ORGANIC LETTERS

2010
Vol. 12, No. 10
2322−2325

Pd-Catalyzed Carboamination of Oxazolidin-2-ones: A Stereoselective Route to *trans*-2,5-Disubstituted Pyrrolidines

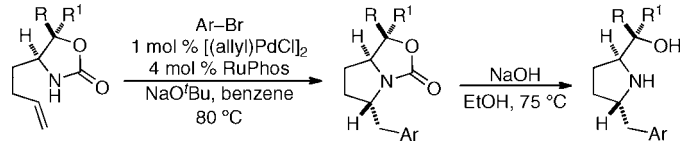
Georgia S. Lemen and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan 48109-1055

jpwolfe@umich.edu

Received March 23, 2010

ABSTRACT



Palladium-catalyzed carboamination reactions between aryl bromides and 4-(but-3-enyl)-substituted oxazolidin-2-ones are described. These transformations afford bicyclic oxazolidin-2-one derivatives that can be converted to *trans*-2,5-disubstituted pyrrolidines in one step. The starting materials are easily prepared from amino acid precursors, and products that contain up to three stereocenters are generated with >20:1 dr.

The development of convergent, stereoselective methods for the synthesis of *trans*-2,5-disubstituted pyrrolidines is of significant importance due to the presence of this motif in chiral auxiliaries, ligands, and catalysts.[1,2] These heterocycles are also displayed in several interesting biologically active compounds such as the highly potent β3 andrenergic receptor agonist **1** (Figure 1).[3] In addition, polysubstituted pyrrolidines with a *trans*-relationship between the C2 and C5 substituents are found in many natural products, including the potent glycosidase inhibitor broussonetine C (**2**).[4]

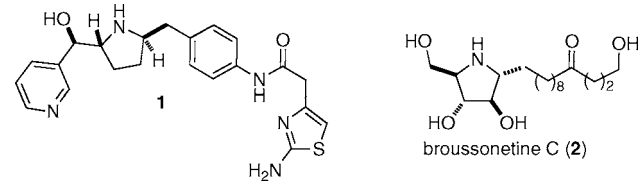


Figure 1. Biologically active *trans*-2,5-disubstituted pyrrolidine derivatives.

Our group has devised an efficient approach to the construction of substituted pyrrolidines via Pd-catalyzed carboamination reactions of γ-aminoalkene derivatives.[5−7] For example, treat-

(1) For recent approaches to the synthesis of *trans*-2,5-disubstituted pyrrolidines, see: (a) Enkisch, C.; Schneider, C. *Eur. J. Org. Chem.* **2009**, 5549. (b) Davis, F. A.; Zhang, J.; Qiu, H.; Wu, Y. *Org. Lett.* **2008**, *10*, 1433. (c) Hernandez, J. N.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S. *Org. Lett.* **2008**, *10*, 2349. (d) Moloney, M. G.; Panchal, T.; Pike, R. *Org. Biomol. Chem.* **2006**, *4*, 3894. (e) Davis, F. A.; Song, M.; Augustine, A. *J. Org. Chem.* **2006**, *71*, 2779, and references therein. (f) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927.

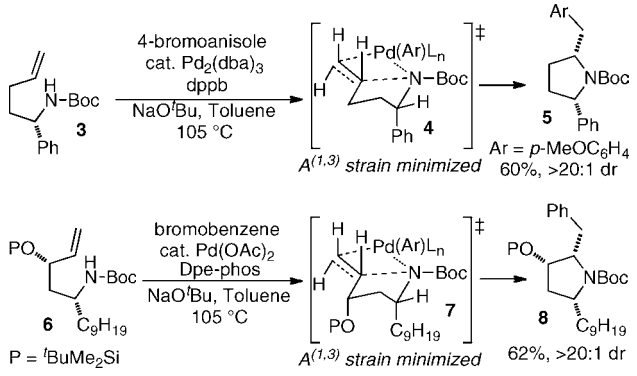
(2) For selected recent examples of pyrrolidine-derived ligands and catalysts see: (a) Chen, H.; Sweet, J. A.; Lam, K.-C.; Rheingold, A. L.; McGrath, D. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1672. (b) Simonini, V.; Benaglia, M.; Pignataro, L.; Guizzetti, S.; Celentano, G. *Synlett* **2008**, 1061. (c) Liu, Z.; Qu, H.; Gu, X.; Min, B. J.; Nyberg, J.; Hruby, V. J. *Org. Lett.* **2008**, *10*, 4105. (d) Frisch, K.; Landa, A.; Saaby, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058. (e) Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465.

