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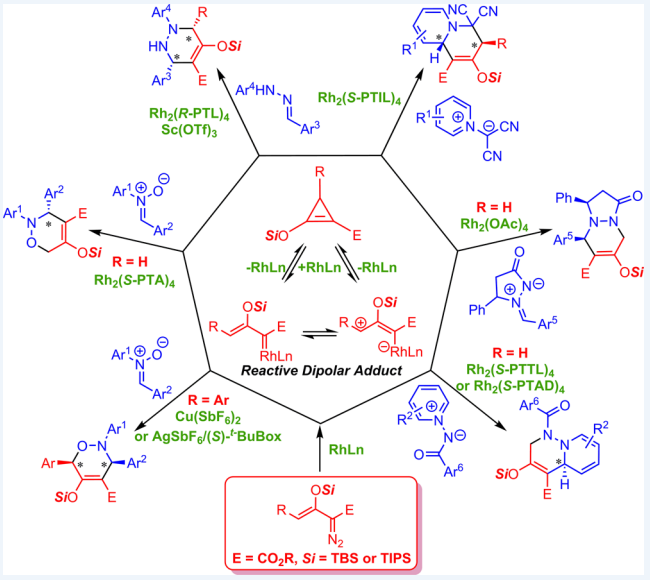
The [3 + 3]-Cycloaddition Alternative for Heterocycle Syntheses: Catalytically Generated Metalloenolcarbenes as Dipolar Adducts

Xinfang Xu and Michael P. Doyle*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States

CONSPECTUS: The combination of two or more unsaturated structural units to form cyclic organic compounds is commonly referred to as cycloaddition, and the combination of two unsaturated structural units that forms a six-membered ring is formally either a [5 + 1]-, [4 + 2]-, [2 + 2 + 2]-, or [3 + 3]-cycloaddition. Occurring as concerted or stepwise processes, cycloaddition reactions are among the most useful synthetic constructions in organic chemistry. Of these transformations, the concerted [4 + 2]-cycloaddition, the Diels−Alder reaction, is by far the best known and most widely applied. However, although symmetry disallowed as a concerted process and lacking certifiable examples until recently, stepwise [3 + 3]-cycloadditions offer advantages for the synthesis of a substantial variety of heterocyclic compounds, and they are receiving considerable attention.



In this Account, we present the development of stepwise [3 + 3]-cycloaddition reactions from virtual invisibility in the 1990s to a rapidly growing synthetic methodology today, involving organocatalysis or transition metal catalysis. With origins in organometallic or vinyliminium ion chemistry, this area has blossomed into a viable synthetic transformation for the construction of six-membered heterocyclic compounds containing one or more heteroatoms. The development of [3 + 3]-cycloaddition transformations has been achieved through identification of suitable and compatible reactive dipolar adducts and stable dipoles. The reactive dipolar species is an energetic dipolar intermediate that is optimally formed catalytically in the reaction. The stepwise process occurs with the reactive dipolar adduct reacting as an electrophile or as a nucleophile to form the first covalent bond, and this association provides entropic assistance for the construction of the second covalent bond and the overall formal [3 + 3]-cycloaddition. Organocatalysis is well developed for both inter- and intramolecular synthetic transformations, but the potential of transition metal catalysis for [3 + 3]-cycloaddition has only recently emerged. The key to the rapid development of the transition metal-based methodology has been recognition that certain catalytically generated vinylcarbenes are effective dipolar adducts for reactions with stable dipolar compounds, including aryl and vinyl ylides. In particular, metallo-enolcarbenes that are generated catalytically from conveniently prepared stable enoldiazoacetates or from donor−acceptor cyclopropenes are highly effective dipolar adducts for [3 + 3]-cycloaddition. The electron-donating oxygen of the silyl ether enhances electrophilic ring closure to the metal-bound carbon of the initial adduct from vinylogous addition, and this enhancement inhibits the alternative [3 + 2]-cycloaddition across the carbon−carbon double bond of the vinylcarbene.

Catalytically generated metallo-enolcarbenes react under mild conditions with a broad spectrum of compatible stable dipoles, including nitrones, azomethine imines, ylides, and certain covalent precursors of stable dipoles, to form [3 + 3]-cycloaddition products having the β-ketoester functionality (in dihydrooxazines, tetrahydropyridazines, pyrazolidinone and pyraxole derivatives, dihydroquinolines, and quinolizidines, for example) in high yield. Two ways to access these metallo-enolcarbenes, either by dinitrogen extrusion from enoldiazoacetate esters or by rearrangement of donor−acceptor cyclopropenes, enhance the versatility of the process. The [3 + 3]-cycloaddition methodology is a complementary strategy to [4 + 2]-cycloaddition for the synthesis of heterocyclic compounds having six-membered rings. High levels of enantioselectivity are obtained with the use of chiral ligands on transition metal catalysts that include those on dirhodium(II) and silver(I).

1. INTRODUCTION

Two reviews in 1996 and 1997[1,2] reported that [3 + 3]-cycloadditions were rare and that very few reports of these processes existed. They included palladium-catalyzed generation of trimethylenemethanes as dipolar adducts, which underwent stepwise cycloaddition with stable dipoles that included β-diketones and β-ketoesters,[3] as well as aziridines.[4]

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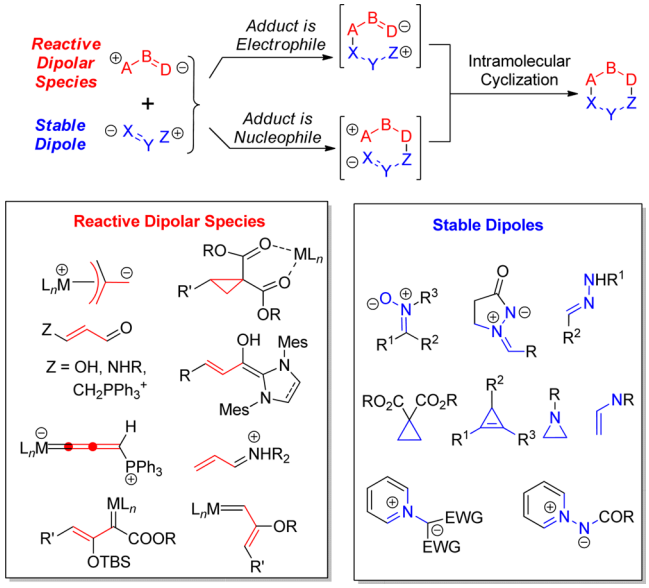
Scheme 1. Reactive Dipolar Species and Stable Dipoles Form [3 + 3]-Cycloaddition Products



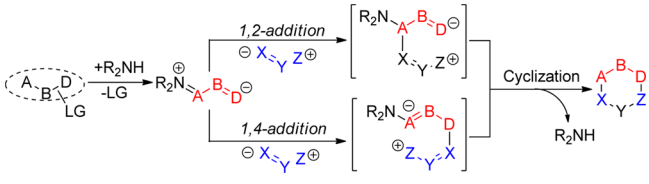
Lithiated alkoxyallenes were subsequently established in reactions with aldonitrones to provide an efficient [3 + 3]-methodology to oxazines.[5] Organometallic reagents provided the first reports that were often unexpected outcomes. These examples were followed by reports of vinyliminium reactions with vinylogous amides and enols to form an intermediate triene that underwent pericyclization to a cyclic six-membered heterocyclic diene.[6]

The development of [3 + 3]-cycloaddition transformations has been achieved through identification of suitable and compatible reactive dipolar adducts and stable dipoles (Scheme 1). The reactive dipolar species is an energetic dipolar intermediate that is generally catalytically formed in the reaction. The stable dipole is any one of a spectrum of nitrones, ylides, and covalent precursors to dipolar species. The two-step process occurs with the reactive dipolar adduct reacting as an electrophile or as a nucleophile to form the first covalent bond, and this association provides entropic assistance for the construction of the second covalent bond and the overall formal [3 + 3]-cycloaddition. The success of the overall process is a function of the compatibility of the two reacting dipolar partners and, of course, of the catalytic or stoichiometric species employed for the generation of the reactive dipolar adduct.

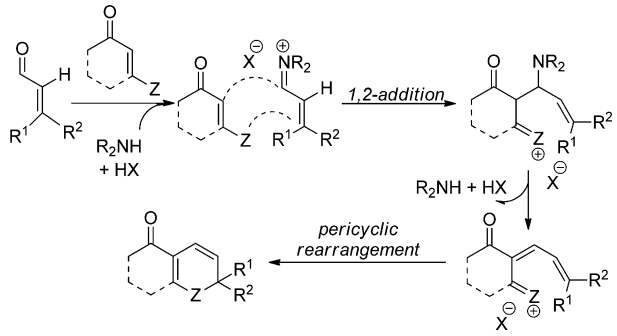
2. ORGANOCATALYSIS

There are two basic catalytic pathways with which to enter [3 + 3]-cycloaddition transformations: organocatalysis and transition metal catalysis. Organocatalysis is commonly based on

Scheme 2. Vinyliminium Ions Initiate [3 + 3]-Cycloaddition by 1,2- or 1,4-Addition



Scheme 3. Mechanistic Outline for Intermolecular Formal [3 + 3]-Cycloaddition of Enamines with Vinyliminium Salts



vinyliminium ion chemistry,[7] but phosphine catalysis might also be compatible,[8] and *N*-heterocyclic carbene catalysis has been reported.[9] Its formal relationship to [3 + 3]-cycloaddition is similar to that of the linkage of the Robinson annulation reaction to [4 + 2]-cycloaddition in that the overall process is stepwise, rather than concerted, involving addition and condensation. The vinyliminium ion is activated for either 1,2- or 1,4-addition (Scheme 2), and both processes are observed.

