Organic LETTERS

Letter

pubs.acs.org/OrgLett

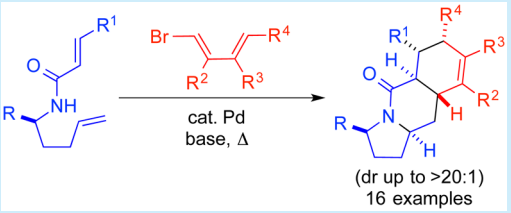
Synthesis of Polycyclic Nitrogen Heterocycles via Cascade Pd-Catalyzed Alkene Carboamination/Diels–Alder Reactions

Derick R. White and John P. Wolfe*

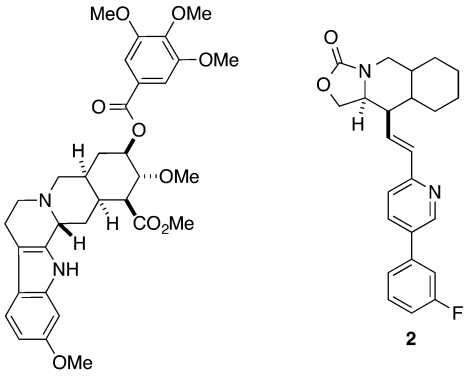
Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055, United States

Supporting Information

ABSTRACT: Cascade Pd-catalyzed alkene carboamination/Diels–Alder reactions between bromodienes and amines bearing two pendant alkenes are described. These transformations generate 4 bonds, 3 rings, and 3–5 stereocenters to afford polycyclic nitrogen heterocycles with high diastereoselectivity.



Polycyclic scaffolds that contain a nitrogen heterocycle fused to a six-membered carbocycle are common features of many biologically active molecules. These structures are displayed in natural products such as the yohimbine alkaloids (e.g., reserpine, **1**)[1] and molecules of potential pharmaceutical relevance such as thrombin receptor antagonist **2**.[2]

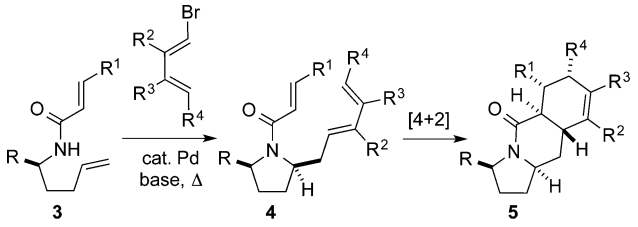


Reserpine, **1**

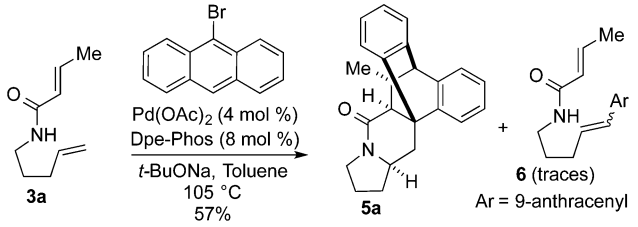
2

Our group has previously illustrated that Pd-catalyzed alkene carboaminations between aryl or alkenyl halides or triflates and alkenes bearing pendant nitrogen nucleophiles are a concise, efficient, and stereoselective means of generating nitrogen heterocycles.[3,4] We reasoned that coupling our Pd-catalyzed alkene carboamination method with a Diels–Alder cycloaddition could provide a rapid and efficient approach to the synthesis of polycyclic heterocycles with a high degree of stereocontrol. As shown in Scheme 1, a γ-aminoalkene derivative such as **3**, which bears a second pendant alkene unit, could be coupled with a bromodiene in the presence of a Pd-catalyst and a base to afford intermediate **4**. This intermediate could then undergo a Diels–Alder [4 + 2] cycloaddition[5] to yield **5**. Our prior studies have illustrated that most Pd-catalyzed alkene carboamination reactions proceed with high diastereoselectivity, and examples of stereocontrolled intramolecular Diels–Alder reactions are well-established. In addition, a few prior examples of Pd-catalyzed cross-coupling/Diels–Alder reactions supported the overall feasibility of this transformation.[6] Importantly, given the broad scope of the carboamination reactions, this strategy should not be limited to the synthesis of polycyclic pyrrolidine derivatives such as **5**, but rather a much broader array of heterocyclic architectures could be obtained by employing different alkene-tethered nucleophiles.

