

Unexpected Dual Role of Titanium Dioxide in the Visible Light Heterogeneous Catalyzed C–H Arylation of Heteroarenes

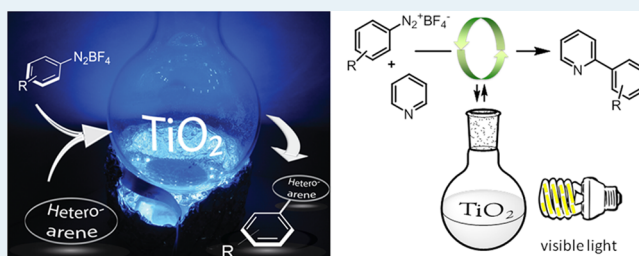
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Supporting Information

ABSTRACT: The direct arylation of heteroaremetics with an easily accessible and recyclable, heterogeneous TiO₂ catalyst and visible light was developed. Electron-rich as well as electron-poor heteroarenes could be applied in this transformation, and the corresponding products were isolated in very good yields. Azoethers were detected as reactive intermediates, and the unexpected role of TiO₂ in their formation as well as reaction was established.

KEYWORDS: photocatalysis, heterogeneous catalysis, cross coupling, C–H activation, photoredox catalysis



INTRODUCTION

The use of titanium dioxide as a heterogeneous catalyst offers an environmentally friendly alternative to homogeneous photocatalysis. Due to its low cost, nontoxicity, and high chemical stability, titanium dioxide is one of the most popular photochemical materials.^{1–11} Titanium dioxide is predominantly used to degrade pollutants^{3,9,10} being also well-known in the photocatalytic oxidation of alcohols and hydrocarbons.^{12–20} However, the use of titanium dioxide with visible light is not very effective in organic synthesis as its activation requires UV light ($\lambda = 385$ nm) due to the band gap of 3.2 eV (anatase). Due to the use of UV light, the substrate range and compatibility with various functional groups is limited so that only a few organic transformations have been described.^{21–30}

Recently, the use of visible light in combination with metal- and metal-free catalysts^{31–50} attracted attention as a promising method for the C–H arylation with diazonium salts.^{51–57} Whereas typically cross coupling and transition metal catalyzed reactions are applied for the synthesis of biaryl building blocks, the direct arylation of C–H bonds is, if feasible, more efficient.⁵⁸ Pioneering work in this area is represented by the copper catalyzed Meerwein-arylation,^{59,60} which is nowadays not commonly used due to its low yields. Recently, Heinrich described a highly interesting TiCl₃-mediated arylation with diazonium salts.^{61–63} Not only diazonium salts could successfully be applied, but also sulfonyl chlorides,^{64,65} aryl iodides,^{66–68} sulfonium,⁶⁹ and iodonium^{70–73} salts proved to be efficient aryl sources. Furthermore, König reported on an elegant light-mediated, direct arylation of heteroarenes, enol acetates, and alkenes with diazonium salts using Eosin Y as photoredox catalyst.^{74–77} In addition, the successful conduction of redox reactions making use of visible light and titanium dioxide modified with ruthenium complexes or gold nanoparticles was reported.^{78,79}

Based on these considerations and our own results in the field of photocatalysis with visible light, we decided to investigate the direct arylation of heteroarenes by using a heterogeneous catalyst.^{49,50,80} In order to develop a practicable protocol, the catalyst should be easily accessible, recyclable, applicable to a broad substrate spectrum and the products should be delivered in good yields under mild and environmentally friendly reaction conditions.

RESULTS AND DISCUSSION

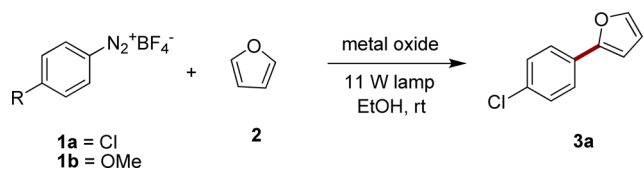
To accomplish our goal, we started our investigations with the TiO₂-mediated direct arylation of arenes with diazonium salts. First attempts showed that the arylation of furan with aryl diazonium salt **1a** in the presence of commercially available and cheap titanium dioxide (Evonik-Degussa Aeroxide P25) indeed provided, under irradiation with an 11 W household lamp, the desired product **3a** (Table 1). Background reactions without light or catalyst delivered the product only in traces. In pure furan, the product could only be isolated in 40% yield. Among the different solvents tested, chlorinated and polar aprotic solvents delivered only traces or led to decomposition, respectively.⁸¹ Surprisingly, the reaction in alcohols provided the desired product in good yields. Next to methanol and ethanol, the reaction could surprisingly also be conducted in isopropanol.

