Carbocyclization

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Palladium(II)-Catalyzed Oxidative Carbocyclization of Aza-Enallenes**

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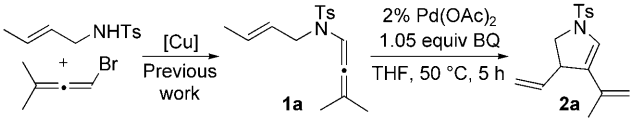
Metal-mediated C–H bond functionalizations offer the synthetic chemist a powerful tool in the quest for producing ever more complex and demanding organic structures.[1] This process transforms various C–H bonds into more synthetically useful C–O, C–N, or C–C bonds.[2] In particular, the metal-catalyzed activation of allylic C–H bonds has received much attention, and, as a consequence, there are numerous examples of metal-mediated allylic oxidations in the literature.[3] Early procedures suffered from moderate selectivity and the use of stoichiometric amounts of metal.[4] Most of these drawbacks have long since been overcome, which has resulted in a vast array of catalytic allylic oxidations,[5–9] including asymmetric protocols,[6] being made available to the synthetic chemist. More recent work on palladium(II)-catalyzed allylic oxidation reactions has extended the synthetic utility of these protocols, and has also allowed the selective formation of carbon–carbon bonds.[8–10] In all of these oxidation reactions, an efficient re-oxidation system is key to their success, with molecular oxygen as the preferred terminal oxidant.[11]

We have previously reported various palladium-catalyzed transformations of allenes.[12–14] These studies have focused on a variety of C-allenyl compounds that contain olefinic side chains. Such substrates are well-suited for palladium(II)-catalyzed carbon–carbon bond-forming oxidative cyclization reactions,[13] as well as palladium(0)-catalyzed cyclization reactions.[14] In a recent investigation, we showed that water (aqueous media) can act as a nucleophile in the oxidative carbocyclization[15] of diene–allene compounds using molecular oxygen as the terminal oxidant.[13c]

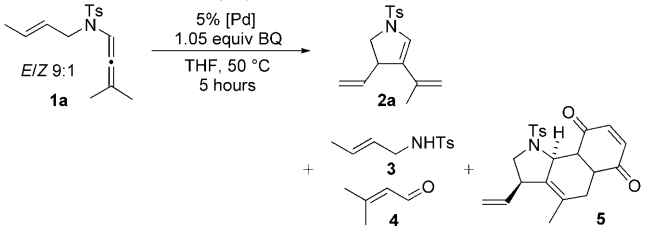
We recently reported a copper-catalyzed coupling of sulfonamides and halo-allenes that provided access to aza-enallenes,[16] which might be suitable for a carbocyclization protocol. Herein, we report that aza-enallenes **1a** react with catalytic amounts of $Pd(OAc)_2$ in an overall oxidative carbocyclization process to give **2a** (Scheme 1).

In our previous work on the preparation of aza-enallenes,[16] we noticed that these compounds were highly sensitive towards acidic conditions. Initially, we studied the reaction of **1a** with different palladium sources. As shown in Table 1, the only simple palladium(II) salt that resulted in an acceptable yield of **2a** was $Pd(OAc)_2$. Under these conditions, the only by-product detected was the Diels–Alder adduct **5**



Scheme 1. Preparation and carbocyclization of aza-enallenes. BQ = *para*-benzoquinone, THF = tetrahydrofuran.

Table 1: Investigation of different Pd^{II} sources in the oxidative carbocyclization of aza-enallene (**1a**).[a]



Entry	[Pd^{II}]	Conv. [%][b]	Product ratio (**2a**/**3**/**4**/**5**)	Yield of **2a** [%][c]
1	$Pd(OAc)_2$	100	90:0:0:10	80
2	$[PdCl_2(CH_3CN)_2]$	100	5:45:45:5	< 5
3	$Pd(tfa)_2$	95	1:49:49:1	< 1
4	$Pd(acac)_2$	0	s.m.	0
5	$Pd(OAc)_2$, L1[d]	0	s.m.	0
6	none	0	s.m.	0

[a] Reaction conditions: Pd^{II} source (5 mol%), BQ (1.05 equiv), aza-enallene (1.00 equiv) THF, 50 °C, 5 h. [b] Product distribution and conversion determined using NMR analysis. [c] Yield based on an internal standard (anisole). [d] L1 = 1,10-phenanthroline. s.m. = starting material.

