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Cycloaddition reactions of enoldiazo compounds

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Enoldiazo esters and amides have proven to be versatile reagents for cycloaddition reactions that allow highly efficient construction of various carbocycles and heterocycles. Their versatility is exemplified by (1) [2+*n*]-cycloadditions (*n* = 3, 4) by the enol silyl ether units of enoldiazo compounds with retention of the diazo functionality to furnish α-cyclic-α-diazo compounds that are themselves subject to further transformations of the diazo functional group; (2) [3+*n*]-cycloadditions (*n* = 1–5) by metallo-enolcarbenes formed by catalytic dinitrogen extrusion from enoldiazo compounds; (3) [2+*n*]-cycloadditions (*n* = 3, 4) by donor–acceptor cyclopropenes generated *in situ* from enoldiazo compounds that produce cyclopropane-fused ring systems. The role of dirhodium(II) and the emergence of copper(I) catalysts are described, as are the different outcomes of reactions initiated with these catalysts. This comprehensive review on cycloaddition reactions of enoldiazo compounds, with emphasis on methodology development, mechanistic insight, and catalyst-controlled chemodivergence, aims to provide inspiration for future discoveries in the field and to catalyze the application of enoldiazo reagents by the wider synthetic community.

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1. Introduction

Diazo compounds (N_2 = CRR′) are among the most important reagents in organic synthesis.[1–14] One of their major applications is for highly efficient carbon–carbon/carbon–heteroatom bond formation, thus allowing the construction of various carbocycles and heterocycles. In cycloaddition reactions with unsaturated compounds, diazo compounds are directly utilized as N–N- or N–N–C-type dipolar components.[15–19] They also serve as effective metal carbene precursors in a wide range of transition metal-catalyzed cyclization processes, including cyclopropanation,[20–26]

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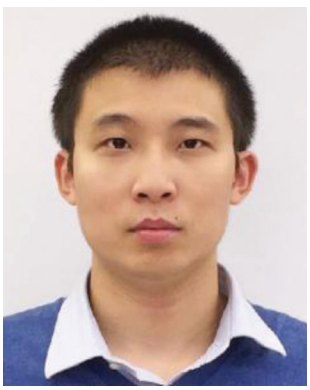
Qing-Qing Cheng was born in Binzhou of Shandong province, China in 1987. He received his BSc from Tianjin University in 2009. Then he began his graduate study at Nankai University under the supervision of Professor Qi-Lin Zhou, and obtained his PhD in organic chemistry in 2014. Subsequently, he joined the research group of Professor Michael P. Doyle at the University of Texas at San Antonio as a postdoctoral fellow. His research interests include the development of synthetic methodologies and their application in the syntheses of biologically active products, asymmetric catalysis, and medicinal chemistry. His current research in the Doyle group has focused on highly selective catalytic metal carbene transformations, in particular the cycloaddition reactions of enoldiazo compounds.



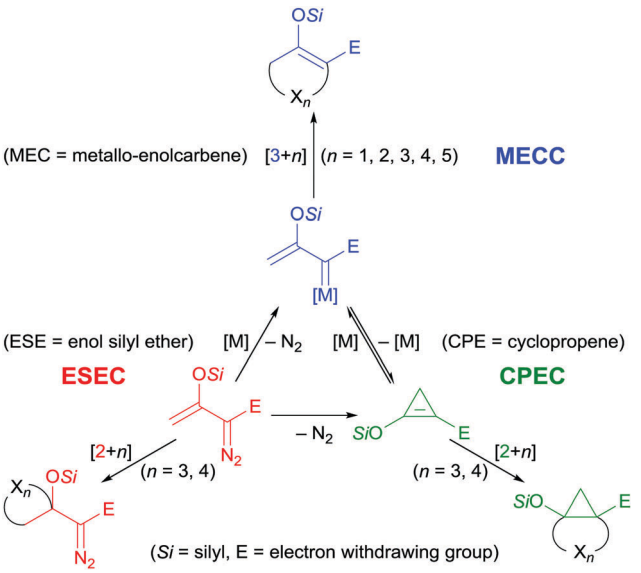
Yongming Deng

Yongming Deng received his BSc from Shandong University in 2009. In 2014, he obtained his PhD from Miami University (Ohio) under the supervision of Dr Hong Wang. At MIAMI, he was engaged in the development of enamine/metal Lewis acid cooperative catalysis for new chemical reactions discovery. In the same year, he began his postdoctoral studies with Professor Michael P. Doyle at University of Maryland then moved to the University of Texas at San Antonio. His research in the Doyle group has focused on developing assessments of new catalysts and reagents to access catalytic metal carbene reactions and on investigating selective catalytic transformations of enoldiazo compounds.

cyclopropenation,[27–30] and intramolecular carbene transformations (C–H insertion, O–H insertion, N–H insertion, dimerization, *etc.*).[31–41] Furthermore, several reactive intermediates, such as carbonyl ylides, oxonium ylides, azomethine ylides, and nitrones, can be generated from diazo compounds in the presence of transition metal catalysts and then undergo intermolecular cycloaddition or intramolecular ring closure.[16,32,34,39,42–53] Additionally, the successful combination of metal carbene chemistry and other catalytic strategies (*e.g.*, C–H activation,[45,54–62] C–C cleavage,[63–66] and gold catalysis[17,46,67–70]) is fully illustrated by recent advances in cycloaddition reactions of diazo compounds.

Bearing both enol and diazo functionalities, enoldiazo compounds have proven to be one of the most versatile tools for the development of cycloaddition reactions. As depicted in Scheme 1, (1) the Enol Silyl Ether (ESE) units of enoldiazo compounds can participate in [2+*n*]-cycloadditions (*n* = 3, 4) with retention of the diazo functionality to furnish α-cyclic-α-diazo compounds (ESEC pathway); (2) the Metallo-EnolCarbenes (MEC) formed by dinitrogen extrusion from enoldiazo compounds can act as three-carbon synthons in transition metal-catalyzed [3+*n*]-cycloadditions (*n* = 1–5, MECC pathway); (3) the donor–acceptor CycloPropEnes (CPE) generated *in situ* from enoldiazo compounds can undergo [2+*n*]-cycloadditions (*n* = 3, 4) to produce cyclopropane-fused carbocycles and heterocycles (CPEC pathway). Notably, these three reaction pathways can be switched from one to another simply by the choice of catalyst, which allows divergent cycloaddition outcomes from identical reactants and thus demonstrates the controllable versatility of enoldiazo compounds.

Despite tremendous achievements made so far in this area, a comprehensive review on cycloaddition reactions of enoldiazo compounds is still unavailable. Herein, we present a systematic overview of cycloaddition transformations involving enoldiazo compounds, with emphasis on methodology development and mechanistic insight. This review is organized based on the aforementioned cycloaddition pathways in the sequence of ESEC, MECC, and CPEC reactions, followed by a discussion of catalyst-controlled switchable chemoselectivity in these processes. While we focus on representative examples from the past two decades, early pioneering works are included as well. With the present review article we aim to inspire researchers to explore new avenues in this field, and to add enoldiazo compounds, a reagent with controllable versatility, to the toolbox of synthetic chemists.



Scheme 1 Cycloaddition reactions of enoldiazo compounds.

Marianne Lankelma

Marianne Lankelma (1994) obtained her BS and MS degrees from the University of Amsterdam, with a specialization in molecular design, synthesis, and catalysis. After her undergraduate project in the group of Prof. Dr Olivia Reinaud (Université Paris Descartes) and her graduate project in the group of Prof. Dr Joost N. H. Reek (University of Amsterdam), she completed her studies with an extracurricular internship in the group of Prof. Dr Michael P. Doyle at the University of Texas at San Antonio. Currently she investigates rhodium-mediated carbene (C1) polymerization as a PhD student under the supervision of Prof. Dr Bas de Bruin at the University of Amsterdam.

Michael P. Doyle

Michael P. (Mike) Doyle is the Rita and John Feik Distinguished University Chair in Medicinal Chemistry at the University of Texas at San Antonio. He is a graduate of the College of St. Thomas and Iowa State University, has had academic appointments at undergraduate institutions (Hope College and Trinity University) and graduate universities (University of Arizona and University of Maryland), as well as being Vice President, then President, of a science foundation (Research Corporation) before taking his current position. Doyle is a Fellow of the American Chemical Society, the American Association for the Advancement of Science, and the Royal Society of Chemistry, and he is widely recognized for his research in catalytic methods for metal carbene transformations.

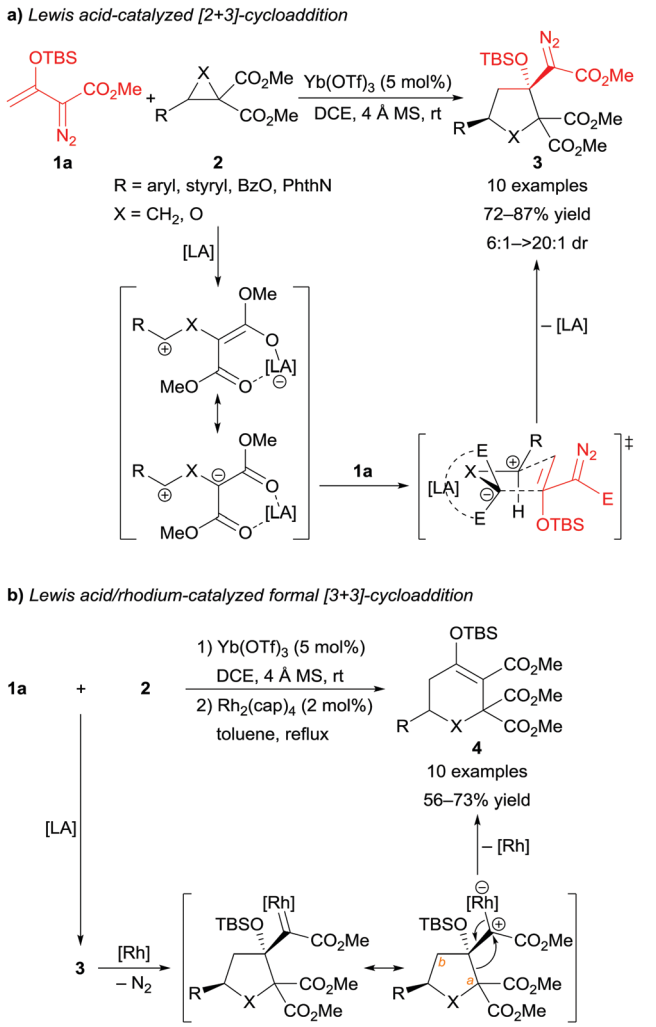
2. ESEC reactions of enoldiazo compounds

The enol-silyl-ether cycloaddition (ESEC) reactions of enoldiazo compounds, usually facilitated by Lewis or Brønsted acids, are cycloaddition reactions of the enol silyl ether units of enoldiazo compounds that retain the diazo functionality. In the presence of transition metal catalysts, the resulting α-cyclic-α-diazocarbonyl compounds undergo dinitrogen extrusion and selective 1,2-migration to furnish structurally different cyclic products. In these reactions the enol group serves as unsaturated two-carbon component in [2+3]- or [2+4]-cycloaddition transformations that leave the diazo unit intact and adjacent to a quaternary carbon, providing pathways for 1,2-migrations to the metal carbene carbon other than the common 1,2-hydrogen migration. Alternatively, acid catalysis can effect substitution or addition reactions with enoldiazoacetates to form functionalized diazoketoesters that can further undergo intramolecular cyclization processes upon dinitrogen extrusion under catalytic or thermal conditions.

