

Article

Expanded access to vinyl diazo compounds and their catalytic enantioselective applications

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SUMMARY

The catalytic uses of metal carbenes for addition, insertion, and cycloaddition reactions are dependent on their carbene precursor. The limited methods available for the preparation of diazo esters, which are the most common carbene precursors, restricts their ability to impart structural diversity in metal carbene reactions. Here we report a new methodology for the preparation of diverse vinyl diazoacetate esters and their effective uses in highly enantiocontrolled cyclopropanation, N-H bond insertion, O-H bond insertion, and [3+2]-cycloaddition reactions. 1,2,3-Triazine 1-oxides with a sp^3 -C-H bond at the 5-position undergo base catalyzed Dimroth-type rearrangement to form multiply substituted oximido vinyl diazoacetates in high yields at or below room temperature, and these diverse vinyl diazo compounds undergo catalytic metal carbene transformations to produce oximido vinyl cyclopropanes, α -oximido vinyl- α -amino acids and α -hydroxy acids, as well as tricyclic indole derivatives in high yields and enantioselectivities. The new access to vinyl diazo compounds has applicability to a vast array of metal carbene transformations.

INTRODUCTION

Advances in the synthesis and applications of diazo esters have expanded rapidly^{1,2} since their discovery.³ Originally a curiosity, they found essential uses throughout the chemical sciences in diverse application including carbene sources,⁴ dipolar species,⁵ and biological probes.⁶ Ethyl diazoacetate was prominent in early applications that included the first reported example of asymmetric homogeneous transition-metal catalysis.⁷ Structural modifications to increase functionality and selectivity in chemical reactions of diazo compounds led to the evolution of diazoacetates into diazomalonates and similar “acceptor-acceptor” diazo compounds,^{1,2} then to aryl- and vinyl diazoacetates and other derivative “donor-acceptor” diazo compounds,⁸⁻¹⁰ as well as to “donor-donor” diazo compounds such as diaryl diazomethane.¹¹ A variety of reactions have been employed to prepare diazo compounds,¹² the methods dependent on the specific application, but hydrazone oxidation, the Bamford–Stevens reaction, and diazo transfer are the most widely used. The preparation and uses of vinyl diazo compounds, especially for [3+ n]-cycloaddition reactions¹³ but also for cyclopropanation¹⁴ and carbon-hydrogen insertion,¹⁵ are developments that have rapidly expanded. However, in spite of the apparent generality of methods for their synthesis (Figure 1a), each has

THE BIGGER PICTURE

Diazoesters are primary precursors to metalcarbenes, and vinyl diazoesters provide a rich array of synthetic transformations, but their availability is limited. In this study we report a strikingly straightforward catalytic synthesis of diverse aryl- and alkyl-substituted, cyclic and branched, oximido vinyl diazoesters from stable 1,2,3-triazine 1-oxide ester precursors. Their applications in highly enantioselective cyclopropanation, N-H insertion, O-H insertion, and cycloaddition transformations with the use of chiral catalysts provide access to a diverse array of products that are not available with existing methods. Notably, the oximido group does not hinder the catalytic reactions. Our findings significantly broaden the applicability of vinyl diazo compounds in catalytic metal carbene transformations and offer a new platform for asymmetric synthesis. Furthermore, these results suggest the suitability of multiple variants of the reported structures.

limitations, and methods to generate vinyldiazo compounds for late-stage functionalization have been limited, as has been their stability. *N*-Sulfonylimidodiazao compounds, formed as unstable reaction intermediates from *N*-sulfonyl-1,2,3-triazoles (Figure 1b),¹⁶ were the most recent widely-investigated class of compounds to access α,β -unsaturated diazo compounds and, despite the higher temperatures required to generate their diazo intermediates, they have seen wide applications. We have discovered a new source for vinyldiazo compounds that greatly expands access to diverse vinyldiazoacetates (Figure 1c), and we also report that these complex compounds undergo in high yields and stereocontrol the common catalytic metallo-vinylcarbene reactions expected of them.

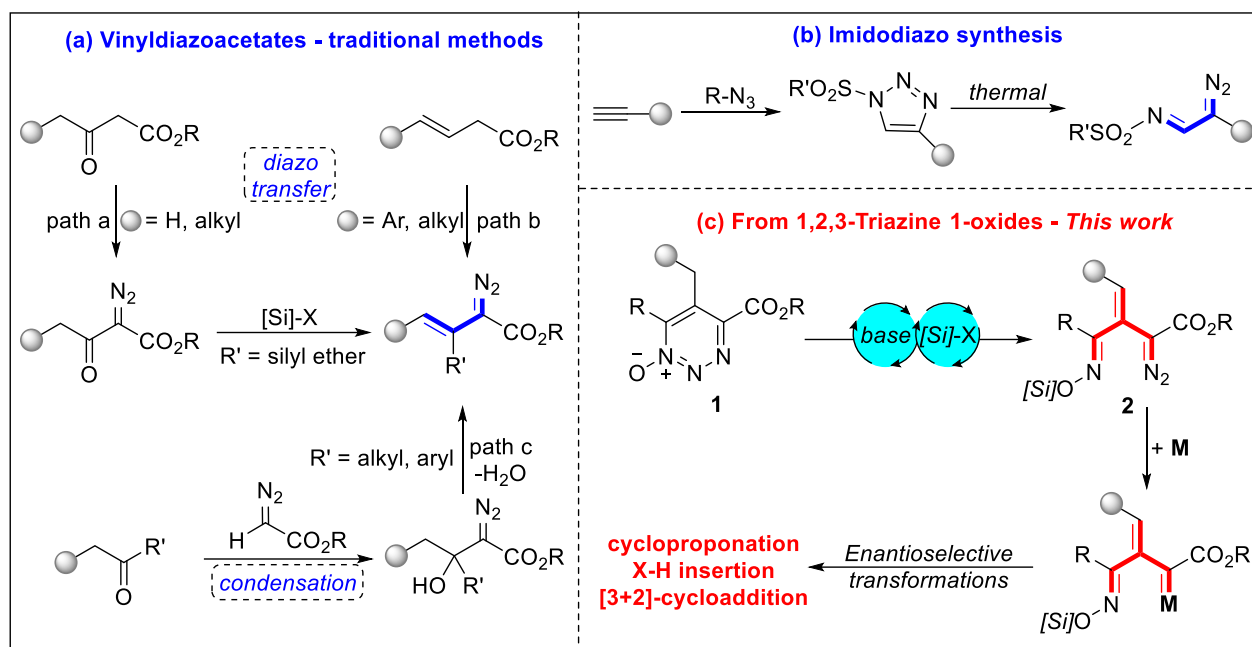


Figure 1. Synthesis of vinyldiazo esters

- (a) Traditional methods that include diazo transfer to β -ketoesters, to 4-aryl-3-butenate esters, and by condensation of diazoacetates with ketones.
(b) Thermal rearrangement of *N*-sulfonyl-1,2,3-triazoles.
(c) Base promoted rearrangement of 1,2,3-triazine 1-oxides (this work).

