Intramolecular Aminoazidation of Unactivated Terminal Alkenes by Palladium-Catalyzed Reactions with Hydrogen Peroxide as Oxidant

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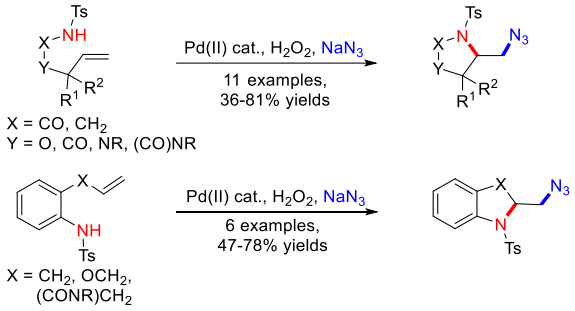
Supporting Information Placeholder



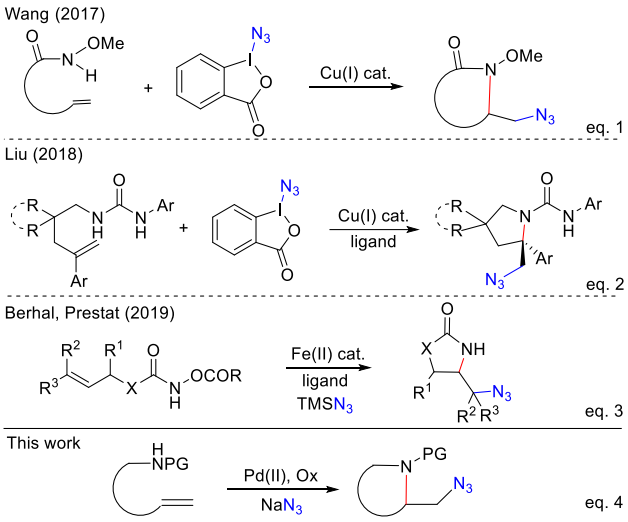
ABSTRACT: The palladium-catalyzed aminoazidation of aminoalkenes yielding azidomethyl substituted nitrogen-containing heterocycles was developed. The procedure requires oxidative conditions and occurs at room temperature in the presence of hydrogen peroxide and NaN_3 as azide source. These conditions provide selective *exo*-cyclization/azidation of the carbon-carbon double bond furnishing a versatile approach toward five-, six-, and seven-membered heterocyclic rings.

Vicinal difunctionalization of unactivated alkenes has recently become a powerful tool.[1] Various combinations of functional groups have been installed on hydrocarbons in intra/intermolecular procedures resulting in bicyclic structures or differently functionalized heterocyclic systems.[2] In this context, despite organoazides are versatile intermediates in organic synthesis,[3] reactions involving the introduction of an azido group are rather rare and this is true for aminoazidation procedures as well. In one isolated example, Chemler and co-workers reported that treatment of an allylurea with [NaN_3/excess Cu(2-ethylhexanoate)$_2$] allows the formation of the corresponding azidomethyl-imidazolidin-2-one resulting from an intramolecular amination/intermolecular azidation sequence.[4] Another aminoazidation procedure starting from β,γ-unsaturated hydrazones in the presence of stoichiometric amount of $Cu(OAc)_2$ and NaN_3 was reported by Wang, Li and co-workers.[5] More recently, Wang and co-worker developed a copper-catalyzed aminoazidation of alkenyl *N*-methoxy amides using an azidoiodinane reagent (Scheme 1, eq. 1).[6] A dual [Cu(I)/chiral phosphoric acid]-based catalyst, in the presence of the same azide source as that of the previous example has been used by Liu and co-workers to provide the enantioselective aminoazidation of alkenyl ureas (Scheme 1, eq. 2).[7] Very recently, Berhal and Prestat reported the aminocyclization/azidation of alkenyl oxy-ureas, oxy-carbamates, and oxy-amides with a [$Fe(OAc)_2$/phenanthroline]-catalytic system and $TMSN_3$ giving azido-containing 5-membered heterocyclic rings (Scheme 1, eq. 3).[8] The NCS-promoted one-pot conversion of a series of unsaturated amines into the corresponding 3-azidopiperidines has been obtained

by Kang and co-workers in the presence of NaI and NaN_3.[9] Studer and co-worker and Li and co-workers performed the intermolecular aminoazidations of olefins by copper- or iron-catalysis, respectively, using $TMSN_3$ in the presence of *N*-fluorobenzensulfonimide.[10] Overall, only few other cyclization/azidation synthetic protocols are reported in the literature, specifically concerning Cu-catalyzed oxyazidations.[11]

