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Complex Polycyclic Scaffolds by Metathesis Rearrangement of Himbert Arene/Allene Cycloadducts

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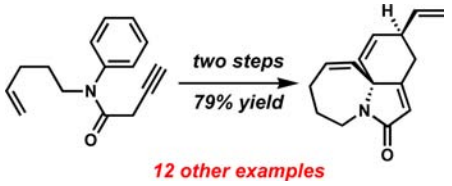
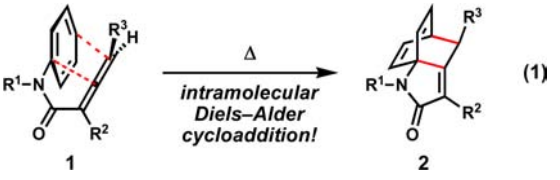
ABSTRACT



The intramolecular arene/allene cycloaddition first described 30 years ago by Himbert and Henn permits rapid access to strained polycyclic compounds. Alkene metathesis processes cleanly rearrange appropriately substituted cycloadducts into complex, functional-group-rich polycyclic lactams of potential utility for natural product synthesis and medicinal chemistry.

In certain instances, dearomatization of simple benzene rings via pericyclic reactions can be facile. For example, the aromatic Claisen rearrangement results in the transient loss of aromaticity, and in some cases, the barrier to these processes can be surprisingly low.[1] Of course, in these and related sigmatropic rearrangements, a facile mechanism for restoration of aromaticity is usually available, positively affecting the equilibrium of the overall process. Cycloaddition reactions to aromatic rings are also well-known but are most common in extended aromatic systems or heteroaromatic rings with somewhat compromised aromatic stabilization, such as anthracene[2] or furan,[3] respectively, or those that provide a postcycloaddition–fragmentation pathway to generate a new aromatic system, as with six-membered-ring azadienes.[4] Certain transition metal complexes of benzene also undergo Diels–Alder reactions with potent dienophiles.[5] On the other hand, direct thermal cycloadditions to simple carbocyclic aromatic nuclei are rare, and it seems reasonable to credit both high kinetic barriers and unfavorable equilibria with the apparent dearth of reports of these reactions.[6–8]

Three decades ago, Himbert and Henn disclosed a fascinating thermal intramolecular Diels–Alder cycloaddition of allenecarboxanilides (eq 1).[9] This reaction



(1)

[†] These authors contributed equally.

(1) For example, the aromatic Claisen reaction of a tyrosine-derived reverse-prenyl ether occurs under "physiological conditions" (37 °C in aqueous buffers): McIntosh, J. A.; Donia, M. S.; Nair, S. K.; Schmidt, E. W. *J. Am. Chem. Soc.* **2011**, *133*, 13698–13705.

(2) See: Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; Wiley & Sons: New York, 1990; Section 6.2 "Aromatic Hydrocarbons"; pp 262–275.

(3) For a review of furan Diels–Alder reactions, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233.

(4) For a review of the cycloaddition reactivity of heterocyclic azadienes, see: Boger, D. L. *Chem. Rev.* **1986**, *86*, 781–793.

(5) For a representative example, see: Chordia, M. D.; Smith, P. L.; Meiere, S. H.; Sabat, M.; Dean Harman, W. *J. Am. Chem. Soc.* **2001**, *123*, 10756–10757.

(6) Photochemically induced cycloadditions to simple benzene rings, especially the arene–olefin photocycloaddition, are well-known but most often provide the *meta*-regioisomer. For reviews, see: (a) Wender, P. A.; Ternansky, R.; deLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* **1990**, *62*, 1597–1602. (b) Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615–669. (c) Hoffmann, N. *Synthesis* **2004**, 481–495. (d) Streit, U.; Bochet, C. G. *Beilstein J. Org. Chem.* **2011**, *7*, 525–542.

(7) For a recent interesting intramolecular dearomatizing 1,3-dipolar cycloaddition of a nitrile oxide to an unactivated benzene ring, see: Yonekawa, M.; Koyama, Y.; Kuwata, S.; Takata, T. *Org. Lett.* **2012**, *14*, 1164–1167.

