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Stereocontrolled Synthesis of Bicyclic Sulfamides via Pd-Catalyzed Alkene Carboamination Reactions. Control of 1,3-Asymmetric Induction by Manipulating Mechanistic Pathways

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Abstract

A new annulation strategy for the synthesis of trans-bicyclic sulfamides is described. The Pd-catalyzed alkene carboamination reactions of 2-allyl and cis-2,5-diallyl pyrrolidinyl sulfamides with aryl and alkenyl triflates afford the fused bicyclic compounds in good yields and with good diastereoselectivity (up to 13:1 dr). Importantly, by employing reaction conditions that favor an anti-aminopalladation mechanism, the relative stereochemistry between the C3 and C4a stereocenters of the products is reversed relative to related Pd-catalyzed carboamination reactions that proceed via *syn*-aminopalladation.

Over the past decade our group has developed a series of Pd-catalyzed alkene carboamination reactions between aryl or alkenyl halides and alkenes bearing pendant nitrogen nucleophiles.[1] These reactions have proven useful for the stereoselective construction of a broad array of nitrogen heterocycles,[2,3,4] and have been demonstrated to proceed through a mechanism involving *syn*-aminopalladation of an intermediate palladium amido complex which leads to net *syn*-addition of the heteroatom and the aryl/alkenyl group to the double bond (Scheme 1).[5] Although these transformations are synthetically useful, the relative stereochemistry of the heterocyclic products formed from substrates that contain stereogenic centers is invariably substrate controlled. For example, we have demonstrated that Pd-catalyzed carboamination reactions between aryl or alkenyl bromides and 2-allylpyrrolidinyl urea substrates such as **1** provide products **2** that contain a *cis*-relationship between the C-3 alkyl chain and the C-4a hydrogen atom when a mixture of $Pd_2(dba)_3$ and PCy_3 is employed as the catalyst along with NaO^tBu as a base (eq 3).[6] This relative stereochemistry arises through *syn*-aminopalladation of the alkene via boat-like transition state **3**.[6]

Recently, our group developed a method for the synthesis of cyclic sulfamides via Pd-catalyzed carboamination reactions between *N*-allylsulfamides or *N*-allylureas and aryl

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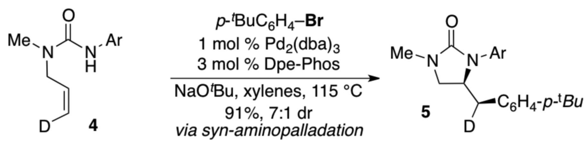
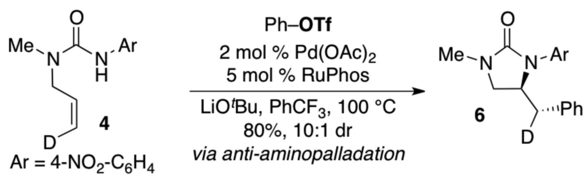
The authors declare no competing financial interest.

ASSOCIATED CONTENT
Supporting Information
Experimental procedures, characterization data, descriptions of stereochemical assignments, and copies of ^1H and ^{13}C NMR spectra for all new compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

triflates or bromides.[7] During the course of these studies we demonstrated that either *syn*- or *anti*-addition products could be obtained under appropriate conditions.[8] For example, coupling of **4** with an aryl bromide using a Pd/Dpe-Phos catalyst with NaO^{t}Bu as base and toluene as solvent afforded *syn*-addition product **5 (**eq 1). In contrast, coupling of **4** with an aryl triflate using Pd/RuPhos and LiO^{t}Bu in $PhCF_3$ solvent provided *anti*-addition product **6** (eq 2).