Although oxidative palladium-catalysis occupies a relevant role in alkene 1,2-difunctionalization protocols,[12] to the best of our knowledge, no such catalysis has been reported involving the inter- or intramolecular installation of an azido group on an alkene.

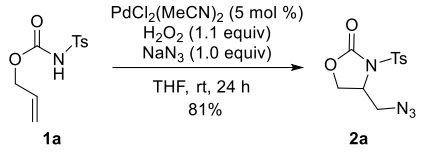
Scheme 1. Intramolecular aminoazidation of olefins: previous and present works



In the frame of a longstanding collaboration between our groups,[13] and as part of our ongoing studies on the synthesis of nitrogen-containing heterocyclic as well as on intramolecular oxidative palladium-catalyzed functionalization of alkenes,[14] we report herein a novel palladium-catalyzed aminoazidation of alkenylamines as a straightforward procedure to access azidomethyl substituted azaheterocycles (Scheme 1, eq. 4).

We chose *O*-allyl-*N*-tosylcarbamate (**1a**) as our initial model substrate, selecting hydrogen peroxide as the stoichiometric oxidant.[15] After some preliminary experimentation (see SI), we found that the reaction conditions [$PdCl_2(MeCN)_2$ (5 mol %), H_2O_2 (1.1 equiv), NaN_3 (1.0 equiv), in THF, r.t., 24 h] afforded the azidomethyl oxazolidinone **2a** in 81% yield, according to a 5-*exo*-amination/azidation sequence (Scheme 2). Change of the catalyst [$Pd(OAc)_2$, $Pd(O_2CCF_3)_2$] or of the stoichiometry of H_2O_2 (1.5, 2.0 or 4.0 equiv), or of the solvent (MeCN, dioxane, DMF) deteriorated the purity of the crude mixture.[16] The use of $TMSN_3$ as azide source did not furnish the desired product in a detectable amount.

Scheme 2 *Exo*-amination/azidation of *O*-allyl-*N*-tosylcarbamate 1a[a]

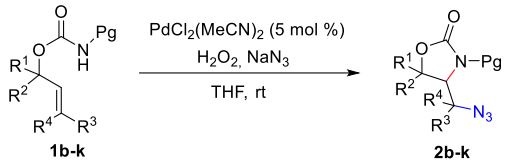


[a] Reaction conditions: **1a** (1.00 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol), H_2O_2 (1.10 mmol), NaN_3 (1.00 mmol), THF (5 mL).

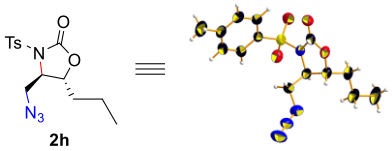
First, we examined the reactivity of *O*-allyl-*N*-arylcarbamates **1b-d** bearing substituents with different electronic properties on the aryl group. Working with the reaction system [$PdCl_2(MeCN)_2$ cat., H_2O_2, NaN_3] in THF, at room temperature the sole recovery of unreacted substrates was obtained. Only the 4-nitrophenyl derivative **1b** gave the expected oxazolidin-2-one **2b** (53% yield) upon treatment with the above catalytic system under microwave irradiation at 60 °C for 1 h (Scheme 3, entries 1-3). Furthermore, the palladium-catalyzed aminoazidation reaction was successful also on *N*-(2-nitrophenyl)sulfonyl carbamate **1e**, although in moderate yield, indicating that the high acidity of a *N*-sulphonyl carbamate was essential to promote the process.[17]