2.1 [2+3]-Cycloaddition

Donor–acceptor cyclopropanes/epoxides. Based on earlier uses of donor–acceptor cyclopropanes as efficient three-carbon synthons in Lewis acid-catalyzed cycloaddition reactions,[71–77] the [2+3]-cycloaddition of *tert*-butyldimethylsilyl (TBS)-protected enoldiazoacetate **1a** with donor–acceptor cyclopropanes or epoxides **2** (X = CH_2 or O) proceeded smoothly at room temperature with catalysis of ytterbium(III) triflate [$Yb(OTf)_3$], furnishing cycloadducts **3** in good yields with high diastereocontrol (Scheme 2a).[78] This cycloaddition process did not interfere with the diazo functionality, thereby presenting a structure that, upon catalytic dinitrogen extrusion, was capable of 1,2-migration with three migration products possible. However, using rhodium(II) caprolactamate [$Rh_2(cap)_4$] as the catalyst, highly chemoselective ring expansion of **3** produced six-membered ring products **4** *via* metal carbene formation and consecutive 1,2-migration of the quaternary carbon (C_a) to the electrophilic carbene carbon (Scheme 2b).[78] Note that the migration of secondary carbon (C_b) or silyloxy moiety (TBSO) was not observed in these reactions.

Azomethine imines. Lewis acid-catalyzed [2+3]-cycloaddition reactions of enoldiazoacetate **1a** with azomethine imines **5** also delivered the expected β-methylene-β-amido-β-silyloxy-α-diazoacetates **6** with exclusive diastereocontrol (Scheme 3a).[79] Various transition metal catalysts effected dinitrogen extrusion/1,2-migration from cycloadducts **6**, and three catalyst-dependent bond migrations were identified. Intriguingly, rhodium(II) caprolactamate [$Rh_2(cap)_4$], copper(I) hexafluorophosphate [$Cu(MeCN)_4PF_6$], and rhodium(II) α,α,α′,α′-tetramethyl-1,3-benzenedipropionate [$Rh_2(esp)_2$] directed the migration by carbon, nitrogen, and oxygen substituents, respectively, to afford a diverse array of dinitrogen-fused heterocyclic compounds (**7**–**9**) in an efficient and controllable manner that was reported to be conformationally dependent on the metal carbene intermediate (Scheme 3b).[79]



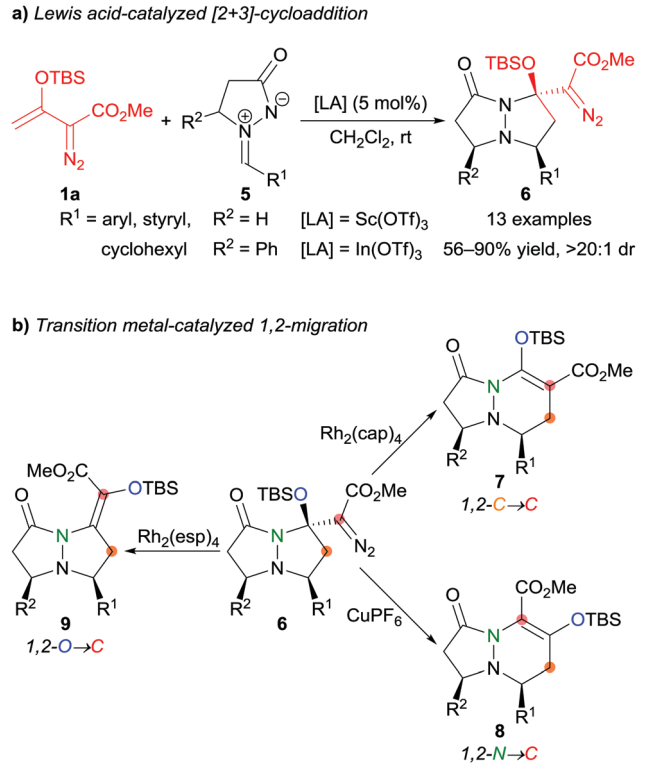
Scheme 2 Cycloaddition reactions of enoldiazoacetate with donor–acceptor cyclopropanes/epoxides.

2.2 [2+4]-Cycloaddition

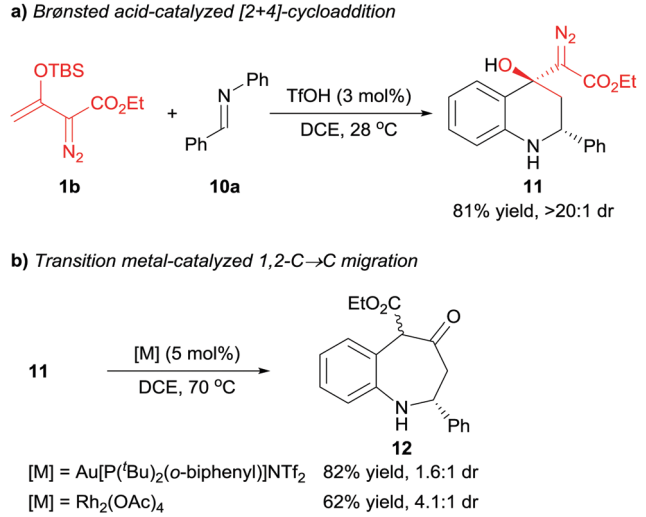
Besides [2+3]-cycloaddition, the enol silyl ether units of enoldiazo compounds provide ideal polarized two-carbon synthons for potential [2+4]-cycloaddition reactions.

***N*-Aryl imines.** Triflic acid (TfOH)-catalyzed Povarov reactions of vinyldiazoacetates with *N*-aryl imines have been reported earlier, for which the reaction between enoldiazoacetate **1b** and *N*-benzylideneaniline **10a** produced the diazo-containing cycloadduct **11** in 81% yield with excellent diastereoselectivity (Scheme 4a).[80] A plausible stepwise mechanism involving a chair-like transition state was proposed to rationalize the stereochemical course, which is differentiated from the concerted pathway for reactions of other vinyldiazoacetates.[80] Furthermore, in the presence of gold(I) or dirhodium(II) catalysts, the functionalized diazo compound **11** underwent metal carbene-mediated ring expansion (1,2-migration) to provide seven-membered azacycle (**12**, Scheme 4b).[80]

Azoalkenes. [2+4]-Cycloaddition reactions of enoldiazoacetates with azoalkenes have recently been developed.[81] As depicted in Scheme 5, the reactive azoalkenes were readily accessed by

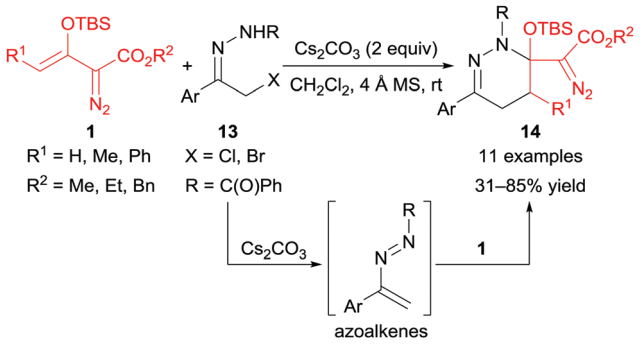


Scheme 3 Cycloaddition reactions of enoldiazoacetate with azomethine imines.



Scheme 4 Cycloaddition reaction of enoldiazoacetate with *N*-benzylidene-aniline.

treating α-halohydrazones **13** with stoichiometric amounts of inorganic base (Cs_2CO_3), which subsequently reacted with a wide range of enoldiazoacetates **1** to afford tetrahydropyridazinyl-substituted diazoacetates **14** in moderate to good yields. It is noteworthy that an unexpected tetrahydropyridazine derivative was obtained when cycloadduct **14** was treated with copper(I) catalysts, which was due to acetyl migration from nitrogen, and



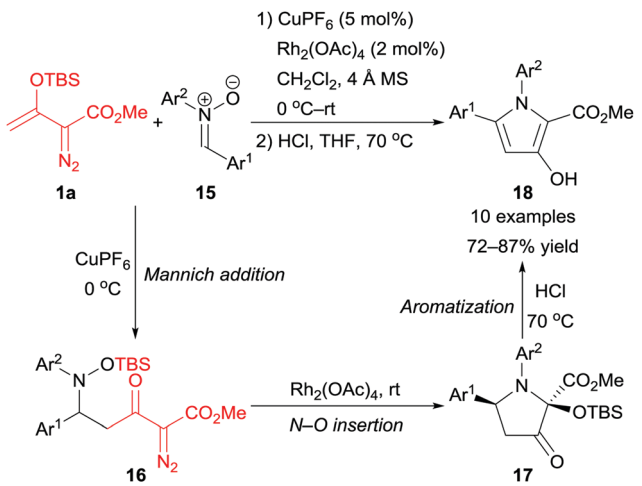
Scheme 5 Cycloaddition reactions of enoldiazoacetates with α-halohydrazones.

the formation of an intermediate oxazolium salt accounted for the acetyl migration outcome.[81]

2.3 Miscellaneous

Besides their direct ESEC reactions described above, enoldiazo compounds were also employed in Lewis (or Brønsted) acid-catalyzed nucleophilic substitution[82–87] and nucleophilic addition (Mukaiyama Aldol,[88] Mukaiyama–Michael,[89–98] and Mukaiyama–Mannich[99] reactions) to furnish complex organodiazo frameworks (the enol silyl ether unit serving as a general nucleophile with the diazo functionality maintained). Subsequent intramolecular cyclization, triggered by dinitrogen extrusion, produced various carbocyclic and heterocyclic ring systems.[82–97,99] A representative example is illustrated in Scheme 6.

A three-step, one-pot cascade approach to synthesize multi-functionalized 3-hydroxypyrroles **18** from enoldiazoacetate **1a** and nitrones **15** demonstrates the importance of the catalyst.[99] In this report, copper(I) hexafluorophosphate activated the nitrones through Lewis-acid coordination for electrophilic addition to the enol ether moieties (at 0 °C) that with silyl group transfer to the nitrone oxygen produced stable Mannich addition products (**16**); subsequent dirhodium(II)-catalyzed N–O bond insertion (at room temperature) followed by acid-promoted

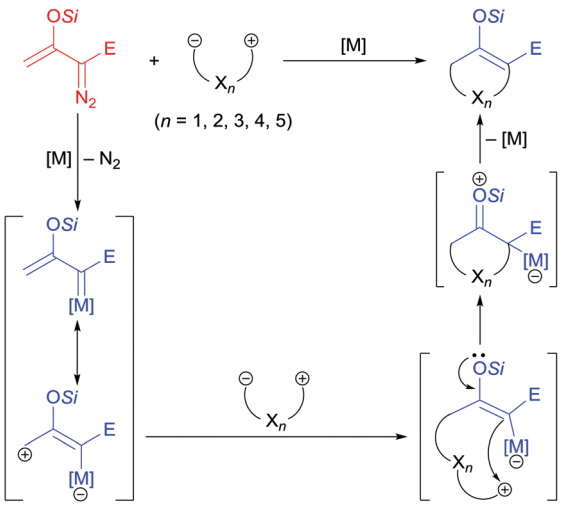


Scheme 6 Cyclization reactions of enoldiazoacetate with nitrones.

deprotection and aromatization (at 70 °C) completed the transformation.[99] Catalysis of the same combination of reagents by dirhodium(II) acetate effected dinitrogen extrusion from the enoldiazoacetate without activation of the nitrone, thus allowing [3+3]-cycloaddition between the resulting metal carbene and the nitrone (see Section 3.3). However, use of both catalytic copper(I) hexafluorophosphate and dirhodium(II) acetate in the same pot at the same time gave initial copper(I)-catalyzed Mannich addition, then dirhodium(II)-catalyzed N–O insertion, resulting in the same products (**17**) as were formed in the two-step process.[99] The striking feature of this study is the significant difference in the reactivity of copper(I) and rhodium(II) towards enoldiazoacetates (see also Section 5.1).