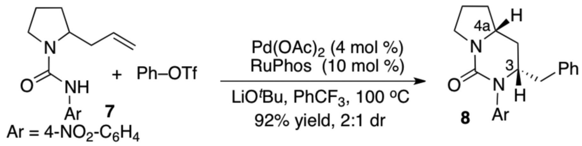
(1)



(2)

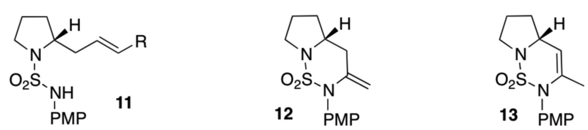
The influence of *syn*- vs. *anti*- addition pathways on 1,2-asymmetric induction is quite obvious: 1,2-disubsituted alkenes such as **4** will be transformed to different stereoisomeric products depending on reaction mechanism, as the 1,2-addition to the alkene generates two stereocenters. However, we reasoned that *syn*- vs. *anti*-addition pathways may also influence relative stereochemistry in systems involving mono-substituted alkene substrates that also contain stereocenters in relatively close proximity to the alkene. Herein we report the first examples of reactions in which *syn*- vs. *anti*-aminopalladation pathways can be manipulated to control 1,3-asymmetric induction. These transformations generate synthetically useful bicyclic sulfamide products that are potentially valuable intermediates in the synthesis of polycyclic alkaloids.[9,10,11]

To probe the influence of aminopalladation mechanism on 1,3-asymmetric induction we initially elected to examine the Pd-catalyzed carboamination between 2-allylpyrrolidinyl urea **7** and phenyl triflate (eq 3) using the optimized *anti*-aminopalladation conditions described for the synthesis of cyclic ureas and sulfamides.[7] Gratifyingly, the desired product **8** was generated in excellent yield (92%) and the product stereochemistry was reversed (2:1 dr *trans*:*cis*) from that obtained using *syn*-aminopalladation conditions (Scheme 1). However, efforts to improve the selectivity of the transformation through the use of other protecting groups, ligands, solvents, and reaction temperatures were largely ineffective.[12]



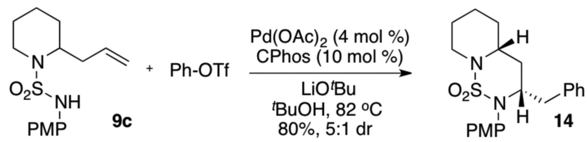
(3)

Although our preliminary studies with urea substrate **7** did not provide fully satisfactory results, the observed reversal in stereoselectivity was encouraging. We felt that selectivities might be higher in transformations of analogous sulfamide derivatives due to the differences in atomic geometry (pyramidal vs. trigonal *N*-atom geometry, tetrahedral sulfur bearing two O-atoms vs. trigonal carbon bearing one) and nitrogen nucleophilicity. To probe this hypothesis, 2-allylpyrrolidinyl sulfamide substrate **9a** was synthesized and treated with PhOTf using several different catalysts (Table 1).[13,14] The coupling of **9a** and phenyl triflate under the previously optimized conditions led to an improvement in selectivity, affording **10a** in 6:1 dr favoring the *trans*-stereoisomer (entry 1).[15] Unfortunately, several of the ligands screened led to low yields of desired product **9a** and generated significant amounts of side products resulting from Heck-arylation of the alkene (**11**) and/or β-hydride elimination from intermediate palladium complexes (**12-13**) (Figure 1). CPhos provided the best results but side products **11–13** were still formed in substantial quantities (entry 5). Moreover, the coupling of **9a** with phenyl triflate proved to be highly variable, making it difficult to obtain consistently high and reproducible yields. After some experimentation, it was discovered that changing the solvent from benzotrifluoride to *tert*-butanol led to significantly improved and reproducible yields, and just as importantly, side products **11**–**13** were generated in only trace amounts (entry 6).[16,17]



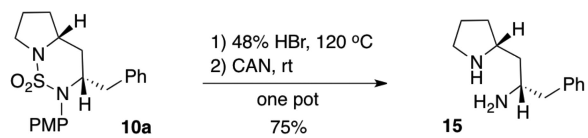
With optimized conditions in hand, the scope of the Pdcatalyzed carboamination methodology was examined by coupling *N*-PMP-protected pyrrolidinyl sulfamide substrates **9a** and **9b** with a variety of different aryl triflates (Table 2). Aryl triflates bearing either electron-donating or electron-withdrawing groups afforded bicyclic sulfamide products **10** in good yields and selectivities (entries 2–4 and 9). Additionally, the reaction of an *ortho*-substituted aryl triflate proceeded in good yield and with similar diastereoselectivity (entry 5). Alkenyl triflates also proved to be viable substrates, providing the desired bicyclic products with good selectivity but decreased yields (entries 6 and 7). Improved selectivities were observed for the cross-coupling reactions involving *meso*-2,5-diallyl-pyrrolidinyl sulfamide substrate **9b** (entries 8 and 9), although shorter reaction times were required to minimize undesired isomerization of the remaining terminal olefin. In most cases the Pd-catalyzed carboamination reactions did not lead to significant amounts of undesired side products, however the competing formation of small amounts of **11–13** were occasionally observed.[18]