(3) Berger, R.; Chang, L.; Edmonson, S. D.; Goble, S. D.; Harper, B.; Kar, N. F.; Kopka, I. E.; Li, B.; Morriello, G. J.; Moyes, C. R.; Shen, D.-M.; Wang, L.; Wendt, H.; Zhu, C. PCT Int. Appl. WO 2009/123870 A1, October 8, 2009; *Chem. Abstr.* **2009**, *151*, 448256.

10.1021/ol1006828
Published on Web 04/20/2010

ment of **3** with 4-bromoanisole and NaO^{t}Bu in the presence of a palladium catalyst affords *cis*-2,5-disubstituted pyrrolidine **5** in 60% yield as a single diastereomer (Scheme 1).[6b]

Scheme 1. Formation of *cis*-2,5-Disubstituted Pyrrolidines



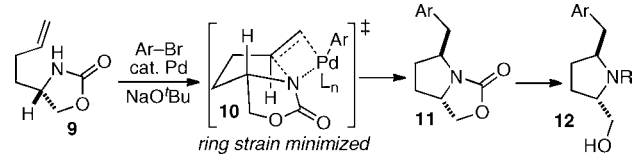
The installation of different groups can be achieved by simply varying the starting aryl or alkenyl bromide. Thus, many different pyrrolidine analogues can be prepared from a single γ-aminoalkene substrate.

Despite the utility of Pd-catalyzed carboamination reactions for preparation of *cis*-2,5-disubstituted pyrrolidines such as **5**, the analogous synthesis of pyrrolidines with a *trans*-relationship between substituents at C2 and C5 has not yet been accomplished. However, such a transformation would be of significant synthetic utility. For example, these carboamination reactions could potentially be used to optimize properties of *trans*-2,5-disubstituted pyrrolidine derived ligands, auxiliaries, catalysts, or pharmaceutical lead compounds such as **1**. In addition, an assortment of nitrogen-containing sugar analogues, including the broussonetine alkaloids, could be accessed in a straightforward manner from a common aminoalkene precursor.

As shown in Scheme 1, transformations of **3** and related substrates are believed to occur through transition states such as **4**, in which the C2-substituent is oriented in a pseudoaxial position. This transition state geometry minimizes A$^{(1,3)}$-strain between the Boc group and the C2-phenyl group and leads to the observed *cis*-2,5-disubstituted pyrrolidine products (e.g., **5**). Moreover, the stereochemical outcome of reactions that generate molecules with more than two stereocenters is also dictated by minimization of A$^{(1,3)}$-strain interactions. For example, the Pd-catalyzed carboamination of **6** yields **8** with >20:1 dr even though the substrate C4-ether group is in a pseudoaxial orientation in transition state **7** and suffers from a 1,3-diaxial interaction with the C2-alkyl group.[6d] Thus, the conversion of substrates such as **3** to *trans*-2,5-disubstituted pyrrolidines does not appear to be feasible using this method.

The allylic strain model shown in Scheme 1 suggests two possible substrate modifications that could yield *trans*-2,5-disubstituted pyrrolidines. The first would simply involve use of primary amine substrates, as absence of the *N*-Boc group should favor equatorial orientation of the C2-substituent and lead to preferential formation of *trans*-disubstituted products.[8] Unfortunately, all efforts to effect carboamination reactions of primary aliphatic amines have thus far resulted in substrate *N*-arylation, with no observed pyrrolidine formation.[9] A second approach to the construction of *trans*-2,5-disubstituted pyrrolidines would employ carboamination reactions of 4-(but-3-enyl)-substituted oxazolidin-2-ones such as **9** (Scheme 2). These substrates should undergo ring

Scheme 2. Approach to *trans*-2,5-Disubstituted Pyrrolidines



formation via transition state **10**, as other possible transition states suffer from significant ring strain.[10,11] Reaction via transition state **10** would give rise to bicyclic products **11**, which could be hydrolyzed or reduced to yield *trans*-2,5-disubstituted pyrrolidines **12** (R = H or Me).

