Oxidative Amination

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

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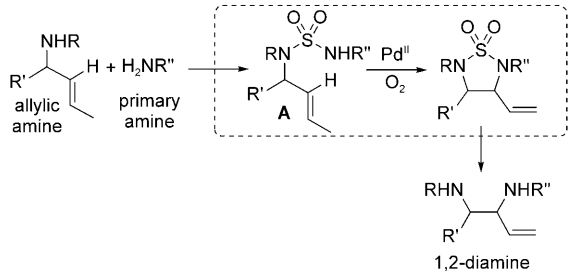
Vicinal diamines are prevalent in biologically active molecules and as ligands for transition metals. Consequently, these structures have been the target of considerable synthetic effort.[1] A number of novel palladium-catalyzed methods for the synthesis of diamines from alkenes and dienes have been reported recently.[2–6] 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,[7] prompted us to consider whether analogous diamines could be prepared using O_2 as the oxidant. Herein, we describe a versatile method for the stereocontrolled synthesis of 1,2-diamine derivatives by the palladium-catalyzed aerobic oxidative cyclization of allylic sulfamides (**A**, Scheme 1), substrates which are readily prepared in multigram quantities from their corresponding allylic and primary amines.[8] These reactions were made possible by identification of a very simple catalyst system consisting of a 2:1 ratio of dimethyl sulfoxide and $Pd(TFA)_2$ (TFA = trifluoroacetate), which is capable of promoting the oxidative cyclization reactions at room temperature with molecular oxygen as the sole stoichiometric oxidant.



Scheme 1. Synthesis of 1,2-diamines by palladium-catalyzed aerobic oxidative cyclization of allylic sulfamides.

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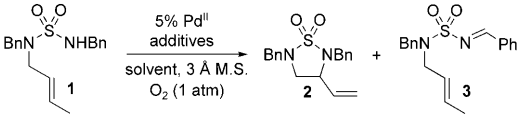
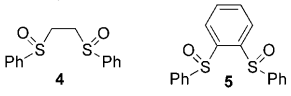
Initial reaction development efforts employed sulfamide **1** as the substrate (Table 1). We tested a number of catalyst systems that have been reported previously for aerobic oxidative heterocyclization reactions, the most prominent of which include $Pd(OAc)_2$ in dimethyl sulfoxide (Ac = acetyl),[9] $Pd(OAc)_2$/pyridine in toluene, and other closely related variants.[10] These catalyst systems were only moderately successful (Table 1, entries 1–3; for full screening data, see the Supporting Information). For example, the $Pd(OAc)_2$/pyridine catalyst system we originally reported for tosyl-substituted γ-aminoalkenes[10a] afforded the desired cyclic

Table 1: Optimization of the palladium-catalyzed aerobic oxidative cyclization of sulfamides.[a]



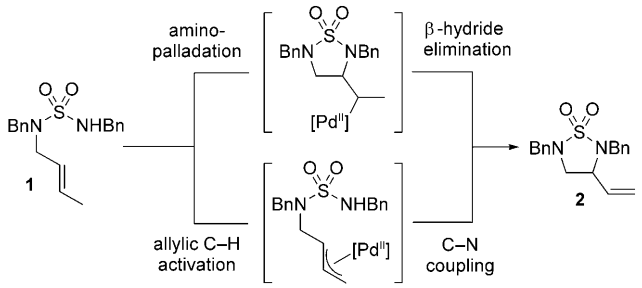
Entry	Catalyst (5 mol%)	Additive (mol%)	Base (mol%)	Solvent	*T* [°C]	Yield **2** (**3**) [%][b]
1	$Pd(OAc)_2$	–	NaOBz (200)	DMSO	80	24
2	$Pd(OAc)_2$	py (10)	–	toluene	80	39 (25)
3	$Pd(TFA)_2$	py (20)	NaOAc (100)	toluene	80	68 (17)
4	$Pd(TFA)_2$	py (20)	NaOBz (20)	1,4-dioxane	80	35
5	$Pd(TFA)_2$	py (20)/ DMSO (10)	NaOBz (20)	1,4-dioxane	80	48
6	$Pd(TFA)_2$	DMSO (10)	NaOBz (20)	1,4-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 M.S. (20 mg), 1 atm O_2, solvent (0.75 mL), 24 h. [b] Determined by ^1H NMR spectroscopy, internal standard = 1,3,5-trimethoxybenzene. [c] 10 h. [d] Yield of isolated product (0.3 mmol scale). Bz = benzoyl, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran.



