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Oxidative 1,4-Diamination of Dienes Using Simple Urea Derivatives

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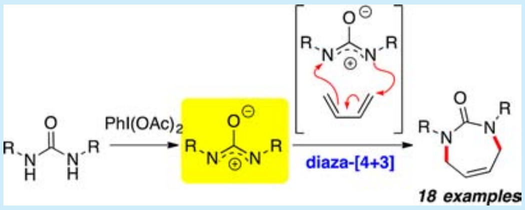
Supporting Information

ABSTRACT: Diamination of alkenes and dienes has found widespread use in the synthesis of biologically active target molecules. Although the 1,2-diamination of alkenes has been comprehensively explored, versatile methods that install higher order 1,*n*-diamine moieties (e.g., *n* = 3−5) are not broadly developed. Herein, we report the development of an oxidative 1,4-diamination of dienes. This method represents one of the scarce examples of exclusive regioselectivity for 1,4-diamination. The reaction is easy to perform, uses simple reagents, works with a variety of functionalized dienes, and provides unique heterocyclic products.

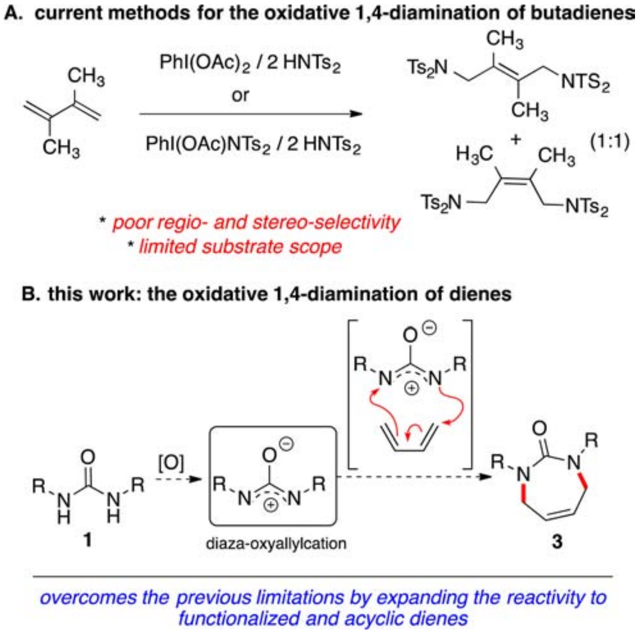


The direct 1,4-diamination of conjugated dienes represents a challenging but highly desirable strategy for the synthesis of biologically active molecules.[1,2] A few methods for the direct 1,4-diamination of dienes using metal catalysis have been reported.[3,4] Unfortunately, these methods suffer from a lack of regioselectivity and have a limited substrate scope. The development of new heterocycloaddition approaches using simple amination reagents represents an attractive solution for the 1,4-diamination of dienes.

Simple urea derivatives are common reagents used in 1,2 diamination reactions.[5,6] Our group has recently developed a new class of heterocycloaddition reactions that utilize aza-allylic cation intermediates as dienophiles for formal [4 + 3] cycloaddition.[7] The aza-allylic cations are generated by the dehydrohalogenation of halo alkylhydroxamate esters and are stabilized by *O*-alkyl substituents on the nitrogen atom. We recently found that diaza-oxyallylic cations underwent a [4 + 3]-cycloaddition reaction with cyclic dienes providing highly functionalized heterocyclic building blocks for organic synthesis.[7b,8] This reaction provided exclusive selectivity for the 1,4-functionalization process. However, it suffered from a limited substrate scope and poor regioselectivity in reactions with monosubstituted furans. These problems prompted our group to pursue methods for the direct oxidative 1,4-diamination of dienes using simple urea derivatives **1**.

Lishchynskyi, Muñiz, et al. have recently reported the oxidative 1,4-diamination of substituted butadienes using hypervalent iodide oxidants and sulfonimides. However, this method suffered from low regio- and stereoselectivity for the diamination process, resulting in a relatively low substrate scope (Scheme 1, panel A).[3a] Alternatively, reaction of an oxidatively generated diaza-oxyallylic cationic intermediate **2** with a diene would provide exclusive selectivity for the 1,4-difunctionalization product **3** due to the Woodward−Hoffmann requirements for the reaction of allylic cations with dienes (Scheme 1, panel B).[9]

Scheme 1. Previous Examples of an Oxidative 1,4-Diamination Reaction Using Sulfonimides (A) and Our Approach to This Transformation (B)



overcomes the previous limitations by expanding the reactivity to functionalized and acyclic dienes

