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An Atom-Economic Synthesis of Bicyclo[3.1.0]hexanes by Rhodium N-Heterocyclic Carbene-Catalyzed Diastereoselective Tandem Hetero-[5 + 2] Cycloaddition/Claisen Rearrangement Reaction of Vinylic Oxiranes with Alkynes

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Supporting Information

ABSTRACT: The first synthetic application of a vinylic oxirane as a heteroatom-containing five-atom component in transition-metal-catalyzed cycloaddition reactions is reported. A new, efficient, diastereoselective tandem intramolecular hetero-[5 + 2] cycloaddition/Claisen rearrangement of vinylic oxirane-alkyne substrates that uses a rhodium NHC complex and provides strategically novel, atom-economic, regiospecific, and diastereoselective access to [3.1.0] bicyclic products has been developed.

Transition-metal-catalyzed cycloaddition reactions have proven reliable for the construction of polycyclic carbocycles and heterocycles.[1] Many impressive examples in the area of polycyclic carbocycle synthesis have emerged. For example, the research groups of Wender,[2] Trost,[3] and Yu[4] have done seminal work on the cycloadditions of vinylcyclopropanes (VCPs) and π systems. Alternatively, the [4 + 3] cycloaddition of allyl cations and dienes is an efficient method for making seven-membered rings.[5] Lautens,[6] Motherwell,[7] Nakamura,[8] and Mascareñas[9] have developed intramolecular [3 + 2] cycloadditions of methylenecyclopropanes (MCPs) with various unsaturated compounds for the synthesis of five-membered rings. Evans has described the merit of the rhodium-catalyzed [2 + 2 + 2] and [4 + 2 + 2] reactions of 1,6-enynes with alkynes and 1,3-butadienes.[10] Recently, Tanaka has demonstrated an elegant system for enantioselective [2 + 2 + 2] cycloadditions.[11] On the other hand, the formation of polycyclic heterocycles by these processes has focused mainly on using carbonyl compounds,[12a−d] 1-azadienes,[12e] azomethine imines,[12f] nitrones,[12g−j] isocyanates,[12k,l] etc.,[1e] as heteroatom components.

Vinylic oxiranes are easily made, versatile synthons[13] that are commonly used as substrates in metal-catalyzed substitution reactions,[14] rearrangements,[15] and [3 + 2] cycloadditions.[16] However, there has been no report on the utilization of vinyl oxiranes as a heteroatom-containing five-atom partner in cycloaddition reactions. If this approach is successful, it will give new insight into the synthetic application of vinylic oxiranes, but it faces many obstacles and challenges, considering that epoxides activated by an adjacent aryl or vinyl substituent easily undergo isomerization to carbonyl compounds in the presence of complexes of metals such as Rh,[15a−c] Ru,[15d] Pd,[15e−j] etc.[15k,l]

During the course of our ongoing development of rhodium-catalyzed cyclization[17a−e] and oxirane chemistry,[17f,g] we became interested in whether vinylic oxiranes could be used as heteroatom-containing five-atom components in metal-catalyzed intramolecular hetero-[5 + 2] cycloadditions via C−O bond cleavage of the epoxide motif to afford the 2,5-dihydrooxepin (Scheme 1). The 2,5-dihydrooxepin would then readily undergo a subsequent Claisen rearrangement,[18] providing a strategically novel, atom-economic route to [3.1.0] bicycles, which are widely found in natural products[19a] and pharmaceutical agents.[19b,c] Among those methods for synthesizing bicyclo[3.1.0]hexanes, the most common and well-known process is intramolecular cyclopropanation of suitably functionalized substrates, including transition-metal-catalyzed decomposition of diazo compounds followed by intramolecular alkene insertion,[20] organocatalytic Michael-initiated ring closure,[21] intramolecular Simmons-Smith cyclopropanation,[22] cyclization of lithiated epoxides,[23] and others.[24] However, atom-economic methods for the synthesis of these compounds are relatively rare, except for transition-metal-catalyzed cycloisomerization of enynes.[25] Herein we report the first Rh N-heterocyclic carbene (NHC)-catalyzed tandem intramolecular hetero-[5 + 2] cycloaddition/Claisen rearrangement reaction of vinylic oxirane−alkyne substrates, which provides practical, regiospecific, and diastereoselective access to bicyclo[3.1.0]hexanes. To the best of our knowledge, this is the first example of the use of vinylic oxiranes as a heteroatom-containing five-atom component in transition-metal-catalyzed cycloadditions.

