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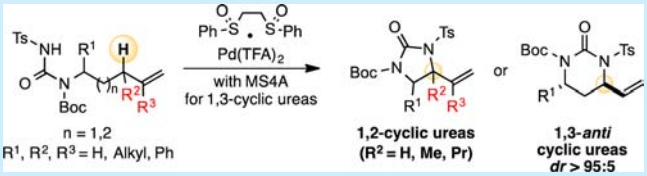
Pd(II)-Catalyzed Allylic C−H Amination for the Preparation of 1,2- and 1,3-Cyclic Ureas

Yasuhiro Nishikawa,* Seikou Kimura, Yuri Kato, Natsuka Yamazaki, and Osamu Hara*

Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan

Supporting Information

ABSTRACT: A general synthesis of 1,2- and 1,3-cyclic ureas is accomplished by intramolecular allylic C−H amination employing $Pd(TFA)_2$/bis-sulfoxide as a catalyst. By careful modification of substrates and catalyst, a variety of 1,2-cyclic ureas are accessible from not previously employed terminal olefins substituted in allylic or vinylic positions. Furthermore, MS4A is found to be an effective additive for the synthesis of 1,3-cyclic ureas in good yields and excellent diastereoselectivities.

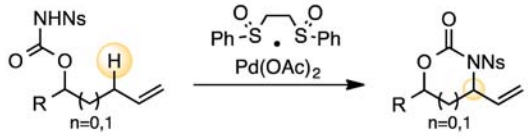


1,2- and 1,3-cyclic ureas and their derivatives such as guanidines are important motifs in natural products and pharmaceuticals.[1] In addition, these motifs can be lead compounds to structurally and biologically diverse 1,2- and 1,3-diamines.[2] Among the various useful approaches to cyclic ureas, C−H amination of the corresponding acyclic ureas seems to be attractive since the preparation of substrates and their C−N functionalization can be performed with minimal functional group manipulations.[3−6] One of the most powerful methods is Rh-catalyzed C−H amination to afford 1,2- and 1,3-diamines through the corresponding ureas, guanidines, sulfamates, and sulfamides.[7] While a variety of C−H bonds can be functionalized via Rh-nitrenoids, one drawback is that olefin aziridination outcompetes the desired allylic C−H insertion in cases where homoallyl and bis-homoallyl derivatives are used.[7b−d] On the other hand, Pd-catalyzed amination favors allylic C−H bond functionalization and further functionalization of the resulting olefin moiety. Pioneering work in this field is the Pd(II)/bis-sulfoxide catalyzed C−H amination first reported by White et al. to produce 1,2- and 1,3-cyclic carbamates leading to 1,2-*anti* and 1,3-*syn* amino alcohols (eq 1).[8,9] Very recently, the same group reported a new synthetic method for 1,2-cyclic ureas by an olefin isomerization/amination protocol employing a Pd(II) catalyst with a Lewis acid cocatalyst (eq 2).[10]

Inspired by these results, we started to investigate the synthesis of a variety of cyclic ureas, because of not only their inaccessibility by Pd(II) catalyzed C−H oxidation but also the limited availability of suitable substrates for olefin isomerization/amination, yielding 1,2-cyclic ureas only. In particular, substrates that are branched at the allylic (R^2) or vinylic (R^3) positions have yet to be employed in Pd(II) catalyzed C−H oxidation (eq 3).[8a] Furthermore, it has yet to be applied to the preparation of 1,3-cyclic ureas (eq 4).