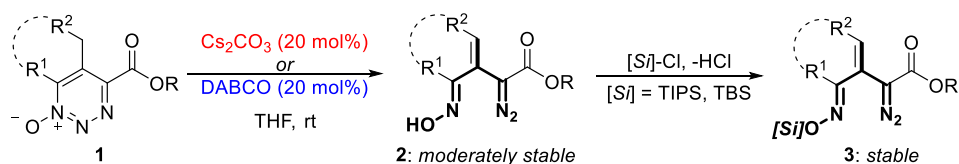
RESULTS AND DISCUSSION

Synthesis of oximidovinyldiazoacetate

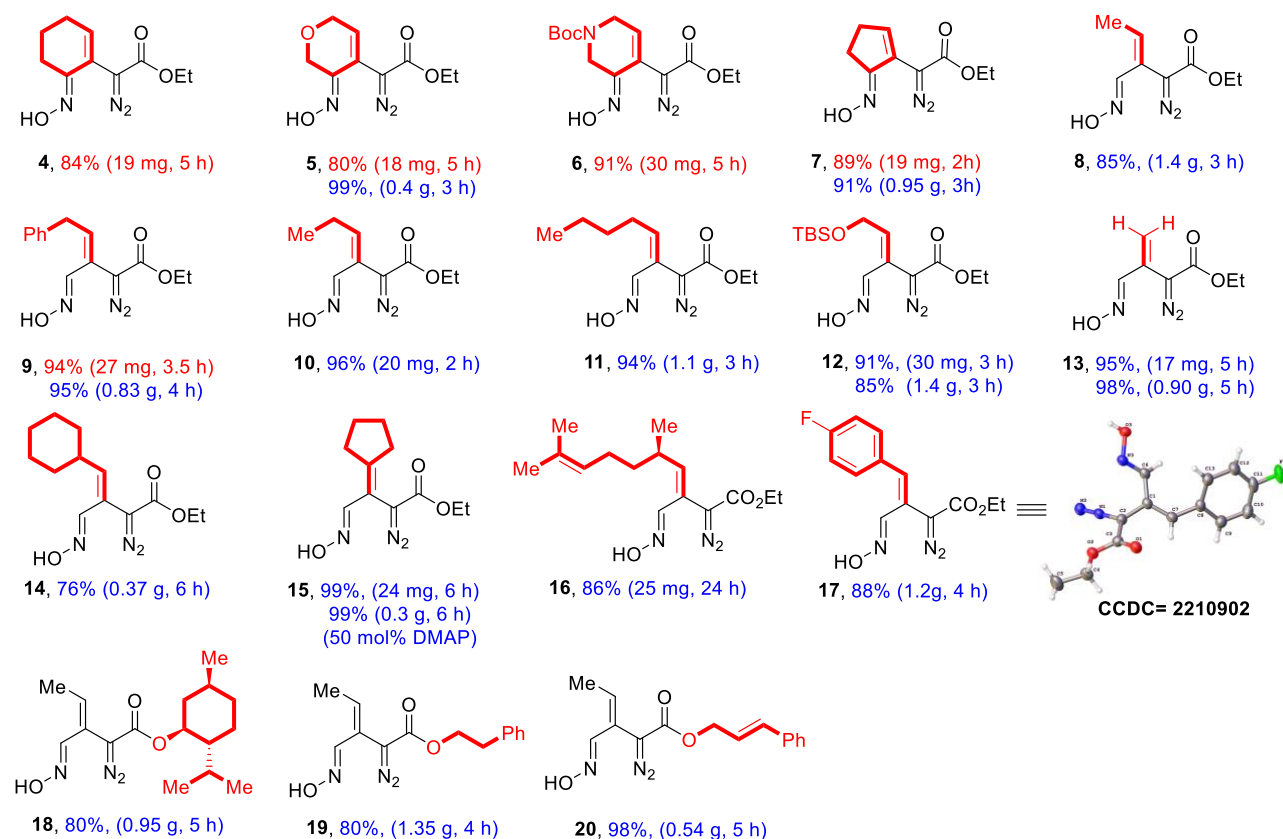
We have previously reported the facile synthesis of 1,2,3-triazine 1-oxides (**1**).¹⁷ They are stable aromatic compounds (from Figure 1a) that are rapidly formed by treatment of vinyldiazoacetates with an alkyl nitrite at room temperature without the use of a catalyst, but they undergo the expulsion of dinitrogen in refluxing chlorobenzene with near quantitative formation of isoxazoles. More recently we discovered that these compounds readily undergo inverse electron demand Diels-Alder reactions under basic conditions to form highly substituted pyridine and other heterocycle derivatives.¹⁸ In the course of the latter investigations, with 1,2,3-triazine-1-oxides having an alkyl group containing an

α -C-H bond at the 5-position, a new product was formed that we originally thought might be a tautomer of the intact triazine-1-oxide. However, spectroscopic analyses, especially IR spectroscopy, revealed that this product had the diazo functionality and was an oxime. Like *N*-sulfonyl-1,2,3-triazoles which undergo thermal rearrangement to imidodiazocompounds (Figure 1b), 1,2,3-triazine 1-oxides undergo base promoted rearrangement to diazovinylloximes, but, unlike 1,2,3-triazoles, this rearrangement occurs at or below room temperature (Figure 1c). These uniquely constructed, highly functionalized vinyl diazo compounds are stable at room temperature for days and at 0°C for much longer times. Probing reaction conditions for the rearrangement with 5,6,7,8-tetrahydrobenzo-1,2,3-triazine 1-oxide **4** (see SI) with base and solvent disclosed that use of either Cs₂CO₃ or DABCO as the base, and with THF as the solvent, gave optimum results. Results with less than stoichiometric amounts (20 mol%) of base demonstrated the catalytic nature of this process and the mild conditions required for this transformation. A broad spectrum of these vinyl diazo compounds has been produced under these conditions (Figure 2). Reactions with bicyclic 1,2,3-triazine 1-oxides form the corresponding oximidovinyl diazo esters **4-7** in high isolated yield. To our surprise, the monocyclic 1,2,3-triazine 1-oxides produced their oximidovinyl diazoacetate esters in excellent yields but, also, with exceptional diastereocontrol for the (*Z*)-alkene isomer. The triazine with a tertiary C-H bond at the 5-position required a stronger base (DMAP) to produce oximidovinyl diazoacetate **15**. X-Ray diffraction of **17** confirmed the oximidovinyl diazoacetate structure, and NOE NMR experiments established the diastereoisomer assignments. These reactions are not limited to small scale transformations; gram-scale reactions give comparable product yields.

(a) General transformation:



(b) Reaction scope:

**Figure 2. Synthesis of oximidovinyl diazoacetates**

(a) General reaction with sub-stoichiometric amounts of Cs_2CO_3 or DABCO.
 (b) Synthesis of diverse oximidovinyl diazo esters by base promoted rearrangement of 1,2,3-triazine 1-oxides: structure, product yield, scale of reaction, and reaction time.

Catalytic enantioselective cyclopropanation

The applicability of these oximidovinyl diazo compounds as carbene sources was initially evaluated in intermolecular catalytic reactions with styrene for which dirhodium(II) and copper(I) complexes are the most widely used catalysts. Reactions of vinyl diazoacetates with styrenes undergo addition at the diazo carbon resulting in the formation of vinylcyclopropane compounds^{19,20} and they are amenable to a rich stream of subsequent transformations.²¹⁻²³ However, consistent with previously reported examples of cyclopropanation reactions with diazoesters containing the oxime functional group,²⁴ neither copper(I) nor dirhodium(II) catalysts generated the desired cyclopropane product(s) with the

oxime reactant. In contrast, the near quantitative conversion of the oximidovinylidiazole reactant to its *tert*-butyldimethylsilyl (TBS) ether (Figure 3a) provided a much more stable reactant (at least one month in storage at 0 °C), and this derivative underwent dirhodium tetraacetate catalyzed cyclopropanation of styrene at room temperature in high yield. However, copper(I) catalysts with and without chiral Box ligands gave low product yields (<20%) with low enantiocontrol of cyclopropane products and produced complex product mixtures.

As previously documented in catalytic reactions of β -substituted vinylidiazole compounds involving the extrusion of dinitrogen,²⁵ a principal competing reaction of silyl-protected metallo-oximidovinylcarbenes is loss of dinitrogen resulting in the formation of cyclopropene products **22**. Unlike previous reports,¹¹ however, these oximidocyclopropenes are unstable and undergo an ene reaction to form dimers (**23** in Figure 3a),²⁶ but unlike donor-acceptor cyclopropenes formed from silyl-protected enoldiazoacetates²⁷ they do not reform the metallo-vinylcarbene intermediate. With $\text{Rh}_2(\text{OAc})_4$ as catalyst, this cyclopropene dimer was produced in only one isomeric form as the only major byproduct. Reactions using copper catalysts did not produce this cyclopropene dimer.

