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Palladium Catalysis

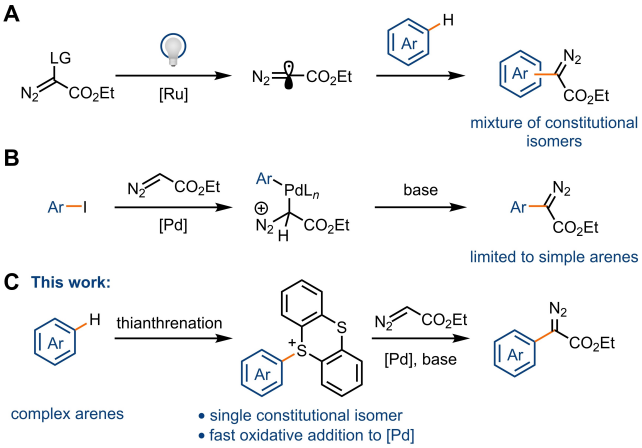
Late-Stage Diazoester Installation via Arylthianthrenium Salts

*Le Li, Sven Müller, Roland Petzold, and Tobias Ritter**

Abstract: By leveraging the fast oxidative addition of arylthianthrenium salts (aryl-TT$^+$) to palladium(0), a regioselective diazoester installation has been developed. This approach enables the introduction of a diazo moiety to densely functionalized arenes at a late stage. The installed diazo group is amenable to facile further derivatization.

Aryl diazoalkanes are valuable building blocks in organic synthesis due to their versatile reactivity as α-carbon nucleophiles,[1] terminal nitrogen electrophiles,[2] 1,3-dipoles,[3] and radical precursors.[4] Additionally, under heating, metal catalysis or irradiation, aryl diazoesters give donor/acceptor carbenes, which are widely used in facile structural modifications of organic molecules.[5] Electron-rich diazoalkanes are unstable, explosive and toxic.[6–8] While diazoalkanes with acceptor substituents at the α–C are more stable, they undergo rapid dediazotization when exposed to acids, heat, or transition metals.[6,9] Synthesis of complex aryl diazo compounds is therefore limited due to facile decomposition of the diazo products, once formed, by side reactions. Herein, we report the first general method for the synthesis of aryl diazoacetates via arylthianthrenium salts. The two-step procedure leverages the site-selective C–H thianthrenation of arenes, followed by the fast oxidative addition of the resulting arylthianthrenium salts to Pd, to afford aryl diazo compounds, which are currently inaccessible from other aryl (pseudo)halides.

Most modern approaches to aryl diazoalkanes can be classified into two categories, namely free radical-based photocatalytic C–H functionalization[10] and palladium-catalyzed cross-coupling reactions of aryl iodides (Scheme 1).[11] The photocatalytic procedure reported by Suero and associates describes a light-induced assembly of aryl diazoesters from medicinally relevant arenes (Scheme 1A).[10b] This method does not require a pre-functionalization step, yet, the presence of multiple C–H bonds in a given arene can result in a mixture of constitutional isomers. The cross-coupling process was pioneered by Wang and co-workers who reported a palladium-catalyzed functionalization of ethyl diazoacetate (EDA) with aryl iodides to afford aryl diazoesters (Scheme 1B).[11a] This procedure requires the addition of half an equivalent of silver salts for electron-rich aryl iodides and is limited to simple arenes.[11d] Despite progress in the field, a site-selective, late-stage synthesis of aryl diazo compounds with a broad scope of arenes has not yet been accomplished. Here we report a method that overcomes the current limitations because reaction of the arylthianthrenium salt with the catalyst can proceed at conditions mild enough, so that the product diazo compound is not destroyed at a competitive rate.



Scheme 1. A, B: Modern approaches to aryl diazoalkanes and their limitations. C: Our method for the site-selective C–H functionalization of complex arenes with α-diazoacetate.

The combination of C–H thianthrenation with Pd-catalyzed functionalization can achieve site-selective α-diazoester installation to complex arenes (Scheme 1C). First, C–H thianthrenation is performed on an arene to obtain a single constitutional isomer with a thianthrenium linchpin. Other (pseudo)halide linchpins can often not be introduced with comparable positional selectivity for simple and complex arenes alike.[12] Second, the aryl thianthrenium salt undergoes fast oxidative addition to Pd to afford the complex aryl diazo compounds by outcompeting deleterious follow-on reactions of the diazo product. Thus, our method provides straightforward access to densely functionalized α-diazoesters that were outside the reach of previous methodologies.

