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Convergent Synthesis of Dihydropyrans from Catalytic Three-Component Reactions of Vinylcyclopropanes, Diazoesters, and Diphenyl Sulfoxide

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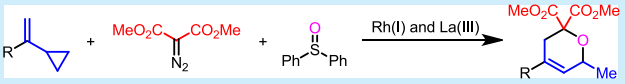
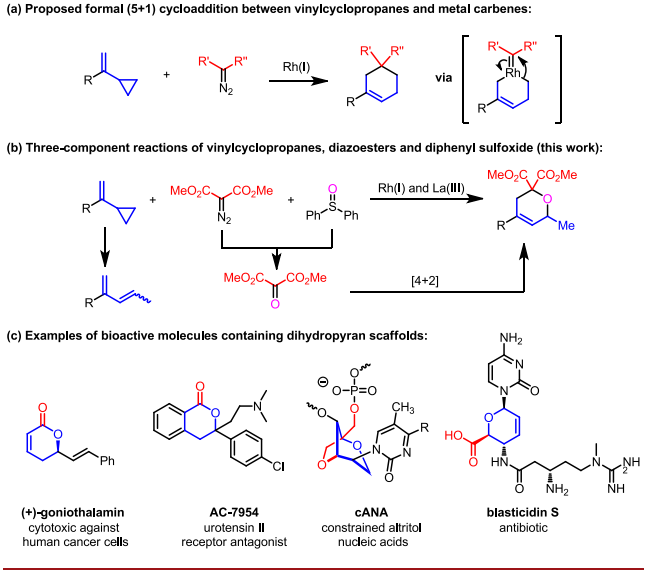
ABSTRACT: A novel Rh(I)/La(III) cocatalytic three-component reaction of vinylcyclopropanes, diazoesters, and diphenyl sulfoxide has been developed. The reaction gives polysubstituted dihydropyrans as the reaction products. Mechanistic studies indicate that isomerization of vinylcyclopropanes gives conjugated dienes, which then undergo [4 + 2]-cycloaddition with vicinal tricarbonyl compounds generated by oxygen atom transfer from diphenyl sulfoxide to diazoesters.



Vinylcyclopropanes (VCPs) are highly versatile substrates in transition-metal-catalyzed C−C bond activation reactions. Their uses in building cyclic, bicyclic, and polycyclic ring structures have been well documented.[1] In particular, as the pioneer, Wender established rhodium-catalyzed (5 + 2) cycloadditions of VCPs with various π-systems such as alkynes, alkenes, and allenes.[2] Yu further advanced the field by developing rhodium-catalyzed (3 + 2) intramolecular cycloadditions of unactivated VCPs.[3] Moreover, CO as a donor−acceptor ligand could participate in the cycloadditions to provide (5 + 2 + 1) and (3 + 2 + 1) products.[4] These works generally utilized VCPs as three-carbon or five-carbon components for cycloadditions.

Our interest in C−C bond activation reactions[5] prompted us to study the activation reactions of VCPs. Our initial plan was to achieve the carbene migration insertion to the rhodacyclohexene intermediate obtained from rhodium-mediated C−C activation of vinylcyclopropanes (Scheme 1a). And upon reductive elimination, the (5 + 1) cycloaddition product would be formed.[6] However, this proposed reaction did not occur in our hands. Instead, we accidentally discovered a novel three-component reaction of VCPs with diazoesters and diphenyl sulfoxide, which produced polysubstituted dihydropyrans (Scheme 1b). In this reaction, VCPs have been found to serve as a four-carbon component for cycloaddition. Mechanistic studies suggest that VCPs are converted to conjugated dienes, which then undergo hetero-Diels−Alder reactions with vicinal tricarbonyl compounds obtained from the oxygen atom transfer from diphenyl sulfoxide to diazoesters. Because dihydropyrans are the core structure of many bioactive molecules and pharmaceuticals, such as (+)-goniothalamin,[7a] AC-7954,[7b] cANA,[7c] and blasticidin S[7d] (Scheme 1c) and the methods for directly accessing such structures are limited,[8] we believe that this reaction would be particularly attractive for medicinal chemists. Herein, we would like to elaborate the study of this reaction.

