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Regioselective Rh-Catalyzed Allylic Amination/Ring-Closing Metathesis Approach to Monocyclic Azacycles: Diastereospecific Construction of 2,5-Disubstituted Pyrrolines

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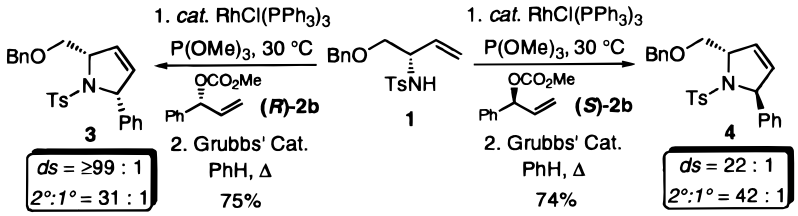
ABSTRACT



Regioselective rhodium-catalyzed allylic amination followed by ring-closing metathesis, using the Grubbs' catalyst, provides an expeditious route to monosubstituted azacycles. The enantiomerically enriched allylamine 1 can also be resubjected to the reaction sequence with (*R*)- and (*S*)-2b to facilitate the diastereospecific construction of 2,5-disubstituted pyrrolines 3/4.

The stereoselective construction of nitrogen heterocycles remains a topic of intense synthetic interest.[1,2] This may be attributed to their ubiquity in biologically interesting natural and unnatural products, in addition to the challenges associated with the design of stereochemical and architecturally flexible approaches to these molecules. Hence, although a number of interesting and synthetically useful methods have been developed, they are often specific to a particular ring size and/or stereochemical motif which imparts limitations to their utility as general methods.[1] In a program directed toward controlling the regioselectivity in metal-catalyzed allylic substitution reactions,[3] we demonstrated that Wilkinson's catalyst [$Rh(PPh_3)_3Cl$)] can be modified *in situ* with trimethyl phosphite to furnish a catalyst that facilitates the regioselective and enantioselective allylic amination of unsymmetrical acyclic allylic carbonates, to afford the secondary substituted products in excellent yield and with almost complete retention of absolute configuration.[4,5]

Herein, we describe the combination of the regioselective allylic amination with ring-closing metathesis as a strategy for the construction of mono- and disubstituted azacycles, *vide infra*.[6,7] This strategy requires that the allylic amination be tolerant of homologated alkenyl substituents in order to

(1) For a recent review of methods for constructing saturated nitrogen heterocycles, see: Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493.

(2) For recent examples of general azacycle construction, see: (a) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Suárez-Sobrino, A. *J. Org. Chem.* **1997**, *62*, 9229. (b) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871. (c) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421. (d) Larock, R. C.; Ty, C.; Pace, P. *J. Org. Chem.* **1998**, *63*, 6859. (e) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S,; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160. (f) Naito, T.; Nakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem.* **1999**, *64*, 2003 and pertinent references therein.

(3) (a) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *39*, 1725. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(4) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

(5) For a recent review on allylic amination, see: Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689 and pertinent references therein.

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Table 1. Regioselective Allylic Amination/Ring-Closing Metathesis Approach to Monocyclic Azacycles

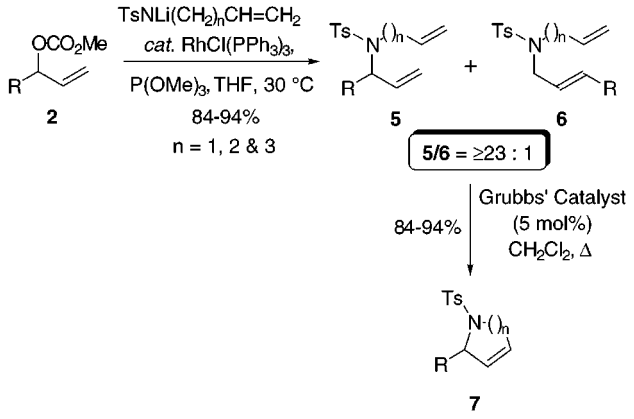
entry	allylic carbonate **2**	Nu[a]		yield (%)[b]	ratio of **5**:**6**[c]		yield of **7** (%)[b,d]
1	Me	**a**	$n = 1$	89	**a**	≥99:1	91
2	Ph	**b**		91	**b**	32:1	86
3	$BnOCH_2$	**c**		84	**c**	≥99:1	84
4	Me	**a**	$n = 2$	85	**d**	23:1	84
5	Ph	**b**		87	**e**	44:1	89
6	$BnOCH_2$	**c**		94	**f**	35:1	84
7	Me	**a**	$n = 3$	87	**g**	≥99:1	94
8	Ph	**b**		92	**h**	89:1	93
9	$BnOCH_2$	**c**		86	**i**	84:1	89