Extensive contributions in the organocatalysis approach have been made by Richard P. Hsung[7] who initially recognized[6] that reactions of vinyliminium ions with vinylogous amides formed an initial adduct that, upon elimination of amine, formed a conjugated hexatriene, which could undergo pericyclic rearrangement (tandem Knoevenagel/6π-electron electrocyclic ring closure pathway) to azacyclohexadienes (Scheme 3),[10] which are precursors for piperidinyl heterocycles or to 2*H*-pyrans.[11] In this pathway, a heteroatom (Z, mainly nitrogen, but also oxygen) activates 1,2-addition onto the iminium ion, and reversible β-elimination occurs to form a heterotriene that undergoes pericyclic rearrangement to form the formal [3 + 3]-cycloaddition product. Often the enamine (Z = NR_2) and the iminium ion are derived from the same unsaturated aldehyde or ketone. An extensive array of heterocyclic compounds have resulted from this methodology.[7] However, enantiocontrol for these intermolecular reactions is not straightforward due to the azatriene intermediate, although a high level of stereocontrol has been achieved with the use of chiral auxiliaries (Z = *N*-chiral auxiliary),[12] and structural modifications in the reactant pairs have formed [3 + 3]-cycloaddition products by mechanisms that circumvent the azatriene intermediate and provide high enantioselectivity.[13]

Although the structural outcome is similar to that for intermolecular reactions, the operative mechanism for intramolecular [3 + 3]-cycloaddition allows greater opportunity for enantiocontrol (Scheme 4).[10f] In this case, initial 1,4-addition occurs, followed by tautomerization and 1,2-addition with elimination of the amine and tautomerization to the final product. Asymmetric induction is controlled by the amine catalyst used to form the iminium ion reactant. Although enamine reactants are most common for this transformation, 1,3-diketones or ketoesters are suitable alternatives that form oxygen heterocycles via intramolecular reaction with an imbedded dicarbonyl[10c] or by initial Michael addition that forms the reactant for intramolecular cycloaddition.[11c,14]

Procedural variants in the sequence of reactions of Schemes 3 and 4,[11] including sequences that employ bulky amine catalysts to effect intermolecular vinylogous Michael addition to

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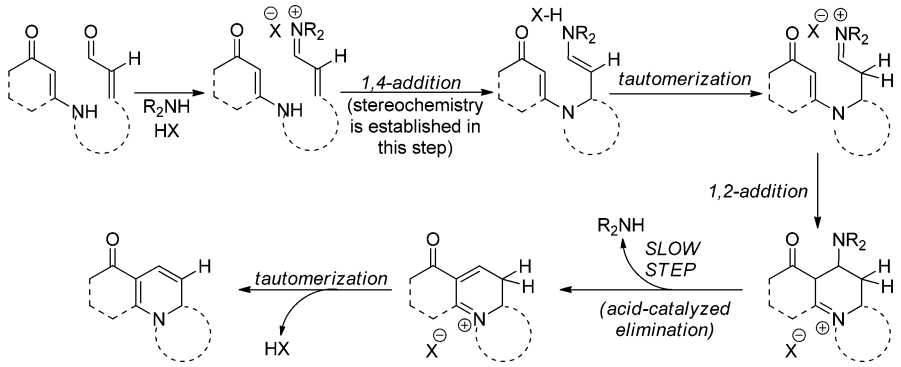
Scheme 4. Mechanistic Outline for Intramolecular Formal [3 + 3]-Cycloaddition of Enamines with Vinyliminium Salts



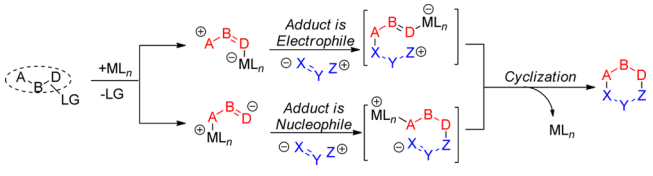
the vinyliminium ion,[13a,b,d] have been reported. In addition, diverse enamine methods have been developed that utilize enones and enals in combination with acid catalysts for the construction of six-membered ring heterocyclic[7,15] and carbocyclic[13d,16] compounds. Reactants other than enamines that include acrylic acid chlorides and esters[17] as well as allenes[18] and phosphorus ylides[19] and dipolar species that include aziridines[15a,20] and cyclopropanes[21] have been employed. Several reviews have summarized the diversity of heterocyclic compounds that can be prepared through the organocatalytic approach.[7]

3. TRANSITION METAL CATALYSIS: PRIOR INVESTIGATIONS

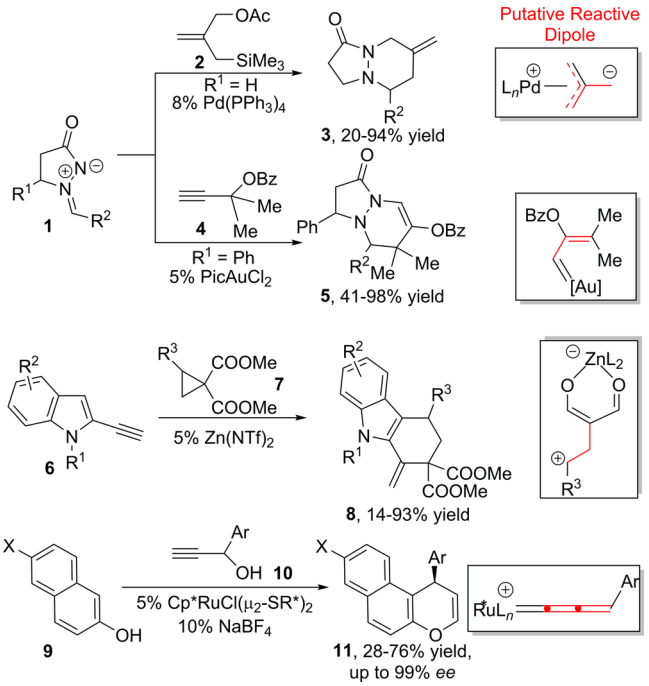
Until recently, scarce attention has been given to transition metal-catalyzed [3 + 3]-cycloaddition reactions other than for their uses as Lewis acids. Following reports by Huang and co-workers with enolates and presumed palladium acetate generated trimethylenemethane,[3] Hayashi reported a palladium-catalyzed [3 + 3]-cycloaddition between azomethine imines, as well as between an *N*,*α*-diarylnitrone and the reactive dipole trimethylenemethane, generated from [2-(acetoxymethyl)-2-propenyl]trimethylsilane, that occurred in high yield.[22] In these cases, the catalyst converts the precursor molecule to a reactive dipolar molecule that contains the ligated transition metal, which then undergoes stepwise dipolar cycloaddition to a stable dipole (Scheme 5). Although both electrophilic and nucleophilic adducts are conceivable in transition metal-catalyzed reactions, only the electrophilic adducts have been reported thus far.

Azomethine imines have proven to be a model stable dipole template for [3 + 3]-cycloaddition reactions with trimethylenemethane (Pd catalysis)[22] and propargyl esters (Au catalysis),[23] but other pairings have been limited (Scheme 6).[24] However, the variety of proposed metal-associated reactive dipoles indicates a high potential for such reactive intermediates. Although [3 + 3]-cycloaddition between 1,3-dipoles (*C*-heteroarylimines) and electrophilic Fischer vinylcarbene

Scheme 5. Transition Metal Catalyzed Generation of the Reactive Dipolar Species for [3 + 3]-Cycloaddition

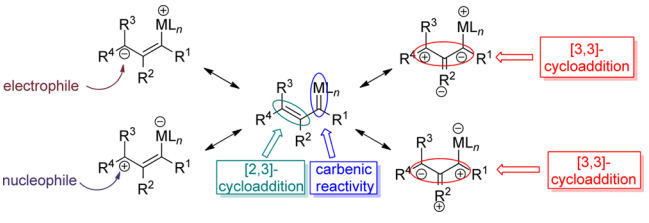


Scheme 6. Transition Metal Catalyzed [3 + 3]-Cycloaddition Reactions



complexes was reported 15 years ago,[25] it was Toste and co-workers' presentation of a gold-catalyzed reaction between a propargyl benzoate, involving a putative vinylcarbene intermediate, and azomethine imines that suggested the catalytic potential of vinylcarbene species for [3 + 3]-cycloaddition processes.[23]

Scheme 7. Resonance Contributing Structures of Vinylcarbenes Suggest Reaction Outcome