To further demonstrate the utility of this methodology, 2-allylpiperidinyl sulfamide substrate **9c** was prepared and subjected to the optimized reaction conditions (eq 4). Gratify-ingly, the coupling of **9c** and phenyl triflate afforded the desired 6,6-fused bicyclic ring system in good chemical yield (80%) and with good stereocontrol (5:1 dr).



(4)

In order to illustrate the potential of these compounds as potential intermediates in the total synthesis of polycyclic alkaloid natural products, we sought to effect cleavage of the sulfamide bridge and removal of the *N*-PMP group. After some experimentation we found that treatment of **10a** with HBr to effect de-sulfonylation[19] followed by addition of CAN to oxidatively cleave the *N*-aryl group led to the formation of **15** in 75% yield (eq 5).



(5)

The mechanism of the Pd-catalyzed reactions for the formation of bicyclic sulfamides likely proceeds as depicted in Scheme 2.[7] The catalytic cycle is initiated by oxidative addition of the aryl triflate to palladium (0) to generate cationic palladium complex **16**.[20] Activation of the olefin through coordination of the Pd-complex produces 17 and leads to outersphere nucleophilic attack of the sulfamide group onto the alkene (*anti*-aminopalladation). Reductive elimination from Pd-alkyl intermediate **18** affords the desired sulfamide product (10) and regenerates the palladium catalyst.

The stereochemical outcome of the Pd-catalyzed reactions for the synthesis of *trans*-bicyclic sulfamides is particularly interesting given the stereoselectivity of related carboamination reactions and the low selectivity generally observed for transformations involving *anti*-aminopalladation.[21] Despite seemingly minor changes to the substrate, catalyst and reaction conditions, the stereoselectivity of the carboamination reactions are dramatically altered, reversing a preference for the *cis*-stereoisomer (up to 20:1 dr) to form the *trans*-bicycle as the major product with good levels of stereocontrol (up to 13:1 crude dr). One possible explanation for the observed selectivity is the stereochemical outcome is thermodynamically controlled and arises due to differences in the stability of chair-like intermediates **19** and **20**, and/or **21** and **22** (Scheme 3).[22,23] It appears that there are unfavorable 1,3-diaxial interactions in intermediates **20** and **22**, where the olefin or alkylpalladium moiety occupies a pseudo-axial position. These steric interactions drive the equilibria towards **19** and **21**. This model is consistent with the observed stereochemical outcome as aminopalladation from **19** and reductive elimination from **21** both lead to the major stereoisomer, whereas reductive elimination from **22** generates the minor diastereomer. The aminopalladation step is likely reversible in this system given the electron-deficient nature of the cyclizing nitrogen atom.[5e,24] Since there are not obvious reasons why the relative rates of reductive elimination from **21** vs **22** should be significantly different we favor a model where selectivity is thermodynamically controlled rather than dictated by kinetic factors.

