JOC Perspective

pubs.acs.org/joc

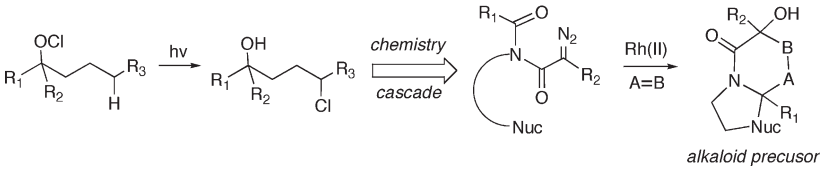
A Chemistry Cascade: From Physical Organic Studies of Alkoxy Radicals to Alkaloid Synthesis†

Albert Padwa

Department of Chemistry, Emory University, Atlanta Georgia 30322

chemap@emory.edu

Received June 17, 2009



In this Perspective, I present a personal account of a succession of chemical projects that I was involved with, each of which triggered or initiated my next research undertaking. It started with my early work in the field of physical organic photochemistry, which, in turn, guided me to my current research dealing with the synthesis of biologically active alkaloids. The article highlights some of the dominant themes of my research program over the past 48 years. Subject matter that is discussed includes the generation of reactive intermediates by photoexcitation, [1,3]-dipolar cycloaddition chemistry, rhodium(II)-catalyzed domino reactions of α-diazo carbonyl compounds, intramolecular [4 + 2]-cycloaddition of 2-amidofurans, and the utilization of various thio fragments for the synthesis of nitrogen heterocycles.

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

"*How did you get here from there?*" is a question often asked of one who has achieved what passes for "*success*". That question assumes there is a rational explanation which, once understood, can help others become "*successful*". However, the most truthful response to this question is simply "*the randomness of life is primarily responsible for change*". Retracing a road traveled over the past 50 years provides for a nostalgic journey, both in terms of the scientific challenges along the way as well as the many pleasant interactions with numerous colleagues and collaborators who passed through my "*space*" at three different universities. This perspective constitutes a personal account of how our current projects in the area of heterocyclic synthesis of natural products developed over a period of five decades. It begins with some of the early success we achieved in the area of physical organic radical chemistry that eventually led us into the field of alkaloid synthesis.

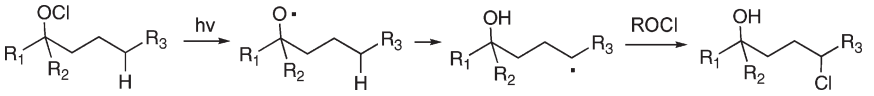
I was drawn to chemistry as a young student attending William Howard Taft High School in New York City in 1954. I found that I enjoyed science; it came to me easily and it was fun. After graduation from Taft, I enrolled as an undergraduate at Columbia University. I was a student there from 1955 to 1959 and lived at the AEΠ fraternity house with a cluster of frat brothers. The intellectual climate in the fraternity house was vibrant and full of debate and discussion about society, politics, life, and even organic chemistry since many of my premed contemporaries had signed up for that required course. My enjoyment of chemistry turned to a passion when I met my first great teacher, Julian Miller, at Columbia University in 1955 who taught an outstanding general chemistry course. Together with two other Columbia classmates (Roald Hoffmann (Cornell) and Bob Pecora (Stanford), class of 59), we three successfully completed all of the requirements for a BA major in chemistry. I was fortunate to take the follow-up sophomore organic chemistry class from Cheves Walling, one of the great pioneers of free radical chemistry. He subsequently invited me to do research with him on hypochlorite chemistry in my junior year at Columbia.

As a rather provincial native New Yorker I did not want to go elsewhere for my graduate studies and elected to stay on at

† I was honored to have been asked to chair the morning session of the Centennial Symposium of the Division of Organic Chemistry at the 236th ACS National Meeting in Philadelphia on August 18, 2008. This perspective was written in response to that invitation and presents a personal account of my research program over the past 48 years. To further celebrate ORGN's Centennial, a series of video interviews of the participants, including myself, of the symposium were conducted and are now available via the ORGN website: http://organicdivision.org/.

DOI: 10.1021/jo901300x Published on Web 08/10/2009
© 2009 American Chemical Society

SCHEME 1



Columbia working with Cheves for my Ph.D. from the fall of 1959 until the summer of 1962. My Ph.D. dissertation was on "*Some Reactions of Organic Hypohalites*", which was a classical physical organic investigation of alkoxy radical behavior including fragmentation and intramolecular hydrogen transfer studies (Scheme 1). Although the Walling hypochlorite C−H activation reaction[1] was published in the same issue of *The Journal of the American Chemical Society* (1961) as the related Barton reaction,[2] it attracted far less attention from the synthetic community. Clearly, the clever "*chemical packaging*" by Barton starting with steroidal alcohols for the key internal H-transfer step was well appreciated and duly recognized by the organic community and also provided me with a good lesson for my future research.

Cheves Walling (Figure 1) was a wonderful mentor but not a particularly demanding research supervisor. Students in his group worked on their own and were encouraged to develop their individual passion for the discipline. Over the years, Cheves has been described as a "deep thinker, a low-key mischievous child, a founding father of free radical chemistry, a statesman in the world of science, a man with a quirky sense of humor, and the classic gentleman scholar".[3] He taught me the essential art of self-criticism in research—the need to be as critical of one's own ideas and arguments as of any others—and left me alone to work out the day-to-day details of experimentation. It was with the greatest of pleasures that I attended Cheves 70th birthday/retirement symposium in Park City, UT, in 1986. I brought along a collection of "*Emory Chemistry Softball Team T-shirts*" for all the speakers (Figure 2), which coincidentally happen to have a "*Free Radicals*" logo printed on the front of the shirt. For many years thereafter, I would regularly receive e-mails from some participants at the Gordon Research Conference on free radicals in New Hampshire who had been informed by Cheves that I could provide such T-shirts at a very reasonable price.

My tastes in organic chemistry during my Columbia years were also being subtly influenced by my attendance at the Thursday evening organic chemistry problem-solving sessions supervised by Ronald Breslow, Tom Katz, and Gilbert Stork. These three gentlemen, whom I came to admire very much, had a lasting influence on me since their approach to organic chemistry was so strikingly different from Cheves' interests. It was Gilbert Stork who suggested that I do my postdoctoral studies at some place far removed from my comfortable roots in New York City. Consequently, I decided to broaden my horizon and work in the newly developing area of organic photochemistry with Howard Zimmerman (Figure 3) at Madison, WI, studying the di-π-methane photorearrangement of cyclohexadienones.[4] So with my wife and two very young children (ages 3 and 1), we set off for the hinterlands of the USA. The early 1960s was the golden age of mechanistic organic photochemistry, and I soon became involved in a study of quantum yield measurements and the determination of the rates of excited state reactions of substituted cyclohexadienones using Stern−Volmer kinetics. Howard was very determined that all of

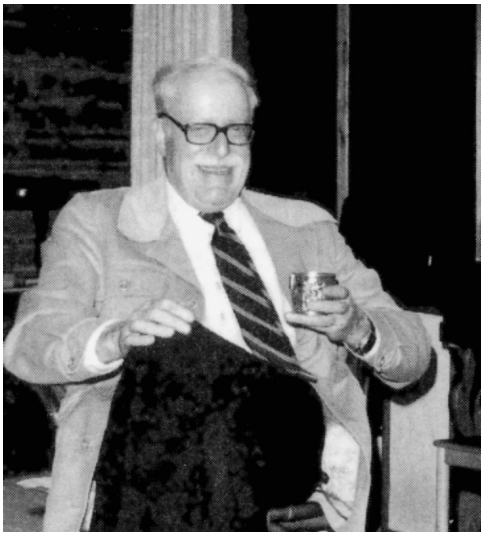


FIGURE 1. Cheves Walling, Ph.D. Research Advisor.

his postdocs should take to an academic career, and he pushed us all in that direction. Although my photochemical studies with Howard were going well, I created a problem for myself by turning down an interview at the University of Kansas. I believed at the time that my wife would have divorced me on the spot if I had accepted such an appointment, since she was a strictly native "*New Yorker*" who could not fathom living in the middle of the country. At that point in time, Assistant Professor offers were privately arranged in "*back-room*" corridors among the "*power-mongers*" of academia. It was not until early April 1963 that I finally received my first offer for a faculty position from the University of California at Berkeley, even though I had never applied for the position. At first I thought that Harry Morrison (Purdue), another postdoc in the Z-group, was pulling my leg. As it turned out, the offer was indeed arranged by Bill Dauben and Howard with a subsequent telegram to me. It seemed as though Berkeley needed someone to handle the sophomore organic chemistry laboratory. Phil Eaton had occupied such a position at Berkeley for several years before joining the faculty at the University of Chicago. After speaking with Phil, he advised me that it was not in my best interest to accept such a position. Young organic faculty at Berkeley in those years were not allowed access to graduate students nor were expected to do much in the way of research. Of course all of that changed once Clayton Heathcock joined the faculty at Berkeley the following year. In some ways, my decision to turn down Berkeley's offer may have been one of the highlights of my academic career. After all, about the only thing that could be more rewarding than accepting a position at Berkeley was to "*turn down*" the offer. Eventually, all the other postdocs with Howard found suitable positions and I was finally granted an interview and a subsequent offer of an Assistant Professorship at the Ohio State University. Armed with an understanding of the

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

FIGURE 2. Speakers at the Walling retirement symposium in Park City, UT, 1986. Left to right: Keith Ingold, Wes Bentrude, Pete Wagner, Athel Beckwith, Bob Neuman, Cheves Walling, Dennis Tanner, Al Padwa, Jay Kochi, Gilbert Stork, and Ned Porter.

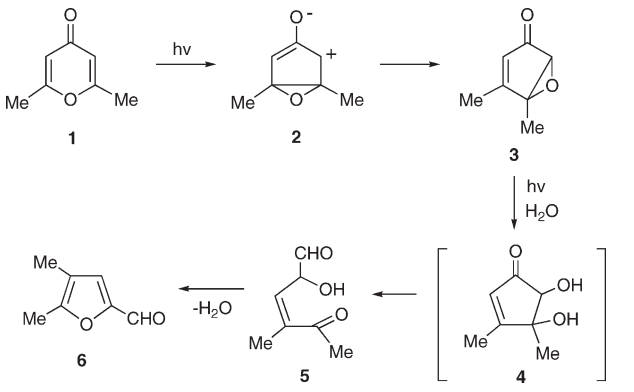
Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

FIGURE 3. Howard Zimmerman, Postdoc Research Mentor (note the famous HZ map of the world in background with push-pins indicating locations of his academic students).

principles of organic photochemistry and with some good advice from Howie Zimmerman, I migrated east in August 1963 to start my academic career in Columbus, OH.

In early 1963, the late Peter Yates published a paper in *The Journal of the American Chemical Society* describing the photochemistry of several 4-pyrone derivatives.[5] Contained within the manuscript was a brief description of an unusual photorearrangement reaction whereby the dimethyl-substituted 4-pyrone **1** was transformed into an isomeric furan aldehyde **6** on exposure to UV light. I reasoned that the transformations shown in Scheme 2 must have taken place. The key step seemingly involved a di-π-methane reaction of the starting 4-pyrone **1** to produce a transient epoxy ketone **3** as an intermediate. I found this to be a rather novel photorearrangement and made a mental note to keep track of any future developments in the area of epoxy ketone

SCHEME 2



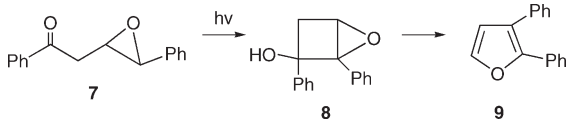
photochemistry. It was during this period of the early 1960s that I (and others) developed an awareness that the photochemistry of carbonyl compounds containing tethered heteroatoms had the enormous potential for synthesizing a variety of heterocyclic compounds that could not be prepared by more traditional methods.

Mechanistic Organic Photochemistry Period (1962−1977)

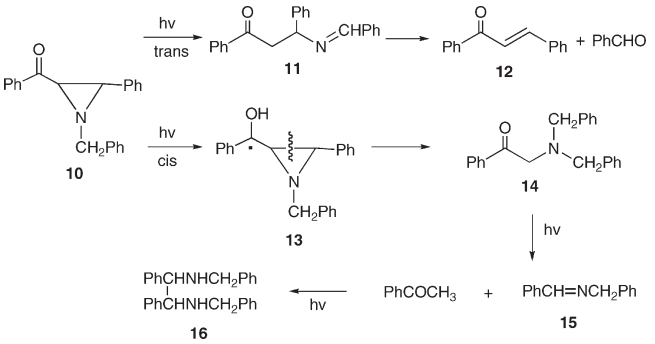
At Ohio State, I was now in a position to write a modest research grant to the Petroleum Research Fund proposing a study of the excited state behavior of α,β-epoxy ketones.[6] I was encouraged by the alacrity with which my new colleagues (especially Paul Gassman and Leo Paquette, Figure 4) accepted the feasibility of my proposal. Both Paul and Leo had a major impact on my career as they were excellent mentors for an aspiring young Assistant Professor still wet behind the ears. It was at this point that I was joined by my first graduate student, Richard Hartman, who undertook an exploration of the above photochemistry as part of his efforts to obtain a Ph.D. degree. During the course of his work, I thought it worthwhile to extend our investigations toward related β,γ-epoxy ketones, and so we discovered another interesting photorearrangement whereby the epoxy ketone **7**

FIGURE 4. Paul Gassman and Leo Paquette, former colleagues at OSU.

