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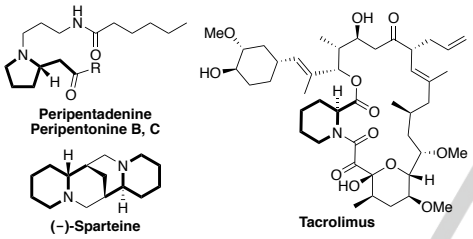
Rhodium-Catalyzed Asymmetric Intramolecular Hydroamination of Allenes

Dino Berthold, Arne G. A. Geissler, Sabrina Giofré and Bernhard Breit*

Abstract: The rhodium-catalyzed asymmetric intramolecular hydroamination of sulfonyl amides with terminal allenes is reported. It provides selective access to 5- and 6-membered *N*-heterocycles, scaffolds found in a large range of different bioactive compounds. Moreover, gram scale reactions, as well as the application of suitable product transformations to natural products and key intermediates thereof are demonstrated.

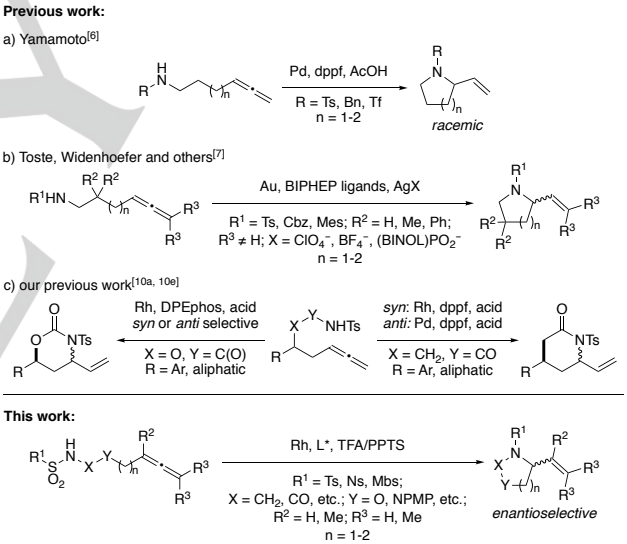
Nitrogen-containing heterocycles are core scaffolds in many bioactive and functional molecules. In particular, pyrrolidines and piperidines bearing an α-chiral carbon center are important structural motives in natural products (Peripentadenine and Peripentonines), pharmaceuticals (Tacrolimus) and as chiral ligands (Sparteine) (Scheme 1).[1]



Scheme 1. Bioactive and functional compounds possessing an α-chiral *N*-heterocyclic scaffold.

For this reason, several asymmetric methods, like allylic substitution,[2] allylic oxidation[3] and nucleophilic substitution/addition[4] have been disclosed for the preparation of these branched, α-chiral *N*-heterocyclic compounds. However, these approaches come along with limitations with regard to the requirement of stoichiometric amounts of a leaving group or an oxidant, thus rendering these synthesis economically unattractive. Thus, a more atom efficient[5] pathway involving a transition metal catalyzed, intramolecular hydroamination/cyclization of C–C multiple bonds is of greater interest. In this respect, various groups contributed to the field of hydroamination of alkynes and allenes. Beginning in 1998, Yamamoto and co-workers introduced sulfonyl amides as suitable pronucleophiles for the Pd-catalyzed intramolecular addition to alkynes and allenes.[6] More recently, Toste, Widenhoefer and Liu utilized chiral Au^{I}-complexes and chiral Brønstedt acids for the asymmetric addition of amides and amines to internal allenes. Unfortunately, these reactions are limited to rather special substrate classes.[7,8]

Throughout the last years, we reported on a series of rhodium-catalyzed chemo-, regio- and enantioselective coupling reactions involving allenes[9, 10] and alkynes[11] with various pronucleophiles, thus establishing an atom efficient alternative to the classic allylic substitution. Especially in light of our previously reported diastereoselective addition of tosylated carbamates[10a] and tosylated amides[10e], we envisioned that a suitable chiral catalyst might be able to realize an intramolecular, enantioselective hydroamination of alkynes or allenes (Scheme 2).