3. MECC reactions of enoldiazo compounds

Catalytically generated metallo-enolcarbenes have proven to be efficient and versatile three-carbon synthons in the construction of various carbocycles and heterocycles that are generally formed with high regio- and stereocontrol. As depicted in Scheme 7, the metallo-enolcarbene exhibits vinylogous electrophilic reactivity that enables nucleophilic coupling to form an intermediate dipolar metallo-vinyl complex which completes the intramolecular cyclization with the aid of electron donation by the ether oxygen. This latter step distinguishes reactions of enoldiazo compounds from those of other vinyldiazo compounds (*e.g.*, styryldiazoacetate). The metallo-enolcarbene cycloaddition (MECC) reactions of enoldiazo compounds are cycloaddition reactions of the metallo-enolcarbenes formed by dinitrogen extrusion from enoldiazo compounds, which are facilitated by transition metal catalysts. They include [3+1]-, [3+2]-, [3+3]-, [3+4]-, and [3+5]-cycloaddition reactions, many of which occur with high enantiocontrol.



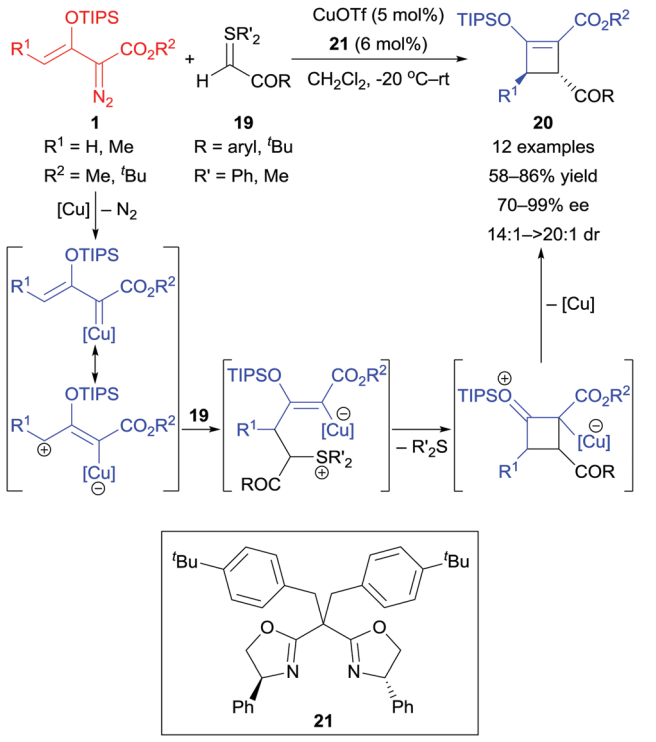
Scheme 7 [3+*n*]-Cycloaddition reactions of enoldiazo compounds.

3.1 [3+1]-Cycloaddition

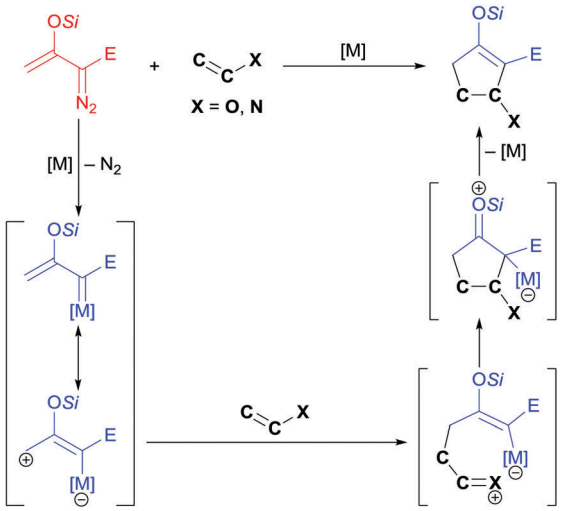
Cyclobutane and cyclobutene are important structural elements in many natural products and biologically active compounds. As an alternative to the well-established [2+2]-cycloaddition and an attractive approach to structurally diverse four-membered rings, [3+1]-cycloaddition, especially its asymmetric version, has remained underexploited.[100,101] The first highly stereoselective [3+1]-cycloaddition between enoldiazoacetates and sulfur ylides has recently been reported.[102] As depicted in Scheme 8, a chiral copper(I) catalyst, generated *in situ* from copper(I) triflate [CuOTf·Tol$_{1/2}$] and double-sidearmed bisoxazoline ligand **21**, facilitated dinitrogen extrusion from triisopropylsilyl (TIPS)-protected enoldiazoacetates **1**. Consecutive nucleophilic addition of sulfur ylides **19** to the vinylogous position of the resulting copper-enolcarbenes, followed by intramolecular cyclization with displacement of the thioether (R′$_2$S) and the catalyst produced enantioenriched multifunctionalized cyclobutenes **20**. Notably, the first-generation Grubbs catalyst was also successfully employed as stoichiometric one-carbon component to furnish the corresponding [3+1]-cycloaddition product in 71% yield, in which case the cyclization was accomplished by presumed nucleophilic displacement of a ruthenium leaving group.[102]

3.2 [3+2]-Cycloaddition

Polarized alkenes, such as enol ethers[103,104] and enamides,[105–107] have been widely applied in [3+2]-dipolar cycloaddition reactions. As illustrated in Scheme 9, the resonance contributing structure of catalytically generated metallo-enolcarbenes provides an ideal dipolar three-carbon scaffold for [3+2]-cycloaddition reactions



Scheme 8 Cycloaddition reactions of enoldiazoacetates with sulfur ylides.



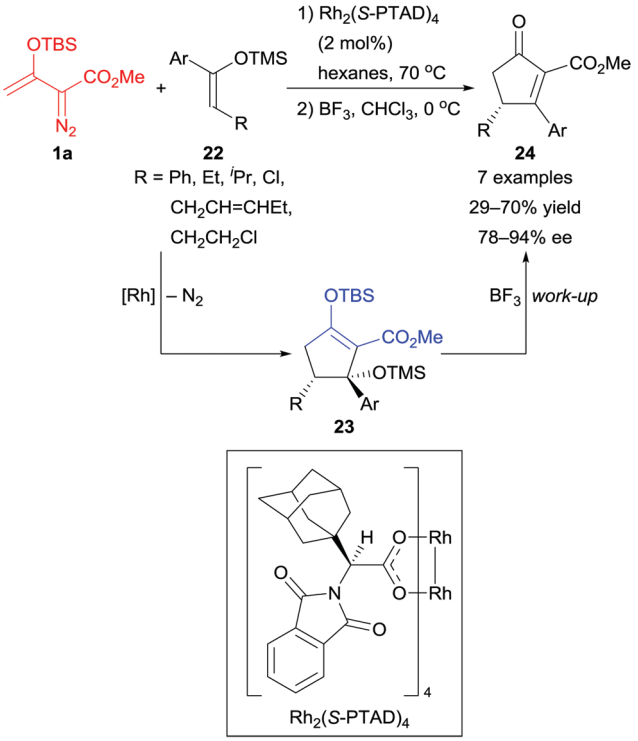
Scheme 9 [3+2]-Cycloaddition reactions of enoldiazo compounds.

with polarized alkenes. These transformations are proposed to go through a plausible stepwise pathway involving initial nucleophilic addition of polarized alkenes to the vinylogous position of electrophilic metallo-enolcarbenes. Subsequent intramolecular electrophilic addition of oxonium or iminium ions to the metal-bound vinyl carbon is enhanced by the electron-donating silyloxy group originated from enoldiazo compounds, and consecutive release of the ligated metal completes the [3+2]-cycloaddition process.

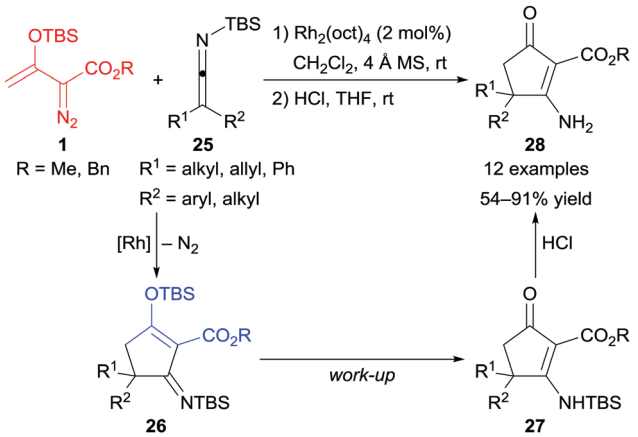
Enol silyl ethers. Dirhodium(II)-catalyzed [3+2]-cycloaddition reactions of enoldiazoacetate **1a** with enol silyl ethers **22** formed cyclopentene derivatives **23**, and subsequent removal of silyl protecting groups (TBS and TMS) produced cyclopentenone derivatives **24** (Scheme 10).[108] The chiral dirhodium(II) catalyst [Rh_2(*S*-PTAD)$_4$] allowed high levels of enantiocontrol in this process. Although this transformation was limited to sterically demanding substrates with modest to moderate yields, it demonstrates the capability of catalytically generated rhodium-enolcarbenes to undergo [3+2]-cycloaddition reactions and provided new access to enantioenriched cyclopentenone building blocks.

Silyl ketene imines. An application of [3+2]-cycloaddition between enoldiazoacetates **1** and silyl ketene imines **25** was subsequently reported.[109] As depicted in Scheme 11, rhodium(II) octanoate [Rh_2(oct)$_4$] efficiently catalyzed the cycloaddition process to furnish five-membered ring products **26**, which further underwent acid-promoted deprotection to produce 3-amino-2-cyclopentenone derivatives **28** in moderate to high overall yields.

Enecarbamates. Chiral carbocyclic β-amino acids are key structural elements of many natural products and antibiotics and, also, important building blocks in peptide synthesis. A recent report[110] described a highly enantio- and diastereoselective approach to multifunctionalized cyclopentyl β-amino esters **30** through chiral dirhodium(II) [Rh_2(*S*-TCPTTL)$_4$]-catalyzed [3+2]-cycloaddition of enoldiazoacetates **1** with enecarbamates **29** (Scheme 12). Notably, a series of aryl/hydroxyl-substituted



Scheme 10 Cycloaddition reactions of enoldiazoacetate with enol silyl ethers.

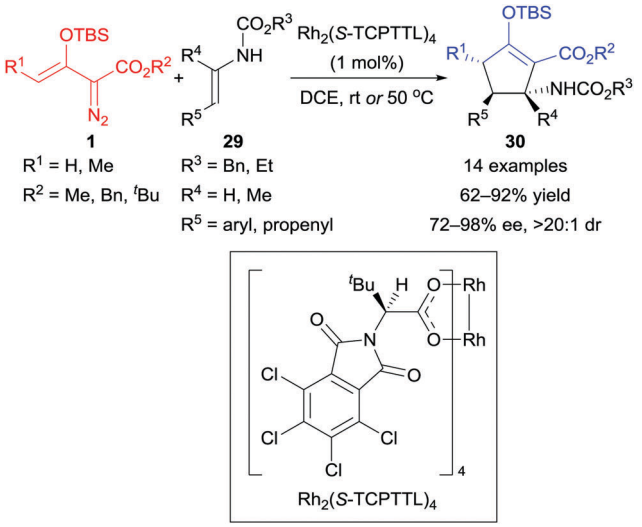


Scheme 11 Cycloaddition reactions of enoldiazoacetates with silyl ketene imines.