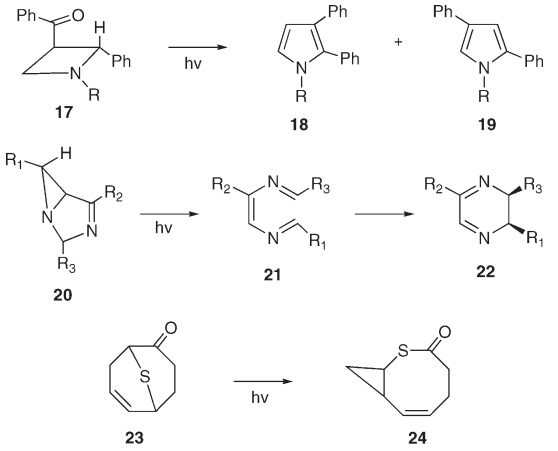
SCHEME 3



SCHEME 4



SCHEME 5



shown in Scheme 3 was converted into 2,3-diphenylfuran **9**.[7] With some care, it was possible to isolate a labile epoxy cyclobutanol derivative **8** formed by γ-hydrogen abstraction followed by biradical coupling. Treatment of this tertiary alcohol with a trace of acid afforded our first legitimate heterocycle.

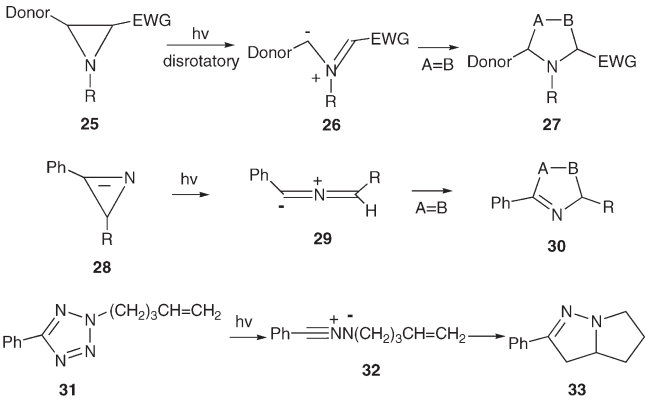
By the end of my first year at OSU, we had tested a range of epoxy ketones and started to extend our photochemical studies toward the structurally related aziridine system.[8] In early 1964, Lou Hamilton, my second Ph.D. student, set about to examine the photochemical behavior of several *cis*- and *trans*-benzoyl aziridines **10** shown in Scheme 4.[9] At first, we were surprised to discover such fundamentally different photobehavior from this class of small ring heterocycles. The *trans*-isomer underwent a photoinduced Norrish type II reaction to eventually produce benzaldehyde and chalcone **12** via a ring opened intermediate **11**. Since it was not possible for the *cis*-isomer to undergo a related internal hydrogen transfer due to steric crowding, bimolecular abstraction occurred ultimately providing an amino-substituted ketone **14**. A subsequent photoreaction via electron transfer[10] produced a benzaldimine derivative **15** which was further converted into 1,2-diamine **16** by a novel chemical sensitization reaction.[11]

In the fall of 1966, I was offered an Associate Professorship at the State University of New York at Buffalo and decided to return to my native state. At SUNY Buffalo we continued our ongoing photochemical program using a variety of small ring heterocyclic systems and encountered some remarkably interesting photorearrangements along the way.[12] A few of the many systems that were examined are outlined in Scheme 5.

It was in the late 1960s when Lou Hamilton made an experimental observation that eventually directed us toward the field of alkaloid synthesis. In connection with his photochemical studies, Lou noticed that several of the benzoyl aziridines **25** that he was working with developed a deep pink coloration on exposure to light and this pink color faded on standing in the dark. The colored species produced in this photoinduced reversible reaction was assigned as 1,3-dipole **26** (i.e., an azomethine ylide).[13] In a continuing series of investigations, we proceeded to study the photochemical cleavage reaction of aroyl-substituted aziridines, their orbital symmetry controlled disrotation, and subsequent 1,3-dipolar addition to reactive multiple π-bonds (Scheme 6).[14] We soon discovered that irradiation of the closely related 2*H*-azirine system **28** resulted in irreversible ring-opening

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 6



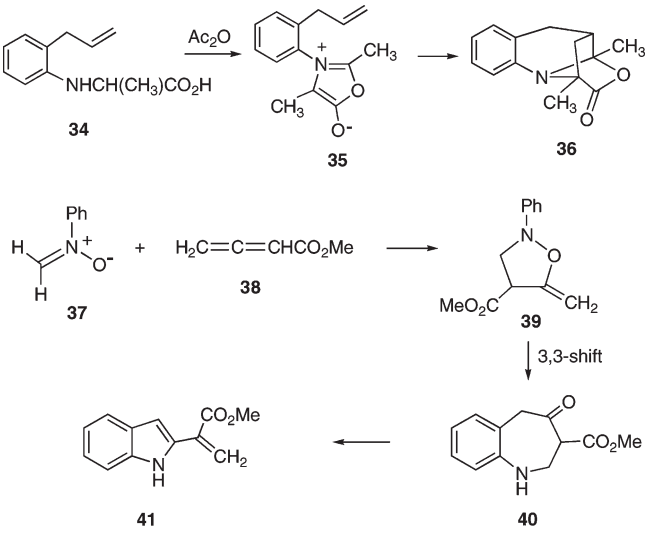
and formation of nitrile ylide **29** as a reaction intermediate.[15] This dipole was intercepted with a variety of dipolarophiles to furnish five-membered heterocycles **30**. Over the next several years, we came to recognize that the 1,3-dipolar cycloaddition reaction, popularized by Rolf Huisgen and his students,[16] represents an astonishingly fruitful method that allowed for the synthesis of many different five-membered ring heterocycles. Numerous possibilities for variation are possible by simply changing the structure of both the dipolarophile and dipole. In the early 1970s, we made extensive use of photochemical activation as a method to generate a wide assortment of 1,3-dipoles and to study their cycloaddition chemistry.[17]

Dipolar Cycloaddition Period (1977−1987)

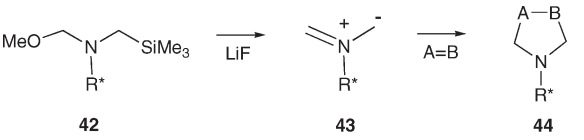
By 1977, we had abandoned our physical organic photochemical program and had immersed ourselves in research which focused primarily on various aspects of dipolar cycloaddition chemistry.[18] The facility of the [3 + 2]-cycloaddition, the rapid accumulation of functionalities in a relatively small molecular framework, the high stereochemical control of the cycloaddition, and the good predictability of its regiochemistry were some of the factors that led us in this direction. I owe a special debt of gratitude to Rolf Huisgen (Figure 5, University of Munich), the father of [3+2]-cycloaddition chemistry, for both his encouragement to get involved in this area as well as his kindness and helpfulness over the years. Some of the various systems that we examined during this period of time are shown in Scheme 7. Studies were carried out using mesoionic heterocycles such as sydnones and münchnones as a method to synthesize various pyrroles and pyrrolidines.[19] The 1,3-dipolar cycloaddition of *N*-phenyl-*C*-phenylnitrone (**37**) with several allenes containing electron-withdrawing groups was also investigated.[20] The cycloaddition was found to proceed in good yield to furnish a substituted benzazepin-4-one **40** which was further transformed into vinyl indole **41** in the presence of a trace of acid. The results are consistent with a mechanism that involves dipolar cycloaddition of the nitrone across the more activated π-bond of the allene to generate a transient 5-methyleneisoxazolidine **39** (Scheme 7). This compound undergoes rapid N−O bond cleavage, and the resulting diradical intermediate cyclizes onto the ortho position of the phenyl group to afford benzazepinone **40**.

FIGURE 5. Rolf Huisgen, the father of 1,3-dipolar cycloaddition chemistry.

SCHEME 7



SCHEME 8



The 1,3-dipolar cycloaddition of azomethine ylides also attracted our attention as a particularly appealing method for pyrrolidine synthesis, especially since this ring system is found in many alkaloids. We found that the desilylation reaction of *N*-(trimethylsilyl)methylamino ethers was a very convenient method for azomethine ylide generation.[21] Treatment of these compounds with LiF in the presence of a reactive dipolarophile afforded dipolar cycloadducts in high yield. Our interest in the asymmetric synthesis of substituted pyrrolidine derivatives by this process led us to study the [3 + 2]-cycloaddition of chiral azomethine ylides. The dipole precursors were prepared from enantiomerically pure α-methylbenzylamines, and the diastereoselectivity of the [3 + 2]-cycloaddition was studied in some detail (Scheme 8).

It was in late January 1977 that a winter storm dropped more than four feet of snow in Buffalo over an 8-h period.

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

FIGURE 6. Buffalo vs Atlanta, Winter 1977 (note: Buffalo is on the left!).

By the early afternoon I was stranded in my office since a state of emergency was in effect, with all nonessential vehicles barred from the streets. Because the roads were impassable, I was unable to return to my home for 3 days. About 30 disoriented students and a few faculty managed to survive on food procured from the vending machines in the building, and we slept on the floor of our laboratories and offices. Not a particularly pleasant memory, but one that was certainly unforgettable! It was during this period that I received a phone call from Leon Mandell, chairman of the chemistry department at Emory University. Two weeks later I was met at the airport by Leon in his open convertible on a rather balmy spring-like day (see Figure 6 for weather contrast between these two east coast cities). This initial visit eventually led to my moving to Emory University (Atlanta, GA) during the summer of 1979. Soon thereafter, we started a program at Emory dealing with intramolecular dipolar cycloaddition chemistry and its application toward heterocyclic synthesis.[22] We rapidly discovered that when the reacting components are themselves cyclic or contain ring substituents, complex multicyclic arrays such as those contained in drugs and natural products could be constructed in a single step.

Rhodium(II)-Catalyzed Cycloaddition Chemistry

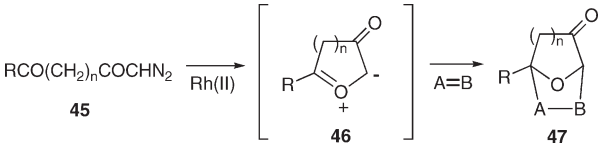
A major challenge in organic synthesis is to devise reactions that can form several carbon−carbon bonds in one operation leading to the construction of polycyclic structures with proper regio- and stereochemical control. In a series of papers published in the early 1980s, we described the formation of bridged oxabicyclo[3.2.1]heptanes **47** from the rhodium(II)-catalyzed reaction of 1-diazopentanediones **45** (Scheme 9).[23] The reaction involves the formation of a rhodium(II) carbenoid, cyclization of the electrophilic carbon onto the adjacent keto group to generate a cyclic carbonyl ylide **46**, followed by 1,3-dipolar cycloaddition.

Over the next several years, we demonstrated that carbonyl ylide formation in transition-metal-catalyzed reactions of diazo compounds depends on the nature of the catalyst, the diazo species, the interacting C=O group, as well as competition with other processes.[24] Our investigations indicated that once the metal-complexed carbonyl ylide is formed, there are two possibilities for the subsequent cycloaddition. One option is that the catalyst rapidly dissociates from the dipole, and therefore, a metal-complexed carbonyl ylide is not involved in the subsequent dipolar cycloaddition. Alternatively, if the catalyst remains associated with the dipole during the [3 + 2] reaction, then asymmetric induction may be observed. Subsequent studies from my team[25] as well as research from the Hashimoto[26] and Hodgson[27] groups showed that a complex blend of electronic effects from the dipole and dipolarophile, together with the nature of the catalyst, contribute to the origin of asymmetric induction.

Of course, I was not the only person working in the field of rhodium(II)-carbenoid chemistry in the early 1980s. A great deal of innovative research was also being carried out by my good friends Mike Doyle (then at Hope College)[28] and Huw Davies (then at Wake Forest),[29] especially for catalytic chiral cyclopropanation and C−H insertion chemistry (Figure 7). What really endeared me to Mike and Huw early on was their willingness to provide us with samples of many different chiral catalyts to study. Huw's generosity ultimately led me to spearhead a movement to "*steal*" him away from SUNY Buffalo, and he is now ensconced at Emory with his extensive collection of chiral rhodium(II) catalysts. While I am on this topic, I also want to acknowledge my good friend and colleague Lanny Liebeskind, who I first met in 1970 when he was an undergraduate student at SUNY Buffalo. Lanny was primarily my source of wisdom and inspiration in my delving into the mechanistic details of organometallic chemistry of these rhodium(II) carbenoids.

Application of the Rh(II)−carbenoid methodology toward the synthesis of both *exo*- and *endo*-brevicomin was subsequently carried out.[30] The *exo* (**51**) and *endo* isomers of brevicomin (**52**) are exuded by the female Western Pine Beetle, and the *exo* isomer is known to be a key component of the aggregation pheromone of this destructive pest. Cycloaddition of 1-diazo-2,5-hexanedione **48** with rhodium(II) acetate using propionaldehyde as the dipolarophile afforded the 6,8-dioxabicyclo[3.2.1]octane ring system in high yield as a 2:1-mixture of *exo* (**49**) and *endo* (**50**) isomers. Separation of the diastereomers followed by reduction of the carbonyl group afforded *exo*- and *endo*-brevicomin in good yield (Scheme 10).

