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# Silver-Catalyzed N–H Functionalization of Aryl/Aryl Diazoalkanes with Anilines

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**ABSTRACT:** Herein, we report on the N–H functionalization reaction of primary and secondary anilines with diaryldiazoalkanes using simple  $AgPF_6$  as catalyst. We demonstrated broad applicability in the reaction of diaryldiazoalkanes with different anilines (31 examples, up to 97% yield). Furthermore, we propose a possible reaction mechanism for the N–H functionalization.

arbon-nitrogen bonds are one of the most important carbon-heteroatom bonds and can be found in organic compounds across all disciplines, from natural products to drugs and materials. The development of efficient methods for the construction of this bond is thus of ongoing interest in organic synthesis methodology.<sup>1</sup> In particular, amination reactions under mild and environmentally benign reaction conditions are attractive as they bear the potential for the direct amination of complex molecules.<sup>2</sup> One approach toward this goal harnesses reactive intermediates, such as carbenes that allow for the direct amination of primary and secondary amines.<sup>3</sup> The carbene itself can be readily obtained by decomposition reaction of diazoalkanes under metal-catalyzed, thermal, or photochemical reaction conditions.<sup>5</sup> In the majority of studies, either acceptor or donor/acceptor type diazoalkanes were employed,<sup>4,5</sup> whereas aryl/aryl diazoalkanes remained underexplored and underestimated. Only until recently, applications of such aryl/aryl diazoalkanes remained rare and often only single experiments were reported. First, more general applications of these were reported in early 2020. Aryl/aryl diazoalkanes are of particular interest as they allow the introduction of a diarylmethylene unit onto organic building blocks. In this context, the Davies group reported on asymmetric Rh-catalyzed cyclopropanation reactions of aryl/aryl diazoalkanes and uncovered a marked influence of the substitution pattern of the aromatic rings on the stereoselectivity of the cyclopropanation reaction (Figure 1a, 4).<sup>6a</sup> Furthermore, the Davies and Stahl groups reported on a copper-catalyzed aerobic oxidation of hydrazones to the corresponding aryl/aryl diazoalkanes and subsequent trapping of the aryl/aryl diazoalkane with acetic acid.<sup>6b</sup> In a different approach, the Zhou<sup>7a</sup> and the Franz<sup>7b</sup> groups studied Rhcatalyzed asymmetric Si-H insertion reactions (Figure 1a, 5).

Our group reported on the metal-free reactions of aryl/aryl diazoalkanes, which allows access to three different reaction pathways depending on the electronic properties of the diazoalkanes under photochemical conditions (Figure 1a, 6-8)<sup>8a</sup> or a benzhydryl cation under Brønsted acid-catalyzed conditions that can be used in C–H functionalization.<sup>8b</sup>

Despite the significance of amination reactions in organic synthesis, studies on the N–H functionalization of aniline derivatives with aryl/aryl diazoalkanes are rare. In 2020, Che et al. investigated Fe-porphyrin complexes in diaryl carbene transfer reactions. Using a large excess (10 equiv) of the reaction partner (9a), the corresponding N–H functionalization products (10a) were obtained in moderate to excellent yield and a good functional group tolerance after 12 h reaction time.<sup>9a</sup> Apart from Che's work, previous reports are frequently limited to singular examples—often as part of studies on acceptor-only or donor/acceptor diazoalkanes (Figure 1b).<sup>9</sup>

Therefore, studies on the N–H insertion reaction of aryl/ aryl diazoalkanes are highly demanded as these would provide insight into the reactivity of aryl/aryl diazoalkanes in X–H functionalization reactions and provide applications for the introduction of a benzhydryl amine protecting groups.<sup>10</sup>

Based on our interest in carbene chemistry<sup>11</sup> and N–H functionalization reactions via carbene intermediates,<sup>12</sup> we became intrigued in studying the N–H insertion reactions of aryl/aryl diazoalkanes (Figure 1c). We therefore studied the

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Figure 1. Application of diaryl carbenes in organic synthesis.

reaction of diphenyl diazomethane 1a with aniline 9a in the presence of different metal catalysts or under photochemical conditions (for details, please see the Supporting Information (SI), Table S1).

