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Palladium-catalyzed aerobic oxidative coupling of enantioenriched primary allylic amines with sulfonyl hydrazides leading to optically active allylic sulfones†

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A range of highly enantioenriched primary allylic amines underwent palladium-catalyzed oxidative coupling with sulfonyl hydrazides open to air at room temperature to give structurally diverse allylic sulfones in moderate to excellent yields with excellent retention of ee.

The allyl sulfone moiety is not only present in some biologically relevant compounds such as anticancer agents[1a] and antibacterials,[1b] but also serves as a versatile building block in chemical synthesis.[2] To gain direct access to allylic sulfones in a convergent fashion, much attention has been paid to the coupling of allylic electrophiles with sulfonyl nucleophiles.[3] In this regard, sulfinate salts have been widely employed as sulfonyl nucleophiles to couple with symmetrical (α-substituent = γ-substituent) or α-unbranched allylic esters, carbonates, and chlorides in the presence of chiral transition metal complexes.[4,5] Complementarily, transition metal-catalyzed allylation of sulfinate salts with enantioenriched allylic carbonates or amines has been developed for the asymmetric synthesis of unsymmetrical (α-substituent ≠ γ-substituent) allylic sulfones, which, however, requires high temperature and excess additives and in most cases exhibits significant erosion of ee.[6] In addition, a single example has been disclosed for the asymmetric sulfonylation of an enantioenriched allylic carbonate with 1-phenyl-3-(phenylsulfonyl)-pyrrolidine-2,5-dione.[7] To our knowledge, no other type of sulfonyl nucleophile has previously been reported to couple with allylic electrophiles for the asymmetric synthesis of allylic sulfones.

In the course of exploring new chemistry of hydrazine derivatives,[8] we found that the $NHNH_2$ group and the SO_2 group of an arylsulfonyl hydrazide were removed successively by Pd under oxygen at 70 °C.[8a,9] This result prompted us to envision that milder conditions would just remove the $NHNH_2$ group from a simple sulfonyl hydrazide (RSO_2NHNH_2) and the remaining part (RSO_2) could serve as a sulfonyl source.[10–12] On the basis of the ability of Pd to catalyze allylic substitution *via* π-allylpalladium intermediates,[5] we further envisioned that a single Pd source would catalyze the oxidative coupling of allylic electrophiles with simple sulfonyl hydrazides yielding allylic sulfones. In connection with our recent studies on the substitution of primary allylic amines,[6b,13–15] we planned to develop an oxidative coupling reaction of sulfonyl hydrazides with enantioenriched primary allylic amines. Reasoning that H_2O, N_2, and NH_3 would be generated as small-molecule byproducts, we expected that the reaction would proceed at much lower temperature than that for the reaction with sulfinate salts (100 °C),[6b] and consequently, the erosion of ee would be significantly minimized through selective attack of sulfonyl nucleophiles on π-allylpalladium intermediates, which, ideally, would be racemization-free under certain conditions.[5,6b]

To our delight, a variety of sulfonyl hydrazides underwent $Pd(OAc)_2$–BINAP-catalyzed oxidative coupling with amine **1a** open to air at room temperature and the reaction proceeded in an α-selective fashion with retention of configuration and alkene geometry to give structurally diverse allylic sulfones in moderate to excellent yields with excellent retention of ee (Table 1, entries 1–13).[16] This chemistry was successfully extended to a range of enantioenriched primary allylic amines, wherein the α-substituents were alkyl groups and the γ-substituents were aryl, bulkier alkyl, or ester groups (entries 14–19). To avoid significant erosion of ee in some cases, the reaction was carried out with a lower catalyst loading under oxygen (entries 5, 6, 9, and 16) or at a lower concentration (entry 8).

In line with typical allylic substitution,[5] the regioselectivity was determined by the steric and electronic properties of the α- and γ-substituents in the allylic amines. In sharp contrast to the examples shown in entries 1–19 of Table 1, the reaction proceeded in a γ-selective fashion when the α-substituent was an aryl group and the γ-substituent was an alkyl group (entry 20). The γ-selectivity was speculated to arise from both maximizing conjugation and minimizing steric hindrance prior to the formation of the C–S bond between the π-allylpalladium intermediate and the sulfonyl nucleophile (see below). As expected, effective chirality transfer was not applicable to a symmetrical allylic amine because of the symmetry of the π-allyl unit in the resulting π-allylpalladium intermediate (entry 21).