Scheme 1. Cascade Carboamination/Diels–Alder Reaction



Scheme 2. Preliminary Experiment: Optimal Conditions

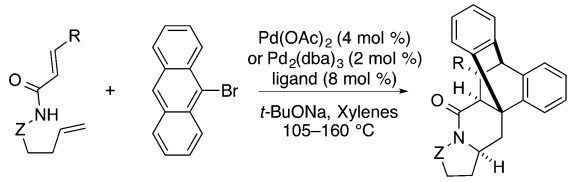


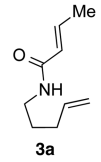
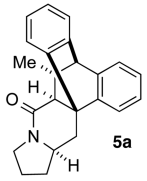
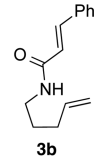
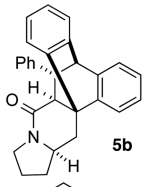
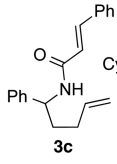
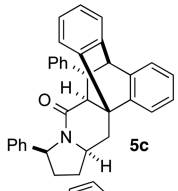
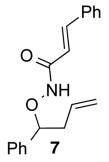
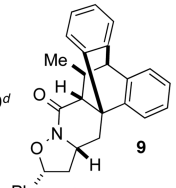
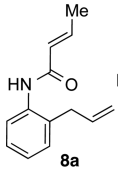
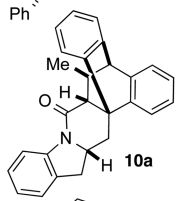
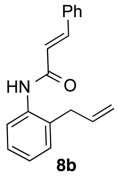
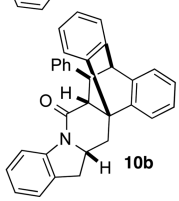
In our initial experiments we elected to employ 9-bromoanthracene as the bromodiene substrate, as this compound is commercially available and would allow us to explore the diastereoselectivity (relative face selectivity) of the Diels–Alder reaction in a simple system with no possible stereoisomers resulting from *endo*- vs *exo*-cycloaddition. As shown in Scheme 2, after exploring a range of phosphine

Received: March 27, 2015

DOI: 10.1021/acs.orglett.5b00896
Org. Lett. XXXX, XXX, XXX–XXX

Table 1. Cascade Carboamination/Diels–Alder Reactions of Amides and Hydroxylamines[a]

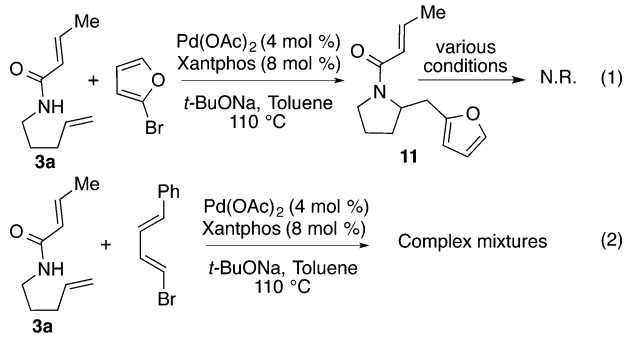


substrate	ligand	t (°C)	product	dr[b]	yield (%)[c]
 **3a**	Dpe-Phos	105	 **5a**	>20:1	57
 **3b**	Xantphos	130	 **5b**	>20:1	64
 **3c**	Cy_4Dpe-Phos	130	 **5c**	5:1	77
 **7**	RuPhos	90-130[d]	 **9**	>20:1 (3.5:1)[e]	39 51[e]
 **8a**	Dpe-Phos	130	 **10a**	>20:1	52
 **8b**	Dpe-Phos	160	 **10b**	>20:1	55

[a]Conditions: 1.0 equiv of substrate, 2.0 equiv of 9-bromoanthracene, 2.0 equiv of *t*-BuONa, 4 mol % $Pd(OAc)_2$ or 2 mol % $Pd_2(dba)_3$, 8 mol % ligand, xylenes (0.07 M), 24 h. [b]Diastereomeric ratio of isolated material. Diasteromeric ratios were similar for crude reaction mixtures unless otherwise noted. [c]Isolated yield (average of two experiments). [d]The reaction was conducted at 90 °C for 24 h until the carboamination step had proceeded to completion, then 1 equiv of LiOTf was added to the reaction mixture, and the temperature was increased to 130 °C for an additional 24 h. [e]Diastereomeric ratio and yield for initial purification in which diastereomers were not separated. One pure diastereomer was isolated following a second chromatography

ligands, palladium precatalysts,[7] and reaction conditions for the coupling of **3a** with 9-bromoanthracene we discovered that the best results were obtained using a catalyst composed of $Pd(OAc)_2$ and Dpe-Phos. Other phosphine ligands provided various amounts of Heck arylation side product **6** or failed to efficiently promote the carboamination step.