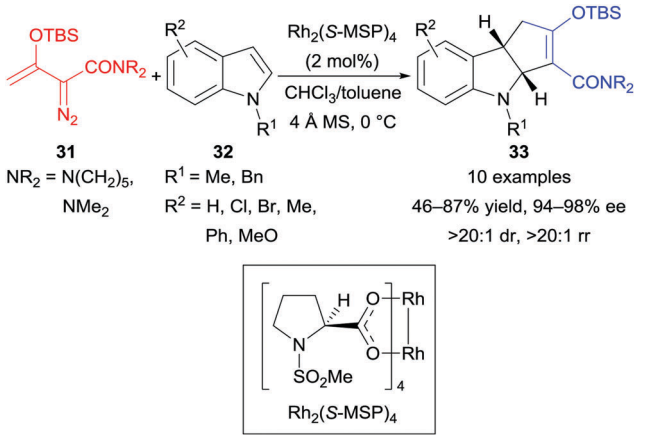
cyclopentyl β-amino acids were successfully produced from the cycloadducts *via* a deprotection/reduction/hydrogenolysis process.[110]

Furthermore, an unprecedented hydrogen-bond association between the intermediate rhodium-enolcarbene and the enecarbamate was proposed to explain the observed geometrical constraints from both reactants.[110]

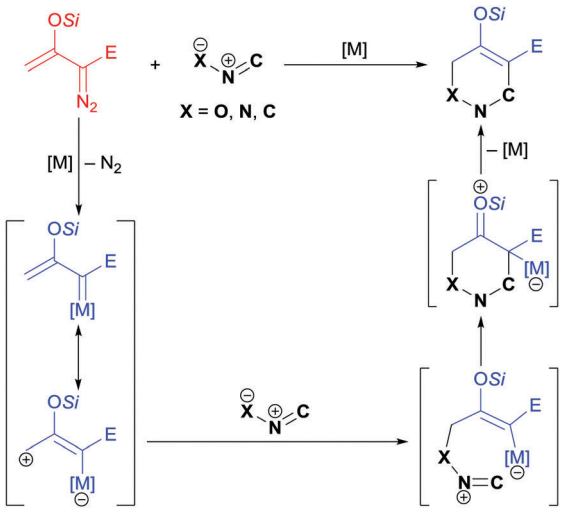
Indoles. Besides polarized alkenes, considerable efforts have been devoted to develop [3+2]-cycloaddition of indoles.[111–115] In the previous studies, substituents at the C2- and/or C3-positions of indoles were required for appropriate regiocontrol.[111–114]



Scheme 12 Cycloaddition reactions of enoldiazoacetates with enecarbamates.



Scheme 13 Cycloaddition reactions of enoldiazoacetamides with indoles.



Scheme 14 [3+3]-Cycloaddition reactions of enoldiazo compounds.

For example, the dirhodium(II)-catalyzed [3+2]-cycloaddition reaction between (*E*)-styryldiazoacetate and *N*-methylindole **32a** only afforded moderate regioselectivity (4 : 1 rr).[112] Recently, this limitation has been overcome by the employment of enoldiazoacetamides **31** in dearomatizing [3+2]-cycloaddition with C2,C3-unsubstituted indoles **32**, which provided cyclopentane-fused indoline derivatives **33** with exceptional regio-, diastereo-, and enantiocontrol (Scheme 13).[115] Note that the highest enantioselectivity was achieved with the chiral dirhodium(II) catalyst bearing the least sterically encumbered prolinate ligand [Rh_2(*S*-MSP)$_4$] of those that have been previously utilized.[115]

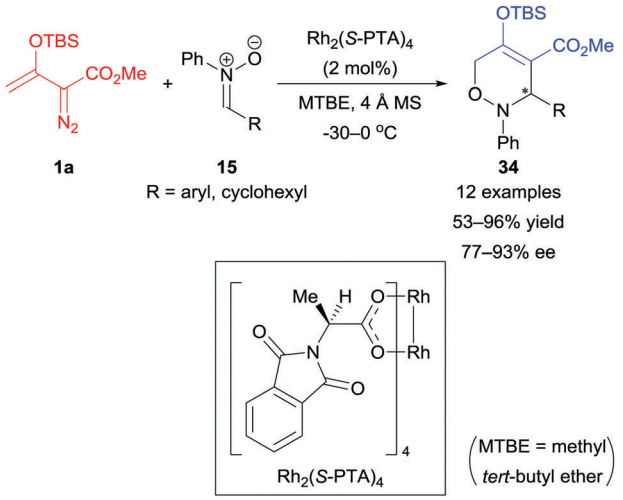
Allenes. The exploration of allenes in [3+2]-cycloaddition with vinyldiazo compounds was also reported recently.[116] However, a gold(I)-catalyzed reaction between enoldiazoacetate **1a** and 1,1-diphenylallene only afforded the corresponding [3+2]-cycloadduct in 25% yield.

3.3 [3+3]-Cycloaddition

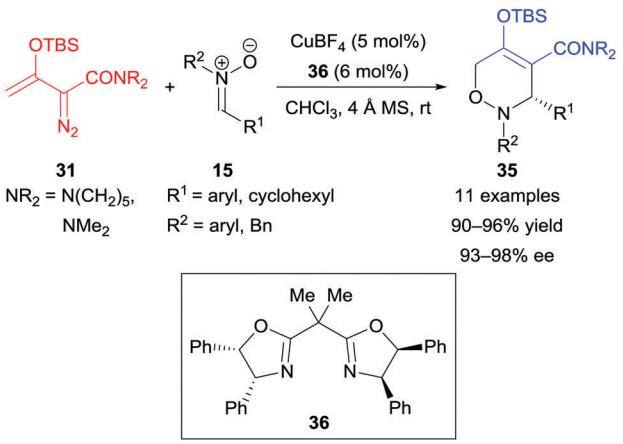
[3+3]-Cycloaddition of enoldiazo compounds, which contributes to the efficient and highly selective synthesis of six-membered heterocyclic compounds, has attracted burgeoning interest over the past six years.[117] As depicted in Scheme 14, transition metal complexes [such as those of rhodium(II) and copper(I)] facilitate dinitrogen extrusion from enoldiazo compounds to form metallo-enolcarbenes, which can serve as effective 1,3-dipole equivalents. A subsequent cycloaddition process starts with nucleophilic attack by a 1,3-dipole at the vinylogous position of the electrophilic metallo-enolcarbene. Importantly, the electron-donating silyloxy group enhances electrophilic ring closure to the metal-bound vinyl carbon, and this step demonstrates the unique advantage of enoldiazo compounds for this transformation. Final elimination of the metal catalyst delivers the [3+3]-cycloaddition product.

Nitrones. The first [3+3]-cycloaddition of enoldiazo compounds was reported in 2011.[118] Under the catalysis of Rh_2(*S*-PTA)$_4$, chiral 3,6-dihydro-1,2-oxazine derivatives **34** were formed from enoldiazoacetate **1a** and nitrones **15** in moderate to high yields with good enantiocontrol (Scheme 15). In contrast, [2+3]-cycloaddition products were obtained from dirhodium(II)-catalyzed reactions between β-unsubstituted vinyldiazoacetates and nitrones, in which the metallo-vinylcarbenes participated only as two-carbon components (the carbon–carbon double bond).[119] This comparison indicates that the β-silyloxy substituents of enoldiazo compounds play a crucial role in enhancing the [3+3]-cycloaddition process[118] and in inhibiting other competing reaction pathways.[119–121]

While the field is dominated by chiral dirhodium(II) catalysts, the first highly enantioselective base metal-catalyzed vinylcarbene transformation was recently uncovered.[122] As depicted in Scheme 16, a chiral copper(I) catalyst, generated *in situ* from copper(I) tetrafluoroborate [$Cu(MeCN)_4BF_4$] and bisoxazoline ligand **36**, exhibited high catalytic activity and excellent enantiocontrol in [3+3]-cycloaddition reactions between enoldiazoacetamides **31** and nitrones **15**, which also furnished the first example of an intermolecular reaction with vinyldiazoacetamides.



Scheme 15 Cycloaddition reactions of enoldiazoacetate with nitrones.

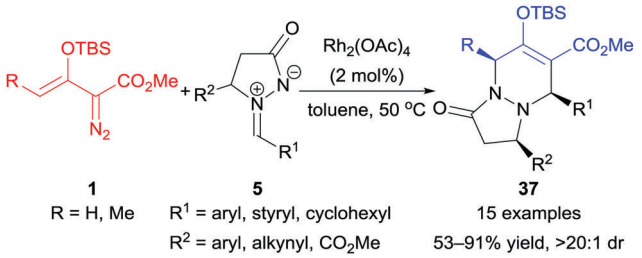


Scheme 16 Cycloaddition reactions of enoldiazoacetamides with nitrones.

Notably, dirhodium(II) catalysts [$Rh_2(OAc)_4$, Rh_2(*S*-PTA)$_4$, Rh_2(*S*-PTTL)$_4$, and Rh_2(*S*-DOSP)$_4$] were also evaluated in this system, which surprisingly afforded very low reactivities and the recovery of nitrones under otherwise identical conditions.[122]

Moreover, γ-substituted enoldiazoacetamides[122] and enoldiazoacetates[123,124] were also successfully employed in [3+3]-cycloaddition reactions with nitrones. Copper(I)[122] and copper(II)[123] salts, as well as a combination of dirhodium(II) and silver(I) complexes[124] were utilized as the catalysts in these transformations. Additionally, dirhodium(II)-catalyzed [3+3]-cycloaddition of enoldiazoacetates with silyl nitronates was presented recently, which produced a series of *N*-silyloxy-3,6-dihydro-1,2-oxazine derivatives in good yields.[125]

Azomethine imines. In pioneering studies on transition metal-catalyzed [3+3]-cycloaddition, azomethine imines **5** have proven to be effective dipolar reactants (in palladium-catalyzed reactions with trimethylenemethane[126] and gold-catalyzed reactions with propargyl esters[127]). Their [3+3]-cycloaddition reactions with enoldiazoacetates **1** were also realized in the presence of a dirhodium(II) catalyst [$Rh_2(OAc)_4$], which

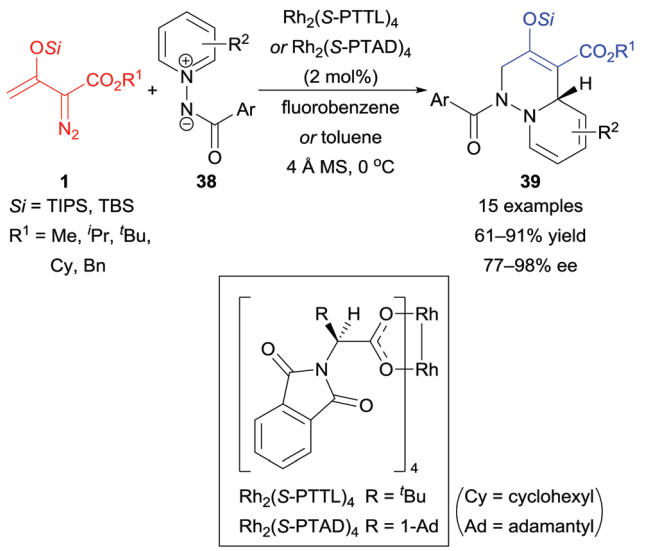


Scheme 17 Cycloaddition reactions of enoldiazoacetates with azomethine imines.