We thus decided to focus on N-sulfonyl protected alkenyl substrates for further investigations. Tests on functionalized *O*-allyl-*N*-Ts carbamates indicated that the success of this tandem sequence depends on the location of the substituents. On the one hand, substrates **1f-i**, carrying substituents at the α-allylic position, afforded the corresponding oxazolidinones **2f-i** in 65-81% isolated yields (Scheme 3, entries 5-8). Here again, products derived from a 6-endo-amination/azidation process were not isolated, even in traces. Furthermore, in the case of entries 5-7, the reactions were totally diastereoselective, affording exclusively one azidated oxazolidinone, although the *i*-Pr- substituted substrate **1h** gave additionally a small amount of the hydroxymethyl-substituted oxazolidinone **3h**.[18] The single crystal X-ray structure analysis of **2h** in combination with the analogy of its ^{1}H-NMR spectrum with those of **2f** and **2g** allowed to assign the trans 4*R**,5*R** relative configuration of the oxazolidinone ring. On the other hand, allyl substituents incorporating an 1,2-disubstituted alkene impede the reaction to take place (Scheme 3, entries 9 and 10). Reactions on homoallyl carbamates furnished only complex mixtures of degradation compounds.

Scheme 3. Aminoazidation reaction of *O*-alkenyl-*N*-substituted-carbamates 1b-k[a]



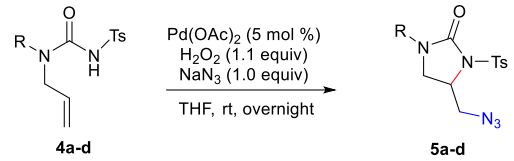
Entry	Substrate	Time (h)	Product	Yield (%)
1[b]	Ar = 4-NO_2-C_6H_4 **1b**	24	**2b**	53[c]
2[b]	Ar = 4-Cl-C_6H_4 **1c**	48	**2c**	-
3[b]	Ar = 4-MeC_6H_4 **1d**	48	**2d**	-
4	Ar = o-Ns **1e**	16	**2e**	56
5	R = Me **1f**	20	**2f** (R' = N_3)	61
6	R = Et **1g**	24	**2g** (R' = N_3)	68
7	R = Pr **1h**	16	**2h** (R' = N_3)	55[d]
			3h (R' = OH)	15
8	**1i**	20	**2i**	52
9	R = Me **1j**	20	degradation products	
10	R = Ph **1k**	24	degradation products	



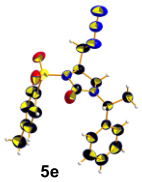
[a] Reaction conditions: **1a** (1.00 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol), H_2O_2 (1.10 mmol), NaN_3 (1.00 mmol), THF (5 mL), r.t., 24 h. [b] Reaction temperature: 60 °C, MW irradiation; reaction time: 1 h. [c] Unreacted substrate (39%) was recovered beside **2b**. [d] For **2h**, the molecular structure as retrieved by single crystal X–ray diffraction at room temperature is also given. Thermal ellipsoids are drawn at the 50 % probability level. See Supporting Information for more details. CCDC 1970338 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

To confirm the totally selective 5-*exo*-*trig* cyclization observed in the aminoazidation of *O*-allyl-carbamates, we tested our conditions on *N*-allyl-*N*'-tosylureas, which are structurally analogous compounds. Accordingly, treatment of ureas **4a-e** with the system [$Pd(OAc)_2$ (5 mol %), H_2O_2, NaN_3] at room temperature gave, after an overnight stirring, the corresponding 4-azidomethyl-imidazolidinones **5a-e** in fairly satisfactory yields as the major products (Scheme 4).

