Benzazepine Synthesis

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Palladium-Catalyzed Oxidative Cycloaddition through C–H/N–H Activation: Access to Benzazepines**

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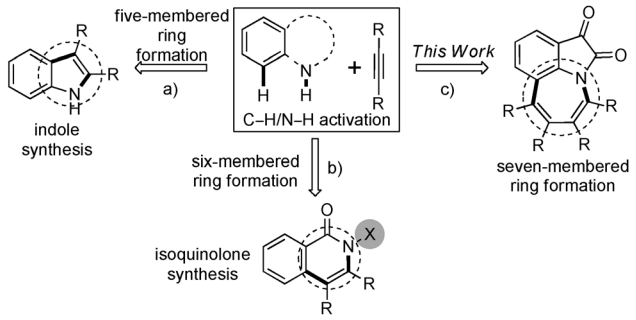
The biological applications of many nitrogen-containing heterocycles have encouraged chemists to develop efficient methods for their synthesis.[1] Recently, chemists have turned their attention to solving the problem of finite chemical feedstocks coupled with the negative impact of manufacturing waste.[2] In this regard, directed C–H activation towards the formation of C–C and C-heteroatom bonds has received the most attention owing to its sustainable and environmentally benign features.[3] In particular, the Pd-catalyzed oxidative cycloaddition of alkynes by C–H/N–H bond cleavage has proven reliable in forming the corresponding nitrogen-containing heterocycles in an atom- and step-economical synthetic manner.[4] In recent reports, Jiao et al. described an elegant approach to constructing indoles from anilines and alkynes using Pd-catalyzed oxidative C–H/N–H activation, involving a five-membered ring cyclization (Scheme 1a).[5] Other transition metals (such as Ru and Rh) have been applied to assembling indole and other five-membered-ring structures based on nitrogen-containing heterocycles through a similar strategy.[6] Recently, a one-pot Pd-catalyzed C–H/N–H activation of alkynes was reported to facilitate isoquinolinone synthesis, which includes the formation of a nitrogen-containing six-membered ring.[7] Although these methods have been shown to be highly efficacious in the construction of five- or six-membered N-heterocyclic systems, there are very few reports on the direct synthesis of more challenging higher-order nitrogen-containing seven-membered rings by Pd-catalyzed oxidative cyclization (Scheme 1c).



Scheme 1. Pd-catalyzed oxidative cycloaddition for five- to seven-membered ring formation involving C–H/N–H activation. a) Indole synthesis. b) Isoquinolone synthesis. c) Benzazepine synthesis.

Benzazepines are well-known seven-membered nitrogen-containing heterocycles that form the structural scaffold of many pharmaceutical compounds; therefore, they are often used as structural elements in medicinal chemistry.[8] For example, Mozavaptan (Figure 1) is used as an orally effective, nonpeptide arginine vasopressin V-2 receptor antagonist.[9] Lotensin is a prescription medication licensed for treating high blood pressure (hypertension), congestive heart failure, and chronic renal failure by inhibiting angiotensin-converting enzyme (ACE) in human subjects.[10] Anafranil is identified as an antiobsessional drug that belongs to the class of pharmacologic agents known as tricyclic antidepressants.[11] In addition to Anafranil, its analogues, Tienopramine and Amezepine, are also classified as antidepressants.[12]

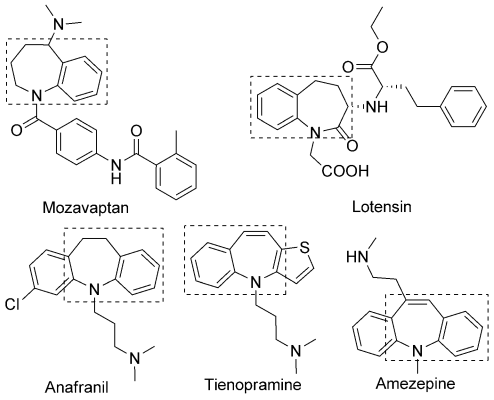


Figure 1. Examples of benzazepine pharmaceuticals.

