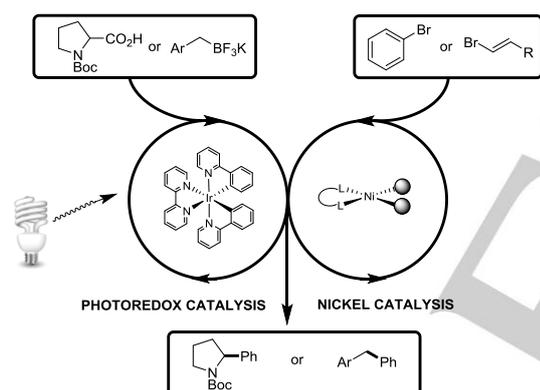


Merging Visible-light Photoredox and Nickel Catalysis

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Sunlight is a safe, renewable, abundant, inexpensive and non-polluting source of energy, all of this means that sunlight is one of the most “green” energy that we can use. Therefore, the development of methodologies to use the solar energy has become a one of the biggest challenge in the scientific community in the last century.^[1] Specifically, the conversion of solar energy into chemical energy is an important topic from the point of sustainability.^[2] Therefore for an efficient development of photochemical reactions will be required the use of the wavelengths of visible-light that are abundant in the sunlight. Nevertheless, one of the drawbacks for the photochemical reactions is that the major part of the organic molecules doesn't absorbed light in the visible region. For this purpose, some photocatalysts that absorb strongly in the visible-light spectrum have been developed to transfer this energy to the organic molecules. These photoredox catalysts absorb the visible-light and transform it into electric potential energy. In this context, transition metal polypyridyl complexes^[3] have been extensively used, and the combination with transition metal catalysis open a wide range of possibilities.^[4]



Scheme 1. The merger of photoredox and nickel catalysis for cross-coupling reactions.

Dual catalysis^[5] is wherein two catalysts work in concert to create a single new bond, and has emerged as a powerful new approach to develop new methodologies for organic synthesis. Successfully synergistic combinations of photoredox and transition metal catalysis, such palladium,^[6] copper,^[7] gold^[8] or rhodium,^[9] has been recently described in the literature. Despite these examples, the combination of nickel and photoredox catalysis is elusive. Nickel catalysis is a pivotal methodology that has provided numerous examples in cross-coupling reactions over the past century and has a great potential for chemical synthesis.^[10] Very recently, the groups of MacMillan^[11] and Molander,^[12] independently, described the combination of nickel

and photoredox catalysis for the Csp³-Csp² cross-coupling reactions (Scheme 1). This highlight focuses on the synthetic scope and limitations of these two methodologies.

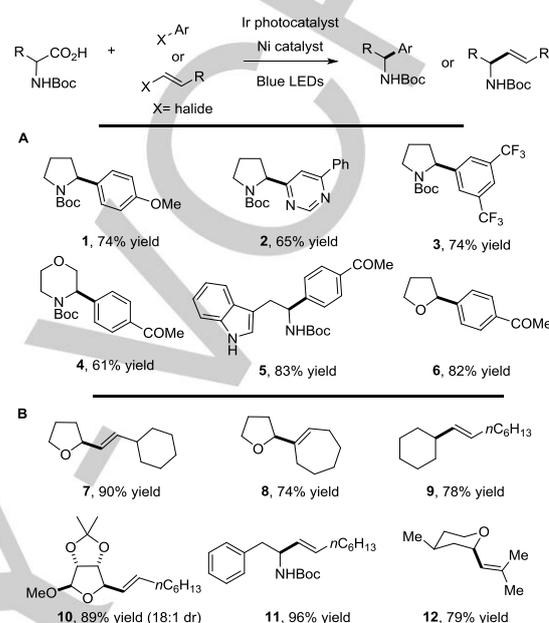


Figure 1. Photoredox-nickel catalysed decarboxylative cross-coupling.

MacMillan and Doyle groups,^[11] introduced a new dual catalysis methodology where a decarboxylative coupling of Csp³ carboxylic acids with aryl halides was possible thanks to the combination of visible-light photoredox catalysis and nickel catalysis (Part A, Figure 1). In this communication a Csp³-Csp² cross-coupling is described with a great scope. Different α -amino acids, including **1-5** (74-83% yield), or α -oxy acids (**6**, 82% yield) were successfully coupled with a wide range of aryl and heteroaryl halides with great yields. This year, MacMillan and coworkers,^[13] continue studying the decarboxylative cross-coupling of α -amino or α -oxy acids (also simple hydrocarbon substituted acid) with simple vinyl halides, the corresponding olefins are obtained with high efficiency under mild conditions (Part B, Fig. 1). For example, product **7-11** were isolated with 74-96% yields. Moreover, *trans*-Rose Oxide **12** (widely used fragrance) could be synthesized in high yield (79%).