In conclusion, we have developed a new method for the synthesis of bicyclic sulfamides via the Pd-catalyzed alkene carboamination of 2-allylpyrrolidinyl sulfamides. The reactions proceed in good yields and with good control of stereoselectivity (up to 13:1 dr). Importantly, this work illustrates that control of 1,3-asymmetric induction in Pd-catalyzed carboamination reactions of closely related substrates can be achieved by varying catalyst structure, reaction conditions, and substrate structure (e.g. sulfamides vs. ureas). These transformations provide access to synthetically useful bicyclic sulfamides and substituted pyrrolidin-2-yl-ethylamine derivatives. Studies on applications of this chemistry towards the total synthesis of polycyclic alkaloid natural products are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Employing the ligand Trixiephos did lead to some improvement in diastereoselectivity (2.6:1 dr) without compromising the chemical yield of the reaction (91% NMR yield).
13. The sulfamide substrates 9a, 9b and 9c were prepared in 3-4 steps from commercially available materials.
14. Structures of the ligands named in Table 1 are provided in the Supporting Information.
15. Other protecting groups provided inferior results, see the Supporting Information for further details.
16. The use of tBuOH in the carboamination of 7 with phenyl triflate led to the formation of 8 in diminished yield and selectivity (1.2:1 dr).
17. For selected examples of other Pd-catalyzed cross-coupling reactions where tBuOH solvent leads to improved rates, yields, or selectivities, see: Huang X, Anderson KW, Zim D, Jiang L, Klapars A, Buchwald SL. J. Am. Chem. Soc. 2003; 125:6653. [PubMed: 12769573] Bagdanoff JT, Ferreira EM, Stoltz BM. Org. Lett. 2003; 5:835. [PubMed: 12633084] Shekhar S, Dunn TB, Kotecki BJ, Montavon DK, Cullen SC. J. Org. Chem. 2011; 76:4552. [PubMed: 21510695] Lucciola D, Keay BA. Synlett. 2011:1618.Garcia-Fortanet J, Buchwald SL. Angew. Chem. Int. Ed. 2008; 47:8108.
18. When benzotrifluoride was employed as the solvent, substantial quantities of 11–13 were generated in a number of reactions. For example, when the coupling of 9b and phenyl triflate was conducted in benzotrifluoride, the yield of the desired product (10h) was modest (57%) and was not separable from β-hydride elimination side products 12–13 (~25%) via flash chromatography.
19. The O-methyl group present on the N-PMP substituent was also cleaved under these conditions. However, oxidative cleavage of the N-p-hydroxyphenyl group proceeded smoothly.
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23. The possibility that these transformations are actually under kinetic control and/or that the selectivity arises from boat-like transition states/intermediates similar to those described in reference 6 cannot be ruled out. However, this type of model does not seem consistent with the selective formation of trans-bicyclic sulfamides, as the boat-like transition state leading to the observed major isomer appears to suffer from unfavorable steric interactions and overall appear to be much higher in energy than the analogous chair-like intermediates 19 and 20.
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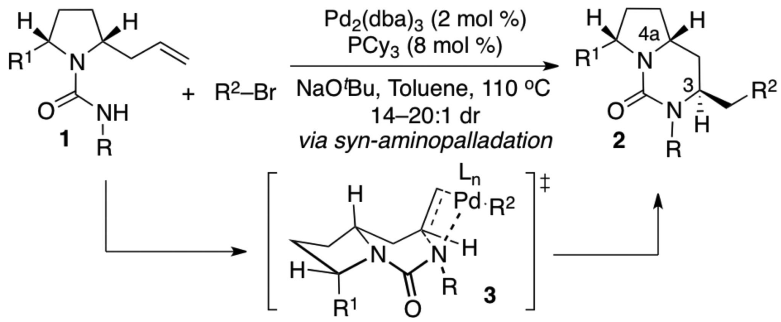
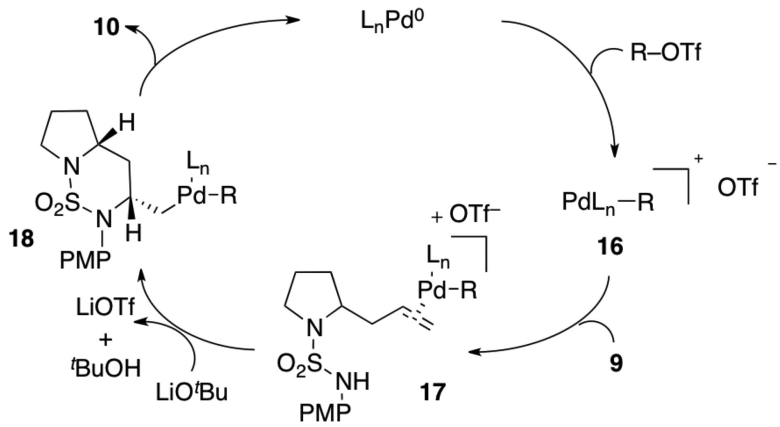
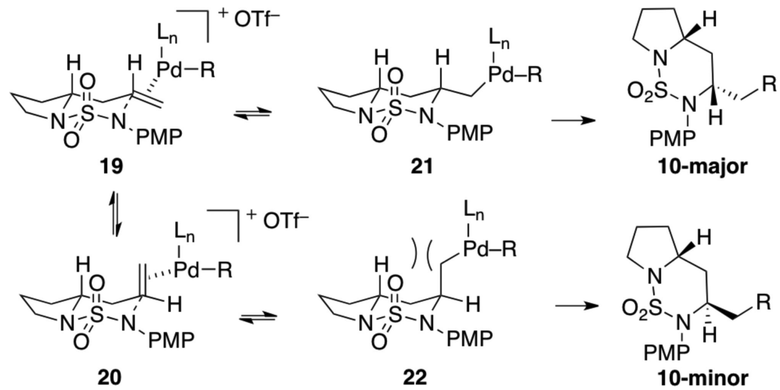


