ACS Catalysis

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Research Article

Catalyst-Directed Divergent Catalytic Approaches to Expand Structural and Functional Scaffold Diversity via Metallo-Enolcarbene Intermediates

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Cite This: *ACS Catal.* 2021, 11, 4712–4721

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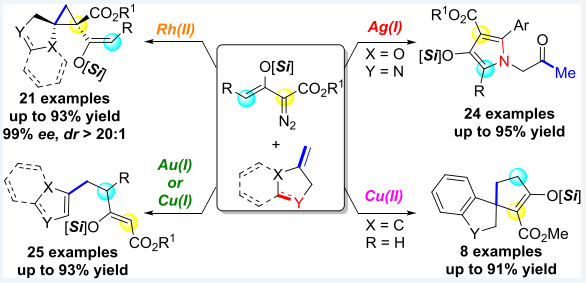
ABSTRACT: Catalyst-directed access to divergent products involving three different metals that exclusively form three different products from the same reactants is reported. Each catalyst directs an individual metallo-enolcarbene pathway from enoldiazoacetates and alkenes to a specific product. These include highly selective intermolecular cyclopropanation catalyzed exclusively by dirhodium(II) carboxylates, providing spiro-substituted dihydrooxazoles with greater than 20:1 diastereoselectivity and up to 99% *ee*; vinylogous addition with subsequent 1,6-proton transfer occurring independently with either Au(I) or Cu(I) catalysis or [3 + 2]-cycloaddition with a Cu(II) catalyst; and direct cycloaddition with the C═N bond of methylenedihydrooxazoles followed by rearrangement forming multiply substituted pyrroles in the presence of a silver catalyst. Allylic aromatization via vinylogous addition selectively delivers aromatic oxazole derivatives from methylenedihydrooxazoles, and when aromatization does not occur by 1,6-proton transfer, [3 + 2]-cycloaddition is the outcome. This catalyst-dependent formation of metallo-enolcarbene intermediates with alkenes demonstrates the tremendous potential of this approach to diversity-oriented-synthesis.



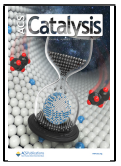
KEYWORDS: *divergent catalysis, metallo-carbene, cyclpropanation, cycloaddition, pyrrole*

INTRODUCTION

The complete control over products formed in catalytic reactions is a preeminent goal of organic synthesis and continues to be challenging.[1] Catalyst control over stereoselectivity in product formation has been a major achievement in chemistry, and the stereoelectronic factors that provide this selectivity are increasingly well documented.[2] In catalytic metal carbene chemistry, for example, stereoselectivity grew from very modest diastereocontrol and enantioselectivity for cyclopropanation in the 1960s[3] to virtually complete stereocontrol today.[4] Similarly, catalyst controlled regioselectivity for which the catalyst ligands impart selectivity has advanced remarkably in carbon−hydrogen insertion transformations.[5] These achievements have been primarily due to the development of chiral ligands that are suitable for the challenge of selectivity. However, the nature of ligand coordination around the metal and the electronic state of the metal also play significant roles in the control of product formation.[6,7] In contrast, metal catalysts control over chemoselective products formation, specifically, different catalysts directing one set of reactants to different products in synthetically useful yields, is meaningful but rare.[8] This approach to "divergent" product selection differs from the widely practiced redirection of a reaction pathway to different products by changing the reactant or reaction conditions.[9]

Metallocarbenes are important and useful intermediates in the construction of complex molecular frameworks. Their versatility is exemplified in numerous transition metal catalyzed transformations, including those of addition, insertion, and ylide formation, that offer abundant and selectable methods to construct various C−C and C-heteroatom bonds in both intramolecular and intermolecular reactions.[10] These reactions can occur in competition, and different catalysts have been selected to favor one pathway over another. Traditionally, two classifications of catalytic reactions exemplify diversity in metal carbene transformations: Type I involves reaction of a metallocarbene at two or more nucleophilic sites of a reactant (Figure 1a, Type I) whose selectivity is primarily based on steric effects from the ligand, and Type II occurs by formation of two or more metallocarbene intermediates from the same

Received: March 6, 2021
Revised: March 29, 2021
Published: April 5, 2021



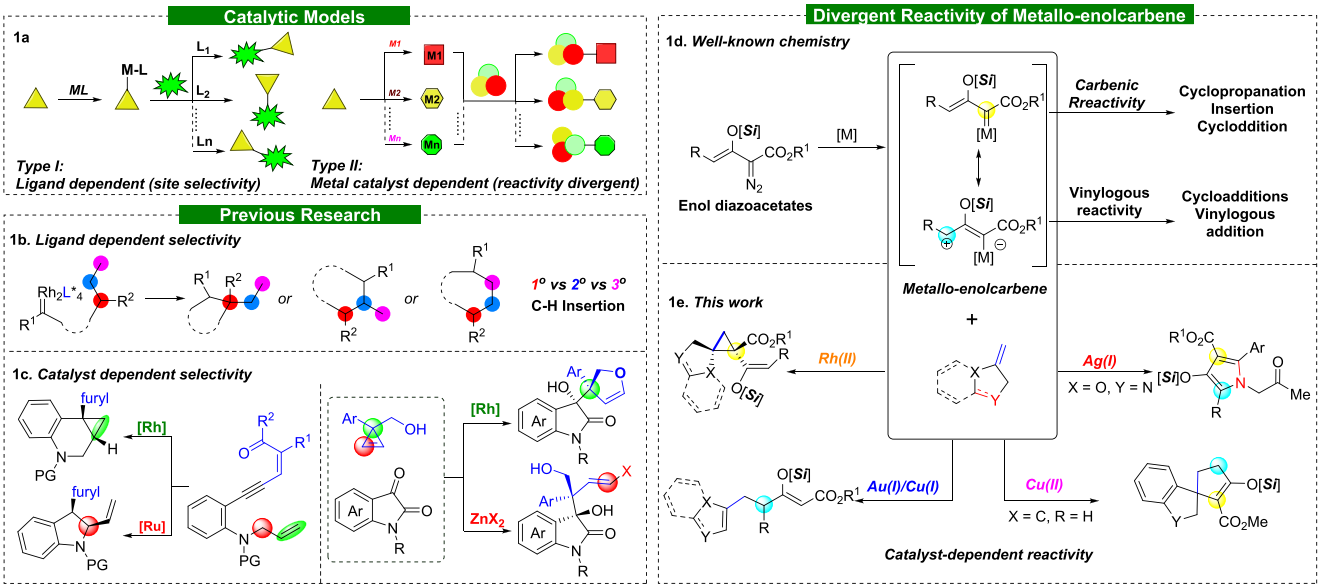


Figure 1. Previous Research and This Contribution.