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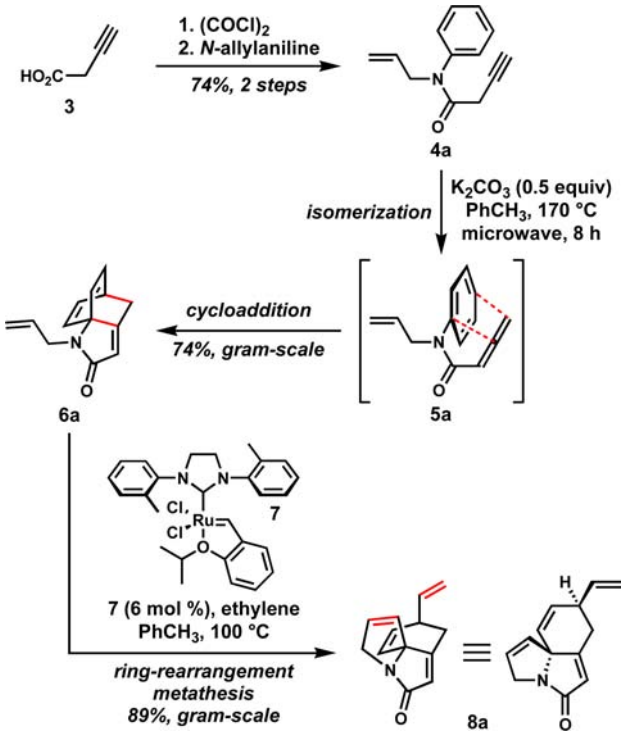
efficiently dearomatized the unactivated benzene ring without recourse to oxidative, reductive, or photochemical conditions, nor did it take advantage of an arene with low aromatic stabilization or with the ability to engage in a post-cycloaddition thermodynamically favored process.[10] This unusual reaction rejects the conventional wisdom that "normal" benzene rings do not readily behave as dienes in the Diels–Alder reaction. Furthermore, it provides easy access to complex polycycles from readily available starting materials. The scope of the reaction is relatively broad with respect to substitution both on the arene and on the allene; furthermore, ester, thioester, imide, phosphinamide, and phosphinic ester tethers can be used in place of the amide.[11] Extensive studies of the reaction characteristics can be found in more than 20 publications from the Himbert group since their first disclosure;[11−13] this significant body of work has apparently gone largely unappreciated by organic chemists—to date, we are unaware of any applications of this complexity-generating transformation.

Scheme 1. Facile Synthesis of Cycloaddition Precursors, Tandem *in Situ* Allene Formation and Cycloaddition, and Metathesis Rearrangement



Our laboratory is interested in underutilized processes that permit the conversion of readily available aromatic systems into complex organic scaffolds.[14] In that context, we became intrigued by the idea of using Himbert cycloadducts as starting points for the synthesis of topologically and stereochemically complex molecules that might find application in natural product synthesis and medicinal chemistry. Our first efforts involved alkene-metathesis-based rearrangement reactions of these cycloadducts;[15,16] our initial results are described in this communication.

The Himbert group used a variety of methods to access the allene-containing cycloaddition substrates. Most often, they performed Wittig olefination reactions on *in situ* generated ketenes,[11a,b] and they also took advantage of the reactivity of silylated ynamines with ketenes that they had developed themselves.[11c] While these methods certainly enabled access to a variety of substrates, we sought more general preparations of a broad range of allenecarboxylic acid derivatives. We have found that readily available deconjugated alkynoic amides can be easily isomerized to the desired allenes (**4a** → **5a**, Scheme 1).[17] As a result, acylation of the corresponding aniline provides straightforward access to allene precursors. An *in situ* base-catalyzed isomerization/cycloaddition reaction serves to convert alkynes of type **4** directly into the Himbert cycloadducts; for example, **6a** is generated in good yield on gram scale in this manner. With the appropriately tethered alkene included in the cycloaddition substrate, the cycloadduct is poised for rearrangement via alkene metathesis. After significant screening efforts, we found that the Hoveyda–Grubbs-type ruthenium catalyst **7**[18] smoothly converted the lactam cycloadduct **6a** into the complex polycyclic product **8a**.

(8) For a review describing synthetic equivalents to "cyclohexatriene" for Diels–Alder cycloadditions, see: Cossu, S.; Fabris, F.; De Lucchi, O. *Synlett* **1997**, 1327–1334.

(9) Himbert, G.; Henn, L. *Angew. Chem., Int. Ed.* **1982**, *21*, 620.