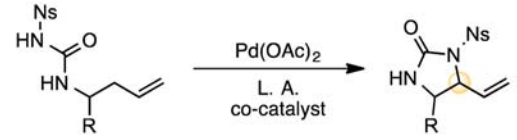
An initial attempt at the cyclization of **1a** under the same conditions as used in the synthesis of cyclic carbamates[8] furnished cyclic urea **2a** in an unsatisfactory yield (Table 1, entry 1). While replacing $Pd(OAc)_2$ with $PdCl_2$ further reduced the yield, the use of $Pd(TFA)_2$ dramatically improved this

White (2007, 2009): C-H oxidation



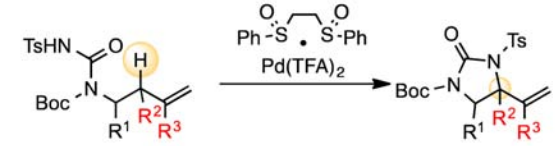
(1)

White (2013): olefin isomerization/amination



(2)

This work: C-H oxidation



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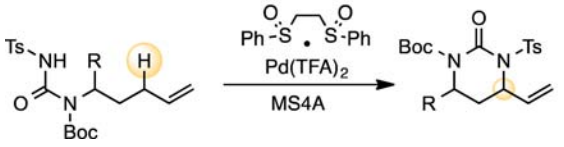

(4)

reaction in terms of yield as well as reaction time (entries 2−4). This is in contrast with the synthesis of cyclic carbamates in which the use of $Pd(TFA)_2$ led to insignificant amounts of cyclized product unless an external acetate source was added (Scheme 2, vide infra).[8a] Next, we turned our attention to the effect of the protecting group on the cyclization reaction. Boc protected acyclic urea **1b** gave a better yield than that of **1a** (entry 5). On the other hand, unprotected (**1c**) and Bn protected

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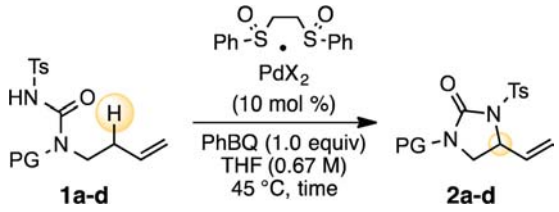
Table 1. C−H Oxidation for 1,2-Cyclic Ureas by C−H Oxidation



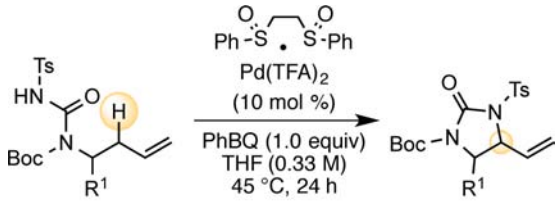
entry[a]	PdX_2	protecting group		time	% yield[b]
1	OAc	Cbz	(**1a**)	48	**2a** (38)
2	Cl	Cbz	(**1a**)	48	**2a** (13)
3	TFA	Cbz	(**1a**)	48	**2a** (90)
4	TFA	Cbz	(**1a**)	24	**2a** (85)
5	TFA	Boc	(**1b**)	24	**2b** (93)
6	TFA	H	(**1c**)	48	**2c** (ND)
7	TFA	Bn	(**1d**)	48	**2d** (ND)

[a]Reactions were performed with 0.2 mmol of acyclic urea (**1a−d**), 10 mol % of Pd(II)/bissulfoxide complexes, and 1.0 equiv of phenyl-1-benzoquinone (PhBQ) in THF (0.3 mL) at 45 °C. [b]Determined by ^{1}H NMR analysis.

acyclic urea **1d** formed no cyclized product (entries 6 and 7). These results implied that the acidity of the urea is an important factor in this reaction as an electron-withdrawing group on the urea enhances the acidity of the N−H on the urea.[8b]

Next, we examined the range of substrates for the synthesis of 1,2-cyclic ureas (Table 2). The acyclic urea bearing a phenyl

Table 2. Substrate Range for the Synthesis of 1,2-Cyclic Ureas



entry	R^1	% yield[c]	dr (*anti:syn*)[d]
1[a]	H (**1b**)	**2b** (87)	–
2[a]	Ph (**1e**)	**2e** (75)	38:62
3[b]	Ph (**1e**)	**2e** (65)	33:67
4[b]	CH_2CH_2Ph (**1f**)	**2f** (53)	65:35
5[b]	*n*Pr (**1g**)	**2g** (99)	65:35
6[b]	*i*Pr (**1h**)	**2h** (79)	>95:5
7[b]	*t*Bu (**1i**)	**2i** (69)	>95:5