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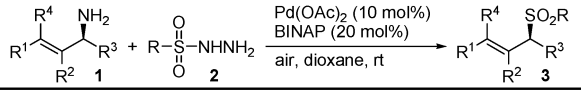
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and copies of ^1H NMR and ^{13}C NMR spectra and HPLC traces. See DOI: 10.1039/c4cc00275j

Table 1 Oxidative coupling of allylic amines with sulfonyl hydrazides[a]



Entry	1, R^1, R^2, R^3, R^4	2, R	3	Yield[b] (%)	ee[c] (%) 1 (3)
1	**1a**, Ph, H, Me, H	**2a**, 4-Me-Ph	**3a**	79	95 (95)
2	**1a**, Ph, H, Me, H	**2b**, Ph	**3b**	80	95 (95)
3	**1a**, Ph, H, Me, H	**2c**, 4-MeO-Ph	**3c**	72	95 (94)
4	**1a**, Ph, H, Me, H	**2d**, 4-AcNH-Ph	**3d**	66	95 (92)
5[d]	**1a**, Ph, H, Me, H	**2e**, 4-Cl-Ph	**3e**	77	95 (95)
6[d]	**1a**, Ph, H, Me, H	**2f**, 4-F-Ph	**3f**	72	95 (93)
7	**1a**, Ph, H, Me, H	**2g**, mesityl	**3g**	54	95 (93)
8[e]	**1a**, Ph, H, Me, H	**2h**, 2-Np	**3h**	80	95 (93)
9[d]	**1a**, Ph, H, Me, H	**2i**, 2-thienyl	**3i**	71	95 (94)
10	**1a**, Ph, H, Me, H	**2j**, Me	**3j**	90	95 (95)
11	**1a**, Ph, H, Me, H	**2k**, $Me(CH_2)_7$	**3k**	91	95 (94)
12	**1a**, Ph, H, Me, H	**2l**, $Me(CH_2)_{15}$	**3l**	62	95 (95)
13	**1a**, Ph, H, Me, H	**2m**, $PhCH_2$	**3m**	74	95 (94)
14	**1b**, Ph, Me, Me, H	**2a**, 4-Me-Ph	**3n**	51	97 (96)
15	**1c**, 2-Cl-Ph, H, Me, H	**2a**, 4-Me-Ph	**3o**	75	98 (96)
16[d]	**1d**, 2-Np, H, Me, H	**2a**, 4-Me-Ph	**3p**	80	90 (89)
17	**1e**, Cy, H, Me, H	**2a**, 4-Me-Ph	**3q**	57	97 (95)
18	**1f**, Ph, H, Et, H	**2a**, 4-Me-Ph	**3r**	68	99 (98)
19	**1g**, CO_2Et, H, ^iPr, Me	**2a**, 4-Me-Ph	**3s**	58	99 (99)
20[f]	**1h**, Me, H, Ph, H	**2a**, 4-Me-Ph	**ent-3a**	75	95 (95)
21	**1i**, Ph, H, Ph, H	**2a**, 4-Me-Ph	**3t**	65	96 (0)
22	**1j**, X = $NHCH_2Ph$	**2a**, 4-Me-Ph	**3a**	88	95 (92)
23	**1k**, X = $N(CH_2CH_2)_2O$	**2a**, 4-Me-Ph	**3a**	80	95 (87)

[a] Conditions: **1** (0.20 mmol), **2** (0.30 mmol), $Pd(OAc)_2$ (10 mol%), BINAP (20 mol%), dioxane (1.2 mL), air, rt and 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Run with 5 mol% $Pd(OAc)_2$ and 10 mol% BINAP under oxygen. [e] 2.0 mL of dioxane was used. [f] **ent-3a** = enantiomer of **3a**.

Moreover, replacement of the NH_2 group in the amine with a bulkier amino group was found to decrease the efficiency of chirality transfer (entries 22 and 23).

