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Highly Stereoselective Synthesis of Imine-Containing Dibenzo-[b,d]azepines by a Palladium(II)-Catalyzed [5+2] Oxidative Annulation of *o*-Arylanilines with Alkynes

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Abstract: A novel palladium(II)-catalyzed [5+2] oxidative annulation of readily available o-arylanilines with alkynes has been developed for building a seven-membered N-heterocyclic architecture containing a biaryl linkage. This method is applicable to a wide range of unprotected o-arylanilines and internal alkynes, and results in the chemoselective preparation of imine-containing dibenzo[b,d]azepines in high yields with excellent diastereoselectivity with respect to the two types of stereogenic elements.

Dibenzo[*b*,*d*]azepines represent an important class of medium-sized N-heterocycles because they are the key structural motifs in many natural products and bioactive compounds (Figure 1). For example, dimeric erythrivarine B, which contains the seven-membered skeleton, was isolated from cultivated *E. variegata*.^[1] LY-411575 was identified as an effective γ -secretase inhibitor for the treatment of melanoma and Alzheimer's disease.^[2] Functionalized dibenzo[*b*,*d*]azepines were also investigated as serotonin (5-HT) receptor^[3] and potassium channel inhibitor.^[4] Therefore, the search for new reliable synthetic approaches for the preparation of dibenzo[*b*,*d*]azepines from readily available starting materials is of great interest.



Figure 1. Selected examples bearing the dibenzo[*b*,*d*]azepine core structure.

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Recently, transition-metal-catalyzed C-H functionalization has emerged as an efficient and versatile method for accessing various heterocycles and carbocycles.^[5] In particular, nitrogen-group-assisted heteroannulations of nitrogencontaining coupling partners with alkynes by a C-H cleavage/ alkyne insertion/cyclization cascade have been widely used to generate structurally diverse N-heterocyclic compounds, such as indoles,^[6] pyrroles,^[7] isoquinolines,^[8] isoquinolinones,^[9] and so on.^[10] Remarkably, most of these transformations were realized by formal [3+2] or [4+2] cycloadditions to give fiveor six-membered rings, but the construction of larger rings by means of related annulations is quite rare.^[10c,e] In this context, we set out to develop a new type of [5+2] annulation between simple biaryl precursors and alkynes involving a C-H activation step for the synthesis of functionalized dibenzo-[b,d]azepines. $^{[11]}$

This work originated from our recent studies on ruthenium(II)-catalyzed oxidative annulation of o-arylphenol derivatives with alkynes through a C-H activation strategy (Scheme 1 a).^[12] It is noteworthy that the reaction proceeded exclusively by a dearomatizing [3+2] annulation pathway to generate spirocyclic enones as the sole product, but not dibenzoxepines through a possible [5+2] cycloaddition route. Presumably, a clear steric clash between the two twisted aromatic groups of the intermediate A played a key role in driving the essential ring contraction from A to B, thus hampering the reductive elimination of A to form a dibenzoxepine and rendering the [3+2] spiroannulation more favorable than a seven-membered ring formation. Moreover, a recent seminal report from the group of Mascareñas and Gulías demonstrated that simple o-vinylphenols (R = H), which cannot engage in a similar steric interaction, were well suited for a rhodium(III)-catalyzed [5+2] annulation to give benzoxepines (Scheme 1b).^[13] These prior studies imply that adapting the sterically more hindered biaryl coupling partner for a potential [5+2] annulation with alkynes represents a formidable challenge, and to date, no example of such transformations has been realized. To address this limitation, we switched gears to attempt analogous o-arylaniline derivatives by exchanging the hydroxy group for an amino group. Herein, we report the successful development of a palladium-(II)-catalyzed [5+2] annulation of easily accessible o-arylanilines with alkynes for the direct synthesis of imine-containing dibenzo[b,d]azepines (Scheme 1 c).