SCHEME 9



Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

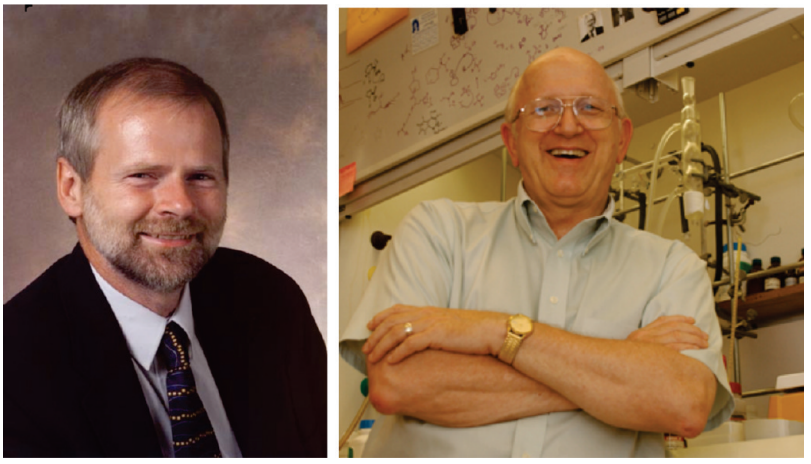
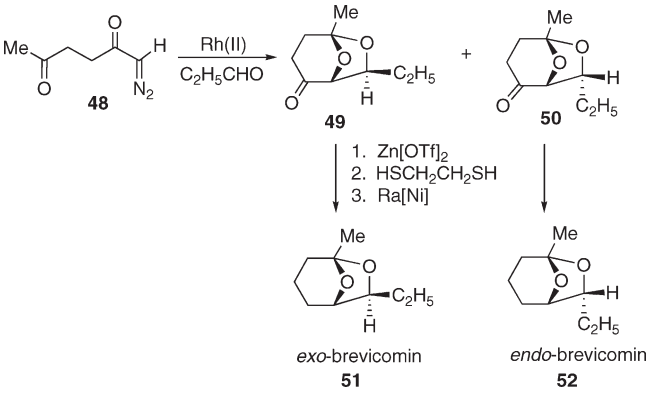


FIGURE 7. Huw Davies and Mike Doyle, members of the Rh(II) gang.

SCHEME 10



It was at this point in time (mid-1980s) that I discovered that another passion in my life lied in climbing tall mountains. To me mountains are like life...you see them from the bottom up and the summit seems hard to reach. However, once you are on the top, everything is clear. I associate the top of mountains with success, achievement, and freedom. In contrast, the lower part of the mountain possesses many obstacles and challenges which need to be overcome. This is really not so different from bringing a chemical project to fruition and getting it published. My first real mountaineering experience was a climb to the top of Mount Rainier in 1984 (Figure 8). Over the next 25 years, I have climbed extensively in Ecuador, Bolivia, Peru, Argentina, Chile, Tanzania, Western China, and Nepal (Figure 9). A few photos of some of these adventures are included in this perspective together with a Table of Climbs (Table 1).

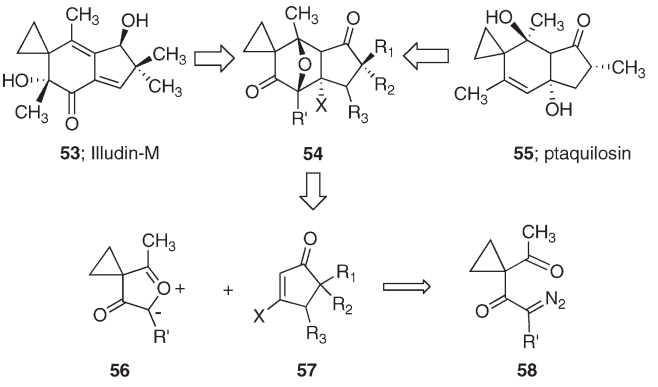
Application of Rhodium(II) Catalysis toward Natural Product Synthesis

After returning from an exhilirating climb to the summit of Mt. Rainier, I was pleased to learn that my group had been quite active in my absence as they had discovered that diazoketone **58** could be used to prepare the core structure of the illudin **53** and ptaquilosin **55** family of sesquiterpenes (Scheme 11). This strategy ultimately provided for a rapid assembly of the basic core unit of these novel target molecules with most of the requisite functionality already in place.[31]

TABLE 1. Various Climbs by Al Padwa over the Past Two and a Half Decades

year	mountain	country	altitude (ft)
1984	Mt. Rainier	USA	14400
1987	Mt. Cotopaxi	Ecuador	19800
1988	Mt. Cayambe	Ecuador	20700
1992	Mt. Fuji	Japan	12400
1994	Mt. Aconcagua	Argentina	22840
1996	Mt. Kilimanjaro	Tanzania	19340
1997	Mt. Ausangate	Peru	17160
1999	Mt. Cabezade Condor	Bolivia	18640
2000	Mt. Quandry, Lincoln, Democrat	USA	14280
2001	Mt. Kala Pittar − Everest trek	Nepal	18300
2003	Mt. Cuyoc - Huayhuash	Peru	19000
2005	Mt Kosciuszko	Australia	7300
2006	Mt. Elbert, Mt. Massive	USA	14400
2007	Torres del Paine, Patagonia	Chile	10000
2008	Mustagh Ata	West China	16300
2009	Annapurna trek, Thorung-La Pass	Nepal	17870

SCHEME 11



(±)-Illudin M (**53**), a toxic sesquiterpene isolated from the Jack-o-lantern mushroom, was eventually prepared via this approach.[32] The key step of the synthesis consisted of a carbonyl ylide 1,3-dipolar cycloaddition reaction with a substituted cyclopentenone to form the dipolar cycloadduct **61** which had undergone the [3 + 2]-cycloaddition with high diastereoselectivity. Several functional group manipulations were carried out to eventually give illudin M (Scheme 12).

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

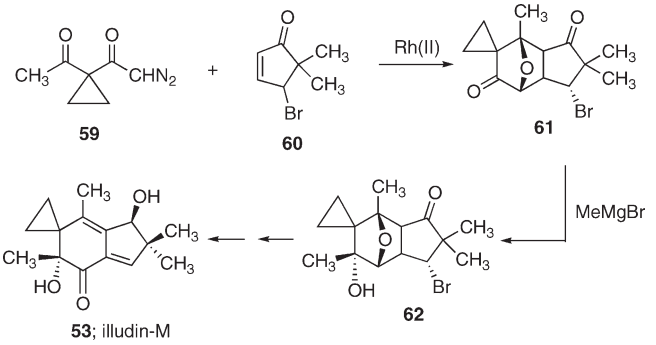
FIGURE 8. On the way to the summit of Mt. Rainier, 1984.

FIGURE 9. On the way to the summit of Mt. Aconcagua, Argentina, 1994, and Annapurna trek, Nepal, 2009.

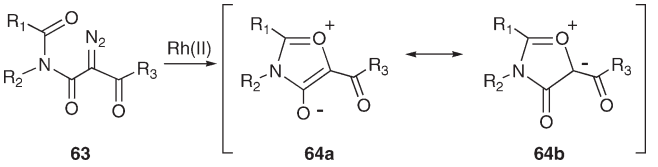
Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

By the early 1990s we had started work in our laboratory to synthesize ring-fused poly-heterocycles based on a *sequential dipolar cycloaddition-N-acyliminium ion cyclization* process.[33] These two types of reactions provided an opportunity for linking two disparate ring-forming reactions in a novel sequential manner. The combination of a sequence of individually powerful methods often has a value significantly greater than the sum of individual reactions and has become of great interest to the synthetic community. We believed that this protocol would provide one-pot access to target molecules possessing a high degree of complexity which would otherwise require technically demanding multistep syntheses. Our early studies showed that 1,3-oxazolium 4-oxides (isomünchnones) **64** can be generated by the rhodium(II)-catalyzed cyclization of a suitable diazo imide **63** (Scheme 13).[34] This type of mesoionic ylide corresponds to the cyclic equivalent of a carbonyl ylide and was found to readily undergo [3 + 2]-cycloaddition with suitable dipolarophiles. Construction of the prerequisite diazo imides necessary for betaine generation was accomplished by the

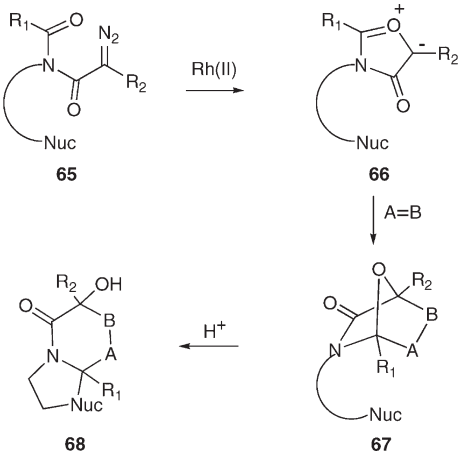
SCHEME 12



SCHEME 13



SCHEME 14

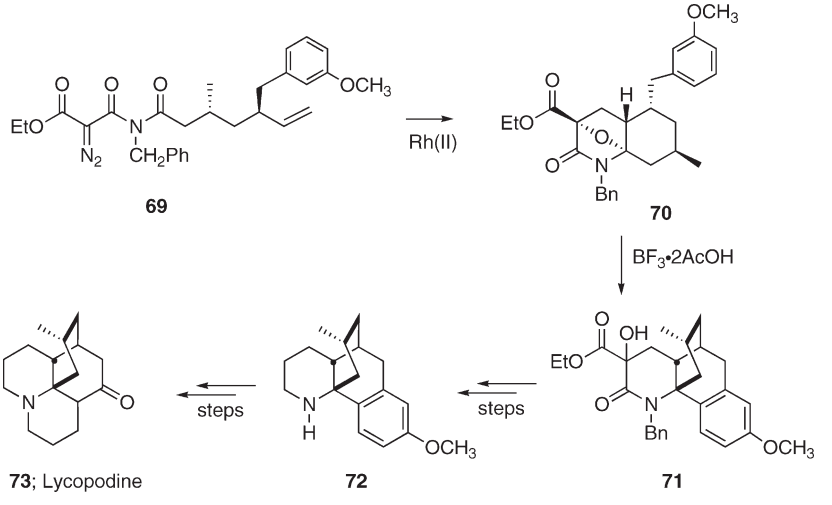


transformation of the corresponding carboxylic acids to their respective amides. Conversion to the diazo imides was straightforward using established malonyl-acylation and diazotization procedures.[35] Formation of the isomünchnone ring proceeds by initial generation of a rhodium carbenoid species, followed by an intramolecular cyclization onto the neighboring carbonyl oxygen to form the mesoionic ylide **64**. The resultant isomünchnone may be trapped with electron-rich or electron-deficient dipolarophiles to give the cycloadducts in high yield. These uniquely functionalized cycloadducts (i.e., **67**) contain a "*masked*" *N*-acyliminium ion which can be generated by treatment with a Lewis acid.[36] By incorporating an internal nucleophile on the tether, annulation of the original cycloadduct **67** allows for the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologues of the erythrinane family of alkaloids. Starting from simple acyclic diazo imides of type **65**, we established a *domino carbenoid cyclization*−[*3*+*2*]-*cycloaddition*−*cationic* π-*cyclization* protocol as a method for the construction of complex nitrogen polyheterocycles of type **68** (Scheme 14). This sequence represented the first example where a [3 + 2]-cycloaddition and *N*-acyliminium ion cyclization were coupled in a one-pot sequence. The novelty of the process lies in the method of *N*-acyliminium ion generation, which was unprecedented at the time that the research was carried out. *N*-Acyliminium ions are traditionally generated from the *N*-acylation of imines, *N*-protonation and oxidation of amides, electrophilic additions to enamides, and the heterolysis of amides bearing a leaving group adjacent to nitrogen.[37] These reactive intermediates readily react with a wide assortment of nucleophiles to effect an overall α-amido alkylation.