Scheme 4. Aminoazidation reactions of *N*-allyl-*N*'-tosylureas 4a-e[a]



Entry	Substrate	Product	Yield (%)
1	R = Me **4a**	**5a** (R' = N_3)	79
2	R = Cy **4b**	**5b** (R' = N_3)	78
3	R = Ph **4c**	**5c** (R' = N_3)	46
		6c (R' = OH)	14
4	R = Bn **4d**	**5d** (R' = N_3)	81
5	**4e**	**5e**	52[b,c]



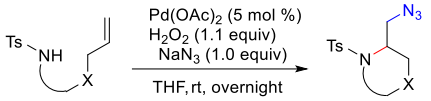
[a] Reaction conditions: **4** (1.00 mmol), $Pd(OAc)_2$ (0.05 mmol), H_2O_2 (1.10 mmol), NaN_3 (1.00 mmol), THF (5 mL).[b] Major diasteroisomer (isolated yield); minor diasteroisomer not isolated; diastereomeric ratio 78:22 determined by ^1H NMR analysis of the crude reaction mixture.[c] The experimental molecular structure of **5e** is given, with same specs as in Scheme 3. See Supporting Information for more details. CCDC 1970339 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

In this case, $Pd(OAc)_2$ proved to be the best performing palladium source. Only when starting from the *N*-allyl-*N*-phenyl-urea **4c** a small amount of the amination/hydroxylation byproduct **6c** was isolated. In contrast to some literature precedents,[19] no product arising from intramolecular C-O bond formation was detected. The application of standard conditions to the (*R*)-*N*-α-methylbenzyl-*N*-allylurea **4e** afforded the optically active imidazolidinone **5e**, whose α*R*,4*R* absolute configuration was determined by single crystal X-ray structure analysis.

We further extended the scope of the reaction. *N*-tosyl-2-allylanilines **7a,b** reacted as expected, providing the corresponding 2-azidomethylindolines **8a,b**, albeit in moderate yields (Scheme 5, entries 1 and 2). The *N*-allylamides of *N*-tosylglycine **9a,b** and *O*-allyl-*N*-tosyl-2-aminophenol (**11**) were then considered in view of obtaining rings of greater size. Accordingly, treatment of these substrates under the above reaction conditions gave the piperazinones **10a,b** and the 1,4-benzoxazine **12** in satisfactory yields (Scheme 5, entries 3-5). The reactions successfully proceeded also on *N*-allyl-anthranilamides **13a-c**, yielding the 1,4-benzodiazepines **14a-c** through selective

7-*exo*-aminoazidation (Scheme 5, entries 6-8), with, in the case of **13c**, a small amount of the hydroxymethyl-substituted compound **15c**.

Scheme 5. The scope of the aminoazidation reaction

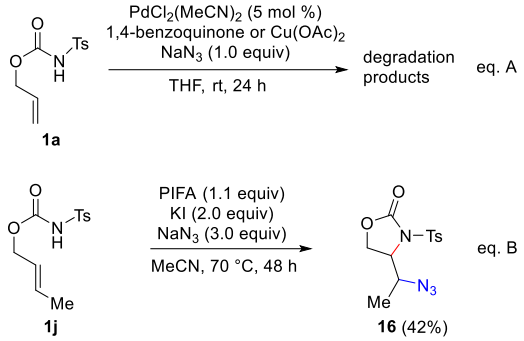


Entry	Substrate	Product	Yield (%)
1 R = H	**7a**	**8a**	47
2 R = OMe	**7b**	**8b**	51
3 R = Cy	**9a**	**10a**	52
4 R = Ph	**9b**	**10b**	74
5	**11**	**12**	78
6 R = Me	**13a**	**14a** ($R^1 = N_3$)	50
7 R = Bn	**13b**	**14b** ($R^1 = N_3$)	70
8 R = Cy	**13c**	**14c** ($R^1 = N_3$)	58
		15c (R^1 = OH)	24

[a] Reaction conditions: substrate **7, 9, 11, 13** (1.00 mmol), $Pd(OAc)_2$ (0.05 mmol), H_2O_2 (1.10 mmol), NaN_3 (1.00 mmol), THF (5 mL).

