ORGANOMETALLICS

Article

Cite This: *Organometallics* 2019, 38, 4043−4050

pubs.acs.org/Organometallics

Role of Donor−Acceptor Cyclopropenes in Metal Carbene Reactions. Conversion of *E*-Substituted Enoldiazoacetates to *Z*-Substituted Metallo-Enolcarbenes

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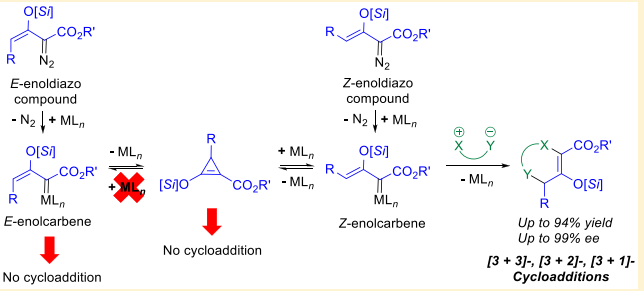
Supporting Information

ABSTRACT: The influence of geometrical isomers of silyl-protected γ-substituted enoldiazoacetates has been examined in transition-metal-catalyzed vinylcarbene cycloaddition reactions. These reactions often occur with the intervention of donor−acceptor (D-A) cyclopropenes that can serve as metal carbene sources. Pathways to cycloaddition products that occur with and without D-A cyclopropene involvement have been identified. *E*-γ-Substituted enoldiazoacetates do not undergo cycloaddition reactions unless they first form D-A cyclopropene intermediates. When cycloaddition reactions occur from the metallocarbene only after formation of the D-A cyclopropene, *E*-γ-substituted enoldiazoacetates are converted to *Z*-γ-substituted metallo-enolcarbenes, and both geometrical isomers of silyl-protected γ-substituted enoldiazoacetates result in the same product selectivity.

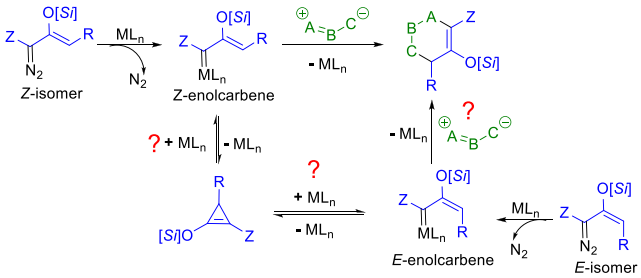


INTRODUCTION

The rearrangement of cyclopropenes to carbenes has been widely investigated as a thermally induced process.[1] Although cyclopropenes and alkylcyclopropenes undergo ring-opening reactions at temperatures above 200 °C, the introduction of electron-donating and electron-withdrawing substituents is known to dramatically reduce the temperature at which ring opening occurs. Catalytic ring opening of cyclopropenes is an outcome of the conceptual relationship between cyclopropenes and carbenes, and gold catalysis provided the first successes in 2008, albeit with controversy over the nature of the intermediate.[2] Extensive studies with a wide variety of cyclopropenes have established the formation of gold carbene intermediates in many cases,[3] and an increasing number of examples of carbene intermediates formed from cyclopropenes with rhodium catalysts have been reported.[4]

The recent discovery of donor−acceptor cyclopropenes as precursors to silyl-protected metallo-enolcarbenes and their uses in cycloaddition reactions has explained, in part, the remarkable versatility of silyl-protected enoldiazo acetates, acetamides, ketones, and sulfones in asymmetric [3 + *n*]-cycloaddition reactions.[5] Donor−acceptor cyclopropenes serve as a resting state for the corresponding metal carbenes, increasing their lifetime and providing increased product yields.[6] They are generated from silyl-protected enoldiazo compounds both thermally and catalytically,[7] but because of their ease of access diazoaceto compounds have been their principal sources. Only two γ-substituted enoldiazoacetates have been reported (R = Me, Ph in Scheme 1),[8,9] and the enoldiazoacetate with R = Ph did not undergo dirhodium(II)-catalyzed cycloaddition with nitrones under conditions where its unsubstituted analogue was highly reactive.[10] With the traditional base-promoted conversion of α-diazo-β-keto esters to enoldiazoacetates,[11] substituents at the γ-position are formed in the *E* and *Z* configurations, and each of them is expected to have its own reactivity and selectivity in reactions with catalysts that form metal carbenes (Scheme 1). However, formation of the donor−acceptor cyclopropene from these diastereomeric enoldiazoacetates provides only one cyclopropene isomer, but its metal-catalyzed ring opening may give access to either or both diastereomeric metallo-enolcarbenes. We report that the donor−acceptor cyclopropene formed from (*E*)- and (*Z*)-enoldiazoacetates undergoes catalytic ring opening to produce

Scheme 1. Role of Donor−Acceptor Cyclopropene in Cycloaddition Reactions of Enoldiazo Compounds



Special Issue: Asymmetric Synthesis Enabled by Organometallic Complexes

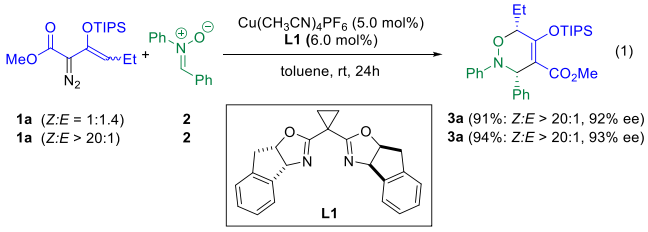
Received: June 26, 2019
Published: August 8, 2019

DOI: 10.1021/acs.organomet.9b00427
Organometallics 2019, 38, 4043−4050

only the *Z*-diastereomeric metallo-enolcarbene, but that dipolar cycloaddition can occur either before or after D-A cyclopropene formation.