Scheme 1. Metal-Mediated Ring-Opening of VCPs and Subsequent Reactions with Diazo Compounds



We began our study by reacting 1-(1-cyclopropylvinyl)-benzene (**1a**) with dimethyl diazomalonate (**2a**) in the presence of $[Rh(cod)Cl]_2$ (5 mol %) in dioxane at 120 °C, in a hope to get the (5 + 1) cycloaddition product (Table 1). However, after reacting for 12 h, no cycloaddition product was formed (entry 1). Interestingly, when we added AgOTf (10

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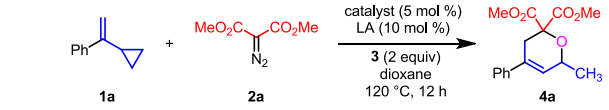
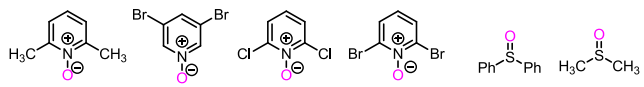
Table 1. Study of Reaction Conditions[a]



1a 2a 4a

Oxygen Atom Transfer Reagent **3**:



3a 3b 3c 3d 3e 3f

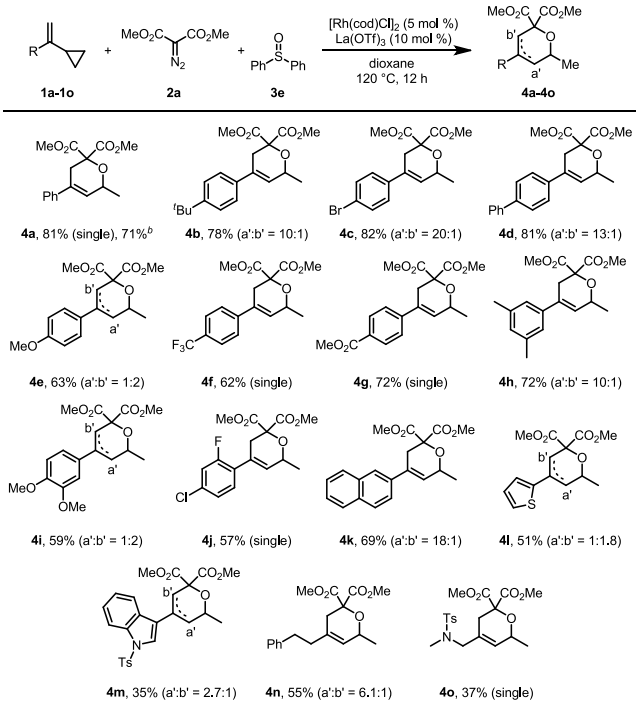
entry	catalyst	3	Lewis acid	yield[b] (%)
1	$[Rh(cod)Cl]_2$	none	none	none
2	$[Rh(cod)Cl]_2$	none	AgOTf	8
3	$[Rh(cod)Cl]_2$	none	AgOTf[c]	25
4	$[Rh(cod)Cl]_2$	none	$Cu(OTf)_2$[c]	22
5	$[Rh(cod)Cl]_2$	**3a**	$Cu(OTf)_2$	20
6	$[Rh(cod)Cl]_2$	**3b**	$Cu(OTf)_2$	42
7	$[Rh(cod)Cl]_2$	**3c**	$Cu(OTf)_2$	trace
8	$[Rh(cod)Cl]_2$	**3d**	$Cu(OTf)_2$	trace
9	$[Rh(cod)Cl]_2$	**3e**	$Cu(OTf)_2$	69
10	$[Rh(cod)Cl]_2$	**3f**	$Cu(OTf)_2$	30
11	$[Rh(cod)Cl]_2$	**3e**	none	11
12	$[Rh(cod)Cl]_2$	**3e**	AgOTf	68
13	$[Rh(cod)Cl]_2$	**3e**	$Sc(OTf)_3$	63
14	$[Rh(cod)Cl]_2$	**3e**	$La(OTf)_3$	87 (81[d])
15	$[Rh(cod)Cl]_2$	**3e**	$Yb(OTf)_3$	79
16	$[Rh(cod)Cl]_2$	**3e**	TMSOTf	48

[a]Unless otherwise specified, all reactions were performed with 0.2 mmol of **1a**, 0.4 mmol of **2a**, and 0.4 mmol of **3** in 1 mL of dioxane. [b]NMR yields. [c]Used 40 mol % of Lewis acids. [d]Isolated yield.