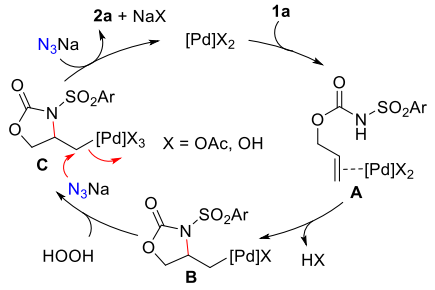
Relevant information on the mechanism of this reaction was obtained by inspecting the role of the oxidant and the nature of the alkene moiety. In relation to the former point, we found that oxidizing agents that typically work by Pd(0)/Pd(II) cycles were unable to provide the aminoazidation process. Indeed, when carbamate **1a** was treated under standard conditions, but using 1,4-benzoquinone or $Cu(OAc)_2$ instead of H_2O_2, no azidomethyl oxazolidinone **2a** was detected in the resulting intractable reaction mixtures (Scheme 6, eq. A). This is likely due to the competitive paths of protonolysis and/or β-hydride elimination that become dominant when the oxidant is incapable of bringing the Pd(II) complex to the Pd(IV) oxidation state.[20] As to the latter point, reaction of carbamate **1j** with the system [PIFA, KI, and NaN_3] provided the cyclization/azidation product **16** as a single diastereoisomer, isolated in 42% yield (Scheme 6, eq. B).[21] This result confirms that the failure to obtain the aminoazidation products from substrates **1j** and **1k** (Scheme 3, entries 9 and 10) is not due to the intrinsic instability of the final product.

Scheme 6. Experiments to inspect the role of the oxidant and the nature of the alkene moiety



On the basis of the above results, we propose a plausible mechanism as depicted in Scheme 7. Exocyclic nucleopalladation on the σ-olefin complex **A** generates the π-alkyl-palladium(II) intermediate **B**, which undergoes oxidation by H_2O_2 to afford the Pd(IV)-intermediate **C**.[22] Following azide anion direct substitution of the C-Pd(IV) bond affords the final product with regeneration of the starting catalyst. Hints about the mechanism of the last step are given by the above mentioned failure of substrates **1j** and **1k**. Indeed, the fact that the reaction is viable when the attacked carbon atom is secondary, but fails when it is tertiary strongly speaks in favor of a direct substitution mechanism. On the other hand, an alternative mechanism involving azide addition to the palladium atom followed by reductive elimination is not expected to be sensitive to the degree of substitution of alkene β-carbon atom. Furthermore, an analogous S_N2 step was found operative in the substitution of a $C(sp^3)$-Pd(IV) bond by acetate anion,[23] and should be *a fortiori* so in the case of the softer azide anion.[24]

Scheme 7. Plausible reaction mechanism



In summary, we have developed a new palladium-catalyzed procedure for the cyclization/azidation of unactivated alkenes bearing a -NHTs group. The reaction proceeds in mild conditions with NaN_3 as azide anion source and H_2O_2 as inexpensive oxidant agent to yield azidomethyl-substituted heterocycles. The use of H_2O_2 is essential to generate a Pd(IV)-intermediate which avoids competitive reactions such as the β-hydride elimination. In summary, we have developed a new palladium-catalyzed procedure for the cyclization/azidation of unactivated alkenes bearing a -NHTs group. The reaction proceeds in mild conditions with NaN_3 as azide anion source and H_2O_2 as inexpensive and green oxidant agent to yield az-

idomethyl-substituted heterocycles. The use of H_2O_2 is essential to generate a Pd(IV)-intermediate which avoids competitive reactions such as the β-hydride elimination. Overall, this approach is the first example of successful palladium-catalyzed aminoazidation and appears as a valid and useful alternative to the copper-promoted intramolecular aminoazidation. The procedure based on the palladium-catalysis runs at room temperature, while the use of copper-catalyst requires heating at 50-60 °C. The mechanism of the reaction does not involve radical intermediates as in the case of copper-catalyzed reactions and a broader range of different heterocycles, especially 6-membered ones, could be accessed in comparison to the more limited scope of the copper protocol. Further work is aimed to the investigation of the asymmetric aminoazidation of aminoalkenes as well as to the study of oxyazidation reactions of alkenols.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data including copies of ^1H and ^{13}C NMR spectra, and X-ray data (CIF) for **2g** and **5e** are provided (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1)] (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368-3398. (b) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269-275. (c) Romero, R. M.; Woste, T. H.; Muñiz, K. *Chem. - Asian J.* **2014**, *9*, 972-983. (d) Koike, T.; Akita, M. *Org. Chem. Front.* **2016**, *3*, 1345-1349. (e) Lan, X.-W.; Wang, N.-X.; Xing, Y. *Eur. J. Org. Chem.* **2017**, 5821-5851. (f) Sauer, G. S.; Lin, S. *ACS Catal.* **2018**, *8*, 5175-5187.