[a] All rhodium-catalyzed allylic amination reactions were carried out on a 1 mmol reaction scale using 2 equiv of the nucleophile. [b] Isolated yields. [c] Ratios of regioisomers were determined by crude HPLC. [d] All ring-closing metathesis reactions were carried out on a 0.5 mmol reaction scale using 5 mol % of Grubbs' catalyst.

provide the versatility required for a general approach to this problem.

Table 1 summarizes the results for the rhodium-catalyzed allylic amination using the lithium anion of the *N*-*p*-toluenesulfonyl alkenylamines as nucleophiles with a variety of racemic allylic carbonates **2a**−**c** (Scheme 1). The allylic

Scheme 1. General Strategy for Monosubstituted Azacycles

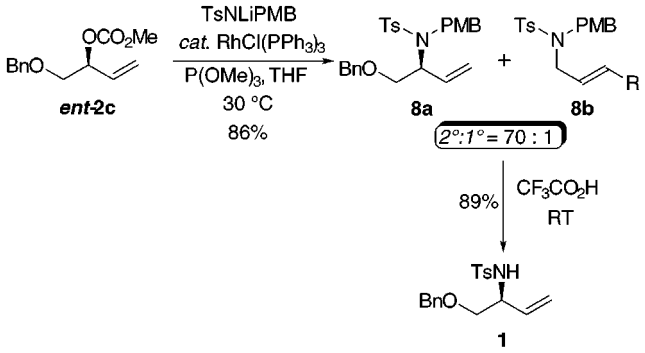


amination reaction furnished products **5/6a**−**i** in 84−94% yield with excellent regioselectivity (≥23:1) in favor of **5**. The dienes **5a**−**i** were then subjected to ring-closing metathesis, using Grubbs' catalyst, to furnish monosubstituted nitrogen-containing heterocycles **7a**−**i** in 84−94% yield.

The application of this strategy to the diastereospecific construction of 2,5-disubstituted pyrrolines was anticipated to provide a stereochemically versatile route to this type of heterocycle.[8] Furthermore, this approach provided the ideal system to determine whether the enantiospecific rhodium-catalyzed allylic amination with a chiral non-racemic nucleophile occurs through matched and mismatched transition states.[3b]

This strategy required an alternative protecting group, to facilitate the formation of the *N*-*p*-toluenesulfonyl allylamine **1**. Scheme 2 summarizes how this was accomplished.

Scheme 2. Preparation of the Allylamine **1**



Treatment of the enantiomerically enriched allylic carbonate ***ent*-2c** (≥99% ee)[4] with trimethyl phosphite modified Wilkinson's catalyst and the lithium anion of *N*-*p*-toluenesulfonyl *p*-methoxybenzylamine furnished the allylamines **8a/b** in 86% yield as a 70:1 mixture of regioisomers favoring **8a**. Treatment of **8a** with trifluoroacetic acid at room temperature furnished the allylamine **1** (≥99% ee by HPLC) in 89% yield.