We started our investigation with the selection of a suitable palladium catalyst and found that 58 % of *p*-meth-

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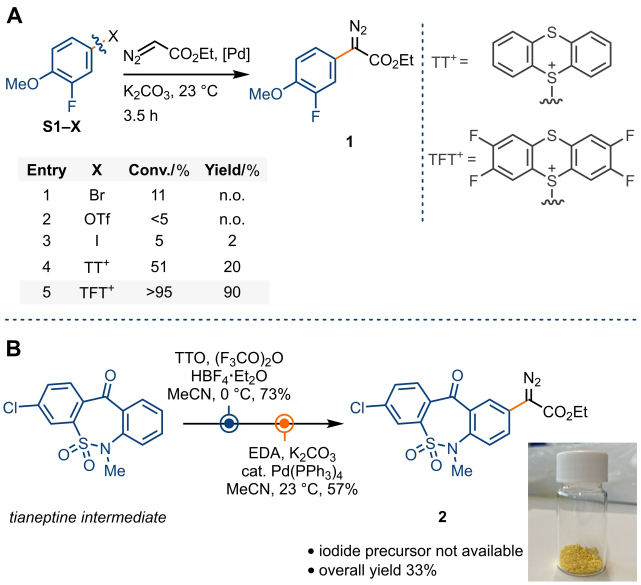
oxylphenyl diazoacetate (0.1 M in CD_3CN) underwent dediazotization when mixed with 10 mol% $Pd(PPh_3)_4$ for 18 h at 23 °C, presumably via formation of a palladium carbene complex.[13] Under similar conditions, 73% of the diazoester was consumed when mixed with $Pd(OAc)_2$ or $Pd(^tBu_3P)_2$ (see Supporting Information for details, p. S35). A smaller rate of dediazotization is desirable in order to maximize the difference of the relative rates of productive diazomethylation and destructive dediazotization. Evaluation of palladium catalysts, bases, and solvents showed that a combination of 10 mol% $Pd(PPh_3)_4$ with 1.5 equivalent of K_2CO_3 in MeCN (0.1 M) resulted in satisfactory yields of the diazoester products.

Fast conversion and careful choice of the reaction time of the diazoester installation procedure are essential for the isolation of the aryl diazo products. Monitoring of the reaction of ethyl diazoacetate with a tetrafluorothianthrenium salt by ^{19}F NMR spectroscopy revealed an initial steady increase in the concentration of the product **1** (see Figure 1). However, reaction times longer than 3.5 hours lead to a decrease in the concentration of **1**, which may be due to side reactions with palladium,[13] free phosphine ligands[14] or acidic impurities.[9a] An additional 40 minutes of reaction time resulted in a 10% lower yield of **1**. Therefore, conversion has to be carefully monitored, and the reaction must be stopped at full conversion to avoid subsequent decomposition of product.

A comparison of the reactivity of aryl-TT^+ salts with the corresponding aryl (pseudo)halides confirmed the advantages of arylsulfonium salts. Without the addition of extra phosphine ligands or leaving group scavengers, the reaction of ethyl diazoacetate with *p*-methoxylphenyl tetrafluorothianthrenium salt **S1–TFT** reached full conversion in less than 4 hours with 90% yield as determined by quantitative NMR spectroscopy (Scheme 2A). We have also observed an unusual superiority of the tetrafluorothianthrenium salts when compared to the parent thianthrenium salts, which under identical conditions, only proceeded in half the conversion (Scheme 2A). Under the same conditions, the corresponding aryl iodide **S1–I** reached 5% conversion with only trace amounts of the desired product formed. Slow conversion was also observed for aryl triflates (<5%) and -bromides (11%) under the same reaction conditions. The higher conversions of arylsulfonium salts is consistent with fast and irreversible oxidative addition of the arylthianthrenium salts to Pd(0).[15] The higher reactivity of Ar-TT^+ may also be supported by faster nucleophilic attack of EDA to the cationic Pd center, which is also consistent with the requirement for silver salts when aryl iodides are used.[11d] The diazoester installation process to thianthrenium salts can be carried out on a gram scale to obtain for example antidepressant drug derivative **2** (Scheme 2B). Because C–H thianthrenation of the complex arenes can be accomplished regioselectively,[12,16] subsequent Pd-catalyzed diazomethylation of the arylthianthrenium salt provides **2** in 33% yield over two steps from the parent C–H molecule.