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4. [3 + 3]-CYCLOADDITION REACTIONS OF ENOLDIAZOACETATES

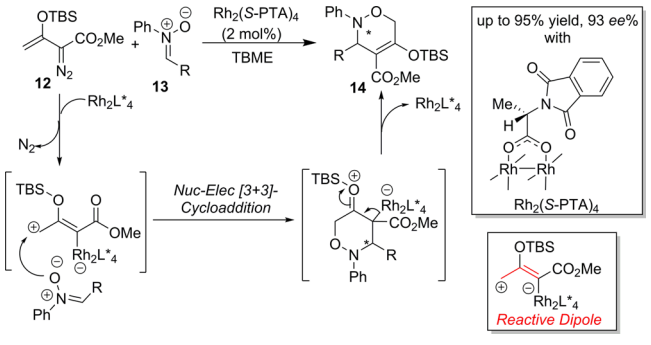
Vinylcarbenes are potential reactive dipolar adducts for [3 + 3]-cycloaddition reactions. Their resonance contributing structures (Scheme 7) suggest a variety of transformations if the dipolar characteristics of the vinylcarbene can dominate over both its carbenic character[26] and activation of the conjugated double bond for [2,3]-cycloaddition.[27] The transition metal and its associated ligands establish the nucleophilic or electrophilic character of the carbene, and R^1 enhances or diminishes its reactivity.[28] Vinyl substituents R^3 and R^4 enhance the electrophilic or nucleophilic character of the carbon to which they are attached, but it is the substituent R^2 that determines the viability of the [3 + 3]-cycloaddition transformation. Conceivably, both electrophilic and nucleophilic vinylcarbenes could undergo [3 + 3]-cycloaddition transformations, but this transformation has only been observed with electrophilic metal vinylcarbenes.

4.1. [3 + 3]-Cycloaddition Reactions of Enoldiazoacetates with Nitrones

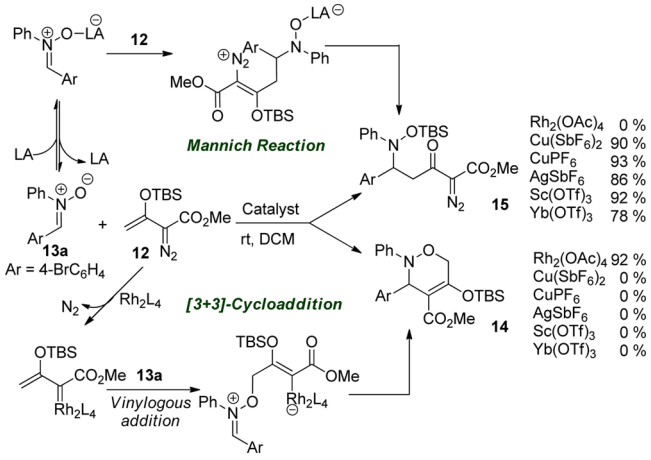
The Doyle group recently reported an enantioselective formal [3 + 3]-cycloaddition of nitrones with an enoldiazoacetate.[28] 3,6-Dihydro-1,2-oxazines are produced in high yields with high enantiocontrol when catalyzed by Hashimoto's chiral dirhodium carboxylate Rh_2(*S*-PTA)$_4$ catalyst. The reaction mechanism is proposed to involve initial dirhodium-catalyzed dinitrogen extrusion to form an intermediate metal enolcarbene. Nucleophilic attack by the nitrone at the vinylogous position of the vinylcarbene followed by intramolecular iminium ion electrophilic addition to the catalyst-activated vinyl ether functional group with elimination of the dirhodium catalyst, in a stepwise or concerted fashion (*Nuc-Elec* [3 + 3]-cycloaddition), completes the transformation. During the cyclization, iminium ion addition is facilitated by stabilization from the TBSO group, and subsequent or concurrent release of the catalyst is a favorable process (Scheme 8). Enantioselection is conferred by the catalyst in the ring-closing step, and the degree of enantiocontrol obtained is consistent with the intimate involvement of the catalyst in the transition state for cyclization. Although [3 + 2]-cycloaddition between nitrones and α,β-unsaturated carbonyl compounds,[29] and even with rhodium vinylcarbenes,[27] is known, this transformation did not occur in the reactions of enoldiazoacetate **12** with nitrones.

The reaction product is dependent on the transition metal compound used with enoldiazoacetate **12** and nitrones.[28,30] Dirhodium(II) catalysts direct the overall process solely to the

Scheme 8. [3 + 3]-Cycloaddition of Catalytically Generated Enolcarbene Reactive Dipoles with Nitrones



Scheme 9. Competition between Metal Carbene Formation and Diazonium Ion Generation



product from [3 + 3]-cycloaddition, whereas Lewis acids promote Mannich-type addition as the sole outcome from both copper(I) and other Lewis acid catalysts (Scheme 9).[31] Both transformations occur from the vinylogous position of the diazo compound or its corresponding carbene. Reaction selectivity for diazonium ion generation is determined, at least in part, by the ability of the catalyst to coordinate with the stable dipole, which enhances its electrophilic character relative to undergoing addition at the diazo carbon, which results in metal carbene formation following extrusion of dinitrogen. The absence of dinitrogen extrusion from reaction between enoldiazoacetate and copper(I) catalysts is particularly surprising in view of the known ability of copper(I) catalysts to generate carbene intermediates with diazo compounds.[26]

4.2. Stepwise [3 + 3]-Cycloaddition Reactions of Enoldiazoacetates with Hydrazones and Azomethine Imines

The stepwise nature of the cycloaddition process is evident in the reaction of hydrazones with enoldiazoacetate **16**.[32] A vinylogous 1,4-N–H insertion/Mannich addition cascade reaction gives 1,2,3,6-tetrahydropyridazines **18** in good overall yields with up to 97% ee (Scheme 10). In this formal [3 + 3]-cycloaddition transformation excellent enantioselectivities and high diastereoselectivities are controlled by the chiral dirhodium(II) catalyst and Lewis acid, respectively. The transformation is initiated by Rh(II)-catalyzed dinitrogen extrusion followed by a previously unprecedented vinylogous 1,4-N–H insertion into the hydrazone's N–H bond, presumably through ammonium ylide intramolecular proton transfer with elimination of the catalyst.[33] The dirhodium catalyst is insufficiently Lewis acidic to activate the imine for ring closure; instead, Lewis acid promoted Mannich addition of **19** smoothly generates 1,2,3,6-tetrahydropyridazines **18** with high diastereocontrol (Scheme 11).

Guided by the formal [3 + 3]-cycloaddition reactions of enoldiazoacetates with nitrones and hydrazones, various 1,3-dipoles have been examined for their compatibility. With azomethine imines, a highly regio- and diastereoselective [3 + 3]-annulation reaction with enoldiazoacetates gives bicyclic pyrazolidinone derivatives **20** when R^1 is an alkyl, an aryl, or a vinyl group (Scheme 12).[34] However, when R^1 is hydrogen, N–N-cleavage of the azomethine imine occurs, and imine derivative **21** is obtained. The two different outcomes in this

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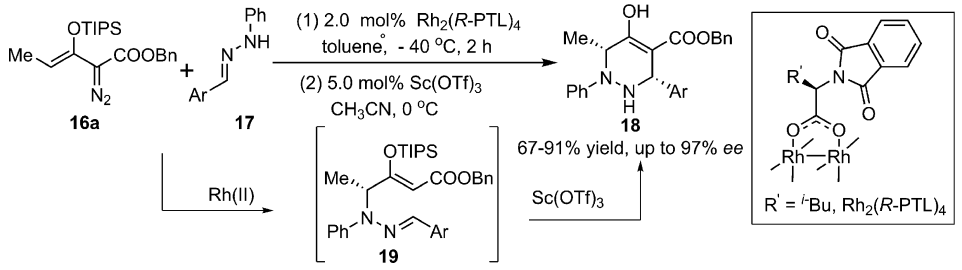
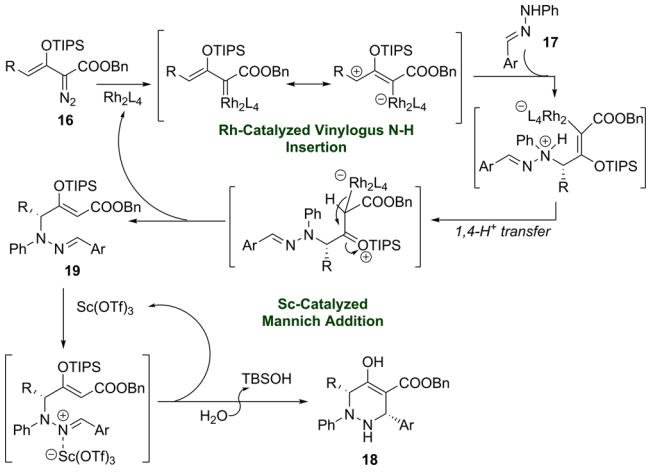
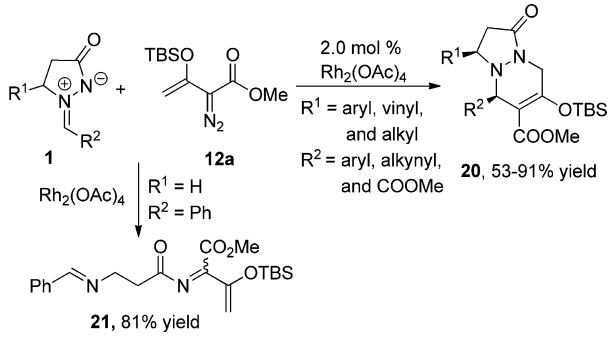
Scheme 10. Two-Step, One-Pot [3 + 3]-Cycloaddition of Catalytically Generated Enolcarbene Reactive Dipoles with Hydrazones