carbene precursor, but different metals, followed by a different transformation of each metallocarbene with the same substrate (Figure 1a, Type II) with selectivity based on the metal that is employed. Type I behavior is described in competition reactions, such as regiocontrol in 1°, 2°, and 3 °C−H insertion reactions (Figure 1b).[11,12] Type II selectivity is seen in chemoselectivity between C−H insertion and cyclopropanation[13] or in reactions of nucleophilic and electrophilic carbene-related intermediates, with variations in product distribution dependent on the transition metal catalyst that is employed (Figure 1c).[14] For virtually all of these cases, unique selectivities have been achieved between only two catalysts, and comparisons between a broader selection of catalysts give selectivities that fall between the two extremes. Except for a very limited number of additional reports,[15−17] there are few examples of transformations with diazo compounds whose product is determined by the catalyst that is employed.

Enoldiazo compounds are a distinctive vinylcarbene source that have had significant impact on chemical methodology.[18,19] They undergo electrophilic addition at the diazo carbon or at the vinylogous carbon, providing access to diazonium ion or vinyldiazonium ion intermediates (Figure 1d). In reactions with select transition metal compounds they form electrophilic metallo-enolcarbenes, whose dipolar nature allows nucleophilic attack at the carbenic carbon to undergo direct carbene addition (e.g., cyclopropanation)[20] or remote vinylogous addition with subsequent atom transfer[19,21] or cycloaddition.[22] Competition between nucleophilic addition to the carbenic carbon and its vinylogous position with the same reactant(s) has not been reported, which suggests that obtaining diverse products with chemocontrol is a significant challenge.

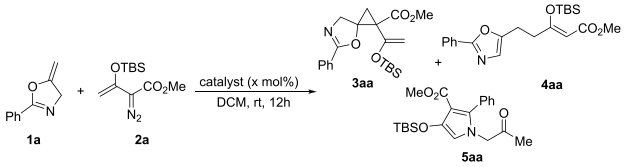
We have been intrigued with the diversity of transformations that occur with enoldiazo compounds, and especially with their possible reaction pathways using different catalysts.[15−17] As a continuation of our research interests in this area, we envisioned that the use of 5-methylene-4,5-dihydrooxazole with its nonconjugated C═C and C═N bond, as well as a basic nitrogen, in a structure that is formally a tautomer of an aromatic oxazole might provide sufficient nucleophilic sites to afford catalyst-directed product diversity. The C═C double bond allows feasible access to cyclopropanation, [3 + 2]-cycloaddition or vinylogous addition, and the C═N moiety offers a basic nucleophilic center for ylide formation that with resultant cycloaddition could lead to pyrrole derivatives. By adjusting the catalyst, this design could allow the selective formation of three or more different products from the same substrates (Figure 1e).

RESULTS AND DISCUSSION

Reaction Development. Our efforts began with investigation of the catalytic reactions of silyl-protected enoldiazoacetate with methylenecycloalkanes, recognizing a prior disparity in the outcome of dirhodium(II) catalyzed reactions with monosubstituted alkenes and trisubstituted alkenes. Cyclopropanation occurred in high yields and stereoselectivities in reactions with styrenes,[23] whereas trisubstituted vinyl ethers underwent exclusive [3 + 2]-cycloaddition, and both processes were catalyzed with dirhodium(II) carboxylates.[24] 5-Methylene-2-phenyl-4,5-dihydrooxazole **1a** was selected as the target methylenecycloalkene because of the convenience of its preparation and the suitability of its products for further synthetic elaboration. Its reactions were surveyed over a 12-h reaction time with catalysts known to convert **2a** to the corresponding metallo-enolcarbene. We were concerned that the basic nitrogen of the dihydrooxazole might inhibit catalyst activity, but we did not anticipate the diversity of products obtained (Table 1). Cyclopropanation of the carbon−carbon double bond that formed spiro-cyclopropane **3aa** with complete diastereocontrol was the outcome of reactions with dirhodium(II) carboxylate catalysts (entries 1 and 2). Cationic gold(I) and copper(I) catalysts gave product **4aa** that formally occurred by vinylogous addition of the vinylcarbene followed by 1,6-proton transfer with a synchronous aromatization of the heterocyclic ring (**VA-PT**), and the silver(I) catalyst, $AgSbF_6$, formed pyrrole **5aa** as an unexpected rearrangement product that formally occurred by initial C═N cycloaddition and was completed with C−O bond cleavage and 1,5-proton transfer (**C−C−PT**, entry 5). That these reactions were not Lewis acid catalyzed processes was indicated by the absence of any of

https://doi.org/10.1021/acscatal.1c01051
ACS Catal. 2021, 11, 4712−4721

Table 1. Divergency in Catalyst Influences on Metal-catalyzed Reactions[a]



entry	catalyst (x mol %)	conv. (%)[b]	yield (%)[c] 3aa	4aa	5aa
1	$Rh_2(OAc)_4$ (1)	40	26	<5	<5
2	$Rh_2(esp)_2$ (1)	40	33	<5	<5
3[d]	Au(JohnPhos)$(CH_3CN)SbF_6$ (5)	80	<5	51	<5
4	$Cu(CH_3CN)_4PF_6$ (5)	30	<5	21	<5
5	$AgSbF_6$ (5)	60	<5	14	36
6[e]	$Sc(OTf)_3$(5)	NR			
7[e]	$ZnBr_2$(5)	NR			

[a]Reactions were carried out at room temperature on a 0.10 mmol scale of **1a** with 0.15 mmol of enoldiazoacetate **2a**. [b]Yield from ^{1}H NMR spectral analysis with 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yields after flash-chromatography. [d]The reaction was carried out at 60 °C. No reaction occurred at rt. [e]No reaction was occurred over 48 h, and most of **1a** and **2a** were recovered. NR = No reaction.

these products in reactions using classic Lewis acids $Sc(OTf)_3$ and $ZnBr_2$ even over 48h (entry 6 and 7).