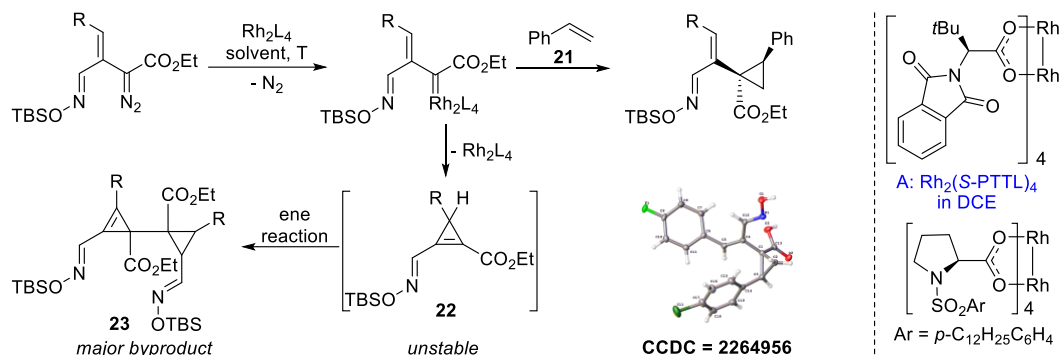
To assess the extent of asymmetric induction in intermolecular cyclopropanation reactions with styrene, we selected the TBS derivative of **8** as the vinylidiazole compound and surveyed chiral dirhodium(II) carboxylate catalysts for their competitiveness in both cyclopropanation versus cyclopropene/ene dimerization and cyclopropanation enantiocontrol. As expected for cyclopropanation reactions of vinylidiazoleacetates,¹⁴ diastereoselectivity was high. Among the chiral phthalimide-amino acid ligated dirhodium(II) carboxylate catalysts, $\text{Rh}_2(\text{S-PTTL})_4$ ²⁸ was found to provide the highest level of enantiocontrol (87% *ee*) and the highest yield of cyclopropane product (90%). This product was formed as a single diastereoisomer (NOE determination from the ester reduction product, see SI), with minimal cyclopropene dimer formation (<10%) when the reaction was performed in 1,2-dichloroethane at 0°C. The absolute configuration of the cyclopropanation product is (1*R*,2*S*), as determined from the crystal structure of the hydrolysis/desilylation product **31'** (Figure 3b), which is identical to that formed with a similar chiral carboxylate catalyst from silyloxyvinylidiazoleacetates.²⁰

Solvent also played a significant role in determining cyclopropanation product yield and enantioselectivity. Although the sulfamido-prolinate ligated $\text{Rh}_2(\text{S-DOSP})_4$ catalyst²⁹ provided a high yield (90%) but low 68% *ee* in DCE, not surprisingly this catalyst gave an even higher yield (95%) and enantioselectivity (91% *ee*) in the formation of **24** when the reaction was performed in the less polar toluene at 0°C. These differences in yields and selectivities suggest that determination of the optimum chiral carboxylate ligand for dirhodium(II) or the optimum solvent may not be predictable for the broad spectrum of oximidovinylidiazole esters that are available, and further research is expected to reveal improvements.

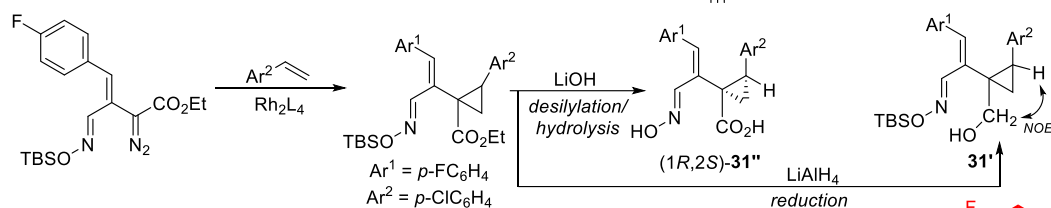
Using the two different chiral dirhodium(II) carboxylate catalysts, $\text{Rh}_2(\text{S-PTTL})_4$ and $\text{Rh}_2(\text{S-DOSP})_4$, we surveyed product yields and stereoselectivities for reactions of TBS-protected oximidovinylidiazole esters with styrene under the optimized conditions, and these results are presented in Figure 3c. The $\text{Rh}_2(\text{S-DOSP})_4$ catalyst generally provides the highest yields and %*ee* values.

Exceptional diastereocontrol for the *E*-isomer was obtained using all the oximido vinyl diazo esters and dirhodium catalysts that were employed. Substituents on the benzene ring of styrene have a minor influence on yield and stereocontrol. With cyclopropanation product yields normally greater than 80%, the dominant or exclusive by-product formed in variable, but low, yields were due to the competing process that formed cyclopropene dimer **23** via internal cyclopropene formation and subsequent ene reaction (Figure 3a). Surprisingly, the oxime attachment of **3**, which is a notable Lewis base, did not inhibit these reactions. When the *t*Bu ester of silyl-protected oximido vinyl diazoacetate **17** was used in a rhodium acetate catalysed reaction, the *t*Bu ester analog of **28** was not formed; instead cyclopropene dimer **23** was produced in 80% yield. We have selected 4-phenyl-1-butene as a substrate to conduct the cyclopropanation reaction, but only the cyclopropane dimers **23** were obtained. In the case of 1-(vinyl oxy)butane, the cyclopropanation product was obtained in 86% yield and >20:1 *dr* in the presence of Rh₂(PTTL)₄, which suggests the potential for further expansion of cyclopropanation applications.

(a) General transformation:



(b) Stereochemical determination



(c) Cyclopropanation scope:

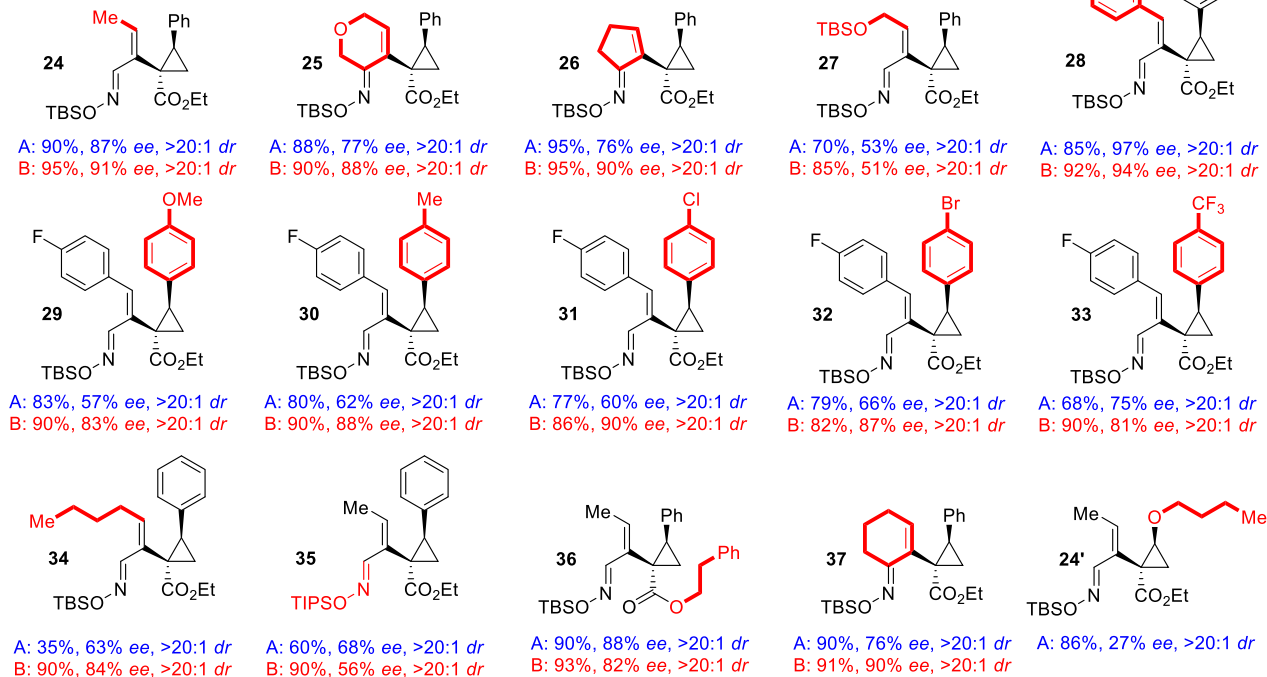


Figure 3. Highly enantioselective catalytic intramolecular cyclopropanation of styrenes by of diverse oximidyldiazo esters

(a) The general transformation and its major competing reaction. General conditions: diazo compound was added over a period of 3 h *via* syringe pump in vial containing Rh catalyst (1 mol%) and the styrene derivate under an argon atmosphere.

