C–H Activation

Deutsche Ausgabe: DOI: 10.1002/ange.201508850
Internationale Ausgabe: DOI: 10.1002/anie.201508850

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.

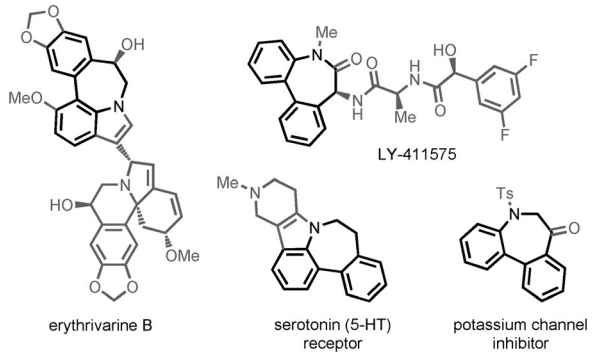

Figure 1. Selected examples bearing the dibenzo[*b*,*d*]azepine core structure.

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 nitrogen-containing 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 five- or 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 1 b).[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

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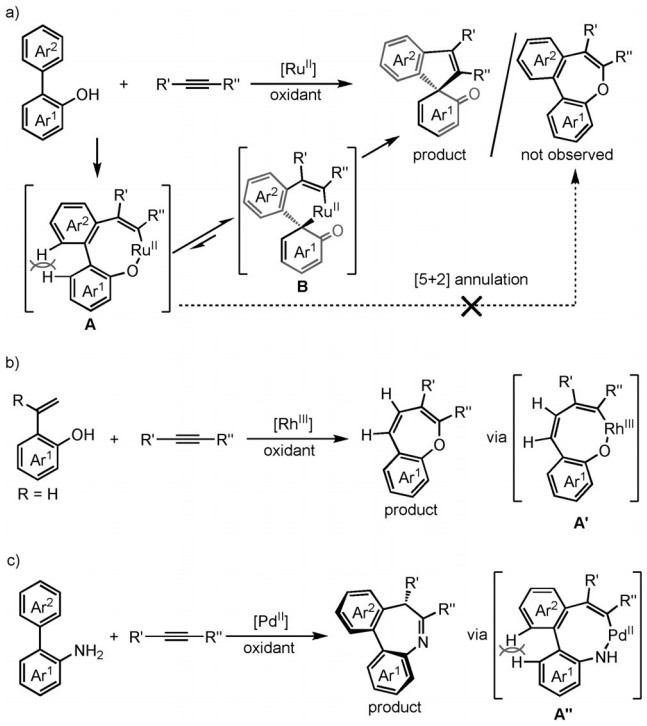
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201508850.

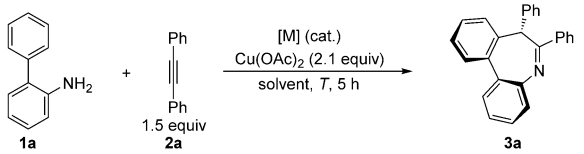


Scheme 1. Development of [5+2] oxidative annulations of biaryls with alkynes. a) Ruthenium(II)-catalyzed annulation of *o*-arylphenol derivatives with alkynes (Ref. [12]). b) Rhodium(III)-catalyzed [5+2] annulation of *o*-vinylphenols with alkynes (Ref. [13a]). c) This work: Palladium(II)-catalyzed [5+2] 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 2-phenylaniline (**1a**) as an effective substrate for the envisioned transformation. It has long been known that N-unprotected *o*-arylanilines could undergo cyclometalation by transition-metal-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 $[\{Cp^*RhCl_2\}_2]$ or $[RuCl_2(p\text{-cymene})_2]$, 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]



Entry	[M]	mol%	Solvent	*T* [°C]	Yield [%][b]
1	$Pd(OAc)_2$	5.0	DMF	100	57
2	$Pd(OAc)_2$	5.0	1,4-dioxane	100	29
3	$Pd(OAc)_2$	5.0	THF	100	18
4	$Pd(OAc)_2$	5.0	CH_3CN	100	23
5	$Pd(OAc)_2$	5.0	*t*AmOH	100	16
6	$Pd(OAc)_2$	5.0	DMSO	100	72
7	$Pd(OAc)_2$	5.0	DMSO	120	91
8	$[\{Cp^*RhCl_2\}_2]$	2.5	DMSO	120	0
9	$[RuCl_2(p\text{-cymene})_2]$	2.5	DMSO	120	0
10	–	0	DMSO	120	0

[a] Reactions were conducted with 0.30 mmol of **1a**. [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 **1o**, 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.