To improve the reactivity and selectivity of the cyclopropanation process yielding **3aa**, an array of chiral dirhodium(II) carboxylate catalysts was evaluated (see Table S1 in the Supporting Information, SI). No product formation was observed from reactions performed in refluxing dichloromethane catalyzed by chiral prolinate-ligated catalysts, possibly because of their coordination with the basic imine of reactant **1a**. However, most chiral phthalimide-carboxylate ligated catalysts produced **3aa** in modest yields (56−71%) and high enantioselectivities (>89% *ee*). Optimum enhancement was achieved by Rh_2(*S*-TCPTTL)$_4$ (71% yield, 95% *ee*). Results from the screening of solvents showed that both yield and enantioselectivity were improved when the reaction was performed in the mixed solvent of 1:1 DCM and TBME, generating **3aa** in 91% isolated yield with 97% *ee* using 2.0 equiv of **2a**. Notably, only one diastereoisomer of spirocyclopropane **3aa** was observed in all reactions (*dr* > 20:1 by NMR analysis; *dr* > 40:1 by chiral HPLC analysis).

Considering the different reactivities and selectivities between the **VA-PT** process yielding **4aa** and the **C−C−PT** rearrangement yielding **5aa**, we searched for improved differentiation between the two processes. A γ-methyl substituent on the enoldiazoacetate (**2j**) reactant markedly increased its reactivity and process differentiation (see Table S2). Use of [Au(JohnPhos)(CH_3CN)]SbF_6 significantly improved both the yield and chemoselectivity of the aromatization process (77% yield, **4**:**5** > 20:1). No further enhancements were obtained by switching the counteranion of the gold catalyst from SbF_6^- to NTf_2^-, OTf^-, or Cl^-. Alternatively, the tetrakis(acetonitrile) coordinated copper(I) catalyst $Cu(MeCN)_4BF_4$ and $Cu(OTf)_2$, as well as $AgSbF_6$, provided modest to good product yields but moderate chemoselectivities. Further screening revealed that yield and chemoselectivity were improved, exclusively generating **5ar** in 89% isolated yield, when the reaction was performed with γ-ethyl substituted triisopropylsilyl (TIPS)-protected enoldiazoacetate (**2r**) with molecular sieves added to inhibit hydrolysis of oxazole **1a**.

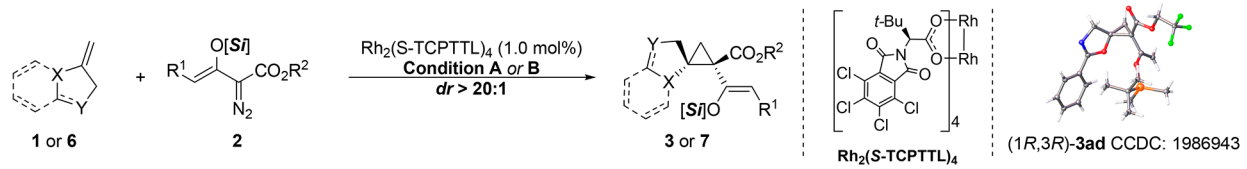
Substrate Scope for Asymmetric Cyclopropanation. With the optimized reaction conditions in hand, the applicability of the protocol was extended to a variety of methylene-substituted dihydrooxazoles **1** and enoldiazoactates **2**. As shown in Scheme 1, a series of enoldiazoactates **2** with different ester groups including isopropyl (**3ab**), *tert*-butyl (**3ac**) and trifluoroethyl (**3ad**) gave high yields (up to 91%) with excellent enatioselectivities (>96% *ee*). Moreover, **2** with benzyl ester groups also gave comparable yields (**3ae**-**3ai**, up to 93%) with excellent enatioselectivities (>91% *ee*), without any adverse effect on reactivity or selectivity due to electronic or steric influences from the benzyl ester. Furthermore, enoldiazoactates having a γ-ethyl substituent (**3an**, 83% yield, 96% *ee*) or a TIPS protective group (**3ap**,88% yield, 96% *ee*) showed little effect on the either reactivity or selectivity. Notably, the γ-phenyl-substituted styryldiazoacetate (**2z**) smoothly produced the desired product **3az** in 94% yield with 91% *ee* at room temperature. Comparable high enantiocontrol (94−97% *ee*, **3ba**-**3fa**) and yields (78−90%) were observed in reactions of **2a** with **1** bearing electron-neutral, electron-rich, or electron-deficient substituents on the aryl group. 1-Naphthyl and heterocyclic 2-furyl substituted dihydrooxazoles (**1g** and **1h**) delivered the desired product (**3ga** and **3ha**) with isolated yields above 85% and enantioselectivities up to 97% *ee*. The introduction of dimethyl substituted dihydrooxazole (**1i**) and even the six-membered ring dihydrooxazine (**1j**) resulted in similar yields (**3ia**, 92% and **3ja**, 85%) and excellent enantioselectivities (**3ia**, 99% *ee* and **3ja**, 97% *ee*). However, internal 2-(*R*)-methylenedihydrooxazole **1m** (R = C_6H_5) failed to give the desired cyclopropanation product, mainly because of its decreasing reactivity; diazo compound **2** decomposed during the reaction time. The absolute configuration of *syn*-**3ad** was (*1R*,*3R*) by single crystal X-ray crystallography, and the absolute configurations of the other products were assigned by analogy. To show the synthetic potential of this strategy, a gram-scale reaction of **2a** was performed with 0.5 mol % catalyst loading that yielded pure **3aa** with comparable results (1.25g, 81% yield, 96% *ee*).