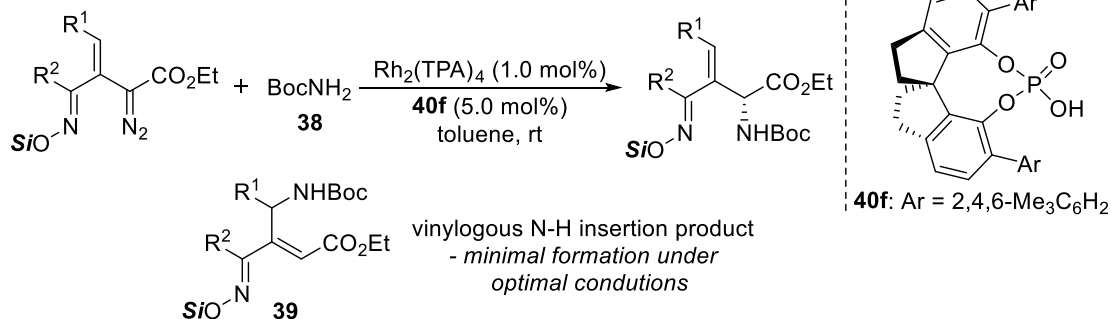
(b) Stereochemical determinations.

(c) Comparison of % yields and % *ee* values for cyclopropanation reactions catalyzed by $\text{Rh}_2(\text{S-PTTL})_4$ and $\text{Rh}_2(\text{S-DOSP})_4$.

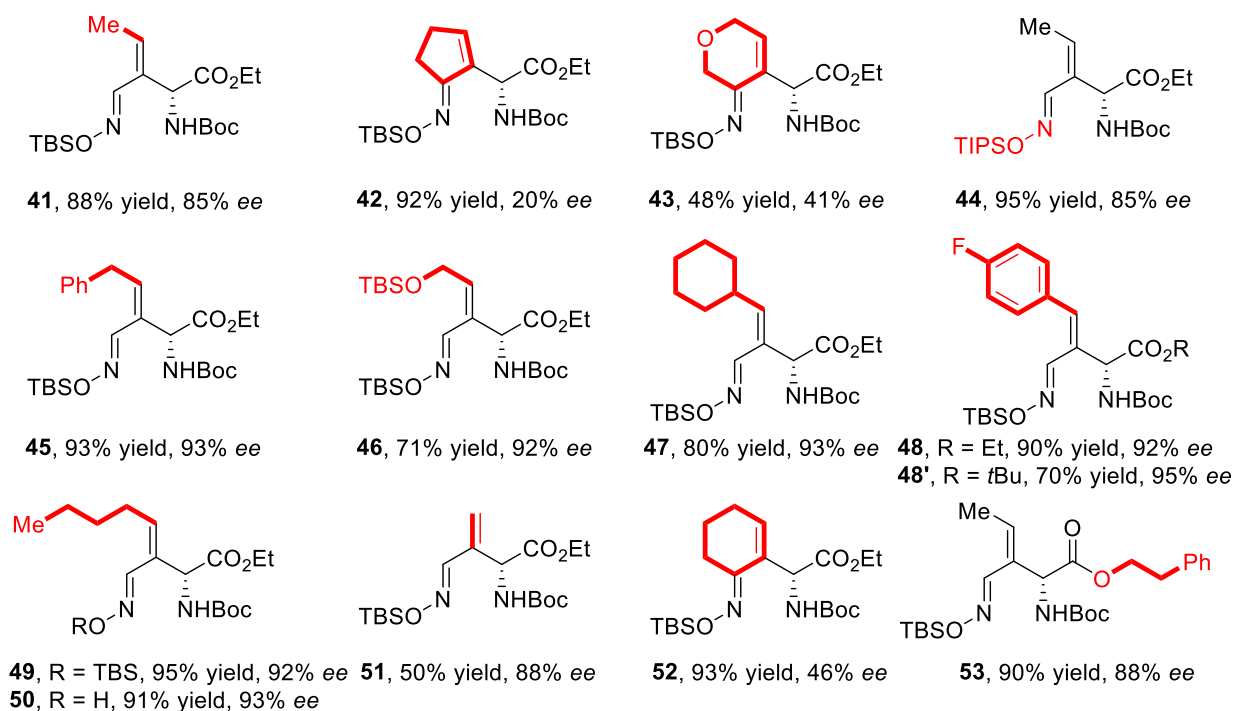
Catalytic enantioselective N-H insertion

Another intriguing metal carbene transformation is that of N-H insertion that can transform diazo esters to amino acid esters. This transformation has been the target, with some notable successes,^{30–32} of many investigations seeking high enantioselection for conversions of alkyl- and aryl diazoacetates to amino acid derivatives. However, until the recent report by Zhou and coworkers,³³ its applicability to vinyl diazoacetates has been severely limited. We had previously found that 3-(trialkylsiloxy)-2-diazobutanoate underwent highly enantioselective exclusive vinylogous N-H insertion, instead of insertion at the original diazo carbon, with aldehyde-derived hydrazones using chiral dirhodium catalysts.³⁴ The Zhou group developed a high yielding and highly enantioselective synthesis of γ -substituted α -alkenyl- α -amino acids by N-H insertion between vinyl diazoacetates at the diazo carbon and *tert*-butyl carbamate that was cooperatively catalyzed by achiral dirhodium(II) carboxylates, of which dirhodium tetra(triphenylacetate), $\text{Rh}_2(\text{TPA})_4$, was optimal, and a chiral spiro phosphoric acid (**SPA**) catalyst under mild, neutral conditions. The **SPA** catalyst promoted proton transfer of the ylide intermediate by functioning as a proton shuttle catalyst. Using this methodology, optimized from the TBS-protected oximido vinyl diazoacetate **8** for the formation of **41** with $\text{Rh}_2(\text{TPA})_4$ and spirophosphoric acid **SPA**, the corresponding N-H insertion product was produced in high yield (88%) and stereocontrol (85% *ee*). Vinylogous N-H insertion was observed as a minor product in pre-optimized investigations but was minimal or not observed with reactions performed under optimum conditions (Figure 4a). The observed N-H insertion is, as was previously noted,³³ very rapid; and the competing side reaction of vinyl diazoacetates (to form cyclopropene ene dimers **23**) is suppressed. Using the optimized reaction conditions, we then carried out reactions with other oximido vinyl diazoacetates, and these results are presented in Figure 4b. High product yields and consistently high enantioselectivities are obtained, even with the unprotected oxime **11** yielding **50**. The *t*Bu ester of compound **48** was formed in 95% *ee* (70% yield) which was only a slight improvement from the 92% *ee* obtained with the ethyl ester. The amino acid of N-H insertion product **48** was obtained by hydrolysis³³ (Figure 4c) and its absolute configuration was determined to be *R* using a chiral aldehyde chemical shift reagent (**55**) that forms resonance-assisted hydrogen bonded imines with amino acids (Figure S3).³⁵ The *R*-configuration of amino acid **54** is the same as the α -alkenyl- α -amino acids obtained from styryl diazoacetates and *tert*-butyl carbamate with the same catalysts and under the same conditions.³³

(a) General transformation:



(b) N-H Insertion scope:



(c) Absolute configuration:

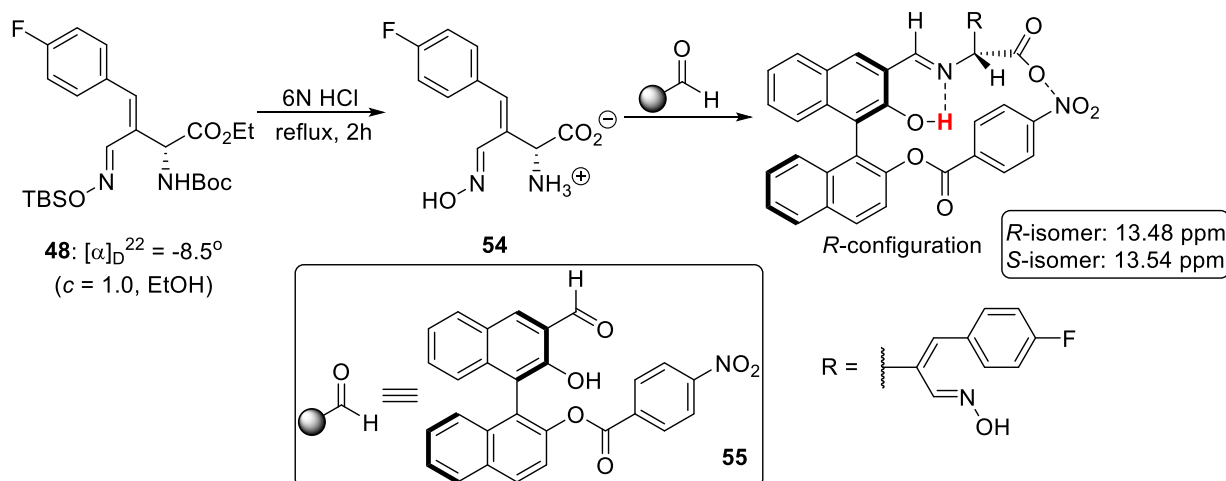


Figure 4. Catalytic enantioselective N-H insertion

(a) General transformation of oximidovinyl diazo esters with *tert*-butyl carbamate catalyzed by dirhodium(II) tetra(triphenylacetate) [Rh₂(TPA)₄] and the chiral **SPA** Brønsted acid in toluene at room temperature. Formation of the vinylogous N-H insertion product **39** was not observed or was a minor competing reaction.

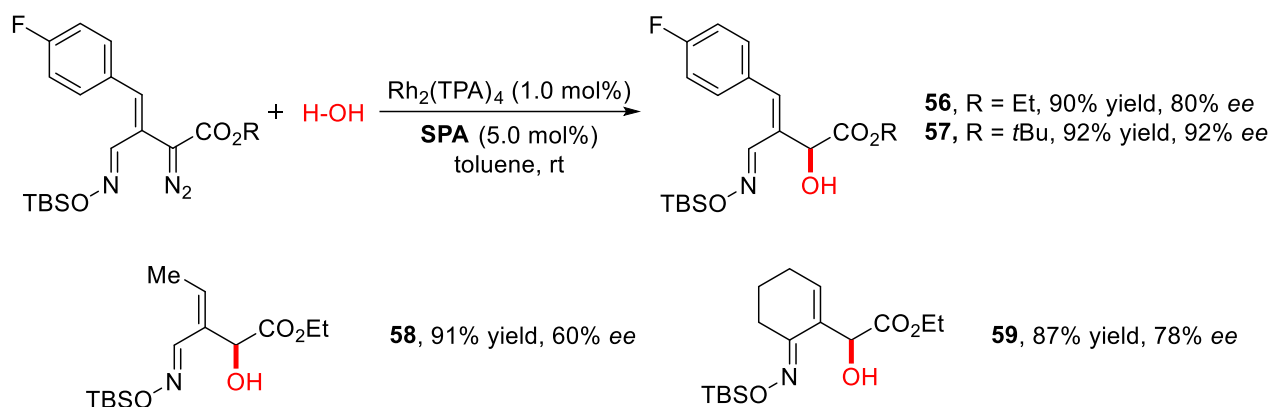
(b) % Yields and % *ee* values for N-H insertion reactions.

(c) Absolute configuration of N-H insertion products.

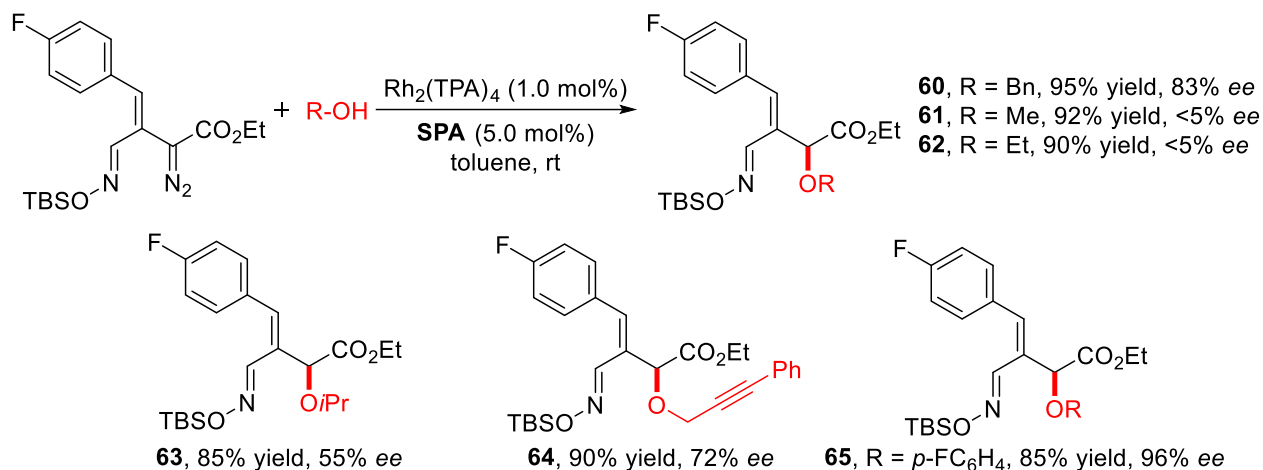
Catalytic enantioselective O-H insertion

To further expand the scope of this insertion transformation we examined the potential of this methodology for O-H insertion. Prior attempts to achieve high enantiocontrol in O-H insertion reactions that used aryldiazoacetates with iron(II) catalysts having chiral spirobox ligands achieved greater than 90% *ee*,³⁶ and with copper(I) catalysis using chiral box ligands attained greater than 80% *ee*³⁷ for O-H insertion with alcohols, but neither reported a successful O-H insertion with water. However, Zhou and coworkers reported³⁸ highly enantioselective O-H insertion of water with α -alkyl- and α -alkenyl- α -diazoacetates using modifications of the same catalytic methodology that they previously reported for N-H insertion.³³ Using a 20% molar excess of water for reactions performed under the same conditions as with BocNH₂ (Figure 4b), α -hydroxy ester **56** was obtained in high yield with 80% *ee* (Figure 5a). With benzyl alcohol, the corresponding benzyl ether (**60**) was formed in higher yield and similar enantioselectivity (Figure 5b). A sampling of results with various alcohols showed (**61-65**) that product yields are highly dependent on the structure of the alcohol, ranging from <5% *ee* for reactions with methanol and ethanol to greater than 95% *ee* in the reaction with *p*-florophenol. Similarly, the % *ee* from water insertion was dependent on the diazo ester alkyl group.

(a) O-H Insertion with water:



(b) O-H Insertion with alcohols:

**Figure 5. Catalytic enantioselective O-H insertion**

(a) % Yields and % ee of products from insertion with water.

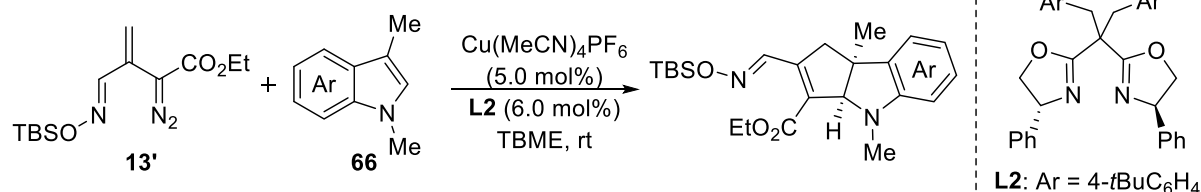
(b) % Yields and % ee of products from insertion with alcohols.