We began to examine this hypothesis by subjecting substrate **1a** to a solution of various rhodium catalysts (Table 1). To our surprise, the reaction did not occur when $[Rh(CO)_2Cl]_2$[2a,b] or $(PPh_3)_3RhCl/AgSbF_6$[2c,d] was used as the catalyst, even though these are commonly used in intramolecular [5 + 2] cycloadditions (entries 2 and 3). No reaction occurred in the absence of rhodium catalyst (entry 1). With 5 mol % $[Rh(COD)Cl]_2$/$AgSbF_6$ in 1,2-dichloroethane (DCE) at room temperature, a mixture of **2a** and some unidentified aldehydes was obtained (entry 4). Increasing the temperature to 75 °C did not improve the yield (entry 5). When used alone, $[Rh(COD)Cl]_2$ failed to catalyze this reaction (entry 6). On the other hand, use of $AgSbF_6$ alone induced isomerization of the epoxide to the aldehyde derivatives (entry 7). Hence, we carried out this reaction in the

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Scheme 1

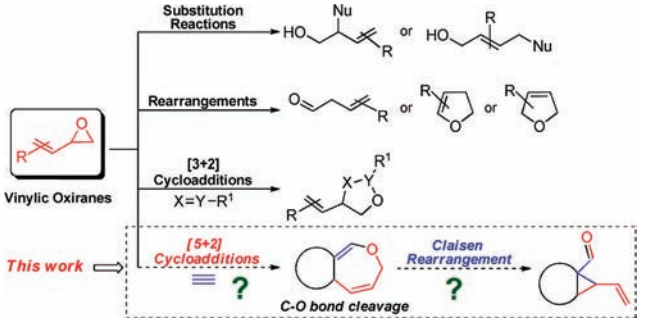
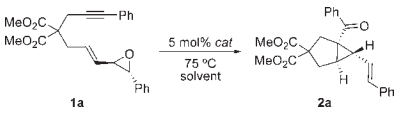


Table 1. Optimization of Reaction Conditions[a]



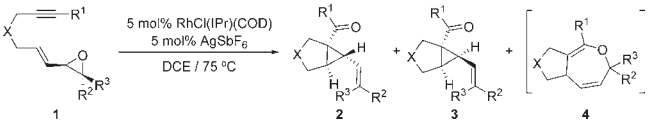
entry	catalyst (mol %)	solvent[g]	time (h)	% yield[d]
1	none	DCE	24	NR[h]
2	$[Rh(CO)_2Cl]_2$	DCE	24	–[e]
3[b]	$(PPh_3)_3RhCl/AgSbF_6$	DCE	8.0	–[e]
4[b,c]	$[Rh(COD)Cl]_2/AgSbF_6$	DCE	1.5	73
5[b]	$[Rh(COD)Cl]_2/AgSbF_6$	DCE	0.5	57
6	$[Rh(COD)Cl]_2$	DCE	12	NR[h]
7[c]	$AgSbF_6$	DCE	1.5	–[e]
8[c]	$[Rh(\eta^6\text{-}C_{10}H_8)(COD)]^+SbF_6^-$	DCE	0.5	50
9[c]	$[Rh(\eta^6\text{-}C_6H_6)(COD)]^+SbF_6^-$	DCE	0.5	80
10[b,c]	$RhCl(IPr)(COD)/AgSbF_6$	DCE	36	80 (75)
11[b,f]	$RhCl(IPr)(COD)/AgSbF_6$	DCE	3.0	86 (81)
12[b]	$RhCl(IPr)(COD)/AgSbF_6$	DCE	2.0	94 (92)
13[b]	$RhCl(IMes)(COD)/AgSbF_6$	DCE	2.0	94 (92)
14	RhCl(IPr)(COD)	DCE	24	NR[h]
15[b]	$RhCl(IPr)(COD)/AgSbF_6$	DMF	24	–[e]
16[b]	$RhCl(IPr)(COD)/AgSbF_6$	CH_3CN	24	–[e]
17[b]	$RhCl(IPr)(COD)/AgSbF_6$	EtOH	24	10
18[b]	$RhCl(IPr)(COD)/AgSbF_6$	toluene	24	80