To examine the scope of the reaction, arylthianthrenium salts of structurally diverse arenes were prepared via C–H thianthrenation, followed by cross coupling with the diazoacetate. Under optimized conditions, most aryl diazo esters were obtained from the arylthianthrenium salts within approximately four hours, with yields ranging from 41 to 83% (Scheme 3). In cases where conversion was slow, DMF (0.25 M) was used as the solvent instead. The formation of a



Scheme 2. A: Introduction of diazoester group to different substrates (reaction condition: 10 mol% $Pd(PPh_3)_4$, 2.5 equivalent EDA, 1.5 equivalent K_2CO_3, MeCN (0.1 M), 23 °C, 3.5 h). B: A gram-scale reaction of tianeptine intermediate-derived thianthrenium ion to obtain diazo ester **2** (reaction conditions: thianthrenation: 1.0 equivalent thianthrene-*S*-oxide (TTO), 3.0 equivalent trifluoroacetic anhydride, 1.2 equivalent $HBF_4 \cdot Et_2O$, MeCN (0.2 M), 0 °C to 23 °C, 12 h;[17] diazoester installation: 10 mol% $Pd(PPh_3)_4$, 2.5 equivalent EDA, 1.5 equivalent K_2CO_3, DMF (0.25 M), 23 °C, 2 h).

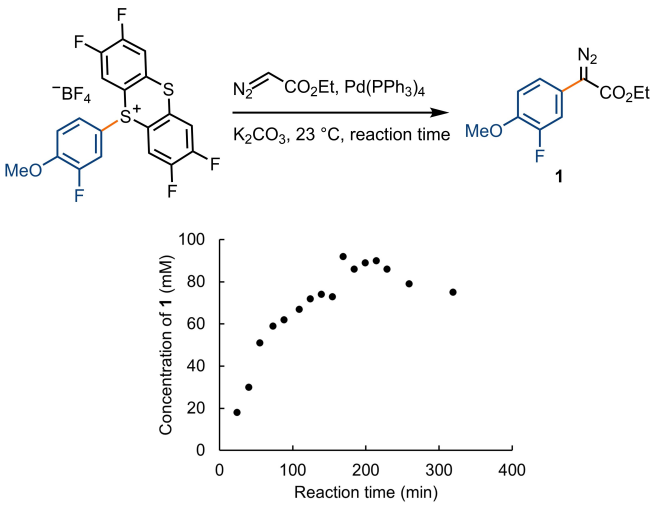
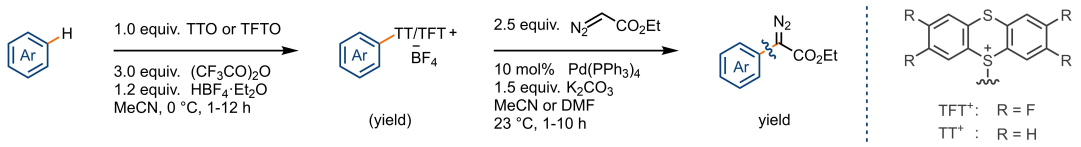
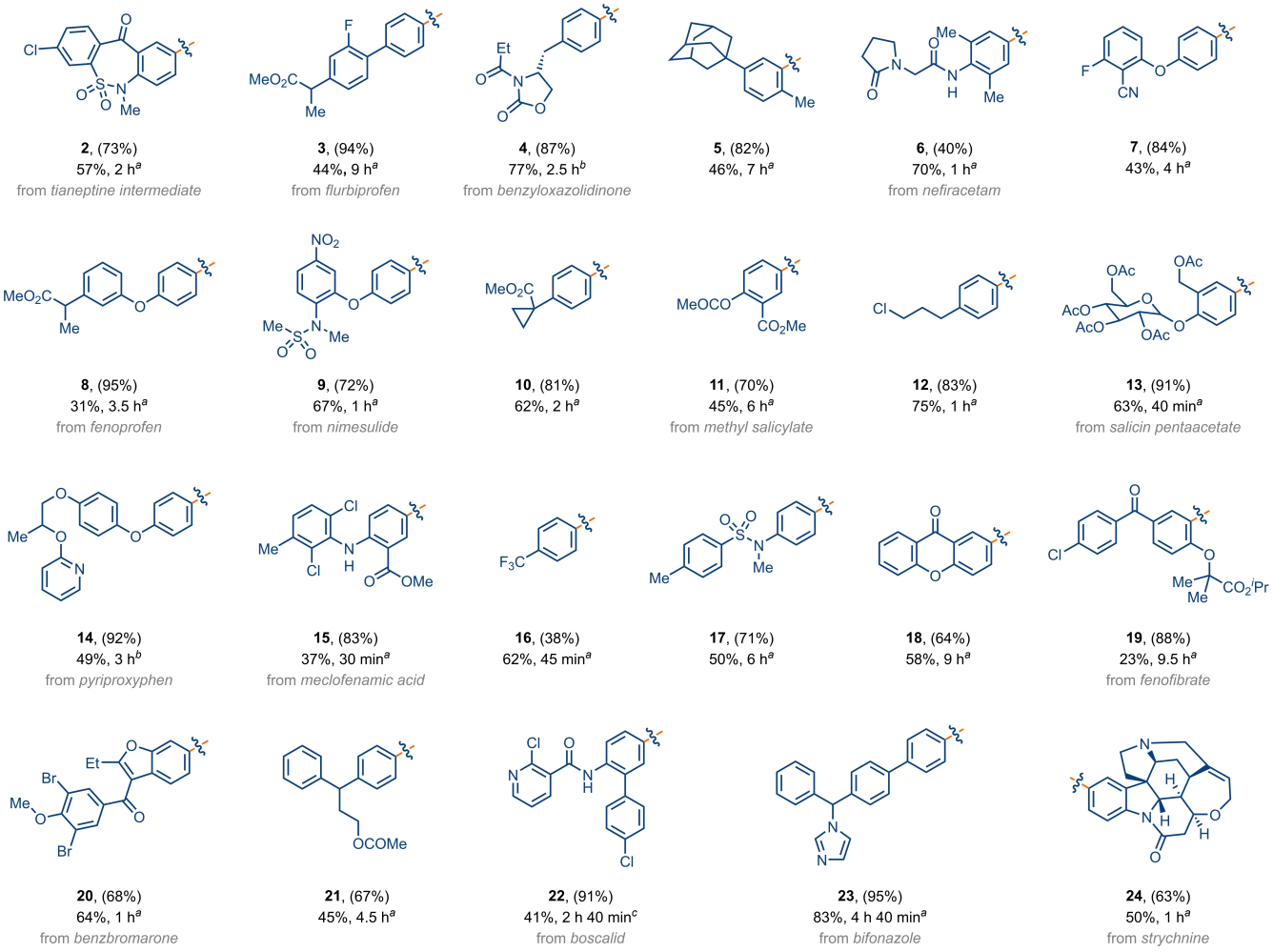