Preparation of such benzazepine-containing compounds generally requires multiple synthetic steps.[13] A direct synthetic method utilizing simple and readily available starting materials, would not only enable the construction of a new class of scaffolds, but would also facilitate late-stage modification of existing compounds that are biologically active. To address this limitation, we devised a direct C–H/N–H activation method to construct a benzazepine scaffold. We

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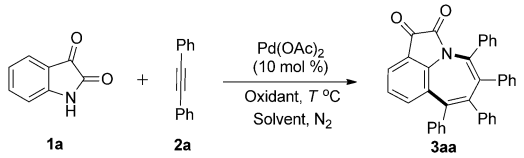
envisioned that this strategy could be applied to the production of valuable benzazepine heterocycles from simple and readily available alkynes and isatins by a direct oxidative cycloaddition.

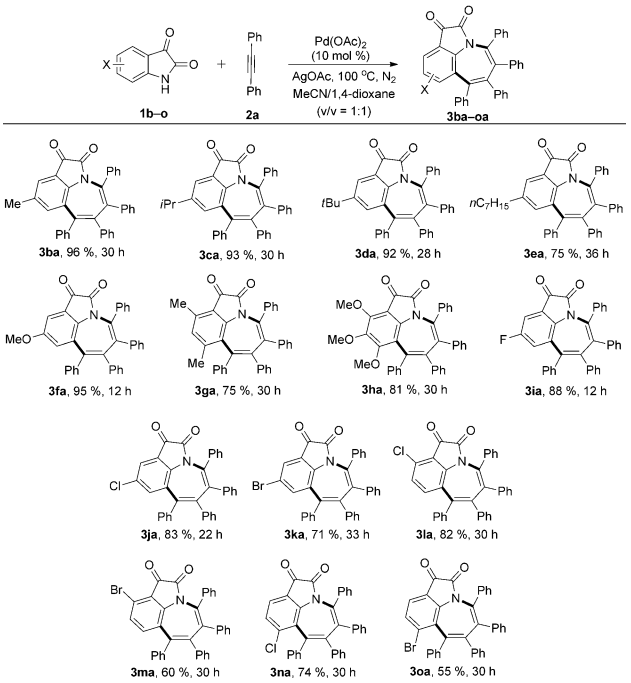
Our investigation began with the Pd-catalyzed oxidative cycloaddition of isatin **1a** and diphenylacetylene **2a** to give the corresponding benzazepine **3aa** (Table 1). Based on optimization experiments, the best results were obtained using $Pd(OAc)_2$ as catalyst with stoichiometric amounts of AgOAc as the oxidant in a mixed solvent of MeCN/1,4-dioxane (v/v = 1:1) (Scheme 2, entry 13). Under these conditions, conversion was complete within 24 h at 120 °C (entry 13, 83% yield of isolated product). Variation of oxidants (Table 1, entries 2–12), or solvents (see the detailed solvent screening in the Supporting Information) led to a decrease in chemical yield. The effects of temperature were summarized in Table 1 (entries 13–17), and a similar yield was achieved at lower temperature (entry 15, 100 °C, 81%). However, further lowering of the temperature led to slow conversion (entries 16–17, 56% and 18%, respectively). Moreover, product formation was also highly sensitive to the ratio of starting materials (**1a**/**2a**) used. When the ratio of **2a** was decreased from 1:5 (**1a**/**2a**, entry 3) to 1:3 (**1a**/**2a**, entry 4), a significant decrease in yield was observed. An inert atmosphere (N_2) was found to be essential to the reaction. When the reaction was carried out in air, only moderate yield was obtained (entry 14, 55%).