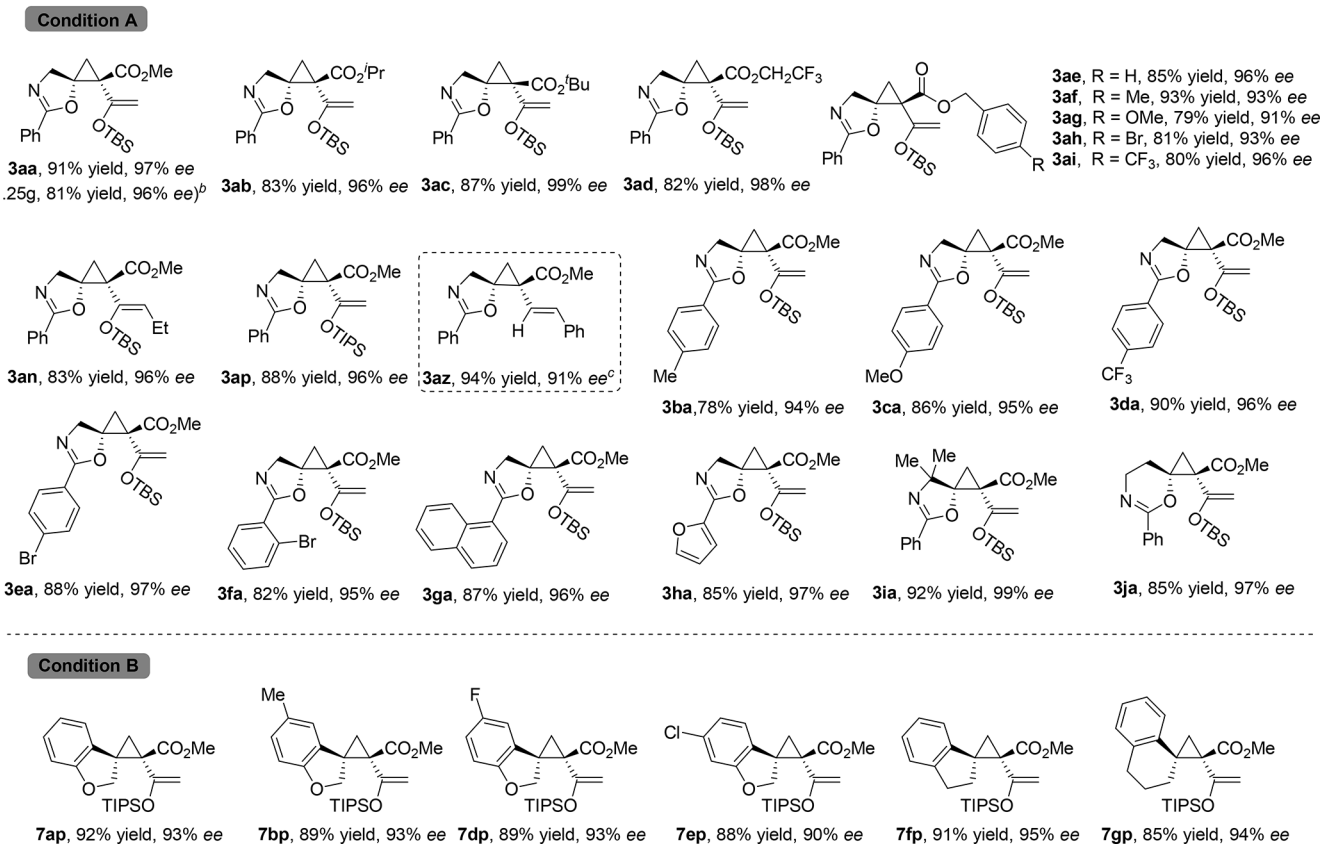
To assess the generality for cyclopropanation of exocyclic methylenes with the same Rh_2(*S*-TCPTTL)$_4$ catalyst, 3-methylene-2,3-dihydrobenzofurans **6a−6e** also smoothly generated spiro-cyclopropanation products in excellent yields with high enantioselectivities and exclusive diastereocontrol. Notably, this transformation can be realized at room temperature since benzofurans do not coordinate with the dirhodium(II) catalyst as do the dihydrooxazoles. Substituents on the benzene ring have no significant electronic or steric effect on yields and enantioselectivities; spiro-cyclopropane products **7** were obtained in greater than 88% yield and 90% *ee* (**7ap**-**7ep**). Furthermore, methylene-dihydroindene **6f** and methylene-tetrahydronaphthalene **6g**, both without heteroatoms, also underwent cyclopropanation to give **7fp** (91% yield, 95% *ee*) and **7gp** (85% yield, 94% *ee*), respectively.

Substrate Scope of the VA-PT Reaction. Vinylogous addition of vinyl ethers to metallo-vinylcarbenes that form open-chain products are commonly found as a compliment to [3 + 2]-cycloaddition reactions, and they have been reported as divergent outcomes between different catalysts operating on the same reactants.[25] The formation of **4aa** also arises from

https://doi.org/10.1021/acscatal.1c01051
ACS Catal. 2021, 11, 4712−4721

Scheme 1. Substrate Scope in Asymmetric Cyclopropanation by Enoldiazoacetates[a]





[a]**Condition A**: to Rh_2(*S*-TCPTTL)$_4$ (1.0 mol %), and **1** (0.2 mmol) in TBME/DCM solvent (*v*:*v* = 1:1, 2.0 mL) was added **2** (0.4 mmol) in the same solvent (2.0 mL) via syringe pump over 1 h under an argon atmosphere at 45 °C. **Condition B**: to Rh_2(*S*-TCPTTL)$_4$ (1.0 mol %) and **1** (0.2 mmol) in DCM (2.0 mL) was added **2** (0.24 mmol) in DCM (2.0 mL) via syringe pump over 1 h under an argon atmosphere at room temperature. The yields are given in isolated yields after flash-chromatography. Unless otherwise noted, the *dr* ratio was determined from the ^{1}H NMR spectrum of the reaction mixture, and *ee*s were determined by HPLC analyses with chiral columns. [b]The reaction was carried out on a 4.0 mmol scale with 0.5 mol % catalyst loading. [c]The reaction was carried at room temperature.

vinylogous addition of a vinyl ether (**1a**) to a metallo-vinyl carbene (from **2a**), but in this case no complementary [3 + 2]-cycloaddition product was detected. Instead, this transformation is formally a vinylogous addition followed by proton transfer that results in aromatization of the dihydrooxazole. To further understand this catalyst directed reaction pathway its substrate generality was investigated, and the results are presented in Scheme 2. Enoldiazoacetates **2** with electron-deficient and halogen substituents on its benzyl ester reacted smoothly with **1a**, generating the corresponding aromatization products in good yields (77−83%, **4aj**−**4am**), The steric influence of changes in the size of the γ-substituent on enoldiazoacetate **2** is evident inproduct yields, with the ethyl substituent delivering **4an** in 78% yield. Electronic influences from the introduction of a CF_3 group (**1d**), a naphthyl group (**1g**), or halogen substituents at the para- or ortho-positions of the aromatic ring (**1e** and **1f**) had virtually no effect on product yields (**4dj**-**4gj** in 77−84% yields). However, **1** with 2-furanyl or 2-phenethyl substituents at the 2-position and γ-methyl-TBS-protected **2j** led to the **C−C−PT** rearrangement process dominating the **VA-PT** allylic aromatization process, generating pyrrole derivatives **5hj** and **5kj** in high yields (81% and 85%, respectively). The TIPS protected enoldiazoacetate **2**, formed the vinylogous addition products with moderate yields (**4aq** and **4ar** with 72% and 65% yield, respectively).

