Title: Asymmetric Palladium-Catalyzed Alkene Carboamination Reactions for the Synthesis of Cyclic Sulfamides

Authors: John P. Wolfe; Zachary J Garlets; Kaia Parenti

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Asymmetric Palladium-Catalyzed Alkene Carboamination Reactions for the Synthesis Of Cyclic Sulfamides

Zachary J. Garlets, Kaia R. Parenti, and John P. Wolfe*

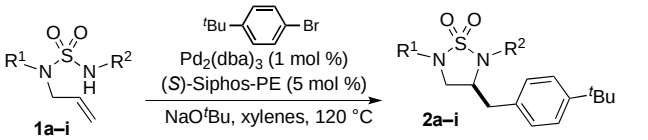
Abstract: The synthesis of cyclic sulfamides via enantioselective Pd-catalyzed alkene carboamination reactions between *N*-allyl sulfamides and aryl or alkenyl bromides is described. High levels of asymmetric induction (up to 95:5 er) are achieved using a catalyst composed of $Pd_2(dba)_3$ and (*S*)-Siphos-PE. Deuterium labelling studies indicate the reactions proceed via *syn*-aminopalladation of the alkene and suggest that control of *syn*- vs. *anti*-aminopalladation pathways is important for asymmetric induction.

Cyclic sulfamides are present in a wide variety of natural products and pharmaceuticals.[i] In addition, the sulfonyl group can easily be cleaved from these compounds to afford synthetically useful 1,2-diamines.[ii, iii] Although a number of approaches have been developed for the synthesis of racemic cyclic sulfamides,[iv] few methods exist for the enantioselective generation of these compounds. Enantiomerically enriched cyclic sulfamides are often prepared from amino acids via multistep routes,[v] and only one asymmetric metal-catalyzed reaction for the synthesis of cyclic sulfamides has been previously reported.[vi]

Our group recently developed a new method for the synthesis of racemic cyclic sulfamides via Pd-catalyzed alkene carboamination reactions between *N*-allylsulfamides and aryl halides or triflates.[vii,viii] We reasoned that an asymmetric variant of this transformation could provide straightforward access to enantiomerically enriched cyclic sulfamides. However, our prior studies had illustrated that the sulfamide-forming carboamination reactions may proceed via either *syn*- or *anti*-aminopalladation of the alkene depending on catalyst structure and reaction conditions.[vii] Since the two different C–N bond forming (and potentially enantiodetermining) aminopalladation pathways proceed through very different transition states, it seemed likely that achieving high selectivity for one pathway over the other would be critical for asymmetric induction.[ix,x]

We have previously found that palladium catalysts supported by the chiral ligand (*S*)-Siphos-PE provide good to excellent results in Pd-catalyzed asymmetric carboamination reactions that afford pyrrolidines,[xi] cyclic ureas,[xii] or benzo-fused six-membered nitrogen heterocycles.[xiii] All of these transformations were demonstrated to proceed via *syn*-aminopalladation of the alkene. As such, we elected to focus on reaction conditions that would promote *syn*-aminopalladation over *anti*-aminopalladation: use of aryl bromide electrophiles, xylenes as a nonpolar solvent, and NaO^{t}Bu as a base. In our previous studies on asymmetric carboamination reactions of ureas we discovered that the nature of the protecting group on the cyclizing nitrogen atom has a large influence on enantioselectivity.[xii] The best results were obtained with substrates bearing electron-poor aryl groups (e.g., *p*-nitrophenyl or *p*-chlorophenyl) on the cyclizing nitrogen atom. Thus, we initially examined the reactivity of substrates **1a-b** bearing an *N*-aryl group on the cyclizing nitrogen atom and a *tert*-butyl group on the other nitrogen atom. Unfortunately, these reactions failed to provide satisfactory results; products **2a-b** were generated in low yield and modest er (Table 1, entries 1–2). However, we subsequently discovered that substrates **1c-e** with an *N*-benzyl group (or substituted *N*-benzyl group) on the cyclizing N-atom were transformed to the desired products **2c-e** in good yields with useful levels of enantioselectivity (entries 3–5). Further exploration of substrate structure indicated the presence of the *tert*-butyl group on the non-cyclizing nitrogen atom was essential for reactivity, as substrates **1f-i** were not transformed to the desired cyclic sulfamides (entries 6–9).[xiv]