Catalytic enantioselective [3+2]-cycloaddition

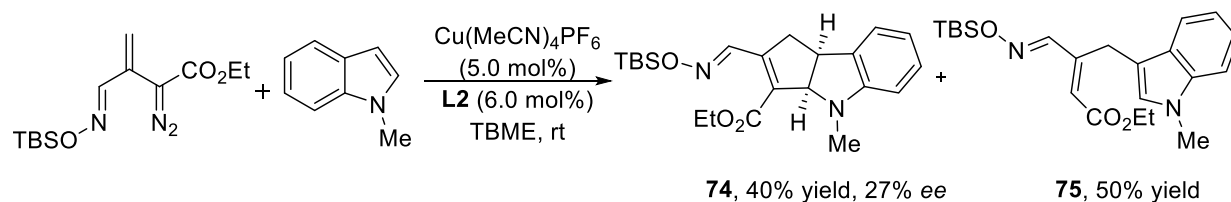
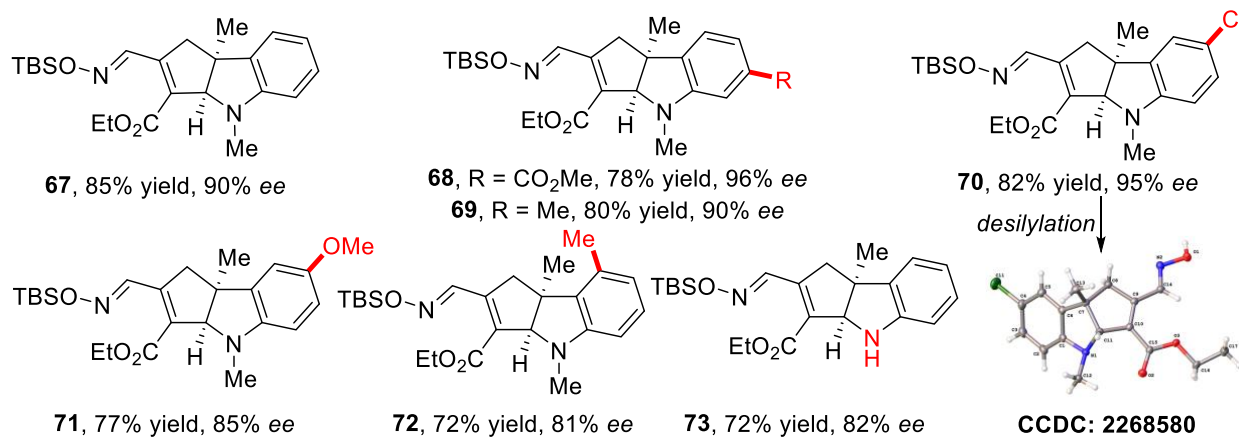
Another common reaction of metal carbenes is cycloaddition,²⁷ and the [3+2]-cycloaddition of vinyl diazoesters with indoles is among the most thoroughly investigated.³⁹⁻⁴¹ A survey of catalysts revealed that copper(I) tetrakis(acetonitrile) hexafluorophosphate with Sabox ligands was optimum for providing the [3+2]-cycloaddition products in high yields and high enantioselectivities without evidence for a competing production of cyclopropene dimer **23** (Figure 6a). Treatment of 3-methyl-*N*-methylindole with the parent TBS-protected oximido vinyl diazoacetate of **13** using the optimized Cu(I) catalyst with chiral SaBox ligand **L2** produced the [3+2]-cycloaddition product **67** in 85% yield with 90% ee. Reactions with substituted 3-methyl-*N*-methylindoles using the same catalyst and under the same conditions gave their cycloaddition products in comparable yields, but with % ee values that were dependent on the indole substituents (Figure 6b); electron withdrawing substituents gave higher enantiomeric excesses than did electron donating

substituents. The crystal structure of **70** describes its (*R,S*) absolute configuration. Interestingly, 3-methylindole without the *N*-methyl group gave cycloaddition product **73** with a somewhat lower % yield and % *ee*, but *N*-methylindole without the 3-methyl substituent gave both the [3+2]-cycloaddition product **74** with low enantiocontrol and a vinylogous product (**75**) by formal Csp²-H insertion. Reactions of 3-methyl-*N*-methylindole with methyl- and *p*-fluorophenyl-substituted oximidovinyl diazoacetates **76** and **77** formed the corresponding cycloaddition products in good yields but in low diastereocontrol, although with a high % *ee* for the *cis* diastereoisomer and a low % *ee* for the *trans* diastereoisomer (Figure 6c). The low diastereocontrol is indicative of a stepwise cycloaddition reaction, and efforts are underway to control diastereoselectivity.

(a) General transformation:



(b) [3+2]-Cycloaddition scope:



(c) Reactions of vinyl-substituted oximidovinyl diazoacetates with 3, *N*-dimethylindoles:

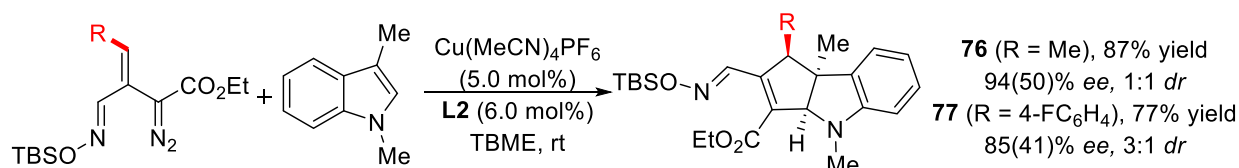


Figure 6. Catalytic enantioselective [3+2]-cycloaddition with indoles

(a) General reaction of oximidovinyl diazoacetate **13'** with substituted indoles catalyzed by Cu(MeCN)₄PF₆ with chiral SaBox ligand **L2** at room temperature in TBME.

(b) % Yields and % *ee* values for copper(I) catalyzed [3+2]-cycloaddition products from **13'** and substituted indoles.

(c) % Yields and % *ee* values for copper(I) catalyzed [3+2]-cycloaddition products from substituted oximidovinyl diazoacetate and 3-methyl-*N*-methylindole

Conclusion

This work provides the synthesis of diverse oximidovinyl diazoacetates that are conveniently formed by base catalyzed Dimroth-type rearrangement of multiply-substituted 1,2,3-triazine 1-oxides. These diazo compounds have β,γ -unsaturation with an oxime functional group at the β -position. The oxime hydroxyl group is unsuitable for most metal carbene reactions, but silylation generates the diazo reactant that is effective for metal carbene formation and reactions. Addition, insertion, and cycloaddition processes were selected to exemplify the suitability of silylated oximidovinyl diazoacetates for catalytic metal carbene transformations, and high product yields with exceptional enantiocontrol were achieved under very mild conditions, suggesting that these new vinyl diazoacetates will be appropriate for use in a larger array of metal carbene transformations, as well as in the increasing number of non-metal transformations of vinyl diazoacetates. The diazo compound reactants formed from 1,2,3-triazine 1-oxides and their metal carbene derived products possess the oxime functionality, which is among the most common nitrogen-containing biological motifs,⁴² whose pharmacological applications include antibacterial, anti-fungal, anti-inflammatory, anti-oxidant and anti-cancer activities.^{43,44} Furthermore, the oxime functional group is amenable to conversions into other functionalities.^{45,46} Overall, oximidovinyl diazoacetates offer a new platform for catalytic asymmetric syntheses

EXPERIMENTAL PROCEDURES**Resource availability***Lead contact*

Requests for further information and resources should be informed to and will be fulfilled by the lead contact, Michael P. Doyle (michael.doyle@utsa.edu).

Materials availability

New products generated in this study will be made available on request, but we might require a payment and/or a completed material transfer agreement if there is potential for commercial application.

Data and code availability

This study did not generate any datasets.

GENERAL

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Reagents and solvents were purified by standard means. See Supplementary Methods for detailed conditions, reaction optimizations, and product characterizations.

General procedure for the preparation of oximidovinylidiaoacetates

To a solution of triazine 1-oxide (0.1 mmol, 0.2 M in THF) in a dry 10-mL tube was added all at once Cs_2CO_3 (20 mol%, 0.020 mmol, 6.5 mg) or DABCO (20 mol%, 0.020 mmol, 2.2 mg). The solution was stirred at room temperature under air. When the reaction was complete (monitored by TLC), the reaction mixture was purified by flash column chromatography on silica gel without additional treatment (hexanes:EtOAc = 10:1) to give the oximidovinylidiao ester compounds.

