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Modular Synthesis of 1,2-Diamine Derivatives via Palladium-Catalyzed Aerobic Oxidative Cyclization of Allylic Sulfamides**

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Abstract

Allylic sulfamides undergo efficient aerobic oxidative cyclization at room temperature, mediated by a new Pd catalyst system consisting of 5% Pd(TFA)₂/10% DMSO in THF. The synthetic utility of these reactions is enhanced by several features: (1) the sulfamide substrates are accessible in multi-gram scale from the corresponding allylic and primary amines, (2) the cyclic sulfamide products are readily converted to the corresponding 1,2-diamines upon treatment with LiAlH₄, and (3) substrates derived from chiral allylic amines cyclize with very high levels of diastereoselectivity.

Keywords

catalysis; diamines; dioxygen; oxidation; oxidative cyclization; palladium

Vicinal diamines are prevalent in biologically active molecules and as ligands for transition metals. Consequently, these structures have been the target of considerable synthetic effort.^[i] A number of novel palladium-catalyzed methods for the synthesis of diamines from alkenes and dienes have been reported recently.^[ii–vi] Limitations of these reactions with respect to substrate scope and identity of the stoichiometric oxidant (e.g., benzoquinone, PhI(OAc)₂, and di-*tert*-butyldiaziridinone), together with our interest in aerobic oxidation reactions,^[vii] prompted us to consider whether analogous diamines could be prepared with O₂ as the oxidant. Here, we describe a versatile method for the stereocontrolled synthesis of 1,2-diamine derivatives via Pd-catalyzed aerobic oxidative cyclization of allylic sulfamides (**A**, Scheme 1), substrates which are readily prepared in multigram quantities from the corresponding allylic and primary amines.^[viii] These reactions were made possible by identification of a very simple catalyst system consisting of a 2:1 ratio of DMSO and Pd(O₂CCF₃)₂, which is capable of promoting the oxidative cyclization reactions at room temperature with molecular oxygen as the sole stoichiometric oxidant.

Initial reaction development efforts employed sulfamide **1** as the substrate (Table 1). We tested a number of catalyst systems that have been reported previously for aerobic oxidative heterocyclization reactions, the most prominent of which include Pd(OAc)₂ in DMSO,^[ix]

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$\text{Pd}(\text{OAc})_2/\text{pyridine}$ in toluene, and closely related variants.^[x] These catalyst systems were only moderately successful (Table 1, entries 1–3; for full screening data, see Supporting Information). For example, the $\text{Pd}(\text{OAc})_2/\text{pyridine}$ catalyst system we originally reported for Ts-substituted γ -aminoalkenes^[xa] afforded the desired cyclic sulfamide **2** in only 39% yield and generated the imine byproduct **3** in 25% yield (entry 2). In the course of testing other solvents and reaction conditions, we observed that addition of catalytic quantities of DMSO improved the yield of **2** when $\text{Pd}(\text{TFA})_2/\text{pyridine}$ ($\text{TFA} = \text{CF}_3\text{CO}_2^-$) was used as the catalyst in dioxane (entries 4 and 5). Substantially better results were obtained by eliminating pyridine altogether (entry 6). The formation of Pd black in these reactions prompted us to examine whether the catalyst might be more stable, but retain good activity, at lower temperature. Additional optimization studies led to conditions in which quantitative product formation could be obtained in 10 hours at room temperature in THF (entry 7). The stoichiometry of DMSO affects the reaction outcome (entries 7–11). The product yield is substantially lower at $\text{Pd}^{\text{II}}:\text{DMSO}$ ratios less than 2:1 (entries 8 and 9), and the yield also diminishes at higher [DMSO], falling to 47% yield when DMSO is used as the solvent (entries 10 and 11). The identity and quantity of the added base is also important, and use of 20 mol % sodium benzoate proved to be optimal.^[xi]

This oxidative cyclization reaction could proceed via two different mechanisms (Scheme 2): aminopalladation of the alkene followed by β -hydride elimination^[xa] or allylic C-H activation to form a π -allyl- Pd^{II} intermediate followed by C–N coupling.^[xiib,d,e] The chelating sulfoxides **4** and **5** were tested as replacements for DMSO because these ligands have been shown to facilitate allylic C-H activation;^[xiib,d,e] however, only low yields of the sulfamide product **2** were obtained in these reactions (Table 1, entries 12 and 13). To further distinguish between the two mechanisms, the homoallyl amine derivative **6** was synthesized. Effective cyclization of this substrate would provide evidence in favor of an allylic C–H activation pathway. Subjecting this substrate to the optimized reaction conditions, however, resulted in complete recovery of starting material after 24 hours. This result suggests allylic C–H activation does not occur under the reaction conditions.