Table 1: Optimization of reaction conditions.[a]



Entry	Oxidant	Solvent	T [°C]	Yield [%][b]
1	–	DMF	120	< 5
2	CuI	DMF	120	16
3	**AgOAc**	DMF	120	**77**
4	AgOAc	DMF	120	38[c]
5	$AgCO_2CF_3$	DMF	120	28
6	$AgSbF_6$	DMF	120	< 5
7	$CuBr_2$	DMF	120	< 5
8	$Cu(OAc)_2$	DMF	120	40
9	BQ	DMF	120	15
10	$(NH_4)_2S_2O_8$	DMF	120	< 5
11	$PhI(OAc)_2$	DMF	120	24
12	oxone	DMF	120	< 5
13	AgOAc	MeCN/1,4-dioxane	120	83
14	AgOAc	MeCN/1,4-dioxane	120	55[d]
15	AgOAc	**MeCN/1,4-dioxane**	**100**	**81**
16	AgOAc	MeCN/1,4-dioxane	80	56
17	AgOAc	MeCN/1,4-dioxane	60	18

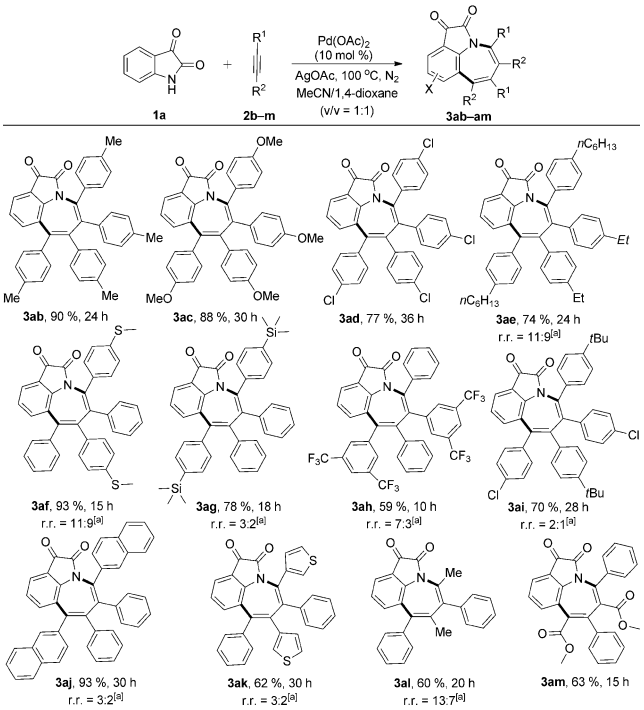
[a] Reaction conditions: MeCN/1,4-dioxane (v/v = 1:1; 2 mL), **1a** (0.2 mmol, 1.0 equiv), **2a** (1.0 mmol, 5.0 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), 24 h, under N_2. [b] Yield of isolated product after purification by column chromatography. [c] **1a**/**2a** = 1:3. [d] Reaction conducted in air. Ac = acetyl, BQ = 1,4-benzoquinone, DMF = dimethylformamide.



Scheme 2. Scope of isatins. Reaction conditions: MeCN/1,4-dioxane (v/v = 1:1; 2 mL), **1b–o** (0.2 mmol, 1.0 equiv), **2a** (1.0 mmol, 5.0 equiv), $Pd(OAc)_2$ (10 mol%), 100 °C, 24 h, under N_2. For the crystal structure of compound **3da**, see the Supporting Information.

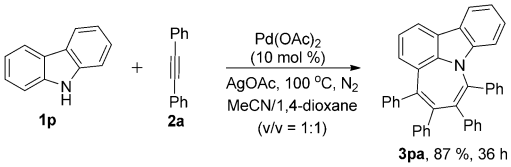
After identifying the optimized conditions, we examined the scope of isatins **1**. Scheme 2 illustrates the substitution pattern on the istains we validated. Electron-withdrawing, electron-neutral, and electron-donating substituents at the C5 position were tolerated and gave high yields (**3ba–fa, 3ja–ka**).[14] Substrates with electron-withdrawing and/or electron-donating substituents at the C4 or C7 positions also showed moderate to high reactivity and afforded the corresponding benzazepine products (Scheme 2, **3ga–ha**, **3la–oa**).[15]