mol %) as an additive in order to in situ generate cationic $[Rh(cod)_2]OTf$, a cyclic compound **4a**, which was determined to be a polysubstituted dihydropyran, was produced in 8% yield (entry 2). We suspected that the oxygen atom in **4a** came from AgOTf, so we increased the loading of AgOTf to 40 mol %. Indeed, the yield of **4a** was enhanced to 25% (entry 3). Use of $Cu(OTf)_2$ (40 mol %) instead of $Ag(OTf)_2$ was also able to afford **4a** (22% yield, entry 4). However, further increasing the loading of $Ag(OTf)_2$ or $Cu(OTf)_2$ failed to improve the yield, only resulting in decompositions of the starting materials. Then, we reconsidered the reaction mechanism. We speculated that the OTf anion had transferred its oxgen atom to the diazoester to provide the C−O fragment in the ring. Actually, metal-catalyzed oxygen atom transfer from an oxidant to a metal carbene is a known reaction, which was studied in detail by Doyle and co-workers.[9] Dimethyldioxirane, dimethyl sulfoxide, and pyridine *N*-oxides are suitable oxidants for this transfer reaction. Therefore, we tested the addition of an oxidant to our reaction. When 2,6-dimethylpyridine *N*-oxide (**3a**) was used in the presence of 10 mol % of $Cu(OTf)_2$, **4a** was obtained in 20% yield (entry 5). Encouragingly, when 3,5-dibromopyridine *N*-oxide (**3b**) was used, the yield was improved to 42% (entry 6). Further screening of oxidants revealed that diphenyl sulfoxide (**3e**) was optimal, which afforded **4a** in 69% yield (entry 9). Furthermore, the Lewis acid was found to be very important for the reactivity because the yield dropped to only 11% when the reaction was run in the absence of any Lewis acids (entry 11). Additional tests of other Lewis acids, including AgOTf, $Sc(OTf)_3$, $La(OTf)_3$, $Yb(OTf)_3$, and TMSOTf, showed that $La(OTf)_3$ gave the highest yield (87%, entry 14).

With the optimal reaction conditions in hand, we first explored a number of VCPs bearing various α substituents (Scheme 2). Electron-donating and electron-withdrawing

Scheme 2. Scope of VCPs Bearing Various α-Substituents[a]



[a]Unless otherwise specified, all reactions were performed with 0.2 mmol of VCPs, 0.4 mmol of **2a**, and 0.4 mmol of **3e** in 1 mL of dioxane. [b]When the reaction was run at 2.0 mmol scale.

groups, including ^{t}butyl (**4b**), bromo (**4c**), phenyl (**4d**), methoxy (**4e**), trifluoromethyl (**4f**), and methoxycarbonyl (**4g**), at the *para* position of the α phenyl ring were tolerated; the cycloaddition products were obtained in 62−82% isolated yields. In these reactions, we also obtained an isomerization product, which has the olefin unit migrating to the adjacent C−C bond (b′ in each structure). Substrates bearing electron-donating groups tend to produce more of this isomer. Especially, for the *para*-methoxy-substituted substrate, the isomerization product became the major product (**4e**, a′:b′ = 1:2). Disubstituted phenyls (**4h**−**4j**) were also compatible. Moreover, other aryl rings, including 2-naphthyl (**4k**), 2-thienyl (**4l**), and 3-indolyl (**4m**), at the α position were also acceptable; the cycloaddition products were isolated in 35−69% yields. Furthermore, reactions of VCPs bearing phenethyl (**4n**) and aminomethyl (**4o**) were feasible. When the reaction of **1a** was performed at 2.0 mmol scale, product **4a** was isolated in 71% yield. Therefore, this reaction can be scaled up.

VCPs bearing substituents at other locations were next investigated (Scheme 3). When the cyclopropane ring was substituted with a methyl group at a carbon adjacent to the vinyl-substituted carbon (**1p**), the bond cleavage occurred at both proximal C−C bonds (bonds **A** and **B**), providing two isomeric products (**4p**) in a ratio of 1.5:1. When the same carbon was substituted with a phenyl group (**1q**), the ratio of the two isomers (**4q**) became 2:1. A 1,1-disubstituted cyclopropane (**1r**) gave a single product (**4r**) in 47% yield. And the reaction of bicyclic VCP **1s** selectively cleaved the less

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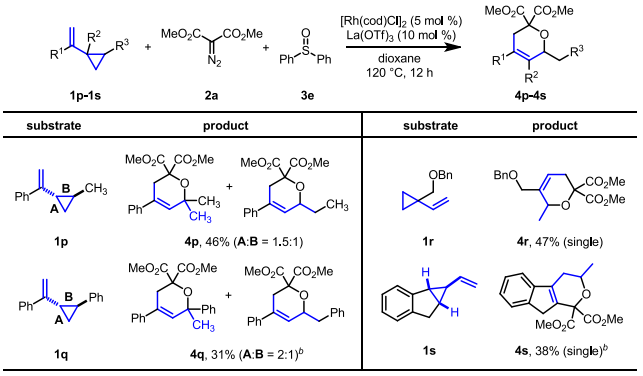
Scheme 3. Scope of VCPs Bearing Substituents at Other Locations[a]