However, carbene transfer catalysts based on rhodium, gold, copper, ruthenium or palladium did not provide the desired product in reasonable yield (Table 1, entries 1-5). In the case of JohnPhos(AuCl) and CuOTf, the N-H functionalization product 10a was formed in low yield and the diazine was formed as the major byproduct (Table 1, entries 4 and 5). In a next step, we investigated the borane-catalyzed reaction, using  $B(C_6F_5)_3$  as catalyst we isolated the N–H functionalization product in 15% yield after reaction overnight (Table 1, entry 6). Unexpectedly, simple  $AgPF_6$  proved highly efficient and the reaction was completed after only 10 min of reaction time at ambient temperature and we were able to isolate 10a in 84% yield (Table 1, entry 7). Intrigued by the promising results using  $AgPF_6$  as catalyst, we further investigated different silver salts, catalyst loadings, solvents and the stoichiometry of the model reaction (for details, please see the SI, Table S1).<sup>13</sup> However, no further improvement of the reaction yield was obtained. A 1:1 stoichiometry of 1a and 9a in DCM as solvent proved optimal to yield the product 10a in 86% yield (Table 1, entry 8). To evaluate the participation of  $HPF_6$  as a hidden Brønsted acid catalyst, we investigated HPF<sub>6</sub> as a catalyst. Yet, even after 24 h of reaction time, we did not observe any reaction and both starting materials remained untouched. This excludes the participation of  $HPF_6$  as catalyst, which can be

#### Table 1. Reaction Optimization



<sup>*a*</sup>Reaction conditions: In an oven-dried test tube, catalyst (3 mol %) was put under vacuum and flushed with Argon for three times. Dry, degassed DCM (0.5 mL) was added. Aniline **9a** (0.4 mmol) and aryl/aryl-diazo **1a** (0.2 mmol) was dissolved in 0.5 mL of dry, degassed DCM and added to the reaction mixture in one portion. The reaction mixture was stirred at rt until the aryl/aryl diazo **1a** was consumed. <sup>*b*</sup>Isolated reaction yield of **10a**. <sup>*c*</sup>Both staring materials were recovered. <sup>*d*</sup>NaBArF<sub>4</sub> (5 mol %) was used as an additive. <sup>*e*</sup>A 1:1 stoichiometry of aniline **9a** and aryl/aryl-diazo **1a** was used. dec = decomposition

rationalized by an acid base reaction between the Brønsted acid catalyst and aniline 9a that shuts down catalytic activity of the Brønsted acid (Table 1, entry 9).

With the optimized conditions in hand, we next studied different anilines 9 in the reaction with diphenyl diazomethane 1a (Scheme 1). Different electron-donating, electron-withdrawing substituents and halogens were well tolerated in all positions of the aromatic ring of 9, and the corresponding N– H functionalization products 10a-o were isolated in high yield. We observed slightly reduced reaction yields in the case of *ortho*-substituted anilines, which can be reasoned by increased sterical hindrance due to the *ortho* substituent (10k-o). Moreover, 1-naphtylamine and benzo[d][1,3]dioxol-S-amine proved compatible with the present reaction conditions and the products were formed in 68% and 56%, respectively (10p,q). Additionally, we investigated the synthesis of 10a on a 1 mmol scale, and to our delight we were able to isolate 10a in slightly reduced yield (78%).