between carbocyclization product and *para*-benzoquinone (BQ). Replacing $Pd(OAc)_2$ with $Pd(TFA)_2$ (TFA = trifluoroacetate) or $[PdCl_2(CH_3CN)_2]$ gave only trace amounts of carbocyclization product (Table 1, entries 2 and 3), and instead the formation of tosylamide derivative **3** and aldehyde **4** predominated.[17]

No conversion was observed with $[Pd(acac)_2]$ or $Pd(OAc)_2$ with 1,10-phenanthroline, and the starting material was recovered in these cases (Table 1, entries 4 and 5). A control experiment without palladium, under the same conditions, showed no decomposition or conversion of **1a** by NMR spectroscopy (Table 1, entry 6). The catalyst screening showed that $Pd(OAc)_2$ was the most effective catalyst

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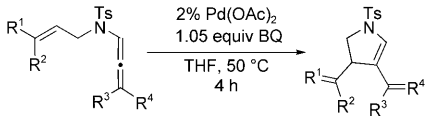
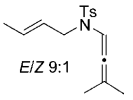
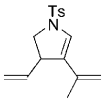
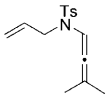
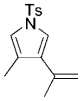
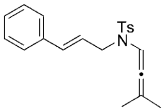
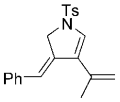
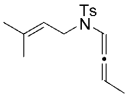
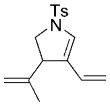
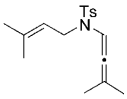
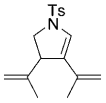
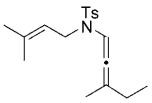
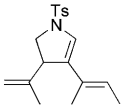
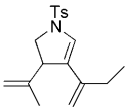
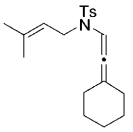
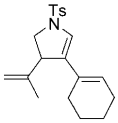
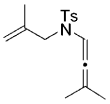
among the simple Pd^{II} catalysts that were tested. To gain some insight into the formation of the Diels–Alder adduct in the catalytic reaction, some in situ NMR experiments were performed. The reaction of aza-enallene **1a** with 1.05 equivalents of BQ in the presence of 2 mol% of $Pd(OAc)_2$ in [D_8]THF at 48 °C was monitored by ^{1}H NMR spectroscopy, which showed that a Diels–Alder product was formed when the reaction had reached around 40% conversion. (see the Supporting Information, Figure S1) This observation suggests that the byproduct arises from a reaction between carbocyclized product **2a** and BQ. After 2.5 hours, products **2a** and **5** were formed in a 91:9 ratio, and the yield of **2a** was 82%, based on the internal standard. Interestingly, the formation of **2a** shows a sigmoidal growth curve (Figure S1, Supporting Information). A plausible explanation for this phenomenon is that the commercially available trimeric palladium acetate needs to be activated or dissociated in order to produce the monomeric species required for catalysis.[18] Another explanation could be that the Diels–Alder adduct participates as a ligand in the reaction; this type of activation has been previously suggested for the diacetoxylation of 1,3-dienes.[19]

Table 2: Substrate scope.[a]



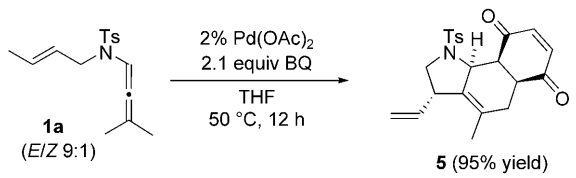
Entry	Aza-enallene		Product		Yield [%][b]
1	 *E*/*Z* 9:1	**1a**		**2a**	74 94[c]
2		**1b**		**2b**	64[d]
3		**1c**		**2c**	95 (*Z*)
4		**1d**		**2d**	71
5		**1e**		**2e**	84
6		**1f**	 **2f** (*E*/*Z* = 4:1)  **2f′**		70 **2f**/**2f′** 3:1
7		**1g**		**2g**	81 86[c]
8		**1h**	no reaction		0[e]

[a] Reaction conditions (unless otherwise noted): $Pd(OAc)_2$ (2 mol%), BQ (1.05 equiv), aza-enallene (1.00 equiv), THF, 50 °C, 4 h. [b] Yield of isolated product. [c] $Pd(OAc)_2$ (5 mol%), [Co] cat. **6** (5 mol%)/O_2, 6 h. [d] 24 h reaction time. [e] Starting material can be recovered.