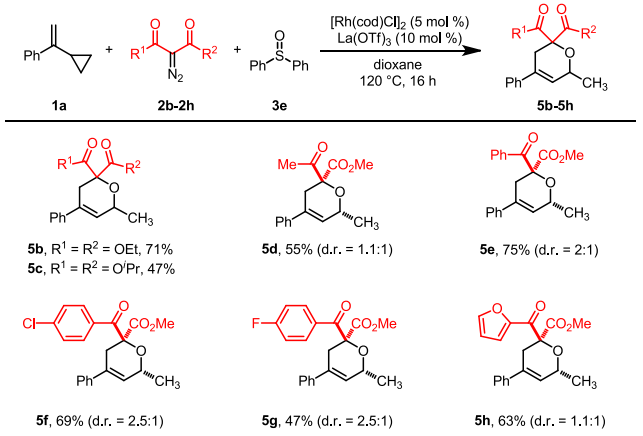


[a]Unless otherwise specified, all reactions were performed with 0.2 mmol of substrates, 0.4 mmol of **2a**, and 0.4 mmol of **3e** in 1 mL of dioxane. [b]Reaction time: 20 h.

hindered C−C bond, affording a single product (**4s**) in 38% yield.

The scope of diazoesters was subsequently investigated (Scheme 4). Diethyl and diisopropyl diazomalonates (**2b** and

Scheme 4. Scope of Diazoesters[a]

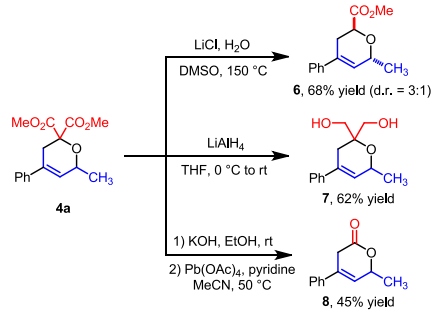


[a]Unless otherwise specified, all reactions were performed with 0.2 mmol of **1a**, 0.4 mmol of diazoesters, and 0.4 mmol of **3e** in 1 mL of dioxane.

2c) were reactive; the yields dropped with the increase of the steric bulk. Methyl diazoacetoacetate (**2d**) was reactive, but the diastereoselectivity (**5d**) was very poor. The reaction was also compatible with dicarbonyl-stabilized diazo compounds bearing aryl and heteroaryl substituents (**5e**−**5h**). However, this reaction is not feasible with diazo compounds stabilized by only one carbonyl group (e.g., ethyl diazoacetate and methyl phenyldiazoacetate; for limitations of the reaction, see the Supporting Information).

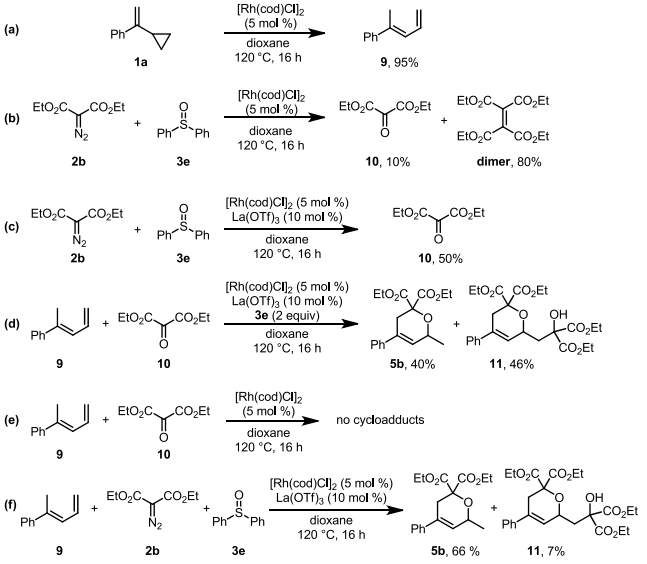
To demonstrate the utility of this cycloaddition reaction, we studied the transformations of product **4a** (Scheme 5). Treatment of **4a** with LiCl and water at 150 °C gave the decarboxylation product **6** in 68% yield (d.r. = 3:1). Reduction of the diesters by excess $LiAlH_4$ gave diol **7** in 62% yield. Finally, hydrolysis of **4a** followed by oxidation with $Pb(OAc)_4$ delivered lactone **8** in 45% yield. It is worth mentioning that these obtained structures exist in many bioactive molecules (e.g., examples shown in Scheme 1c).