Hypervalent iodide reagents are effective oxidants for the direct generation of stabilized *N*-acylnitrenium ions from the oxidation of *O*-alkyl hydroxamates.[10] It was our vision that the desired diaza-oxyallylic cation could be generated directly from a urea **1** through a series of deprotonation and oxidation events. Following this hypothesis, a solution of the *N*,*N*′-dibenzyloxyurea (**1**) and 2-methylfuran (**2a**) was treated with (diacetoxy)iodobenzene and 2,2,3,3-tetrafluoropropanoxide (TFP-Na) in 2,2,3,3-tetrafluoropropanol (TFP)[11] and provided the desired cycloadduct (**3a**) in 40% yield. This promising result motivated

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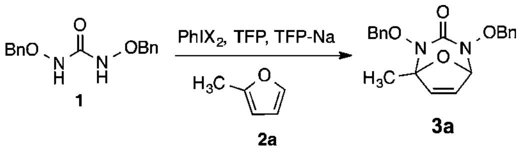
our efforts to optimize this reaction and explore the substrate scope.

Table 1. Optimization of the Oxidative Diamination Reaction of 2 Using *N*,*N*′-Dibenzyloxyurea (1)



oxidant[a]	diene (equiv)	addition time	temp (°C)	% yield
$PhI(OCOCF_3)_2$	5	3 h	0	
PhI(OH)(OTs)	5	3 h	0	
$PhI(tBuCO_2)_2$	5	3 h	0	52
$PhI(OAc)_2$	5	3 h	0	70
$PhI(OAc)_2$	5	3 h	−20	49
$PhI(OAc)_2$	5	3 h	25	67
$PhI(OAc)_2$	5	2 h	0	64
$PhI(OAc)_2$	5	6 h	0	54
$PhI(OAc)_2$	5	~1 min	0	40
$PhI(OAc)_2$	2	3 h	0	70
$PhI(OAc)_2$	0.5	3 h	0	42[b]
$PhI(OAc)_2$	1	3 h	0	
$PhI(OAc)_2$	1	3 h	0	69[c]

[a] 2.0 equiv of oxidant was used in each case. [b] Yield based upon stoichiometry of the urea. [c] Reaction was conducted by adding $PhI(OAc)_2$ to a solution of 2-methylfuran (**2**), the urea **1**, and base in tetrafluoropropanol.

Slow addition of the urea **1** was found to significantly increase the yield of the desired product (Table 1), presumably due to competitive oxidative decomposition of the urea by the hypervalent iodide reagent. Using other oxidants [PIFA, PhI(OH)(OTs), $PhI(tBuCO_2O)_2$] resulted only in diminished yields and revealed $PhI(OAc)_2$ as the optimal oxidant. A solvent screen revealed TFP as the optimal solvent. A diminished yield (56% cf. 70%) of the cycloadduct was obtained when the reaction was run without TFP-Na. Using 5.0 compared to 1.0 equiv of the diene had only a marginal effect on the yield of the cycloadduct. Addition of the oxidant to the diene and urea resulted in no significant improvement in yield in this case.

Cyclic dienes and aromatic heterocycles have proven to be optimal substrates for the [4 + 3] cycloaddition reaction of oxyallylic cations and related species.[7,9] Likewise, the oxidative diaza-[4 + 3] cycloaddition of **1** with aromatic heterocycles provided the diaminated product in good to excellent yield in all cases (Figure 1). Electron-rich and oxidatively labile furans required the addition of the $PhI(OAc)_2$ to a solution of the urea, base, and diene in order to achieve the best results (**3d** and **3j**, Figure 1). Furans substituted with electron-withdrawing groups, like carboxylate or a MIDA boronate, were found to be unreactive in the previous studies using *N*-chlorourea diamination agents.[7b] To our delight, the diamination of both methyl 2-furancarboxylate and 3-MIDA boronate substituted furan provided good to excellent yields of the desired cycloadduct (**3h** and **3k**, Figure 1). These examples demonstrate the high degree of functionality compatible with the reaction conditions and provide handles for the further functionalization of these scaffolds. Diamination of cyclic nonaromatic dienes was explored using the optimized conditions. All cyclic dienes provided good yields of the diaminated product (**3c**, **3l**, **3m**, **3n**, and **3o**, Figure 1). Fulvene and 2,2,2-spiroheptadiene were found to be unstable to $PhI(OAc)_2$ and required addition of the oxidant to a solution of the urea, diene, and base (**3m** and **3n**, Figure 1). The exclusive formation of the [4 + 3] cycloadduct with fulvene supports the proposal of a diaza-allylic cation intermediate. Oxidative diamination of cyclohexadiene derivatives provided excellent yields of the cyclic urea (**3l** and **3o**, Figure 1). In the case of α-phellandrene (**3l**, Table 2), the cycloaddition was diastereoselective (dr =70:30) for approach opposite of the isopropyl substituent.