Scheme 3. Limitations



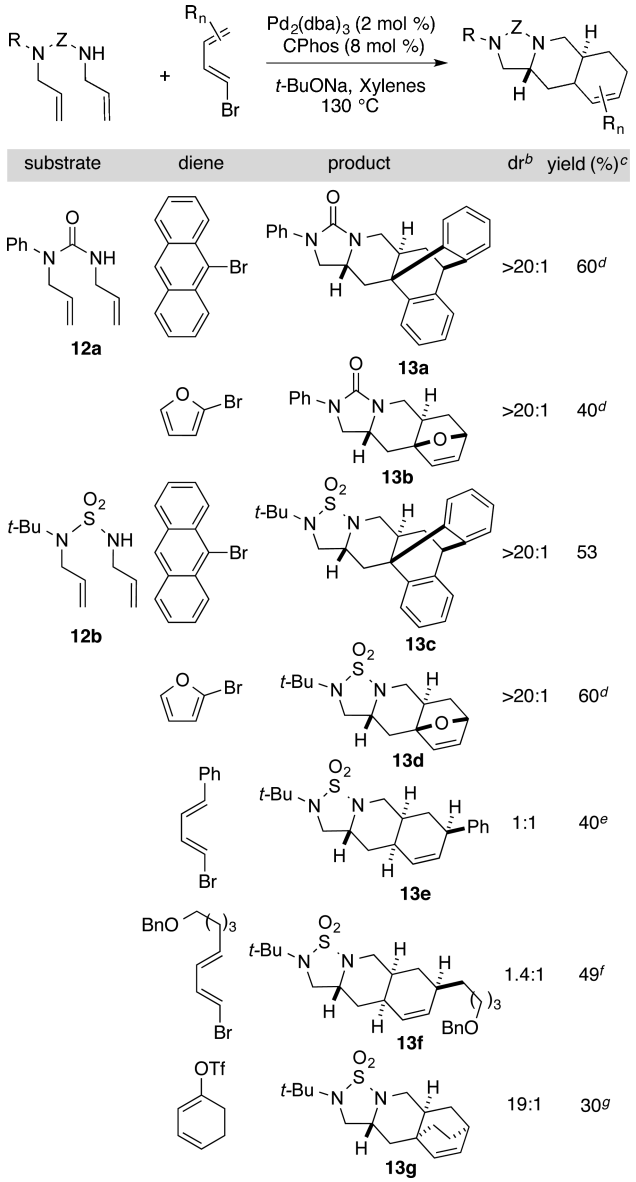
Once suitable reaction conditions had been identified we began to explore the scope of this one-pot reaction sequence. Since chemical yields were modest in some instances, a few different phosphine ligands were examined for most substrate combinations. The Dpe-Phos ligand provided satisfactory results in most cases, but for some substrates other ligands such as Xantphos, Cy_4Dpe-Phos, or RuPhos proved superior. As shown in Table 1, pentenylamine derivatives **3a–b** bearing a *N*-crotonyl group or an *N*-cinnamyl group were coupled with 9-bromoanthracene to afford polycyclic products **5a–b** with high diastereoselectivity.[8] The presence of a phenyl substituent adjacent to the N-atom was tolerated in the reaction of **3c**, although the desired product **5c** was generated with lower, but still useful, diastereoselectivity (5:1 dr). A similar outcome was observed in the reaction of 3-phenylhydroxylamine derived substrate **7** (3.5:1 dr). In both of these cases the diminished stereocontrol occurred during the Diels–Alder step, as the diasteromeric products differed in the configuration of the stereocenters generated in the cycloaddition relative to those formed in the carboamination step. Substrates **8a–b** obtained via acylation of 2-allylaniline also underwent the carboamination/Diels–Alder reaction sequence to afford **10a** and **10b** in moderate yield and high dr. In most instances satisfactory outcomes were achieved simply through extended heating of the reaction mixture at a constant temperature (usually 130 °C). However, for substrate **7** the best results were obtained when the carboamination step was conducted at 90 °C until the substrate had been completely consumed, at which point 1 equiv of LiOTf was added and the temperature was raised to facilitate the cycloaddition.[9]