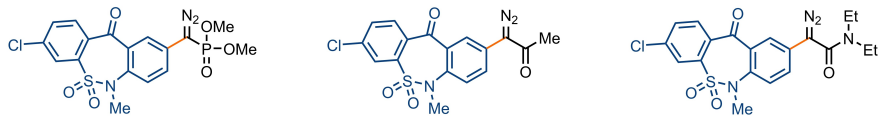
Figure 1. Monitoring of the concentration of **1** over time by ^{19}F NMR spectroscopy at 23 °C. Individual reactions were stopped at the indicated times, 1,4-difluorobenzene (0.2 M) was added, and the yield of **1** assessed by ^{19}F NMR spectroscopy (reaction conditions: 10 mol% $Pd(PPh_3)_4$, 2.5 equivalent EDA, 1.5 equivalent K_2CO_3, MeCN (0.1 M).



arene scope



diazo scope



Scheme 3. Substrate scope of the palladium-catalyzed functionalization of aryl-TT^+/TFT^+ salts with α-diazoacetate. [a] starting from aryl thianthrenium ions ($ArTT^+$) in DMF (0.25 M); [b] starting from aryl tetrafluorothianthrenium salts ($ArTFT^+$) in MeCN (0.1 M); [c] starting from $ArTFT^+$ salts in MeOH (0.1 M). Reaction times for substrates are indicated below each structure. TTO, thianthrene-*S*-oxide. TFTO, 2,3,7,8-tetrafluorothianthrene-*S*-oxide.

single constitutional isomer and the distinct yellow color of the product facilitate identification and purification by chromatography.[18] The palladium-catalyzed α-diazoester installation is compatible with arylthianthrenium salts of electron-rich (**3**–**10**, **12**–**14**, **17**, **20**–**24**), electron-neutral (**2**, **15**, **18**, **19**), and electron-deficient (**11**, **16**) arenes. Strained cyclic ring systems (**5**, **10**, **24**), protic NH groups (**6**), and basic heterocycles (**14**, **22**, **23**), which can be problematic in