(2) (a) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671-2681. (b) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009-3019. (c) Chemler, S. R. *J. Organomet. Chem.* **2011**, *696*, 150-158. (d) Schultz, D. M.; Wolfe, J. P. *Synthesis*, **2012**, *44*, 351-361. (e) Chemler, S. R.; Bovino, M. T. *ACS Catal.* **2013**, *3*, 1076-1091.

(3) (a) *The Chemistry of the Azido Group* (Ed.: S. Patai), Wiley, New York, **1971**. (b) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188-5240. (c) Shen, S.-J.; Zhu, C.-L.; Lu, D.-F.; Xu, H. *ACS Catal.* **2018**, *8*, 4473–4482. (d) Zhu, H.-T.; Arosio, L.; Villa, R.; Nebuloni. M.; Xu, H. *Org. Process. Res. Dev.* **2017**, *21*, 2068-2072.

(4) Sequeira, F. C; Turnpenny, B. W.; Chemler, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6365-6368.

(5) Wang, L.-J.; Ren, P.-X.; Qi, L.; Chen, M.; Lu, Y.-L.; Zhao, J.-Y.; Liu, R.; Chen, J.-M.; Li, W. *Org. Lett.* **2018**, *20*, 4411-4416.

(6) Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2017**, *139*, 13110-13116.

(7) Wang, L.-J.; Dong, X.-Y.; Lin, J.-S.; Zeng, Y.; Jiao, G.-Y.; Guo, Q.-S.; Ma, C.-L.; Liu, X.-Y. *Chem.* **2017**, *3*, 979-990.

(8) Abi Fayssal, S.; Giungi, A.; Berhal, F.; Prestat, G. *Org. Process Res. Dev.* DOI: 10.1021/acs.oprd.9b00400.

(9) Ortiz, G. X.; Kang, B.; Wang, Q. *J. Org. Chem.* **2014**, *79*, 571-581.

(10) (a) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 1790-1793. (b) Lei, B.; Wang, X.; Ma, L.; Li, Y.; Li, Z. *Org. Biomol. Chem.* **2018**, *16*, 3109-3113. (c) As an example of oxyaminoazidation, see: Nocquet-Thibault, S.; Rayar, A.; Retailleau, P.; Cariou, K.; Dodd, R. H. *Chem. Eur. J.* **2015**, *21*, 14205-14210.

(11) (a) Zhu, L.; Hu, H.; Jiang, X.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1562-1565. (b) Zhu, R.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2015**, *137*, 8069-8077. (c) Alazet, S.; Le Vaillant, F.; Nicolai, S.; Waser, T. *Chem. Eur. J.* **2017**, *23*, 9501-9504. (d) Alazet, S.; Preindl, J.; Simonet-Davin, R.; Nicolai, S.; Nanchen, A.; Meyer, T.; Waser, J. *J. Org. Chem.* **2018**, *83*, 12334-12356.

(12) (a) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142-1152. (b) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083-4088. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318-5365. (d) McDonald, R. I.; Liu, G.; Stahl, S.S. *Chem. Rev.* **2011**, *111*, 2981-3019. (e) Broggini, G.; Borelli, T.; Giofré, S.; Mazza, A. *Synthesis* **2017**, *49*, 2803-2818.