[a]Method A: Isolated $Pd(TFA)_2$/bis-sulfoxide complex was used. [b]Method B: $Pd(TFA)_2$/bis-sulfoxide complex was prepared in the reaction vessel before use. See Supporting Information for more details. [c]Isolated yields. [d]Determined by ^{1}H NMR of the crude products.

group on the homoallylic position was cyclized in good yield and moderate diastereoselectivity (entry 2).[11] At this stage, another method in which the $Pd(TFA)_2$/bis-sulfoxide complex is prepared *in situ* and used without isolation (Method B) was compared with the previous method using the isolated complex (Method A).[12a] We subsequently adopted the simpler method B because both methods resulted in similar yields and selectivities (entries 2 and 3). Further investigation revealed that alkyl-substituted substrates reacted in a similar fashion (entries 4 and 5). Interestingly, opposite diastereoselectivities were observed between entry 3 and entries 4−5.[13] This might be explained by the coordination of the phenyl group to the π-allyl Pd complex during cyclization, which preferentially leads to *syn*-**2e** over sterically favored *anti*-**2e** (Figure 1). Similarly, bulky substituents on the homoallylic position influence the diastereoselectivities to afford only *anti* products in high yield (entries 6 and 7).

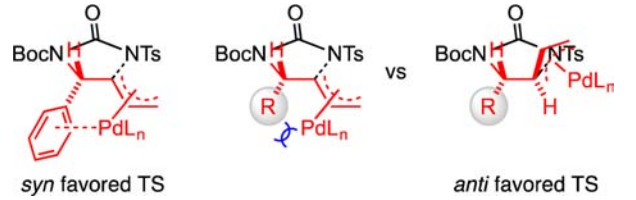
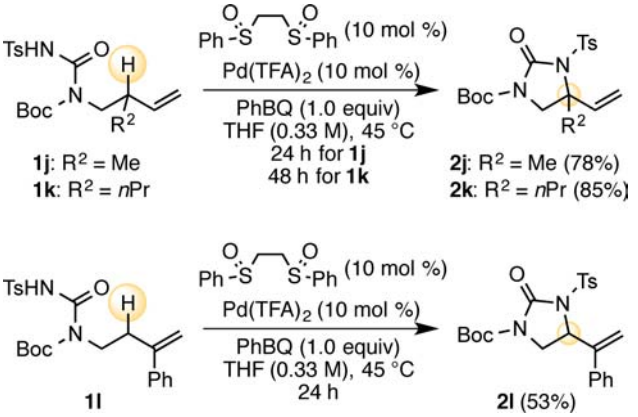


Figure 1. Plausible transition models in cyclization.

In the previous studies of Pd-catalyzed C−H amination, high yielding reactions have been limited to substrates bearing an allyl group.[8] To test the versatility of the protocol in our study, we demonstrated C−H amination of challenging substrates such as homoallylureas substituted in allylic and vinylic positions (Scheme 1). Gratifyingly, the methyl group and an even more

Scheme 1. C−H Oxidation of Substrates Branched at the Allylic or Vinylic Positions



bulky *n*-propyl group on the allylic position had no deleterious effect on C−H amination to give the corresponding cyclic ureas **2j** and **2k** having quaternary carbon centers. In addition, a cyclic urea **2l** bearing a 2-styryl group could be synthesized using the same protocol.