Scheme 2. Strategies for the synthesis of chiral, α-vinylated *N*-heterocycles. Ns = *p*-NO_2-C_6H_4-SO_2; Mbs = *p*-MeO-C_6H_4-SO_2.

We herein disclose the development of a rhodium-catalyzed intramolecular and enantioselective hydroamination of allenyl sulfonyl amides, providing the desired *N*-heterocyclic products without structural limitations.[12]

Initial reactivity assays were carried out using *N*-(hexa-4,5-dien-1-yl)tosylamide (**1a**) in the presence of [{Rh(cod)Cl}$_2$] (2.0 mol%), dppf (**L1**) (5.0 mol%) and PPTS (10 mol%) in DCE at 60 °C (Table 1, entry 1). To our delight, we already obtained the allylated pyrrolidine **2a** in a promising yield of 58%. This result encouraged us to screen numerous chiral bidentate ligands.[13] We were pleased to find that JosPOphos ligand J688-1 (**L2**) furnished the desired product in a low yield (28%) but in a promising enantioselectivity (77% *ee*) (entry 2).

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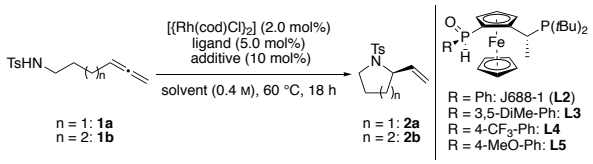
Table 1. Rhodium-catalyzed intramolecular, enantioselective addition of tosylamides to allenes.[a]

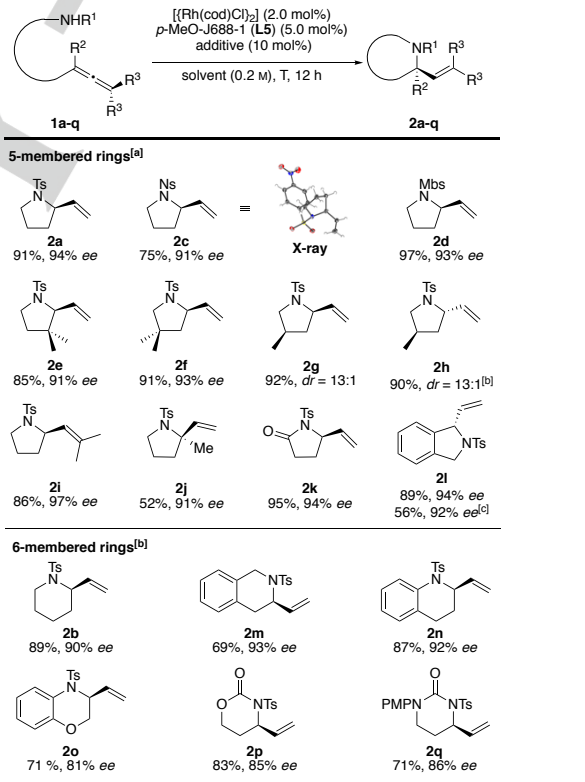


Entry	n	Ligand	Additive	Solvent	Yield [%][b]	*ee* [%][c]
1	1	**L1**	PPTS	DCE	58%	*rac*
2	1	**L2**	PPTS	DCE	28%	77%
3	1	**L3**	PPTS	DCE	27%	78%
4	1	**L4**	PPTS	DCE	35%	77%
5	1	**L5**	PPTS	DCE	47%	88%
6[d]	1	**L5**	TFA	DCE	63%	91%
7[e]	1	**L5**	TFA	CH_2Cl_2	91%	94%
8[e]	2	**L5**	TFA	CH_2Cl_2	42%	79%
9[f]	2	**L5**	PPTS	DCE	89%	90%

[a] Reactions were performed in 0.4 mmol scales. [b] Yield of isolated product. [c] The *ee* was determined by HPLC analysis using a chiral stationary phase. [d] 10 mol% of TFA were used. [e] Concentration was 0.2 M. [f] Reaction was performed with 10 mol% of PPTS at a concentration of 0.2 M at 80 °C.