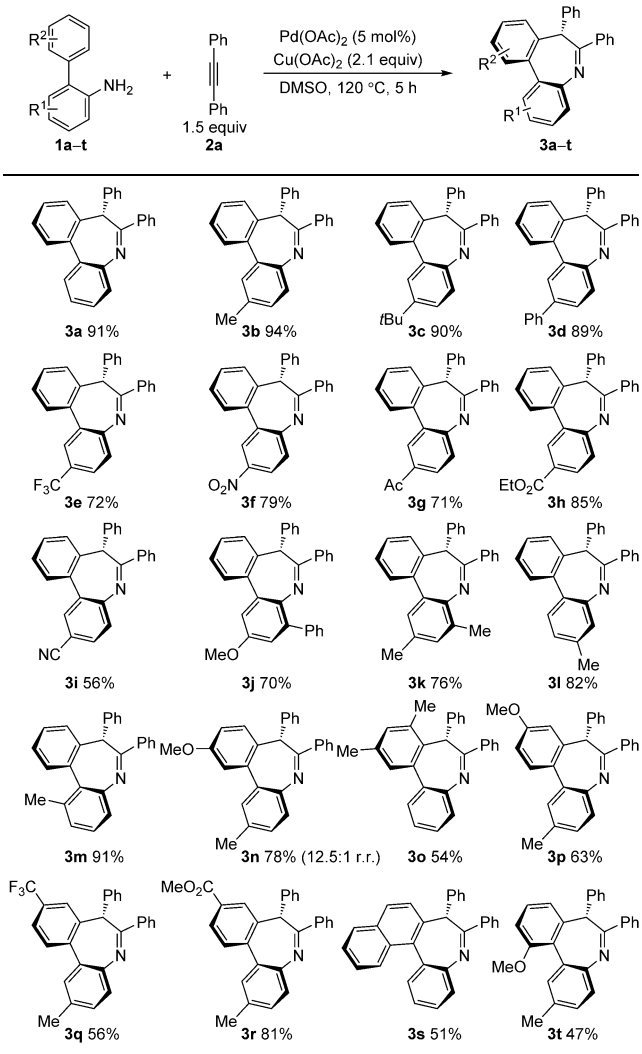
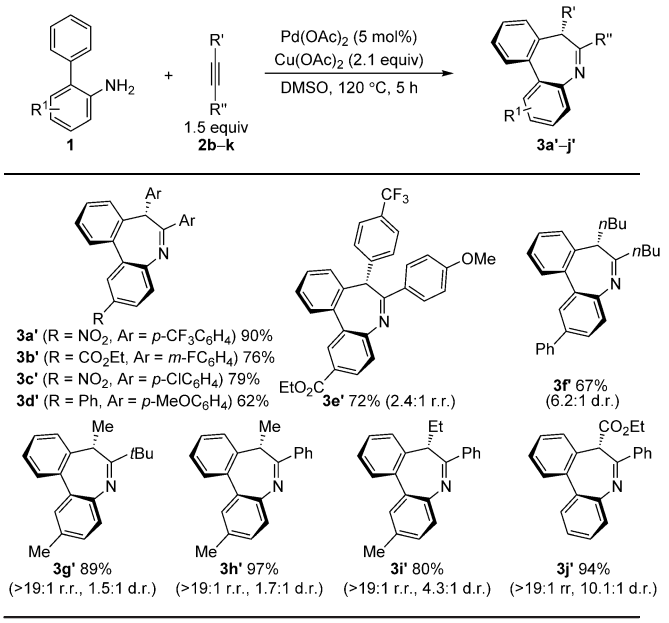


Table 3: The reaction substrate scope of alkynes.