At the outset, we first examined a series of commonly used *o*-arylanilines,^[14] which were N-substituted with a carbonyl, sulfonyl, alkyl, aryl, or heteroaryl groups, for the anticipated [5+2] annulation by using either rhodium(III)-, ruthenium(II)-, or palladium(II)-catalyzed C–H activation



Scheme 1. Development of [5+2] oxidative annulations of biaryls with alkynes. a) Ruthenium(II)-catalyzed annulation of *o*-arylphenol derivatives with alkynes (Ref. [12]). b) Rhodium(III)-catalyzed [5+2] annulation of *o*-vinylphenols with alkynes (Ref. [13a]). c) This work: Palladium(II)-catalyzed [5+2] annulation of *o*-arylanilines with alkynes.

under various reaction conditions. Unfortunately, no desired [5+2] dibenzo[b,d] azepine product was observed. A key breakthrough was ultimately achieved by identifying 2phenylaniline (1a) as an effective substrate for the envisioned transformation. It has long been known that N-unprotected oarylanilines could undergo cyclometalation by transitionmetal-mediated C-H bond cleavage,^[15] whereas the related catalytic processes, which might be suppressed by the tight coordination of the free amino group to the metal center, were not reported until very recently.^[16] In our investigation, the initial observation showed that a [5+2] annulation product, the imine-containing dibenzo [b,d] azepine **3a**, was formed in 57% yield upon treatment of 1a and 2a in the presence of a catalytic amounts of $Pd(OAc)_2$ (5.0 mol%) and 2.1 equivalents of Cu(OAc)₂ in DMF at 100°C for 5 hours (Table 1, entry 1). The optimal reaction conditions were then quickly established by switching the solvent to DMSO (entry 6) and elevating the temperature to 120°C (entry 7), thus providing 3a in 91% yield upon isolation. Control experiments indicated that replacing Pd(OAc)₂ with either [{Cp*RhCl₂}] or [RuCl₂(p-cymene)₂], or removing the catalyst completely shut down the titled reaction (entries 8–10). Notably, 3a was obtained as the sole product under the optimized reaction conditions, without giving either an enamine-containing dibenzo[b,d]azepine or other side products.

Under the optimal reaction conditions, the reaction scope was then surveyed by employing a great number of o-

Table 1: Optimization of the reaction conditions.[a]



[a] Reactions were conducted with 0.30 mmol of **1 a**. [b] Yield of isolated product. DMF = N,N-dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

arylanilines (1a-t) to react with 2a, and it was found that substrates containing substituents of varying electronic and steric character, at any position of either aromatic ring, were tolerated, thus providing the desired [5+2] annulation products **3a-t** in moderate to good yields (47-94%; Table 2). Notably, the reaction with the substrate 1n, which contains two possible C-H functionalization sites, proceeded preferentially at the least sterically encumbered position to give **3n** as the major regioisomer (12.5:1 r.r.). The substrate 10, featuring the increased steric hindrance for C-H functionalization, also participated in the process, although the yield was slightly lower (54% yield). More importantly, the reaction was compatible with several challenging substrates (1m, 1s,t), which would cause more severe steric clash in the intermediate A" (see Scheme 1), and the anticipated products 3m, 3s, and 3t were isolated in 91, 51, and 47% yield, respectively.

The structure of the dibenzo[b,d]azepines **3** was then further elucidated by X-ray crystallographic studies on **3d**, **3m**, and **3n**.^[17] It is clear that they exist in the imine form. Moreover, the stereochemistry is of particular interest in that, in addition to the one tertiary carbon center, the moiety has a chiral biaryl axis. Notably, a single diastereomer was always observed as the sole product for all the reactions between **1a**– **t** and **2a**, and the relative configuration is depicted in Figure 2.