Evaluation of different members of the JosPOphos ligand family, which we recently introduced for the rhodium-catalyzed allylation of triazoles,[14c] we found that neither more sterically demanding ligand **L3** nor electron-poor ligand **L4** resulted in higher yields and enantioselectivities (entry 3 and 4). However, the electron-rich ligand **L5** provided the desired product **2a** in significantly higher yield (47%) together with an improved enantioselectivity (entry 5). We were pleased to observe that by using TFA (10 mol%) instead of PPTS (10 mol%) as an additive the yield and enantioselectivity increased even further (63%, 91% *ee*) (entry 6). Finally, by changing the solvent to CH_2Cl_2 and lowering the concentration to 0.2 M we obtained the desired 5-membered product **2a** in excellent yield and enantioselectivity (91%, 94% *ee*) (entry 7). Regrettably, these optimized conditions were not suitable for the conversion of *N*-(hepta-5,6-dien-1-yl)tosylamide (**1b**) to piperidine **2b**, since the latter was obtained in only 42% yield and with 79% *ee*. However, we were pleased to observe that our initial conditions (entry 5) at a slightly higher temperature of 80 °C proved satisfactory (89%, 90% *ee*) (entry 9).[15]

The substrate scope was examined utilizing the optimized reaction conditions for the synthesis of pyrrolidines and piperidines. Starting with the scope of 5-membered rings we were delighted to see that efficient and enantioselective coupling reactions did not only occur with Tosyl substituted amines but also with Nosyl and Mbs substitution. At this point the absolute configuration could be determined by means of a X-ray crystal structure analysis of Ns-substituted pyrrolidine **2c**. Next, we were interested if substitutions on the alkyl chain or allene affect the outcome of the reaction. For this, two geminal disubstituted substrates were tested, both of them gave the desired products **2e** and **2f** in high yield and *ee*. Employing an already chiral substrate we were pleased to see that by employing ligand **L5** or *ent*-**L5** both diastereomers **2g** and **2h** were obtained in high yield and diastereoselectivity. Next, we examined the suitability of higher substituted allenes, which are prone for facile isomerization to the corresponding diene, as reaction partners. In this respect, both 3,3-disubstituted pyrrolidine **2i** and 1,1-disubstituted pyrrolidine **2j** were obtained in moderate to very good yields and high enantioselectivities.[16] As expected, an amide also reacted smoothly to the γ-lactam **2k**. Finally, we were interested in ring-closing reactions of Ph-substituted allenes and internal alkynes, since the latter ones were already exploited in the past.[13] Remarkably, isoindoline **2l** was obtained for both substrates in great enantioselectivity, albeit the yield for the internal alkyne derived product was only 56% – in comparison to 89% for the allene – owing to the low reaction temperature of 60 °C.[17]

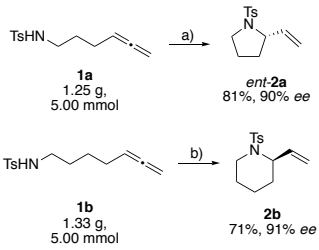


Scheme 3. Scope of intramolecular hydroamination of allenes. [a] [{Rh(cod)Cl}$_2$] (2.0 mol%), **L5** (5.0 mol%), TFA (10 mol%), CH_2Cl_2 (0.2 M), 60 °C, 12 h; [b] [{Rh(cod)Cl}$_2$] (2.0 mol%), **L5** (5.0 mol%), PPTS (10 mol%), DCE (0.2 M), 80 °C, 12 h. Ns = *p*-NO_2-C_6H_4-SO_2; Mbs = *p*-MeO-C_6H_4-SO_2.

