

A New Synthesis of Imidazolidin-2-ones via Pd-Catalyzed Carboamination of *N*-Allylureas

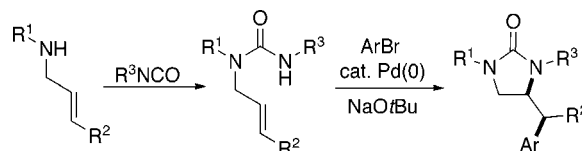
Jonathan A. Fritz, Josephine S. Nakhla, and John P. Wolfe*

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

jpwolfe@umich.edu

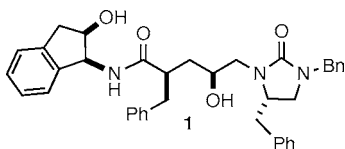
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ABSTRACT



A new strategy for the preparation of substituted imidazolidin-2-ones in two steps from readily available *N*-allylureas is described. Addition of the amine starting materials to isocyanates affords *N*-allylureas, which are converted to imidazolidin-2-one products with generation of two bonds and up to two stereocenters when treated with aryl bromides and catalytic amounts of Pd₂(dba)₃/Xantphos in the presence of NaOtBu.

Cyclic urea moieties are found in a broad array of biologically active molecules¹ and have been employed as monomeric units for biomaterials that exhibit greater stability than many peptides.² For example, imidazolidin-2-ones³ and other cyclic ureas⁴ are utilized as structural elements in a number of molecules with potent anti-HIV activity such as **1**.³



Cyclic ureas are most commonly constructed via treatment of 1,2-diamine precursors with phosgene equivalents such as carbonyl diimidazole.^{5,6} Although a number of 1,2-diamines can be accessed with available methods, many

require multistep sequences for their preparation.⁷ Thus, alternative strategies for the construction of imidazolidin-2-ones would provide more facile access to derivatives that are not readily available. In addition, methods that allow for preparation of a variety of products from a common starting material would allow straightforward generation of analogues that could be used to optimize biological activity or pharmaceutical properties.

We have recently reported a new method for the construction of pyrrolidines via Pd-catalyzed carboamination reactions of γ -aminoalkenes with aryl bromides.^{8–10} We reasoned that a related strategy could potentially be employed in a

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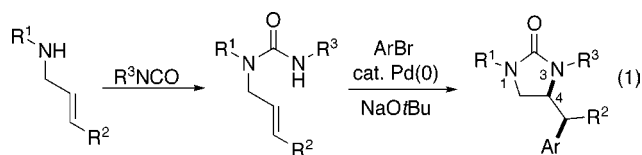
(6) For other recent approaches to the synthesis of cyclic ureas, see: (a) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076. (b) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñoz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587. (c) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251. (d) Kim, M. S.; Kim, Y.-W.; Hahm, H. S.; Jang, J. W.; Lee, W. K.; Ha, H.-J. *Chem. Commun.* **2005**, 3062–3064 and references therein. (e) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309.

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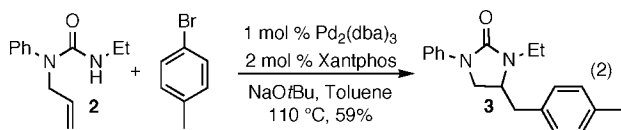
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(9) For related reactions that provide tetrahydrofuran products, see: (a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621. (b) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476.

straightforward, two-step synthesis of cyclic ureas. As shown in eq 1, treatment of readily available allylic amines with isocyanates followed by Pd-catalyzed carboamination would provide a general approach to a diverse array of five-membered cyclic ureas bearing different substituents on N1, N3, and C4. Moreover, this approach would have a significant advantage over existing methods for the synthesis of substituted imidazolidin-2-ones as a C–C bond is formed at the same time the heterocyclic ring is closed.¹¹ In this letter, we describe our preliminary studies on the construction of 4-substituted imidazolidin-2-ones using this strategy.