Table 1. Optimization of Protecting Groups[a]



Entry	R^1	R^2 (substrate)	Yield (%)[b]	er[c]
1	^{t}Bu	C_6H_4-*p*-OMe (**1a**)	47 (**2a**)	78:22
2	^{t}Bu	C_6H_4-*p*-Cl (**1b**)	11 (**2b**)	73:27
3	^{t}Bu	Bn (**1c**)	70 (**2c**)	93:7
4	^{t}Bu	*p*-MeO-Bn (**1d**)	77 (**2d**)	91:9
5	^{t}Bu	*m*-MeO-Bn (**1e**)	60 (**2e**)	91:9
6	Bn	Bn (**1f**)	0 (**2f**)	–
7	C_6H_4-*p*-OMe	Bn (**1g**)	0 (**2g**)	–
8	C_6H_4-*p*-Cl	Bn (**1h**)	0 (**2h**)	–
9	Ph_2CH	Bn (**1i**)	0 (**2i**)	–

[a] Conditions: 1.0 equiv **1**, 2.0 equiv. 4-bromo-*tert*-butylbenzene, 2.0 equiv. NaO^{t}Bu, 1 mol% [$Pd_2(dba)_3$], 5 mol% (*S*)-Siphos-PE, xylenes (0.125 M), 120 °C, 18 h. Reactions were conducted on a 0.30 mmol scale. [b] Isolated yield (average of two experiments). [c] Enantiomeric ratios were determined by chiral HPLC analysis.

Having identified satisfactory reaction conditions and a set of nitrogen-protecting groups that provided acceptable enantioselectivities, we set out to explore the scope of this transformation. Thus, substrate **1c** was treated with a range of aryl and alkenyl halides using the optimized conditions (Table 2). In general, transformations of electron-neutral or electron-rich aryl bromides provided the highest levels of asymmetric induction (entries 1–7), whereas use of electron-poor substrates resulted in slightly lower selectivity (entries 8–10). Transformations of substrates bearing *m*- or *p*-substituents proceeded smoothly, but *o*-substituted aryl bromides were

[*] Z.J. Garlets, K. R. Parenti, Prof. Dr. J. P. Wolfe
Department of Chemistry, University of Michigan
930. N. University Ave, Ann Arbor, MI 48109-1055 (USA)
E-mail: jpwolfe@umich.edu

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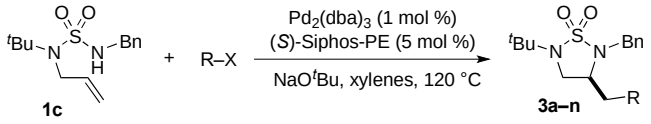
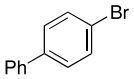
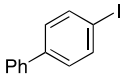
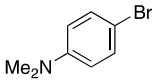
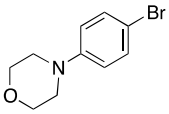
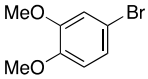
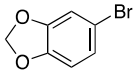
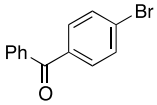
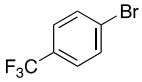
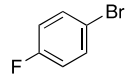
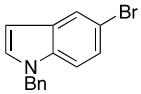
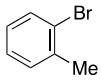
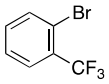
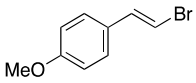
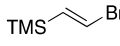
Supporting information for this article is given via a link at the end of the document.

Table 2. Enantioselective Synthesis of Cyclic Sulfamides[a]