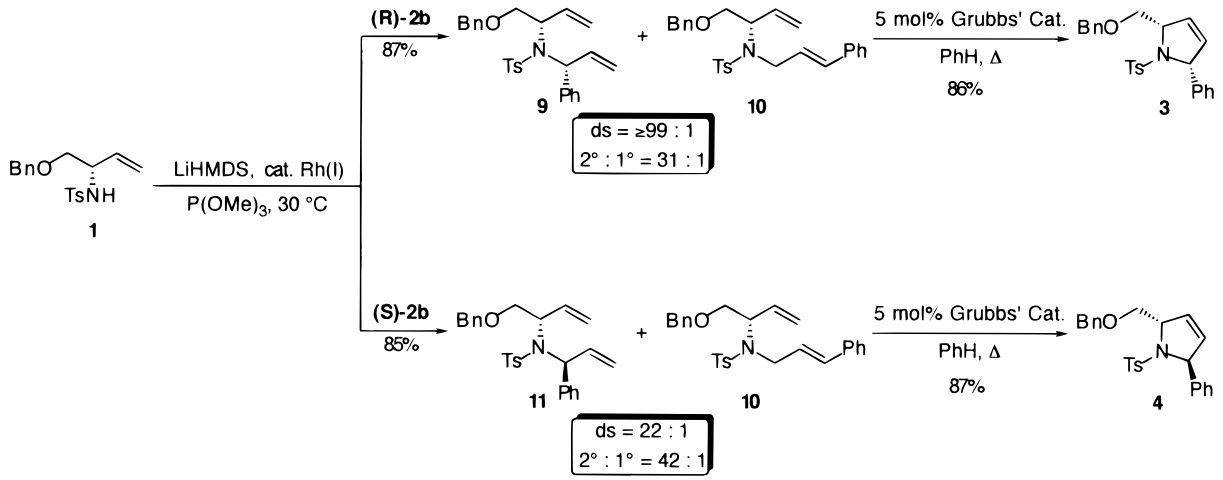
The allylamine **1** was then resubjected to the allylic amination reaction as outlined in Scheme 3. Diastereospecific rhodium-catalyzed allylic amination with the enantiomerically enriched allylic carbonates (***R***)- and (***S***)-**2b** using the lithium anion of **1** furnished the dienes **9/10** and **11/10** in 87% and 85% yield, as 31:1 and 42:1 mixtures of regioisomers, favoring **9** and **11**, respectively. Interestingly, the matched alkylation with (***R***)-**2b** proceeded with excellent diastereospecificity (ds ≥ 99:1), while the analogous alky-

(6) For recent reviews on ring-closing metathesis, see: (a) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Grubbs, R. H. *Tetrahedron* **1998**, *54*, 4413. (d) Pandit, U. K.; Overleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 9.

(7) For recent approaches to nitrogen heterocycles using ring-closing metathesis, see: (a) Fu, G. C,; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (b) Overleeft, H. S.; Bruggeman, P.; Pandit, U. K. *Tetrahedron Lett.* **1998**, *39*, 3869. (c) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359. (d) Veerman, J. J. N.; Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 3. (e) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523. (f) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Synthesis* **1999**, 138. (g) Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427. (h) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J. Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (i) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (j) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695. (k) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189. (l) Jo, E.; Na, Y.; Chang, S. *Tetrahedron Lett.* **1999**, *40*, 5581. (m) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126 and pertinent references cited therein.

(8) For recent examples of 2,5-disubstituted pyrrolidine construction, see: (a) Dhimane, H.; Vanucci-Bacqué, C.; Hamon, L.; Lhommet, G. *Eur. J. Org. Chem.* **1998**, 1955. (b) Kawanami, Y.; Iizuna, N.; Okano, K. *Chem. Lett.* **1998**, 1231. (c) Senboku, H.; Hasegawa, H.; Orito, K. Tokuda, M. *Heterocycles* **1999**, *50*, 333. (d) Grigg, R.; Thornton-Pett, M.; Yoganathan, G. *Tetrahedron* **1999**, *55*, 1763. (e) Katritzky, A. R.; Cui, X.-L. Yang, B. Steel, P. J. *J. Org. Chem.* **1999**, *64*, 1979 and pertinent references therein.

Scheme 3. Diastereospecific Construction of *cis*- and *trans*-2,5-Disubstituted Pyrrolines



lation with the mismatched carbonate (***S***)-**2b** proceeded with the expected lower, but synthetically useful diastereospecificity (ds = 22:1). Treatment of the dienes **9** and **11** with Grubbs' catalyst in refluxing benzene furnished the *cis*- and *trans*-2,5-disubstituted pyrrolines **3** and **4** in 86% and 87% yield, respectively.

In conclusion, we have demonstrated that the rhodium-catalyzed allylic amination may be combined with ring-closing metathesis to provide a general approach to monosubstituted azacycles. Furthermore, the allylic amination product may be deprotected and resubjected to the reaction sequence to facilitate the diastereospecific construction of *cis*- and *trans*-2,5-disubstituted pyrrolines.

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Supporting Information Available: Experimental procedures for the preparation of **3** and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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