We investigated a range of different alkynes **2** that could potentially react with **1a** to study the generality of the method for further synthetic exploitation. The reaction showed broad substrate tolerance among internal alkynes. Electron-rich tolanes reacted to give products in high yield (Scheme 3, **3ab–ac**, **3ae–af**) while electron-deficient systems were less facile (Scheme 3, **3ad** and **3ah**). Heteroaryl, ester-containing and aliphatic alkynes were also tolerated (**3ak**, **3am**, **3al**). When asymmetrical internal alkynes were employed, two regioisomers were usually observed (**3ae–ak**). In the event that the internal alkynes were highly electron-rich (**2f**) or electron-deficient (**2h, 2i, 2m**), the major stereoisomers formed followed Markovnikov's rule for both alkyne additions.[19] The minor isomer formed differed from the major product as a result of anti-Markovnikov addition in the second alkyne addition step.[19] However, when the asymmetrical internal alkynes were less electron-rich (**2e, 2g**), less electron-deficient, or electron-neutral (**2j, 2k**) by virtue of their functional groups, steric considerations became predominant and the least sterically-encumbered product was formed as the major stereoisomer.[19] An exception was 2-butyne, which



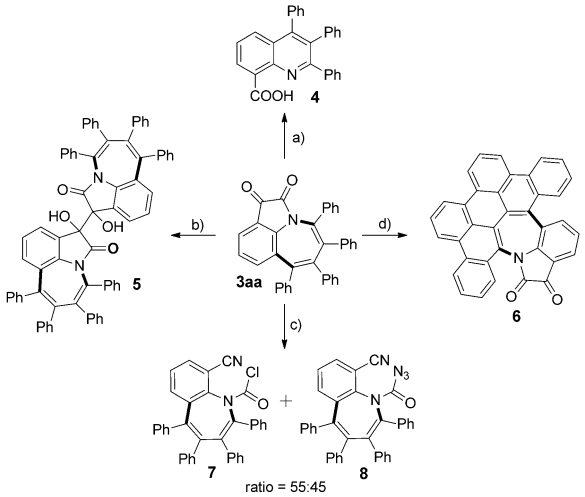
Scheme 3. Scope of alkynes. Reaction conditions: MeCN/1,4-dioxane (v/v = 1:1; 2 mL), **1a** (0.2 mmol, 1.0 equiv), **2b–m** (1.0 mmol, 5.0 equiv), $Pd(OAc)_2$ (10 mol %), 100 °C, 24 h, under N_2. [a] Ratio of regioisomers (r.r.) was determined by NMR spectroscopy.

generated an unknown structure (not shown) under these conditions. When the naphthalene-based isatin **1t** was used, a series of unique and unexpected pyrrole-fused 3-indolinone structures were obtained through a currently unknown reaction mechanism (Scheme 4). Notably, although two molecules of diphenylacetylene **2a** played a part in the reaction, a combination of one phenyl ring, one carbon atom, and one oxygen atom were eliminated from the desired structure. Surprisingly, when a carbazole **1p** reacted with diphenylacetylene **2a**, the corresponding carbazole-fused azepine **3pa** was obtained in 87 % yield [Eq. (1)]. This finding greatly enriches the diversity of our synthetic applications.

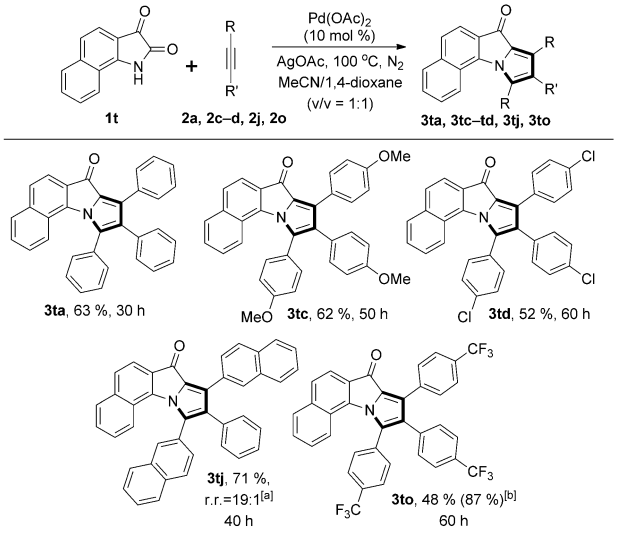


(1)