To probe this hypothesis, a series of oxazolidin-2-ones bearing pendant alkenes were prepared as shown in Scheme 3. The majority of these substrates were generated through conversion of **13** to substituted *N*-Boc-amino alcohols **15a**−**d** (Scheme 3). For example, treatment of **13** with $LiBH_4$ afforded monosubstituted product **15a**.[12] Alternatively, con-

(4) (a) Shibano, M.; Tsukamoto, D.; Kusano, G. *Heterocycles* **2002**, *57*, 1539. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (c) Ribes, C.; Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron* **2009**, *65*, 10612. (d) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem.—Eur. J.* **2006**, *12*, 6607.

(5) Reviews: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (b) Wolfe, J. P. *Synlett* **2008**, 2913.

(6) (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (b) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447. (c) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644. (d) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353. (e) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851.

(7) For Cu- or Au-catalyzed carboamination reactions, see: (a) Fuller, P. H.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 5477. (b) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948, and references therein. (c) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. For alkene carboamination reactions involving solvent C−H bond functionalization, see: (d) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488. (e) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945.

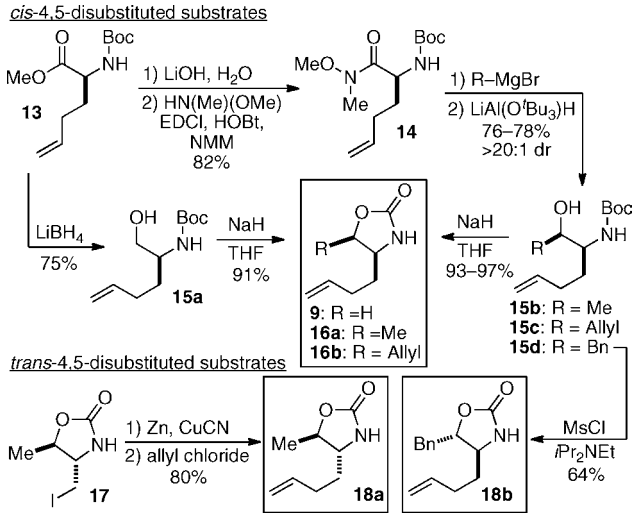
(8) This strategy has successfully been employed in the formation of *cis*- vs *trans*-3,5-disubstituted pyrazolidines. See: Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907.

(9) In some instances tandem *N*-arylation/carboamination reactions of these substrates have been achieved. However, the *N*-arylation precedes the carboamination, and *cis*-2,5-disubstituted pyrrolidines are generated. See: Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575.

(10) During the course of these studies Cacchi described related Pd-catalyzed carboamination reactions of aryl halides with 5-(but-3-enyl)pyrrolidin-2-one that afford *trans*-5,7a-disubstituted pyrrolizidin-3-ones. See: Bagnoli, L.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Scarponi, C.; Tiecco, M. *J. Org. Chem.* **2010**, *75*, 2134.

(11) For other ring-closing reactions of oxazolidin-2-one derivatives that afford substituted pyrrolidines with a *trans*-relationship between groups on C2 and C5, see: (a) Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893. (b) Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. *Tetrahedron* **1999**, *55*, 8953.

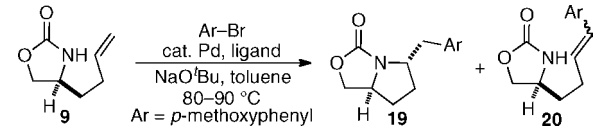
Scheme 3. Synthesis of Oxazolidin-2-one Substrates



version of **13** to Weinreb amide **14** followed by addition of a Grignard reagent and then reduction with $LiAl(O^tBu)_3H$ afforded amino alcohols **15b**−**d** in good yield and with >20:1 diastereoselectivity. The amino alcohols **15a**−**c** were transformed to **9** and **16a**,**b** by treatment with NaH to effect ring closure. The synthesis of *trans*-4,5-disubstituted oxazolidin-2-ones **18a**,**b** was accomplished through two methods. Methyl-substituted derivative **18a** was prepared via allylation of iodide **17**.[13] Alternatively, treatment of amino alcohol **15d** with MsCl and iPr$_2$NEt provided **18b** in 64% yield.