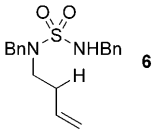
sulfamide **2** in only 39% yield and generated the imine byproduct **3** in 25% yield (Table 1, entry 2). In the course of testing other solvents and reaction conditions, we observed that addition of catalytic quantities of dimethyl sulfoxide improved the yield of **2** when $Pd(TFA)_2$/pyridine was used as the catalyst in 1,4-dioxane (Table 1, entries 4 and 5). Substantially better results were obtained by eliminating pyridine altogether (Table 1, entry 6). The formation of palladium 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 tetrahydrofuran (Table 1, entry 7). The stoichiometry of dimethyl sulfoxide affected the reaction outcome (Table 1, entries 7–11). The product yield was substantially lower at Pd^{II}/DMSO ratios of less than 2:1 (Table 1, entries 8 and 9), and the yield also diminished at higher [DMSO], falling to 47% when dimethyl sulfoxide was used as the solvent (Table 1, entries 10 and 11). The identity and quantity of the added base is also important, and use of 20 mol% sodium benzoate was found to be optimal.[11]

This oxidative cyclization reaction could proceed via two different mechanisms (Scheme 2): aminopalladation of the alkene followed by β-hydride elimination[10a] or allylic C–H activation to form a π-allyl–palladium(II) intermediate fol-



Scheme 2. Possible mechanisms for the palladium-catalyzed oxidative cylization reaction.

lowed by C–N coupling.[12b,d,e] The chelating sulfoxides **4** and **5** were tested as replacements for dimethyl sulfoxide because these ligands are known to facilitate allylic C–H activation;[12b,d,e] however, only low yields of sulfamide product **2** were obtained in these reactions (Table 1, entries 12 and 13). To further distinguish between these 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. However, subjecting this substrate to the optimized reaction conditions resulted in complete recovery of starting material after 24 hours. This result suggests that allylic C–H activation does not occur under these reaction conditions.



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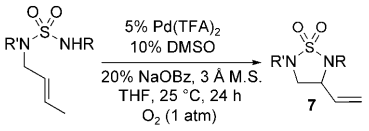
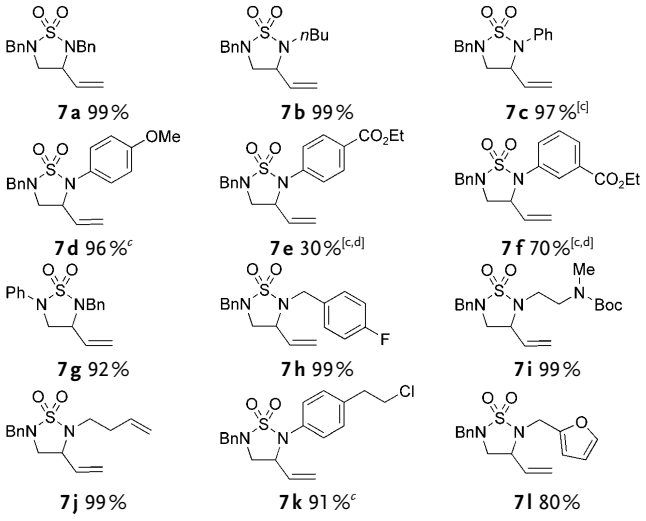
The beneficial effect of dimethyl sulfoxide and other sulfoxides in palladium-catalyzed reactions has been noted previously by a number of groups,[9,12] and we have already reported kinetic studies of aerobic alcohol oxidation catalyzed by $Pd(OAc)_2$ in dimethyl sulfoxide.[13] In the latter studies, the large excess of dimethyl sulfoxide prevented us from gaining fundamental insights into the palladium–dimethyl sulfoxide interaction. The present catalyst system is more amenable to characterization. Spectroscopic studies draw attention to at least two properties of dimethyl sulfoxide that are probably important in these reactions: 1) linkage isomerism and 2) kinetic lability. ^{1}H NMR spectra of the 2:1 DMSO/$Pd(TFA)_2$ mixture in [D_8]tetrahydrofuran revealed several resonances for dimethyl sulfoxide, none of which corresponded to free dimethyl sulfoxide. The chemical shifts of these resonances, together with infrared spectroscopic analysis of the Pd^{II}/DMSO complexes obtained under these conditions, supported the presence of both S- and O-bound dimethyl sulfoxide ligands.[11,14] These observations are consistent with earlier studies of the coordination of dimethyl sulfoxide to palladium(II).[15,16] As we have previously speculated,[13] the ability of dimethyl sulfoxide 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 Pd^0 redox states during the catalytic cycle. Variable-temperature ^{1}H NMR spectroscopic analysis (−60 to 40 °C) revealed the coalescence of dimethyl sulfoxide ligand resonances, the O-bound dimethyl sulfoxide resonances at −40 °C, and the S-bound resonances at +40 °C.[11] These observations highlight the kinetically labile nature of dimethyl sulfoxide coordination to palladium(II) under the reaction conditions. This property contrasts with the behavior of pyridine as a ligand[17] and probably facilitates substrate coordination to palladium(II) and other ligand-exchange processes necessary for efficient catalytic turnover at room temperature.