Subsequently, the influence of different metal oxides as well as their modifications was investigated and the results are summarized in Table 1. Whereas the reaction with ZnO and the TiO₂-modification anatase as catalyst led to the formation of product only in poor yields after 4 h (entries 3 and 4), the product was obtained in excellent yields with the rutile and P25 modification (anatase/rutile 70:30) (entries 1 and 2). A

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Table 1. Optimization of Reaction Conditions^a

entry	metal oxide	equiv	time	yield [%] ^b
1	TiO ₂ (P25)	1	4	96
2	TiO ₂ (rutile)	1	4	95
3	TiO ₂ (anatase)	1	4	44
4	ZnO	1	4	57
5	TiO ₂ (P25)	1	4	96
6	TiO ₂ (P25)	0.1	4	66
7	TiO ₂ (P25)	1	2	61
8	TiO ₂ (rutile)	1	4	95
9	TiO ₂ (rutile)	1	2	95
10 ^c	TiO ₂ (rutile)	0.1	5	92
11	TiO ₂ (P25), blue LEDs	1	4	36
12	TiO ₂ (rutile), blue LEDs	1	4	82
13	TiO ₂ (anatase), blue LEDs	1	4	68

^aReaction conditions: 0.1 mmol **1a**, 0.1–1 equiv. metal oxide, 1 mL solvent, 1 mL furan, irradiation with the 11 W CFL lamp from 3 cm distance for 2–12 h under argon atmosphere. ^bYield after chromatographic purification. ^c0.2 mmol.

subsequent reduction of reaction time and catalyst loading provided the product with P25 in moderate yields (entries 6 and 7). In contrast, under similar reaction conditions, rutile provided the product in very good yields (entries 9 and 10). In further studies, the influence of the light source was investigated. Whereas anatase with a band gap of 3.2 eV requires irradiation with light with a wavelength of 385 nm, rutile has a band gap of 3.0 eV and can therefore be irradiated with only 413 nm. Using an 11 W CFL bulb which provides irradiation of the entire visible light region (400–800 nm), the yield of the product with rutile was indeed higher than with P25 and anatase. Using blue LEDs with an emission spectrum around 455 nm, rutile also showed full conversion, whereas anatase and P25 led to significantly lower yields (entries 11–13).

These results showed that the direct arylation with titanium dioxide and visible light could indeed be conducted. Based on these findings, we decided to record UV–vis solid-state spectra of the reaction. These measurements revealed that absorption of the reaction mixture on titanium dioxide was significantly shifted toward the visible region and can therefore be performed with visible light (Figure S1 in the SI). The fast color change of the reaction solution after start from colorless/slightly yellow to intensive yellow prompted us to investigate the reaction kinetics via UV–vis liquid spectroscopy since both substrate and product show no absorption in the visible light region (Figure S3 in the SI).⁸¹

In the standard reaction with diazo compound **1a** (R = 4-Cl) an absorption maximum at 412 nm could be observed after only a few minutes that vanished immediately afterward. When the reaction was conducted without titanium dioxide, the absorption maximum was still formed, however the intensity decreased rather slow and after 4 h was still present. In the standard reaction without furan, interestingly no maximum was detected over a period of 4 h. This led to the conclusion that the diazonium salt reacts with the alcohol to an intermediate which was assigned to the azoether **4a**.^{82–87} Furan could help in the formation of the

azoether acting as a weak base. To get further evidence we monitored the reaction profile via MS-ESI and established that azoether **4a** could be detected only at the beginning of the reaction, whereas in the reaction without titanium dioxide compound **4a** was present over the whole period (Figure 1).⁸¹

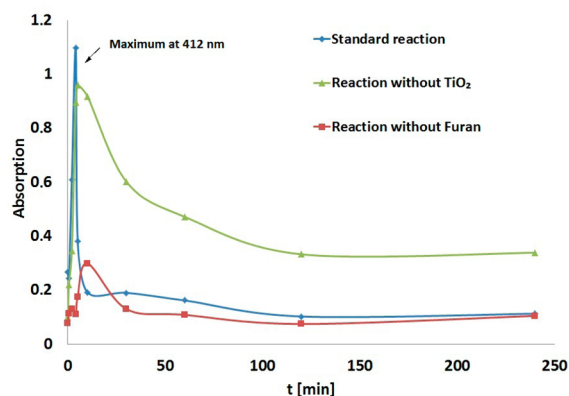


Figure 1. Reaction kinetic of formation and decomposition of azoether **4a** (R = 4-Cl) via detection of absorption maximum at 412 nm.

