50 °C (Figure 1a).<sup>5</sup> The reaction reached 98% yield within five min. Subsequently in 2010, Shi,<sup>6</sup> Shirakawa and Hayashi,<sup>7</sup> and Lei<sup>8</sup> independently reported similar C(sp<sup>2</sup>)-H functionalization using aryl halides and a strong base in the presence of a substoichiometric amount of 1,10-phenanthroline (phen) or *N,N'*-dimethylethane-1,2-diamine (DMEDA) (Figure 1b). In all cases, radical intermediates were identified by trapping with TEMPO, product analysis or competition reactions. Shirakawa and Hayashi proposed a homolytic aromatic substitution mechanism (Figure 1c).<sup>7</sup>



**Figure 1.** (a) Seminal report by Itami. (b) Generalized reaction scheme from reports by various authors. (c) Mechanism proposed by Shirakawa and Hayashi. (d) BHAS mechanism considering the electron as the catalyst.

Later, Studer and Curran classified these transformations as BHAS reactions and highlighted the role of the electron as the catalyst in a radical chain mechanism (Figure 1d).<sup>1</sup>

BHAS has rapidly expanded in the past five years. New transformations such as the transition-metal-free Heck-type reaction,<sup>9</sup> radical cross-dehydrogenative-coupling (CDC) reaction,<sup>10</sup> arene trifluoromethylation,<sup>11</sup> and alkoxyacylation<sup>12</sup> reactions have been reported (Figure 2). Superficially, these reactions are unrelated because the substrates, reagents and outcomes share few common features. However, all of the reactions have been shown to involve radical intermediates and share the mechanism of BHAS<sup>9-12</sup> and as such are recognized as examples of electron catalysis.



**Figure 2.** (a) Heck-type reaction. (b) CDC reaction. (c) Trifluoromethylation reaction. (d) Alkoxyacylation reaction.

## FUTURE DIRECTIONS OF ELECTRON CATALYSIS

At its inception, BHAS was inaccurately placed in context of organocatalysis or C-H activation.<sup>6,12,13</sup> To further explore the possibilities of BHAS, radical chemistry and its related catalysis is a preferable perspective.<sup>1,3,13</sup> Electron catalysis relies on the innate reactivity of radical intermediates, many of which have been well-documented as elementary reactions.<sup>14</sup> This knowledge provides predictability of electron-catalyzed reactions and therefore allows opportunities for future creativity.

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