In our preliminary experiments, we examined the Pd-catalyzed carboamination of **9** with 4-bromoanisole. As shown in Table 1, these reactions afforded mixtures of the desired product **19** and side product **20**, which results from competing Heck arylation of the starting material. Although Dpe-phos or dppe have proven to be useful ligands in other Pd-catalyzed carboamination reactions,[6,14] catalysts derived from these ligands exhibited low reactivity in transformations of **9** and failed to generate significant amounts of **19**. However, after some optimization we found that Buchwald's RuPhos ligand[15] provided satisfactory results. Use of $[(allyl)PdCl]_2$ as precatalyst and benzene as solvent simplified experimental setup, as premixing the ligand and metal complex was not required.[16,17] These optimized conditions provided **19** in 80% yield upon isolation.

Table 1. Optimization of Reaction Conditions[a]



palladium source[b,c]	ligand[14]	conversion (%)	yield **19** (%)[d]	yield **20** (%)[d]
$Pd(OAc)_2$	Dppe	27	0	8
$Pd(OAc)_2$	Dpe-phos	15	2	9
$Pd(OAc)_2$	S-Phos	70	57	3
$Pd(OAc)_2$	PCy_2(*o*-biphenyl)	17	<1	2
$Pd(OAc)_2$	RuPhos	92	87	3
$[(allyl)PdCl]_2$	RuPhos	92	79	4
$[(allyl)PdCl]_2$	RuPhos	96[e]	81 (80)[f]	3

[a] Conditions: 1.0 equiv of **9**, 1.2 equiv of 4-bromoanisole, 1.2 equiv of NaO^tBu, 2 mol % Pd, 4 mol % monodentate ligand/2 mol % bidentate ligand, NaO^tBu, toluene (0.25 M), 80−90 °C. Product **19** was formed with >20:1 dr in all experiments. [b] Experiments with the dinuclear palladium complex $[(allyl)PdCl]_2$ were conducted using 1 mol % of the dimer (2 mol % total Pd). [c] When $Pd(OAc)_2$ was employed, the ligand and palladium source were stirred at rt in toluene for 5 min prior to addition of the substrate and other reagents. [d] Yields for optimization studies were determined by ^{1}H NMR analysis of crude reaction mixtures using phenanthrene as an internal standard. [e] The reaction was conducted using benzene as solvent. [f] Isolated yield (average of two or more experiments).

As shown in Table 2, the optimized conditions outlined above allow the construction of a number of tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one derivatives. Several different electron-neutral or electron-rich aryl bromides proved to be viable coupling partners. However, attempts to employ electron-poor aryl bromides such as 4-bromobenzophenone led to competing *N*-arylation of the oxazolidin-2-one starting material. Competing *N*-arylation was also observed with modestly electron-deficient aryl bromides (e.g., *p*-fluorobromobenzene), but use of PCy_2(*o*-biphenyl) as ligand suppressed this side reaction and provided optimal results with these substrates (entries 7, 11, and 13).

The synthesis of bicyclic products bearing three stereocenters was accomplished using 4,5-disubstituted oxazolidin-2-ones as substrates. In all cases products were obtained with >20:1 dr, and enantiomerically enriched (+)-**18a** and (+)-**16b** were converted to the desired products without loss of optical activity (Table 2, entries 6 and 14). Similar product yields were obtained regardless of the oxazolidin-2-one's relative stereochemistry. For example, *trans*-disubstituted substrate **18a** and *cis*-disubstituted compound **16a** were coupled with 4-bromoanisole to afford **24** and **27** in 83% and 84% yields, respectively (entries 5 and 9).

The bicyclic products formed in the carboamination reactions can easily be transformed to *trans*-2,5-disubstituted pyrrolidines (Scheme 4).[18] For example, hydrolysis of **27** was accomplished using NaOH/EtOH and afforded **33** in 96% yield. Alternatively, the conversion of **27** to *N*-methyl pyrrolidine **34** was achieved via reduction with $LiAlH_4$ (95%

(12) Ester **13** was prepared from commercially available *N*-Boc-serine methyl ester in 62% yield over two steps. See: Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.