Next, we investigated different aryl/aryl diazoalkanes 1 in the reaction with aniline 9a. Electron-donating and chloro substituents were well tolerated in all positions of the aromatic ring (10r-w). Overall, we observed slightly reduced yields compared to the unsubstituted diazoalkane 1a. When introducing electron-withdrawing substituents instead of electron-donating substituents, we observed a strong dependence of the position of the substituent, while a 3-nitro substituent was well tolerated, a 4-nitro substituent reduced the yield significantly (10x-z). This observation could be reasoned by the mesomeric effect of the nitro group leading to an activation of diphenyl diazomethane 1x and subsequent higher reaction yield compared to unsubstituted diphenyl diazomethane 1a (97% vs 86%, respectively). Furthermore, 4nitro substituted diphenyl diazomethanes 1y,z deactivated the diazoalkane and longer reaction times and lower yields were observed (Scheme 1).

Scheme 1. Scope of Different Primary Anilines and Aryl/ Aryl Diazoalkanes



"NMR yield due to inseparable mixture of N-H functionalization product and byproducts.

In further studies, we investigated secondary aniline derivatives. However, *N*-methyl aniline **11a** proved much less reactive and gave a significantly lower yield of the N–H functionalization product **12a** under the optimized conditions after 24 h reaction time. Byproducts arise from decomposition of the diazoalkane **1a**, and we therefore decided to use a slow addition protocol (24 h addition time) and 2 equiv of aniline **11a**. With this adapted procedure, we were able to isolate **12a** in 66% yield. We then investigated different *N*-alkyl and *N*-aryl anilines in the reaction with diazoalkane **1a**. Sterically less demanding substituents were compatible with the reaction conditions, and the corresponding products were isolated in moderate to high yield (**12b–d**). When sterically more demanding groups were introduced, e.g., *ortho* methyl

substituted *N*-methyl aniline, the reaction yield decreased significantly and the products were isolated in moderate yield (12e,f) (Scheme 2).

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When studying aliphatic primary and secondary amines, indole, or carbazole in this silver-catalyzed transformation (13a-e), we did not observe the desired reaction product. Instead, we observed the decomposition of the diazoalkane 1a. Furthermore, we investigated cyclohexanol (14a), phenol (14b), thiophenol (15a), and allyl mercaptan (15b) in O-H and S-H insertion reactions, respectively. However, we did not observe any product formation and diazoalkane 1a decomposed to a complex mixture of byproducts (Scheme 2). Based on literature precedence,<sup>7,14</sup> we propose a reaction

mechanism that involves stabilization of the silver salt by Lewis-basic amine  $(I)^{15}$  that can undergo formation of a silver carbene complex III. Hydrogen bonding of aniline to the carbene carbon results in the formation of intermediate IV, which can further react to intermediate V. It should be noted that the aniline molecule can potentially be both delivered intra- and intermolecularly in this reaction. In a last step, the silver carbon bond is cleaved, releasing the desired product 10a and the catalytically active species I (Scheme 3). Based on the proposed mechanism longer reaction times for secondary anilines 11 can be reasoned by a slower formation of the hydrogen bonding complex IV and subsequent slower C-N bond forming reaction to form intermediate V. Furthermore, sterically demanding substituents suppress the formation of V, especially when secondary anilines are investigated which is in line with the experimental results.

In summary, we developed a method for the efficient N–H functionalization reaction of primary and secondary anilines with aryl/aryl diazoalkanes using a simple silver salt as catalyst.

# Scheme 3. Proposed Reaction Mechanism



While primary anilines smoothly reacted in very short reaction times (10 min), secondary anilines proved less reactive and a slightly adapted protocol had to be used to ensure high yields. We discuss a possible reaction mechanism which gives an explanation for the decreased reactivity of secondary anilines. Overall, the N-H functionalization products were isolated in moderate to high yields and a broad applicability was demonstrated (31 examples, up to 97% isolated yield).

#### ASSOCIATED CONTENT

# **9** Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02289.

Full experimental data for all compounds, experimental procedures, characterizations, and analytical data (PDF)

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#### **Author Contributions**

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# Notes

The authors declare no competing financial interest.

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