Once the optimum conditions for the transformation were found, we investigated the scope of the procedure, and the results are given in Table 2. In general, aza-enallenes cyclized to afford their corresponding heterocycles in good to high yields. Carbocyclization of aza-allene **1a** (Table 2, entry 1) afforded pyrroline **2a** in 74% yield after 4 hours. Aza-enallene **1b**, which has a terminal alkene (Table 2, entry 2), gave *N*-tosyl-protected pyrrole **2b** in 64% yield. This substrate reacted sluggishly and required 24 hours to reach full conversion. We believe that this is due to the fact that β-hydride elimination to form the exocyclic double bond is slow. The initial β-elimination product can be detected by NMR spectroscopy, but it is unstable under the reactions conditions and isomerizes into aromatic compound **2b** during the reaction. Interestingly, substrate **1c** cyclized in 95% yield in 4 hours to give **2c** (>99% *Z*) without any detectable amounts of aromatized product or Diels–Alder adduct (Table 2, entry 3). This result can be explained by the extended conjugation added by the phenyl group, which makes the structure less prone to undergo Diels–Alder reactions and/or isomerization. Although this product is stable under the reaction conditions, purification by column chromatography on basic alumina was necessary to avoid formation of the aromatized product.[20]

Subjecting 1,1-disubstituted olefins **1d–g** to the coupling conditions resulted in good yields of carbocyclization products (Table 2, entries 4–7). In all cases, the reactions proceeded with 100% conversion and the desired products were only accompanied by small amounts of the corresponding Diels–Alder adduct. Substrates that contained an internal substituent on the double bond failed to undergo carbocyclization, even at elevated temperatures and over prolonged reaction times (Table 2, entry 8).

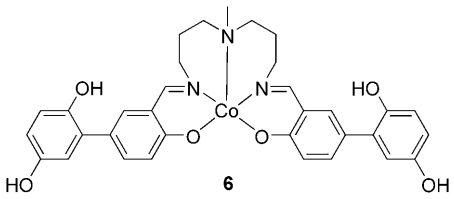
We then decided to investigate the effectiveness of the Diels–Alder reaction and found that increasing the amount of BQ to 2.1 equivalents and running the reaction at 50 °C for 12 hours exclusively afforded *endo*-Diels–Alder adduct **5** in 95% yield (Scheme 2). This result indicates that oxidative



Scheme 2. Selective formation of Diels–Alder product **5**.

carbocyclization proceeds selectively without the formation of any isomerized or over-oxidized products.

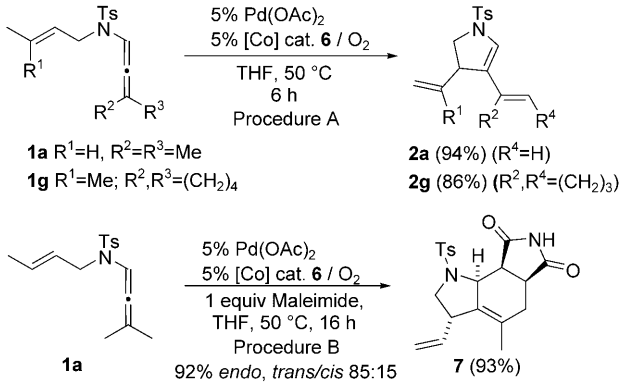
To broaden the synthetic utility of this transformation, an aerobic (biomimetic) version was investigated using catalytic amount of quinone. We have previously reported such procedures for a variety of palladium-catalyzed reactions, where O_2 is employed as a terminal oxidant.[5b,11a,21] Recently, our group developed and utilized a new type of hybrid catalyst (**6**), in which hydroquinone is tethered to the salen-type framework (Scheme 3).[21,22] With **6** as the sole co-



Scheme 3. Structure of oxygen-activating [Co] catalyst **6**.

catalyst a higher yield of cyclized product was expected, as secondary Diels–Alder reactions of **2a** would be minimized. To our delight, subjecting **1a** to 5 mol% $Pd(OAc)_2$ and 5 mol% of cobalt catalyst **6** in tetrahydrofuran at 50 °C under 1 atmosphere of O_2 (balloon) smoothly gave the desired cyclized product **2a** in 94% yield after 6 hours without the formation of any detectable Diels–Alder adducts (Scheme 4, procedure A; Table 2, entry 1). Under the same aerobic conditions, **1g** afforded **2g** in 86% yield (Scheme 4, procedure A; Table 2, entry 7).