The beneficial effect of DMSO and other sulfoxides in Pd-catalyzed reactions has been noted previously by a number of groups,^[ix, xii] and we have performed kinetic studies of aerobic alcohol oxidation catalyzed by $\text{Pd}(\text{OAc})_2$ in DMSO.^[xiii] In the latter studies, the large excess of DMSO prevented us from gaining fundamental insights into the Pd–DMSO interaction. The present catalyst system is more amenable to characterization. Spectroscopic studies draw attention to at least two properties of DMSO that are probably important in these reactions: (1) linkage isomerism and (2) kinetic lability. ^1H NMR spectra of the 2:1 DMSO: $\text{Pd}(\text{TFA})_2$ mixture in THF- d_8 reveal several resonances for DMSO, none of which correspond to free DMSO. The chemical shifts of these resonances, together with infrared spectroscopic analysis of the Pd^{II} –DMSO complexes obtained under these conditions, establishes the presence of both *S*- and *O*-bound DMSO ligands.^[xi,xiv] These observations are consistent with early studies of the coordination of DMSO to Pd^{II} .^[xv,xvi] As we have

speculated previously,^[xiii] the ability of DMSO to serve as a “hard” (*O*) or “soft” (*S*) ligand could play an important role in the interconversion between the relatively hard and soft Pd^{II} and Pd⁰ redox states during the catalytic cycle. Variable-temperature ¹H NMR spectra (–60 – 40 °C) reveal coalescence of DMSO ligand resonances, the *O*-bound DMSO resonances at –40 °C and *S*-bound resonances at +40 °C.^[xi] These observations highlight the kinetically labile nature of DMSO coordination to Pd^{II} under the reaction conditions. This property contrasts the behavior of pyridine as a ligand^[xvii] and probably facilitates substrate coordination to Pd^{II} and other ligand exchange processes necessary for efficient catalytic turnover at room temperature.

This simple catalyst system proved to be quite versatile in reactions with other sulfamides (Tables 2 and 3). Substrates bearing both aliphatic or aryl *N*-substituents undergo efficient cyclization, with the only exception being a substrate derived from an electron-deficient aniline (**7e**). The reactions proved to be remarkably tolerant of functional groups. Compatibility included groups typically stable to oxidizing reaction conditions [an ester (**7f**), aryl fluoride (**7h**), carbamate (**7i**), primary chloride (**7k**), and ether (**7d**; see also, Table 3, entry 7)], but also extended to groups susceptible to oxidation in other Pd-catalyzed reactions, including terminal alkene (**7j**) and furan substituents (**7l**). A substrate with a silyl ether appended to the allyl amine also undergoes cyclization in high yield, affording a silyl enol ether product that is stable under the reaction conditions (Table 3, entry 3). In many of these reactions, analytically pure products could be obtained by simply filtering the reaction mixture through a plug of activated basic alumina. Furthermore, all procedures were performed on the benchtop, and no solvent purification was required prior to performing these reactions.

Sulfamides derived from substituted allylic amines also proved to be excellent substrates (Table 3). Use of a trisubstituted alkene (entry 1) led to quarternary C–N bond formation in quantitative yield. Cyclization onto an alkene with remote C–H bonds experienced little complication associated with alkene isomerization (entry 2). The cyclization reactions exhibit good-to-excellent levels of diastereoselectivity. A sulfamide derived from α -methylbenzylamine as the primary amine (entry 4) underwent cyclization to afford a 6:1 ratio of diastereomers. Substrates derived from chiral allylic amines exhibited substantially higher levels of stereoselectivity: allylic substituents larger than a methyl group provided products with diastereomeric ratios >29:1 (entries 5–9). The latter observation has important implications for the synthetic utility of this cyclization reaction because numerous procedures are available for enantioselective synthesis of chiral allylic amines.^[xviii]

Use of this method to prepare densely functionalized chiral diamines is highlighted in the oxidative cyclization of mannitol-derived substrate **8** (Figure 1). This reaction was carried out at room temperature on a 1 g scale, and it proceeded in quantitative yield, affording a single product diastereomer. Facile removal of the sulfonyl group by treatment of **9** with LiAlH₄ in diethyl ether unveiled the acyclic diamine **10** in 89% yield.^[xi]

The reactions described here are complementary to other metal-catalyzed routes to prepare vicinal diamines.^[ii–vi] Among the most synthetically useful methods currently available are those reported recently by Shi and coworkers, which employ di-*tert*-butylaziridinone as the oxidant and diamination reagent [e.g., Eq. (1)].^[iii] The latter methods are highly diastereoselective, they employ readily available terminal alkenes as substrates, and enantioselective reactions have been achieved.^[iiib] One of the few drawbacks of this method is the requirement for *tert*-butyl groups as the *N*-substituents of the diaziridinone reagent. Removal or replacement of these groups can result in additional steps in the synthesis of a target molecule.^[xix] In contrast, the aerobic oxidation method described here exhibits broad versatility with respect to the *N*-substituents. This feature, together with the extensive

availability of enantiomerically pure allylic amines,^[xviii] could be highly advantageous in the synthesis of many target molecules.