(13) (a) Borelli, T.; Brenna, S.; Broggini, G.; Oble, J.; Poli, G.; *Adv. Synth. Catal.* **2017**, *359*, 623-628. (b) Diamante, D.; Gabrieli, S.; Benincori, T.; Broggini, G.; Oble, J.; Poli, G. *Synthesis* **2016**, *48*, 3400-3412. (c) Broggini, G.; Poli, G.; Beccalli, E. M.; Brusa, F.; Gazzola, S.; Oble, J. *Adv. Synth. Catal.* **2015**, *357*, 677-682. (d) Rigamonti, M.; Prestat, G.; Broggini, G.; Poli, G. *J. Organomet. Chem.* **2014**, *760*, 149-155.

(14) (a) Giofrè, S.; Beccalli, E. M.; Foschi, F.; La Rosa, C.; Lo Presti, L.; Christodoulou, M. *Synthesis* **2019**, *51*, 3462-3470. (b) Liu, Y.; Mao, Z.; Pradal, A.; Huang, P.-Q.; Oble, J.; Poli G. *Org. Lett.* **2018**, *20*, 4057-4061. (c) Foschi, F.; Albanese, D.; Pecnikaj, I.; Tagliabue, A.; Penso, M. *Org. Lett.* **2017**, *19*, 70-73. (d) Mao, Z.; Martini, E.; Prestat, G.; Oble, J.; Huang, P.-Q.; Poli, G. *Tetrahedron Lett.* **2017**, *58*, 4174-4178. (e) Penso, M.; Foschi, F.; Pellegrino, S.; Testa, A.; Gelmi, M. L. *J. Org. Chem.* **2012**, *77*, 3454-3461.

(15) Åkermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729-5733.

(16) See Table S-1 of the Supporting Information for a complete list of the oxidizing agents used

(17) Compound **1e**, when treated with tiophenol in bases, to remove the o-nosyl group, furnished complex mixtures of degradation compounds.

(18) The aminohydroxylation reaction of aminoalkenes promoted by Pd(II)-catalyst in the presence of H_2O_2 is known in the literature (Zhu, H.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 1766-1769).

(19) Representative examples of intramolecular alkoxylation reactions from secondary ureas or amides: (a) Verniest, G.; Padwa, A. *Org. Lett.* **2008**, *10*, 4379-4382. (b) Yu, J.; Yang, H.; Fu, H. *Adv. Synth. Catal.* **2014**, *356*, 3669-3675. (c) Moon, N. G.; Harned, A. M. *Tetrahedron Lett.* **2013**, *54*, 2960-2963. (d) Gazzola, S.; Beccalli, E. M.; Borelli, T.; Castellano, C.; Chiacchio, M. S.; Diamante, D.; Broggini, G. *J. Org. Chem.* **2015**, *80*, 7226-7234.

(20) (a) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442-5445. (b) Zhu, H.; Chen, P.; Liu, G. *Org. Lett.* **2015**, *17*, 1485-1488. (c) Xie, M.-H.; Yang, X.-L.; Wu, C.-D. *Chem. Commun.* **2011**, *47*, 5521-5523. (d) Ouyang, L.; Li, J.; Zheng, J.; Huang, J.; Qi, C.; Wu, W.; Jiang, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 15926-

15930. (e) Huang, J.; Li, J.; Zheng, J.; Wu, W.; Hu, W.; Ouyang, L.; Jiang, H. *Org. Lett.* **2017**, *19*, 3354-3357.

(21) Reaction was carried out following aminoiodination conditions (Giofrè, S.; Sala, R.; Beccalli, E. M.; Lo Presti, L.; Broggini, G. *Helv. Chim. Acta* **2019**, *102*, e1900088) in the presence of NaN_3.

(22) For intramolecular palladium catalyzed alkene diamination reactions that proceed through Pd(IV) intermediates see: (a) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542-14543. (b) Streuff, J.; Hoovelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586-14587. (c)

(23) Liu, G.; Stahl, S. *J. Am. Chem. Soc.* **2006**, *128*, 7179-7181.

(24) This step implies the interaction between the nucleophile HOMO and the carbon-centered orbital involved in the C-N bond-forming step, which is expected to rise with the increasing softness of the nucleophile.