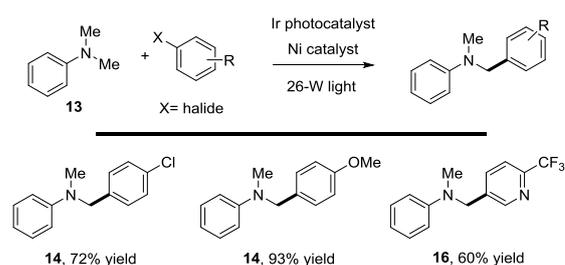


Figure 2. Photoredox-nickel catalysed cross-coupling of dimethylaniline with aryl halides.

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Furthermore, MacMillan group could demonstrate the utility of this methodology for the direct Csp³-H in dimethylaniline **13** with aryl halides (Figure 2).^[11] The α -amino radical from **13** generated via photoredox catalysis, undergoes to the nickel catalysis cycle doing the Csp³-H functionalization possible. Electron-deficient and electron-rich iodoarenes afforded good yields (**14** and **15**, 72% and 93% yields respectively). Moreover heteroaryl bromides were a competent coupling partners for dimethylaniline **13**, obtaining the corresponding product **16** in 60% yield.

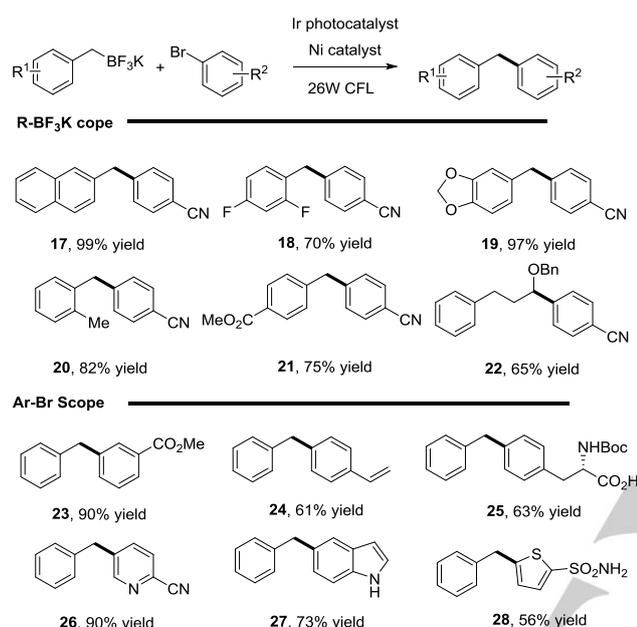


Figure 3. Photoredox cross-coupling of trifluoroborates and aryl bromides.

Concurrently to the first work of MacMillan and Doyle,^[11] Molander published the merger of nickel and photoredox catalysis for the cross-coupling of potassium alkoxyalkyl- and benzyltrifluoroborates with a collection of aryl bromides (Figure 3).^[12] In traditional cross-coupling reactions with Csp³-hybridized boronic acids, the rate-limiting step is the transmetalation (two electron transmetalation), and different strategies have been used for accelerating the rate of transmetalation, such excess of base and high temperatures. Molander group take the advantage of potassium organotrifluoroborates that have been shown their ability to function as a carbon radical sources in single-electron transmetalation to develop this methodology. In this communication, potassium organotrifluoroborates showed low activation energy to form alkyl radical, thanks to the photoredox iridium catalytic cycle, and the advantages are that requires no base or heat. The corresponding alkyl radical form is captured by the nickel catalytic cycle, generating the corresponding product after the reductive elimination. High levels of versatility and functional group tolerance were observed in the scope of the reaction, both benzylic trifluoroborate and aryl bromides (Figure 3). For example, heterocyclic bromides underwent successfully to the cross coupling reaction, and products **26-28**, were obtained with high

yields (56-90%). The absence of and strong base allowed the coupling of the amino acid derivative **25** in good yield, with no observable epimerization. Moreover, 4-bromostyrene, could be used under the optimized conditions, affording the product **24** in 61% yield, without competitive radical capture or polymerization. Remarkably, this methodology was extended to the use of a secondary (α -alkoxy)alkyltrifluoroborate, and the corresponding product **22** was obtained in 65% yield.