Scheme 11. Mechanism of [3 + 3]-Cycloaddition by 1,4-N−H Insertion of Catalytically Generated Enolcarbene Reactive Dipoles with Hydrazones Followed by Lewis Acid Directed Ring Closure



Scheme 12. [3 + 3]-Cycloaddition of Catalytically Generated Enolcarbene Reactive Dipoles with Azomethine Imines

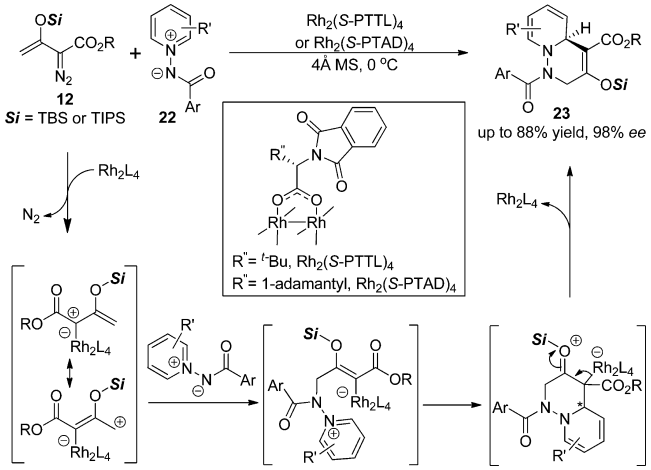


reaction occur by nucleophilic attack of the azomethine imine on the metal enolcarbene at the vinylogous position (R^1 = alkyl, aryl, or vinyl) or at the metal carbene center (R^1 = H), but the precise cause is unknown.

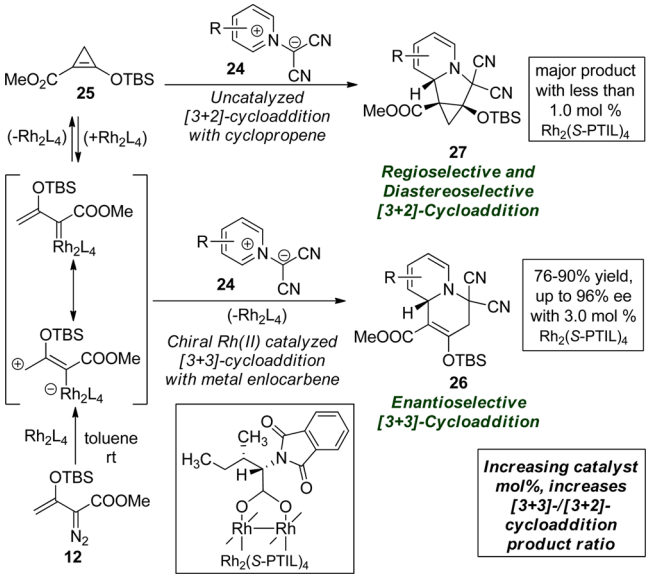
4.3. Dearomatization in [3 + 3]-Cycloaddition Reactions of Enoldiazoacetates

Unlike in reactions of nitrones, hydrazones, and azomethine ylides with enolcarbene intermediates, reactions with *N*-iminopyridinium ylides afford a barrier to cycloaddition due to dearomatization, and for this reason, it is perhaps not surprising that [3 + 3]-cycloaddition reactions with *N*-iminopyridinium ylides have only been reported in limited cases with 1,1-cyclopropane diesters.[35] However, application of

Scheme 13. [3 + 3]-Cycloaddition of Catalytically Generated Enolcarbene Reactive Dipoles with *N*-Iminopyridinium Ylides



Scheme 14. [3 + 3]-Cycloaddition of Catalytically Generated Enolcarbene Reactive Dipoles with Isoquinolinium/Pyridinium Methylides



N-acyliminopyridinium ylides (**22**) as stable dipoles in reactions with enoldiazoacetates catalyzed by dirhodium(II) catalysts gave the [3 + 3]-cycloaddition product in high isolated yields and with exceptional enantiocontrol when catalyzed by Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTAD)$_4$ (Scheme 13).[36] In this

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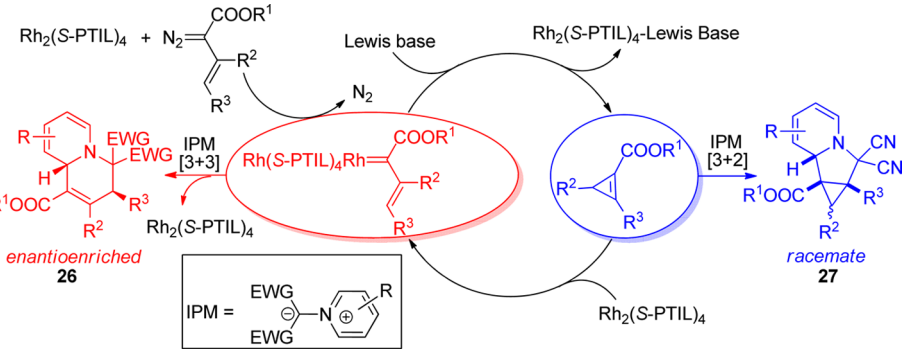
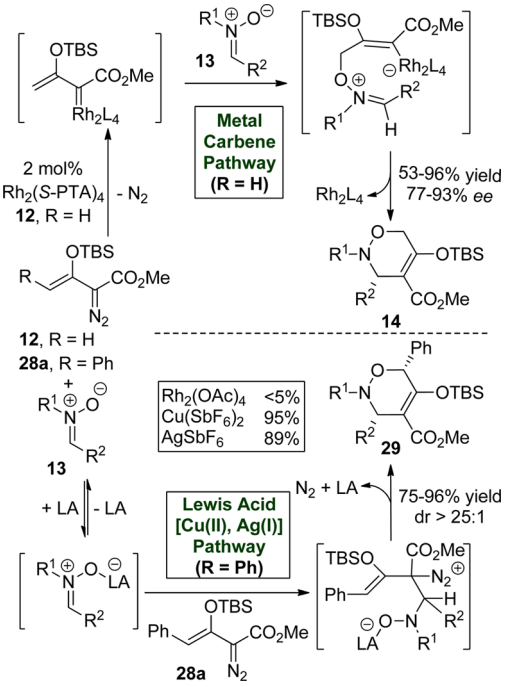
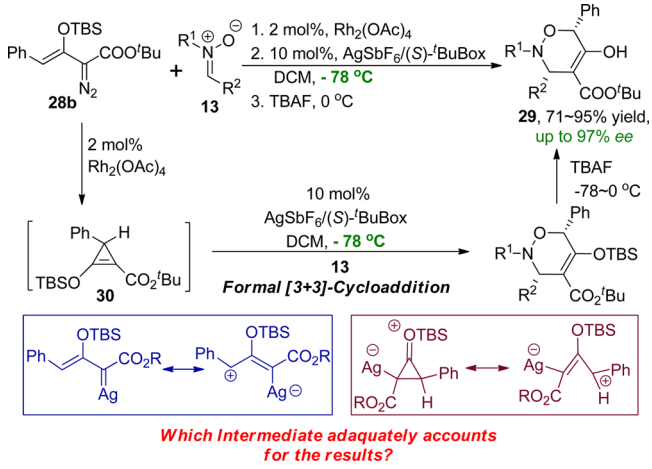
Scheme 15. Involvement of Donor–Acceptor Cyclopropenes in Cycloaddition Reactions of Catalytically Generated Enolcarbene Reactive Dipoles with Isoquinolinium/Pyridinium Methylides



Scheme 16. Dipolar Intermediates Catalytically Generated for Metal Carbene or Lewis Acid Adduct [3 + 3]-Cycloaddition Reactions



Scheme 17. [3 + 3]-Cycloaddition of Silver(I)-generated Reactive Dipoles from Donor–Acceptor Cyclopropenes with Nitrones



transformation, steric effects have an important influence on the control of selectivity since dirhodium catalysts with bulky ligands [Rh_2(*S*-PTTL)$_4$ instead of Rh_2(*S*-PTA)$_4$] give dramatic improvements in selectivity control. Either pyridine, quinoline, or isoquinoline derived ylides work very well in these [3 + 3]-cycloaddition reactions, giving up to 98% ee in reactions with enoldiazoacetates.