The versatility of this palladium-catalyzed oxidative cycloaddition can be exploited in chemoselective transformations to access various frameworks with high degrees of molecular complexity. As outlined in Scheme 5, the oxidative



Scheme 5. Synthetic transformations of benzazepine **3aa**. Reaction conditions: a) **3aa** (0.1 mmol), *m*-CPBA (0.2 mmol), CH_2Cl_2 (2 mL), RT, 0.5 h, 85 %; b) **3aa** (0.1 mmol), 10 % Pd/C, H_2 (balloon), THF (2 mL), RT, 0.5 h, 95 %; c) **3aa** (0.1 mmol), $FeCl_3$ (0.5 mmol), $TMSN_3$ (2 mmol), DCE (3 mL), 60 °C, 6 h, 57 %; d) **3aa** (0.1 mmol), $Cu(OTf)_2$ (4.5 mmol), $AlCl_3$ (5 mmol), CS_2 (10 mL), RT, 24 h, 61 %. For crystal structures of compounds **4**,**5**,**7**, and **8**, see the Supporting Information. DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

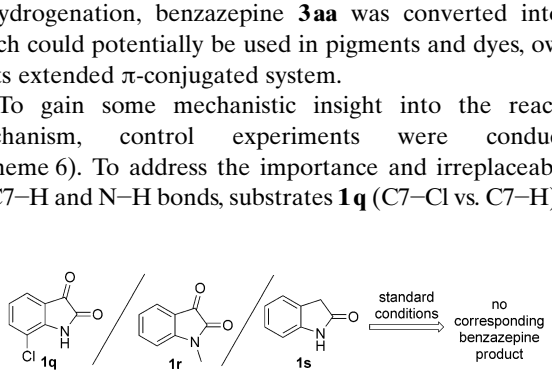


Scheme 4. Synthesis of pyrrole-fused 3-indolinones. [a] Ratio of regioisomers (r.r.) was determined by NMR spectroscopy. [b] Value in parentheses is the yield of isolated product based on recovered starting material. For the crystal structure of compound **3ta**, see the Supporting Information.

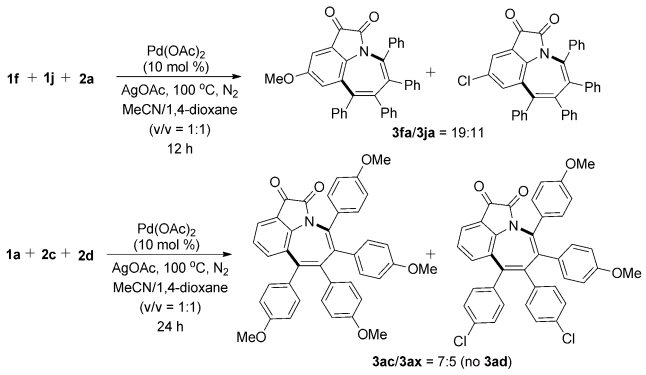
adduct **3aa** was readily converted into polysubstituted quinoline **4** through the use of 2.0 equivalents of *meta*-chloroperoxybenzoic acid (*m*-CPBA). Polysubstituted quinoline **4** was structurally characterized by single crystal X-ray diffraction analysis.[16] Under standard Pd-catalyzed hydrogenation conditions (10 mol % Pd/C, 1 atm H_2), **3aa** unexpectedly afforded dimer **5** in 0.5 h, which was structurally confirmed by X-ray diffraction analysis.[17] C1–C2 bond cleavage could also be carried out in the presence of an $FeCl_3$ catalyst to yield **7** and **8** (55:45),[18] which bear acyl chloride and acyl azide functional groups on the N atom, respectively. Notably, using $Cu(OTf)_2$ and $AlCl_3$ to promote

dehydrogenation, benzazepine **3aa** was converted into **6**, which could potentially be used in pigments and dyes, owing to its extended π-conjugated system.

