

## Photo Meerwein Addition

The Photoredox-Catalyzed Meerwein Addition Reaction:  
Intermolecular Amino-Arylation of Alkenes\*\*

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**Abstract:** A variety of amides are efficiently accessible under mild conditions by intermolecular amino-arylation using a photo Meerwein addition with visible light. The reaction has a broad substrate scope, tolerates a large range of functional groups, and was applied to the synthesis of a 3-aryl-3,4-dihydroisoquinoline.

The Meerwein arylation is a valuable synthetic transformation based on aryl radical chemistry.<sup>[1]</sup> The classic Meerwein arylation has two alternative reaction pathways: a) Meerwein arylation–elimination, in which aryl–alkene cross-coupling products are formed exclusively, and b) Meerwein arylation–addition, in which the aryl radical and a halogen atom add to an olefinic substrate.<sup>[1b]</sup> The addition of atoms other than halogen has also been reported.<sup>[1b]</sup> However, photo Meerwein arylations have been applied so far only for the formation of aryl–alkene coupling products and have not been extended to the valuable alkene addition products<sup>[2]</sup> obtainable under classical Meerwein arylation conditions.<sup>[3]</sup> The challenge in obtaining the addition product is the competing reaction of the trapping reagent or nucleophile with the diazonium salt leading to undesired products (Scheme 1).<sup>[1b]</sup>

The Ritter-type amination reaction is a most useful transformation for the formation of C–N bonds and has

been used in industrial processes for the synthesis of the anti-HIV drug Crixivan, the alkaloid aristotelone, and amantadine.<sup>[2d,4]</sup> We utilize the Ritter reaction conditions to trap the carbenium ion, which is generated during the photoredox Meerwein arylation, thus allowing the intermolecular amino-arylation of alkenes mediated by visible light.

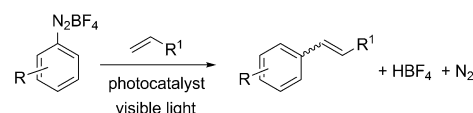
Our initial studies began with the attempted reaction of diazonium salt **1a** (0.25 mmol) with 5 equiv of styrene **2a** using 2 mol % of [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> in 1.0 mL of CH<sub>3</sub>CN containing 10 equiv of water under visible-light irradiation for 4 h at 20 °C; the desired product **3a** was obtained in 42 % yield (Table 1, entry 1) along with 1,2-diphenylethanol as a byprod-

Table 1: Optimizing reaction conditions.

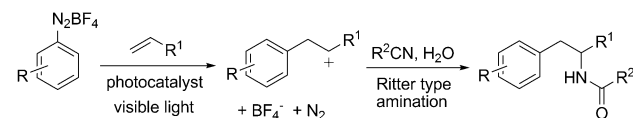
| Entry | Conditions                                                                                                       | Yield [%] <sup>[a]</sup> |
|-------|------------------------------------------------------------------------------------------------------------------|--------------------------|
| 1     | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (2 mol %), <b>2a</b> (5 equiv)                                            | 42 <sup>[b]</sup>        |
| 2     | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (2 mol %), <b>2a</b> (5 equiv)                                            | 75                       |
| 3     | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (2 mol %), <b>2a</b> (5 equiv)                                            | 65 <sup>[c]</sup>        |
| 4     | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (2 mol %), <b>2a</b> (5 equiv)                                            | 74 <sup>[d]</sup>        |
| 5     | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (0.5 mol %), <b>2a</b> (5 equiv)                                          | 75                       |
| 6     | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (0.5 mol %), <b>2a</b> (2 equiv)                                          | 88                       |
| 7     | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (0.5 mol %), <b>2a</b> (1.1 equiv)                                        | 72                       |
| 9     | Eosin Y (0.5 mol %), <b>2a</b> (2 equiv)                                                                         | 38                       |
| 10    | [Ir(ppy) <sub>3</sub> ] (0.5 mol %), <b>2a</b> (2 equiv)                                                         | 76                       |
| 11    | Rhodamine B (0.5 mol %), <b>2a</b> (2 equiv)                                                                     | 5                        |
| 12    | Rose bengal (0.5 mol %), <b>2a</b> (2 equiv)                                                                     | 37                       |
| 13    | C <sub>50</sub> H <sub>40</sub> CuF <sub>6</sub> N <sub>2</sub> OP <sub>3</sub> (0.5 mol %), <b>2a</b> (2 equiv) | 21                       |
| 14    | no photocatalyst, <b>2a</b> (2 equiv)                                                                            | 5                        |
| 15    | [Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> (0.5 mol %), <b>2a</b> (2 equiv), no light                                | 0                        |