The stable dipoles described thus far were not sufficiently basic to cause inhibition of dirhodium catalysts toward metal carbene formation. These dirhodium(II) compounds are mild Lewis acids that coordinate with Lewis bases,[37] sometimes causing diminished reactivity toward diazo compounds. Isoquinolinium/pyridinium methylides are readily accessible nucleophiles of variable base strengths[38] that readily undergo [2 + 3]-cycloaddition reactions.[39] Testing the limits of stable dipoles in their reactions with metalloenolcarbenes, isoquinolinium/pyridinium methylides were treated with enoldiazoacetate **12** in the presence of dirhodium catalyst without obvious catalyst inhibition, and instead of 1,3-dipolar cyclization through [2 + 3]-cycloaddition, [3 + 3]-cycloaddition readily occurred to give substituted quinolizidines **26** in high yield and high enantioselectivity when the reaction was catalyzed by Rh_2(*S*-PTIL)$_4$ (Scheme 14).[40] The reaction outcome was solvent, catalyst, and temperature dependent with a competing process that formed an apparent product from [3 + 2]-cycloaddition of **24** to donor–acceptor cyclopropene **25**.

4.4. Donor–Acceptor Cyclopropenes as Reactive Enolcarbene Sources in [3 + 3]-Cycloaddition Reactions

During investigations with isoquinolinium/pyridinium methylides, a unique equilibrium was revealed by the competitive formation of [2 + 3]-cycloaddition product **27** in amounts that varied with the amount of catalyst employed. Coordination of Lewis basic methylides to dirhodium(II) was established, and this association was proposed to prompt rearrangement of the enolcarbene bound to dirhodium(II) to produce donor–acceptor cyclopropene **25**. However, independently formed donor–acceptor cyclopropene **25** was also demonstrated to be a precursor of the same metal carbene intermediate that formed **26** (identical enantioselectivities), and via this process, the donor–acceptor cyclopropene is in equilibrium with the dirhodium-bound enolcarbene (Scheme 15). The reaction pathways in this system involve enantioselective [3 + 3]-cycloaddition from the dirhodium-bound enolcarbene and uncatalyzed diastereoselective [3 + 2]-cycloaddition of cyclopropene **25** with isoquinolinium or pyridinium methylides.

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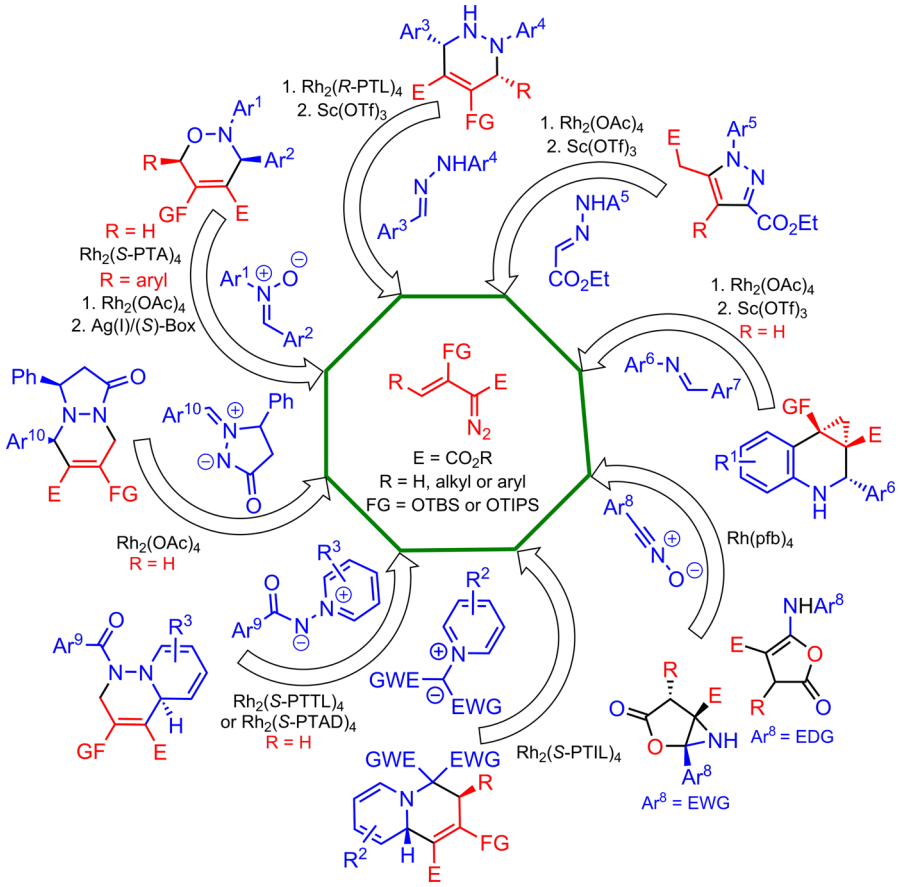
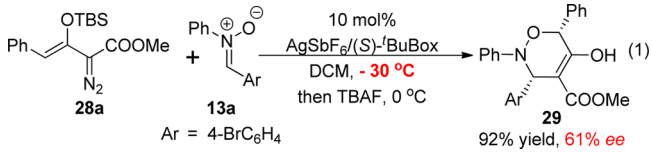
Scheme 18. Heterocyclic Syntheses from Cycloaddition Reactions with Enoldiazoacetates



Variation in the silyl ether and carboxylate ester groups of enoldiazoacetates maintains the [3 + 3]-cycloaddition process that occurs through a metal carbene pathway in dirhodium(II)-catalyzed reactions, but changing the substituents at the vinylogous position can inhibit this cycloaddition pathway. For example, when γ-phenyl enoldiazoacetate **28** underwent dinitrogen extrusion with rhodium(II) acetate in the presence of diphenylnitrone **13**, there was no observable product from [3 + 3]-cycloaddition even though O−H insertion into benzyl alcohol readily occurred. However, catalysis by $Cu(SbF_6)_2$ and $AgSbF_6$ gave the [3 + 3]-cycloaddition product in high yield within 5 min under the same conditions (Scheme 16).[41] The reaction pathway with Cu(II) and Ag(I) changed from that with dirhodium(II) and is consistent with one involving Lewis acid addition to the diazo carbon to form a diazonium ion intermediate (Scheme 16).

In an effort to effect enantiocontrolled cycloaddition of γ-phenyl-enoldiazoacetate **28a** with nitrones, $AgSbF_6$/(*S*)-^{t}BuBox catalyst was found to be superior to all other Lewis acid/ligand combinations used, giving the [3 + 3]-cycloaddition product in 92% yield but with only 61% ee under conditions limited by the temperature necessary to initiate the reaction (eq 1, −30 °C). However, with the corresponding donor−acceptor cyclopropene generated *in situ* from γ-phenyl-enoldiazoacetate **28** through catalysis by rhodium(II) acetate, formation of the [3 + 3]-cycloaddition product could be optimized (Scheme 17) to 93% yield with 90% ee (at −78 °C with the ^{t}Bu ester **28b**).[42] Here the question arises of whether the silver(I)-catalyzed reaction is the result of a process that occurs through an organometallic intermediate formed by electrophilic addition of Ag(I) to the carbon−carbon double bond of the donor−acceptor cyclopropene or, as is suggested from results with dirhodium(II) catalysts on the cyclopropene analogues without the phenyl substituent, through a silver-enolcarbene intermediate.[43] Enantioselectivities from the reactions of **28** and the corresponding donor−acceptor cyclopropene (**30**) with $AgSbF_6$/(*S*)-^{t}BuBox are not exactly the same (61% ee vs 67% ee), so both intermediates must be considered.



5. SUMMARY AND OUTLOOK

The success of enoldiazoacetates in achieving highly selective [3 + 3]-cycloaddition transformations can be attributed to several factors, among which are steric influences around the metal carbenic center that inhibit attachment of nucleophiles at the carbonic center lending preference to vinylogous attachment. Another advantage is the electrophilic character imparted to the vinylogous position by the ligated transition metal of the metal carbene (Scheme 7). However, it is the electron-donating oxygen of the silyl ether that enhances the viability of electrophilic ring closure to the metal-bound carbon (Schemes 8, 11, 13, and 16) and inhibits the alternative [3 + 2]-cycloaddition. The extent to which other electron-donating substituents will favor [3 + 3]-cycloaddition is yet to be determined, but replacement of the silyl ether by hydrogen (but

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not phenyl) in reactions with an isoquinolinium methylide (Scheme 14) that produces the [3 + 3]-cycloaddition product exclusively in modest yield suggests broad application.[40] That donor−acceptor cyclopropenes are suitable precursors to the same enolcarbene intermediates formed by catalytic dinitrogen extrusion of enoldiazoacetates provides an alternative entry to [3 + 3]-cycloaddition reactions that is just now being investigated; however, just as with enoldiazoacetates and as was found with organocatalysis, multiple mechanistic pathways to the same reaction products are possible, and alternatives to dirhodium(II) catalysts may be viable.

In conclusion, catalytically generated enolcarbenes are effective reactive dipolar species for reactions with stable dipolar compounds, and they are key to the development of [3 + 3]-cycloaddition reactions as a complementary strategy to alternative [4 + 2]-cycloaddition for the synthesis of heterocyclic compounds. In particular, metallo-enolcarbenes that are generated catalytically from conveniently prepared and highly stable enoldiazoacetates or from donor−acceptor cyclopropenes are highly effective dipolar adducts that give six-membered ring heterocyclic products, not only with nitrones,[28,41,42] hydrazones,[32] and ylide derivatives,[36,40] but also with nitrile oxides,[44] oximes,[45] imines,[46] and donor−acceptor substituted hydrazones[47] (Scheme 18). With this methodology, one or more heteroatoms can be introduced into the six-membered ring in high yields and with high levels of stereocontrol obtained through the use of asymmetric catalysts.[48] Further applications of these enoldiazoacetates are worth pursuing with new catalyst development for the stereoselective synthesis of functionalized heterocyclic compounds.