In our initial experiments, we examined the carboamination of 1-allyl-3-ethyl-1-phenylurea (**2**), which was prepared in 92% yield via addition of *N*-allylaniline to ethyl isocyanate. Treatment of **2** with 4-bromotoluene and NaOtBu in the presence of 1 mol % of Pd₂(dba)₃ and 2 mol % of Xantphos¹² afforded the desired imidazolidin-2-one **3** in 59% isolated yield. The major side products observed in this reaction derive from the base-mediated decomposition of **2** to afford *N*-allylaniline.¹³ Other ligands examined for this transformation including dppe,¹² dppf,¹² and P(*o*-tol)₃ provided lower yields of **3** because of the formation of a side product resulting from oxidative cyclization without incorporation of the *p*-tolyl group.¹⁴



With suitable reaction conditions in hand, we examined the Pd-catalyzed carboamination of several different acyclic ureas. As shown in Table 1, the nature of the *N*-substituents affected the yield of the cyclization reactions. For example, the carboamination of 1-allyl-3-ethyl-1-methylurea (**7**)¹⁵ with

(10) For a two-step carboamination strategy involving ureidomercuration followed by radical-mediated alkylation, see: Danishefsky, S.; Taniyama, E.; Webb, R. R., II. *Tetrahedron Lett.* **1983**, *24*, 11–14.

(11) Tamaru has described Pd(II)-catalyzed Wacker-type carbonylation reactions of *N*-allylureas and *O*-allylcarbamates that effect ring closure with concomitant C–C bond formation to afford imidazolidin-2-ones and oxazolidin-2-ones bearing carbonyl functionality at C-4. See: (a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002. (b) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113–2122.

(12) Xantphos = 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene; dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1'-bis(diphenylphosphino)-ferrocene.

(13) The formation of *N*-allylaniline was observed in reactions of **2** that were monitored by ¹H NMR spectroscopy. The *N*-allylaniline underwent further transformation to provide mixtures of unidentified products. The formation of *N*-allylaniline was also observed when **2** was heated with NaOtBu in the absence of Pd.

(14) This product was assigned as 3-ethyl-4-methyl-1-phenyl-1,3-dihydroimidazol-2-one on the basis of ¹H NMR analysis.

Table 1. Imidazolidin-2-one Synthesis^a

entry	substrate	ArBr	product	yield ^b
1				73%
2				97%
3				83%
4				92%
5				85%
6				75%
7				71%
8				80%
9				58%
10				63%
11				35%
12				68%

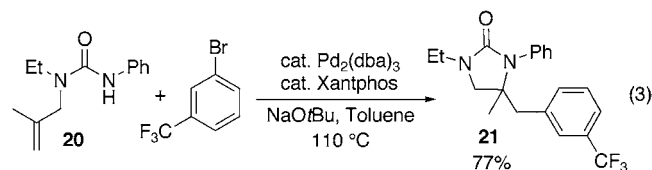
^a Conditions: 1.0 equiv of substrate, 1.2 equiv of ArBr, 1.2 equiv of NaOtBu, 1 mol % of Pd₂(dba)₃, 2 mol % of Xantphos, toluene (0.17–0.25 M), 110 °C. Reactions were complete in 30 min–8 h; reaction times have not been minimized. ^b Isolated yield (average of two or more experiments).

2-bromonaphthalene proceeded in comparable yield (68%, entry 12) to the analogous transformation of **2** (73% yield, entry 1). However, treatment of 1-allyl-1-methyl-3-phenylurea (**4**) with 2-bromonaphthalene under identical conditions provided 97% isolated yield of **9** (entry 2).

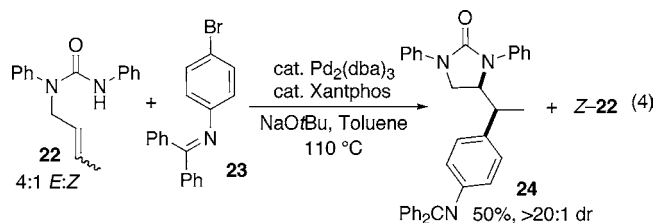
Substrates bearing N1-methyl and N3-benzyl groups (**6**, entry 8) and N1-benzyl and N3-(*p*-methoxyphenyl) groups (**5**, entries 6 and 7) were also transformed to the desired products in moderate to good yield.¹⁶ The efficient reactivity of the latter substrate (**5**) is particularly noteworthy, as the *N*-benzyl and *N*-(4-methoxyphenyl) substituents can potentially be cleaved from the product under orthogonal conditions to allow further functionalization.¹⁷ Unfortunately, the method was not effective for transformation of a urea substrate in which N3 was unprotected.¹⁸ In addition, attempts to cyclize a substrate bearing a N3-(α -methylbenzyl) group failed to provide the cyclic urea product.

