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

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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 β 3 adrenergic receptor agonist **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

Our group has devised an efficient approach to the construction of substituted pyrrolidines via Pd-catalyzed carboamination reactions of γ -aminoalkene derivatives.^{5,6,7} For example, treatment of **3** with 4-bromoanisole and NaOtBu in the presence of a palladium catalyst affords *cis*-2,5-disubstituted pyrrolidine **5** in 60% yield as a single diastereomer (Scheme 1).^{6b} The installation of different groups can be achieved by simply varying the starting aryl or alkenyl bromide. Thus, many different pyrrolidine analogs 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 analogs, including the broussonetine

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

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-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 LiBH₄ afforded monosubstituted product **15a**.¹² Alternatively, conversion of **13** to Weinreb amide **14** followed by addition of a Grignard reagent, and then reduction with LiAl(O^{*i*}Bu)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 *i*Pr₂NEt 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 ligand¹⁵ 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.

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 PCy₂(*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 13). 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 LiAlH₄ (95% 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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13. Iodide 17 was prepared from threonine methyl ester in 40% yield over four steps.
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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.
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Figure 1.
Biologically Active *trans*-2,5-Disubstituted Pyrrolidine Derivatives

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

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

cis-4,5-disubstituted substrates trans-4,5-disubstituted substrates

Scheme 3.
Synthesis of Oxazolidin-2-one Substrates

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

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 (<i>o</i> -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 **9**, 1.2 equiv 4-bromoanisole, 1.2 equiv 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 ¹H 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).

Table 2

product	yield ^b
26	70%

yield ^b	product
84%	27

yield ^b	product
61%
77%

yield ^b	product
78%

30

31

product	yield ^b
<chem>Cc1ccc(cc1)[C@H]2CC[C@@H]3C(=O)OC[C@H]3[C@H]2C=C</chem> (-)-32	79% (97% ee)

^cThe reaction was conducted with 2 mol % $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and 8 mol % RuPhos.

^dThe reaction was conducted with 2 mol % $\text{Pd}(\text{OAc})_2$.

^eThe reaction was conducted with 2.5 mol % $[(\text{allyl})\text{PdCl}]_2$ and 10 mol % Cy2JohnPhos.