The aerobic oxidative coupling reaction failed to occur with *N*′-substituted sulfonyl hydrazides, such as $TsNHNHCH_2Ph$ (**4a**) and TsNHNHBoc (**4b**), and these results indicate that the $NHNH_2$ group is essential for the reaction to take place. To gain more insights into the reaction mechanism, we carried out electrospray ionization mass spectrometric analysis of the $Pd(OAc)_2$–BINAP-catalyzed reaction mixture of **1a** with **2a**. Gratifyingly, π-allylpalladiums **5a** and **6a**, sulfinic acid **7a**, sulfonyl hydrazide **8a**, and diazene **9a** were successfully assigned (Fig. 1).[17]

7a failed to couple with **1a** to give **3a** under the standard reaction conditions, and it suggests that neither **5a** nor **6a**, generated from **1a** and Pd(0),[13b] is active enough to couple with the sulfinate anion generated from **7a** and **1a**. Instead, the π-allylpalladium intermediate could be attacked by **2a**, a more active *N*-nucleophile, to give **8a**, which was subjected to Pd(II)-catalyzed aerobic oxidation to yield **9a**. We further speculated that the π-allylpalladium intermediate

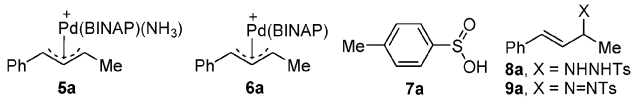
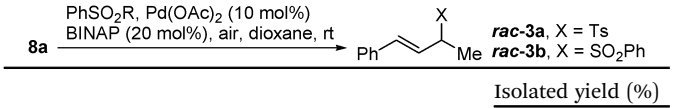


Fig. 1 Intermediates **5a–9a**.

Table 2 Reactions of sulfonyl hydrazide **8a**[a]



Entry	$Pd(OAc)_2$	$PhSO_2R$	Isolated yield (%) rac-3a	rac-3b
1	Yes	None	24	—
2	No	None	0	—
3	Yes	$PhSO_2H$ (**7b**)	3	30
4	Yes	$PhSO_2NHNH_2$ (**2b**)	17	57

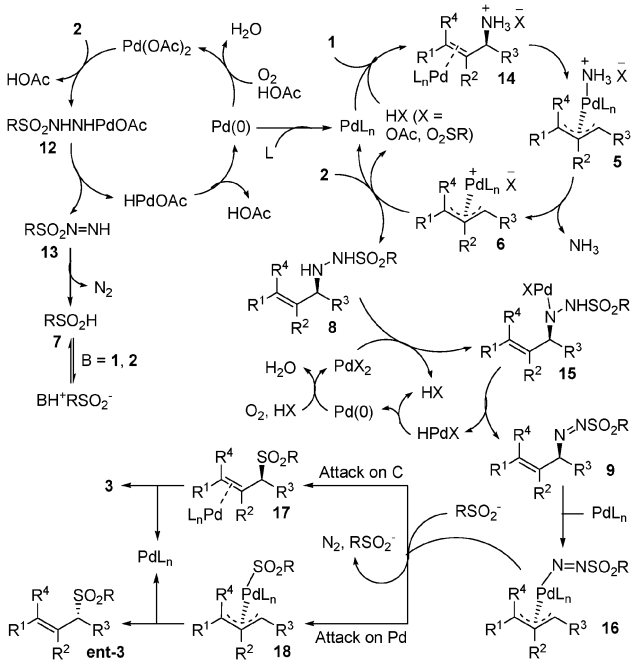
[a] Conditions: **8a** (0.20 mmol), $PhSO_2R$ (0.30 mmol), $Pd(OAc)_2$ (10 mol%), BINAP (20 mol%), dioxane (1.2 mL), air, rt and 24 h.

generated from **9a** and Pd(0) could be active enough to couple with the sulfinate anion to give **3a**.

While **8a** could not be isolated from the reaction mixture by silica gel chromatography because of decomposition, it was successfully prepared by condensation of (*E*)-4-phenylbut-3-en-2-one with **2a** followed by reduction, and purified by recrystallization.[18] **8a** was treated with $Pd(OAc)_2$–BINAP open to air to give **rac-3a** in 24% yield, but this product was not detected in the reaction without $Pd(OAc)_2$ (Table 2, entries 1 and 2). Interestingly, addition of **7b** to the mixture gave **rac-3a** and **rac-3b** in 3% and 30% yields, respectively (entry 3). Moreover, alternative addition of **2b** gave the same two sulfones but in much higher yields probably due to the ability of the sulfonyl hydrazide to reduce Pd(II) to Pd(0) (entry 4). Clearly, these results are not in accord with Yamamoto's proposal that Pd(0) would convert *N*′-allyl sulfonyl hydrazides to π-allylpalladium(II)-*S*-sulfinate intermediates (with release of N_2 and H_2) and subsequent reductive elimination would give sulfones.[10] Instead, they suggest that sulfinate anions would most likely be kicked off from the initially-generated π-allylpalladium intermediates prior to their attack on the allylic carbons (see below).