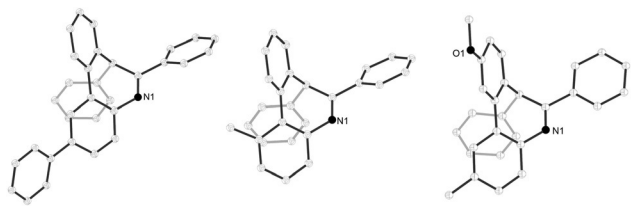
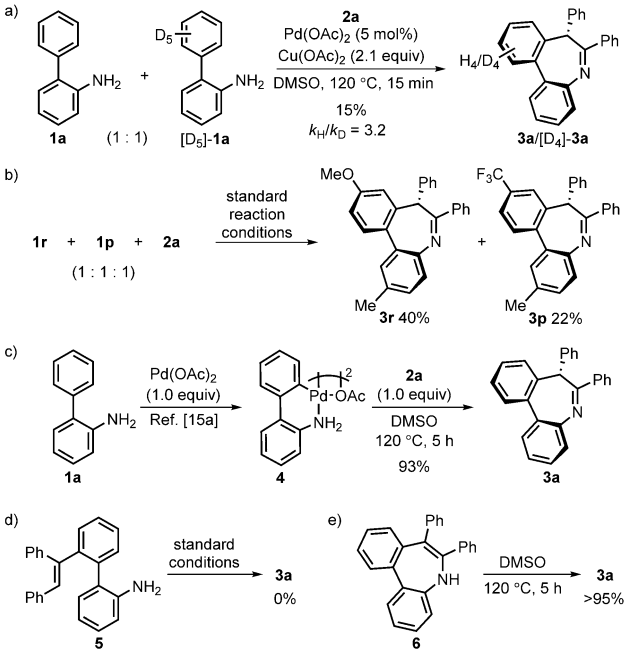


Figure 2. X-ray structures of **3d**, **3m**, and **3n** (from left to right). Thermal ellipsoids shown at 60% probability.

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 (**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]

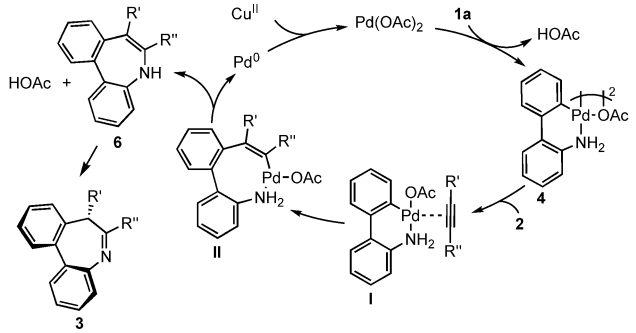
We conducted a series of experiments to probe the reaction mechanism (Scheme 2). An intermolecular competition between **1a** and [D_5]-**1a** demonstrated a kinetic isotope effect ($k_H/k_D = 3.2$; Scheme 2a), which suggests that the C–H activation is probably involved in the rate-determining step. Treatment of the *o*-arylanilines **2r** (4-MeO) and **2p** (4-CF_3)



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 atom-economical access to a new class of fascinating imine-containing dibenzo[*b*,*d*]azepines in high yields and stereoselectivities by using readily available *o*-arylanilines and alkynes as starting materials.

Acknowledgements

This work was supported by the NSFC (21222201, 21271147, 51202192) and the "1000 Youth Talents Plan".

Keywords: annulations · arenes · C–H activation · heterocycles · palladium

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15385–15389
Angew. Chem. **2015**, *127*, 15605–15609

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[17] CCDC 1422296 (**3d**), 1422295 (**3m**), 1422299 (**3n**), 1422297 (**3e′**$_{major}$), 1422298 (**3e′**$_{minor}$), and 1430680 (**3j′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Received: September 21, 2015
Published online: November 2, 2015