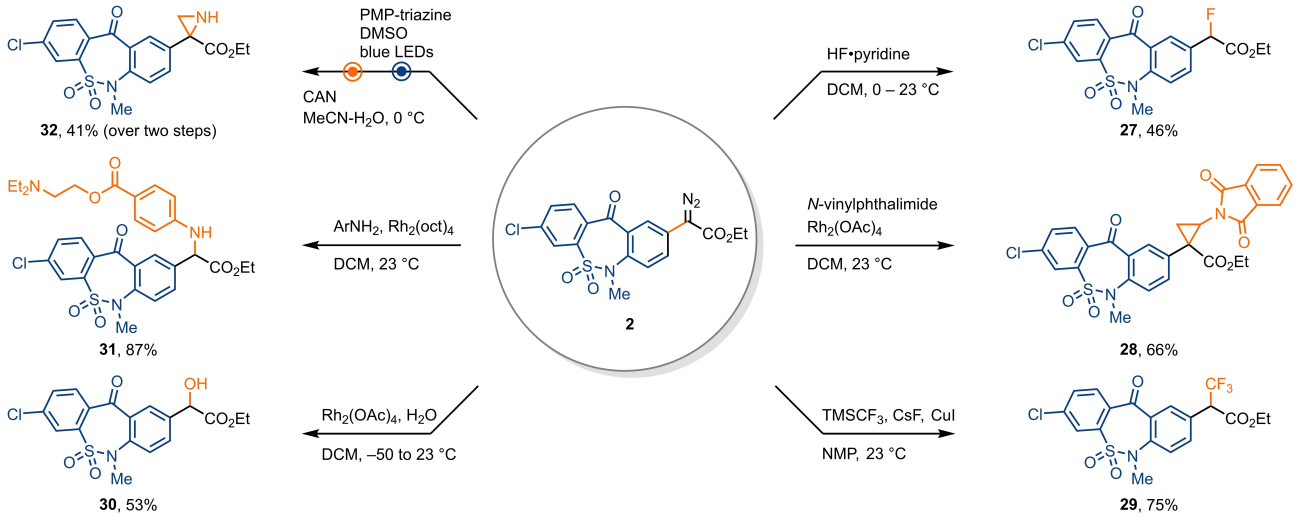
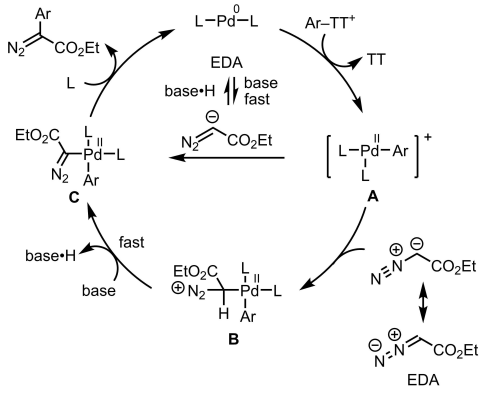


Figure 2. Diversification of tianeptine intermediate-derived diazo ester **2**.

transition-metal catalyzed reactions,[19] could be coupled efficiently. Furthermore, the methodology tolerates nitro groups, esters, ketones, alkyl and aryl chlorides, amides, sulfonamides, and lactams. Sterically encumbered *o*-substituted aryls (**5**, **19**) are also reactive, albeit with lower yields of 46 % and 23 %, respectively. Other α-diazo compounds containing electron-withdrawing groups such as a phosphonate (**25**) or a ketone group (**26**) can also be used. The cross-coupled diazoester products can be conveniently diversified, e.g. by fluorination (**27**),[20] cyclopropanation (**28**),[21] trifluoromethylation (**29**),[22] O–H (**30**)[10b] and N–H insertion (**31**),[23] as well as aziridination (**32**)[24] in two steps (Figure 2). Access to structures **27**–**32** from the corresponding arenes would otherwise be challenging.

A plausible reaction mechanism is presented in Scheme 4, and begins with Ar-TT$^+$ oxidative addition to Pd(0) to afford the cationic Pd(II) intermediate **A**. Nucleophilic attack of EDA to cationic Pd(II) species **A** gives intermediate **B**, which leads to **C** after deprotonation. The absence of a kinetic isotope effect in two independent reaction rate measurements with ethyl diazoacetate and α-D-diazoacetate (see SI, p. S62) is consistent with either oxidative addition of Ar-TT$^+$ or formation of **B** being turnover-limiting. Addition of iodide to the Ar-TT$^+$ reaction inhibits product formation, which is consistent with inhibition of formation of **B** and explains the superiority of Ar-TT$^+$ over aryl halides for this transformation.

In summary, a late-stage functionalization of complex arenes with a diazo group via arylthianthrenium salts under palladium catalysis is reported. It promotes structural variation of a large scope of arenes with high positional selectivity and practicality.



Scheme 4. Plausible reaction pathway.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Arylthianthrenium salts · Diazoesters · Palladium · Synthetic methods · Arenes

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