Molander and co-workers also applied their photoredox-nickel methodology to the cross-coupling of secondary alkyl trifluoroborates with aryl bromides.^[14] Single-electron-transmetalation allows the use of mild conditions for the cross-coupling. In contrast of the normal secondary alkyl boron reagents were significant isomerization and byproducts are observed, unless electronic or functional groups stabilization is used for an effective reaction. In this communication, the combination of photoredox and nickel catalysis allows the successfully cross-coupling of secondary alkyltrifluoroborates with a wide range of (hetero)aryl bromides (Figure 4), under very mild reactions conditions. Moreover, this dual catalytic system tolerates the coupling of 2-methylcycloalkylborons in high yields and no isomerization was observed. For example products **33-36**, were isolated in 75-78% yield without isomerization of the secondary alkyl chain.

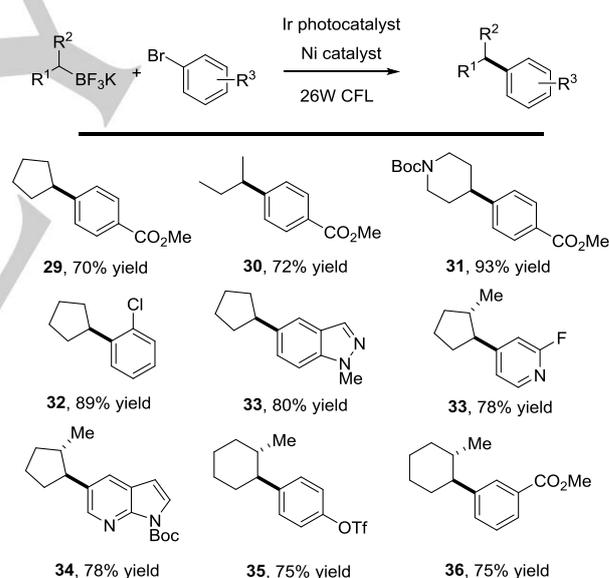


Figure 4. Photoredox cross-coupling of secondary alkyl trifluoroborates and aryl bromides.

The proposed mechanism in both methodologies is similar. The photoexcitation of Ir (III) with visible-light generates the photoexcited Ir(III)* that is a strong oxidant that undergoes a single electron transfer (SET) with an α -amino acid or alkyltrifluoroborate, to generate the reduced Ir(II) and affording the corresponding alkyl radical. Subsequent capture of the alkyl radical at the Ni(II) complex, generating the high valent complex Ni(III), that finally undergoes reductive elimination affording the desired cross-coupling product and the Ni(I) complex (Figure 5).

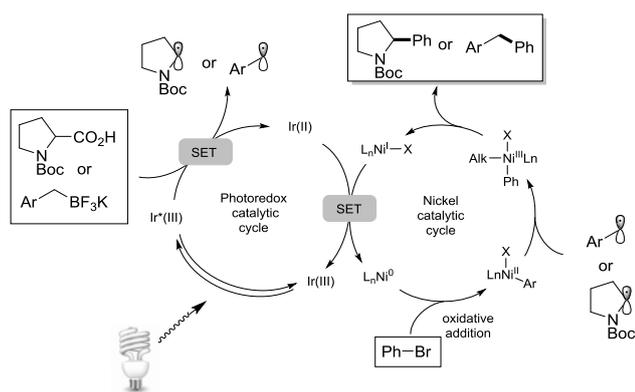


Figure 1. Proposed mechanism for the photoredox-nickel cross-coupling.

In summary, the merging of visible-light photoredox catalysis and nickel catalysis has been successfully achieved for the cross-coupling reactions and has much synthetic potential. This methodology is very attractive due to its operational simplicity and very mild conditions used. This dual catalysis represents a significant advancement to Csp³-Csp² cross-coupling reactions and the synthetic community will be await for the next developments in this area such asymmetric Csp³-Csp² bond formation^[15] or Csp²-heteroatom bond formation^[16] using visible-light photoredox-nickel catalysis.

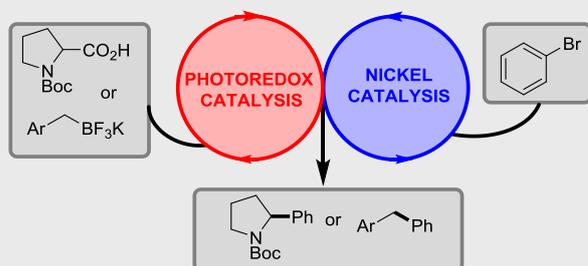
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Keywords: photoredox • nickel • visible-light • cross-coupling • synthetic methods

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HIGHLIGHT



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