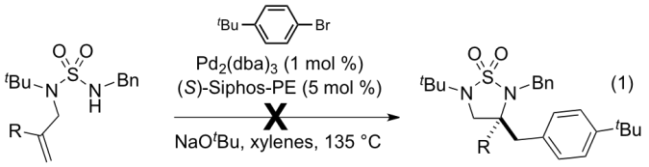


Entry	R–X	Product	Yield (%)[b]	er[c]
1a		**3a**	51	93:7
1b[d]			96	93:7
2a		**3b**	62	94:6
2b[d]			95	94:6
3a		**3b**	46	81:19
3b[d]			77	75:25
4a		**3c**	48	94:6
4b[d]			85	95:5
5a		**3d**	70	94:6
5b[d]			89	94:6
6a		**3e**	67	94:6
6b[d]			75	94:6
7a		**3f**	50	91:9
7b[d]			74	92:8
8a		**3g**	65	87:13
8b[d]			74	90:10
9a		**3h**	62	89:11
9b[d]			77	88:12
10a		**3i**	53	88:12
10b[d]			69	90:10
11a		**3j**	60	90:10
11b[d]			72	92:8
12a		**3k**	46	76:24
12b[d]			58	68:32
13a		**3l**	22	57:43
13b[d]			21	62:38
14a		**3m**	56	94:6
14b[d]			44	94:6
15a		**3n**	44	93:7
15b[d]			34	95:5

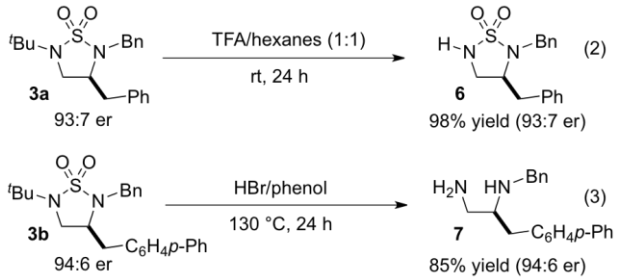
[a] Conditions: 1.0 equiv **1c**, 2.0 equiv. R-X, 2.0 equiv. NaO^{t}Bu, 1 mol% [$Pd_2(dba)_3$], 5 mol% (*S*)-Siphos-PE, xylenes (0.125 M), 120 °C, 18 h. Reactions were conducted on a 0.30 mmol scale. [b] Isolated yield (average of two or more reactions). [c] Enantiomeric ratios were determined by chiral HPLC analysis. [d] The reaction was conducted with 2.0 equiv of water added.

converted to the desired products with dramatically lower enantioselectivities and yields (entries 12–13). Reactions of alkenyl bromides proceeded with high enantioselectivity (>93:7 er) but low yields were obtained due to competing Heck alkenylation of the *N*-allylsulfamide starting material (entries 14–15).

In our previous investigations of asymmetric Pd-catalyzed carboamination reactions of ureas, we discovered that the addition of 2 equivalents of water improved enantioselectivities in transformations of electron-poor aryl bromides.[xiia] For example, the use of 4-bromobenzotrifluoride as an electrophile in the asymmetric carboamination of 1-allyl-1-methyl-3-(4-nitrophenylurea) under standard conditions resulted in the formation of the desired cyclic urea product with only 77% ee. However, when this reaction was conducted in the presence of water the enantioselectivity improved to 95% ee.[xiia] In our present studies on transformations of *N*-allylsulfamides we found that addition of 2 equivalents of water led to slight improvements in enantioselectivity with some electron-deficient electrophiles (Table 2, entries 8, 10, and 13), but did not have an impact on asymmetric induction with most electron-neutral or –rich aryl or alkenyl halides. However, we were surprised to discover that in almost all cases, water exhibited a significant positive influence on the chemical yield of these reactions (an increase of 10–20% for most electrophiles and a 45% increase with bromobenzene). As observed with urea substrates, use of an aryl iodide rather than an aryl bromide led to a significant decrease in both yield and enantioselectivity (entry 3). The addition of water to this reaction improved the yield of the product, but interestingly the enantioselectivity was diminished. Substrates **4a-b** that contain substituents at the internal alkene position proved to be unreactive even when the reaction temperature was increased to 135 °C [Eq. (1)].

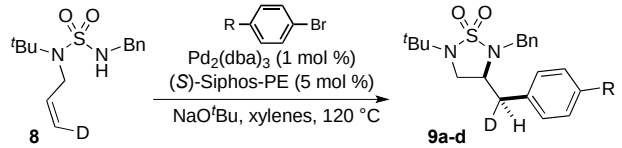


To further illustrate the synthetic utility of this method we examined the deprotection and desulfonylation of products **3a** and **3b**. As shown in [Eq. (2–3)], the *tert*-butyl group is easily and selectively cleaved by trifluoracetic acid[xv] to afford **6** in near quantitative yield with no loss of optical purity. In contrast, subjection of **3b** to more strongly acidic conditions[ii] (HBr/phenol) leads to formation of chiral 1,2-diamine **7** (in high yield and er) by removal of both the *tert*-butyl and SO_2 groups. Thus, overall this method provides straightforward access to enantiomerically enriched chiral diamines, which are useful building blocks for organic synthesis.[iii]