With these results in hand, we sought to examine the scope of 6-membered *N*-heterocycles. Beside piperidine **2b**, we also obtained the tetrahydroisoquinoline **2m** and tetrahydroquinoline **2n** in good yields and very good enantioselectivities. Both

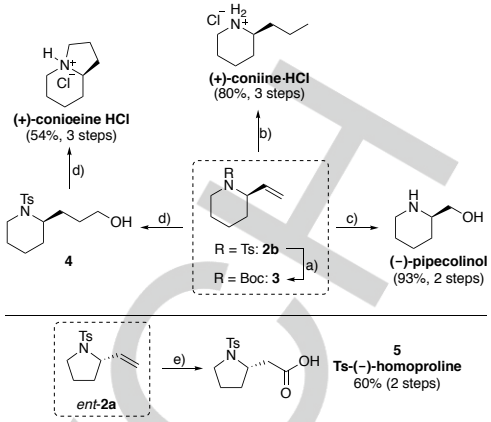
substrates might serve as valuable building blocks for natural product synthesis.[18] As an example for substitution of the alkyl chain by a heteroatom, 1,4-benzoxazine **2o** was prepared in good yields and a slightly lower enantioselectivity. Finally, we obtained the synthetically valuable carbamate **2p** and urethane **2q** in very good yields along with high enantioselectivities.[19,20]

Inspired by these synthetic possibilities, this new intramolecular allylation was applied to the syntheses of different natural products and key intermediates. By using both substrates for pyrrolidine **1a** and piperidine **1b** in the previously described rhodium-catalyzed coupling, we could synthesize *ent*-**2a** and **2b** in gram quantities in a straightforward fashion.



Scheme 4. Gram-scale catalysis. Reagents and conditions: a) [{Rh(cod)Cl}$_2$] (2.0 mol%), *ent*-**L5** (5.0 mol%), TFA (10 mol%), CH_2Cl_2 (0.2 M), 60 °C, 18 h; 81%, 90% *ee*. b) [{Rh(cod)Cl}$_2$] (2.0 mol%), **L5** (5.0 mol%), PPTS (10 mol%), DCE (0.2 M), 80 °C, 18 h; 71%, 91% *ee*.

To explore the synthetic utility of allylated 5- and 6-membered *N*-heterocycles, we subjected *ent*-**2a** and **2b** to various transformations. On one hand, we demonstrated the utility of the tosyl group as an activating protection group of the amine by cleaving it under reductive conditions and introducing a Boc protection group. Piperidine **3** represents, for instance, a key intermediate for the total synthesis of aloperine.[21] On the other hand, the olefin moiety could be functionalized by metathesis and subsequent hydrogenation and deprotection to yield (+)-coniine•HCl in an overall yield of 80%. Moreover, C1 cleavage by ozonolysis of **2b** and cleavage of the tosyl group provided (–)-pipecolinol, a common starting material in alkaloid syntheses.[22] Tandem hydroformylation/hydrogenation of the terminal alkene, using our supramolecular catalyst system,[23] furnished alcohol **4** in high yield (84%) and with an excellent linear/branched selectivity (95:5). After deprotection of the tosyl group and ring closure under Mukaiyama redox condensation conditions (+)-coniceine•HCl was obtained as a colourless solid. Finally, by hydroboration and subsequent oxidation we obtained tosylated (–)-homoproline (**5**), which is, for instance, a valuable intermediate in glycoheterocylic chemistry.[24]



