Domino reactions of rhodium(II) carbenoids for alkaloid synthesis†

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In this tutorial review, the rhodium(II)-catalyzed domino reactions of α-diazo carbonyl compounds are summarized. The article will emphasize some of the more recent synthetic applications of the rhodium carbenoid cyclization/cycloaddition domino cascade for alkaloid synthesis. The many structurally diverse and highly successful examples of both oxa and azapoly cyclic ring formation cited in this tutorial review clearly demonstrate that the domino cyclization/cycloaddition cascade of metallo carbenoids has evolved as an important strategy for the synthesis of nitrogen containing natural products.

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† Part of the rapid formation of molecular complexity in organic synthesis themed issue.

Albert Padwa received his BA and PhD from Columbia University and after a NSF Postdoctoral fellowship at the University of Wisconsin, he was appointed Assistant Professor at Ohio State University. He moved to SUNY Buffalo in 1966 as an Associate Professor and advanced to the rank of Professor in 1969. Since 1979 he has been the William P. Timmie Professor of Chemistry at Emory University. He has authored over 700 publications in such diverse areas as organic photochemistry, heterocyclic chemistry, and the synthesis of alkaloids. He was Chairman of the Organic Division of the American Chemical Society in 1985 and is currently an Associate Editor of the Journal of Organic Chemistry. Aside from Chemistry, his other passion is mountain climbing in various parts of the world.
Domino reactions
(reactions in which several bonds are formed in one sequence without the isolation of intermediates, the changing of reaction conditions, or the addition of reagents),
multi-component reactions, and the so-called “telescoping” of reactions
(the sequencing of multiple transformations in a single reaction vessel through the changing of conditions and/or adding of reagents at appropriate times)
allow for a rapid increase in molecular complexity in a single chemical operation.
The terms “cascade” and “tandem” have also been applied to all three of these reaction types and are thus used as general descriptors in this field.
This review contains a representative sampling from the last 20 years of Rh(II)-catalyzed reactions of a-diazo carbonyl compounds that have been sequenced into domino cascades to produce novel heterocyclic molecules.
Application of rhodium carbenoids in heterocyclic synthesis

In 1986 we* started work in our laboratory to synthesize bridged hetero-substituted bicycloalkanes from the rhodium(II)-catalyzed cyclization/cycloaddition cascade of 1-diazo- alkanediones.

The carbonyl ylide dipole generated from the treatment of α-diazo ketoester 4 with Rh$_2$(OAc)$_4$ underwent intramolecular cycloaddition with the tethered p-bond to form the C$_6$, C$_9$-oxido bridge **tigliane** ring system 5
Heterocyclic synthesis using 1,3-oxazolium-4-oxides (isomünchnones)

An extension of the above cyclization cascade is the formation of 1,3-oxazolium-4-oxides (isomünchnones) by treating a-diazo imides of type 6 with a Rh(II) catalyst.

The resulting mesoionic ylide 7 corresponds to the cyclic equivalent of a carbonyl ylide and this dipole undergoes [3 + 2]-cycloaddition with suitable dipolarophiles.
Cyclization/cycloaddition/cationic $\pi$-cyclization reactions

By starting from simple acyclic $\alpha$-diazooimides 19, our research group has established a domino cyclization/cycloaddition/cationic $\pi$-cyclization protocol as a method for the construction of complex nitrogen polyheterocycles of type 21.
Cycloaddition of isomünchnones across heteroaromatic $\pi$-systems

The ability of diazoimide 31 to undergo this intramolecular cycloaddition across a heteroaromatic ring is presumably due to proper orbital overlap between the dipole and dipolarophile which is also assisted by formation of a six-membered ring.
Alkaloid synthesis using isomünchnones as key intermediates

Given the success in forming novel azabicyclic systems derived from an intramolecular isomünchnone cycloaddition reaction, we applied this domino strategy for a formal synthesis of **vallesamidine (40)** via the key Heathcock intermediate **39**
Cycloaddition chemistry of thioisomünchnones for the synthesis of heterocycles

Dipole cascade processes

Rh(II)-catalyzed equilibration of carbonyl and ammonium ylides

Cycloaddition of push-pull carbonyl ylides
3. Conclusion

Domino carbonyl ylide generation from the reaction of metallo carbenoids with carbonyl compounds continues to be of great interest both mechanistically and synthetically. Effective carbonyl ylide formation in transition metal catalyzed reactions of diazo compounds depends on the catalyst (ligand), the diazo species, the nature of the interacting carbonyl group and competition with other processes. The many structurally diverse and highly successful examples of azapolycyclic ring formation cited in this tutorial review clearly demonstrate that the domino cyclization/cycloaddition cascade of metallo carbenoids has evolved as an important strategy for the synthesis of nitrogen containing natural products.