This simple catalyst system was also quite versatile in reactions with other sulfamides (Table 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 are remarkably tolerant of functional groups, being compatible with groups that are typically stable to oxidizing reaction conditions, such as ester (**7f**), aryl fluoride (**7h**), carbamate (**7i**), primary chloride (**7k**), and ether groups (**7d**; see also, Table 3, entry 7), whilst also tolerating groups that were susceptible to oxidation in other palladium-catalyzed reactions, including terminal alkene (**7j**) and furan substituents (**7l**). A substrate with a silyl ether appended to the allyl amine also underwent cyclization in high yield, affording a silyl enol ether product that was stable under the reaction conditions (Table 3, entry 3). In many of these reactions, analytically pure products were obtained by simply filtering the reaction mixture through a plug of activated basic alumina. Furthermore, all procedures were performed on the bench, and no solvent purification was required prior to performing these reactions.

Sulfamides derived from substituted allylic amines were also excellent substrates (Table 3). The use of a trisubstituted alkene (Table 3, 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 (Table 3, entry 2). The cyclization reactions exhibited good-to-excellent levels of diastereoselectivity. A sulfamide derived from α-methylben-

Table 2: Aerobic oxidative cyclization of sulfamides with various N-substituents.[a,b]



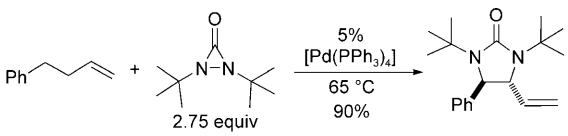


[a] Conditions: substrate (0.3 mmol), $Pd(TFA)_2$ (15 μmol), DMSO (30 μmol), NaOBz (60 μmol), 3 Å MS (75 mg), THF (3 mL), 25 °C, 24 h. [b] Yield of isolated product. [c] NaOAc used instead of NaOBz. [d] 48 h.

zylamine as the primary amine (Table 3, 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 the enantioselective synthesis of chiral allylic amines.[18]

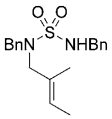
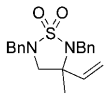
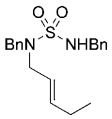
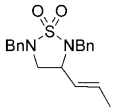
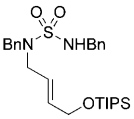
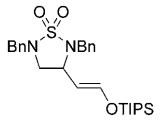
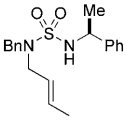
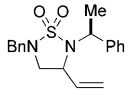
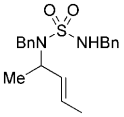
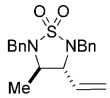
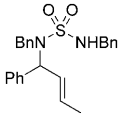
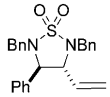
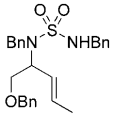
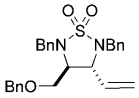
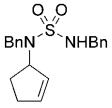
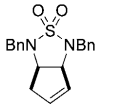
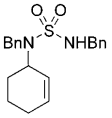
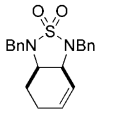
The use of this method to prepare densely functionalized chiral diamines is highlighted in the oxidative cyclization of mannitol-derived substrate **8** (Scheme 3). This reaction was carried out at room temperature on a 1 gram scale, and it proceeded in quantitative yield, affording the product as a single diastereomer. Facile removal of the sulfonyl group by treatment of **9** with $LiAlH_4$ in diethyl ether gave the acylic diamine **10** in 89% yield.[11]

The reactions described here are complementary to other metal-catalyzed routes to prepare vicinal diamines.[2–6] Among the most synthetically useful methods currently available are those reported recently by Shi and co-workers, which employ di-*tert*-butylaziridinone as the oxidant and diamination reagent [e.g., Eq. (1)].[3] The latter methods are highly diastereoselective, they employ readily available

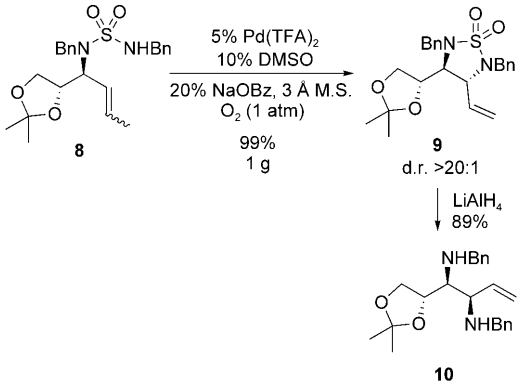


(1)

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)
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), 3 Å M.S. (75 mg), THF (3 mL), 25 °C, 24 h. [b] Yield of isolated product; d.r. determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Isolated as a 12:1 mixture of internal/terminal olefins. [d] 48 h. [e] Isolated as a 2.1:1 mixture of *E*/*Z* olefins.



Scheme 3. Demonstration of 1,2-diamine synthesis by aerobic oxidative cyclization of a mannitol-derived allylic sulfamide.

terminal alkenes as substrates, and enantioselective reactions have been achieved.[3b] 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 requires additional steps in the synthesis of a target molecule.[19] 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,[18] could be highly advantageous in the synthesis of many target molecules.

Overall, these palladium-catalyzed aerobic oxidative cyclization reactions provide a highly modular, efficient and scalable approach for the preparation of 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 that use molecular oxygen as the stoichiometric oxidant.

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Keywords: cyclization · diamines · homogeneous catalysis · oxidation · palladium

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