We had initially postulated the mechanism of these transformations should proceed via *syn*-aminopalladation under our chosen reaction conditions. In order to directly probe the alkene addition stereochemistry and test this hypothesis we prepared deuterated substrate **8** and investigated its coupling with several different aryl bromide electrophiles under our standard conditions (Table 3). In all cases examined the major product stereoisomer resulted from *syn*-addition of the N-atom and the aryl group to the alkene, confirming the *syn*-aminopalladation pathway was operational. However, both the alkene addition stereoselectivity and the enantioselectivity changed depending on whether the electrophile was electron rich or electron poor. For example, the use of 4-bromo-*tert*-butylbenzene as the electrophile led to formation of the desired product **9a** in 17:1 dr and 94:6 er (entry 1) whereas the analogous reaction with 4-bromobenzotrifluoride provided product **9d** in 7:1 dr and 88:12 er (entry 4). The diminished diastereoselectivity likely results from the competing *anti*-aminopalladation mechanistic pathway,[xvi] and this competing pathway also is likely responsible for the decreased enantioselectivity in reactions of electron-poor aryl halides.[xvii] Addition of water to the reaction between **8** and 4-bromobenzotrifluoride led to a significant improvement in yield, but little change to diastereoselectivity or enantioselectivity.[xviii,xix]

Table 3. Deuterium Labelling Studies[a]



Entry	R	Yield (%)[b]	dr[c]	er[d]
1	^{t}Bu	58 (**9a**)	17:1	94:6
2	H	67 (**9b**)	8:1	95:5
3	Ph	65 (**9c**)	9:1	92:8
4a	CF_3	58 (**9d**)	7:1	88:12
4b[e]		78 (**9d**)	5:1	89:11

[a] Conditions: 1.0 equiv **8**, 2.0 equiv. Ar-X, 2.0 equiv. NaO^{t}Bu, 1 mol% [$Pd_2(dba)_3$], 5 mol% (*S*)-Siphos-PE, xylenes (0.125 M), 120 °C, 18 h. Reactions were conducted on a 0.25 mmol scale. [b] Isolated yield (result of a single experiment). [c] Diastereomeric ratios were determined by ^{1}H NMR integration [d] Enantiomeric ratios were determined by chiral HPLC analysis. [e] The reaction was conducted with 2.0 equiv of water added.

In conclusion, we have developed an enantioselective Pd-catalyzed alkene carboamination between *N*-allyl sulfamides and aryl or alkenyl bromides that affords cyclic sulfamide products in good yield with high enantioselectivity. The sulfamide starting material is easily prepared in one step from the corresponding allylic amine. Deprotection and/or desulfonylation of the products can be achieved in good yield, thus providing access to enantiomerically enriched substituted 1,2-diamines. These transformations constitute rare examples of asymmetric metal-catalyzed reactions that afford cyclic sulfamides. These studies also illustrate the importance of controlling *syn*- vs. *anti*- alkene aminopalladation pathways in asymmetric Pd-catalyzed alkene carboamination reactions.

Keywords: asymmetric catalysis •heterocycles • palladium • enantioselective

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[vii] a) R. M. Fornwald, J. A. Fritz, J. P. Wolfe, *Chem. Eur. J*. **2014**, *20*, 8782–8790. For an extension of this work to the synthesis of bicyclic sulfamides, see: b) N. R. Babij, G. M. McKenna, R. M. Fornwald, J. P. Wolfe, *Org. Lett*. **2014**, *16*, 3412–3415.

[viii] For reviews on Pd-catalyzed alkene carboamination reactions between aryl/alkenyl halides/triflates and alkenes bearing pendant amines, see: a) J. P. Wolfe, *Top. Heterocycl. Chem.* **2013**, *32*, 1–38; b) D. M. Schultz, J. P. Wolfe, *Synthesis* **2012**, *44*, 351–361.