The urea carboamination reactions were found to be effective with a broad array of aryl bromides, including substrates bearing functional groups such as nitriles (entry 8), *tert*-butyl esters (entry 6), trifluoromethyl substituents (entry 4), nonenolizable ketones (entry 5), and ortho substituents (entries 7 and 10). Although reactions involving electron-poor and electron-neutral aryl halides generally provided good to excellent yields of the substituted imidazolidin-2-one products, modest yields were obtained with the electron-rich 4-bromoanisole (entry 11).

To probe both the scope and the mechanism of these transformations further, three substrates bearing internal alkenes and one substrate bearing a 1,1-disubstituted alkene were prepared and subjected to the carboamination reaction conditions. The 1,1-disubstituted compound **20** was converted to **21** in 77% yield under our standard reaction conditions (eq 3).

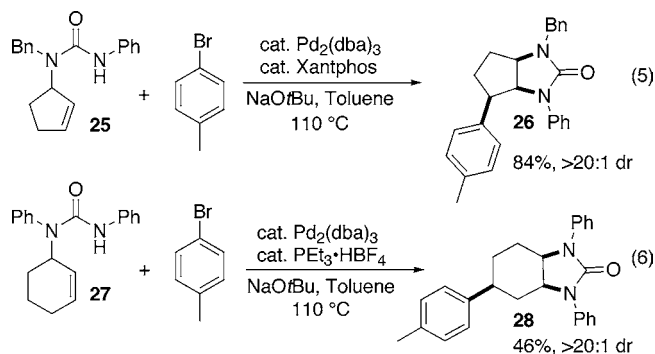


As shown in eq 4, treatment of butenyl-substituted urea **22** with **23** in the presence of NaO*t*Bu and the Pd₂(dba)₃/Xantphos catalyst generated **24** in 50% yield. Interestingly, although **22** was employed as a 4:1 mixture of *E/Z* isomers,



product **24** was obtained as a single diastereomer. The unreacted *Z*-isomer was observed by ¹H NMR analysis of the crude reaction mixture, which suggests the *E/Z* mixture is effectively resolved to a single product diastereomer because of the differences in kinetic reactivity between the two isomers. Crystallographic analysis of **24** indicated that the reaction had proceeded with syn addition of the arene and the urea nitrogen across the carbon–carbon double bond. This syn addition selectivity is analogous to that previously observed in Pd-catalyzed carboamination reactions of γ -unsaturated amines.⁸

The Pd-catalyzed carboamination of cyclopentene derivative **25** with 4-bromotoluene proceeded under our standard conditions to afford syn-addition product **26** in excellent yield (84%) with >20:1 diastereoselectivity (eq 4).¹⁹ However, attempts to effect the cyclization of the cyclohexene-containing substrate **27** using the Pd/Xantphos catalyst provided only trace amounts of the desired product. After some experimentation, a catalyst composed of Pd₂(dba)₃ and PEt₃ was found to provide the cyclized product **28** in 46% yield with >20:1 dr (eq 5). Interestingly, the product **28** was



determined to be arylated at C-5 rather than at the expected C-4 position; the addition again occurred with syn stereochemistry.^{20,21}

The stereochemical and regiochemical outcomes of the transformations of **22**, **25**, and **27** suggest the mechanism of the *N*-allylurea carboaminations is analogous to that previously described for related transformations of γ -aminoalkenes.^{8,20} As shown in Scheme 1, oxidative addition of the aryl bromide to Pd(0) would generate **29**, which could be

(15) The formation of side products resulting from base-mediated isomerization of the *N*-allyl group to a *N*-1-propenyl group was observed in reactions of **7**. This isomerization also occurred when **7** was heated with NaO*t*Bu in the absence of Pd.

(16) Substrates **4–7**, **20**, **22**, **25**, and **27** were obtained in 79–97% yield from treatment of the corresponding allylamine with the appropriate isocyanate as described above.