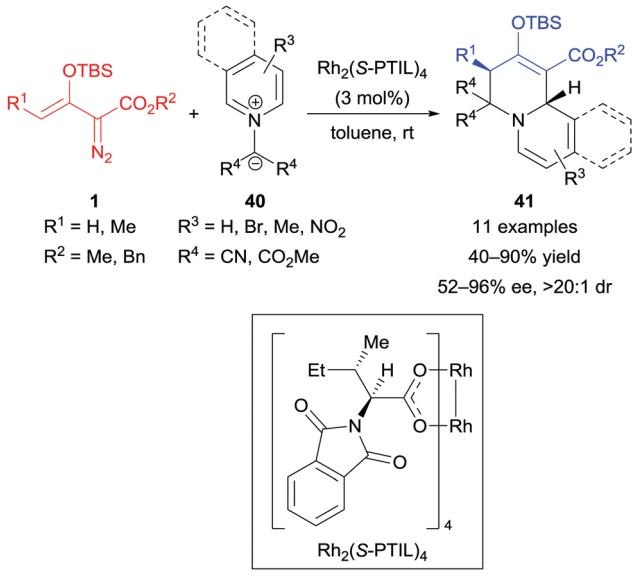
produced bicyclic pyrazolidinone derivatives **37** in moderate to high yields with exclusive diastereocontrol (Scheme 17).[128]

***N*-Acyliminopyridinium ylides.** Inspired by previously reported nickel-catalyzed [3+3]-cycloaddition of donor–acceptor cyclopropanes as dipolar reactants with *N*-iminopyridinium ylides,[129,130] catalytic reactions between dipolar metallo-enolcarbene precursors (*i.e.*, enoldiazoacetates **1**) and *N*-acyliminopyridinium ylides **38** were investigated.[131] By using appropriate combinations of chiral dirhodium(II) catalyst [Rh_2(*S*-PTTL)$_4$ or Rh_2(*S*-PTAD)$_4$] and solvent (fluorobenzene or toluene), bicyclic tetrahydropyridazine derivatives **39** were formed in a highly enantioselective manner (Scheme 18).

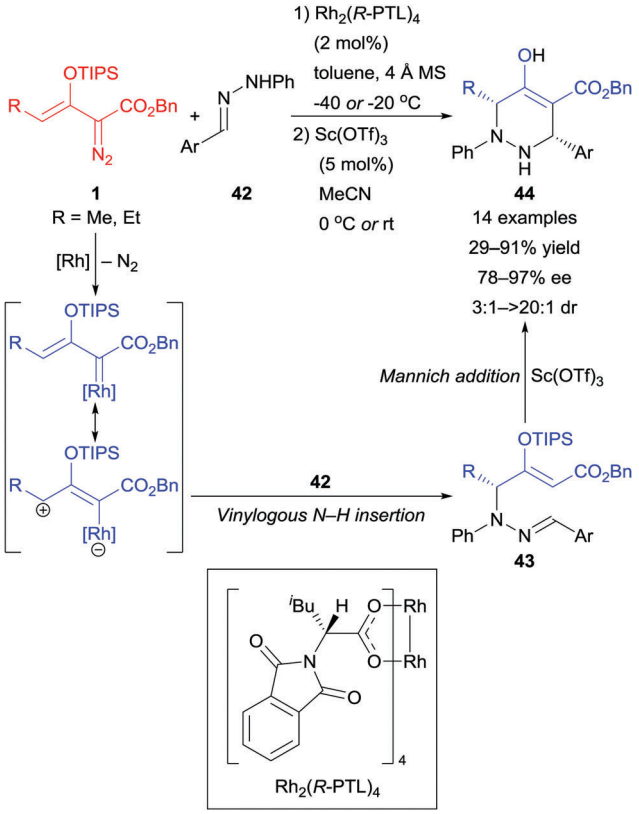
Isoquinolinium/pyridinium methylides. In addition to the aforementioned C–N–O (nitrones **15**) and C–N–N (azomethine imines **5** and *N*-acyliminopyridinium ylides **38**) dipolar species, the C–N–C-type dipoles were also evaluated. As illustrated in Scheme 19, isoquinolinium or pyridinium methylides **40** smoothly underwent [3+3]-cycloaddition with enoldiazoacetates **1** in the presence of a chiral dirhodium(II) catalyst [Rh_2(*S*-PTIL)$_4$].[132] Dearomatization occurred in these cycloaddition reactions, as well as those with *N*-acyliminopyridinium ylides (**38**, Scheme 18),[131] furnishing enantioenriched quinolizidine derivatives **41** in moderate to high yields and enantioselectivities.[132] It is worth mentioning



Scheme 18 Cycloaddition reactions of enoldiazoacetates with *N*-acylimino-pyridinium ylides.



Scheme 19 Cycloaddition reactions of enoldiazoacetates with isoquinolinium/pyridinium methylides.



Scheme 20 Cycloaddition reactions of enoldiazoacetates with hydrazones.

that the outcome of this reaction was found to be highly catalyst-dependent, and further discussion is presented in Section 5.3.

Hydrazones. Besides 1,3-dipolar species, hydrazones **42** were also successfully utilized in an overall [3+3]-cyclization process.[133] Initially, rhodium-enolcarbenes formed from enoldiazoacetates **1** and chiral dirhodium(II) catalyst [Rh_2(*R*-PTL)$_4$] underwent enantioselective vinylogous N–H bond insertion to furnish intermediate products **43**, and subsequent Lewis acid [Sc(OTf)$_3$]-catalyzed intramolecular Mannich addition produced multifunctionalized chiral tetrahydropyridazine derivatives **44** (Scheme 20). Additionally, when donor/acceptor-substituted hydrazones (*N*-aryl hydrazonoacetates) were used instead of diarylhydrazones **42**, a series of pyrazole derivatives were formed *via* dirhodium(II)-catalyzed vinylogous addition followed by Lewis acid-catalyzed cyclization and aromatization.[134]

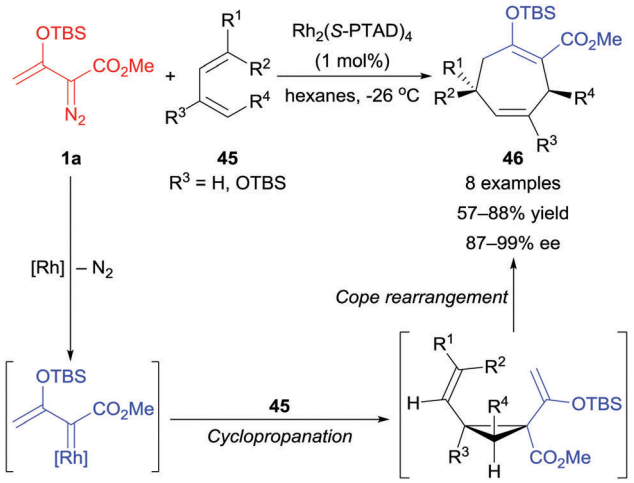
3.4 [3+4]-Cycloaddition

[3+4]-Cycloaddition of enoldiazo compounds has become an attractive tool for the establishment of seven-membered cycles, which are abundant in natural products and, hence, of interest to many synthetic chemists. Since the disclosure of tandem cyclopropanation/Cope rearrangement reactions,[135–153] the Davies group has been a major contributor to this area. Recently, they[154] and others[155] also developed [3+4]-methodologies that shared similar mechanistic pathways (vinylogous addition/ring closure) with the aforementioned [3+*n*]-cycloaddition reactions (*n* = 1–3). Like the chemistry described in the previous two subsections, this field is dominated by dirhodium(II) catalysts,[135–152,154] although cooperation between rhodium and copper[153] as well as a gold-catalyzed reaction[155] have been observed and are included in the following subsection.

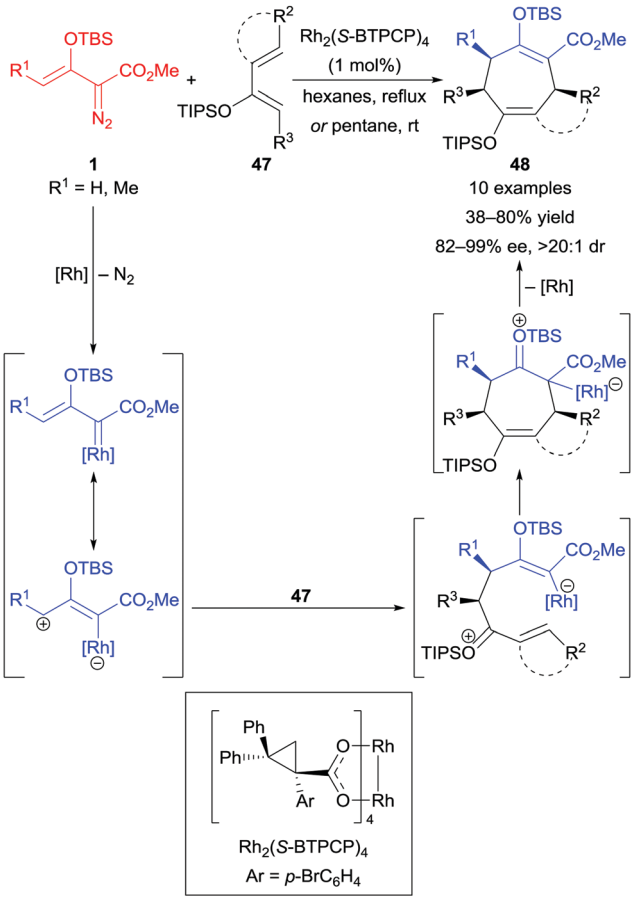
Dienes. Two mechanistically different [3+4]-cycloaddition pathways between enoldiazoacetates and dienes have been discovered. In the first approach, the rhodium-enolcarbene generated from enoldiazoacetate **1a** and Rh_2(*S*-PTAD)$_4$ underwent enantioselective cyclopropanation with dienes **45**, and subsequent Cope rearrangement of the resulting *cis*-1,2-divinylcyclopropanes delivered chiral 1,4-cycloheptadiene derivatives **46** with excellent stereocontrol (Scheme 21).[138] Notably, in a comparison among structurally different vinyldiazo compounds, the reactions of enoldiazoacetates exhibited higher enantioselectivities (up to 91% ee) than those of β-unsubstituted vinyldiazoacetates (up to 57% ee).[138] Moreover, this strategy has already found applications in the total synthesis of natural products, such as (−)-5-*epi*-vibsanin E,[138] (+)-barekoxide,[139] and (−)-barekol.[139]

Whereas Rh_2(*S*-DOSP)$_4$[137,154] and Rh_2(*S*-PTAD)$_4$[138,154] preferentially induced rhodium-enolcarbenes to be attacked at their carbene carbon (to undergo the tandem cyclopropanation/Cope rearrangement sequences), sterically crowded tetrakis(triarylcyclopropanecarboxylate) dirhodium(II) catalysts have proven to be effective promoters of their vinylogous reactivity. The use of Rh_2(*S*-BTPCP)$_4$ in cycloaddition reactions of enoldiazoacetates **1** with 2-silyloxy-1,3-dienes **47** is illustrative (Scheme 22).[154] Nucleophilic attack by the dienes at the vinylogous position of rhodium-enolcarbenes produced enantioenriched 1,4-cycloheptadiene derivatives **48**, rather than forming their regioisomers (**46**-type cycloadducts) by reaction at the carbene carbon.

Furans. Analogous to dienes **45** (Scheme 21), furans **49** are also suitable substrates for dirhodium(II)-catalyzed [3+4]-cycloaddition

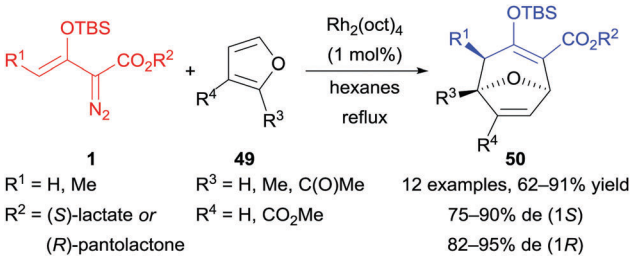


Scheme 21 Rh_2(*S*-PTAD)$_4$-catalyzed cycloaddition reactions of enoldiazoacetate with dienes.