Since dihydrobenzofuran derivatives did not decrease the reactivities of catalysts as did dihydrooxazoles, Cu-$(CH_3CN)_4PF_6$ was also chosen to investigate its reactions with enoldiazo esters **2**. In our experience, copper(I) catalysts have higher reactivity than those of gold, and they are less expensive. TBS- or TIPS-protected enoldiazoacetates **2** bearing different γ-substituents generated the **VA-PT** allylic aromatization products (**8aa**-**8ar**) in good to excellent yields (>80% yield) in dichloromethane at room temperature. Dihydrobenzofurans (**6b**, **6c**, **6e**) and dihydrofurans **6h** were found to have similar reactivity, giving aromatization products in good to excellent yields (**8bj**−**8hj**, up to 93% yield). To our surprise, the [3 + 2] cycloaddition product **9fj** was detected as sole

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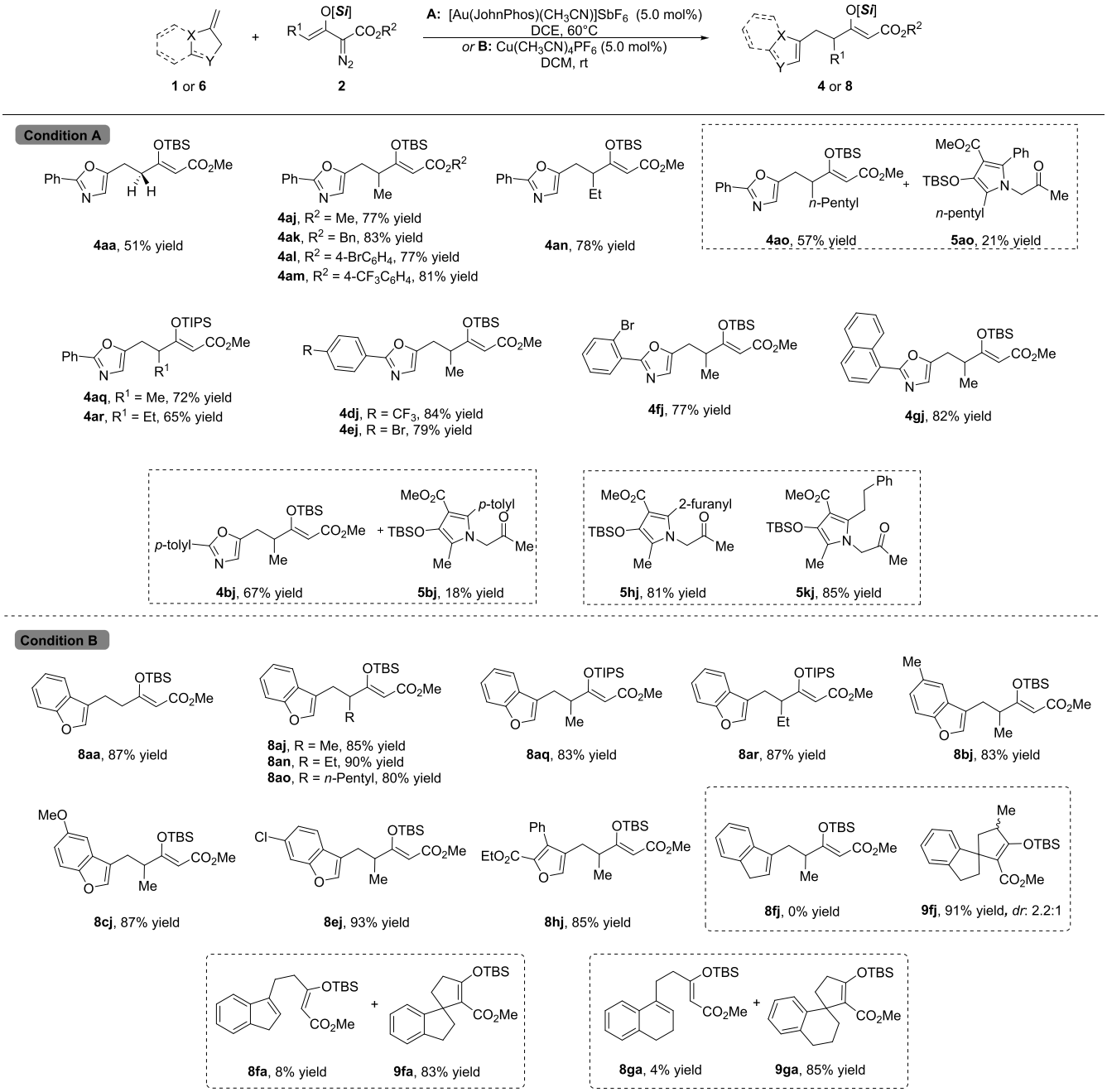
Scheme 2. Substrate Scope of the VA-PT Reaction[a]



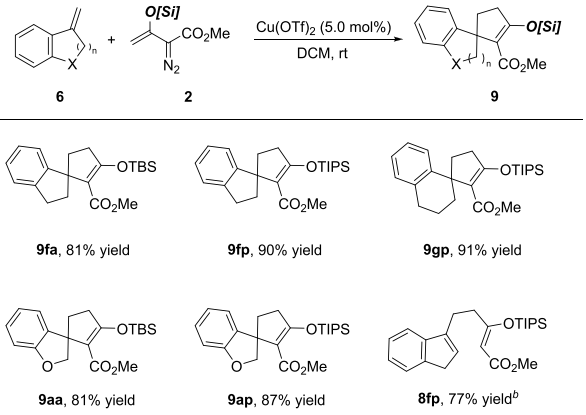
[a]**Condition A**: to the Au(I) catalyst (5.0 mol %), **1** (0.2 mmol) in DCE (2.0 mL) was added **2** (0.3 mmol) in the DCE (2.0 mL) under an argon atmosphere at 60 °C; **Condition B**: to the $Cu(CH_3CN)_4PF_6$ catalyst (5.0 mol %), **6** (0.2 mmol) in DCM (2.0 mL) was added **2** (0.3 mmol) in DCM (2.0 mL) via syringe pump over 1 h under an argon atmosphere at room temperature. The yields are given in isolated yields after flash-chromatography.

outcome in 91% yield with moderate diastereocontrol (*dr* = 2.2:1) in the reaction of the enoldiazoacetate **2j** with the Indane analogue of dihydrobenzofuran, which we explain as due to lack of a driving force from aromatization. Only 8% yield and 4% yield of **VA-PT** products were detected when 1-methyleneindane **6f** and 1-methylenetetralin **6g**, respectively, were employed with enoldiazoacetate **1a**; instead, the [3 + 2] cycloaddition products **9fa** (83% yield) and **9ga** (85% yield) were formed as the dominant products. Notably, when **6a** and **2r** were subjected to $Cu(CH_3CN)_4PF_6$/(*R*,*S*)-BDTBIn-SaBOX catalysis, the **VA-PT** product **8ar** was generated with 73% *ee* in 91% yield (Scheme S3e).