Scheme 5. Various functionalizations of allylated *N*-heterocycles *ent*-**2a** and **2b**. Reagents and conditions: a) 1. Mg powder (5.0 eq), ultrasonification, MeOH/THF (2.5:1, 0.1 M), rt, 3 h; 2. Boc_2O (1.2 eq), K_2CO_3 (2.0 eq), CH_2Cl_2 (0.3 M), rt, 12 h, 79% (2 steps). b) 1. Grubbs II (10 mol%), 2-butene (167 eq), neat, 40 °C, 24 h, 89%, 91% *ee*; 2. Pd/C (10 w.%, 10 mol%), H_2 (1 atm), MeOH (0.2 M), rt, 92%; 3. Na (6.0 eq), naphthalene (5.0 eq), THF (0.1 M), –78 °C, 2 h, 98%. c) 1. O_3, CH_2Cl_2/MeOH (1:1, 0.1 M), –78 °C; then $NaBH_4$ (3.0 eq), –78 °C - rt, 2 h, 96%, 91% *ee*; 2. Na (6.0 eq), naphthalene (5.0 eq), THF (0.1 M), –78 °C, 2 h, 92%. d) 1. [Rh(CO)$_2$acac] (0.50 mol%), 6-DPPon (5.0 mol%), **L6** (5.0 mol%), CO/H_2 (1:1, 20 bar), toluene (0.25 M), 80 °C, 72 h, 84%, 91% *ee*; 2. Na (6.0 eq), naphthalene (5.0 eq), THF (0.1 M), –78 °C, 2 h, then I_2 (3.0 eq), PPh_3 (3.0 eq), imidazole (3.0 eq), CH_2Cl_2 (0.05 M), 0 °C - rt, 6 h, 59%. e) 1. 9-BBN (1.1 eq), THF (0.5 M), 0 °C - rt, 4 h; then NaOH sol. (2.0 M), H_2O_2, 0 °C - rt, 2 h, 85%, 90% *ee*; 2. CrO_3 (2.2 eq), H_2SO_4 (4.2 eq), acetone/H_2O (2:1, 0.15 M), 0 °C - rt, 2 h, 91%. 6-DPPon = 6-diphenylphosphinopyridin-2-(1*H*)-one.

In summary, we have accomplished an enantioselective, intramolecular addition of sulfonyl amides to allenes in an atom efficient manner by using a rhodium/JosPOphos catalyst system. α-Chiral α-vinyl-substituted pyrrolidines and piperidines were obtained in high yields and high stereoselectivities tolerating a broad range of sulfonyl amides and differently substituted allenes. Moreover, several *N*-heterocycles including a lactam were accessed in high yields alongside with high enantioselectivities. Furthermore, we presented synthetic possibilities for either deprotection and introduction of an orthogonal protection group, or, alternatively, the elaboration of the allylic moiety enabling the straightforward synthesis of alkaloid natural products and intermediates thereof. Further studies on extending this strategic approach of intramolecular allylation of allenes and alkynes with different pronucleophiles, as well as their application in target-oriented synthesis, are ongoing in our laboratories.

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Keywords: allenes • heterocycles • allylic products • asymmetric catalysis • rhodium

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[13] For ligand screening, see supporting information.

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[15] For reaction optimization, see supporting information.

[16] Hydroamination of 1,3-disubstituted internal allenes were not successful under these reaction conditions, since the products were only obtained in poor yield and enantioselectivity.

[17] Hydroamination of other internal alkynes were not successful under these reaction conditions, since the products were only obtained in low yield and enantioselectivity.

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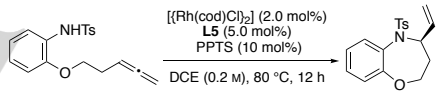

1r **2r** 38%, 84% *ee*

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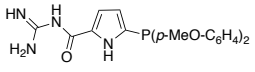

L6

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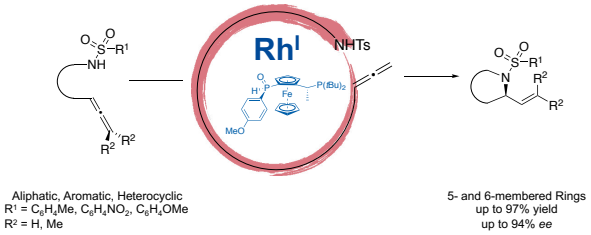

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Rhodium-Catalyzed Asymmetric Intramolecular Hydroamination of Allenes

The rhodium-catalyzed asymmetric intramolecular hydroamination of sulfonyl amides with terminal allenes is described furnishing enantioselective access to 5- and 6-membered *N*-heterocycles, scaffolds found in a wide variety of bioactive molecules. Moreover, gram scale reactions, as well as the application of suitable product transformation to natural products or key intermediates thereof are demonstrated.