Scheme 22 Rh_2(*S*-BTPCP)$_4$-catalyzed cycloaddition reactions of enoldiazoacetates with dienes.

reactions of enoldiazoacetates **1** (tandem cyclopropanation/Cope rearrangement pathway). The employment of (*S*)-lactate or (*R*)-pantolactone as a chiral auxiliary allowed the efficient construction of stereoenriched 8-oxabicyclo[3.2.1]octene



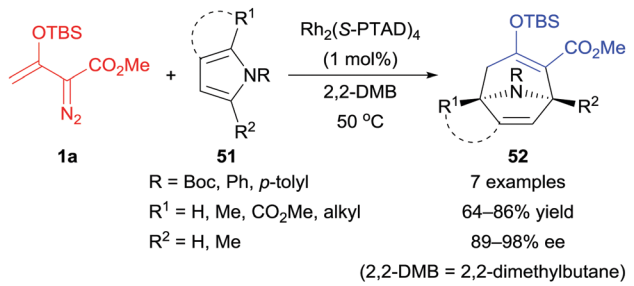
Scheme 23 Cycloaddition reactions of enoldiazoacetates with furans.

derivatives **50** (Scheme 23).[140] Additionally, this method served as the key step in the formal synthesis of (−)-englerin A.[143,144]

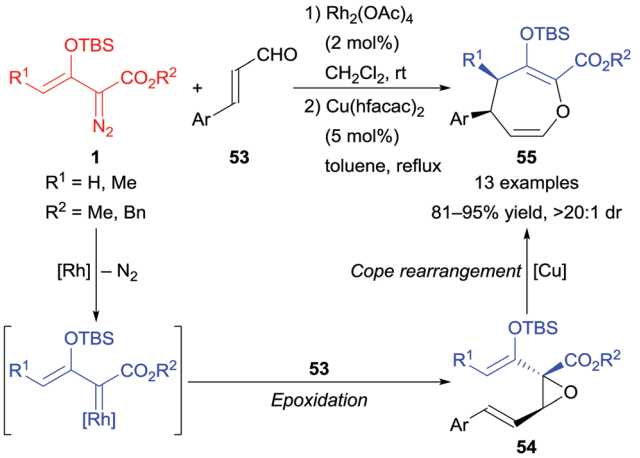
Pyrroles. Related to their oxygen-analogues (furans **49**, Scheme 23), pyrroles **51**, along with enoldiazoacetate **1a**, have proven to be excellent building blocks for the 8-azabicyclo[3.2.1]-octane (tropane) skeleton (**52**, Scheme 24).[147] It is worth mentioning that simple vinyldiazoacetate (in the absence of β-silyloxy group) only gave moderate yields and enantioselectivities (up to 58% yield and 65% ee).[147] The potential of this strategy was fully illustrated by upscaling to multi-gram quantities[146] and by the syntheses of (−)-anhydroecgonine methyl ester,[146] (−)-ferruginine,[146] isostemofoline,[147] (+)-batzelladine B,[148] and scopolamine.[149]

Cinnamaldehydes. In comparison with dienes, furans, and pyrroles (Schemes 21, 23 and 24), cinnamaldehydes **53** underwent epoxidation (in preference to cyclopropanation) with rhodium-enolcarbenes formed from enoldiazoacetates **1** and rhodium(II) acetate, furnishing *trans*-2,3-divinylepoxides **54** that are more stable than the aforementioned *cis*-1,2-divinylcyclopropane intermediates. Subsequent Cope rearrangement was facilitated by copper(II) hexafluoroacetylacetonate [Cu(hfacac)$_2$] under thermal conditions, which completed the overall [3+4]-cyclization process (Scheme 25).[153] This two-step, one-pot approach allowed the formation of 4,5-dihydrooxepine derivatives **55** in high yields with exclusive regio- and diastereocontrol.

Hexahydro-*s*-triazines. In the [3+4]-cycloaddition reactions described so far, the use of vinyldiazoacetates that are devoid of β-silyloxy substituents had a negative influence on product yields and selectivities. A more profound effect was observed in gold(I)-catalyzed cycloaddition reactions between vinyldiazo compounds and hexahydro-*s*-triazines **56**.[155] Gold-enolcarbenes generated from either enoldiazoacetates **1** or enoldiazoacetamide



Scheme 24 Cycloaddition reactions of enoldiazoacetate with pyrroles.

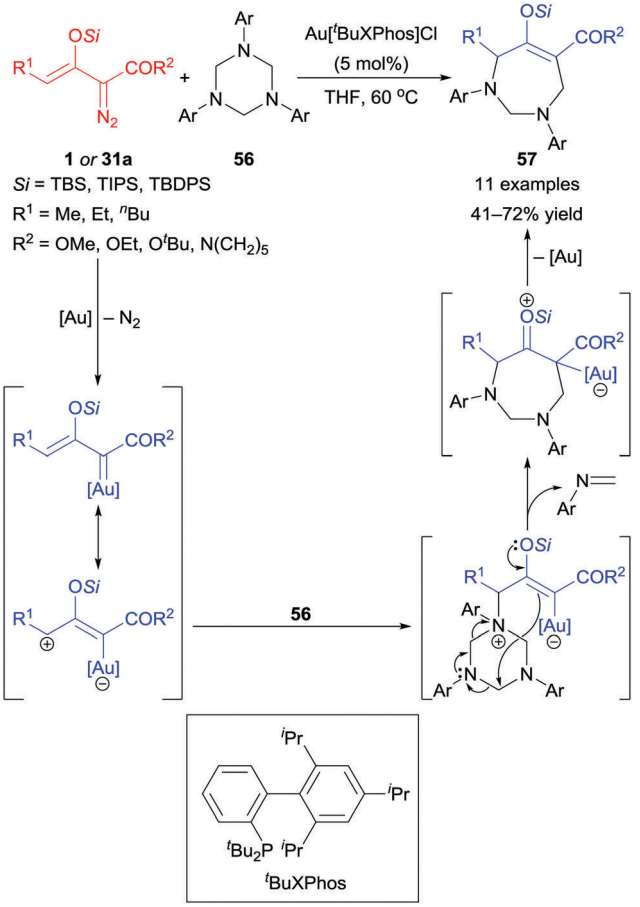


Scheme 25 Cycloaddition reactions of enoldiazoacetates with cinnamaldehydes.

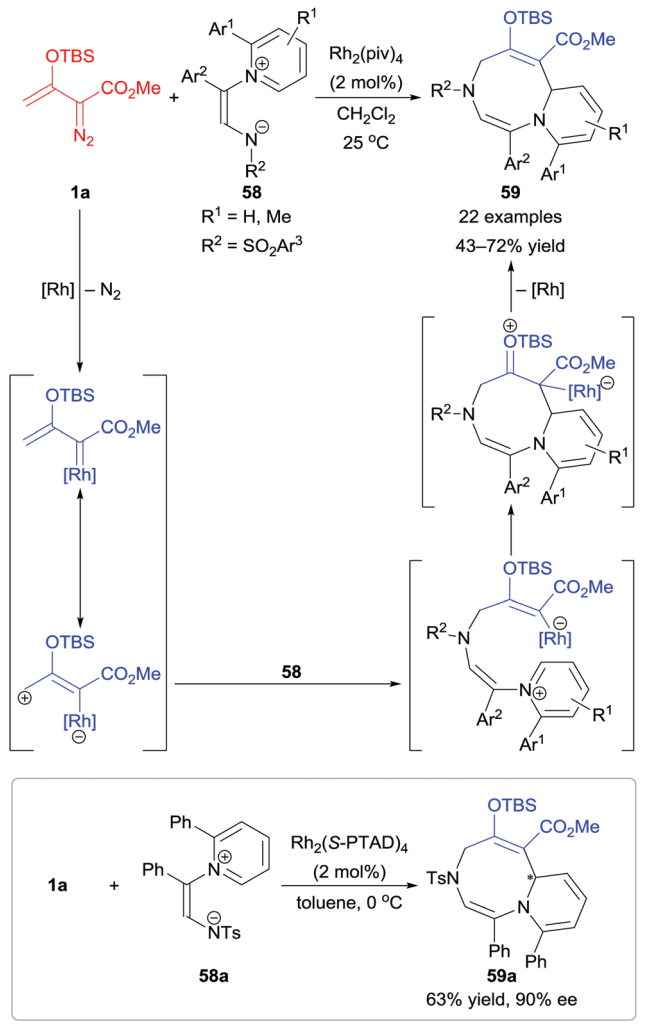
31a furnished [3+4]-cycloadducts **57** *via* vinylogous addition and consecutive ring closure (Scheme 26). By contrast, gold-vinylcarbenes formed from β-unsubstituted vinyldiazoacetates participated only as one-carbon components (the carbene carbon) to afford the corresponding five-membered ring products.[155]

3.5 [3+5]-Cycloaddition

To the best of our knowledge, there exists only a single report on [3+5]-cycloaddition involving enoldiazo compounds, and this report was only recently published. Inspired by their previous observation[156] that isolable pyridinium zwitterions **58** could participate in cycloaddition reactions with activated alkynes as 1,5-dipole equivalents, Yoo *et al.*[157] accomplished the first [3+5]-cycloaddition of enoldiazo compounds. As illustrated in Scheme 27, rhodium(II) pivalate [$Rh_2(piv)_4$] facilitated dinitrogen extrusion from enoldiazoacetate **1a** to form rhodium-enolcarbene, and consecutive vinylogous addition/ring closure yielded diazocine derivatives **59**. Furthermore, the asymmetric version of this process was preliminarily attempted, and high enantioselectivity (90% ee) was achieved with chiral dirhodium(II) catalyst [Rh_2(*S*-PTAD)$_4$].[157] Although the field is clearly still in its infancy, the few results available are promising and merit further investigation.



Scheme 26 Cycloaddition reactions of enoldiazo compounds with hexahydro-*s*-triazines.



Scheme 27 Cycloaddition reactions of enoldiazoacetate with pyridinium zwitterions.

3.6 Miscellaneous

Besides all of the [3+*n*]-cycloaddition reactions (*n* = 1–5) described above, enoldiazo compounds were also employed as carbene precursors in several well-established metal carbene transformations, such as cyclopropanation,[158–165] cyclopropenation,[166] and the Buchner reaction.[167,168] In these [1+*n*]-cycloaddition processes (*n* = 2, 6), catalytically generated metallo-enolcarbenes served as one-carbon synthons (the carbene carbon) to furnish the corresponding cyclopropane,[158–165] cyclopropene,[166] and cycloheptatriene[167,168] derivatives.

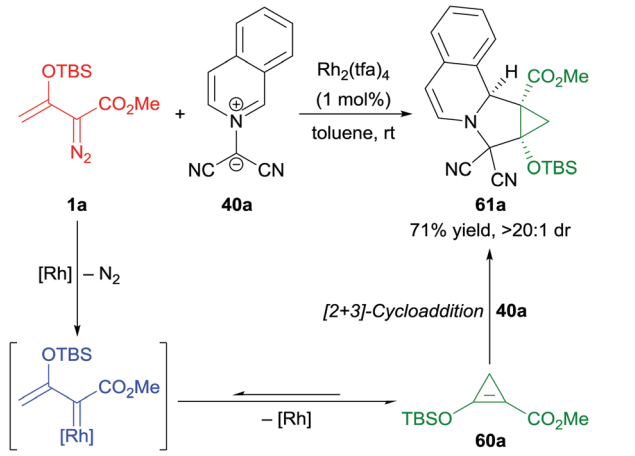
4. CPEC reactions of enoldiazo compounds

The cyclopropene cycloaddition (CPEC) reactions of enoldiazo compounds are cycloaddition reactions of the donor–acceptor cyclopropenes catalytically generated from enoldiazo compounds. The resulting highly strained cyclopropane-fused cyclic scaffolds provide further access to other ring systems *via* selective ring opening and rearrangement. The link between donor–acceptor cyclopropenes and metallo-enolcarbenes was discovered in the investigation of dirhodium(II)-catalyzed [3+3]-cycloaddition reactions between enoldiazoacetates and isoquinolinium/pyridinium methylides.[132] In these reactions, the methylides trapped the donor–acceptor cyclopropene by [2+3]-cycloaddition at low catalyst loading, but this process did not occur at higher catalyst loading. The conclusion drawn from this investigation was that the donor–acceptor cyclopropene was a carbene resting state that was rapidly formed from the metallo-enolcarbene and was rapidly reconverted to the metallo-enolcarbene by reacting with an electrophilic metal catalyst. The efficacy of donor–acceptor cyclopropenes as metal carbene precursors compared to the corresponding diazo-precursors was also investigated.[132] Moreover, the metal-free thermal conversion of enoldiazoacetates and enoldiazoacetamides to donor–acceptor cyclopropenes has been reported to occur under mild conditions (50 °C),[165] but the donor–acceptor cyclopropenes are quite stable at room temperature.