To gain some mechanistic insight into the reaction mechanism, control experiments were conducted (Scheme 6). To address the importance and irreplaceability of C7–H and N–H bonds, substrates **1q** (C7–Cl vs. C7–H), **1r** (N–Me vs. N–H) and **1s** (oxindole vs. isatin **1a**) were tested and the desired cycloaddition adducts were not detected (Scheme 6). This result reveals that C7–H and N–H are both vital reaction sites. To further understand the effects of the functional group, two comparative experiments were conducted (Scheme 7). Electron-rich isatin **1f** reacted more rapidly than electron-deficient isatin **1j** (Scheme 7; **3fa**/**3ja** = 19:11). Similarly, electron-rich alkyne **2c** is favored in this oxidative cycloaddition as electron-deficient alkyne **2d** failed to generate the targeted product **3ad** in the presence of **2c**. Instead, a new oxidative adduct, **3ax**, was obtained.

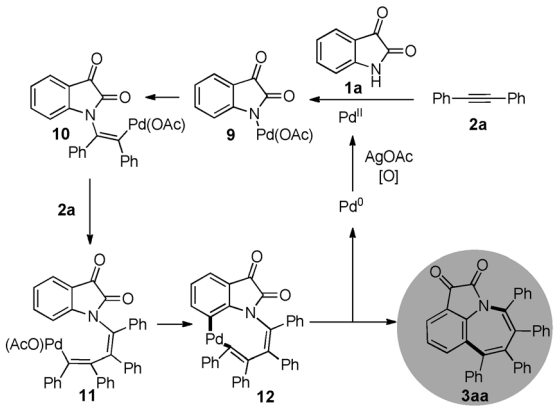


Scheme 6. Control experiments. Reaction conditions: MeCN/1,4-dioxane (v/v = 1:1; 2 mL), **1q–s** (0.2 mmol, 1.0 equiv), **2a** (1.0 mmol, 5.0 equiv), $Pd(OAc)_2$ (10 mol%), 100 °C, 24 h, under N_2.



Scheme 7. Competition experiments.

On the basis of known transition-metal-catalyzed C–H activation/oxidative cycloaddition reactions, we propose a mechanism to account for product formation (Scheme 8). Formation of benzazepine **3aa** presumably commences with the palladation of isatin **1a** to yield the palladium intermediate **9** (Scheme 8). This is followed by *syn*-addition of intermediate **9** to diphenylacetylene (**2a**) to generate vinylpalladium intermediate **10**. Insertion of another **2a** affords butadienylpalladium intermediate **11**. Finally, intramolecular palladation of **11** leads to the formation of palladabenzocycloheptatriene **12**, which can subsequently undergo reductive elimination to yield benzazepine **3aa**.



Scheme 8. Proposed catalytic cycle.

In summary, we have developed a synthesis of benzazepine heterocycles that utilizes simple and readily available isatins and alkynes, and employs direct Pd^{II}-catalyzed oxidative cycloaddition. Heterocycles are well tolerated in the reaction, which allows access to a number of unique molecular structures. The significance of the benzazepine scaffold as a structural element should render this method attractive for both synthetic and medicinal chemistry, thus paving the way for the synthesis of other complex biologically active heterocyclic systems.

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[14] CCDC 849053 (**3da**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] CCDC 857373 (**3ta**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] CCDC 903588 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] CCDC 894859 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] CCDC 894859 (**7** and **8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] To determine the regioselectivity of asymmetric internal alkynes, the regioisomers of compound **3ag** and **3ah** were established by X-ray crystal analysis. For details, see the Supporting Information.