AUTHOR INFORMATION

Corresponding Author

*E-mail: mdoyle3@umd.edu.

Notes

The authors declare no competing financial interest.

Biographies

Xinfang Xu was born in Zhejiang in 1981. He received his B.S. in 2005 and his Ph.D. in 2010 from East China Normal University (Shanghai China) under the direction of Professor Wenhao Hu, after which he joined Mike Doyle's research group at the University of Maryland. His current research interest is asymmetric cycloaddition reactions for the synthesis of heterocyclic compounds.

Michael P. Doyle began his academic career at Hope College in 1968, moved to Trinity University (San Antonio, TX) in 1984, to Tucson, AZ in 1997 as Vice President and then President of Research Corporation and Professor at the University of Arizona, then to the University of Maryland in 2003. The development of new catalytic strategies and chemical processes with diazocarbonyl compounds is a major focus of his research efforts.

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REFERENCES

(1) Lautens, M.; Klute, W.; Tam, W. Transition Metal-Mediated Cycloaddition Reactions. *Chem. Rev.* **1996**, *96*, 49−92.
(2) Frühauf, H. Metal-Assisted Cycloaddition Reactions in Organo-transition Metal Chemistry. *Chem. Rev.* **1997**, *97*, 523−596.
(3) (a) Huang, Y.; Lu, X. Novel Palladium Catalayzed Synthesis of Pyran Derivatives. *Tetrahedron Lett.* **1987**, *28*, 6219−6220. (b) Huang, Y.; Lu, X. Palladium Catalyzed Annulation Reaction Using a Bifunctional Allylic Alkylating Agent. *Tetrahedron Lett.* **1988**, *29*, 5663−5664.
(4) Bambal, R. B.; Kemmitt, R. D.W. [3 + 3] Cycloaddition of Trimethylenemethane to Activated Aziridines: Palladium-catalysed Synthesis of Piperidines. *J. Organomet. Chem.* **1989**, *362*, C18−C20.
(5) (a) Schadw, W.; Reissig, H.-U. A New Diastereoselective Synthesis of Enantiomerically Pure 1,2-Oxazine Derivatives by Addition of Lithiated Methoxyallene to Chiral Nitrones. *Synlett* **1999**, 632−634. (b) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fisera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. Stereodivergent Syntheses of Highly Substituted Enantiopure 4-Alkoxy-3,6-dihydro-2*H*-1,2-oxazines by Addition of Lithiated Alkoxyallenes to Carbohydrate-Derived Aldonitrones. *Eur. J. Org. Chem.* **2005**, 1003−1019. (c) Al-Harrasi, A.; Reissig, H.-U. Synthesis of Enantiopure Carbohydrate Mimetics by Lewis Acid Catalyzed Rearrangement of 1,3-Dioxolanyl-Substituted 1,2-Oxazines. *Angew. Chem., Int. Ed.* **2005**, *44*, 6227−6231.
(6) (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. Sequential 1,2-Addition−Electrocyclic Ring Closures Involving Acyclic α,β-Unsaturated Iminiums: A Formal [3 + 3] Cycloaddition Strategy to Unique Pyranyl Spirocycles. *J. Org. Chem.* **1999**, *64*, 690−691. (b) Sklenicka, H. M.; Hsung, R. P.; Wei, L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J. Highly Stereoselective Formal [3 + 3] Cycloaddition Reactions of Chiral Vinylogous Amides with α,β-Unsaturated Iminiums. *Org. Lett.* **2000**, *2*, 1161−1164.
(7) (a) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. A Formal [3 + 3] Cycloaddition Approach to Natural-Product Synthesis. *Eur. J. Org. Chem.* **2005**, 23−44. (b) Buchanan, G. S.; Feltenberger, J. B.; Hsung, R. P. Aza-[3 + 3] Annulations: A New Unified Strategy in Alkaloid Synthesis. *Curr. Org. Synth.* **2010**, *7*, 363−401. (c) Deng, J.; Wang, X.-N.; Hsung, R. P. A Formal [3 + 3] Cycloaddition Approach to Natural Product Synthesis. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*; Nishiwaki, N., Ed.; Wiley-VCH: Weinheim, Germany, 2013, Chapter 12.
(8) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Guo, H.; Kwon, O. Phosphine-Catalyzed Annulations of Azomethine Imines: Allene-Dependent [3 + 2], [3 + 3], [4 + 3], and [3 + 2+3] Pathways. *J. Am. Chem. Soc.* **2011**, *133*, 13337−13348.
(9) Chan, A.; Scheidt, K. A. Highly Stereoselective Formal [3 + 3] Cycloaddition of Enals and Azomethine Imines Catalyzed by N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2007**, *129*, 5334−5335.
(10) (a) Luo, S.; Zificsak, C. A.; Hsung, R. P. Intramolecular Formal Aza-[3 + 3] Cycloaddition Approach to Indoloquinolizidine Alkaloids. A Stereoselective Total Synthesis of (±)-Tangutorine. *Org. Lett.* **2003**, *5*, 4709−4712. (b) Cole, K. P.; Hsung, R. P. Intramolecular Formal *oxa*-[3 + 3] Cycloaddition Approach to the ABD System of Phomactin A. *Org. Lett.* **2003**, *5*, 4843−4846. (c) Sydorenko, N.; Hsung, R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. Tetronamides as Latent Acyclic Vinylogous Amides in Formal *Aza*-[3 + 3] Cycloaddition Reactions with α,β-Unsaturated Iminium Salts. An Unexpected Rearrangement and an Approach to Synthesis of Substituted Piperidines. *J. Org. Chem.* **2004**, *69*, 6732−6738. (d) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. A Formal [3 + 3] Cycloaddition Reaction. 5. An Enantioselective Intramolecular Formal Aza-[3 + 3] Cycloaddition Reaction Promoted by Chiral Amine Salts. *J. Org. Chem.* **2005**, *70*, 4248−4256. (e) Wang, Y.; Fang, D.; Liu, R. Theoretical Studies on Formal Hetero [3 + 3] Cycloaddition Reaction Between Vinylogous

Amide and α,β-Unsaturated Imine Cation. *Tetrahedron* **2005**, *61*, 5663−5669. (f) Kurdyumov, A. V.; Lin, N.; Hsung, R. P.; Gullickson, G. C.; Cole, K. P.; Sydorenko, N.; Swidorski, J. J. A Lewis Acid-Catalyzed Formal [3 + 3] Cycloaddition of α,β-Unsaturated Aldehydes with 4-Hydroxy-2-pyrone, Diketones, and Vinylogous Esters. *Org. Lett.* **2006**, *8*, 191−193.

(11) (a) Luo, S.; Zhao, J.; Zhai, H. A Fast Assembly of Pentacyclic Benz[*f*]indolo[2,3-*a*]quinolizidine Core by Tandem Intermolecular Formal Aza-[3 + 3] Cycloaddition/Pictet−Spengler Cyclization: A Formal Synthesis of (±)-Tangutorine. *J. Org. Chem.* **2004**, *69*, 4548−4550. (b) Hong, B.; Tseng, H.; Chen, S. Synthesis of Aromatic Aldehydes by Organocatalytic [4 + 2] and [3 + 3] Cycloaddition of α,β-Unsaturated Aldehydes. *Tetrahedron* **2007**, *63*, 2840−2850. (c) Hubert, C.; Moreau, J.; Batany, J.; Duboc, A.; Hurvois, J.; Renaud, J. Brønsted Acid-Catalyzed Synthesis of Pyrans *via* a Formal [3 + 3] Cycloaddition. *Adv. Synth. Catal.* **2008**, *350*, 40−42.

(12) (a) Sklenicka, H. M.; Hsung, R. P.; Wei, L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J. Highly Stereoselective Formal [3 + 3] Cycloaddition Reactions of Chiral Vinylogous Amides with α,β-Unsaturated Iminiums. *Org. Lett.* **2000**, *2*, 1161−1164. (b) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.; Gerasyuto, A. I.; Brennessel, W. B. Stereoselective Formal [3 + 3] Cycloaddition Approach to cis-1-Azadecalins and Synthesis of (−)-4a,8a-diepi-Pumiliotoxin C. Evidence for the First Highly Stereoselective 6π-Electron Electrocyclic Ring Closures of 1-Azatrienes. *J. Am. Chem. Soc.* **2002**, *124*, 10435−10442.