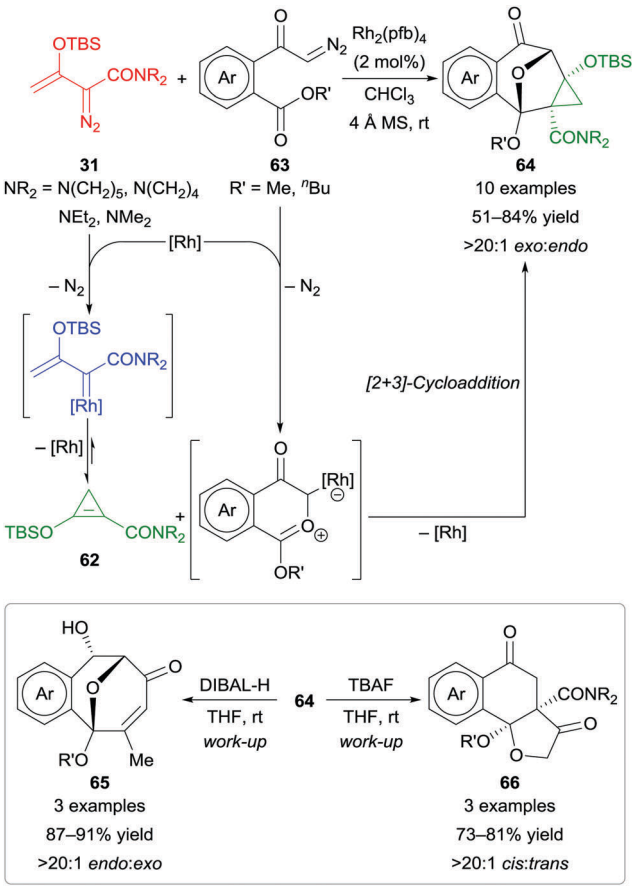
4.1 [2+3]-Cycloaddition

Isoquinolinium methylide. During the catalyst screening of the cycloaddition reaction between enoldiazoacetate **1a** and isoquinolinium methylide **40a**, [2+3]-cycloadduct **61a** was obtained as the sole reaction outcome when rhodium(II) trifluoroacetate [$Rh_2(tfa)_4$] was utilized as the catalyst.[132] As illustrated in Scheme 28, rhodium-enolcarbene, formed through dinitrogen extrusion from the enoldiazoacetate, underwent intramolecular cyclization with elimination of the dirhodium(II) catalyst to deliver donor–acceptor cyclopropene **60a**; and consecutive uncatalyzed cycloaddition between 1,3-dipole equivalent **40a** and highly activated carbon–carbon double bond of the cyclopropene completed this transformation.

Carbonyl ylides. Recently, a novel cycloaddition reaction between two structurally different diazo compounds has been reported (Scheme 29).[169] By adding the mixture of



Scheme 28 Cycloaddition reaction of enoldiazoacetate with isoquinolinium methylide.



Scheme 29 Cycloaddition reactions of enoldiazoacetamides with α-diazoketones.

enoldiazoacetamides **31** and α-diazoketones **63** to the solution of rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$], catalytically generated cyclopropenes **62** and carbonyl ylides (*via* carbene formation/intramolecular cyclization from **31** and **63**, respectively) underwent [2+3]-cycloaddition to furnish donor–acceptor cyclopropane-fused benzoxa[3.2.1]octane scaffolds **64** with excellent chemo-,

regio-, and diastereoselectivities. The key feature of this efficient transformation is the rapid conversion of **31** to **62** to create a reservoir of donor–acceptor cyclopropenes for [2+3]-cycloaddition with the carbonyl ylides formed from **63**. With rhodium(II) perfluorobutyrate as the catalyst, the rhodium-enolcarbenes were significantly diluted relative to other reaction components so that [3+3]-cycloaddition products were not observed. Moreover, the cycloadducts (**64**) can be readily transformed into benzoxa-[3.3.1]nonane (**65**) and hexahydronaphthofuran (**66**) derivatives with exact stereocontrol.[169] This synthetic methodology allowed the efficient construction of three fused and bridged ring systems, all of which are important skeletons of numerous biologically active natural products.

4.2 [2+4]-Cycloaddition

Cyclopentadiene. Early investigations by Davies *et al.*[170–173] indicated the catalytic formation of donor–acceptor cyclopropenes from a series of vinyldiazo compounds. Among them, cyclopropenes generated *in situ* from enoldiazo compounds were successfully trapped by cyclopentadiene to deliver the corresponding [2+4]-cycloadducts.[172] The synthetic application of these intriguing donor–acceptor cyclopropenes was later explored by Doyle and co-workers.

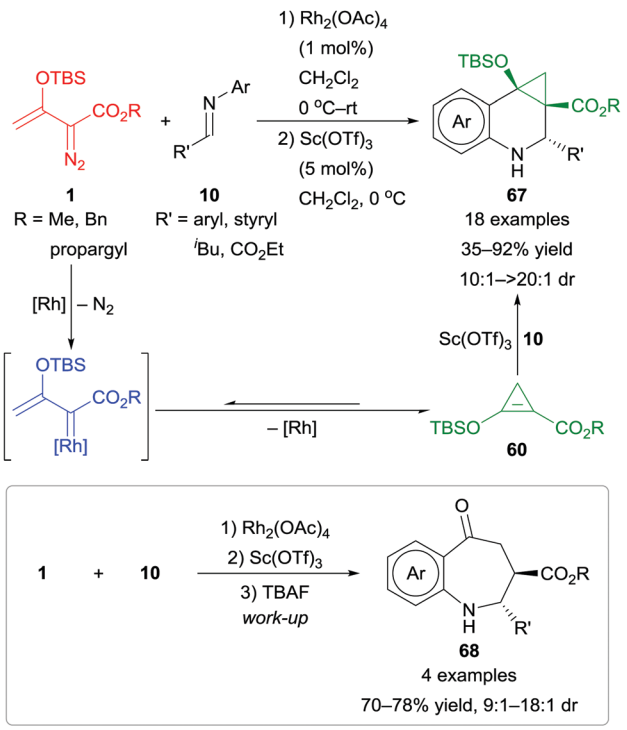
***N*-Aryl imines.** As depicted in Scheme 30, rhodium/Lewis acid-catalyzed [2+4]-cycloaddition reactions of enoldiazoacetates **1** with *N*-aryl imines **5** were accomplished *via* a two-step, one-pot approach.[174] Initially, cyclopropenes **60** were formed from the enoldiazoacetates with catalysis of rhodium(II) acetate; subsequent treatment with scandium(III) triflate catalyzed the Povarov reaction between the donor–acceptor cyclopropenes and the imines to produce cyclopropane-fused tetrahydroquinoline derivatives **67**. In addition, cyclopropane ring opening of the cycloadducts was triggered by the removal of *tert*-butyldimethylsilyl group, furnishing benzazipine derivatives **68** in good yields.[174]

Azoalkenes. As part of their continuous efforts to explore the synthetic potential of enoldiazo compounds, Doyle, Xu, and co-workers[81] recently developed dirhodium(II)-catalyzed/base-promoted [2+4]-cycloaddition reactions of enoldiazoacetates **1** with α-halohydrazones **13** (Scheme 31). This transformation occurred through [2+4]-cycloaddition between donor–acceptor cyclopropenes **60** and azoalkenes, which were generated *in situ* from **1** and **13** in the presence of rhodium(II) acetate and caesium carbonate, respectively. Moreover, the resulting cyclopropane-fused tetrahydropyridazine scaffolds **69** were readily transformed into tetrahydrodiazepine derivatives **70** upon deprotection.[81]

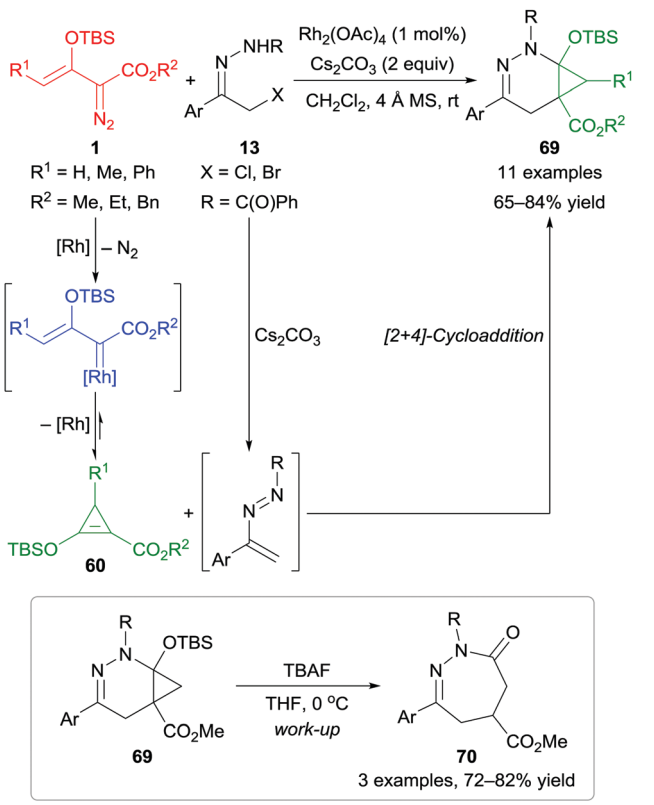
4.3 Miscellaneous

Besides their direct CPEC reactions described above, enoldiazo compounds were also employed in composite cyclization processes, triggered by the formation of donor–acceptor cyclopropenes, to afford a diverse array of carbocyclic and heterocyclic ring systems.[175–177] A representative example is illustrated in Scheme 32.

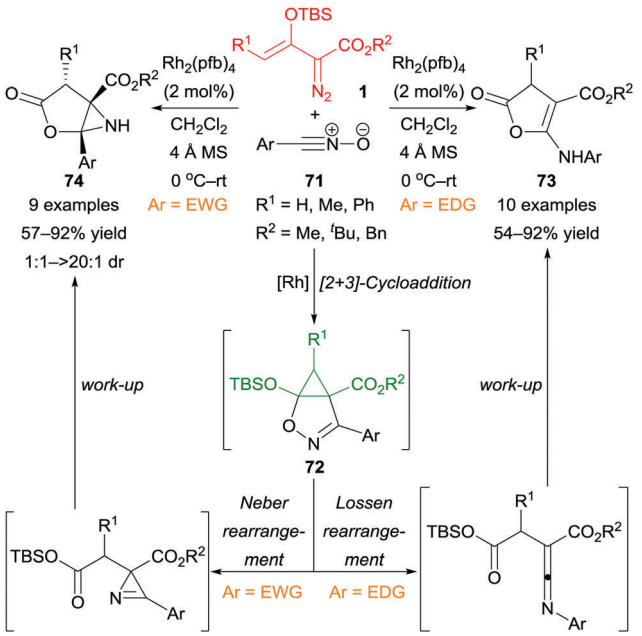
An unexpected product duality was obtained from dirhodium(II)-catalyzed cyclization reactions of enoldiazoacetates **1** with nitrile oxides **71**.[176,177] Unstable compounds **72**, formed by



Scheme 30 Cycloaddition reactions of enoldiazoacetates with *N*-aryl imines.