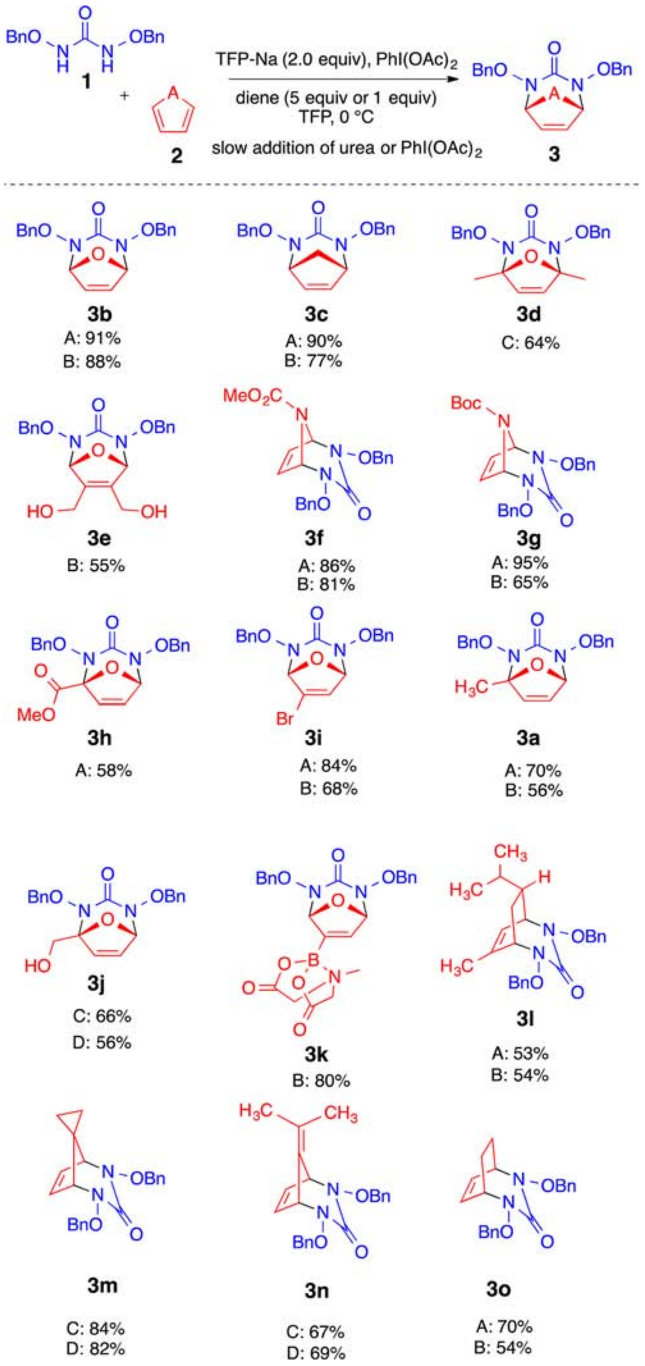
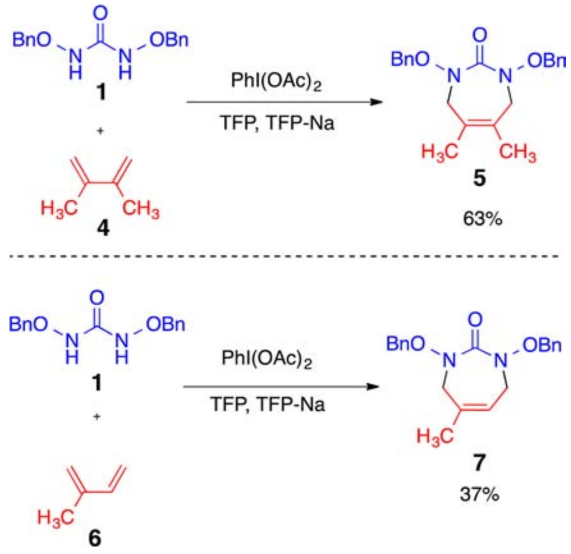


Figure 1. Scope of the oxidative 1,4-diamination reactions of *N*,*N*′-dibenzyloxyurea with cyclic aromatic dienes. (a) Conditions: A = slow addition of urea to 5.0 equiv of diene; B = slow addition of urea to 1.1 equiv of diene; C = slow addition of the $PhI(OAc)_2$ to diene (5.0 equiv) and urea; D = slow addition of $PhI(OAc)_2$ to the diene (1.1 equiv) and urea. (b) Yield based upon stoichiometry of the urea.