Scheme 5. Transformations of 4a



We then performed several control experiments to look into the reaction mechanism (Scheme 6). First, VCP **1a** was heated

Scheme 6. Mechanistic Experiments



at 120 °C in dioxane in the presence of $[Rh(cod)Cl]_2$ (5 mol %) for 16 h; diene **9** was produced in 95% yield (Scheme 6a).[10] We then reacted ethyl diazomalonate (**2b**) with diphenyl sulfoxide under rhodium catalysis; vicinal tricarbonyl compound **10** was formed in 10% yield via the oxygen atom transfer reaction. At the same time, the majority of the diazo compound underwent dimerization (Scheme 6b). By comparison, when we tested the same reaction with the addition of $La(OTf)_3$ (10 mol %), the yield of **10** improved to 50% (Scheme 6c). Therefore, the oxygen atom transfer reaction is promoted by the Lewis acid. We then subjected **9** and **10** to the standard reaction conditions; cycloadduct **5b** was obtained in 40% yield, with formation of another cycloaddition product **11** in 46% yield (Scheme 6d). Apparently, **5b** was generated by hetero-Diels−Alder reaction[11] of **10** with a conjugated diene isomerized from diene **9**; **11** was generated by a cascade process of the addition of **9** to **10** (Prins reaction[12]), followed by hetero-Diels−Alder reaction of the resulting adduct with another molecule of **10**. When **9** and **10** were reacted in the absence of $La(OTf)_3$, no cycloadducts were formed (Scheme 6e), demonstrating the importance of the Lewis acid for cycloaddition. Finally, when diene **9** was reacted with ethyl diazomalonate (**2b**) and diphenyl sulfoxide (**3e**), product **5b** was obtained in 66% yield with only 7% of **11** coproduced (Scheme 6f). This result shows that the in situ generation of

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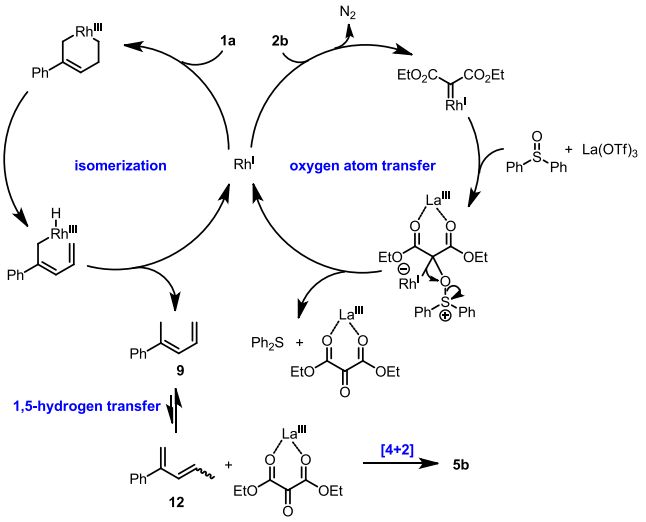
10 from the oxygen atom transfer reaction is better than direct use of **10** for inhibition of byproduct formation perhaps because of the kinetics of the coexisting processes.

Based on the results of the control experiments, we propose a reaction mechanism shown in Scheme 7. In the cycle for

Scheme 7. Proposed Reaction Mechanism



VCP isomerization, oxidative addition of VCP **1a** to rhodium(I) gave the rhodacyclohexene intermediate, which then underwent β-H elimination and reductive elimination to give diene **9**. In the cycle of oxygen atom transfer, rhodium(I) reacted with the diazo compound to give the metal carbene. The Lewis-acid-activated metal carbene was subsequently trapped by diphenyl sulfoxide to give the oxonium ylide. Elimination of diphenyl sulfide gave vicinal tricarbonyl compound **10**. Metal-catalyzed[10,13] 1,5-hydrogen transfer in diene **9** would give diene **12**, which underwent [4 + 2] cycloaddition with the Lewis-acid-activated tricarbonyl compound to give the observed product.

In summary, we have developed a new three-component reaction of VCPs, diazoesters, and diphenyl sulfoxide. The reaction features several coexisting reaction pathways, including VCP isomerization, oxygen atom transfer, 1,5-hydrogen transfer, and [4 + 2] cycloaddition, all occurring in one pot. Moreover, the reaction is suitable to scale up and the obtained polysubstituted dihydropyrans can be converted to other useful scaffolds by simple transformations. The application of this reaction toward natural product synthesis is currently being explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01992.

Experimental details, compound characterization data, and spectra (PDF)

Accession Codes

CCDC 1985208−1985209 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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