Scheme 31 Cycloaddition reactions of enoldiazoacetates with α-halohydrazones.



Scheme 32 Cycloaddition reactions of enoldiazoacetates with nitrile oxides.

[2+3]-cycloaddition between catalytically generated donor–acceptor cyclopropenes and nitrile oxides, were proposed as plausible intermediates; and consecutive rearrangements were found to be highly substrate-dependent. Electron-donating substituents of the nitrile oxides directed the formation of ketenimine intermediates *via* the Lossen rearrangement, furnishing multifunctionalized 5-aminofuran-2(3*H*)-ones **73**;[176] whereas the electron-withdrawing substituents favored the Neber rearrangement to deliver azirine intermediates, which further produced 2-oxa-6-azabicyclo[3.1.0]hexan-3-one derivatives **74**.[177]

5. Catalyst-controlled switchable chemoselectivity

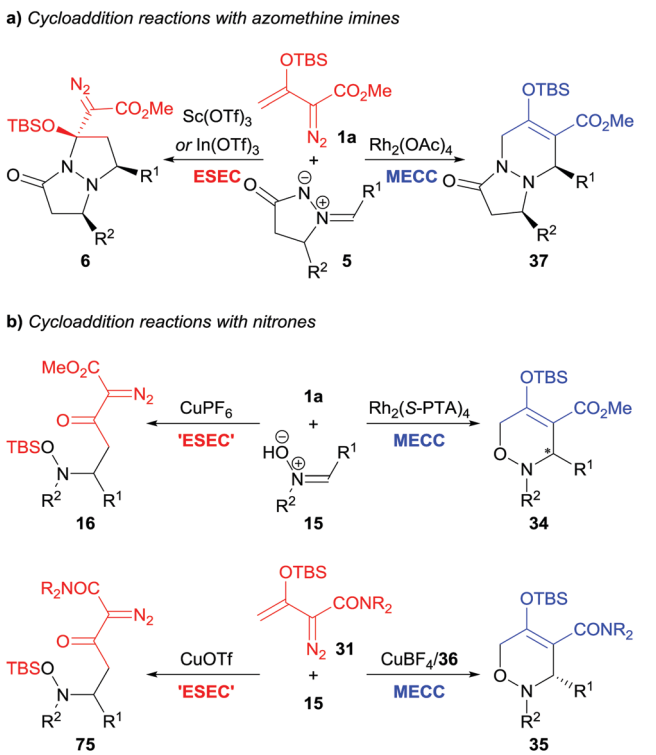
Complete control over the product distribution of catalytic reactions is a significant and long-standing goal in synthetic organic chemistry. Under similar reaction conditions, divergent products can be obtained from identical reactants solely controlled by different catalysts.[178–180] In previous studies, α-diazocarbonyl compounds, such as α-hydro-,[181] α-alkyl-,[182] α-vinyl-,[183,184] and α-aryl-α-diazoacetates,[185] have proven to be versatile reagents in several catalyst-dependent processes. The controllable versatility of enoldiazo compounds (catalyst-controlled switchable chemoselectivity) in cycloaddition reactions is discussed in this section.

5.1 MECC *vs.* ESEC pathways

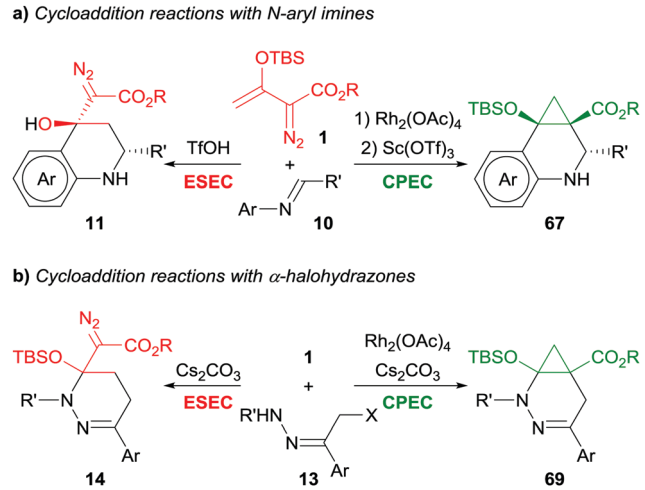
In cycloaddition reactions between enoldiazo compounds and dipolar species, transition metal catalysts facilitate dinitrogen extrusion from the enoldiazo compounds to form metallo-enolcarbenes, and their vinylogous position is then attacked by the nucleophilic site of the dipoles (MECC pathway). In contrast, Lewis acid catalysts promote vinylogous association of the enoldiazo compounds with the dipole's electrophilic site, and the diazo functionality is maintained (ESEC pathway). For example, rhodium(II) acetate directs the formation of [3+3]-cycloadducts **37** from enoldiazoacetate **1a** and azomethine imines **5**;[128] whereas scandium(III) or indium(III) triflate-catalyzed reactions produce [2+3]-cycloadducts **6** (Scheme 33a).[79] Similarly, [3+3]-cycloaddition[118] and Mannich addition[99] reactions of enoldiazoacetate **1a** with nitrones **5** are efficiently catalyzed by $Rh_2(S\text{-PTA})_4$[118] and copper(I) hexafluorophosphate,[99] respectively (Scheme 33b). More interestingly, when the diazo reagent is changed to enoldiazoacetamides **31**, copper(I) catalysts exhibit their unique advantages by switching the reaction pathway between [3+3]-cycloaddition and Mannich addition (Scheme 33b).[122] The catalyst with more open coordination sites [copper(I) triflate] favors the latter pathway by facilitating the migration of *tert*-butyldimethylsilyl group to the nitrone oxygen.[122]

5.2 ESEC *vs.* CPEC pathways

As documented in Sections 2 and 4, the enol silyl ether units of enoldiazo compounds participate in [2+*n*]-cycloadditions with retention of the diazo functionality to furnish α-cyclic-α-diazocarbonyl compounds (ESEC pathway); and the donor–acceptor cyclopropenes catalytically generated from enoldiazo compounds also serve as two-carbon components in cycloaddition reactions to produce cyclopropane-fused carbocycles and heterocycles (CPEC pathway). As illustrated in Scheme 34a, Povarov reactions of enoldiazoacetates **1** with *N*-aryl imines **10** are achieved by using triflic acid as the catalyst.[80] Alternatively, donor–acceptor



Scheme 33 MECC *vs.* ESEC pathways in cycloaddition reactions of enoldiazo compounds.



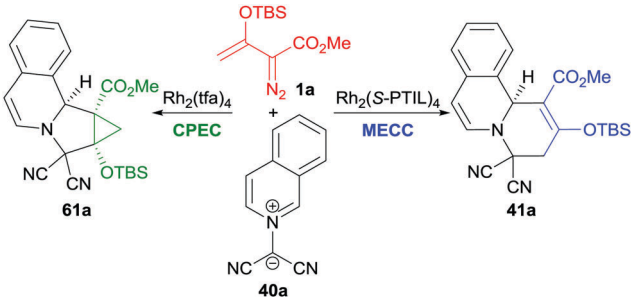
Scheme 34 ESEC *vs.* CPEC pathways in cycloaddition reactions of enoldiazoacetates.

cyclopropenes are formed from the enoldiazoacetates in the presence of the dirhodium(II) catalyst, which further undergo scandium(III) triflate-catalyzed Povarov reactions with the *N*-aryl imines.[174]

An analogous catalyst-dependent process has also been discovered in [2+4]-cycloaddition reactions between enoldiazoacetates **1** and α-halohydrazones **13** (Scheme 34b).[81] In the absence of transition metal catalysts, tetrahydropyridazinyl-substituted diazoacetates **14** are obtained under basic conditions; whereas cyclopropane-fused tetrahydropyridazines **69** are produced with catalysis of rhodium(II) acetate under otherwise identical conditions.

5.3 CPEC *vs.* MECC pathways

Donor–acceptor cyclopropenes,[186] generated *in situ* from enoldiazo compounds, are not only direct participants in CPEC reactions[81,132,169–177] but also important intermediates (in equilibrium with the corresponding metallo-enolcarbenes) in MECC reactions (detected during ^{1}H NMR monitoring).[102,122,132,152,167,168] Furthermore, the cyclopropenes, preformed from enoldiazo compounds under catalytic or thermal conditions, have proven to be effective metallo-enolcarbene precursors in several MECC reactions.[102,115,122,124,132,165,167,168] As depicted in Scheme 35, catalyst-controlled divergent outcomes are obtained from cycloaddition reactions of enoldiazoacetate **1a** with isoquinolinium methylide **40a**.[132] Coordination of the Lewis basic methylide to the carbene-bound dirhodium catalyst promotes the formation of donor–acceptor cyclopropene from rhodium-enolcarbene. Thus, the more Lewis acidic catalyst [rhodium(II) trifluoroacetate] preferentially provides [2+3]-CPEC product **61a**. Alternatively, the *in situ* generated cyclopropene reforms the rhodium-enolcarbene in the presence of Rh_2(*S*-PTIL)$_4$, which further delivers [3+3]-MECC product **41a**. Note that when the cyclopropene, preformed from **1a**, is subjected to the same reaction conditions, the results are the same (product ratio and enantioselectivity) as those obtained with **1a**.[132]



Scheme 35 CPEC *vs.* MECC pathways in cycloaddition reactions of enoldiazoacetate.

6. Conclusions

Enoldiazo compounds have enormous flexibility in their chemical reactions. Their enol silyl ether unit is active for cycloaddition that occurs on the activated carbon–carbon double bond, producing a quaternary carbon and leaving the adjacent diazo functionality intact for subsequent reactions (Schemes 2–4). Enoldiazo compounds have a directive advantage over other vinyldiazo compounds for cycloaddition reactions of metal carbene intermediates. The silyloxy group plays a crucial role in enhancing the nucleophilic character of the original carbenic carbon in order to complete the two-step cycloaddition process (Schemes 7, 9 and 14). Enoldiazoacetates and enoldiazoacetamides are stable at room temperature and below for weeks or months, yet they undergo thermal dinitrogen extrusion at temperatures as low as 50 °C (3–4 h) to quantitatively form donor–acceptor cyclopropenes that are precursors to the same metallo-enolcarbenes which are generated from the corresponding enoldiazo compounds. These donor–acceptor cyclopropenes are themselves highly reactive dipolarophiles or dienophiles that form bi- or tricyclic structures which are subject to further transformations (Schemes 29–31). Enoldiazoacetamides are more stable than are enoldiazoacetates, and so are their corresponding donor–acceptor cyclopropenes. In these intermolecular transformations of enoldiazo compounds, their basicity relative to that of the dipolar reactant determines product formation, so that the Lewis acidity of the catalyst can be used to direct the enoldiazo compound selectively to different products. Although, highly selective cycloaddition reactions of enoldiazo compounds have been established with dirhodium(II) catalysts, recent efforts have shown advantages of copper(I) catalysts for several of these processes (Schemes 8, 16 and 33). Besides the exploration of other dipolar reactants in cycloaddition reactions with enoldiazo compounds, the development and investigation of new subclasses of enoldiazo compounds, as well as the application of these cycloaddition reactions in the syntheses of natural products and pharmaceutical analogues, should be expected in the near future.

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