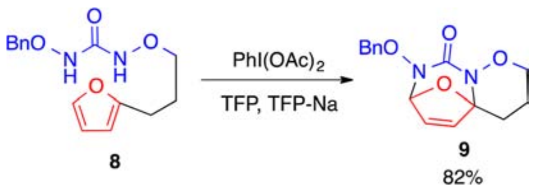
Acyclic dienes are not typically compatible reactants in [4 + 3] cycloadditions of allylic cations, including aza- and diaza-oxyallylic cations.[9] The reaction of isoprene **6** and 2,3-dimethylbutadiene **4** with the urea **1** provided the diaminated products in fair to good yield, representing one of few examples of a cycloaddition of an acyclic diene with an allylic cation (Scheme 2). The higher yield of the reaction with the 2,3-disubstituted butadiene **4** is attributed to the greater population of the reactive *s-cis* conformation. Other aminated byproducts are likely to account for the mass balance in the conversion of **6** to **7**. However, all attempts to recover byproducts from this reaction failed.

Scheme 2. Oxidative Diamination of Acyclic Dienes



Intramolecular tethering of amination agents has been established as an effective strategy to enforce regio- and stereoselectivity in C−H functionalization and 1,2-diamination reactions.[5,12] The competitive *N*-halogenation in the presence of dienes provides significant complications in rendering these aza-[4 + 3] reactions intramolecular. A direct oxidation would permit the intramolecular diaza-[4 + 3] cycloaddition reaction by avoiding prefunctionalization of the urea. The urea **8** was prepared from a known hydroxylamine[7c] in one step and was treated to the oxidative diamination conditions (Scheme 3).

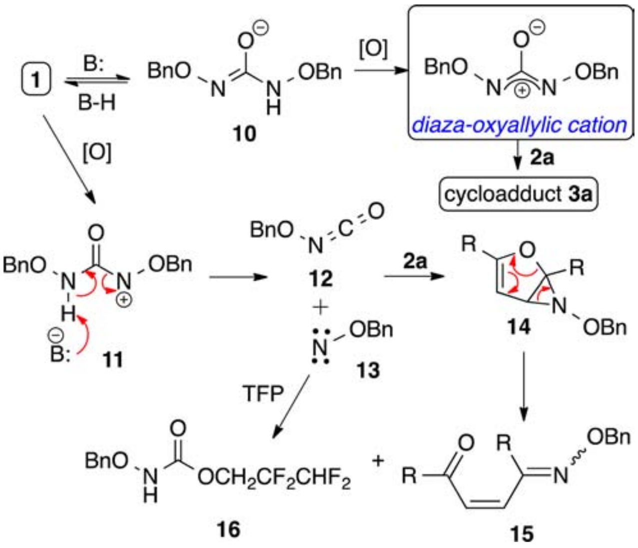
Scheme 3. Intramolecular Oxidative 1,4-Diamination Reaction



Consistent with our hypothesis, oxidation of the urea **8** with the established conditions provided the poly heterocyclic product **9** in excellent yield. Attempts to pursue the identical reaction through prechlorination of **8** were met with failure.

Mechanistically, we propose that the diamination is the result of a formal [4 + 3] cycloaddition reaction of a diaza-oxyallylic cation **8** (2π) and a diene (4π) (Scheme 4). Deprotonation and oxidation to form the azaoxyallylic cation could occur in any order. The observation of the byproducts **15** and **16** from the reaction with 2-methyl furan (**2a**) suggests that the order of events could play an important role in the product distribution. It is clear that the rate of addition is important to this process and that optimal results are obtained when the rate of addition of urea is equivalent or slower than the rate of consumption of the imidate **10**. This is supported by the observation of a greater proportion of the oxime **15** in the crude mixture when the urea **1** is added rapidly [50:50, 3a:15 (1 min addition) vs 70:30, 3a:15 (3 h addition)] and suggests that oxidation to the nitrenium **11**, decomposition of **11** to the nitrene **13**, aziridination of 2-methylfuran (**2a**), and ring opening of **14** is more favorable under these conditions. Alternatively, the ratio of **15** to **3a** could be determined by competitive elimination vs deprotonation of **11** to form **13** or the diaza-oxyallylic cation. While either pathway cannot be ruled out without further mechanistic study, it is clear by the isolation of the byproduct **15** that nitrene **13** and the desired diazaoxyallylic cation formation are competitive and favor cycloadduct formation under the optimized conditions. Ongoing investigations of this approach to the generation of *O*-alkoxynitrenes are underway.