[3 + 2] Cycloaddition vs Allylic Alkylation. To further improve the chemoselectivity of the copper-catalyzed reactions of dihydrobenzofuran derivatives with enoldiazoacetates, the stronger Lewis acidic $Cu(OTf)_2$ catalyst was employed but, instead of the vinylogous ene-type addition, [3 + 2] cycloaddition products were generated exclusively Scheme 3). Use of TIPS-protected enoldiazoactate (**2p**) further improved the yield to 90% (**9fa**, **9fp**). When dihydrobenzofuran **6a** (X = O, *n* = 1) was treated with TBS- or TIPS-

https://doi.org/10.1021/acscatal.1c01051
ACS Catal. 2021, 11, 4712−4721

Scheme 3. Substrate Scope of [3 + 2] Cycloaddition and Allylic Alkylation[a]

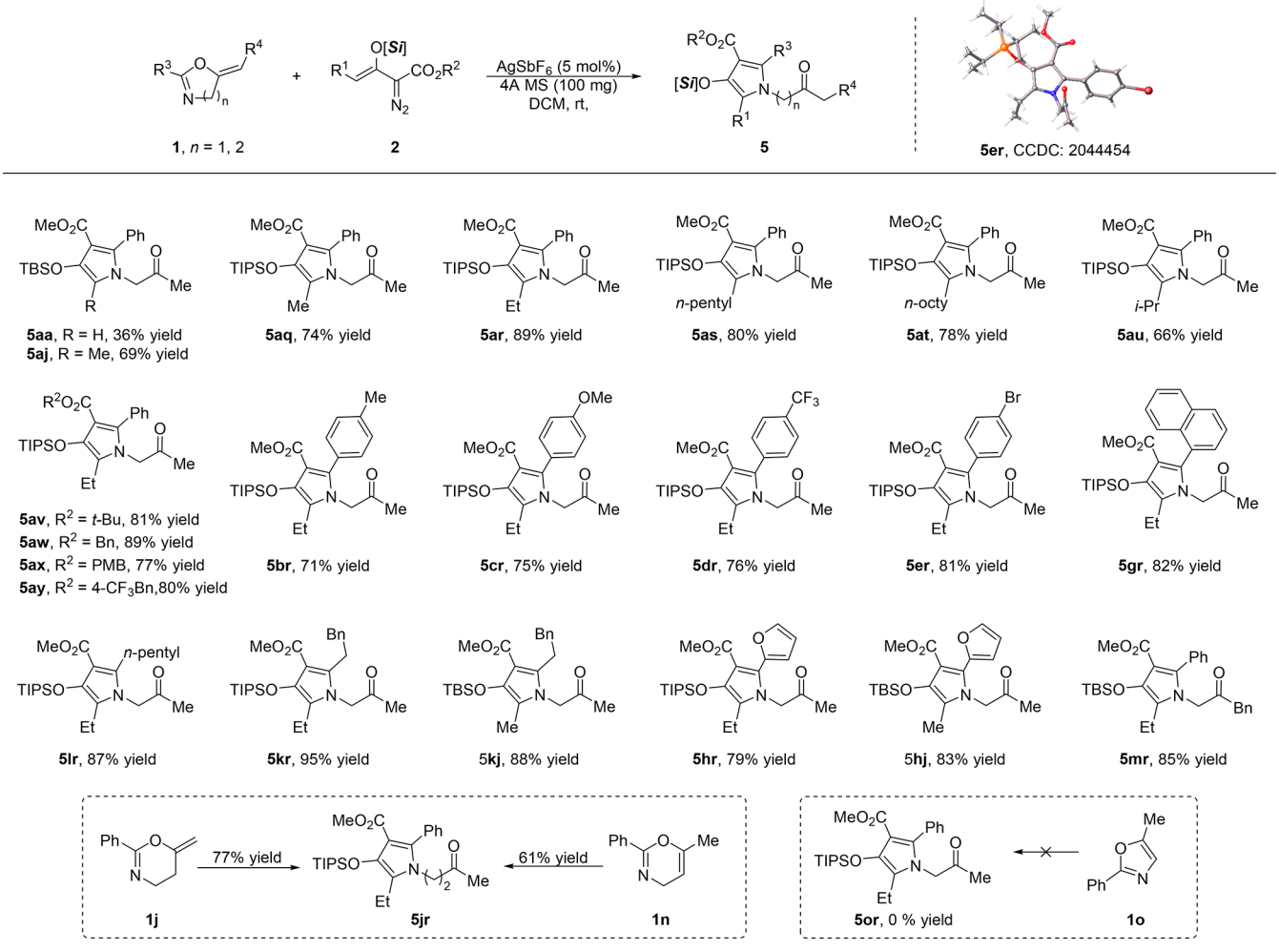


[a]The reaction was carried out on a 0.2 mmol scale: to the $Cu(OTf)_2$ catalyst (5.0 mol %), **6** (0.2 mmol) in DCM (2.0 mL) was added **2** (0.3 mmol) in the DCM (2.0 mL) via syringe pump over 1 h under an argon atmosphere at room temperature. The yields are given in isolated yields after flash-chromatography. [b]The reaction was conducted in the presence of ligand L_4 (see SI for details).

enoldiazoactates under $Cu(OTf)_2$ catalysis, surprisingly, the [3 + 2] cycloaddition products (**9aa** and **9ap**) were also formed in yields up to 87% yield without observable formation of the corresponding **VA-PT** product. To gain insight into the different outcomes between $Cu(CH_3CN)_4SbF_6$ and $Cu(OTf)_2$, chiral Box ligands were introduced and the reaction between methylenedihydroindene **6f** with enoldiazoacetate **2p** was repeated to determine the influence of these ligands on chemoselectivity and enantioselectivity (Table S3). Chiral Box ligands provide high enantiocontrol in copper catalyzed reactions of enoldiazoacetates,[26] but they also decrease reactivity. However, the **VA-PT** product was formed in only 34% yield along with cycloaddition products **9fp** in 46% yield when *t*-BuBox was used (8% *ee*). When the size of the ligand was increased, **8fp** became the dominant product in77% yield.