It was previously shown in the 1980s that under basic conditions aryldiazonium salts (no absorption in the visible range) can be converted into azoethers (absorption in the visible range).^{82–87} Measurements of pH values showed that after formation of azoether **4**, the reaction medium is acidic until the end of the reaction, which can be explained by the formation of HBF₄.⁸¹ Similar compounds were also studied as azosulfides.⁸⁸ Thus, the implicit question was whether titanium dioxide catalyzes only the reaction of azoether **4** or even its formation, in analogy to the titanium dioxide catalyzed transesterification and transesterification. To answer this question, the kinetic of the reaction of an electron-rich diazonium salt (**1b**, R = OMe), which reacts slower, was investigated by UV–vis liquid spectroscopy (Figure 2).

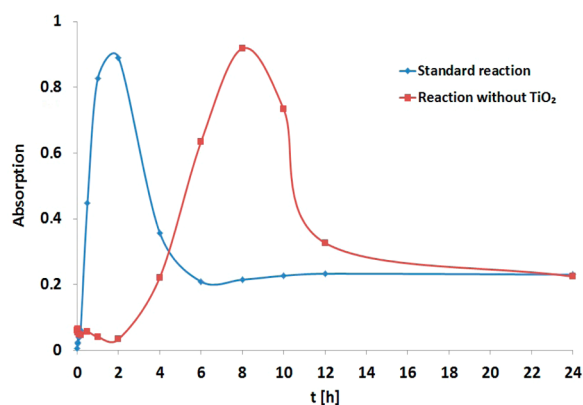


Figure 2. Reaction kinetic for the formation and conversion of azoether **4b** (R = 4-OMe) via detection of absorption maximum at 448 nm.

In the standard reaction with titanium dioxide an absorption maximum at 448 nm could be observed after 30 min. Without titanium dioxide, the absorption maximum was formed only after 8 h, suggesting that the titanium dioxide is not only involved in the conversion but also the formation of the azoethers.

Based on these findings as well as corresponding literature reports,^{12–20,51,61–65,82–90} we assumed that titanium dioxide

catalyzes the formation of azoether **4** under standard reaction conditions (Figure 3a). A transesterification allows the