[a] Yield determined by GC using a calibrated internal standard. [b] The reaction was carried out with 10 equiv of H<sub>2</sub>O. [c] The reaction was carried out in 0.5 mL of CH<sub>3</sub>CN. [d] The reaction was carried out in 2.0 mL of CH<sub>3</sub>CN. Unless otherwise noted, in all other cases the reactions were carried out in 1.0 mL of CH<sub>3</sub>CN using 1 equiv of H<sub>2</sub>O.

## (a) Photo Meerwein arylation-elimination



## (b) Photo Meerwein arylation-addition



**Scheme 1.** Types of photo Meerwein arylation reactions: a) photo Meerwein arylation–elimination, b) photo Meerwein arylation–addition.

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uct. We examined the influence of the amount of water, the catalyst loading, and the number of equivalents of styrene on this multicomponent photoreaction. To our delight, the desired product **3a** was obtained in 88 % yield (Table 1, entry 6) when diazonium salt **1a** (0.25 mmol), 0.5 mol % of [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub>, 2 equiv of styrene **2a**, and 1 equiv of water were used in 1.0 mL of CH<sub>3</sub>CN. The reaction yields of **3a** are significantly affected by the amount of water: a larger amount of water results in the formation of the 1,2-diphenylethanol (Table 1, entry 1 vs. 2).

After having optimized the reaction conditions we screened different photocatalysts (Table 1, entries 6 and 9–13). [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> was found to be the best one for this transformation. To prove the significance of the photoreaction, we carried out control experiments without the photocatalyst and without light. As expected, we observed little (5% yield) or no product, respectively (Table 1, entries 14 and 15). When we employed dichloromethane as a solvent

**Table 2:** Scope of the aryl diazonium salts.<sup>[a]</sup>

| Entry | Substrate | Product | Yield [%] <sup>[b]</sup> |
|-------|-----------|---------|--------------------------|
| 1     |           |         | 82                       |
| 2     |           |         | 92                       |
| 3     |           |         | 70                       |
| 4     |           |         | 82                       |
| 5     |           |         | 76                       |
| 6     |           |         | 70                       |
| 7     |           |         | 73                       |
| 8     |           |         | 87                       |
| 9     |           |         | 50                       |
| 10    |           |         | 75                       |
| 11    |           |         | 70                       |

[a] The reaction was performed with **1** (0.25 mmol), styrene **2a** (2 equiv), [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> (0.005 equiv), and 1 equiv of water in 1.0 mL of CH<sub>3</sub>CN.

[b] Yield of isolated product after purification by flash column chromatography using silica gel.

and 10 equiv of acetonitrile in this photoreaction, product **3a** was obtained in 70% yield.<sup>[5]</sup> This shows that the use of the organic nitrile as a solvent is not required. In addition, we also replaced the photocatalyst and visible light by copper catalysts, which are commonly employed in Meerwein arylations. However, under these conditions the reaction does not proceed showing that the photoredox system is essential.<sup>[5]</sup>

Furthermore, we investigated the scope of the diazonium salts for this photoreaction and the results are summarized in Table 2. Aryl diazonium salts bearing electron-withdrawing, -neutral, and -donating substituents react smoothly affording the corresponding products in good to excellent yields. Several functional groups including ester, nitro, halide, ether, and alkyl groups are tolerated in the photoreaction. In addition to aryl diazonium salts, heteroaryl diazonium salt **1j** was used in this reaction giving the corresponding product **3j** in 75% yield (Table 2, entry 10).