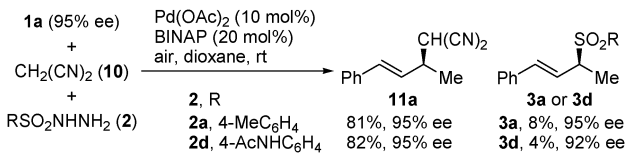
The chirality of the phosphine ligand affected both the yield and the stereochemical outcome *via* formation of diastereomeric π-allylpalladium intermediates. When compared to racemic BINAP, the use of (*R*)-BINAP in the reaction of **1a** (95% ee) with **2a** gave **3a** in a higher yield (87%) with higher ee (97%), and the use of (*S*)-BINAP gave a lower yield (59%) and lower ee (92%). Moreover, the reaction with racemic amine **rac-1a** in the presence of (*R*)-BINAP gave **3a** in 65% yield with 30% ee and the remaining **ent-1a** was recovered in 25% yield with 6% ee, and similar results were obtained from the reaction with (*S*)-BINAP (**ent-3a**: 60%, 30% ee; the remaining **1a**: 26%, 6% ee). These results suggest that the C–N bond cleavage is much less affected by chiral BINAP than the C–S bond formation, which might be responsible for the slight erosion of ee in some cases, as shown in Table 1 (entries 4, 6–8, 15, and 17).

There could be two possible pathways to account for the erosion of ee: (1) partial racemization of the π-allylpalladium intermediate and (2) attack of the sulfinate anion on the Pd atom. To our delight, the latter pathway was demonstrated to be responsible for the erosion of ee by the experiments shown in eqn (1). Malononitrile (**10**) was selected to trap the π-allylpalladium intermediate because of the extremely high selectivity in its attack on the allylic carbon at room temperature.[13b] While the substitution of **1a** with **10** did not occur under the standard reaction conditions, addition of a sulfonyl



Scheme 1 Proposed reaction pathways.

hydrazide gave **11a** as a major product with complete retention of ee. In contrast, the sulfone was obtained as a minor product with the same ee as that shown in Table 1 (entries 1 and 4). The use of **2d** decreased the ee from 95% to 92%. These results substantially permit us to conclude that the erosion of ee is attributed to the attack of the sulfinate anion on the Pd atom of the π-allylpalladium intermediate.



(1)

On the basis of the above experimental results and previous relevant mechanistic studies,[5,6b,8a] we propose the reaction pathways depicted in Scheme 1. Displacement of $Pd(OAc)_2$ by **2** gives **12**, which undergoes β-hydride elimination to give **13** and releases HPdOAc.[8a] Extrusion of N_2 from **13** gives **7**,[19] which reacts with a base (**1** or **2**) to yield a sulfinate anion. Reductive elimination of HPdOAc gives HOAc and Pd(0), and the latter is oxidized by O_2 to regenerate $Pd(OAc)_2$. On the other hand, Pd(0) cleaves the C–N bond in **1**, activated by an acid, with inversion of configuration to give **5**, which releases NH_3 to yield **6**.[13b] Regioselective attack of **2** on the allylic carbon of **6** proceeds with inversion of configuration to give **8** and regenerate Pd(0) and an acid. **8** is subjected to Pd(II)-catalyzed aerobic oxidation to give **9**, which undergoes oxidative addition with Pd(0) to give **16** with inversion of configuration. The allylic carbon of **16** is attacked regioselectively by a sulfinate anion with inversion of configuration to give **3** and regenerate Pd(0).[6b] The configuration of **1** has been inverted four times in the whole process and **3** is produced with net stereoretention. The standard reaction conditions do not allow **16** to undergo racemization *via* Pd–Pd-exchange,[5] and the slight erosion of ee in some cases originates from the attack of the sulfinate anion on the Pd atom of **16** to form **18**,[6b,20] which undergoes reductive elimination to give **ent-3**.

In summary, a variety of highly enantioenriched primary allylic amines underwent $Pd(OAc)_2$–BINAP-catalyzed oxidative coupling with sulfonyl hydrazides open to air at room temperature and the reaction proceeded in a highly regioselective fashion with retention of configuration to give allylic sulfones in moderate to excellent yields with excellent retention of ee.

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