(17) (a) Suh, M.-J.; Kim, S. W.; Beak, S. I.; Ha, H.-J.; Lee, W. K. *Synlett* **2004**, 489–492. (b) Kise, N.; Kashiwagi, K.; Watanabe, M.; Yoshida, J.-i. *J. Org. Chem.* **1996**, *61*, 428–429. (c) Santos, A. G.; Pereira, J.; Afonso, C. A. M.; Frenking, G. *Chem.–Eur. J.* **2005**, *11*, 330–343.

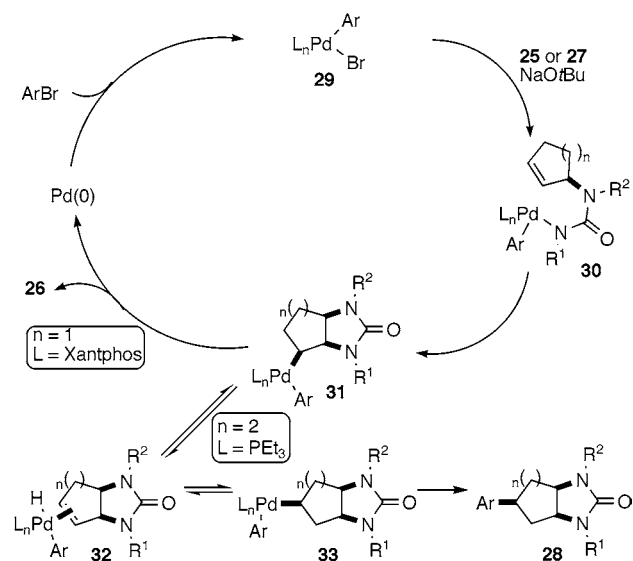
(18) Attempts to transform substrates bearing unprotected N3 moieties led to the formation of products resulting from tandem *N*-arylation and carboamination in low yield (ca. 30%). For a related reaction of aliphatic amines, see: Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575–2578.

(19) The connectivity and stereochemistry of **26** and **28** were determined through ¹H NMR COSY and nOe experiments. See the Supporting Information for complete details of stereochemical assignments.

(20) Related isomers have been observed in Pd/P(*t*-Bu)₂Me-catalyzed carboaminations of *N*-(*p*-methoxyphenyl)-2-(cyclopent-2-enylethyl)amine. See: Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644–8651.

(21) A small amount of *N*-(cyclohex-2-enyl)aniline was observed as a side product in this reaction.

Scheme 1. Mechanism



transformed to **30** ($n = 1$) upon reaction with the urea substrate **25** and NaO*t*Bu. Syn insertion of the alkene into the Pd–N bond would generate **31** ($n = 1$), which would provide **26** upon C–C bond-forming reductive elimination.

The unexpected isomer **28** is likely formed from β-hydride elimination of **31** ($n = 2$) to afford **32**. Reinsertion of the alkene into the Pd–H bond of **32** with reversed regiochemistry followed by reductive elimination from **33** would afford **28**. The conversion of **31** to **32** is presumably thermodynamically favorable, as this transformation would alleviate a steric interaction between the metal and the N–Ph substituent.²⁰ Although this side reaction is not observed in the Pd/Xantphos-catalyzed reaction of **25**, the use of PEt₃

for the coupling of **27** likely slows the rate of C–C bond-forming reductive elimination of **31** ($n = 2$),²² thus allowing access to the alternative mechanistic path.²⁰ The rate of C–C bond-forming reductive elimination from **33** appears to be greater than the rate of alkene displacement from **32**, as oxidative cyclization products are not observed in significant amounts under these conditions.

In conclusion, we have developed a new method that allows the two-step construction of a wide array of imidazolidin-2-ones from readily available starting materials. The key Pd-catalyzed carboamination reaction proceeds in good to excellent yield with excellent levels of diastereoselectivity. These transformations represent the first examples of urea carboamination reactions that proceed with selectivity for products of syn addition and are complementary to existing Wacker-type anti carboaminations¹¹ in terms of both the types of C–C bonds that are formed and the stereochemistry of the products. Further studies directed toward expanding the scope and synthetic utility of these transformations are currently underway.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds reported in the text (78 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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