With the successful synthesis of a variety of 1,2-cyclic ureas in hand, we anticipated that 1,3-cyclic ureas might be obtained in an analogous fashion (Table 3). However, the application of the same conditions as those used for 1,2-cyclic ureas to acyclic bis-homoallylurea **3a** gave 1,3-cyclic urea **4a** in poor yield (entry 1). Increasing the reaction time, reaction temperature, or oxidant equivalents did not improve the reaction (entries 2−4). Fortunately, we found that addition of MS4A accelerated the reaction dramatically to afford the desired product in high yield (entries 5 and 6). As MS4A was usually employed as a dehydrating agent, an experiment to check the influence of water on the reaction was done (entry 7). Almost the same product yields were observed for entries 4 and 7 implying that water does not impair this C−H amination. Thus, the effect of MS4A on the reaction could not be simply explained as drying

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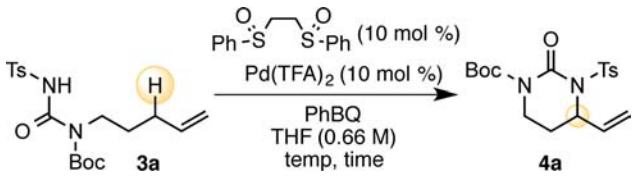
Table 3. C−H Oxidation for 1,3-Cyclic Urea 4a[a]



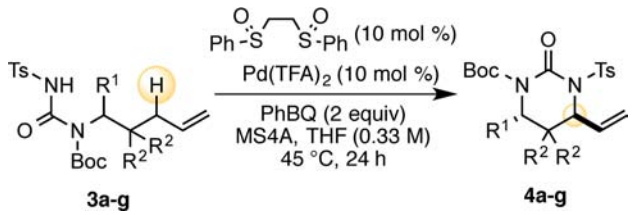
entry	PhBQ (equiv)	temp (°C)	time (h)	additive	yield[b] (%)
1	1	45	24	–	18
2	1	45	48	–	24
3[c]	1	60	48	–	31
4[c]	2	45	48	–	31
5[c]	2	45	48	MS4A[d]	87
6[c]	2	45	24	MS4A[d]	97
7[c]	2	45	48	H_2O[e]	24

[a]0.2 mmol scale. [b]Determined by ^{1}H NMR analysis. [c]Concentration of **3a** was 0.33 M. [d]Powdered MS4A (50 mg) was used. [e]1 equiv.

the reaction medium, though the actual mechanism is still unclear. To the best of our knowledge, this is the first example of the synthesis of a 1,3-cyclic urea via allylic C−H oxidation.[14]

Having established the optimal conditions for the synthesis of 1,3-cyclic urea **4a**, we next applied them to various acyclic bis-homoallylureas (Table 4). Cyclization of the phenyl-substituted

Table 4. Substrate Range for the Synthesis of 1,3-Cyclic Ureas[a]



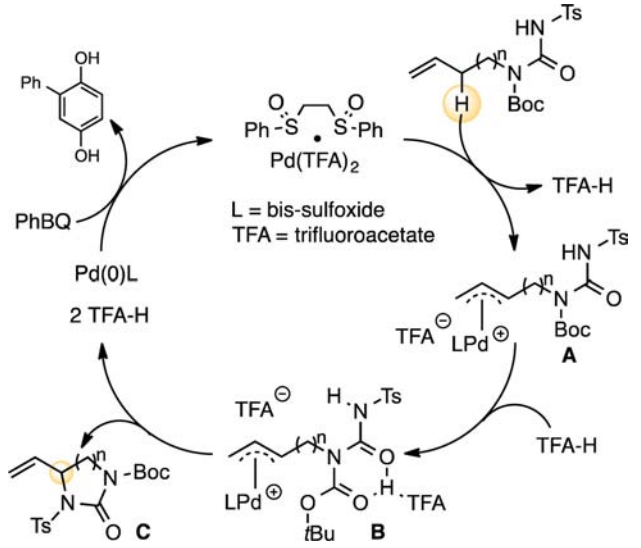
entry		R^1	R^2	yield[b] (%)	*dr*[c] (*anti:syn*)
1	**3a**	H	H	**4a** (86)	–
2	**3b**	Ph	H	**4b** (46)	>95:5
3	**3c**	Et	H	**4c** (52)	>95:5
4	**3d**	CH_2CH_2Ph	H	**4d** (69)	>95:5
5	**3e**	*i*Pr	H	**4e** (83)	>95:5
6	**3f**	*t*Bu	H	**4f** (81)	>95:5
7	**3g**	H	Me	**4g** (84)	–