(10) Of course, there are special features of this substrate that presumably aid in the success of the reaction. The high energy of allenes relative to normal alkenes and the likely diminished entropy of activation from the near perfect alignment of the *sp*-hybridized allene carbon with the *ipso*-carbon of the arene, when the tether is oriented appropriately, are probable contributors to the high reactivity.

(11) Selected, particularly relevant references: (a) Himbert, G.; Diehl, K.; Maas, G. *J. Chem. Soc., Chem. Commun.* **1984**, 900–901. (b) Himbert, G.; Fink, D. *Tetrahedron Lett.* **1985**, *26*, 4363–4366. (c) Henn, L.; Himbert, G.; Diehl, K.; Kaftory, M. *Chem. Ber.* **1986**, *119*, 1953–1963. (d) Himbert, G.; Diehl, K.; Schlindwein, H.-J. *Chem. Ber.* **1986**, *119*, 3227–3235. (e) Himbert, G.; Fink, D.; Diehl, K. *Chem. Ber.* **1988**, *121*, 431–441. (f) Himbert, G.; Fink, D. *Z. Naturforsch., B: Chem. Sci.* **1994**, *49*, 542–550. (g) Himbert, G.; Fink, D. *J. Prakt. Chem.* **1996**, *338*, 355–362. (h) Himbert, G.; Ruppmich, M.; Knöringer, H. *J. Chin. Chem. Soc.* **2003**, *50*, 143–151.

(12) Please see the Supporting Information for the complete listing of the Himbert group references that describe this body of work.

(13) The Orahovats group also studied related cycloadditions in work that began after that of the Himbert group: (a) Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1986**, *69*, 1585–1587. (b) Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1987**, *70*, 262–270. (c) Trifonov, L. S.; Simova, S. D.; Orahovats, A. S. *Tetrahedron Lett.* **1987**, *28*, 3391–3392. (d) Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1987**, *70*, 1732–1736. (e) Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1989**, *72*, 59–64.

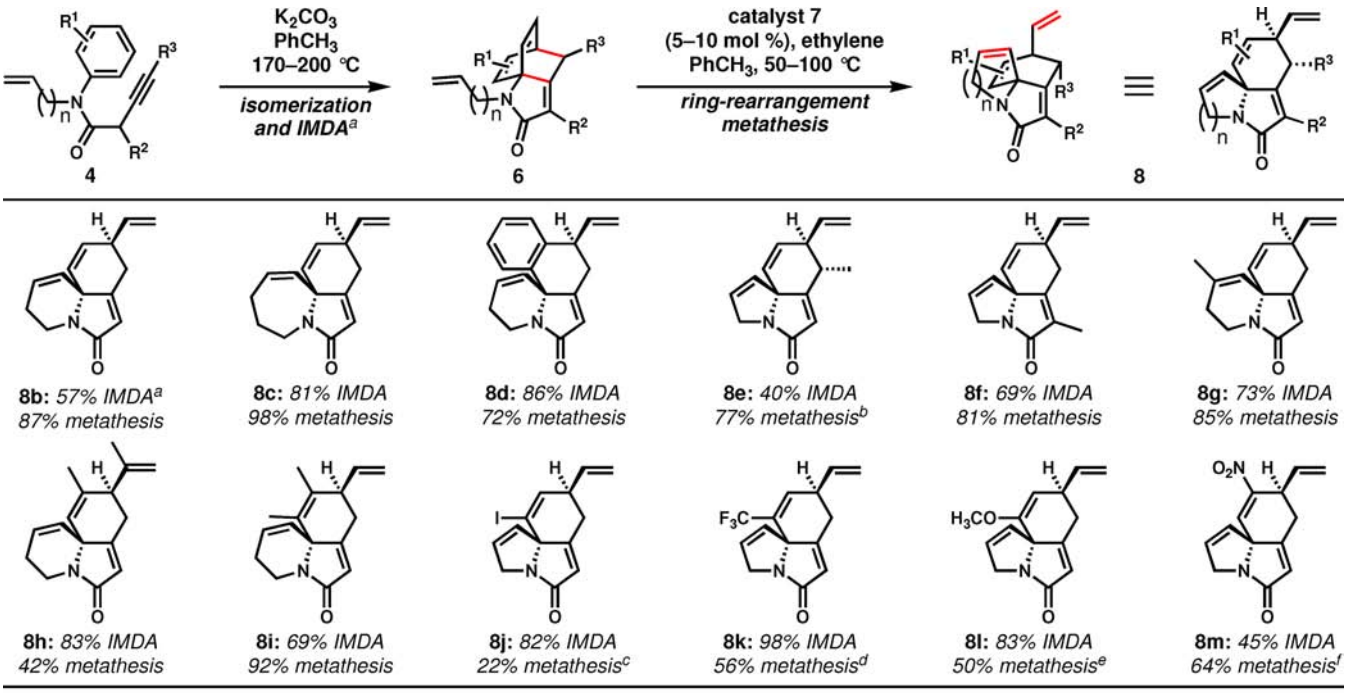
(14) Vanderwal, C. D. *J. Org. Chem.* **2011**, *76*, 9555–9567.