Although the cascade reactions between 9-bromoanthracene and **3a–c**, **7**, and **8a–b** were reasonably efficient, efforts to extend these transformations to other bromodienes were less successful. For example, the Pd-catalyzed carboamination of **3a** with 2-bromofuran proceeded in good yield to afford **11** (Scheme 3, eq 1), but the Diels–Alder cycloaddition of this compound was not achieved even under forcing conditions (170 °C, microwave irradiation).[10] Efforts to employ non-aromatic bromodienes such as 1-bromo-4-phenylbutadiene in the carboamination reactions of **3a–c**, **7**, or **8a–b** led to the formation of complex mixtures of products even at relatively low temperatures (Scheme 3, eq 2).

Given these limitations, we elected to explore the reactivity of urea or sulfamide derived substrates, as our prior studies had illustrated these types of substrates can be efficiently coupled with various alkenyl bromides. As shown in Table 2, *N,N′*-

DOI: 10.1021/acs.orglett.5b00896
Org. Lett. XXXX, XXX, XXX–XXX

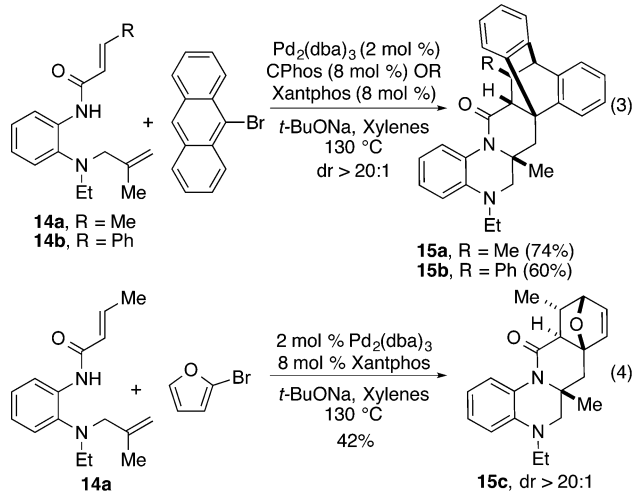
Table 2. Cascade Carboamination/Diels–Alder Reactions of Ureas and Sulfamides[a]



[a]Conditions: 1.0 equiv of substrate, 2.0 equiv of bromodiene, 2.0 equiv of *t*-BuONa, 2 mol % $Pd_2(dba)_3$, 8 mol % ligand, xylenes (0.07 M), 24 h. [b]Diastereomeric ratio of isolated material. Diasteromeric ratios were similar for crude reaction mixtures unless otherwise noted. [c]Isolated yield (average of two experiments). [d]The reaction was conducted at 70 °C for 24 h until the carboamination step had proceeded to completion, and then the temperature was increased to 130 °C for an additional 24 h. [e]The reaction was conducted for 48 h. [f]The reaction was conducted using $P(2\text{-furyl})_3$ as a ligand. [g]The reaction was conducted using 4 mol % $Pd(OAc)_2$, 12 mol % CPhos, 2 equiv *t*-BuOLi, and trifluorotoluene (0.7 M).

diallylureas and sulfamides proved to be viable substrates for the cascade Pd-catalyzed carboamination/Diels–Alder reactions, with a broader substrate scope than was observed with **3a–c**, **7**, and **8a–b**. Reactions of **12a** or **12b** with 9-bromoanthracene or 2-bromofuran proceeded in moderate to good yield and high diastereoselectivity to afford polycyclic products **13a–d**. In some instances the best results were obtained when the carboamination step was conducted at relatively low temperature (70 °C) until the starting material had been consumed, at which time the temperature was raised to promote the Diels–Alder reaction.[7] This protocol helped to minimize competing base-mediated alkene isomerization. Substrate **12b** was successfully coupled with nonaromatic bromodienes to yield **13e** and **13f**. However, in these cases diastereoselectivity was poor (ca. 1:1), presumably due to a low preference for *exo*- vs *endo*-cycloaddition pathways. Finally, cyclohexadienyl triflate also proved to be a viable electrophile in a cascade reaction with **12b**; product **13g** was generated in 30% yield and 19:1 dr. In this case use of modified reaction conditions, in which *t*-BuOLi and $PhCF_3$ were employed as base and solvent, provided results superior to those obtained using standard conditions.