General procedure for cyclopropanation with styrene

Catalysis by $\text{Rh}_2(\text{S-PTTL})_4$: to a 10-mL oven-dried vial with a magnetic stirring bar, styrene (0.20 mmol, 2.0 equiv.), $\text{Rh}_2(\text{S-PTTL})_4$ (1.2 mg, 1.0 mol%), and 4Å MS (50 mg) in anhydrous DCE (1.0 mL) was added a solution of the TBS-protected oximidovinylidiaoacetate (0.1 mmol) in anhydrous DCE (1.0 mL) via a syringe pump over 3 h at 0 °C under an argon atmosphere. When the reaction was complete (monitored by TLC), the reaction mixture was purified by flash column chromatography on silica gel without additional treatment (hexanes:EtOAc = 20:1 to 15:1) to give the pure cyclopropane products.

Catalysis by $\text{Rh}_2(\text{S-DOSP})_4$: to a 10-mL oven-dried vial with a magnetic stirring bar, styrene (0.20 mmol, 2.0 equiv.), $\text{Rh}_2(\text{S-DOSP})_4$ (1.8 mg, 1.0 mol%), and 4Å MS (50 mg) in anhydrous toluene (1.0 mL), was added a solution of the TBS-protected oximidovinylidiaoacetate (0.1 mmol) in anhydrous toluene (1.0 mL) via a syringe pump over 3 h at 0 °C under an argon atmosphere. When the reaction was complete (monitored by TLC), the reaction mixture was purified by flash column chromatography on silica gel without additional treatment (hexanes:EtOAc = 20:1 to 15:1) to give the pure cyclopropane products

General procedure for N-H and O-H insertion

To a 10-mL oven-dried vial with a magnetic stirring bar containing the X-H insertion reagent (*tert*-butyl carbamate, alcohol, or water: 0.12 mmol, 1.2 equiv.), $\text{Rh}_2(\text{TPA})_4$ (1.4 mg, 1.0 mol%), chiral phosphoric acid **40f** (2.8 mg, 5.0 mol%), and 4Å MS (50 mg) in anhydrous toluene (1.0 mL) was added a solution of the oximidovinylidiaoacetate reactant (0.1 mmol) in anhydrous toluene (1.0 mL) via a syringe pump over 2 h at room temperature under an argon atmosphere. When the reaction was complete (monitored by TLC), the reaction mixture was purified by flash column chromatography on silica gel without additional treatment (hexanes : EtOAc = 15:1 to 5:1) to give the pure products.

General procedure for cycloaddition with indoles

The chiral catalyst was prepared by stirring $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (1.8 mg, 0.005 mmol, 5.0 mol %) with the chiral bisoxazoline ligand (3.6 mg, 0.006 mmol, 6.0 mol %) in dry DCM (1.0 mL) in an oven-dried 10 mL vial for 1 h at room temperature under an argon atmosphere, then DCM was removed and dry TBME (0.5 mL) was added. A solution of 1,3-dimethylindole (0.10 mmol, 1.0 equiv.) in dry TBME (0.5 mL) was introduced to the reaction mixture. Then oximidovinylidiaoacetate (0.12 mmol, 1.2 equiv.) in dry TBME (1.0 mL) was added dropwise over 2 min. The reaction solution was stirred at room temperature for 12 h. When the reaction was complete (monitored by TLC), the reaction mixture was purified by flash column chromatography on silica gel

without additional treatment (hexanes : EtOAc = 20:1 to 15:1) to give the pure [3+2]-cycloaddition products.

SUPPLEMENTAL INFORMATION

Document S1. Supplemental experimental procedures, Table S1-S4 and Figures S1–S7.

Table S1. Optimization of the Cyclopropanation Reaction Conditions

Table S2. Optimization of the N-H Insertion Reaction Conditions

Table S3. Optimization of the [3+2]-Cycloaddition Reaction Conditions

Table S4. Crystallographic data and structure refinement for Compounds **17**, **31'** and **70'**

Figure S1. NOE NMR spectra of **31'**

Figure S2. NOE NMR spectra of **31'**

Figure S3. Proton NMR spectra of the imine formed with chiral aldehyde **55** and amino acid **54**

Figure S4. NOE NMR spectra of **75**

Figure S5. NOE NMR spectra of **78**

Figure S6. ORTEP drawing of **17** showing thermal ellipsoids at the 50% probability level

Figure S7. ORTEP drawing of **31'** showing thermal ellipsoids at the 50% probability level

Figure S8. ORTEP drawing of **70'** showing thermal ellipsoids at the 50% probability level

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AUTHOR CONTRIBUTIONS

M. B. performed the catalytic studies of the oximidovinyldiazoacetates and characterization of products. L.D.A. discovered the base-catalyzed formation of oximidovinyldiazoacetates from 1,2,3-triazine 1-oxides, and he, M.S.R., and M. B. prepared the diazo compounds and their silyl-protected derivatives. H. A. performed the reported X-ray analyses, and D.W. assisted with stereochemical NMR determinations. M.B., L.D.A., M.S.R. and M.P.D. conceived and designed the experiments, and M.B., L.D.A., and M.P.D. prepared the manuscript. All authors contributed to discussions and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse and equitable conduct of research.

REFERENCES

1. Doyle, M. P., McKerver, M. A., and Ye, T. (1998). Modern catalytic methods for organic synthesis with diazo compounds, John Wiley & Sons, Inc., New York, NY.
2. Wang, J., and Qiu, D. (2020). Recent developments of diazo compounds in organic synthesis. World Scientific: London.
3. Curtius, T. (1883). Ueber die Einwirkung von salpetriger Säure auf salzsauren Glycocoläther" [On the reaction of nitrous acid with glycine ethyl ester hydrochloride]. Chem. Ber. 16, 2230-2231.
4. Ford, A., Miel, H., Ring, A., Slattery, C. N., Maguire, A. R., and McKerver, M. A. (2015). Modern organic synthesis with α -diazocarbonyl compounds. Chem. Rev. 115, 9981-10080.
5. Breugst, M., and Reissig, H. R. (2020). The Huisgen reaction: milestones of the 1,3-dipolar cycloaddition. Angew. Chem. Int. Ed. 59, 12293-12307.
6. Mix, K. A., Aronoff, M. R.; and Raines, R. T. (2016). Diazo compounds: versatile tools for chemical biology. ACS Chem. Biol. 11, 3233-3244.
7. Nozaki, H., Moriuti, S., Takaya, H., and Noyori, R. (1966). Asymmetric induction in carbenoid reaction by means of a dissymmetric copper chelate. Tet. Lett. 43, 5239-5244.
8. Davies, H. M. L., Clark, D. M., Alligood, D. B., Eiband, G. R. (1987). Mechanistic aspects of formal [3 + 4] cycloadditions between vinylcarbenoids and furans. Tetrahedron 43, 4265-4270.
9. Liao, K. B., and Davies, H. M. L. (2019). Dirhodium tetracarboxylates as catalysts for selective intermolecular C-H functionalization. Nat. Rev. Chem. 3, 347-360.
10. Zhu, D., Chen, L., Fan, H., Yao, Q., and Zhu, S. (2020). Recent progress on donor and donor-donor carbenes. Chem. Soc. Rev. 49, 908-950.
11. Marichev, K. O., Zheng, H., and Doyle, M. P. (2022). Metal carbene cycloaddition reactions in transition metal-catalyzed carbene transformations. Wang, J., Che, C. M., and Doyle, M. P., Eds., Wiley-VCH GmbH, Weinheim, Germany, Chapter 5, pg. 139-168.
12. Regitz, M., and Maas, G. (1986). Diazo compounds: properties and synthesis. Academic Press, London.
13. Cheng, Q. Q., Deng, Y., Lankelma, M., and Doyle, M. P. (2017). Cycloaddition reactions of enoldiazo compounds. Chem. Soc. Rev. 46, 5425-5443.
14. Davies, H. M. L., Clark, T. J., Church, L. A. (1989). Stereoselective cyclopropanations with vinylcarbenoids. Tetrahedron Lett. 30, 5057-5060.
15. Davies, H. M. L., Dai, X., and Long, M. S. (2006). Combined C-H activation/Cope rearrangement as a strategic reaction in organic synthesis: total synthesis of (-)-colombiasin A and (-)-elisapterosin B. J. Am. Chem. Soc. 128, 2485-2490.
16. Davies, H. M. L., and Alford, J. S. (2014). Reactions of metallocarbenes derived from N-sulfonyl-1,2,3-triazoles. Chem. Soc. Rev. 43, 5151-5162.
17. De Angelis, L., Zheng, H., Perz, M., Arman, H.; and Doyle, M. P. (2021). Intermolecular [5+1]-cycloaddition between vinyl diazo compounds and *tert*-butyl nitrite to 1,2,3-triazine 1-oxides and their further transformation to isoxazole. Org. Lett. 23, 6542-6546.
18. Biswas, S., De Angelis, L., Rivera, G., Arman, H., and Doyle, M. P. (2023). Inverse electron demand diels-alder-type heterocycle syntheses with 1,2,3-triazine 1-oxides-expanded versatility. Org. Lett. 25, 3029-3033.
19. Davies, H. M. L., and Hutcheson, D. K. (1993). Enantioselective synthesis of vinylcyclopropanes by rhodium(II) catalyzed decomposition of vinyl diazomethanes in the presence of alkenes. Tetrahedron Lett. 34, 7243-7246.
20. Müller, P., Bernardinelli, G., Allenbach, Y. F.; Ferri, M.; and Flack, H. D. (2004). Selectivity enhancement in the Rh(II)-catalyzed cyclopropanation of styrene with (silyloxyvinyl)diazooacetates. Org. Lett. 6, 1725-1728.
21. Meazza, M., Guo, H., and Rios, R. (2015). Synthetic applications of vinyl cyclopropane opening. Org. Biomol. Chem. 15, 2479-2490.
22. Li, M. M., Xiong, Q., Qu, B. L., Xiao, Y. Q., Lan, Y., Lu, L. Q., and Xiao, W. J. (2020). Utilizing vinylcyclopropane reactivity: palladium-catalyzed asymmetric [5+2] dipolar cycloadditions. Angew. Chem. Int. Ed. 59, 17429-17434.
23. Ebner, C., and Carreira, E. M. (2017). Cyclopropanation strategies in recent total syntheses. Chem. Rev. 117, 11651-11679.
24. Choi, S., Ha, S., and Park, C.-M. (2017). α -Diazo oxime ethers for N-heterocycle synthesis. Chem. Commun. 53, 6054-6064.
25. Deng, Y., Jing, C., and Doyle, M. P. (2015). Dinitrogen extrusion from enoldiazo compounds under thermal conditions: synthesis of donor-acceptor cyclopropenes. Chem. Commun. 51, 12924-12927.
26. Zheng, H., Faghihi, I., and Doyle, M. P. (2021). Copper(I)-catalyzed highly enantioselective [3+3]-cycloaddition of β -aryl/alkyl vinyl diazoacetates with nitrones. Helv. Chim. Acta. 104, e2100081.
27. Marichev, K. O., Zheng, H., and Doyle, M. P. (2022). Metal carbene cycloaddition reactions in transition metal-catalyzed carbene transformations, Wang,