[ix] For studies on factors that influence *syn*- vs. *anti*-aminopalladation pathways in Wacker-type oxidative cyclizations of alkenes bearing pendant amines, see: a) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335; b) A. B. Weinstein, S. S. Stahl, *Angew. Chem.* ***2012,*** 124*, 11673–11677; Angew. Chem. Int. Ed.* **2012**, *51*, 11505–11509; c) X. Ye, P. B. White, S. S. Stahl, *J. Org. Chem.* **2013**, *78*, 2083–2090; d) C. Martinez, Y. Wu, A. B. Weinstein, S. S. Stahl, G. Liu, K. Muniz, *J. Org. Chem.* **2013**, *78*, 6309–6315.

[x] For reviews on stereochemical pathways for alkene nucleopalladation reactions and applications to asymmetric catalysis, see: a) P. Kocovsky, J. E. Bäckvall, *Chem. Eur. J.* **2015**, *21*, 36–56; b) R. I. McDonald, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981–3019; c) K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.* **2008**, *6*, 4083–4088.

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[xii] a) B. A. Hopkins, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2012**, *51*, 9886–9890; *Angew. Chem.* **2012**, *124*, 10024–10028. b) N. R. Babij, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2013**, *52*, 9247–9250; *Angew. Chem.* **2013**, *125*, 9417–9420.

[xiii] B. A. Hopkins, J. P. Wolfe, *Chem. Sci.* **2014**, *5*, 4840–4844.

[xiv] The *N-tert*-butyl group presumably facilitates the carboamination reaction by inducing Thorpe-Ingold type conformational preferences in the substrate. See: M. E. Jung, G. Piizzi, *Chem Rev.* **2005**, *105*, 1735–1766.

[xv] J. D. Catt, W. L. Matier, *J. Org. Chem.* **1974**, *39*, 566–568.

[xvi] In principle, the minor diastereomer could also arise from competing reversible β-hydride elimination/reinsertion/sigma bond rotation pathways. See: M. B. Hay, J. P. Wolfe, *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476. However, this potential competing pathway should not influence enantioselectivity as both the elimination and reinsertion are stereospecific and therefore could not lead to scrambling of the stereocenter.

[xvii] The aminopalladation step in these reactions may be reversible depending on the relative rates of retro-aminopalladation vs. reductive elimination. For studies on reversibility in aminopalladation reactions, see: P. B. White, S. S. Stahl, *J. Am. Chem. Soc*. **2011**, *133*, 18594–18597.

[xviii] The origin of the influence of water on chemical yield is not entirely clear as even reactions that proceed in modest yield (e.g., Table 2, entry 1a) do not generate significant amounts of side products that are observable by ^{1}H NMR analysis of crude reaction mixtures. However, it is possible the starting material may degrade to low molecular weight and/or water soluble side products through allylic oxidative addition or base-mediated alkene isomerisation followed by hydrolysis of the resulting enamine upon workup. Water may play a role in suppressing these competing pathways by consuming the strongly basic sodium *tert*-butoxide to generate the weaker sodium hydroxide base.

[xix] Given the considerably different influences of water on the asymmetric induction in reactions of ureas vs. sulfamides, we currently favour a mechanistic model in which aminopalladation is enantiodetermining in reactions of sulfamides, whereas reductive elimination may be enantiodetermining in reactions of ureas. See reference 12a.

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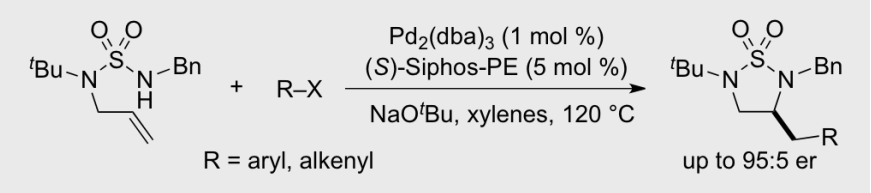

The enantioselective Pd-catalyzed coupling of aryl or alkenyl bromides with *N*-allyl sulfamides affords substituted cyclic sulfamides in good yield with high levels of asymmetric induction. The reactions proceed via stereoselective *syn*-aminopalladation of the alkene, which is important for high enantioselectivity.

*Zachary J. Garlets, Kaia R. Parenti, John P. Wolfe**

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