Next, we sought to investigate the scope with respect to the alkynes (Table 3). Regarding symmetrical alkynes (**2b–e**) containing either electron-rich or electron-deficient aromatic groups, the anticipated [5+2] annulation proceeded smoothly to generate the imines 3a'-d' as single diastereomeric products in good yields (62–90%). When the unsymmetrical diaryl alkyne **2f** was tested, the reaction led to a mixture of two separable regioisomers **3e'** (2.4:1 r.r.) possessing the same relative configuration.^[17] Moreover, the dialkylacetylene **2g** was tolerated under the reaction conditions, thus the providing compound **3f'** in 67% yield with 6.2:1 d.r. Notably, the incorporation of an alkyl group into the tertiary carbon center



Table 2: The reaction substrate scope of o-arylanilines.





eroded the diastereoselectivity in comparison to the examples having diaryl alkynes (>19:1 d.r. for all the cases). To further evaluate the regioselectivity of the reaction with respect to unsymmetrical alkynes, one sterically differentiated alkyne (**2h**) and two alkyl-aryl mixed alkynes (**2i,j**) were studied. Gratifyingly, they participated in the [5+2] annulation to give **3g'-i'** in 80–97 % yields with excellent regioselectivity (>19:1 r.r.), albeit with low diastereoselectivity. Remarkably, the diastereoselectivity for the process with alkyl-aryl alkynes could be enhanced by using alkynes with a larger alkyl group Table 3: The reaction substrate scope of alkynes.



(2j versus 2i). Finally, it should be noted that ethyl 3-phenylpropiolate was also an excellent coupling partner for the [5+2] annulation, thus giving the imine-formed dibenzo-[b,d]azepine 3j' in 94% yield with 10.1:1 d.r., and the structure of its major diastereomer was confirmed by X-ray.^[17]

We conducted a series of experiments to probe the reaction mechanism (Scheme 2). An intermolecular competition between **1a** and $[D_5]$ -**1a** demonstrated a kinetic isotope effect ($k_H/k_D = 3.2$; Scheme 2a), which suggests that the C–H activation is probably involved in the rate-determining step. Treatment of the *o*-arylanilines **2r** (4-MeO) and **2p** (4-CF₃)



Scheme 2. Mechanistic studies.



with alkyne 2a (1.0 equiv) afforded the corresponding products **3r** and **3p**, respectively, in a 1.8:1 ratio (Scheme 2b). The preferential formation of 3r, having an electron-rich substituent, implies that the slow hydrogen abstraction might occur after the electrophilic attack of palladium(II) on the aromatic ring in the C-H activation process.^[18] Moreover, reacting the palladacycle complex 4, which was generated from **1a** by palladium(II)-mediated C–H bond cleavage,^[15a] with an equal molar amount of 2a successfully led to 3a in 93% yield (Scheme 2c), thus providing solid evidence to support a free-amine-directed C-H activation mechanism for the title transformation. Finally, two control reactions were performed, and the experimental data revealed that 3a was not formed from 5 by a possible amination/oxidation sequence (Scheme 2d),^[16a] but generated through the tautomerization of its enamine-counterpart 6 (Scheme 2e).

A plausible reaction mechanism based on the above results is proposed in Scheme 3. The catalytic cycle is initiated with an amino-assisted C–H bond cleavage of 1a by Pd- $(OAc)_2$ to give rise to a stable palladacycle (4). Next, this dimeric palladium complex is broken into its component parts



Scheme 3. Proposed mechanism.

by 2 to form the intermediate I. Notably, it was known from prior work that migratory insertion of the alkyne 2 with 4 favored a regioselective insertion into the Pd–C bond to afford the eight-membered intermediate II.^[15b] Furthermore, C–N reductive elimination takes place to deliver the enamine-containing dibenzo[*b*,*d*]azepine 6 and concomitantly regenerate Pd(OAc)₂ to complete the cycle. Finally, tautomerization of 6 leads to the formation of the thermodynamically more stable 3a as the sole product.

In summary, we have developed an unprecedented palladium(II)-catalyzed [5+2] oxidative annulation of biaryl precursors with alkynes by relying on a C–H activation approach. This method provides a straightforward and atomeconomical access to a new class of fascinating iminecontaining dibenzo[b,d]azepines in high yields and stereoselectivities by using readily available o-arylanilines and alkynes as starting materials.

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Keywords: annulations \cdot arenes \cdot C–H activation \cdot heterocycles \cdot palladium

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15388 www.angewandte.org

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