An early application of the domino cascade process toward the construction of alkaloids involved the synthesis of (±)-lycopodine (**73**) (Scheme 15).[38] The isomünchnone cycloadduct **70** was formed from the Rh(II)-catalyzed reaction of diazo imide **69** and was found to be the precursor of the key Stork intermediate **72** (via **71**). Our plan involved formation of **71** by a Pictet−Spengler cyclization of the *N*-acyliminium ion derived from **70**. Central to this strategy was the expectation that the bicyclic iminium ion originating from **70** would exist in a chairlike conformation.[39,40] Indeed, cyclization of the aromatic ring onto the *N*-acyliminium ion center readily occurred from the axial position.[41] The rearranged product **71** was then converted into the key intermediate previously used by Stork for the synthesis of (±)-lycopodine **73**.[39]

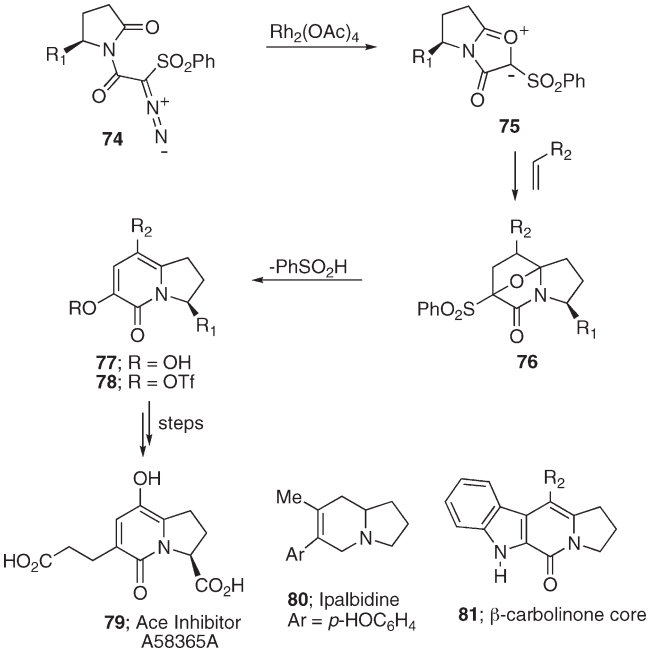
Another implementation of the cascade methodology involves the efficient assembly of the indolizidine ring system by using the Rh(II)-catalyzed [3 + 2]-dipolar cycloaddition of the phenylsulfonyl-substituted diazopyrrolidinone **74** with an appropriately substituted dipolarophile (Scheme 16). The resultant pyridone **77** represents a very versatile synthon. As depicted in Scheme 15, structural manipulation of the pyridinone ring and subsequent functional group interconversions provides access to several indolizidine alkaloids.[42] The C-6 hydroxyl substituent, protected as triflate **78**, allows for an assortment of cross coupling possibilities. Our group

SCHEME 15

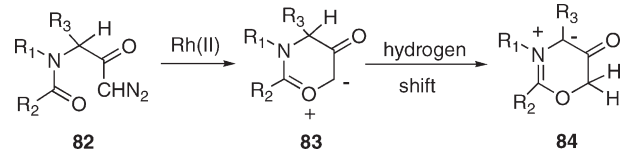


Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 16



SCHEME 17

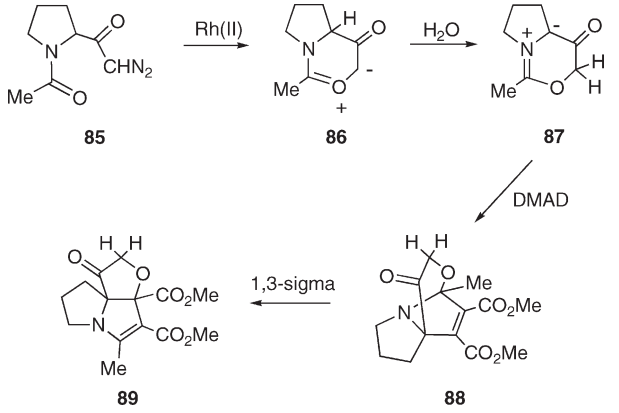


demonstrated the versatility of the method through the synthesis of the angiotensin converting enzyme inhibitor (−)-A58365A (**79**), (±)-ipalbidine (**80**), *β*-carbolinone **81**, and a variety of other novel indolizidine-based compounds.[42] The use of **77** as a key intermediate in total synthesis has also been demonstrated by Greene and co-workers[43] in a recent synthesis of the antiviral agent mappicine ketone, one of the alkaloids isolated together with campothecin from the Indian plant *Nothapodytes fetida*.

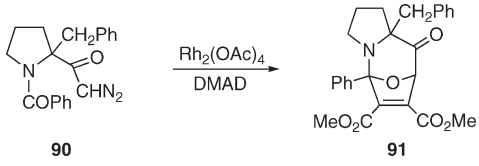
During the course of these studies we were surprise to note that α-diazo carbonyl compounds possessing an interacting *γ*-amido group afforded products derived from an azomethine ylide dipole. This unusual reaction, which we have termed a "*dipole cascade*", involves three distinct classes of 1,3-dipoles.[44] It is initiated by the Rh(II)-catalyzed cyclization of α-diazo ketone **82** onto the neighboring carbonyl group to generate carbonyl ylide dipole **83** which then undergoes a subsequent proton shift to give the cyclic azomethine ylide **84** (Scheme 17).

The wealth of strategically located functionality that results from this novel cascade process was first uncovered during an examination of the Rh(II)-catalyzed reaction of α-diazo ketone **85**. The novel rearranged cycloadduct **89** was obtained when **85** was treated with dimethyl acetylenedicarboxylate (DMAD) in the presence of a Rh(II) catalyst. The mechanism proposed to rationalize the formation of this unusual product involves generation of the expected carbonyl ylide dipole **86** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group.[44]

SCHEME 18



SCHEME 19



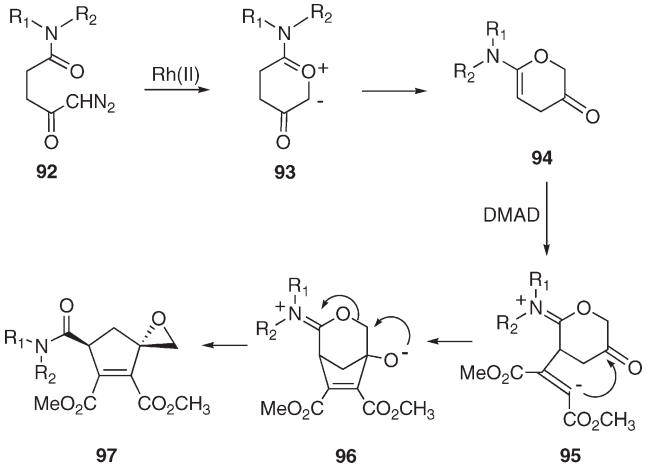
Isomerization of **86** to the thermodynamically more stable azomethine ylide **87** occurs by proton exchange with a small amount of water that was present in the reaction mixture. 1,3-Dipolar cycloaddition with DMAD provided cycloadduct **88** which underwent a subsequent 1,3-alkoxy shift to afford the tricyclic dihydropyrrolizine **89** (Scheme 18). MNDO calculations showed that cyclic carbonyl ylides of type **86** have higher absolute enthalpies (ca. 15 kcal/mol) than the corresponding azomethine ylide **87**. Some of this energy difference is presumably responsible for the rapidity with which the dipole reorganization occurs.

In the dipole cascade reaction, a proton must be removed from the α-carbon atom in order to generate the azomethine ylide. When the α-position was blocked by a benzyl group, formation of the azomethine ylide dipole could not occur. In fact, treatment of α-diazo ketone **90** with $Rh_2(OAc)_4$ in the presence of DMAD afforded only the carbonyl-ylide derived cycloadduct **91** in 95% yield (Scheme 19).

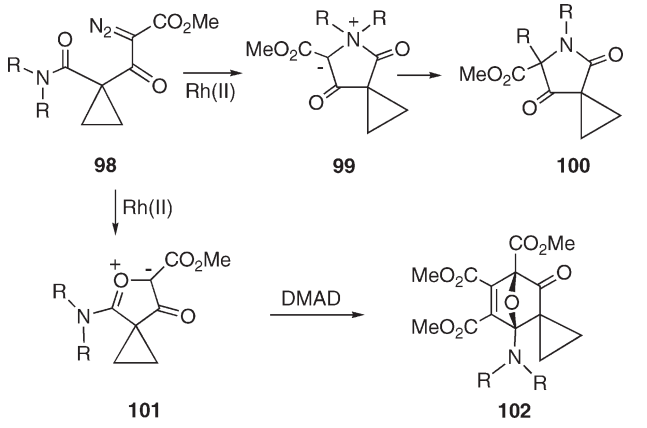
Additional experiments were performed with several related *γ*-amido diazoketones of type **92**. A most unusual addition/rearrangement product (i.e., **97**) was obtained when the Rh(II)-catalyzed reaction was carried out in the presence of DMAD.[45] The initial step involved generation of the expected carbonyl ylide dipole **93** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group (Scheme 20). This highly stabilized dipole does not readily undergo 1,3-dipolar cycloaddition but rather loses a proton to produce the cyclic ketene *N*,*O*-acetal **94**. This transient compound reacts further with the activated *π*-bond of the dipolarophile to produce zwitterion **95**. The anionic portion of **95**, when added to the adjacent carbonyl group, affords a new zwitterionic intermediate **96**. Under anhydrous conditions, epoxide formation occurred with charge dissipation to give the observed cycloadduct **97**. The high efficiency of the dipole cascade, in conjunction with the intriguing chemistry of the resulting cycloadducts, presents numerous synthetic possibilities for the preparation of complex heterocycles.

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 20



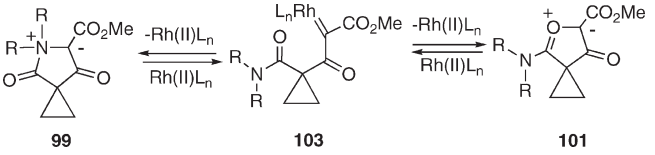
SCHEME 21



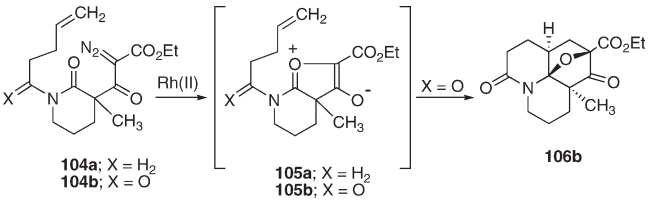
α-Diazo esters containing an amido group in the γ-position have also been found to undergo a novel Rh(II)-catalyzed transformation, producing five-membered ammonium or carbonyl ylides depending on the reaction conditions used.[46] In the absence of an external dipolarophile, ammonium ylides are the exclusive products formed (i.e., **98** → **99** → **100**). In most cases, these ylides cannot be isolated as they readily undergo a 1,2-shift to give products such as **100**. In the presence of typical dipolarophiles such as DMAD or *N*-phenylmaleimide, cycloaddition products such as **102** derived from cyclic carbonyl ylide dipoles **101** are now formed as the major products (Scheme 21). The rhodium carbenoid intermediate generated in these reactions can either attack the lone pair of electrons on the amide nitrogen (ammonium ylide formation) or the lone pair of electrons on the carbonyl oxygen (carbonyl ylide formation). The experimental observations reflect a catalyst-promoted system of equilibria with a clear-cut thermodynamic bias.

In the presence of the Rh(II) catalyst, formation of ammonium ylide **99** was suggested to be reversible, and that it further rearranged to carbonyl ylide **101** via the metallo-carbenoid intermediate **103**. Because of the 1,3-dipolar character of carbonyl ylide **101**, this species can easily undergo cycloaddition with DMAD, ultimately giving cycloadduct **102**. In the first step of the dipole rearrangement process, the transition-metal catalyst would have to add to the ammonium ylide (i.e., **99**) to form a metal-stabilized ylide intermediate which

SCHEME 22



SCHEME 23



then ring opens to give carbenoid **103** (Scheme 22). Attack of the electrophilic carbenoid on the lone pair of electrons on oxygen followed by dissociation then leads to the free carbonyl ylide (i.e., **101**) and regeneration of the rhodium catalyst (Rh(II)Ln). Density functional theory (DFT) calculations indicate that the transition metal-mediated equilibrium between ylides **99** and **101** lies predominantly on the ammonium ylide side.[46]

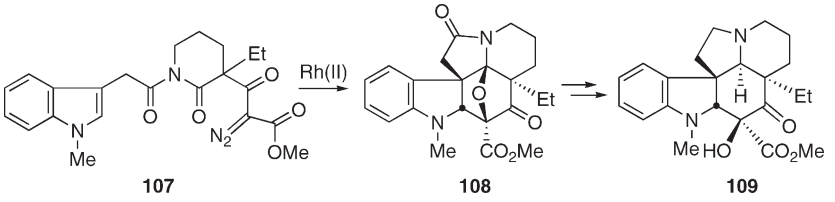
Prompted by our previous work dealing with the internal [3 + 2]-cycloaddition reaction of mesoionic oxazolium ylides,[34] we then became interested in the rhodium(II)-catalyzed reactions of diazo ketoamides such as **104**. Attack of the amido oxygen on to the rhodium carbenoid produced a carbonyl ylide dipole (i.e., **105**) that is isomeric with the isomünchnone class of mesoionic betaines (**64**). We found that the rhodium(II)-catalyzed formation of carbonyl ylide intermediates derived from cyclic diazo amides furnished tetracycles such as **106b** in good yield, provided that the tether engaged in ring formation carried a carbonyl group (i.e., **104b**, X = O) (Scheme 23).[47]

Without the C=O functionality (i.e., **104a**, X = H_2), only decomposition products were observed. By performing ab initio transition-state geometry optimizations, we learned that a severe cross-ring 1,3-diaxial interaction caused by the bridgehead methyl group promoted a boat or twist-boat conformation in the piperidine ring fused to the newly forming one. The presence of a carbonyl group on the tether apparently helps to relieve the steric congestion by favoring a second boat conformation in the latter ring. When the side chain is devoid of a carbonyl group, the calculated reaction barrier is much larger, thereby permitting competing processes to intervene. Thus, the reactivity discrepancy between diazo amido esters **104a** and **104b** can be attributed to steric effects in the transition states.