Substrate Scope of the Cycloaddition/Rearrangement C−C−PT Reaction. The formation of a multisubstituted butanonyl pyrrole **5aa** by silver(I) catalyzed reaction of enoldiazoacetate **2a** with methylene-substituted dihydrooxazole **1a** was an unexpected outcome, and its potential for structural diversity is high. Multisubstituted pyrroles, which are valuable five-membered heterocycles, are found in numerous biologically active natural products,

Scheme 4. Cycloaddition/Rearrangement C−C−PT Reaction[a,b]



[a]The reaction was carried out on a 0.2 mmol scale: to $AgSbF_6$ (5.0 mol %), 4A MS (100 mg), and **1** (0.2 mmol) in DCM (2.0 mL) was added **2** (0.3 mmol) in DCM (2.0 mL) via syringe pump over 0.5 h under an argon atmosphere. [b]Isolated yields after flash-chromatography.

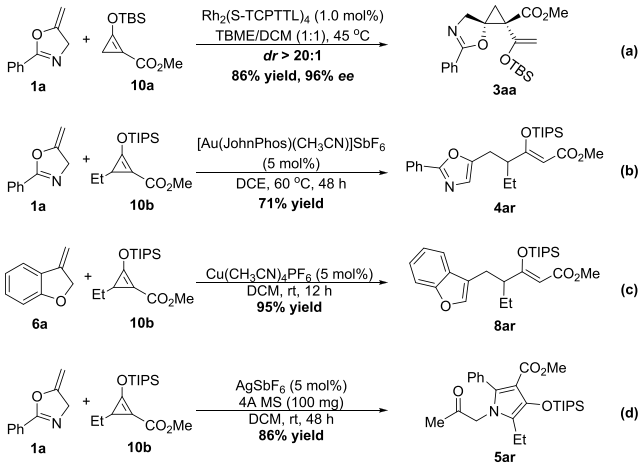
https://doi.org/10.1021/acscatal.1c01051
ACS Catal. 2021, 11, 4712−4721

pharmaceuticals, and materials.[27] Various synthetic strategies have been developed to construct the pyrrole architecture.[28] However, the direct synthesis of multisubstituted pyrroles, especially with variable substituents at each carbon center, remains a significant challenge. With the opportunity provided by Ag(I) catalysis to provide a complementary approach for the synthesis of diverse multisubstituted pyrroles, we developed this transformation to prepare butanonyl pyrroles **5**, which were envisioned to be the outcome of a formal C═N [3 + 2]-cycloaddition reaction that occurred with C−O bond cleavage and hydrogen migration.

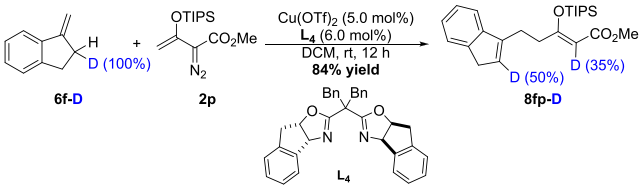
Using the optimized reaction conditions with $AgSbF_6$ catalysis and molecular sieves, the scope of dihydrooxazole starting materials **1** was investigated with a variety of enoldiazoesters **2**, and the results are presented in Scheme 4. Analysis of substituent effects revealed the influence of two variable substitution patterns on reactivity and chemoselectivity that are a function of either or both electronic and steric factors. Increasing the size of the alkyl group at the γ-position of enoldiazoacetate **2** (R^1) from methyl (**2q**) to ethyl (**2r**) led to an improvement in yield and chemocontrol of the reaction. However, introduction of pentyl (**2s**), octyl (**2t**) and isopropyl (**2u**) substituents for R^1 resulted in reduced yield (**5as**−**5au**). These results suggest a significant steric influence by the γ-substituent, and the ethyl substituent at the γ-position was chosen for further studies. No other products that combined **1** and **2** (R^1 = Et and larger) were observed; the lower than quantitative yields were due to the decomposition of enoldiazoacetate **2**. Modest variations in product yields were observed (77−89%) with different enoldiazoacetate esters (R^2, **5av**-**5ay**) that revealed minor electronic influences. The introduction of electron-neutral, -rich, or -deficient substituents on the aryl group (R^1) had minimal influence on product yields (**5br**-**5er**), generating the butanonyl pyrroles in moderate to good yields (71−81%). Naphthyl (**5gr**), aliphatic (**5lr**-**5kr**), and 2-furyl substituents (**5h**) on dihydrooxazole gave even higher yields (79−95%). In contrast with results in Table S2, even enoldiazoacetate **2j** with TBS, instead of TIPS, substituted enoldiazoacetate showed excellent selectivity in forming pyrroles **5kj** and **5hj** as the sole products. Moreover, a phenyl substituent R^3 on the dihydrooxazole methylene (**1m**) also shows high selectivity (**5mr**, 85% yield). Interestingly, when the double bond is in the six-membered dihydrooxazine ring (**1n**) the same pyrrole product **5jr** is generated (61% yield) as when the double bond is exocyclic (**1j**) (77% yield). However, the aromatic analog of **1a**, 5-methyl-2-phenyloxazole (**1o**) was unreactive; no pyrrole product formed, and starting reactants were recovered.

To achieve further insight into the reaction mechanisms, the carbene surrogate for enoldiazoacetate **2**, donor−acceptor cyclopropene **10**, was employed as the reactant for all transformations with **1a** and **6a**. Desired target products were formed with somewhat higher yields (Scheme 5), which we attribute to the increased stability of the D−A cyclopropene over the corresponding enoldiazoacetate to the reaction conditions. These results suggest that metallocarbene intermediates are formed in each of these reaction processes. That these reactions were not Lewis acid catalyzed processes is indicated by the absence of reactions of either **2r** or **10** with the classic Lewis acids $Sc(OTf)_2$ and $ZnBr_2$ (Table 1 and Scheme S3f). Furthermore, an isotope labeling experiment was carried out (Scheme 6) in which monodeuterium **6f** was employed with **2p** using $Cu(OTf)_2$ as the catalyst along with