RESULTS AND DISCUSSION

[3 + 3]-Cycloadditions. We envisioned that there could be three possible pathways for the formation of cycloaddition products: (1) product formation results solely from the metallocarbene without intervention of the D-A cyclopropene, (2) product formation results from the metallocarbene only after formation of the D-A cyclopropene, and (3) product formation results from the metallocarbene both with and without intervention of the D-A cyclopropene. In order to test this hypothesis, we first needed to establish the stereochemical outcome of both *E*- and *Z*-γ-substituted enoldiazoacetate isomers. Using the reaction of the nearly equal mixture of (*E*)- and (*Z*)-γ-ethyl enoldiazoacetate **1a** with nitrone **2** (eq 1) that



results in [3 + 3]-cycloaddition as a guide, the disappearance of the diazo compounds, formation of product **3a**, and the percent ee of **3a** were followed as a function of time; and Figure 1

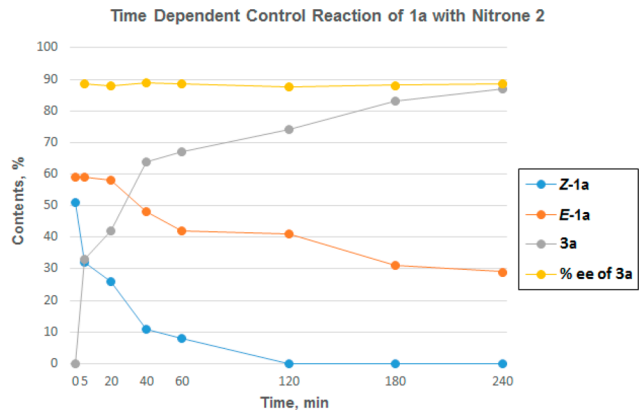
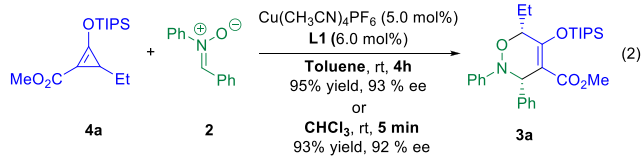


Figure 1. Time course for reaction described in eq 1. The reaction was performed with **1a** (0.24 mmol, *E*:*Z* = 1.2:1) and **2** (0.20 mmol), catalyzed by $Cu(MeCN)_4PF_6$/**L1** (5.0 mol %) in 4.0 mL of chloroform at room temperature.

describes the outcome of these determinations. The ligand selected for this study (**L1**) was optimized from a spectrum of chiral box[12] and sabox[13] ligands (see the Supporting Information).

The rate of loss of *Z*-**1a** is obviously much faster than that of *E*-**1a**, but the percent ee and its diastereomeric ratio (> 20:1) for product **3a** is constant within experimental error over the entire reaction course. For comparison, γ-ethyl enoldiazoacetate **1a** having a *Z*:*E* ratio greater than 20:1 was also reacted with nitrone **2** (eq 1), and its [3 + 3]-cycloaddition product **3a** gave the same percent ee and dr as did the nearly equal *Z*/*E* mixture reported in eq 1. As was established for reactions of **1** without a γ substituent,[14] D-A cyclopropene **4a** was observed in minor, but relatively constant, amounts throughout the reaction.

Use of **4a** instead of **1a** in the same reaction (eq 2) resulted in the formation of the cycloaddition product at about the same



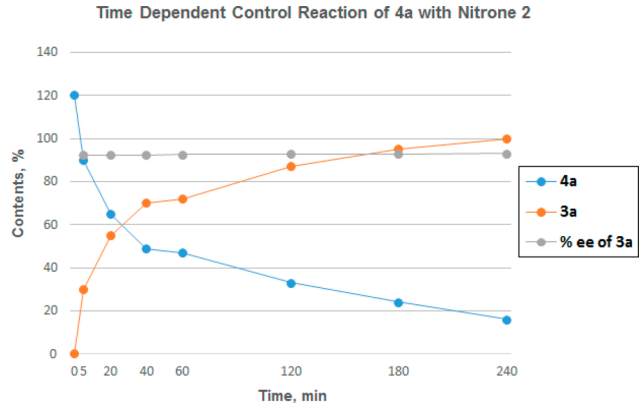
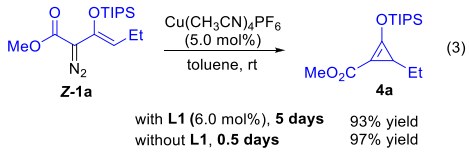


Figure 2. Time course for reaction of **4a** with **2a** under same conditions as described in eq 1. The reaction was performed with **4a** (0.24 mmol) and **2** (0.20 mmol), catalyzed by $Cu(MeCN)_4PF_6$/**L1** (5.0 mol %) in 4.0 mL of toluene at room temperature.

rate as for **1a** and with the same enantioselectivity (Figure 2) in toluene; however, the reaction rate was much higher (the reaction was complete in 5 min) when chloroform was used as a solvent (eq 2). Since both *Z*- and *E*-**1a** give the same product with the same stereocontrol (eq 1), and **4a** reacts at about the same rate as **1a**, the implication is that product formation results from the metallo-carbene only after formation of the donor–acceptor cyclopropene; both *Z*-**1a** and *E*-**1a** form the same D-A cyclopropene (**4a**), but **4a** undergoes catalytic ring opening to produce only the (*Z*)-metallo-enolcarbene that reacts with **2** by [3 + 3]-cycloaddition to form predominantly one stereoisomer of **3a**.

In a reaction of *Z*-**1a** performed under the same conditions without **2** and without **L1**, the rate of formation of **4a** was shown to be fast (complete within 12 h), but the same reaction with **L1** required 5 days to complete the reaction (eq 3).



Because of its electron-withdrawing influence, the sabox ligand inhibits the rate of reaction of **1a** with Cu(I) that forms the donor–acceptor cyclopropene, but the formation of **4a** is accelerated in the presence of **2** (Figure 2). This surprising result points to an additional complexity in the overall mechanism for involvement of copper(I) catalysis that is not expressed in Scheme 1 and is the subject of further investigations.

DOI: 10.1021/acs.organomet.9b00427
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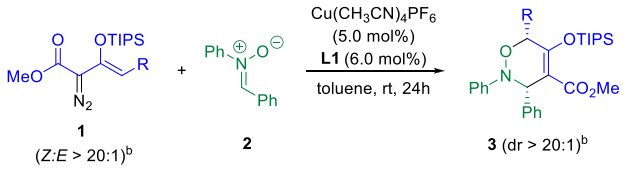
To evaluate the possible generality of [3 + 3]-cycloaddition by γ-substituted enoldiazoacetates with nitrones, TIPS-protected enoldiazoacetates *Z*-**1** with representative γ substituents were subjected to the copper(I)-catalyzed reaction with **2** (Table 1).