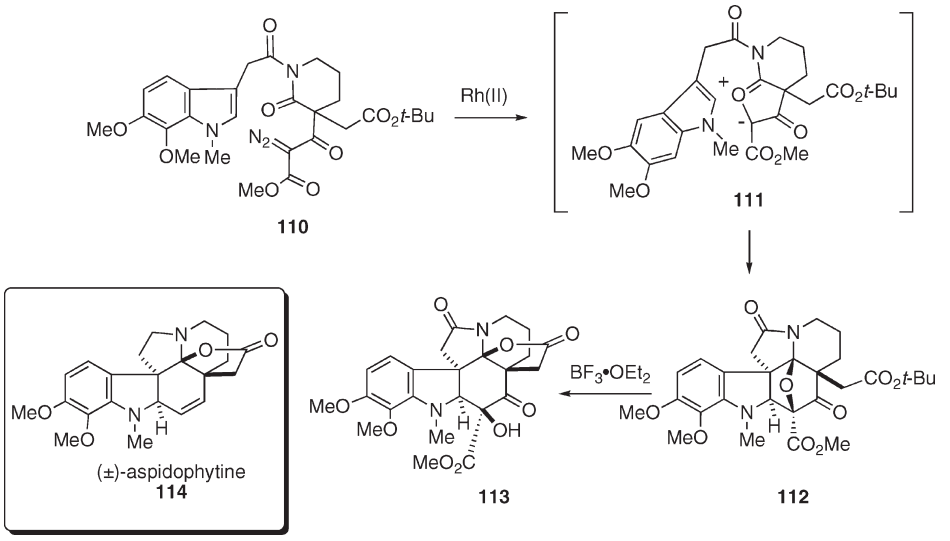
Given the success in forming complex polyheterocyclic systems from the intramolecular cycloaddition reaction of a push−pull carbonyl ylide, we hypothesized that selective modification of the starting α-diazo amido ester would allow application of the method toward the synthesis of the Aspidosperma alkaloid family. In particular, the intramolecular cycloaddition across a tethered indolyl π-bond would bode well for a planned synthesis of this alkaloid skeleton. The key question that needed to be addressed was whether the push−pull dipole would cycloadd across the π-bond of a heteroaromatic system.[48] Indeed, we soon discovered that

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 24



SCHEME 25



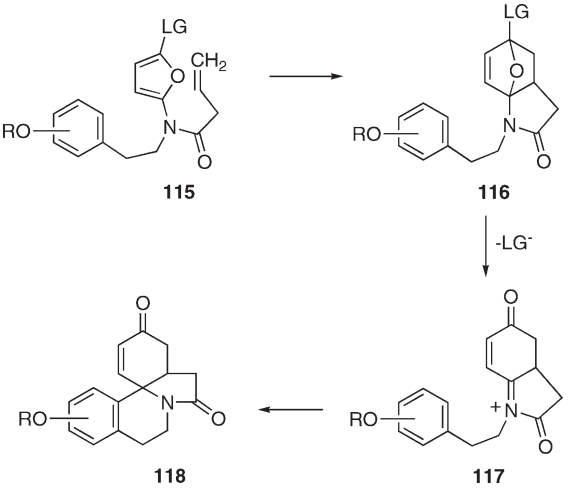
the Rh(II)-catalyzed reaction of α-diazoimide **107** with $Rh_2(OAc)_4$ produced the expected push−pull dipole which subsequently underwent cycloaddition across the tethered indole π-bond.[49] The resulting cycloadduct **108** is the consequence of *endo* cycloaddition with respect to the dipole and this is fully in accord with the reaction proceeding via the lowest energy transition state. The stereospecific nature of the internal cycloaddition reaction results in the correct relative stereochemistry about the four chiral centers of the C-ring. Cycloadduct **108** was converted in three subsequent steps into desacetoxy-4-oxo-6,7-dihydrovindorosine (**109**) (Scheme 24).[49]

A synthesis of the more complex pentacyclic alkaloid (±)-aspidophytine (**114**) was then carried out making further use of the domino dipole cascade sequence. The key sequence of reactions involved a 1,3-dipolar cycloaddition of the push−pull dipole **111** across the indole π-system. Treatment of the resulting dipolar cycloadduct **112** with $BF_3 \cdot OEt_2$ induces a domino fragmentation cascade. The reaction proceeds by an initial cleavage of the oxabicyclic ring and formation of a transient *N*-acyliminium ion which reacts further with the adjacent *tert*-butyl ester and sets the required lactone ring present in aspidophytine. A three-step sequence was then used to remove both the ester and OH groups from lactone **113**. Subsequent functional group manipulations allowed for the high-yielding conversion of **113** into (±)-aspidophytine (**114**) (Scheme 25).[50]

IMDAF Cascade Using 2-Amido-Substituted Furans

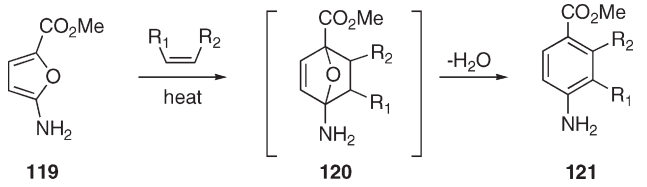
In a more recent phase of our research starting in 2000, we decided to reconsider some aspects of our Rh(II)-cascade strategy with α-diazo carbonyl compounds. It occurred to us that we could also utilize a series of 2-amino substituted furans for the critical cycloaddition step rather than the highly reactive carbonyl ylide dipole, which, on occasion, was prone to undergo hydrolytic decomposition. Our long-range goal involved using 2-amino-substituted furans such as **115** that contain both a suitable leaving group (LG) and an olefinic tether to allow for an intramolecular Diels−Alder reaction (Scheme 26). The resultant cycloadduct was expected to undergo ring-opening to generate a vinylogous C-acyliminium ion of type **117**. Our initial intention was to use this sequence of reactions for a rapid entry into the erythrinane family of alkaloids. With this goal in mind, some model studies

SCHEME 26

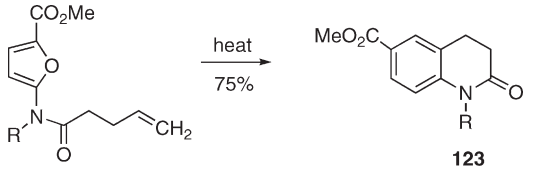


Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 27



SCHEME 28



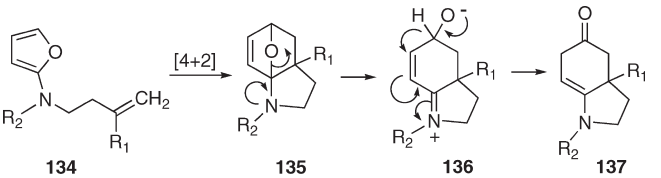
were first undertaken to determine the facility with which 2-aminofurans would undergo Diels–Alder cycloadditions.[51]

Heterocycles such as furan, thiophene, and pyrrole undergo Diels–Alder reactions despite their stabilized 6π-aromatic electronic configuration.[52] MO calculations show that the presence of an electron-donating substituent such as an amino group in the 2-position of the furan nucleus increases its HOMO energy relative to that of furan.[53] A significant increase in the HOMO coefficient at the C-5 position compared to that at the C-2 position also occurs, consistent with an increase in electron density at that position due to resonance interaction with the amino substituent. In this regard, we demonstrated that simple 2-aminofurans such as **119** react with various dienophiles in an intermolecular fashion with high regioselectivity. The initial cycloadducts were not isolated, as they readily underwent ring-opening to anilines **121**, assisted by the lone pair of electrons on the adjacent nitrogen atom (Scheme 27). The influence of the amino group is evident by the extremely facile cleavage of the oxybridge intermediate under the thermal conditions used in the reaction.

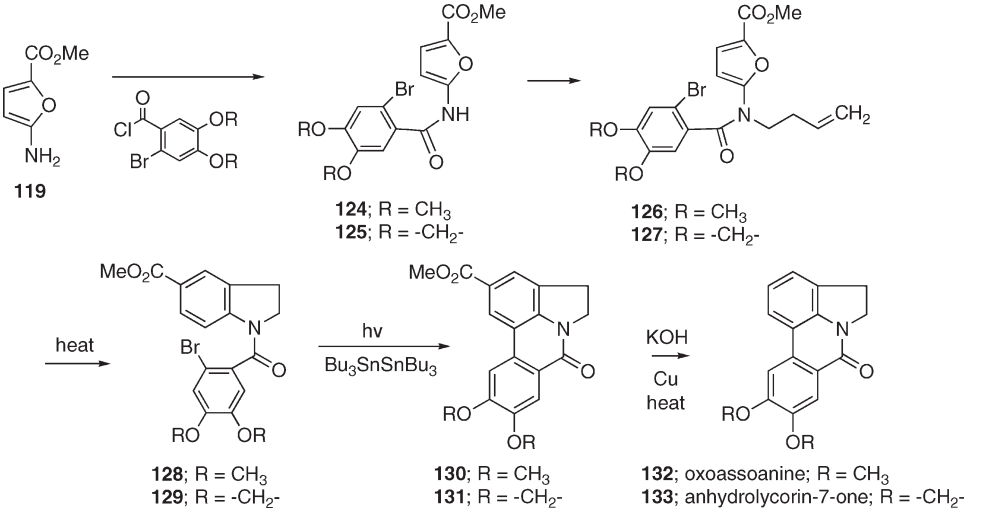
The intramolecular Diels–Alder reaction of furans, often designated as IMDAF, helps to overcome the sluggishness of this heteroaromatic ring system toward [4 + 2]-cycloaddition. Not only do IMDAF reactions allow for the preparation of complex oxygenated polycyclic compounds, they often proceed at lower temperatures than their intermolecular counterparts.[54] Even more significantly, unactivated π-bonds are often suitable dienophiles for the internal cycloaddition. While the carbocyclic IMDAF reaction has been the subject of many reports in the literature, much less is known regarding the cycloaddition behavior of furan Diels–Alder systems that contain heteroatoms. Even rarer are examples in which the heteroatom is directly attached to the furan ring. In an effort to investigate the scope of these reactions, a number of furan substrates were prepared in our laboratory and tested for the cycloaddition cascade. Tethered amidofurans **122** were easily synthesized starting from aminofuran **119** and 4-pentenoyl chloride. The thermal reaction of **122** at 200 °C for 24 h afforded tetrahydroquinolinone **123** in high yield. In both cases, the initial cycloadducts were not isolated, as they readily underwent ring-opening, assisted by the lone pair of electrons on the adjacent nitrogen (Scheme 28).

Having established the suitability of 2-amido furans to generate dihydroindoles, we turned our attention to the application of the methodolgy toward the synthesis of oxoassoanine (**132**)[55] and anhydrolycorin-7-one (**133**).[56] These compounds are members of the pyrrolophenanthridine class of alkaloids which have been isolated from various species of Amaryllidaceae.[57] Although a number of synthetic routes are available for this ring system, many of these suffer from low yields and a lack of generality.[58] A short synthesis of **132** and **133** was carried out as depicted in Scheme 29. This approach is centered on the construction of the key dihydroindoles **128** and **129** which are formed by an IMDAF

SCHEME 30

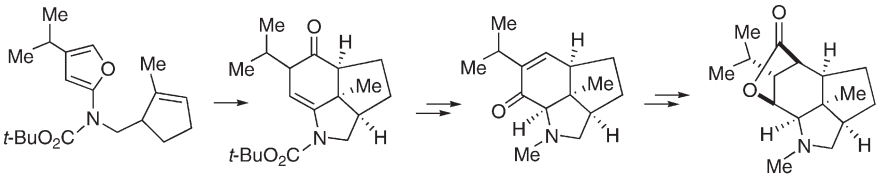


SCHEME 29

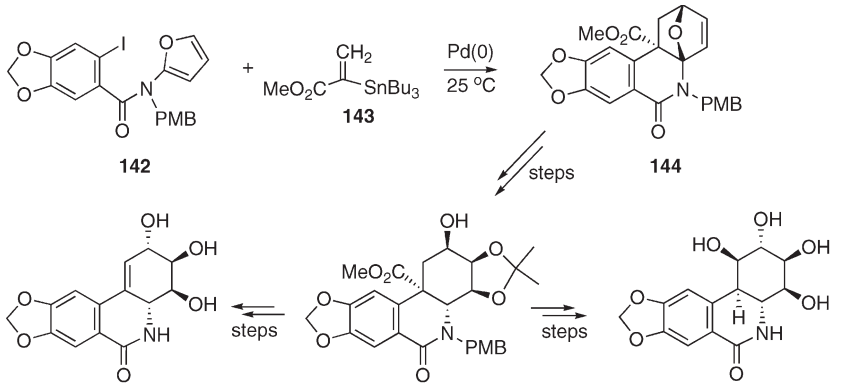


Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 31



SCHEME 32



Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

cycloaddition followed by subsequent nitrogen atom lone pair assisted ring-opening of the initially formed oxabridged cycloadducts. After some experimentation, it was found that using bis(tributyltin) under photochemicalconditions afforded the aryl-coupled products **130** and **131** in high yield from the corresponding dihydroindoles **128** and **129**. Both compounds were converted to the natural products by a saponification−decarboxylation protocol.

The intramolecular [4 + 2]-cycloaddition of 2-amidofurans has also been employed in our group as a new and general method for synthesizing various hexahydroindolin-ones.[59] Subjection of olefinic amidofurans such as **134** to thermolysis affords the rearranged ketone **137**. The initially formed [4 + 2]-cycloadduct **135** undergoes a nitrogen-assisted ring-opening followed by deprotonation of the resulting zwitterion **136** to furnish the rearranged ketone (Scheme 30).

The above IMDAF cascade sequence was subsequently utilized for a synthesis of (±)-dendrobine (**141**), an alkaloid which exhibits antipyretic, hypotensive, and convulsant activity.[60] Upon thermolysis, the unactivated tethered dienophile moiety present in compound **138** underwent cycloaddition with the electron-rich amidofuran system to give the functionalized tricyclic indolinone **139** in 74% overall yield via a transient oxabridge cycloadduct. Conversion of the tricyclic cycloadduct **139** to Kende's intermediate[61] **140** followed by its transformation to alkaloid **141** completed the overall synthesis (Scheme 31).