(1)

Overall, these Pd-catalyzed aerobic oxidative cyclization reactions provide a highly modular, efficient and scalable approach to the preparation to 1,2-diamine derivatives. The straightforward retrosynthetic disconnection evident in Scheme 1 and the excellent diastereoselectivity of the reaction suggest that this reactivity should have broad utility in the synthesis of complex molecules. Moreover, the simple catalyst system identified in this work has clear advantages over previously identified systems, and we anticipate it will find application in numerous other oxidative transformations capable of using molecular oxygen as the stoichiometric oxidant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Demonstration of 1,2-diamine synthesis via aerobic oxidative cyclization of a manitol-derived allylic sulfamide.

Scheme 1.

Synthesis of 1,2-Diamines via Pd-Catalyzed Aerobic Oxidative Cyclization of Allylic Sulfamides.

Scheme 2.
Possible Mechanisms for the Pd-Catalyzed Oxidative Cyclization Reaction.

Table 1

Optimization of the Pd-Catalyzed Aerobic Oxidative Cyclization of Sulfamides.^[a]

Entry	Catalyst (5 mol %)	Additive (mol %)	Base (mol %)	Solvent	Temp [°C]	Yield [%] ^[2] (3/ ^[b]
1	Pd(OAc) ₂	–	NaOBz (200)	DMSO	80	24
2	Pd(OAc) ₂	py (10)	–	toluene	80	39 (25)
3	Pd(TFA) ₂	py (20)	NaOAc (100)	toluene	80	68 (17)
4	Pd(TFA) ₂	py (20)	NaOBz (20)	dioxane	80	35
5	Pd(TFA) ₂	py (20)/DMSO (10)	NaOBz (20)	dioxane	80	48
6	Pd(TFA) ₂	DMSO (10)	NaOBz (20)	dioxane	80	92
7	Pd(TFA)₂	DMSO (10)	NaOBz (20)	THF	25	99 ^[c, d]
8	Pd(TFA) ₂	–	NaOBz (20)	THF	25	9 ^[c]
9	Pd(TFA) ₂	DMSO (5)	NaOBz (20)	THF	25	25 ^[c]
10	Pd(TFA) ₂	DMSO (20)	NaOBz (20)	THF	25	93 ^[c]
11	Pd(TFA) ₂	–	NaOBz (20)	DMSO	25	47
12	Pd(TFA) ₂	ligand 4 (5)	NaOBz (20)	THF	25	9
13	Pd(TFA) ₂	ligand 5 (5)	NaOBz (20)	THF	25	35

^[a] Conditions: **1** (0.075 mmol), 3 Å MS (20 mg), 1 atm O₂, solvent (0.75 mL), 24 h.^[b] Determined by ¹H NMR spectroscopy, internal standard = 1,3,5-trimethoxybenzene.^[c] ¹⁰ hr.^[d] Isolated yield (0.3 mmol scale).

Table 2Aerobic Oxidative Cyclization of Sulfamides With Varying *N*-Substituents.^[a,b]

 7a 99 %	 7b 99 %	 7c 97 % ^c
 7d 96 % ^c	 7e 30 % ^{c,d}	 7f 70 % ^{c,d}
 7g 92 %	 7h 99 %	 7i 99 %
 7j 99 %	 7k 91 % ^c	 7l 80 %

^[a] Conditions: substrate (0.3 mmol), Pd(TFA)₂ (15 μmol), DMSO (30 μmol), NaOBz (60 μmol), 3Å MS (75 mg), THF (3 mL), 25 °C, 24 h.^[b] Isolated yield; d.r. determined by ¹H NMR spectroscopy of crude reaction mixture.^c NaOAc used instead of NaOBz.^d 48 hours.

Table 3

Aerobic Oxidative Cyclization of Sulfamides.^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1			99
2			96 ^c
3			81 ^{d,e}
4			90 ^d (d.r. = 6:1)
5			93 (d.r. = 11:1)

Entry	Substrate	Product	Yield [%] ^[b]
6			95 (d.r. > 30:1)
7			98 (d.r. = 29:1)
8			90 ^d (d.r. > 30:1)
9			73 (d.r. > 30:1)

^[a] Conditions: substrate (0.3 mmol), Pd(TFA)₂ (15 μmol), DMSO (30 μmol), NaOBz (60 μmol), 3Å MS (75 mg), THF (3 mL), 25 °C, 24 h.

^[b] Isolated yield; d.r. determined by ¹H NMR spectroscopy of crude reaction mixture.

^c Isolated as a 12:1 mixture of internal:terminal olefin.

^d 48 hours.

^e Isolated as a 2.1:1 mixture of *E*:*Z* olefin.