Carbon-halogen bonds remain intact during the photoreaction providing access to halogen-substituted amides in a single step (Table 2, entries 5 and 9). The halide functional groups can be used for further transformations in transition-metal-catalyzed or organometallic reactions.

**Table 3:** Scope of nitriles.<sup>[a]</sup>

| Entry | Nitrile            | Product | Yield [%] <sup>[b]</sup> |
|-------|--------------------|---------|--------------------------|
| 1     | CH <sub>3</sub> CN |         | 92                       |
| 2     |                    |         | 84                       |
| 3     |                    |         | 65                       |
| 4     |                    |         | 71                       |
| 5     |                    |         | 80                       |
| 6     |                    |         | 72                       |
| 7     |                    |         | 60                       |

[a] The reaction was performed with **1b** (0.25 mmol), styrene **2a** (2 equiv), [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> (0.005 equiv), and 1 equiv of water in 1.0 mL of nitrile. [b] Yield of isolated product after purification by flash column chromatography using silica gel.

We then expanded the scope of the reaction by varying the nitrile, which proved to be of general applicability in the photoreaction. The products obtained from the reactions of diazonium salt **1b** and styrene **2a** with different nitriles are shown in Table 3. The results demonstrate that primary, secondary, and tertiary alkyl nitriles undergo the transformation cleanly providing the corresponding products in good to excellent yields. We were also pleased to find that cyclopropane carbonitrile was tolerated well affording the corresponding product **3m** in 65% yield after 4 h of irradiation with blue light at room temperature (Table 3, entry 3).

Having established the scope of both diazonium salts and nitriles in this photoreaction, we investigated various alkenes. The results are summarized in the Table 4. Styrenes with

**Table 4:** Scope of alkenes.<sup>[a]</sup>

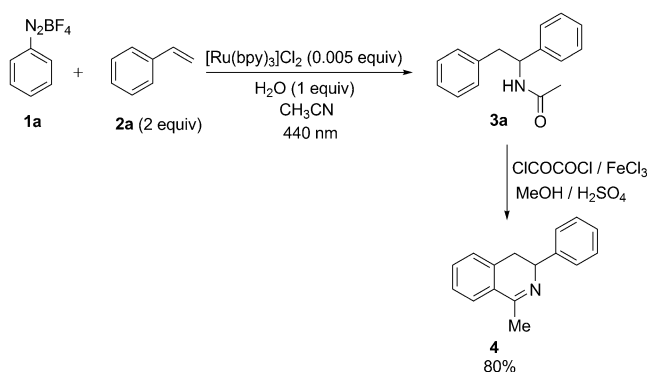
| Entry | R <sup>1</sup> | R <sup>2</sup> | Product | Yield [%] <sup>[b]</sup> |
|-------|----------------|----------------|---------|--------------------------|
| 1     | H              | H              |         | 92                       |
| 2     | Ph             | H              |         | 53                       |
| 3     | H              | Cl             |         | 87                       |
| 4     | COOMe          | H              |         | 20                       |
| 5     | Me             | H              |         | 75 <sup>[c]</sup>        |
| 6     | H              | COOH           |         | 97                       |
| 7     | H              | Me             |         | 55                       |
| 8     | COMe           | H              |         | 43                       |

[a] The reaction was performed with **1b** (0.25 mmol), alkene **2** (2 equiv), [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> (0.005 equiv) and 1 equiv of water in 1.0 mL of CH<sub>3</sub>CN.

[b] Yield of isolated product after purification by flash column chromatography using silica gel. [c] d.r. (65:35).

electron-withdrawing, -neutral, and -donating substituents at the *para* position smoothly give the corresponding products in moderate to excellent yields upon irradiation for 4 h (Table 4, entries 1, 3, 6, and 7). In addition, this photoreaction could also be applied to internal alkenes. The reaction of diazonium salt **1b** with *trans*-β-methylstyrene regioselectively provided the corresponding product **3u** in 75% yield (d.r. 65:35).<sup>[2d]</sup> Notably, *trans*-stilbene, cinnamic acid ester, and benzalacetone can be used in this multicomponent photoreaction and afford the corresponding products as single regioisomers in moderate yields (Table 4, entries 2, 4, and 8).