The development of a biomimetic version that employs O_2 oxidation opens up the possibility of using a variety of



Scheme 4. Biomimetic cyclization and tandem cyclization-Diels–Alder reactions.

dienophiles in a tandem reaction (Scheme 4, procedure B). For example, oxidative cyclization with the addition of 1 equivalent of maleimide resulted in a tandem oxidative-cyclization/Diels–Alder reaction to give polycyclic product **7** in 93% yield after 16 hours at 50 °C (92% *endo*, *trans*/*cis* 85:15).[23,24]

In conclusion, we have extended our oxidative carbocyclization methodology to include aza-enallene substrates. The heterocyclic products are useful intermediates in the synthesis of complex molecules. The biomimetic oxidation can be combined with a Diels–Alder procedure in a tandem oxidative-carbocyclization/Diels–Alder sequence in one pot. Investigation of the scope of the one-pot Diels–Alder reaction sequence is underway.

Experimental Section

Catalyst screening: $Pd(OAc)_2$ (0.6 mg, 0.0026 mmol) and *para*-benzoquinone (5.8 mg, 0.054 mmol) were dissolved in THF (1 mL). Aza-enallene **1a** (15.0 mg, 0.051 mmol) was then added in one portion. The vessel was sealed and stirred for 5 h at 50 °C; after 5 h, the solvent was evaporated and ansiole (5.5 μL, 0.051 mmol) was added. The residual oil was taken up into $CDCl_3$ and analyzed by ^{1}H NMR spectroscopy.

Catalytic carbocyclization of **1a**: Aza-enallene **1a** (50 mg, 0.17 mmol), *para*-benzoquinone (19.5 mg, 0.18 mmol), and $Pd(OAc)_2$ (0.77 mg, 0.0034 mmol) were dissolved in THF (2 mL). The solution was then stirred for 4 h in air. The reaction was monitored using TLC analysis, eluting with pentane/EtOAc (15:1). After cooling to room temperature, the solution was diluted with Et_2O and washed once with 2 M NaOH. The aqueous phase was back-extracted once using Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated. Purification of the slightly brown residue by column chromatography (pentane/EtOAc, 15:1) gave 37 mg of **2a** (74% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ ppm (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 2H), 6.47 (s, 1H), 5.49 (ddd, $J = 17.1$, 10.1, 8.0 Hz, 1H), 4.97 (d, $J = 17.1$ Hz, 1H), 4.93 (d, $J = 10.2$ Hz, 1H), 4.81 (m, 2H), 3.65–3.50 (m, 2H), 3.44–3.40 (m, 1H), 2.43 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.0$, 138.8, 136.1, 132.8, 129.8, 128.4, 127.7, 127.2, 115.8, 112.8, 54.4, 46.5, 21.6, 20.8. HRMS (ESI) calcd for $[M+Na]^+$ $C_{16}H_{19}NNaO_2S$ 312.1028; found 312.1034.

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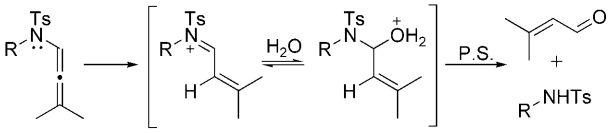
[17] We believe that the formation of **3** and **4** is due to the strong acid (HCl, CF_3COOH) that is formed in these reactions, which then catalyzes the hydrolysis of the *N*-allenyl bond. P.S. = proton shift.



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[20] This product slowly aromatizes in dichloromethane.

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[23] Quenching the reaction before it reached 100% conversion revealed that the reaction mixture consisted of unreacted **1a** and Diels–Alder adduct **7**, but only very small amounts of cyclized product **2a**, thus indicating that the Diels–Alder reaction is faster then the cyclization.

[24] An excess of maleimide slowed the rate of reaction, and the use of 2 equivalents of maleimide gave only 50% conversion after 16 hours. Most likely, the maleimide blocks coordination of *para*-benzoquinone.