Scheme 1.
Pd-Catalyzed Alkene Carboamination Reactions



Scheme 2.
Catalytic Cycle



Scheme 3.
Stereochemical Model

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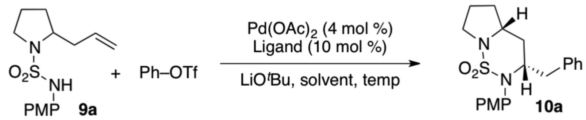
Table 1

Ligand and solvent optimization.[a]



entry	solvent	ligand	NMR yield[b] (isolated yield)[c]	dr
1	$PhCF_3$	RuPhos	50	6:1
2	$PhCF_3$	DavePhos	30	6:1
3	$PhCF_3$	BrettPhos	40	6:1
4	$PhCF_3$	^{t}BuXphos	30	6:1
5	$PhCF_3$	CPhos	80	6:1
6	^{t}BuOH	Cphos	90 (89)[d]	7:1

[a]Reaction Conditions: 1.0 equiv **9a,** 2.0 equiv Ph-OTf, 2.0 equiv LiO^{t}Bu, 4 mol % $Pd(OAc)_2$, 10 mol % ligand, solvent (0.1 M), 100 °C, 16 h.

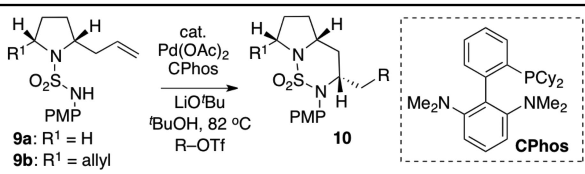
[b]NMR yields were determined using phenanthrene as an internal standard.

[c]Isolated yield (average of two or more runs).

[d]The reaction was conducted at 82 °C.

Table 2

Scope of Pd-Catalyzed Carboamination[a]



fileentry	R^1	R	product	yield (%)[b]	dr[c] (crude)
1	H	Ph	**10a**	89	7:1
2	H	*p*-*t*Bu-C_6H_4	**10b**	78	6:1
3	H	*p*-MeO-C_6H_4	**10c**	70	7:1
4	H	*p*-benzophenone	**10d**	61[d]	8:1 (5:1)
5	H	*o*-Me-C_6H_4	**10e**	87	5:1
6	H	1-cyclohexenyl	**10f**	63[d]	6:1
7	H	1-decenyl	**10g**	45[d]	10:1[f,g]
8	allyl	Ph	**10h**	65[e]	20:1 (12:1)
9	allyl	*P*-MeO-C_6H_4	**10i**	63[e]	>20:1 (13:1)

[a]Reaction Conditions: 1.0 equiv **9a** or **9b,** 2.0 equiv R-OTf, 2.0 equiv LiO^{t}Bu, 4 mol % Pd(OAc)$_2$, 10 mol % C-Phos, ^{t}BuOH (0.1 M), 82 °C, 16 h.

[b]Isolated yield (average of two or more runs).

[c]Diastereomeric ratio of the pure isolated material. Diastereomeric ratios of isolated materials were identical to those of the crude products unless otherwise noted.

[d]The reaction was conducted with 3.0 equiv of LiOtBu and 3.0 equiv R-OTf.

[e]The reaction time was 2 h.

[f]1-Decenyl triflate was employed as 5:1 mixture of *E:Z* isomers.

[g]The dr was determined following hydrogenation of **10g.** The crude dr of **10g** could not be determined directly due to the mixture of diastereomers and *E/Z* isomer products. However, we estimate the crude dr to be ca. 5-10:1.