- J., Che, C. M., Doyle, M. P., Eds., Wiley-VCH GmbH, Weinheim, Germany, Chapter 5, pg. 139-168.
28. Watanabe, N., Ogawa, T., Ohtake, Y., Ikegami, S., and Hashimoto, S. (1996). Dirhodium(II) tetrakis [*N*-phthaloyl-(*S*)-tert-leucinate]: a notable catalyst for enantiotopically selective aromatic substitution reactions of α -diazocarbonyl compounds. *Synlett*. **1**, 85-86.
29. Davies, H. M. L., Bruzinski, P. R., Lake, D. H., Kong, N., and Fall, M. J. (1996). Asymmetric cyclopropanations by rhodium(II) *N*-(arylsulfonyl)prolinate catalyzed decomposition of vinyl diazomethanes in the presence of alkenes. practical enantioselective synthesis of the four stereoisomers of 2-phenylcyclopropan-1-amino Acid. *J. Am. Chem. Soc.* **118**, 6897-6907.
30. Zhu, S. F., and Zhou, Q. L. (2012). Transition-metal-catalyzed enantioselective heteroatom-hydrogen bond insertion reactions. *Acc. Chem. Res.* **45**, 1365-1377.
31. Burtoloso, A. C. B., Santiago, J. V., Bernardim, B. G., and Talero, A. G. (2015). Advances in the enantioselective metal-catalyzed N-H and O-H insertion reactions with diazocarbonyl compounds, *Curr. Org. Synth.* **12**, 650-659.
32. Li, M. L., Yu, J. H., Li, Y. H., Zhu, S. F., and Zhou, Q. L. (2019). Highly enantioselective carbene insertion into N-H bonds of aliphatic amines. *Science* **366**, 990-924.
33. Guo, J. X., Zhou, T., Xu, B., Zhu, S. F., and Zhou, Q. L. (2016). Enantioselective synthesis of α -alkenyl α -amino acids *via* N-H insertion reactions. *Chem. Sci.* **7**, 1104-1108.
34. Xu, X., Zavalij, P. Y., and Doyle, M. P. (2012). Synthesis of tetrahydropyridazines by a metal-carbene directed highly enantioselective vinylogous N-H insertion/Lewis acid catalyzed diastereoselective Mannich addition. *Angew. Chem. Int. Ed.* **51**, 9829-9833.
35. Chin, J., Kim, D. C., Kim, H. J., Panosyan, F. B., and Kim, K. M. (2004). Chiral shift reagent for amino acids based on resonance-assisted hydrogen bonding. *Org. Lett.* **6**, 2591-2593.
36. Zhu, S.-F., Cai, Y., Mao, H. X., Xie, J. H., and Zhou, Q. L. (2010). Enantioselective iron-catalyzed O-H bond insertions. *Nat. Chem.* **2**, 546-555.
37. Maier, T. C., Fu, G. C., Maier, T. C., and Fu, G. C. (2006). Catalytic enantioselective O-H insertion reactions. *J. Am. Chem. Soc.* **128**, 4594-4595.
38. Li, Y., Zhao, Y. T., Zhou, T., Chen, M. Q., Li, Y. P., Huang, M. Y., Xu, Z. C., Zhu, S. F., and Zhou, Q. L. (2020). Highly enantioselective O-H bond insertion of α -alkyl- α -diazoacetates and α -alkenyl- α -diazoacetates with water. *J. Am. Chem. Soc.* **142**, 10557-10566.
39. Barluenga, J., Tudela, E., Ballesteros, A., and Tomas, M. (2009). Asymmetric C2-C3 cyclopentannulation of the indole ring. *J. Am. Chem. Soc.* **131**, 2096-2097.
40. Lian, Y., and Davies, H. M. S. (2010). Rhodium-catalyzed [3+2] annulation of indoles. *J. Am. Chem. Soc.* **132**, 440-441.
41. Jing, C. C., Cheng, Q. -Q., Deng, Y. M., Arman, H., and Doyle, M. P. (2016). Highly regio- and enantioselective formal [3 + 2]-annulation of indoles with electrophilic enol carbene intermediate. *Org. Lett.* **18**, 4550-4553.
42. Dhuguru, J., Zviagin, E., and Skouta, R. (2022). FDA-approved oximes and their significance in medicinal chemistry. *Pharmaceuticals* **15**, 66.
43. Kozłowska, J., Potaniec, B., Żarowska, B., and Anioł, M. (2017). Synthesis and biological activity of novel *O*-alkyl derivatives of naringenin and their oximes. *Molecules* **22**, 1485.
44. Zhmurenko, L. A., Litvinova, S. A., Kutepova, I. S., Nerobkova, L. N., Mokrov, G. V., Rebeko, A. G., Voronina, T. A., and Gudasheva, T. A. (2020). Synthesis of dibenzofuranone-oxime derivatives with anticonvulsant, antihypoxic, and anti-ischemic activity. *Pharm. Chem. J.* **53**, 997-1004.
45. Adams, J. P. (2000). Imines, enamines, and oximes. *J. Chem. Soc., Perkin Trans.* 125-139.
46. Li, Y., Chen, H., Qu, L. B., Houk, K. N., and Lan, Y. (2019). Origin of regiochemical control in Rh(III)/Rh(V)-catalyzed reactions of unsaturated oximes and alkenes to form pyridines. *ACS Catal.* **9**, 7154-7165.