(13) Iodide **17** was prepared from threonine methyl ester in 40% yield over four steps.

(14) dppe = 1,2-bis(diphenylphosphino)ethane; Dpe-Phos = bis(2-diphenylphosphinophenyl)ether; S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl; RuPhos = 2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl.

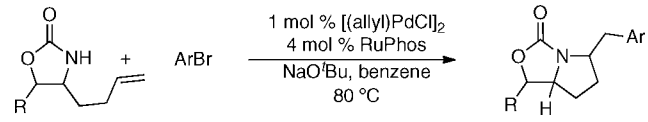
(15) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.

(16) Relatively low yields were obtained when $Pd(OAc)_2$ was used as the palladium source unless the precatalyst and ligand were stirred in toluene for 5 min prior to addition of the substrate and other reagents.

(17) Use of other solvents such as acetonitrile, *tert*-butanol, diglyme, or 1,4-dioxane or palladium sources such as $Pd_2(dba)_3$ led to lower yields and/or incomplete conversion.

(18) (a) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 465. (b) Lakanen, J. R.; Pegg, A. E.; Coward, J. K. *J. Med. Chem.* **1995**, *38*, 2714.

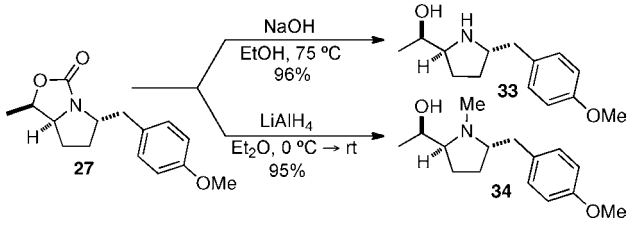
Table 2. Synthesis of Bicyclic Oxazolidin-2-ones[a]



entry	substrate	product	yield[b]	entry	substrate	product	yield[b]
1	(±)-9	19	80%	8[d]	(±)-16a	26	70%
2	(±)-9	21	80%	9	(±)-16a	27	84%
3	(±)-9	22	66%	10	(±)-16a	28	61%
4	(±)-18a	23	63%	11[e]	(±)-16a	29	77%
5[c]	(±)-18a	24	83%	12[d]	(±)-16b	30	78%
6	(+)-18a	(+)-23	69% (99% ee)	13[e]	(±)-16b	31	61%
7[e]	(±)-18b	25	67%	14	(+)-16b	(−)-32	79% (97% ee)

[a] Conditions: 1.0 equiv of substrate, 1.2 equiv of ArBr, 1.2 equiv of NaO^{t}Bu, 1 mol % [(allyl)PdCl]$_2$, 4 mol % RuPhos, benzene (0.25 M), 80 °C. [b] Isolated yield (average of two or more experiments). All products were formed with >20:1 dr. [c] The reaction was conducted with 2 mol % [(allyl)PdCl]$_2$ and 8 mol % RuPhos. [d] The reaction was conducted with 2 mol % Pd(OAc)$_2$. [e] The reaction was conducted with 2.5 mol % [(allyl)PdCl]$_2$ and 10 mol % Cy$_2$JohnPhos.

Scheme 4. Conversion of **27** to *trans*-2,5-Disubstituted Pyrrolidines



yield). In both cases the pyrrolidine products were formed with no loss of stereoisomeric purity.

In conclusion we have developed a concise and convergent approach to the synthesis of *trans*-2,5-disubstituted pyrrolidines. Products bearing up to three stereocenters can be prepared in good yields as single enantiomers from amino acid derived precursors. Further studies on the application of this method to the synthesis of natural products, ligands, and catalysts are underway.

Acknowledgment. The authors thank the NIH-NIGMS (GM071650) for financial support of this work. Additional support was provided by the Camille and Henry Dreyfus Foundation (Camille Dreyfus Teacher Scholar Award), GlaxoSmithKline, Eli Lilly, and Amgen. We acknowledge Ms. Xin Zhou, a summer REU student from Peking University, for help with preliminary experiments.

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

OL1006828