Table 1. Influence of γ-Substituent on Yield and Stereoselectivity in the Reactions of Enoldiazoacetates 1 with Nitrone 2.[a]



1 (*Z*:*E* > 20:1)[b] + **2** → **3** (dr > 20:1)[b]

reactant	product
1a, R = Et	**3a** (94% yield,[c] 93% ee[d])
1b, R = Me	**3b** (91% yield, 86% ee)
1c, R = ^{i}Pr	**3c** (89% yield, 99% ee)
1d, R = Bn	**3d** (89% yield, 96% ee)
1e, R = Ph	**3e** (0% yield)

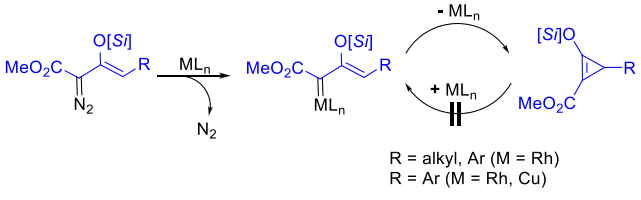
[a]Reactions were carried out on a 0.20 mmol scale of nitrone **2** with 0.24 mmol of enoldiazoacetate **1**. [b]The *Z*:*E* ratios and dr were determined from the ^{1}H NMR spectrum of the reaction solution after evaporation of the solvent. [c]Isolated yields after flash chromatography are reported. [d]Enantiomeric excess was determined using Daicel Chiralpak AD-H and IC-3 and Chiralcel OD-H chiral columns.

High yields and selectivities of **3** were achieved for each reactant, but the more sterically encumbered substituents (R = Bn, *i*Pr) gave higher enantioselectivities and lower percent yield of the products. With R = Ph (**1e**), however, no cycloaddition product was formed; the D-A cyclopropene was obtained but was resistant to ring opening using this catalyst−ligand combination.

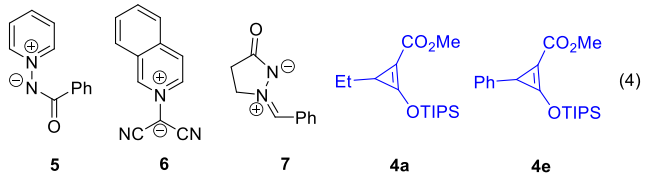
Without **L1**, $Cu(MeCN)_4PF_6$ catalyzed the reaction of **1e** with **2** at room temperature in toluene to form the [3 + 3]-cycloaddition product **3e** in 86% isolated yield. This latter outcome is consistent with the prior observation that the TBS-protected donor−acceptor cyclopropene **4e** does not undergo dirhodium(II) catalyzed [3 + 3]-cycloaddition with **2**, whereas Cu(I) or Ag(I) catalysts, even with chiral box ligands, do facilitate this reaction.[8] With dirhodium(II) catalysts the enoldiazoacetate forms the donor−acceptor cyclopropene, but these catalysts are insufficiently Lewis acidic or are too sterically encumbered to effectively open the cyclopropene to the metallo-enolcarbene (Scheme 2).

Examination of other dipolar species that have been reported to undergo [3 + 3]-cycloaddition with TBS-protected enoldiazoacetates showed the limitations of γ-substituted donor−acceptor cyclopropenes in serving as metal carbene precursors in cycloaddition reactions. Reactions of **1a** or **1e** with

Scheme 2. Influence of γ-Substituent and Metal to Regenerate the Metal Carbene from the Donor−Acceptor Cyclopropene



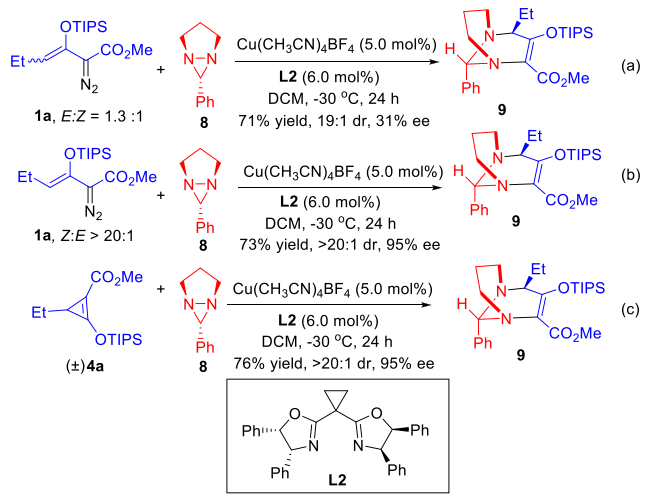
N-benzoylpyridinium ylide **5**,[15] dicyanoisoquinolinium methylide **6**,[6] and azomethine ylide **7**[16] converted **1a** or **1e** to their corresponding D-A cyclopropene **4a** or **4e** (eq 4), which were stable to ring opening by $Rh_2(OAc)_4$, $Cu(MeCN)_4PF_6$, Ag(OTf), and a cationic gold(I) catalyst.



5 **6** **7** **4a** **4e**

[3 + 2]-Cycloadditions. A different outcome is seen in the novel [3 + 2]-cycloaddition of **1a** with diaziridine **8**[17]—a strained ring system that is known to undergo the N−N bond cleavage.[18] The isomeric mixture of **1a** (*E*:*Z* = 1.3:1) gave cycloaddition product **9** with only 31% ee (Scheme 3a), whereas

Scheme 3. Role of Donor−Acceptor Cyclopropene in [3 + 2]-Cycloaddition of Enoldiazoacetate 1a with Diaziridine 8



Z-**1a** yielded **9** with 95% ee under the same conditions and in approximately the same percent yield (Scheme 3b). These results suggest that the initially generated metallo-enolcarbenes undergo cycloaddition at a much faster rate in comparison to their formation of the corresponding D-A cyclopropene **4a**. However, use of **4a** as the metallocarbene source also formed **9** in 95% ee (Scheme 3c), which is consistent with the sole formation of the (*Z*)-metallo-enolcarbene from the substituted D-A cyclopropene.