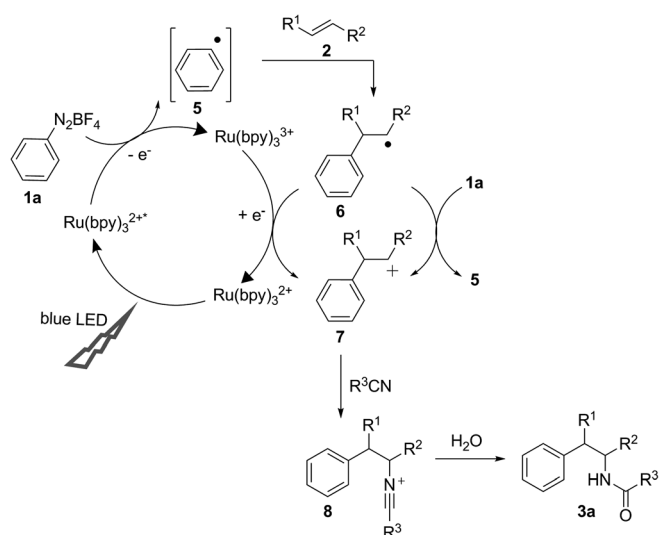
We used the photoreaction product **3a** for the synthesis of 3-aryl-3,4-dihydroisoquinoline to demonstrate its application and adopted a previously reported method by Larsen and co-workers (Scheme 2).<sup>[6]</sup> The reaction of diazonium salt **1a** with styrene **2a** under standard photoreaction conditions provided the corresponding product **3a**, which was then further converted into 3-aryl-3,4-dihydroisoquinoline **4** using oxalyl chloride and FeCl<sub>3</sub>.<sup>[6a]</sup>



**Scheme 2.** Application of the photoreaction in the synthesis of 3-aryl-3,4-dihydroisoquinoline.

The suggested mechanism of the photoreaction based on the trapping of intermediates and related literature reports is depicted in Scheme 3.<sup>[2d,3a,7]</sup> Aryl radical **5** is formed initially by a single-electron transfer from the excited state of the photocatalyst [Ru(bpy)<sub>3</sub>]<sup>2+\*</sup> to diazonium salt **1a**. Addition of aryl radical **5** to alkene **2** yields the corresponding radical intermediate **6**, which is then further oxidized to give carbenium intermediate **7**.<sup>[3e]</sup> Finally, the intermediate **7** is attacked by a nitrile (R<sup>3</sup>CN), followed by hydrolysis to give the amino-arylated product **3a**.<sup>[2d]</sup> Radical intermediate **6** is either oxidized by the strong oxidant [Ru(bpy)<sub>3</sub>]<sup>3+</sup> to complete the photocatalytic cycle or by the diazonium salt **1a** in a chain-transfer mechanism. Radical intermediates **5** and **6** were trapped with TEMPO, which supports radical intermediates during the photoreaction.<sup>[3c-e,5]</sup> In addition, the carbenium ion intermediate was also trapped with water and methanol; these results indicate the formation of intermediate **7** in the reaction.<sup>[5]</sup>

In conclusion, the reported protocol allows the formation of C<sub>alkyl</sub>-N bonds by an intermolecular amino-arylation of alkenes mediated by visible light. It is, to the best of our knowledge, the first example of a photocatalytic Meerwein



**Scheme 3.** Proposed mechanism for the photo Meerwein addition reaction.

addition reaction. The multicomponent reaction gives efficient access to different types of amides under mild reaction conditions and tolerates a broad range of functional groups. The substrate scope of the diazonium salts, nitriles, and alkenes is broad. Many products of the photoreaction are not easily accessible by other methods and have, due to the presence of halide functional groups, the potential for further synthetic elaboration. For example, one photoreaction product was used for the synthesis of a 3-aryl-3,4-dihydroisoquinoline. Experiments to elucidate the mechanism of the reaction in detail, and applications of the reaction to the synthesis of other potential biologically active molecules are ongoing in our laboratory.

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