Scheme 4. Transformations of Phenylenediamine Derivatives



Finally, we briefly explored the formation of six-membered heterocycles using the cascade reaction sequence. Phenylenediamine derivatives **14a–b** were converted to polycyclic products **15a–c** in moderate to good yield with excellent diastereoselectivity (Scheme 4, eqs 3–4). Unfortunately, efforts to employ nonaromatic bromodienes with these substrates did not provide satisfactory results.

In conclusion, we have developed a concise approach to the stereocontrolled synthesis of polycyclic heterocycles via a cascade Pd-catalyzed alkene carboamination/Diels–Alder reaction sequence. The transformations effect the formation of 4 bonds, 3 rings, and 3–5 stereocenters with high levels of diastereoselectivity in most cases examined. Future studies will be directed toward expanding the scope of these reactions to a broader array of diene electrophiles and further exploration of the substrate scope.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, and copies of ^1H and ^{13}C NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00896.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jpwolfe@umich.edu.

DOI: 10.1021/acs.orglett.5b00896
Org. Lett. XXXX, XXX, XXX–XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the NIH (GM 071650) for financial support of this work.

■ REFERENCES

(1) Chan, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671−4706.
(2) Chackalamannil, S.; Wang, Y. U.S. Patent 20070149518A1, June 28, 2007, *Scifinder Scholar* 147:118210.
(3) For reviews on Pd-catalyzed carboamination reactions, see: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571−582. (b) Wolfe, J. P. *Synlett* **2008**, 2913−2937. (c) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351−361. (d) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1−38.
(4) For examples of Pd-catalyzed carboamination reactions that afford *N*-acyl pyrrolidines, isoxazolidines, imidazolidin-2-ones, cyclic sulfamides, or dihydroquinoxalines, see: (a) Bertrand, M. B.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447−6459. (b) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533−2540. (c) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531−2534. (d) Fornwald, R. M.; Fritz, J. A.; Wolfe, J. P. *Chem.—Eur. J.* **2014**, *20*, 8782−8790. (e) Hopkins, B. A.; Wolfe, J. P. *Chem. Sci.* **2014**, *5*, 4840−4844.
(5) For recent reviews on the intramolecular Diels−Alder reaction, see: (a) Parvatker, P. T.; Kadam, H. K.; Tilve, S. G. *Tetrahedron* **2014**, *70*, 2857−2888. (b) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983−2992. (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807.
(6) (a) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317−3320. (b) Brückner, S.; Abraham, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2002**, *4*, 3391−3393. (c) de Meijere, A.; von Zezschwitz, P.; Brase, S. *Acc. Chem. Res.* **2005**, *38*, 413−422. (d) von Zezschwitz, P.; de Meijere, A. *Top. Organomet. Chem.* **2006**, *19*, 49−89. (e) D'Souza, D. M.; Kiel, A.; Herten, D.-P.; Rominger, F.; Mueller, T. J. J. *Chem.—Eur. J.* **2008**, *14*, 529−547. (f) D'Souza, D. M.; Rominger, F.; Mueller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153−158.
(7) See the Supporting Information for a table describing details of optimization studies.
(8) For examples of intramolecular Diels−Alder reactions of anthracene, see: Ciganek, E. *J. Org. Chem.* **1980**, *45*, 1497−1505.
(9) For examples of lithium ion-accelerated Diels−Alder reactions, see: (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595−4596. (b) Auge, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. *Synlett* **2000**, 877−879. (c) Nair, V.; Maliakal, D.; Treesa, P. M.; Rath, N. P.; Eigendorf, G. K. *Synthesis* **2000**, 850−856.
(10) For examples of intramolecular Diels−Alder reactions of furan, see: Padwa, A.; Flick, A. C. *Adv. Heterocycl. Chem.* **2013**, *110*, 1−41.

DOI: 10.1021/acs.orglett.5b00896
Org. Lett. XXXX, XXX, XXX−XXX