Examples in which the metallo-enoldcarbene reacts more quickly with the nucleophilic substrate in comparison to undergoing internal formation of its D-A cyclopropene have been discovered in reactions with *N*-methylindole. Prior investigations of reactions involving metallo-vinyl carbenes with indoles established the influence of catalyst and vinyldiazo compound on regio- and stereoselectivity, but they did not evaluate the influence of *E*- and *Z*-γ-substituted enoldiazoacetates on reaction selectivities.[19] As recently reported,[11] catalysis by rhodium(II) acetate with *Z*-**1a** resulted in the production of substitution product **11** in high yield (Scheme 4a); however, with **1a** (*Z*:*E* = 1:1) under the same conditions, **11** was the major product (but under 50% yield), and donor−acceptor cyclopropene **4a** was also formed but did not react with rhodium(II)

DOI: 10.1021/acs.organomet.9b00427
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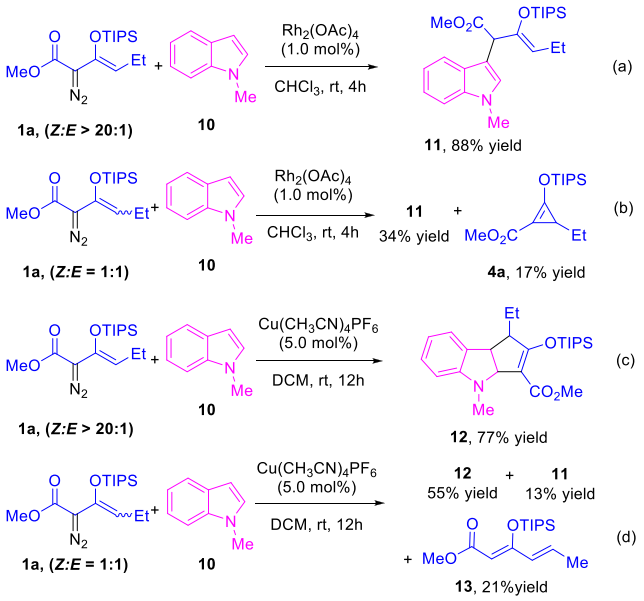
Scheme 4. Role of Donor–Acceptor Cyclopropene in Reactions of Enoldiazoacetate 1a with *N*-Methylindole 10



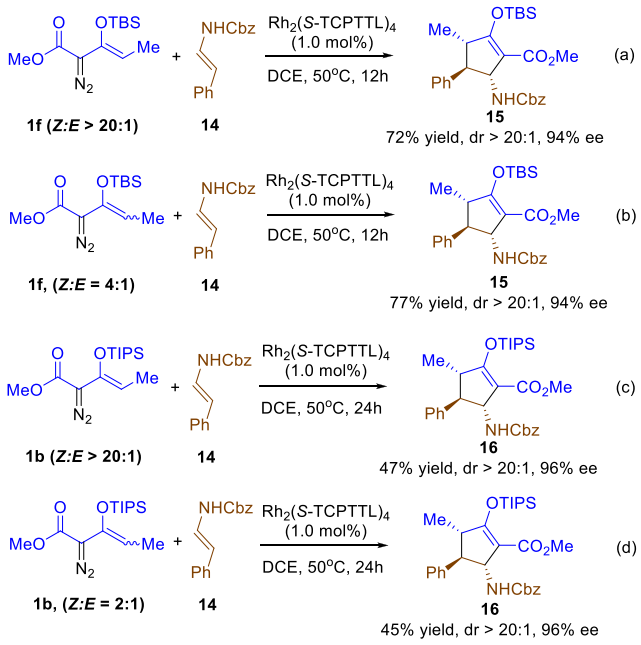
acetate to re-form the intermediate metallo-enolcarbene (Scheme 4b).

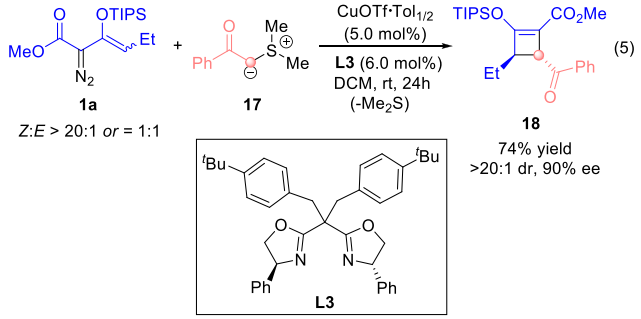
In contrast, the use of $Cu(MeCN)_4PF_6$ as the catalyst with *Z*-**1a** produced cycloaddition product **12** in good yield (Scheme 4c); however, with **1a** (*Z*:*E* = 1:1) under the same conditions (Scheme 4d), **12** was the major product (55% isolated yield) but **11** and a product from intramolecular hydrogen abstraction (**13**), both presumably from *E*-**1a**, were also formed. The disparity between dirhodium(II) and copper(I) catalysts is evident in these results, and so are the differences between *E*- and *Z*-γ-substituted enoldiazoacetates. Reactions of *Z*-**1a** with *N*-methylindole **10** give either **11** with rhodium(II) acetate (by electrophilic addition from the carbenic carbon followed by 1,2-hydrogen transfer) or [3 + 2]-cycloaddition product **12** with copper(I) catalysis (by electrophilic addition from the vinylogous carbon and then cyclization to the original carbenic carbon). In contrast, reactions of *E*-**1a** with *N*-methylindole gave product mixtures with $Cu(MeCN)_4PF_6$ that included **11** but also resulted in what is formally a 1,4-hydride transfer to form **13**. In these cases, product formation results solely from the metallocarbene without intervention of the donor–acceptor cyclopropene.

In another set of [3 + 2]-cycloaddition reactions[20] (Scheme 5) the use of the TBS rather than the TIPS enol protective group was shown to have no obvious influence on selectivity, although the reactivity was lower with the TIPS-enoldiazoacetate (based on yield of product) than with the TBS-enoldiazoacetate. The reactions of **1b** and **1f** with enamide **14** gave product **16** (or **15**) with the same diastereoselectivities and enantiocontrol whether the *Z* isomer or the *E*/*Z* isomeric mixture was used.