Scheme 5. Control Experiments



Scheme 6. Isotope Labeling Experiment

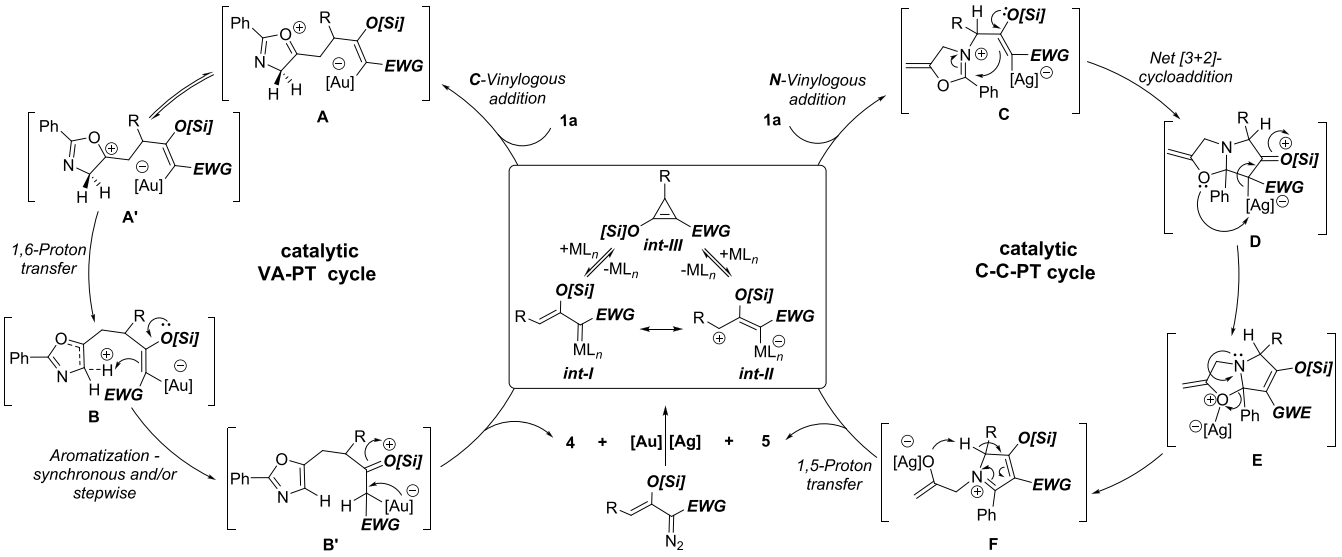


ligand **L4**. Deuterated product was formed with 35% deuterium transfer to the former carbenic center and 50% deuterium remained, as expected, at the original site of deuteration. The loss of 15% deuterium suggested that aromatization via proton transfer occurred prior to proton-induced separation of the catalyst, although 35% deuterium transfer indicated that most of the proton transfer process may be synchronous. The retention of 50% deuterium at the original site portrays the absence of an isotope effect for proton transfer.

On the basis of these results and control experiments, we propose a plausible catalytic cycle between the gold(I) complex catalyzed **VA-HT** reactions and $AgSbF_6$-catalyzed **C−C−PT** for the synthesis of multisubstituted pyrrole derivatives (Scheme 7). Initially, enoldiazoactates undergo dinitrogen extrusion in the presence of metal catalyst to give the corresponding metallo-enolcarbene intermediates. With dirhodium(II) catalysis, the reaction of the metallo-vinylcarbene occurs at the carbenic carbon yielding cyclopropanation products. In the gold(I)-catalyzed transformation nucleophilic addition by the alkene of **1** onto the electrophilic vinylogous carbon of the metallo-enolcarbene forms the oxygen-stabilized carbocationic intermediate **A**. Intramolecular aromatization resulting in the formation of intermediate **B′** via **B**, followed by [1,6]-proton transfer that occurs with aromatization forms the allylic alkylation aromatization product **4**. This process is similar to a vinylogous transformation of vinyldiazo esters with vinyl ethers, catalyzed by Rh_2(*S*-DOSP)$_4$ that was referred to as C−H functionalization/Cope rearrangement;[29] notably Rh_2(*S*-DOSP)$_4$ did not catalyze this transformation in reactions of **1** with **2**. Alternatively, in the silver-catalyzed cycle, the major reaction pathway proceeds by nucleophilic addition of the nucleophilic imine nitrogen to the electrophilic vinylogous carbon of metallo-enolcarbene to generate the iminium ion intermediate

https://doi.org/10.1021/acscatal.1c01051
ACS Catal. 2021, 11, 4712−4721

Scheme 7. Proposed Mechanism for Catalysts-Directed Divergent Catalytic Approach



C, followed by intramolecular cyclization to form **D**. Extrusion of Ag(I) from **D** and association with the vinyl ether oxygen results in **E** for which C−O bond cleavage is activated, and 1,5-proton transfer from carbon with regeneration of the silver catalyst results in aromatization to the polysubstituted pyrrole **5** that completes the catalytic cycle. A distinction between these two processes is that the metal carbene formed with gold and copper carbenes are carbophilic relative to silver, whereas silver(I) is azophilic in its reactions with dihydrooxazoles. Cyclopropanation follows the classical addition mechanism, but its exclusivity with dirhodium catalysts is surprising since vinylogous reactions of vinylcarbenes of dirhodium(II) with vinyl ethers is a common occurrence.[24,25]

CONCLUSIONS

In summary, we have demonstrated distinct multiple catalyst-controlled chemoselective reactions that establish structural and functional scaffold diversity from the same reactants. Cyclopropanation, vinylogous addition or cycloaddition, and multisubstituted pyrrole products formation from a novel rearrangement were enabled by metallo-carbene reactions using selected catalysts that provide exclusive chemocontrol. Previous reports have described product divergence with two different metal-based catalysts that provide high selectivity, but this report takes one set of substrates with three different metal catalysts to three structurally diverse products in high yields and excellent selectivities. With this catalyst-directed diversity, the opportunity to expand structural and functional multiplicity is taken to a higher level of complexity and utility. Overall, the unique, simple, and mild reaction protocol that is reported elaborates the diverse outcome of highly selective catalytic reactions of enoldiazo compounds with a range of carbo- and heterocyclic olefins. Another outcome is a classification of reactivity and selectivity for commonly used metal catalysts, as is evident in the philicity of different metal catalysts for specific reaction centers. Further development of this catalytic diversity is ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01051.

Experimental procedures and spectroscopic data for all new compounds (PDF)

X-ray crystallographic data for **3ad** (CIF)

X-ray crystallographic data for **5er** (CIF)

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Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acscatal.1c01051
ACS Catal. 2021, 11, 4712−4721

■ ACKNOWLEDGMENTS

We acknowledge the U.S. National Science Foundation (CHE-1763168) for funding this research. The x-ray diffractometer used in this research was supported by a grant from the U.S. National Science Foundation (CHE-1920057).

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