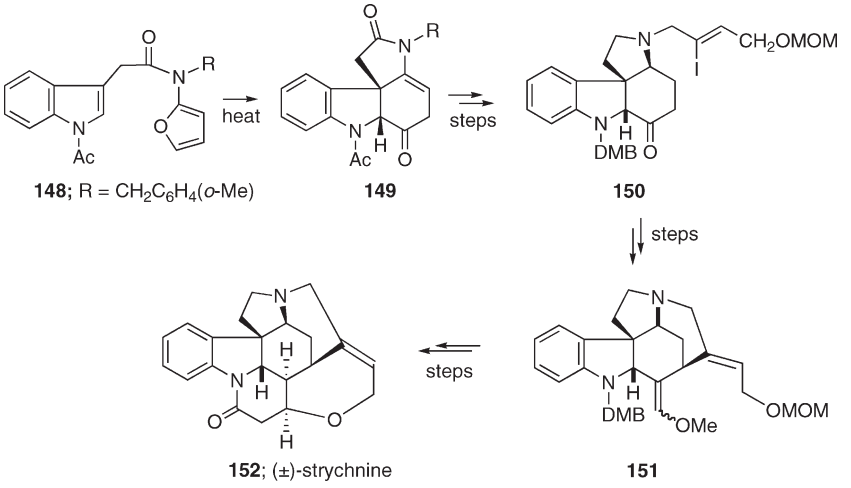
The same general strategy was then used to prepare several members of the hydroxylated Amaryllidaceae alkaloid family.[62] The approach is based on the synthesis of intermediate **145**, which was obtained by a two-step cascade reaction proceeding by a Pd(0)-catalyzed coupling of furanylamide **142** with vinyl stannane **143** followed by an IMDAF cycloaddition to give cycloadduct **144**. Oxidation of **144** with OsO_4/NMO, acetonide formation of the resulting diol with 2,2-dimethoxypropane, followed by reaction with TMSOTf and reduction of the resulting ring-opened iminium ion with $Zn(BH_4)_2$ gave the key intermediate **145**. This compound was then transformed into both (±)-lycoricidine (**146**) and (±)-7-deoxypancratistatin (**147**) in several additional steps (Scheme 32).[62]

A related process was also to synthesize the strychnos alkaloid skeleton. The central step in the synthesis consists of an intramolecular [4 + 2]-cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran **148** which delivers an aza-tetracyclic substructure **149** containing the ABCE-rings of the *Strychnos* alkaloid family. A large substituent group on the amide nitrogen atom causes the reactive *s-trans* conformation of the amidofuran to be more highly populated, thereby facilitating the Diels−Alder cycloaddition. The reaction also requires the presence of an electron-withdrawing substituent on the indole nitrogen in order for the cycloaddition to proceed. The cycloaddition/rearrangement cascade was remarkably efficient given that two heteroaromatic systems are compromised in the reaction. Closure to the remaining D-ring of the *Strychnos* skeleton was carried out from the aza-tetracyclic intermediate **150** by an intramolecular palladium-catalyzed enolate-driven cross-coupling between the *N*-tethered vinyl iodide and the keto functionality. The cycloaddition/rearrangement approach was successfully applied to a synthesis of the heptacyclic framework of (±)-strychnine **152** (Scheme 33).[63] The total synthesis of (±)-strychnine required only 13 steps from furanyl indole **148** and proceeded in an overall yield of 4.4%.

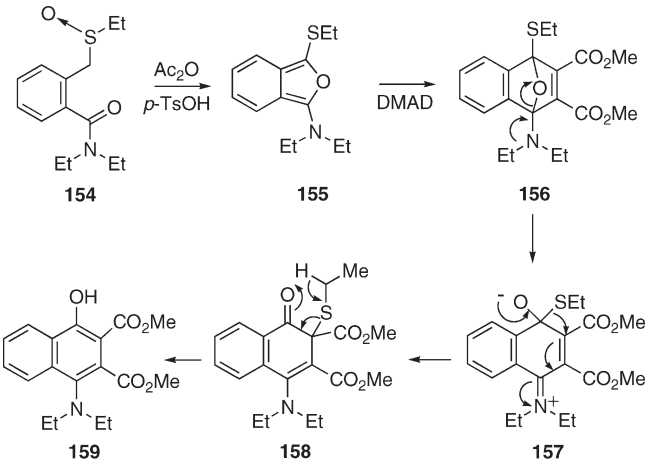
Pummerer-Promoted Cyclization−Cycloaddition Cascade

We came to realize that a limitation of the above IMDAF method is that the 2-amidofuran system is not always easily accessible. In the context of our studies dealing with *domino*

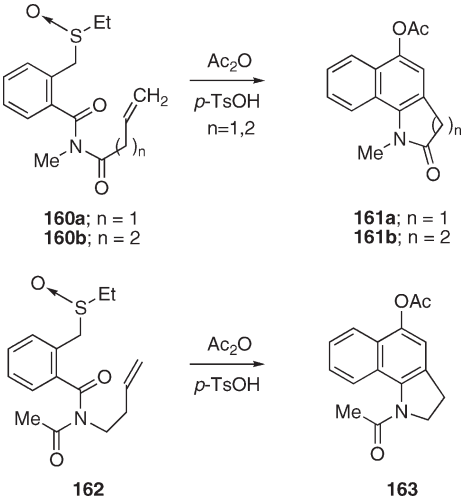
SCHEME 33



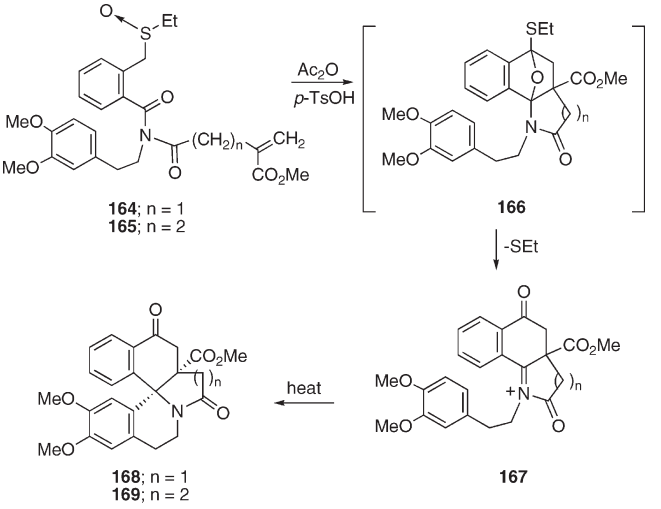
SCHEME 34



SCHEME 35



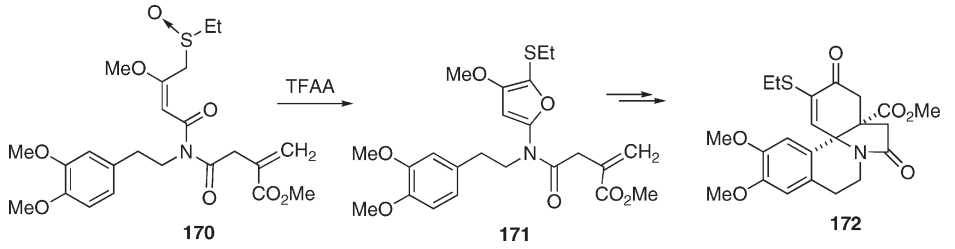
SCHEME 36



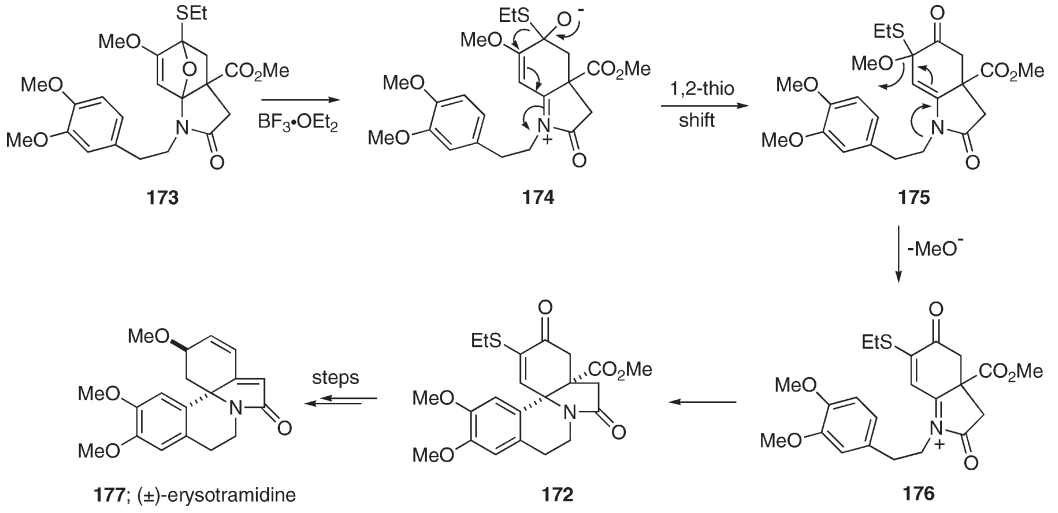
cycloaddition–Mannich cyclizations,[64] we found that the Pummerer reaction can be effectively utilized to prepare the desired 2-aminofurans.[65] α-Acyl thionium ions generated from α-acyl sulfoxides under Pummerer conditions are known to be powerful electrophiles, reacting efficiently with nucleophilic carbon species.[66] Bimolecular addition of the cation to various carbon–carbon double bonds is well established.[67] In the realm of natural product synthesis, most success has been achieved using intramolecular Friedel–Crafts cyclization of the Pummerer thionium ion intermediate.[68] Far fewer examples exist for heteroatom interception of the Pummerer intermediate.[69] The scarcity of examples prompted us to explore the internal trapping of the Pummerer cation with adjacent carbonyl groups as a method to prepare a variety of substituted 2-aminofurans. Indeed, we found that the *domino Pummerer/Diels–Alder sequence* readily afforded 2-amino-substituted isobenzofurans as transient species which were too labile to isolate but underwent rapid [4 + 2]-cycloaddition with added dienophiles.[70] When dimethyl acetylenedicarboxylate (DMAD) was used as the trapping agent, the initially formed iminium ion **157** could not undergo proton loss (Scheme 34). Instead, **157** rearranged by means of a 1,2-ethylthio shift to afford the tetralone derivative **158**. Compound **158** was converted to naphthol **159** in high yield upon further heating. This process presumably proceeds by elimination of thioacetaldehyde in a hetero-retro-ene fashion.[71]

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 37



SCHEME 38



Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

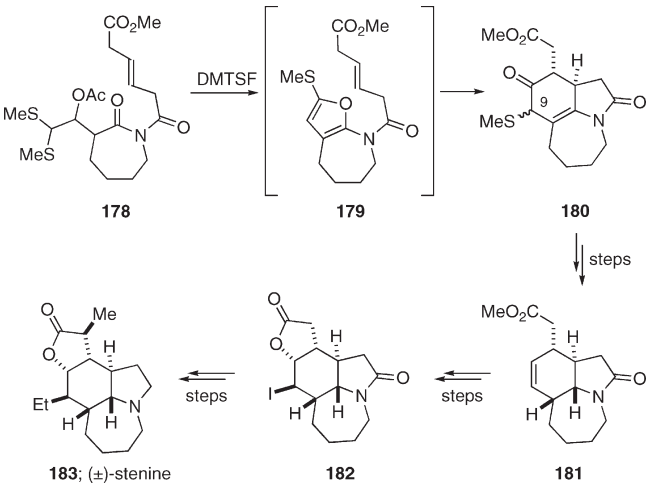
In order to access synthetically more valuable targets, we then focused our attention on an intramolecular variation of the *domino amido-Pummerer−Diels−Alder reaction sequence*. The one-pot intramolecular cascade process occurred smoothly when the olefin tether was activated by an ester or when a carbonyl group was located adjacent to the nitrogen atom of the 2-amino substituted isobenzofuran (Scheme 35).[70] The intramolecular cycloaddition behavior of the incipient isobenzofurans in response to the presence of a C=O group was striking. Five- and six ring-membered precursors **160a** and **160b** delivered cyclized products bearing a carbonyl within the newly formed rings in good to excellent yields. Externalization of the C=O as in **162** likewise led to a facile internal cyclization. Removal of the C=O functionality, however, suppressed intramolecular cycloaddition in favor of the traditional Pummerer reaction.

The amine−amide effect was not limited to isobenzofurans. In our previous study of the intramolecular cycloaddition of carbonyl ylide dipoles and tethered alkenyl π-bonds, a similar phenomenon was observed. Intermediates with carbonyl groups in the tether provided cycloaddition products; those lacking the C=O group failed to cyclize. The reactivity discrepancy in both cases can be traced to steric effects in the transition states. The incorporation of an amido group is clearly of synthetic advantage as it offers the opportunity to accelerate intramolecular cycloaddition by steric adjustment of ground-state and transition state energies either separately or simultaneously. Both examples underscore the unexpected complexity of intramolecular cycloaddition processes that create several fused rings in a domino cascade and simultaneously induce steric effects remote from the reacting centers. Amide tethers have emerged as remote-site promoters of intramolecular cycloaddition for tandem processes yielding products containing multiple fused rings.