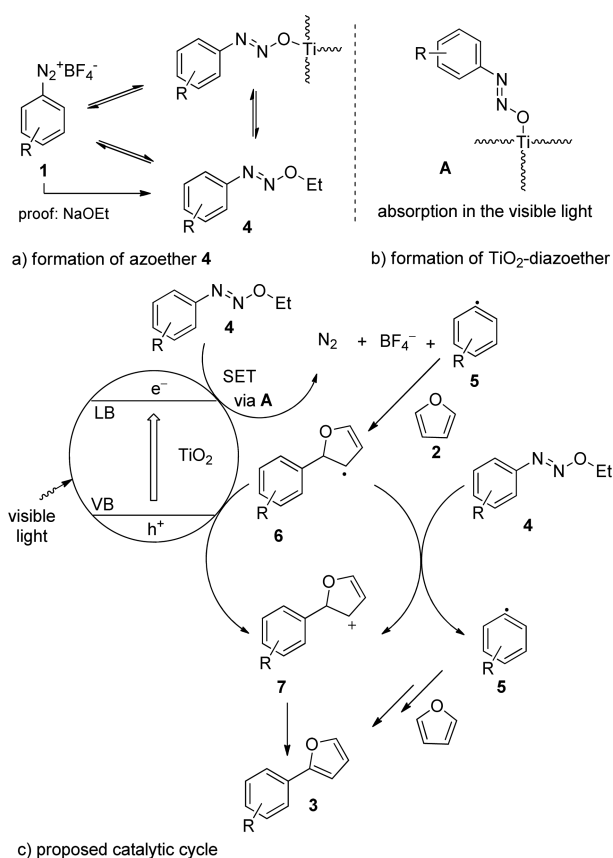


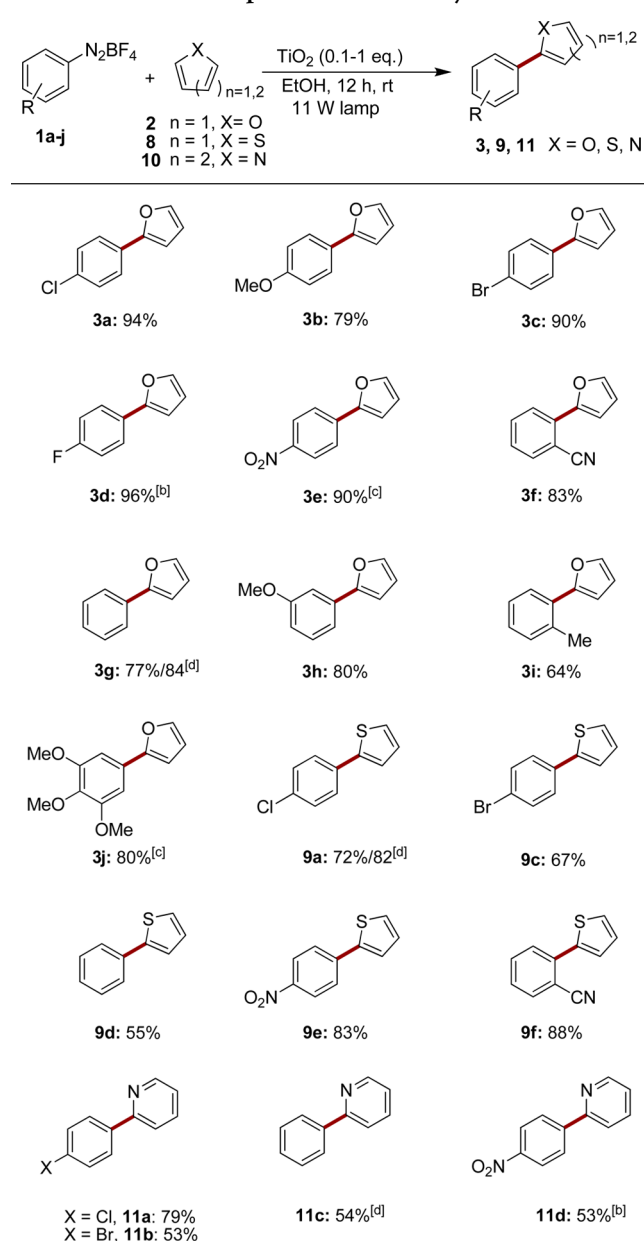
Figure 3. Postulated reaction mechanism for the TiO_2 -mediated direct arylation of heteroarenes.

formation of TiO_2 -azoether **A** (Figure 3b) which shows absorption in the visible light region⁸¹ and behaves similarly to surface modifications of titanium dioxide with ruthenium complexes or gold nanoparticles^{20,78,79}. By excitation of the modified titanium dioxide, a single electron transfer and the formation of aryl radical **5** occurs (Figure 3c). The subsequent addition of the aryl radical onto the heteroaromatic **2** delivers the radical intermediate **6**, which then reacts to the carbenium ion **7**. This step can be mediated by both titanium dioxide or by radical chain mechanisms with azoether **4**. However, it has to be noted that free aryl radical reactions are typically not performed in alcohols due to the hydrogen abstraction. A final rearomatization of **7** leads to formation of the reaction product **3**. The reaction profile also explains why alcohols can be used as solvent. On one hand they work as substrates for the formation of azoethers and on the other hand their polar character allows desorption from the titanium dioxide surface.

Interestingly, metal-catalyzed cross coupling reactions of diazonium salts are also conducted in alcohols. Formations of azoethers are generally not considered in the proposed mechanisms although they indeed proceed via such intermediates. A more detailed study of Pd-catalyzed cross couplings of diazonium salts considering azoether formation would be desirable.

With the optimal conditions and a better understanding of the reaction mechanism in hand, we investigated the substrate scope of the titanium dioxide mediated direct C–H arylation (Table 2).