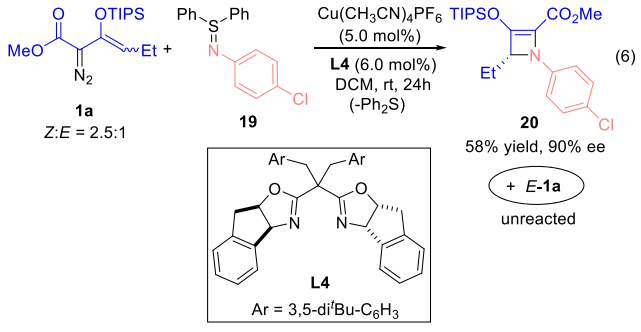
[3 + 1]-Cycloaddition. These recently discovered cycloaddition reactions of enoldiazoacetates[9a] have the potential to exhibit stereoselectivity differences in product formation between *E* and *Z* isomers of enoldiazoacetates. Surprisingly, however, the reaction of **1a** with sulfur ylide **17**[21] catalyzed by [$Cu(MeCN)_4PF_6$/**L3**] showed no detectable selectivity difference between *Z*-**1a** and its 1:1 *E*/*Z* mixture (eq 5), suggesting the intermediate involvement of the donor–acceptor cyclopropene in the overall cycloaddition process.

Scheme 5. Absence of Influence of the *E*/*Z* Geometry on Stereocontrol in Cu(I)- and Rh(II)-Catalyzed Reactions of Enoldiazoacetate 1 with Enamide 14





In contrast, the copper(I) [$Cu(MeCN)_4PF_6$/**L4**] catalyzed reaction of **1a** (*Z*:*E* = 2.5:1) with *N*-(*p*-chlorophenyl)imido diphenylsulfur **19** resulted in [3 + 1]-cycloaddition of *Z*-**1a** to form donor–acceptor azetine **20** with high enantiocontrol (90% ee) but left *E*-**1a** intact (eq 6), suggesting a substantial steric inhibition to dinitrogen extrusion from *E*-**1a**.



CONCLUSION

Using γ-substituted enoldiazoacetates, different reactivities and selectivities are revealed from reactions of the *E* and *Z* geometrical isomers when product formation results solely

DOI: 10.1021/acs.organomet.9b00427
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from the metallocarbene without intervention of the donor−acceptor cyclopropene intermediate. Different reaction outcomes are obtained from reactions of **1a** with diaziridine **8** (Scheme 3) and *N*-methylindole (Scheme 4), indicating that the metallo-enolcarbenes formed from *E*-**1a** and *Z*-**1a** are distinct in their reactivities and/or selectivities. However, product formation resulting from the metallo-enolcarbene both with and without intervention of the donor−acceptor cyclopropene cannot be completely dismissed. In contrast, when the donor−acceptor cyclopropene formed from γ-substituted enoldiazoacetates is the source of the metallo-enolcarbene that undergoes cycloaddition, as is revealed in [3 + 3]-cycloaddition with nitrones (eq 1), for [3 + 2]-cycloaddition with eneamides (Scheme 5) and [3 + 2]-cycloaddition with sulfur ylide **17** (eq 5), the stereoselectivity in product formation from either *E*- or *Z*-γ-substituted enoldiazoacetates is the same. These results are compatible with a more rapid intramolecular cyclization of the metallo-enolcarbene to the D-A cyclopropene in comparison to intermolecular association of the metallo-enolcarbene with a dipole that results in cycloaddition. Cycloaddition occurs from the metallocarbene only after formation of the donor−acceptor cyclopropene to produce only the *Z*-diastereomeric metallo-enolcarbene. This investigation also suggests the limitations of 3-substituted donor−acceptor cyclopropenes for the generation of metallo-enolcarbenes: the absence of reactions with dipoles **5**−**7** implies that basic dipoles that coordinate with electrophilic catalysts can inhibit ring opening of 3-substituted D-A cyclopropenes. In what appears to be an extreme case of selectivity for reactions with γ-substituted enoldiazoacetates, [3 + 1]-cycloaddition of the *Z* isomer of **1a** with **19** occurs, but not the *E* isomer, and *E*-**1a** does not undergo dinitrogen extrusion.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were performed in 10-mL oven-dried (120 °C) glassware under a dinitrogen atmosphere. Solvents were dried using a JC Meyer solvent purification system. Analytical thin-layer chromatography was performed using glass plates precoated with 200−300 mesh silica gel impregnated with a fluorescent indicator (254 nm). Column chromatography was performed on CombiFlash Rf200 and Rf+ purification systems using normal-phase silica gel columns (300−400 mesh). High-resolution mass spectra (HRMS) were performed on a Bruker MicroTOF-ESI mass spectrometer with an ESI resource using CsI or LTQ ESI Positive Ion Calibration Solution as the standard. Accurate masses were reported for the molecular ions $[M + H]^+$. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 and 500 MHz spectrometers. ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 or 500 MHz with residual $CHCl_3$ (δ 7.26 ppm) and H_2O (δ 1.56 ppm). Chemical shifts are reported in ppm with the residual solvent signals as reference, and coupling constants (*J*) are given in Hertz. Peak information is described as s = singlet, d = doublet, dd = doublet of doublets, td = triplet of doublets, t = triplet, m = multiplet, comp = composite of magnetically nonequivalent protons. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 126 MHz with the central resonance of $CDCl_3$ of δ 77.16 ppm. Enantiomeric excess was determined using Daicel Chiralpak AD-H, IB-3, and IC-3 and Chiralcel OD-H columns.

Materials. Enoldiazoacetates **1**,[11] nitrone **2**,[22] diaziridine **8**,[23] enecarbamate **14**,[24] sulfur ylide **17**,[25] and Rh_2(*S*-TCPTTL)$_4$[26] were prepared according to literature procedures. All of the other chemicals were obtained from commercial sources and used without further purification.

General Procedure for Copper(I)-Catalyzed [3 + 3]-Cycloaddition Reaction of γ-Substituted Enoldiazoacetates 1 with Nitrone 2 (Table 1). The chiral copper(I) catalyst was prepared by stirring $[Cu(MeCN)_4]PF_6$ (3.7 mg, 0.010 mmol, 5.0 mol %) and chiral bisoxazoline ligand **L1** (4.3 mg, 0.012 mmol, 6.0 mol %) in dry chloroform (2.0 mL) in an oven-dried 8.0-mL Schlenk tube for 1 h under N_2 at room temperature. Chloroform was then removed, and toluene (2.0 mL) was added. A solution of nitrone **2** (0.20 mmol, 1.0 equiv) in dry toluene (1.0 mL) was introduced to the reaction solution followed by dropwise (over 5 min) addition of TIPS-protected enoldiazoacetate **1** (0.24 mmol, 1.2 equiv) in dry toluene (1.0 mL). The reaction solution was stirred at room temperature for 12 h, and the solvent was then removed under reduced pressure. The product was purified by silica gel column chromatography using a 20/1 to 15/1 gradient of hexane/ethyl acetate (v/v) as the eluent to afford cycloaddition product **3**.