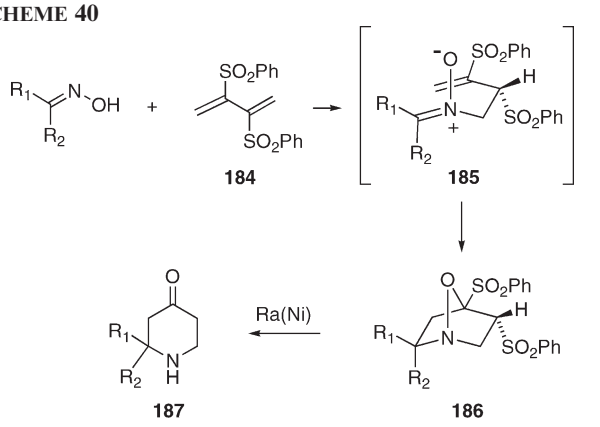
In order to avoid the eventual aromatization step as indicated in Scheme 35, we prepared sulfoxides **164** and **165**, each possessing a carbomethoxy group attached to the olefin tether. This substituent was selected not only to prevent deprotonation and subsequent aromatization but also to enhance the [4+2]-cycloaddition based on FMO considerations. *N*-Acyliminium ion **167** derived from the internal cycloadduct **166** underwent stereoselective spiro-cyclization to furnish the *cis*-3,4-benzoerythrinane **168** or homoerythrinane derivative **169** in good yield (Scheme 36). The overall triple cascade sequence represents an efficient one-pot approach toward the erythrinane alkaloid skeleton in which the spirocyclic ABC skeleton is assembled in a single operation.[72]

At this point, we decided to undertake a synthesis of (±)-erysotramidine (**177**) in order to further test the viability of the triple cascade process as an entry into the erythrinane skeleton.[73] The requisite starting imidosulfoxide **170**, possessing both a dienophilic and diactivated aromatic π-tether, was efficiently synthesized from known starting materials. Subjection of **170** to the Pummerer conditions gave compound **172** as a single diastereomer in 83% yield (Scheme 37). The *cis* A/B ring fusion present in **172** was unequivocally established by an X-ray crystallographic analysis and is identical to the stereochemical relationship found in the naturally occurring Erythrina alkaloids. The conversion of **170** into **172** is believed to follow the pathway outlined below (Scheme 38). The initially formed α-thiocarbocation

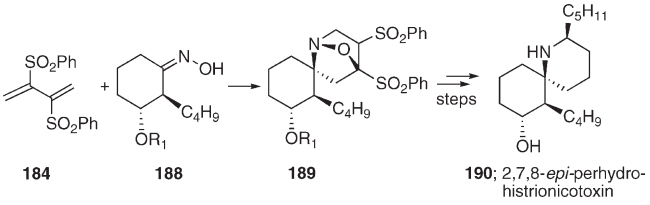
SCHEME 39



SCHEME 40



SCHEME 41



intermediate generated from the Pummerer reaction of **170** is intercepted by the adjacent imido carbonyl to produce the α-amido substituted furan **171**. This transient intermediate undergoes a subsequent intramolecular Diels−Alder cycloaddition across the tethered π-bond to furnish cycloadduct **173**. Nitrogen-assisted ring-opening of the oxabicyclic bridge results in the formation of zwitterionic intermediate **174** which undergoes a 1,2-thioethyl shift followed by methoxide ion ejection to give **175**. Cyclization of the diactivated aromatic tether onto the resulting *N*-acyliminium ion **176** ultimately provides the tetracyclic amide **172**. With a supply of **172** in hand, this enone was eventually transformed into (±)-erysotramidine (**177**).[66,67]

This "*thio-substituted furan-forming Pummerer cascade*" sequence was utilized for the synthesis of several natural products. A typical example involves the total synthesis of (±)-stenine (**183**) (Scheme 39).[74] The reaction of imide **178** with commercially available dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[75] triggered a Pummerer cascade by first transferring a methylthio group in **178**. This was followed by the elimination of methyldisulfide to produce a reactive thionium ion intermediate that was intercepted by the proximal carbonyl group to furnish a dihydrofuran derivative.[76] Elimination of acetic acid under the reaction conditions gave the intermediate furan **179**, which could not be isolated as it spontaneously underwent a Diels−Alder cycloaddition at 0 °C. The resulting cycloadduct rearranged rapidly to give azapinoindole **180** in 80% yield as a 1:1 mixture of epimers about the C(9) stereocenter (Scheme 39).[74] Removal of the methylthio moiety followed by reduction of the ketone, then hydrogenation of the resulting homoallylic alcohol with Crabtree's iridium catalyst[77] and a subsequent dehydration provided the γ,δ-unsaturated ester **181**. Hydrolysis of the ester functionality and iodo-lactonization furnished the expected iodo-lactone **182**. Radical mediated allylation followed by several functional group interconversions eventually afforded (±)-stenine **183**.

Tandem Michael Addition/Dipolar Cycloaddition Cascade

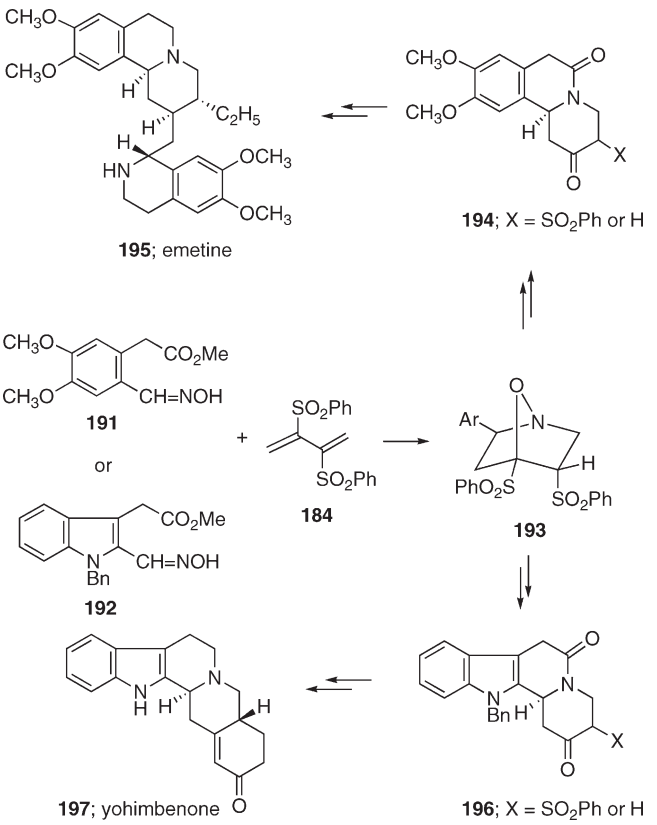
A more recent cascade strategy that we are currently applying to the synthesis of various piperidine alkaloids is founded on a renewed interest in the conjugate addition-dipolar cycloaddition cascade that my group had previously used to prepare 2-substituted-4-piperidones.[78] This cascade utilizes 2,3-bis(phenylsulfonyl)-1,3-butadiene (**184**)[79] as a key reactant which functions as both a Michael acceptor and a dipolarophile. Thus, conjugate addition of an oxime to diene **184** followed by proton transfer creates a transient nitrone **185** that undergoes a 1,3-dipolar cycloaddition with the tethered vinyl sulfone (Scheme 40).[80,81] The regiochemistry of the cycloaddition is controlled by nonbonded interactions in the transition state for the cycloaddition. *N*,*O*-Bond cleavage of the resulting cycloadduct **186** provides efficient access to the 2,2-disubstituted 4-piperidone skeleton **187**.[78]

For cycloalkanone-derived oximes, this methodology provides facile access to 2-substituted azaspirocycles with a high degree of flexibility. Thus, an efficient stereocontrolled synthesis of a spirocyclic perhydrohistrionicotoxin derivative **190** was recently carried out based on the above conjugate addition−dipolar cycloaddition cascade.[82] The reaction of 2-butyl-3-(methoxymethoxy)cyclohexanone oxime (**188**) with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**184**) gave rise to the 7-oxa-1-azanorbornane cycloadduct **189** in high yield. Treatment of the cycloadduct with 5% Na/Hg resulted in reductive nitrogen−oxygen bond cleavage to furnish an azaspiro[5.5]undecane which was eventually converted to (±)-2,7,8-*epi*-perhydrohistrionicotoxin (**190**) (Scheme 41).

As a further demonstration of the potential of the conjugate addition−dipolar cycloaddition cascade, we reported on a route that allowed entry to both the isoquinoline and pentacyclic framework of the Rauwolfia alkaloids.[83] The principal advantage of the method is the presence of the vestigial sulfonyl substituent that allows further elaboration through site-specific enolate chemistry. The appropriately positioned ester in the dipolar cycloadduct **193** undergoes condensation with the resulting secondary amine after reductive N−O cleavage (Scheme 42). This cyclization provides either the pyrido[2,1-*a*]isoquinoline-2,6-dione **194** or the indolo[2,3-*a*]quinolizine-2,6-dione **196** which, after suitable

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

SCHEME 42



modification, gave rise to either (±)-emetine (**195**) or (±)-yohimbenone (**197**).[84]

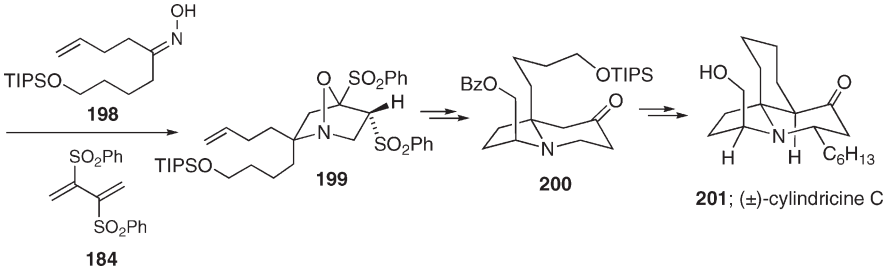
A concise stereocontrolled synthesis of the marine alkaloid (±)-cylindricine C (**201**) was also accomplished wherein the tandem Michael addition/dipolar cycloaddition sequence played a crucial role.[85] The key element of the synthesis consists of a cascade reaction between 2,3-bis(phenylsulfonyl)-1,3-butadiene (**184**) and 9-triisopropylsilanyloxynon-1-en-5-one oxime (**198**). The resulting cycloadduct **199** was converted into cylindricine C (**201**) by (1) a reductive-cyclization reaction of **199** to **200** which sets the BC-ring skeleton, (2) a base-induced cyclization to construct the tricyclic core, and (3) an oxidation−conjugate addition of the *n*-hexyl side chain (Scheme 43). Challenges that were overcome in this approach include the construction of the A and C-rings around the 4-piperidone periphery and the success in epimerizing the C5 and C13 stereocenters within the azatricyclic core to geometries that would adopt the energetically preferred arrangement relative to the central tetrasubstituted C10 carbon prior to the late stage *n*-hexyl group installation at the C2 position. The applicability of the new methodology to other alkaloidal targets is currently under study.

Summary

Looking back, I was indeed fortunate to have grown up in an era where the funding of one's research program was reasonable and it was possible to follow a path of "*curiosity driven*" research. Early on, I was involved in physical organic photochemistry in its "*hey-day*". Some of the experiments that we carried out led us toward a study of 1,3-dipolar cycloaddition chemistry. This, in turn, directed us to the field of rhodium(II) carbenoid cyclizations, and this got me thinking about using cascade chemistry for the synthesis of heterocyclic ring systems. The efficiency with which heterocycles can be constructed is important because it affects not only the production costs for the desired material but also the environmental impact associated with waste disposal, conservation of source materials like petroleum stocks, and energy consumption. The rate of increase in molecular intricacy as one progresses from simple starting materials to the final product can serve as a measure of efficiency. On one end of the continuum, a single synthetic step could convert an inexpensive material into a highly complex heterocyclic product. On the other end lies a linear series of transformations, wherein a single atom or group is added in each step to build complexity. As a prerequisite for an ideally proceeding one-pot sequential transformation, the reactivity pattern of all participating components has to be such that each building block gets involved in a reaction only when it is supposed to do so. The reality of chemical synthesis is somewhere between these extremes, with the one-step process held as the ideal. Because of the rate at which they increase molecular intricacy, cascade reactions have received considerable attention from my research team over the past 25 years. The development of sequences that combine transformations of differing fundamental mechanism broadens the scope of such procedures in synthetic chemistry and provides me with continuing challenges for reaching an "*ideal summit*".

The journey of an academic chemist is a challenging one—teaching students, sitting on various committees, obtaining grants, publishing papers, helping to ensure the success of former Ph.D. students, and making sense of our ongoing chemistry projects. I have often questioned the relevance of what we have done and continue to do, but have come to recognize that organic chemistry is a window of unlimited opportunities. Going to my office is like an adventure every day. To me, chemistry opened up a world of continuing experiences: seeing the world and interacting with young

SCHEME 43



Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

FIGURE 10. Emory faculty (front row: Debbie Mohler, Lanny Liebeskind, Dennis Liotta, Al Padwa, Fred Menger; back row: Frank McDonald, David Goldsmith, Jim Snyder, Craig Hill).

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

students as well as colleagues (Figure 10) and scientists from around the globe. A message that I often relate to my students is that with immense hard work and sincere efforts, anything is possible. While it is essential for us as scientists to keep abreast of new knowledge through research, it is extremely important to maintain a proper balance between professional and nonprofessional activities. Indeed, the flexibility of my schedule has allowed me to develop a myriad of outside interests which are quite varied such as competitive sports (racquet ball in particular), conditioning for mountaineering, yoga, the creation of "rust-art" sculptures, and the time to add new pieces to my ever expanding collection of "mobiles". Would I do anything differently if I had to do it again? Certainly not!