(15) For the first example of the merger of Diels–Alder cycloadditions with metathesis processes in the context of complex molecule synthesis, see: Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855–856.

(16) For some recent outstanding examples of cycloaddition/metathesis rearrangement strategies applied to complex natural product synthesis, see: (a) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334–5335. (b) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094–1095. (c) Henderson, J. A.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8499–8501.

(17) (a) Eglington, G.; Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3197–3200. (b) Hashmi, A. S. K. In *Modern Allene Chemistry*, Vol. 1; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: 2004; pp 3–50.

(18) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592.



a. IMDA = intramolecular Diels–Alder reaction. *b*. IMDA was 52% yield from preformed allene. *c*. 62% recovered starting material from metathesis reaction. *d*. 25% recovered starting material from metathesis reaction. *e*. >10:1 metathesis chemoselectivity. *f*. X-ray structure obtained.[20]

Figure 1. Cycloadditions of *in situ* generated allenecarboxanilides and subsequent alkene metathesis-based rearrangements to generate complex polycyclic lactams (for specific reaction temperatures and times, as well as the X-ray structure of **8m**; please see the Supporting Information).

The two-stage sequence depicted in Scheme 1 proved to be very general, with an additional dozen examples shown in Figure 1. We note the similarity of these architectures to members of the *Erythrina* alkaloids,[19] a large family of natural products, many of which demonstrate interesting biological activities. The two-step sequence generates a variety of ring sizes (see **8a**–**c**), accommodates a broad range of substitution patterns on the arene and allene (see **8e**–**i**), and tolerates a significant range of functional groups (halides, trifluoromethyl, methoxy, and nitro groups; see **8j**–**m**), permitting access to a large collection of complex polycyclic lactams. This diversity of output is readily available from simple starting materials, and an even greater range of product scaffolds can be contemplated when different tethers for both the cycloaddition and the metathesis events are studied. Confirmation of structural identity rests on supportive NMR and mass spectrometric data, as well as X-ray crystallographic analysis of **8m**.[20]

We have used the arene/allene cycloaddition discovered by Himbert to access strained polycyclic lactams that undergo rearrangement by alkene metathesis processes. A key advance put forth herein involves the *in situ* generation of the allene dienophiles from deconjugated alkynes under the conditions for cycloaddition. The topologically complex products[21] that result are available in only two steps from simple starting materials and hold promise for applications in natural product synthesis and medicinal chemistry. The structural similarity of these compounds to members of the *Erythrina* family of alkaloids, many of which exhibit interesting neurobiological activities, suggest the possibility that our products might provide useful lead compounds in this area. This two-step sequence is remarkably general with respect to substitution patterns and is tolerant of a variety of functional groups.

This study constitutes our first foray into the strain-driven rearrangement chemistry of Himbert cycloadducts; given the success of the metathesis reactions, we anticipate access to myriad structures via anion-, cation-, radical-, or transition-metal-mediated rearrangements. In ongoing studies, we are evaluating other tether systems and are also engaged in mechanistic studies of both the cycloaddition and the metathesis rearrangement steps. That work, and applications of the chemistry described herein, will be the subject of future disclosures.

Acknowledgment. We thank Dr. Joe Ziller (UCI) for X-ray crystallographic analysis of **8m**. We acknowledge the NSERC of Canada for a graduate fellowship (J.K.L.)

(19) Parsons, A. F.; Palframan, M. J. *Alkaloids* **2010**, *68*, 39–81.

(20) The crystal structure of compound **8m** has been deposited at CCDC under number 897822.

(21) For a recent example of a complexity building strategy that converts arenes via oxidative dearomatization into products similar to ours, see: Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487–1490.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds, and CIF data for compound **8m**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.