*Methyl (3S,6R)-6-Ethyl-2,3-diphenyl-5-[(triisopropylsilyl)-oxy]-3,6-dihydro-2H-1,2-oxazine-4-carboxylate (**3a**).* Colorless oil; 92 mg, 94% yield. $[\alpha]_D^{20}$ = +129° (*c* = 1.0, $CHCl_3$), 93% ee (HPLC: Chiralpak AD-H column, 1% IPA in hexane (v/v), 1.0 mL/min, 254 nm, t_1 = 4.6 min (*major*), t_2 = 4.9 min (*minor*)). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.25 (comp, 2H), 7.23−7.13 (comp, 5H), 7.02 (d, *J* = 7.7 Hz, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 5.68 (d, *J* = 1.7 Hz, 1H), 4.44−4.34 (m, 1H), 3.62 (s, 3H), 2.19−2.04 (m, 1H), 1.92−1.74 (m, 1H), 1.20−1.13 (comp, 3H), 1.12−1.05 (comp, 21H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 161.7, 148.1, 138.1, 129.5, 128.7, 127.7, 127.5, 122.1, 117.0, 110.0, 78.9, 63.6, 51.4, 24.4, 18.0, 17.9, 13.8, 10.4 ppm. HRMS (ESI): *m*/*z* calcd for $C_{29}H_{42}NO_4Si$ $(M + H)^+$ 496.2878, found: 496.2872.

*Methyl (3R,6S)-6-Methyl-2,3-diphenyl-5-[(triisopropyl-silyl)oxy]-3,6-dihydro-2H-1,2-oxazine-4-carboxylate (**3b**).* Colorless oil; 88 mg, 91% yield. $[\alpha]_D^{20}$ = +121° (*c* = 1.0, $CHCl_3$), 86% ee (HPLC: Chiralcel OD-H column, 0.6% IPA in hexane (v/v), 0.8 mL/min, 254 nm, t_1 = 8.1 min (*major*), t_2 = 9.7 min (*minor*)). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29−7.25 (comp, 2H), 7.23−7.17 (comp, 5H), 7.06−7.01 (comp, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 5.68 (d, *J* = 1.6 Hz, 1H), 4.62 (dd, *J* = 6.7, 1.6 Hz, 1H), 3.63 (s, 3H), 1.59 (d, *J* = 6.7 Hz, 3H), 1.22−1.17 (comp, 3H), 1.16−1.11 (comp, 18H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 162.5, 148.0, 137.7, 129.5, 128.7, 127.7, 127.5, 122.2, 117.1, 109.3, 74.2, 63.9, 51.3, 18.0, 17.95, 16.9, 13.8 ppm. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{40}NO_4Si$ $(M + H)^+$ 482.2721, found: 482.2720.

*Methyl (3R,6S)-6-Isopropyl-2,3-diphenyl-5-[(triisopropyl-silyl)-oxy]-3,6-dihydro-2H-1,2-oxazine-4-carboxylate (**3c**).* Colorless oil; 89 mg, 89% yield. $[\alpha]_D^{20}$ = +133° (*c* = 1.0, $CHCl_3$), 99% ee (HPLC: Chiralcel OD-H column, 0.6% IPA in hexane (v/v), 0.8 mL/min, 254 nm, t_1 = 5.9 min (*minor*), t_2 = 6.4 min (*major*)). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.32 (comp, 2H), 7.25−7.13 (comp, 5H), 7.07−7.01 (comp, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 5.75 (d, *J* = 1.8 Hz, 1H), 4.42−4.36 (m, 1H), 3.63 (s, 3H), 2.57−2.42 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.18−1.14 (comp, 3H), 1.13−1.08 (comp, 21H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 161.4, 148.0, 138.6, 129.4, 128.7, 127.7, 127.3, 121.7, 116.6, 110.4, 81.1, 62.8, 51.3, 29.1, 19.7, 18.0, 17.9, 17.8, 16.2, 13.9 ppm. HRMS (ESI): *m*/*z* calcd for $C_{30}H_{44}NO_4Si$ $(M + H)^+$ 510.3034, found 510.3026.

*Methyl (3S,6R)-6-Benzyl-2,3-diphenyl-5-[(triisopropyl-silyl)oxy]-3,6-dihydro-2H-1,2-oxazine-4-carboxylate (**3d**).* Colorless oil; 99 mg, 89% yield. $[\alpha]_D^{20}$ = +98° (*c* = 1.0, $CHCl_3$), 96% ee (HPLC: Chiralpak IC-3 column, 1% IPA in hexane (v/v), 1.0 mL/min, 254 nm, t_1 = 3.5 min (*major*), t_2 = 4.0 min (*minor*)). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39−7.27 (comp, 5H), 7.17−7.11 (comp, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 2H), 6.91−6.81 (comp, 5H), 5.56 (d, *J* = 1.6 Hz, 1H), 4.78−4.70 (m, 1H), 3.59 (s, 3H), 3.40−3.23 (comp, 2H), 1.30−1.23 (comp, 3H), 1.19 (d, *J* = 8.8 Hz, 18H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 161.0, 148.1, 137.2, 137.1, 130.1, 129.6, 128.6, 128.5, 127.5, 127.3, 126.8, 122.2, 117.3, 111.2, 78.9, 64.8, 51.3, 36.8, 18.2, 18.1, 14.0 ppm. HRMS (ESI): *m*/*z* calcd for $C_{34}H_{44}NO_4Si$ $(M + H)^+$ 558.3034, found 558.3024.

Procedure for Copper(I)-Catalyzed [3 + 3]-Cycloaddition Reaction of 1e with Nitrone 2. In an oven-dried 8.0-mL Schlenk tube under N_2 at room temperature $[Cu(MeCN)_4]PF_6$ (3.7 mg, 0.010 mmol, 5.0 mol %) and dry toluene (2.0 mL) were sequentially introduced, followed by addition of nitrone **2** (40 mg, 0.20 mmol, 1.0 equiv). TIPS-protected enoldiazoacetate **1e** (90 mg, 0.24 mmol, 1.2 equiv) in dry toluene (2.0 mL) was then added dropwise over 5 min. The reaction solution was stirred at room temperature for 24 h, and the

DOI: 10.1021/acs.organomet.9b00427
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solvent was then removed under reduced pressure. The residue was subjected to column chromatography on silica gel using a 15/1 to 10/1 gradient of hexane/ethyl acetate (v/v) as the eluent to afford **3e**.