Table 2. Substrate Scope of Furan with Aryldiazonium Salts^a



^aReaction conditions: 0.1 mmol **1a–j**, 0.1–1 equiv metal oxide, 1 mL EtOH, 1 mL heteroarene, irradiation with 11 W CFL lamp from 3 cm distance, yield after chromatographic purification. ^b0.2 mmol. ^c2 mmol. ^d0.1 equiv TiO_2 (P25).

Using different aryl diazonium salts, the corresponding products were obtained generally in good to excellent yields. The direct arylation could be successfully performed with both electron-withdrawing as well as donating and neutral substituents. The use of ortho, meta, and para, as well as multiple substituted aryl diazonium salts, was possible. In order to examine the efficiency of the heterogeneous catalyst, the reaction scale was increased (**3e** and **3j**) and catalytic amounts of the catalyst were used (**3g**). In both cases, no loss of reactivity or selectivity could be observed emphasizing the potential of the developed protocol as an environmental friendly methodology.

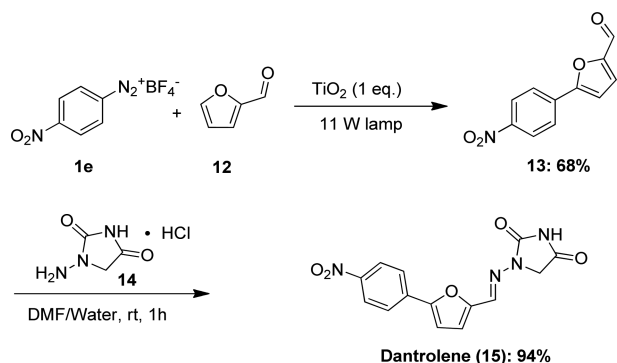
Next other 5- and 6-membered heteroarenes were tested in the heterogeneous catalyzed arylation. The corresponding products **9a** and **c–f** from the arylation of thiophene were obtained in

moderate to high yields. To underline the versatility of the protocol, an extension of the substrate scope was tested and the photocatalyzed C–H arylation of pyridine as electron-poor heteroarene was successfully accomplished for the first time. The corresponding products **11a–d** were obtained in moderate to good yields.

As an extension of the substrate scope substituted heteroarenes were investigated toward their reactivity and regioselectivity.

The arylation of furfural **12** with the aryldiazonium salt **1e** delivered the desired product **13** in good yield. A [2 + 2]-cycloaddition product that can be expected under the use of UV-light, was not observed. The subsequent condensation reaction with 1-aminohydantoin hydrochloride **14** provided dantrolene **15** in a very good yield (Scheme 1). Dantrolene represents a specific and efficient muscle relaxant for the treatment of life threatening disorders during anesthesia.⁹¹

Scheme 1. Synthesis of Dantrolene



For further illustration of the practicability of this cheap and easily accessible heterogeneous catalyzed protocol, TiO₂ was recycled after the reaction and subsequently reused. The catalyst could be easily recovered by centrifugal separation and then reused without loss of reactivity or selectivity in repeated reaction cycles (Table 3).

CONCLUSION

In summary, we developed an environmental friendly, direct arylation of heteroarenes using an easily accessible, cheap and

Table 3. Evaluation of Catalyst Recycling^a

cycle	1	2	3	4	5
yield ^b	93	89	91	88	89

^aReaction conditions: 0.2 mmol **1a**, 1 equiv TiO₂ (P25), 2 mL EtOH, 2 mL furan, irradiation with 11 W CFL bulb from 3 cm distance for 12 h. ^bYield after chromatographic purification.

recyclable heterogeneous catalyst. The TiO₂ catalyst is robust and can be repeatedly applied in the arylation of electron-rich and -poor heteroarenes delivering the products in moderate to excellent yields.

Next to furan and thiophene, pyridine could also be applied in such reactions. Furthermore, easy separation of the catalyst could be accomplished by centrifugation and allowed the repeated use of the catalyst without loss of performance. Moreover, arylation of furfural was successfully conducted enabling the synthesis of the muscle relaxant dantrolene in a very good yield. The combination of UV–vis spectroscopy and mass spectrometry permitted identification of azoethers as reaction intermediates. Interestingly, TiO₂ has a dual role. It is not only catalyzing the formation of the azoether but also initiate their conversion. This explains the shift of absorption toward the visible light region. Further studies based on these interesting observations, as well as the development of TiO₂ mediated reactions with visible light, are the subject of current investigations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00668.

General procedures and full characterization of the products and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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