[a]0.2 mmol scale with powdered MS4A (50 mg). [b]Isolated yields. [c]Determined by ^{1}H NMR of the crude products.

acyclic urea took place in modest yield (entry 2), in contrast to the formation of the analogous 1,2-cyclic urea. It is thought that the coordination of the phenyl group to the π-allyl Pd complex discussed above led to a conformation unfavorable for its cyclization. A variety of substrates having sterically different alkyl groups were effectively oxidized and aminated in modest to good yields (entries 3−6). It is noteworthy that in all cases these cyclizations proceeded with excellent diastereoselectivity to give 1,3-*anti* cyclic ureas.[13] As 1,3-stereoinduction is generally more difficult to achieve than 1,2-induction, this method is valuable for the stereoselective synthesis of 1,3-cyclic urea and diamine derivatives. Additionally, **3g**, incorporating a gem-dimethyl group at the homoallylic position that can sterically hinder C−H activation due to its bulkiness was successfully cyclized to include a highly congested stereocenter in good yield (entry 7).

Finally, the plausible catalytic cycle was speculated on the basis of our experimental results and mechanistic investigations of Pd(II)/bis-sulfoxide catalysis reported previously (Scheme 2).[8,10,12] The catalytic cylcle starts with alkene coordination to

Scheme 2. Plausible Catalytic Cycle



the $Pd(TFA)_2$/bis-sulfoxide complex followed by C−H cleavage to produce the π-allylPd species **A** and trifluoroacetic acid.[8a,10] At this stage, a nitrogen nucleophile is thought to be formed by Pd(II) counterion-mediated deprotonation of a NH moiety to achieve the desired cyclization.[8] We envisioned effective coordination of trifluoroacetic acid with the imide moiety in **B**, which could enhance the acidity of the NH proton. The resulting NH proton should be more susceptible to deprotonation even with a weakly basic trifluoroacetate ion on the π-allylPd complex **B**. The formation of the cyclized product **C** is accompanied by the release of the Pd(0) complex and trifluoroacetic acid, which is oxidized by PhBQ to regenerate a Pd(II) catalyst.[16] However, further studies must be done to prove the above considerations.

In conclusion, we have demonstrated that a $Pd(TFA)_2$/bis-sulfoxide system is effective for intramolecular allylic C−H amination to yield a variety of 1,2-cyclic ureas. Acyclic homoallylureas substituted in allylic or vinylic positions can be employed in this reaction to give synthetically useful cyclic ureas bearing quaternary carbon centers or styryl groups. Furthermore, the combination of MS4A with the $Pd(TFA)_2$/bis-sulfoxide system enables the C−H amination via allylic C−H oxidation to afford 1,3-cyclic ureas for the first time. Excellent 1,3-diastereoselectivity for a broad range of substrates adds value to this procedure, giving access to biologically active compounds and natural products containing 1,3-cyclic ureas and 1,3-diamines.[15]

■ ASSOCIATED CONTENT

Supporting Information

All experimental procedures and spectroscopic data of substrates and cyclized compounds in Scheme 1 and Tables 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: yasuhiro@meijo-u.ac.jp.
*E-mail: oshara@meijo-u.ac.jp.

Notes

The authors declare no competing financial interest.

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(13) For determination of relative stereochemistry of 1,2- and 1,3-cyclic ureas, see Supporting Information.

(14) 1,3-Cyclic sulfamides has been synthesized effectively by Rh-catalyzed C-H insertion. See ref 7d.

(15) The synthesis of 1,3-diamine from **4b** was reported following literature procedure. See: Muorgen, M.; Bretzke, S.; Li, P.; Menche, D. *Org. Lett.* **2010**, *12*, 4494.

(16) No dienes formed from β-hydride elimination were observed in this study. This fact particularly in Tables 3 and 4 may imply the rate of cyclization is sufficiently fast after the formation of π-allylPd complexes with $Pd(TFA)_2$; see: Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892.

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