Scheme 4. Plausible Mechanism for the Formation of the Diazaoxyallylic Cation and the Oxime 15



In conclusion, we have developed an oxidative 1,4-diamination reaction that uses a simple urea derivative and phenyl iododiacetate as the oxidant. The reaction is based upon the reactivity of diaza-allylic cations with 4-π reactants and provides exclusive selectivity for 1,4-difunctionalization. This reaction is simple to perform and provides good yields of functionalized heterocyclic products. The oxidative diamination was found be compatible with a number of substrates, including heterocyclic aromatics, cyclic, and acyclic dienes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and copies of spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) De Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067. (b) De Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190. (c) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (d) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (e) Kotti, S. R. S. S.; Timmons, C.; Guigen, L. *Chem. Biol. Drug Design* **2006**, *67*, 101−114.

(2) For examples of biologically active molecules containing 1,4-diamino motifs, see: (a) Xu, L.; Liu, H.; Murray, B. P.; Callebaut, C.; Lee, M. S.; Hong, A.; Strickley, R. G.; Tsai, L. K.; Stray, K. M.; Wang, Y. *ACS Med. Chem. Lett.* **2010**, *1*, 209. (b) Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N. *Science* **1994**, *263*, 380. (c) Oscarsson, K.; Oscarson, S.; Vrang, L.; Hamelink, E.; Hallberg, A.; Samuelsson, B. *Bioorg. Med. Chem.* **2003**, *11*, 1235. (d) Zuccarello, G.; Bouzide, A.; Kvarnström, I.; Niklasson, G.; Svensson, S. C. T.; Brisander, M.; Danielsson, H.; Nillroth, U.; Karlén, A.; Hallberg, A.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1998**, *63*, 4898.

(3) For examples of methods of 1,4-diamination of conjugated dienes, see: (a) Lishchynskyi, A.; Muñiz, K. *New J. Chem.* **2012**, *18*, 2212. (b) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335. (c) Bäckvall, J.-E.; Nyström, J. E. *J. Chem. Soc. Chem. Commun.* **1981**, 59. (d) Akermark, B.; Bäckvall, J.-E.; Löwenborg, A.; Zetterberg, K. *J. Organomet. Chem.* **1979**, *166*, 33.

(4) (a) Liu, B.; Li, K.-N.; Luo, S.-W.; Huang, J.-Z.; Pang, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 3323. (b) Hisashi, Y.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595 and references cited therein.

(5) (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 7125. (c) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147. (d) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945.

(6) (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523 and references cited therein. (c) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308.

(7) (a) Barnes, K. L.; Koster, A. K.; Jeffrey, C. S. *Tetrahedron Lett.* **2014**, *55*, 4690−4696. (b) Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc.* **2011**, *133*, 7688. (c) Jeffrey, C. S.; Anumandla, D.; Carson, C. R. *Org. Lett.* **2012**, *14*, 5764. (d) Achyara, A.; Eickhoff, J. A.; Jeffrey, C. S. *Synthesis* **2013**, *45*, 1825.

(8) Fishman, J. M.; Kiessling, L. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 5061.

(9) (a) Lohse, A. G.; Hsung, R. P. *Chem.—Eur. J.* **2011**, *17*, 3812. (b) Harmata, M. *Chem. Commun.* **2010**, 8904. (c) Harmata, M. *Chem. Commun.* **2010**, 8886 and references cited therein.

(10) (a) Wardrop, D. J.; Bowen, E. G. Synthetic Applications of Nitrenium Ions. In *Nitrenes and Nitrenium Ions*; Falvey, D. E., Gudmundsdottir, A. D., Eds.; Wiley: Weinhiem, 2013; pp 347−449. (b) Kikugawa, Y. *Heterocycles* **2009**, *78*, 571 and references cited therein.

(11) TFP is a solvent that can be purchased from SynQuest Laboratories for $ 0.07/g and has been demonstrated to be the optimal solvent of other [4 + 3] reactions, see: Föhlisch, B.; Gehrlach, E.; Geywitz, B. *Chem. Ber.* **1987**, *120*, 1815.

(12) Harvey, M. E.; Roizen, J. L.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911 and references cited therein.