Acknowledgment. Finally, I would like to express my heartfelt gratitude to my many talented students and collaborators whose names appear in the appropriate references cited herein. The major funding of our research program has come from the NSF and NIH for which I am eternally grateful. The support and encouragement of various colleagues throughout my career is most appreciated. In particular, I cherish the good fellowship and chemical advice from the late Paul Gassman as well as Leo Paquette (The Ohio State University), Joseph Tufariello (SUNY Buffalo), Howard Zimmerman (University of Wisconsin), David Goldsmith, Lanny Liebeskind, and Huw Davies (Emory University), Mike Doyle (University of Maryland), and Jeff Seeman (University of Richmond). I owe special thanks to Rolf Huisgen (University of Munich) and Gilbert Stork (Columbia) for both their kindness and helpfulness over the years, to the memory of Al Meyers (Colorado State University) who had always been there for me, to my good buddy, Will Pearson, who has been willing to join me in an array of heterocyclic projects, and to my colleague Stefan Lutz for the artwork of the cover page which corresponds to a picture of Annapurna II in Nepal that was taken on our trek in April 2009.

References

(1) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1961**, *83*, 2207.
(2) Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1961**, *83*, 2213.
(3) Walling, C. *Fifty Years of Free Radicals; Profiles, Pathways and Dreams*; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, 1995.
(4) Zimmerman, H. E.; Lewis, R.; McCullough, J.; Padwa, A.; Staley, S.; Semmelhack, M. *J. Am. Chem. Soc.* **1966**, *88*, 159.
(5) (a) Yates, P.; Jorgenson, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 2956. (b) Yates, P.; Still, I. W. J. *J. Am. Chem. Soc.* **1963**, *85*, 1209.
(6) (a) Padwa, A. *Tetrahedron Lett.* **1964**, *15*, 813. (b) Padwa, A.; Hartman, R. *J. Am. Chem. Soc.* **1964**, *86*, 4214.
(7) Padwa, A.; Crumrine, D.; Hartman, R.; Layton, R. *J. Am. Chem. Soc.* **1967**, *89*, 4435.
(8) Padwa, A.; Hamilton, L. *J. Am. Chem. Soc.* **1965**, *87*, 1821.
(9) Padwa, A.; Hamilton, L. *J. Am. Chem. Soc.* **1967**, *89*, 102.
(10) Padwa, A.; Eisenhardt, W.; Gruber, R.; Pashayan, D. *J. Am. Chem. Soc.* **1971**, *93*, 6998.
(11) (a) Padwa, A.; Bergman, W.; Pashayan, D. *J. Am. Chem. Soc.* **1968**, *90*, 4458. (b) Padwa, A.; Bergmark, W.; Pashayan, D. *J. Am. Chem. Soc.* **1969**, *91*, 2653.
(12) (a) Padwa, A.; Gruber, R. *J. Am. Chem. Soc.* **1970**, *92*, 100. (b) Padwa, A.; Albrecht, F.; Singh, P.; Vega, E. *J. Am. Chem. Soc.* **1971**, *93*, 2928. (c) Padwa, A.; Glazer, E. *J. Am. Chem. Soc.* **1972**, *94*, 7788. (d) Padwa, A.; Battisti, A.; Shefter, E. *J. Am. Chem. Soc.* **1969**, *91*, 4000.
(13) Padwa, A.; Hamilton, L. *J. Heterocycl. Chem.* **1967**, *4*, 118.
(14) Padwa, A.; Smolanoff, A. *J. Am. Chem. Soc.* **1971**, *93*, 548.
(15) Padwa, A.; Dharan, M.; Smolanoff, J.; Wetmore, S. I. *J. Am. Chem. Soc.* **1973**, *95*, 1945.
(16) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x

(17) Padwa, A.; Griffin, G. In *Photochemistry of Heterocyclic Compounds*; Buchardt, O., Ed.; J. Wiley and Sons, Inc.: New York, 1976; pp 41−122.
(18) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123.
(19) (a) Padwa, A.; Gingrich, H.; Lim, R. *Tetrahedron Lett.* **1980**, *21*, 3419. (b) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786.
(20) Padwa, A.; Kline, D. N.; Norman, B. H. *J. Org. Chem.* **1989**, *54*, 810.
(21) (a) Padwa, A.; Dent, W.; Parker, K. A.; Cohen, I. D. *Tetrahedron Lett.* **1984**, *25*, 4917. (b) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235. (c) Padwa, A.; Chen, Y. Y.; Chiacchio, U.; Dent, W *Tetrahedron* **1985**, *41*, 3529.
(22) Padwa, A.; Schoffstall A. *Advances in Cycloaddition Chemistry*; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 1−89.
(23) (a) Padwa, A.; Fryxell, G. E.; Zhi, L.; Hornbuckle, S. F. *Tetrahedron Lett.* **1988**, 6889. (b) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 301. (c) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
(24) (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263. (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (c) Padwa, A.; Austin, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.
(25) Padwa, A. *Helv. Chim. Acta* **2005**, *88*, 1357.
(26) (a) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417. (b) Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931.
(27) (a) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471. (b) Hodgson, D. M.; Labande, H.; Pierard, F. Y. T. M.; Castro, M. A. E. *J. Org. Chem.* **2003**, *68*, 6153. (c) Hodgson, D. M.; Glen, R.; Redgrave, A. J. *Tetrahedron Lett.* **2002**, *43*, 3927. (d) Hodgson, D. M.; Glen, R.; Grant, G. H.; Redgrave, A. J. *J. Org. Chem.* **2003**, *68*, 581.
(28) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998.
(29) (a) Davies, H. M. L.; Beckwith, E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1. (c) Davies, H. M. L.; Walji, A. M. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 301−340.
(30) Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 1491.
(31) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667.
(32) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1997**, *62*, 1317.
(33) Marino, J. P. Jr.; Osterhout, M. H.; Price, A. T.; Semones, M. A.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 5518.
(34) (a) Padwa, A.; Marino, J. P. Jr.; Osterhout, M. H. *J. Org. Chem.* **1995**, *60*, 2704. (b) Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418. (c) Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731. (d) Osterhout, M. H.; Nadler, W. R.; Padwa, A *Synthesis* **1994**, 123.
(35) (a) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315. (b) Regitz, M.; Hocker, J.; Leidhergener, A. *Organic Syntheses*; John Wiley: New York, 1973; Collect. Vol. 5, p 179.
(36) Padwa, A.; Brodney, M. A.; Marino, J. P. Jr.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1997**, *62*, 67.
(37) (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(38) Padwa, A.; Brodney, M. A.; Marino, J. P. Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78.
(39) (a) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647. (b) Stork, G. *Pure Appl. Chem.* **1968**, *17*, 383.
(40) Heathcock, C. H.; Kleinman, E.; Binkley, E. S. *J. Am. Chem. Soc.* **1978**, *100*, 8036.
(41) (a) Mondon, A.; Hansen, K. F.; Boehme, K.; Faro, H. P.; Nestler, J. H.; Vilhuber, H. G.; Böttcher, K. *Chem. Ber.* **1970**, *103*, 615. (b) Mondon, A.; Seidel, P. R. *Chem. Ber.* **1971**, *104*, 2937. (c) Mondon, A.; Nestler, H. *J. Chem. Ber.* **1979**, *112*, 1329.
(42) (a) Sheehan, S. M.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 438. (b) Straub, C. S.; Padwa, A. *Org. Lett.* **1999**, *1*, 83. (c) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648. (d) Mmutlane, E. M.; Harris, J. M.; Padwa, A. *J. Org. Chem.* **2005**, *70*, 8055.
(43) (a) Raolji, G. B.; Garcon, S.; Greene, A. E.; Kanazawa, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5059. (b) Anderson, R. J.; Raolji, G. B.; Kanazawa, A.; Greene, A. E. *Org. Lett.* **2005**, *7*, 2989.
(44) (a) Padwa, A.; Dean, D.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *114*, 593. (b) Padwa, A.; Dean, D.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451.
(45) Padwa, A.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *33*, 3273.
(46) Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheehan, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155.
(47) Weingarten, M. D.; Prein, M.; Price, A. T.; Snyder, J. P.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 2001.
(48) (a) Padwa, A.; Lynch, S. M.; Mejiá-Oneto, J. M.; Zhang, H. *J. Org. Chem.* **2005**, *70*, 2206. (b) Mejiá-Oneto, J. M.; Padwa, A. *Tetrahedron Lett.* **2004**, *45*, 9115.
(49) (a) Padwa, A.; Price, A. T. *J. Org. Chem.* **1995**, *60*, 6258. (b) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556.
(50) (a) Mejiá-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275. (b) Mejiá-Oneto, J. M.; Padwa, A. *Helv. Chim. Acta* **2008**, *91*, 285.
(51) (a) Cochran, J. E.; Wu, T.; Padwa, A. *Tetrahedron Lett.* **1996**, *37*, 2903. (b) Schlessinger, R. H.; Bergstrom, C. P. *Tetrahedron Lett.* **1996**, *37*, 2133. (c) Schlessinger, R. H.; Wu, X. H.; Pettus, T. R. R. *Synlett* **1995**, 536. (d) Schlessinger, R. H.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246. (e) Schlessinger, R. H.; Bergstrom, C. P. *J. Org. Chem.* **1995**, *60*, 16.
(52) (a) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179. (b) Woo, W.; Keay, B. *Synthesis* **1996**, 669. (c) Dean, F. M. *Adv. Heterocycl. Chem.* **1981**, *30*, 168.
(53) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088.
(54) (a) Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *J. Org. Chem.* **1984**, *49*, 3427. (b) Jung, M. E.; Gervey, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469. (c) Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770.
(55) Llabres, J. M.; Viladomat, F.; Bastida, J.; Codina, C.; Rubiralta, M. *Phytochemistry* **1986**, *25*, 2637.
(56) (a) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1985**, *24*, 1825. (b) Perez, D.; Bures, G.; Guitian, E.; Castedo, L. *J. Org. Chem.* **1996**, *61*, 1650.
(57) Hill, R. K. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 483.
(58) Hutchings, R. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004 and references cited therein.
(59) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304.
(60) (a) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233. (b) Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119.
(61) Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332.
(62) (a) Zhang, H.; Padwa, A. *Org. Lett.* **2006**, *8*, 247. (b) Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570.
(63) (a) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279. (b) Padwa, A.; Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J. Jr. *J. Org. Chem.* **2008**, *73*, 3539.
(64) (a) Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 3495. (b) Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 3938. (c) Padwa, A.; Cochran, J. E.; Kappe, C. O. *J. Org. Chem.* **1996**, *61*, 3706. (d) Kappe, C. O.; Padwa, A. *J. Org. Chem.* **1996**, *61*, 6166.
(65) DeLucchi, O.; Miotti, U.; Modena, G. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley: New York, 1991; Chapter 3, pp 157−184.
(66) Grierson, D. S.; Husson, H. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 6, pp 909−947.
(67) Kennedy, M.; McKervey, M. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, pp 193−216.
(68) (a) Magnus, P. D.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. (b) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, C.; Deluca, M.; Merrit, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116.
(69) Padwa, A.; Gunn, D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353.
(70) Padwa, A.; Kappe, C. O.; Cochran, J. E.; Snyder, J. P. *J. Org. Chem.* **1997**, *62*, 2786.
(71) Ripoll, J. L.; Vallee, Y. *Synthesis* **1993**, 659.
(72) (a) Padwa, A.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1996**, *61*, 4888. (b) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144.
(73) Tsuda, Y.; Hosoi, S.; Nakai, A.; Sakai, Y.; Abe, T.; Ishi, Y.; Kiuchi, F.; Sano, T. *Chem. Pharm. Bull.* **1991**, *39*, 1365.
(74) (a) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515. (b) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197.
(75) (a) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (b) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719. (c) Kice, J. L.; Favstritsky, N. A. *J. Am. Chem. Soc.* **1969**, *91*, 1751. (d) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. (e) Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544.
(76) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412.
(77) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1971**, *168*, 183.
(78) (a) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 2417. (b) Norman, B. H.; Gareau, Y.; Padwa, A. *J. Org. Chem.* **1991**, *56*, 2154.
(79) Padwa, A.; Watterson, S.; Ni, Z. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. 9, p 82; Vol. 74, p 147.
(80) (a) Grigg, R.; Kemp, J.; Thompson, N. *Tetrahedron Lett.* **1978**, *19*, 2827. (b) Grigg, R.; Gunaratne, H. Q.; Kemp, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 41. (c) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89. (d) Donegan, G.; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett.* **1989**, *30*, 609. (e) Grigg, R.; Dorrity, M. R. J.; Heaney, F.; Malone, J. F. M.; Rajvirongit, S.; Sridhararan, V.; Surendrakumar, S. *Tetrahedron Lett.* **1988**, 4323. (f) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett.* **1990**, *31*, 559. (g) Grigg, R.; Malone, J. F.; Dorrity,

M. R. J.; Heaney, F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron Lett*. **1988**, *29*, 4323.
(81) (a) Hassner, A.; Maurya, R. *Tetrahedron Lett*. **1989**, 2289. (b) Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett*. **1987**, *27*, 683. (c) Hassner, A.; Maurya, R. *Tetrahedron Lett*. **1989**, *30*, 5803. (d) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. *Tetrahedron Lett*. **1988**, *29*, 4169.
(82) Wilson, M. S.; Padwa, A *J. Org. Chem*. **2008**, *73*, 9601.
(83) (a) Cordell, G. A. In *Introduction to Alkaloids - A Biogenic Approach*; Wiley-Interscience: New York, 1981; pp 574−832. (b) Brown, R. T. In *The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; John Wiley: New York, 1983; pp −199. (c) Martin, S. F. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: San Diego, 1989; pp 291−322.
(84) Stearman, C. J.; Wilson, M. S.; Padwa, A *J. Org. Chem*. **2009**, *74*, 3491.
(85) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Org. Lett*. **2008**, *10*, 1871.

Downloaded by Jonathan Berry on September 11, 2009 | http://pubs.acs.org
Publication Date (Web): August 10, 2009 | doi: 10.1021/jo901300x