*Methyl 2,3,6-Triphenyl-5-[(triisopropylsilyl)oxy]-3,6-dihydro-2H-1,2-oxazine-4-carboxylate (**3e**).* Colorless oil; 94 mg, 86% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55−7.50 (comp, 2H), 7.44−7.36 (comp, 5H), 7.22−7.11 (comp, 5H), 7.03 (d, J = 7.7 Hz, 2H), 6.89 (t, J = 7.3 Hz, 1H), 5.78 (d, J = 1.6 Hz, 1H), 5.46 (d, J = 1.7 Hz, 1H), 3.67 (s, 3H), 1.04−0.97 (comp, 3H), 0.95 (d, J = 6.6 Hz, 9H), 0.82 (d, J = 7.1 Hz, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 159.6, 147.9, 138.3, 135.6, 130.4, 129.5, 129.3, 128.8, 127.8, 127.5, 122.3, 117.2, 112.0, 81.0, 63.7, 51.5, 17.8, 17.5, 13.9 ppm. HRMS (ESI): m/z calcd for $C_{33}H_{42}NO_4Si$ $(M + H)^+$ 544.2878, found 544.2861.

*Methyl 3-Phenyl-2-[(triisopropylsilyl)oxy]cycloprop-1-ene-1-carboxylate (**4e**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.26 (comp, 2H), 7.23−7.16 (comp, 3H), 3.74 (s, 3H), 3.41 (s, 1H), 1.36 (td, J = 14.7, 7.5 Hz, 3H), 1.07 (dd, J = 15.8, 7.5 Hz, 18H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 141.7, 141.7, 128.4, 126.4, 126.2, 71.3, 51.7, 34.1, 17.6, 17.5, 12.1 ppm. HRMS (ESI) m/z calcd for $C_{20}H_{31}O_3Si$ $(M + H)^+$ 347.2037, found 347.2030.

Procedure for Copper(I)-Catalyzed [3 + 3]-Cycloaddition Reaction of 4a with Nitrone 2 (eq 2). The chiral copper(I) catalyst was prepared by stirring $[Cu(MeCN)_4]PF_6$ (3.7 mg, 0.010 mmol, 5.0 mol %) and chiral bisoxazoline ligand **L1** (4.3 mg, 0.012 mmol, 6.0 mol %) in dry chloroform (2.0 mL) in an oven-dried 8.0-mL Schlenk tube for 1 h under N_2 at room temperature. Chloroform was evaporated, and toluene (2.0 mL) was added to the system. A solution of nitrone **2** (0.20 mmol, 1.0 equiv) in dry toluene (1.0 mL) was introduced into the reaction solution. Then TIPS-protected cyclopropene **4a** (72 mg, 0.24 mmol, 1.2 equiv) in dry toluene (1.0 mL) was added dropwise over 5 min. The reaction solution was stirred at room temperature for 4 h, and the solvent was then removed under reduced pressure. The residue was subjected to column chromatography on silica gel using a 20/1 to 15/1 gradient of hexane/ethyl acetate (v/v) as the eluent to afford **3a**.

Procedure for Synthesis of Cyclopropene 4a from Enoldiazoacetate 1a. An oven-dried flask containing a magnetic stirring bar was loaded with $Rh_2(OAc)_4$ (1.8 mg, 2.0 mol %) and DCM (1.0 mL), and the system was filled with nitrogen. Enoldiazoacetate **1a** (79 mg, 0.24 mmol) in DCM (0.5 mL) was then added over 10 min via a syringe pump at 0 °C. The reaction solution was stirred for another 20 min, during which time the diazo compound converted to the cyclopropene (the reaction solution turned from yellow to green). $Rh_2(OAc)_4$ was filtered from the reaction solution with a short plug of Celite; the filtrate was washed with DCM (2.0 mL), and the solvent was evaporated to afford **4a**, which was used directly in the next steps without further purification.

*Methyl 3-Ethyl-2-[(triisopropylsilyl)oxy]cycloprop-1-ene-1-carboxylate (**4a**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.73 (s, 3H), 2.39−2.30 (m, 1H), 1.73−1.60 (m, 1H), 1.52−1.36 (comp, 4H), 1.10 (dd, J = 7.4, 2.8 Hz, 18H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.1, 160.5, 148.4, 76.1, 51.5, 31.4, 26.9, 17.6, 12.4, 12.1 ppm, HRMS (ESI): m/z calcd for $C_{16}H_{31}O_3Si$ $(M + H)^+$ 299.2037, found 299.2026.

Procedure for Copper(I)-Catalyzed [3 + 2]-Annulation of 1a with *N*-Methylindole 10 (Scheme 4). In an oven-dried flask containing a magnetic stirring bar, *N*-methylindole **10** (26 mg, 0.20 mmol), $Cu(CH_3CN)_4PF_6$ (3.7 mg, 5.0 mol %), and dry DCM (1.0 mL) were sequentially introduced under a N_2 atmosphere. Enoldiazoacetate **1a** (78 mg, 0.24 mmol) in DCM (1.0 mL) was then added over 30 min via a syringe pump at room temperature. The reaction mixture was stirred for 12 h at room temperature, and then the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexanes/EtOAc 95/5 (v/v) as the eluent to afford products **11** (reported compound),[11] **12**, and **13**.

*Methyl 1-Ethyl-4-methyl-2-[(triisopropylsilyl)oxy]-1,3a,4,8b-tetrahydrocyclopenta[b]indole-3-carboxylate (**12**).* Colorless oil; 66 mg, 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 7.3 Hz, 1H), 7.05 (td, J = 7.7, 1.1 Hz, 1H), 6.64−6.59 (td, J = 7.3, 0.5 Hz, 1H), 6.36 (d, J = 7.7 Hz, 1H), 4.44 (d, J = 7.8 Hz, 1H), 3.70 (s, 3H), 3.59 (d, J = 7.8 Hz, 1H), 2.70 (s, 3H), 2.56 (dd, J = 9.5, 2.4 Hz, 1H), 1.88−1.79 (m, 1H), 1.42−1.34 (m, 1H), 1.23−1.17 (comp, 3H), 1.08 (d, J = 6.8 Hz, 18H), 1.02 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 165.3, 152.8, 130.3, 127.9, 126.4, 117.4, 108.6, 106.1, 70.5, 54.7, 50.5, 48.0, 33.5, 29.9, 24.7, 17.9, 17.8, 13.4, 11.7 ppm. HRMS (ESI): m/z calcd for $C_{25}H_{40}NO_3Si$ $(M + H)^+$ 430.2772, found 430.2770.