(13) (a) Movassaghi, M.; Chen, B. Stereoselective Intermolecular Formal [3 + 3] Cycloaddition Reaction of Cyclic Enamines and Enone. *Angew. Chem., Int. Ed.* **2007**, *46*, 565−568. (b) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. Diphenylprolinol Silyl Ether as a Catalyst in an Enantioselective, Catalytic, Formal Aza [3 + 3] Cycloaddition Reaction for the Formation of Enantioenriched Piperidines. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012−4015. (c) Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. Diphenylprolinol Silyl Ether Catalysis in an Asymmetric Formal Carbo [3 + 3] Cycloaddition Reaction via a Domino Michael/Knoevenagel Condensation. *Org. Lett.* **2009**, *11*, 45−48. (d) Huang, J.; Zhao, L.; Liu, Y.; Cao, W.; Wu, X. Enantioselective Intermolecular Formal [3 + 3] Cycloaddition of 2,3-Disubstituted Indoles with Acrolein. *Org. Lett.* **2013**, *15*, 4338−4341.

(14) Zhu, M.; Wei, Q.; Gong, L. Organocatalytic Asymmetric Formal [3 + 3] Cycloaddition Reactions of α,β-Unsaturated Aldehydes with Nazarov Reagents. *Adv. Synth. Catal.* **2008**, *350*, 1281−1285.

(15) (a) Harrity, J. P. A.; Provoost, O. [3 + 3] Cycloadditions and Related Strategies in Alkaloid Natural Product Synthesis. *Org. Biomol. Chem.* **2005**, *3*, 1349−1358. (b) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. Strategies and Approaches for Constructing 1-Oxadecalins. *Tetrahedron* **2006**, *62*, 10785−10813. (c) Lawrence, A. K.; Gademann, K. Aza-Annulation Strategies in Alkaloid Total Synthesis. *Synthesis* **2008**, 331−351.

(16) (a) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. Enantioselective Organocatalytic Formal [3 + 3]-Cycloaddition of α,β-Unsaturated Aldehydes and Application to the Asymmetric Synthesis of (−)-Isopulegol Hydrate and (−)-Cubebaol. *Org. Lett.* **2006**, *8*, 2217−2220. (b) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. Enantioselective Formal [3 + 3] Annulation for the Direct Construction of Bicyclic Skeletons with Four Stereogenic Centers. *Org. Lett.* **2007**, *9*, 4151−4154. (c) Li, L.; Zhao, M.; Ren, Z.; Li, J.; Guan, Z. $Cu(OAc)_2$/TFA-Promoted Formal [3 + 3] Cycloaddition/Oxidation of Enamines and Enones for Synthesis of Multisubstituted Aromatic Amines. *Org. Lett.* **2012**, *14*, 3506−3509.

(17) (a) Zhong, W.; Lin, F.; Chen, R.; Su, W. An Efficient Synthesis of 2-Hydroxy-7,8-dihydroquinolin-5(6*H*)-ones and 7,8-Dihydroquinoline-2,5(1*H*,6*H*)-diones from Morita-Baylis-Hillman Adduct Acetates. *Synthesis* **2008**, 2561−2568. (b) Pilipecz, M. V.; Varga, T. R.; Mucsi, Z.; Scheiber, P.; Nemes, P. [3 + 3] Cyclization Reactions of β-Nitroenamines and β-Enaminonitriles with α,β-Unsaturated Carboxylic Acid Chlorides. *Tetrahedron* **2008**, *64*, 5545−5550. (c) Alladoum, J.; Toum, V.; Hebbe, S.; Kadouri-Puchot, C.; Dechoux, L. Aza-annulation of β-Enaminolactones: Application to the Synthesis of Enantiopure Difunctionalized Bicyclic Lactams. *Tetrahedron Lett.* **2009**, *50*, 617−619.

(18) Guo, H.; Xu, Q.; Kwon, O. Phosphine-Promoted [3 + 3] Annulations of Aziridines with Allenoates: Facile Entry into Highly Functionalized Tetrahydropyridines. *J. Am. Chem. Soc.* **2009**, *131*, 6318−6319.

(19) (a) Ye, L.-W.; Han, X.; Sun, X.-L.; Tang, Y. Tandem Michael Addition/Ylide Olefination Reaction for the Synthesis of Highly Functionalized Cyclohexadiene Derivatives. *Tetrahedron* **2008**, *64*, 8149−8154. (b) Ye, L.-W.; Wang, S.-B.; Wang, Q.-G.; Sun, X.-L.; Tang, Y.; Zhou, Y.-G. Asymmetric Tandem Michael Addition−Ylide Olefination Reaction for the Synthesis of Optically Active Cyclohexa-1,3-diene Derivatives. *Chem. Commun.* **2009**, 3092−3094. (c) Shu, Z.; Zhu, J.; Liao, S.; Sun, X.; Tang, Y. Facile and Controllable Synthesis of Multiply Substituted Benzenes via a Formal [3 + 3] Cycloaddition Approach. *Tetrahedron* **2013**, *69*, 284−292.

(20) (a) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. A [3 + 3] Annelation Approach to Tetrahydropyridines. *Org. Lett.* **2006**, *8*, 3089−3091. (b) Manceya, N. C.; Butlinb, R. J.; Harrity, J. P. A. Investigation of a Tandem Iminium Ion Allylation Approach to Piperidines. *Synlett* **2008**, *17*, 2647−2650. (c) Wang, S.; Chai, Z.; Zhou, S.; Wang, S.; Zhu, X.; Wei, Y. A Novel Lewis Acid Catalyzed [3 + 3]-Annulation Strategy for the Syntheses of Tetrahydro-β-Carbolines and Tetrahydroisoquinolines. *Org. Lett.* **2013**, *15*, 2628−2631. (d) Fang, X.; Li, J.; Tao, H.; Wang, C. Highly Diastereoselective DABCO-Catalyzed [3 + 3]-Cycloaddition of 1,4-Dithiane-2,5-diol with Azomethine Imines. *Org. Lett.* **2013**, *15*, 5554−5557.

(21) Recent references include: (a) Dias, D. A.; Kerr, M. A. Domino Synthesis of Bridged Bicyclic Tetrahydro-1,2-oxazines: Access to Stereodefined 4-Aminocyclohexanols. *Org. Lett.* **2009**, *11*, 3694−3697. (b) Hu, B.; Zhu, J.; Xing, S.; Fang, J.; Du, D.; Wang, Z. A Highly Site-, Regio-, and Stereoselective Lewis Acid Catalyzed Formal [3 + 3] Cycloaddition of Methylenecyclopropane-1,1-Diesters with *C,N*-Diarylnitrones. *Chem.—Eur. J.* **2009**, *15*, 324. (c) Zhang, Y.; Liu, F.; Zhang, J. Catalytic Regioselective Control in the Diastereoselective 1,3-Dipolar Cycloaddition Reactions of 1-(1-Alkynyl)cyclopropyl Ketones with Nitrones. *Chem.—Eur. J.* **2010**, *16*, 6146−6150. (d) Gorbacheva, E. O.; Tabolin, A. A.; Novikov, R. A.; Khomutova, Y. A.; Nelyubina, Y. V.; Tomilov, Y. V.; Ioffe, S. L. Six-Membered Cyclic Nitronates as 1,3-Dipoles in Formal [3 + 3]-Cycloaddition with Donor_Acceptor Cyclopropanes. Synthesis of New Type of BicyclicNitrosoacetals. *Org. Lett.* **2013**, *15*, 350−353.

(22) Shintani, R.; Hayashi, T. Palladium-Catalyzed [3 + 3] Cycloaddition of Trimethylenemethane with Azomethine Imines. *J. Am. Chem. Soc.* **2006**, *128*, 6330−6331.

(23) Shapiro, N. D.; Shi, Y.; Toste, F. D. Gold-Catalyzed [3 + 3]-Annulation of Azomethine Imines with Propargyl Esters. *J. Am. Chem. Soc.* **2009**, *131*, 11654−11655.

(24) (a) Kanao, K.; Miyake, Y.; Nishibayashi, Y. Ruthenium-Catalyzed Enantioselective [3 + 3] Cycloaddition of Propargylic Alcohols with 2-Naphthols. *Organometalllics* **2010**, *29*, 2126−2131. (b) Grover, H. K.; Lebold, T. P.; Kerr, M. A. Tandem Cyclopropane Ring-Opening/Conia-ene Reactions of 2-Alkynyl Indoles: A [3 + 3] Annulative Route to Tetrahydrocarbazoles. *Org. Lett.* **2011**, *13*, 220−223.

(25) Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. A.; García-Granda, S.; Priede, M. P. Unusual [1,2]- and [1,3]-$M(CO)_5$ Shifts in Fischer Carbene Complexes: [4 + 3] and [3 + 3] Annulation Reactions of Furan and Pyrrole Rings. *J. Am. Chem. Soc.* **1999**, *121*, 3065−3071.

(26) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons, Inc.: New York, 1998.

(27) (a) Wang, X.; Abrahams, Q. M.; Zavalij, P. Y.; Doyle, M. P. Highly Regio- and Stereoselective Dirhodium Vinylcarbene-induced Nitrone Cycloaddition with Subsequent Cascade Carbenoid Aromatic Cycloaddition/N-O Cleavage and Rearrangement. *Angew. Chem., Int. Ed.* **2012**, *51*, 5907−5910. (b) Xu, X.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. Highly Selective Catalyst-Dependent Competitive 1,2-C→C,

-O→C, and -N→C Migrations from β-Methylene-β-silyloxy-β-amido-α-diazoacetates. *J. Am. Chem. Soc.* **2013**, *135*, 1244−12447.
(28) (a) Wang, X.; Xu, X.; Doyle, M. P. Asymmetric Formal [3 + 3] Cycloaddition Reactions of Nitrones with Electrophilic Vinylcarbene Intermediates. *J. Am. Chem. Soc.* **2011**, *133*, 16402−16405. (b) Pagar, V. V.; Jadhav, A. M.; Liu, R. Gold-Catalyzed Formal [3 + 3] and [4 + 2] Cycloaddition Reactions of Nitrosobenzenes with Alkenylgold Carbenoids. *J. Am. Chem. Soc.* **2011**, *133*, 20728−20731.
(29) (a) Wang, X.; Weigl, C.; Doyle, M. P. Solvent Enhancement of Reaction Selectivity: A Unique Property of Cationic Chiral Dirhodium Carboxamidates. *J. Am. Chem. Soc.* **2011**, *133*, 9572−9579. (b) Qin, C.; Davies, H. M. L. Rh_2(*R*-TPCP)$_4$-Catalyzed Enantioselective [3 + 2]-Cycloaddition between Nitrones and Vinyldiazoacetates. *J. Am. Chem. Soc.* **2013**, *135*, 14516−14519.
(30) Xu, X.; Hu, W.-H.; Doyle, M. P. Divergent Outcomes from Catalysis by Dirhodium and Copper Separately or in Combination. *Angew. Chem., Int. Ed.* **2011**, *50*, 11152−11355.
(31) Xu, X.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. Multifunctionalized 3-Hydroxypyrroles in a Three-Step, One-Pot Cascade Process from Methyl 3-TBSO-2-diazo-3-butenoate and Nitrones. *Org. Lett.* **2011**, *13*, 6122−6125.
(32) Xu, X.; Zavalij, P. Y.; Doyle, M. P. Synthesis of Tetrahydropyridazines by a Metal−Carbene-Directed Enantioselective Vinylogous N-H Insertion/Lewis Acid-Catalyzed Diastereoselective Mannich Addition. *Angew. Chem., Int. Ed.* **2012**, *51*, 9829−9833.
(33) (a) Xu, B.; Zhu, S.; Xie, X.; Shen, J.; Zhou, Q. Asymmetric N-H Insertion Reaction Cooperatively Catalyzed by Rhodium and Chiral Spiro Phosphoric Acids. *Angew. Chem., Int. Ed.* **2011**, *50*, 11483−11486. (b) Zhu, S.; Zhou, Q. Transition-Metal-Catalyzed Enantioselective Heteroatom−Hydrogen Bond Insertion Reactions. *Acc. Chem. Res.* **2012**, *45*, 1365−1377. (c) Zhu, S.; Xu, B.; Wang, G.; Zhou, Q. Well-Defined Binuclear Chiral Spiro Copper Catalysts for Enantioselective N−H Insertion. *J. Am. Chem. Soc.* **2012**, *134*, 436−442.
(34) Qian, Y.; Zavalij, P. J.; Hu, W.; Doyle, M. P. Bicyclic Pyrazolidinone Derivatives from Diastereoselective Catalytic [3 + 3]-Cycloaddition Reactions of Enoldiazoacetates with Azomethine Imines. *Org. Lett.* **2013**, *15*, 1564−1567.
(35) (a) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. Cycloadditions of Aromatic Azomethine Imines with 1,1-Cyclopropane Diesters. *Org. Lett.* **2008**, *10*, 689−692. (b) Zhou, Y.; Li, J.; Ling, L.; Liao, S.; Sun, X.; Li, Y.; Wang, L.; Tang, Y. Highly Enantioselective [3 + 3] Cycloaddition of Aromatic Azomethine Imines with Cyclopropanes Directed by π−π Stacking Interactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 1452−1456.
(36) Xu, X.; Zavalij, P. Y.; Doyle, M. P. Highly Enantioselective Dearomatizing Formal [3 + 3]-Cycloaddition Reactions of *N*-Acyliminopyridinium Ylides with Electrophilic Enolcarbene Intermediates. *Angew. Chem., Int. Ed.* **2013**, *52*, 12664−12668.
(37) Xu, X.; Doyle, M. P. Enantiomer Recognition of Amides by Chiral Dirhodium(II) Carboxamidates. *Inorg. Chem.* **2011**, *50*, 7610−7617.
(38) Allgäuer, D. S.; Mayer, P.; Mayr, H. Nucleophilicity Parameters of Pyridinium Ylides and Their Use in Mechanistic Analyses. *J. Am. Chem. Soc.* **2013**, *135*, 15216−15224.
(39) (a) Fernández, N.; Carrillo, L.; Vicario, J. L.; Badia, D.; Reyes, E. Organocatalytic Enantioselective (3 + 2) Cycloaddition Using Stable Azomethine Ylides. *Chem. Commun.* **2011**, *47*, 12313−12315. (b) Kucukdisli, M.; Opatz, T. A Modular Synthesis of Polysubstituted Indolizines. *Eur. J. Org. Chem.* **2012**, 4555−4564. (c) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. Synthesis of Functionalized Indolizines via Copper-Catalyzed Annulation of 2-Alkylazaarenes with α,β-Unsaturated Carboxylic Acids. *Org. Lett.* **2012**, *14*, 957−959. (d) Allgäuer, D. S.; Mayr, H. One-Pot Two-Step Synthesis of 1-(Ethoxycarbonyl)-indolizines via Pyridinium Ylides. *Eur. J. Org. Chem.* **2013**, 6379−6388.
(40) Xu, X.; Zavalij, P. Y.; Doyle, M. P. Catalytic Asymmetric Syntheses of Quinolizidines by Dirhodium-Catalyzed Dearomatization of Isoquinolinium/Pyridinium Methylides−The Role of Catalyst and Carbene Source. *J. Am. Chem. Soc.* **2013**, *135*, 12439−12447.
(41) Qian, Y.; Xu, X.; Wang, X.; Zavalij, P. Y.; Hu, W.; Doyle, M. P. Rhodium(II)- and Copper(II)-Catalyzed Reactions of Enol Diazoacetates with Nitrones: Metal Carbene versus Lewis Acid Directed Pathways. *Angew. Chem., Int. Ed.* **2012**, *51*, 5900−5903.
(42) Xu, X.; Zavalij, P. Y.; Hu, W.; Doyle, M. P. A Donor-Acceptor Cyclopropene as a Dipole Source for a Silver(I) Catalyzed Asymmetric Catalytic [3 + 3]-Cycloaddition with Nitrones. *Chem. Commun.* **2013**, *49*, 10287−10289.
(43) References for silver carbene: (a) Thompson, J. L.; Davies, H. M. L. Enhancement of Cyclopropanation Chemistry in the Silver-Catalyzed Reactions of Aryldiazoacetates. *J. Am. Chem. Soc.* **2007**, *129*, 6090−6091. (b) Urbano, J.; Braga, A. A. C.; Maseras, F.; Álvarez, E.; Díaz-Requejo, M. M.; Péerez, P. J. The Mechanism of the Catalytic Functionalization of Haloalkanes by Carbene Insertion: An Experimental and Theoretical Study. *Organometallics* **2009**, *28*, 5968−5981.
(44) (a) Xu, X.; Shabashov, D.; Zavalij, P. Y.; Doyle, M. P. Unexpected Catalytic Reactions of Silyl-Protected Enol Diazoacetates with Nitrile Oxides That Form 5-Arylaminofuran-2(3*H*)-one-4-carboxylates. *Org. Lett.* **2012**, *14*, 800−803. (b) Xu, X.; Shabashov, D.; Zavalij, P. Y.; Doyle, M. P. Substrate-Dependent Divergent Outcomes from Catalytic Reactions of Silyl-Protected Enol Diazoacetates with Nitrile Oxides: Azabicyclo[3.1.0]hexanes or 5-Arylaminofuran-2(3*H*)-ones. *J. Org. Chem.* **2012**, *77*, 5313−5317.
(45) Xu, X.; Zavalij, P. Y.; Hu, W.; Doyle, M. P. Efficient Synthesis of Oxazoles by Dirhodium(II)-catalyzed Reactions of Styryl diazoacetate with Oximes. *Chem. Commun.* **2012**, *48*, 11522−11524.
(46) Truong, P. M.; Mandler, M. D.; Zavalij, P. Y.; Doyle, M. P. Tetrahydroquinolines and Benzazepines through Catalytic Diastereoselective Formal [4 + 2]-Cycloaddition Reactions between Donor-Acceptor Cyclopropenes and Imines. *Org. Lett.* **2013**, *15*, 3278−3281.
(47) Xu, X.; Zavalij, P. Y.; Hu, W.; Doyle, M. P. Vinylogous Reactivity of Enol Diazoacetates with Donor−Acceptor Substituted Hydrazones. Synthesis of Substituted Pyrazole Derivatives. *J. Org. Chem.* **2013**, *78*, 1583−1588.
(48) Xu, X.; Doyle, M. P. Recent Developments in the Synthetic Uses of Silyl-protected Enoldiazoacetates for Heterocyclic Syntheses. *Aust. J. Chem.* **2013**, DOI: 10.1071/CH13576.