*Methyl (2Z,4E)-3-[(Triisopropylsilyl)oxy]hexa-2,4-dienoate (**13**).* Colorless oil; 13 mg, 21% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (td, J = 13.7, 6.8 Hz, 1H), 5.86 (dd, J = 15.4, 1.5 Hz, 1H), 5.16 (s, 1H), 3.65 (s, 3H), 1.81 (dd, J = 6.8, 1.3 Hz, 3H), 1.33−1.29 (comp, 3H), 1.11 (d, J = 7.4 Hz, 18H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 162.7, 133.1, 130.2, 98.8, 50.7, 29.9, 18.1, 14.0 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{31}O_3Si$ $(M + H)^+$ 299.2037, found 299.2037.

General Procedure for Enantioselective [3 + 2]-Cycloaddition of Enoldiazoacetate 1 with Enecarbamate 14 (Scheme 5). In a 10-mL flame-dried Schlenk flask containing a magnetic stirring bar, Rh_2(*S*-TCPTTL)$_4$ (3.6 mg, 0.0020 mmol), enecarbamate **14** (51 mg, 0.20 mmol, 1.0 equiv), and 1.0 mL of 1,2-dichloroethane (DCE) were sequentially added under a N_2 atmosphere. The reaction flask was then sealed with a rubber septum, and a stirred solution of enoldiazoacetate **1b** (125 mg, 0.40 mmol, 2.0 equiv) in 2.0 mL of DCE was added via a syringe pump over 10 min at room temperature. The reaction solution was heated to 50 °C, and stirring was continued at 50 °C until all enecarbamate **14** was consumed on the basis of TLC analysis (24 h). The reaction solution was then concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using a 10/1 mixture of hexanes/ethyl acetate as the eluent to afford [3 + 2]-cycloaddition product **16**.

*Methyl (3S,4R,5R)-5-[(Benzyloxy)carbonyl]amino-3-meth-yl-4-phenyl-2-[(triisopropylsilyl)oxy]cyclopent-1-ene-1-carboxylate (**16**).* Colorless oil; 51 mg, 47% yield. 96% ee (HPLC: Chiralpak IB-3 column, 7% IPA in hexane (v/v), 1.0 mL/min, 254 nm, t_1 = 6.9 min (*major*), t_2 = 8.8 min (*minor*)). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.21 (comp, 10H), 5.41 (s, 1H), 5.16 (d, J = 12.3 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.70 (s, 1H), 3.62 (s, 3H), 3.31 (s, 1H), 2.92−2.80 (m, 1H), 1.34−1.25 (comp, 3H), 1.13 (dd, J = 7.5, 3.7 Hz, 18H), 0.76 (d, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 164.5, 156.2, 138.0, 136.8, 128.7, 128.6, 128.3, 128.1, 126.8, 108.0, 66.7, 56.0, 53.1, 50.7, 44.6, 18.0, 17.98, 14.4, 13.6 ppm. HRMS (ESI): m/z calcd for $C_{31}H_{44}NO_5Si$ $(M + H)^+$ 538.2983, found 538.2985.

Procedure for Copper(I)-Catalyzed Enantioselective [3 + 1]-Cycloaddition of Enoldiazoacetate 1a with *N*-(*p*-Chlorophenyl)imido Sulfur Ylide 19 (eq 6). In an oven-dried 8.0-mL Schlenk tube equipped with a magnetic stirring bar were sequentially added $Cu(MeCN)_4PF_6$ (3.7 mg, 0.010 mmol, 5 mol %), sabox ligand **L4** (8.8 mg, 0.012 mmol, 6 mol %), and 2.0 mL of dry DCM under a dinitrogen atmosphere. The resulting solution was stirred at room temperature for 1 h. *N*-(*p*-Chlorophenyl)imido diphenylsulfur **19** (62 mg, 0.20 mmol, 1.0 equiv) was then introduced to the reaction solution under a flow of nitrogen, followed by dropwise addition (over 1 min) of enoldiazoacetate **1a** (0.22 mmol, *Z*:*E* = 2.5:1, 1.1 equiv) in dry DCM (2.0 mL). The tube was capped, and stirring was continued at room temperature for 24 h. Subsequently, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using a gradient of hexane/ethyl acetate 49/1 to 4/1 (v/v) as eluent to afford donor−acceptor azetine **20**.

*Methyl (R)-1-(4-Chlorophenyl)-4-ethyl-3-[(triisopropylsilyl)oxy]-1,4-dihydroazete-2-carboxylate (**20**).* Pale yellow oil; 49 mg, 58% yield. 90% ee (HPLC: Chiralpak AD-H column, 2% IPA in hexane (v/v), 0.7 mL/min, 254 nm, t_1 = 5.5 min (*major*), t_2 = 7.8 min (*minor*)). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 3.88 (dd, J = 6.3, 5.0 Hz, 1H), 3.78 (s, 3H), 2.09−2.00 (m, 1H), 1.97−1.87 (m, 1H), 1.36−1.26 (m, 3H), 1.18 (t, J = 7.4 Hz, 3H), 1.14 (d, J = 7.4 Hz, 18H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.5, 153.1, 149.2, 128.7, 127.3, 120.4, 120.3, 80.7, 51.1, 24.2, 17.6, 12.8, 9.8 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{35}ClNO_3Si$ $(M + H)^+$ 424.2069; found 424.2073.

DOI: 10.1021/acs.organomet.9b00427
Organometallics 2019, 38, 4043−4050

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00427.

Catalyst and solvent screening tables, NMR spectra, and HPLC traces of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the U.S. National Science Foundation (CHE-1763168) for funding this research. The acquisition of a NMR spectrometer used in this research was supported by a grant from the U.S. National Science Foundation (CHE-1625963). K.D. acknowledges the support from the National Natural Science Foundation of China and Jiangsu province (21602148).

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DOI: 10.1021/acs.organomet.9b00427
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