[a] Unless otherwise noted, the reaction was performed with 0.2 mmol of **1a** and 5 mol % catalyst in 2.5 mL of DCE at 75 °C. [b] Rh:$AgSbF_6$ = 1:1. [c] Reaction was run at room temperature. [d] Determined by ^1H NMR analysis using CH_2Br_2 as the internal reference; values in parentheses are isolated yields. [e] Complex mixture. [f] Reaction was run at 60 °C. [g] DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide. [h] NR = no reaction.

presence of $[(arene)Rh(COD)]^+SbF_6^-$ (entries 8 and 9).[2e] However, the formation of products isomeric to the epoxides was also observed. Gratifyingly, the use of 5 mol % RhCl(IPr)(COD)/$AgSbF_6$[26] bearing strong σ-donating IPr ligand in DCE at room temperature provided a 80% NMR yield of **2a** and a 20% NMR yield of **1a**. Increasing the temperature to 75 °C significantly improved the yield to 92% (entries 10–12). RhCl(IMes)(COD)/$AgSbF_6$[10e] was also an efficient catalyst for the reaction (entry 13). Treatment of **1a** with RhCl(IPr)(COD) alone did not afford the product (entry 14). Different solvents (entries 15–18) were also tested but failed to improve the process.

Under the optimal reaction conditions, a series of vinylic oxirane–alkynes **1** were prepared and examined (Table 2). The

Table 2. Rh(NHC)-Catalyzed Tandem Intramolecular Hetero-[5 + 2] Cycloaddition/Claisen Rearrangement Reaction[a]



entry	X	$R^1/R^2/R^3$ (**1**)	time (h)	product (% yield[b])
1	$C(CO_2Me)_2$	Ph/Ph/H (**1a**)	2	**2a** (92)
2	$C(CO_2Me)_2$	4-$MeOC_6H_4$/Ph/H (**1b**)	5	**2b** (91)
3	$C(CO_2Me)_2$	4-$NO_2C_6H_4$/Ph/H (**1c**)	8	**2c** (55)
4	$C(CO_2Me)_2$	Ph/Me/H (**1d**)	2	**2d** (80)
5[c]	$C(CO_2Me)_2$	Ph/Me/Me (**1e**)	4	**2e** + **3e** (70)[d]
6[e]	$C(CO_2Me)_2$	Ph/Me/Me (**1e**)	2	**2e** (47)[f]
7	$C(CO_2Me)_2$	Me/Ph/H (**1f**)	4	**2f** (75)
8	$C(CO_2Me)_2$	Me/Me/H (**1g**)	18	**2g** (70)
9	NTs	Ph/Ph/H (**1h**)	7	**2h** (86)[g]
10	NTs	Ph/Me/H (**1i**)	2	**2i** (94)
11	NTs	Ph/Me/Me (**1j**)	7	**2j** (67)
12	O	Ph/Ph/H (**1k**)	2	**2k** (85)
13[h]	O	Ph/Me/H (**1l**)	3	**2l** (60)

[a] Unless otherwise noted, reactions were performed with 0.2 mmol of **1** and 5 mol % RhCl(IPr)(COD)/$AgSbF_6$ (1:1) in DCE at 75 °C. [b] Isolated yields. [c] The reaction was run at 84 °C. [d] NMR yields of 59% for **2e**, 24% for **3e**, and 9% for **4e**. [e] The reaction was run at 80 °C. [f] 80% conversion with NMR yields of 47% for **2e** and 27% for **4e**. [g] Confirmed by X-ray crystallographic analysis. [h] The reaction was run at 60 °C.

results indicate that the present transformation is tolerant of tethers incorporating geminal diester, sulfonamide, and ether functionalities. The substituent R^1 or R^2 can be an aromatic or alkyl group (entries 1–8). Compound **1b** bearing *p*-methoxy group gave [3.1.0] bicyclic compound **2b** exclusively in 91% yield, whereas a reasonable 55% yield of **2c** was isolated from **1c** having a *p*-nitro group on the aromatic R^1 substituent, as a result of the formation of a product isomeric to the epoxide. Epoxide moieties with a quaternary carbon also afforded the corresponding products in good yields (entries 5 and 11). The structure and relative stereochemistry of bicyclic **2h** were confirmed by X-ray crystallography analysis.[27] It is noteworthy that substrate **1e** in the presence of 5 mol % RhCl(IPr)(COD)/$AgSbF_6$ in DCE for 4 h at 84 °C gave **2e** and **3e** in 70% yield together with a 9% NMR yield of the [5 + 2] cycloadduct **4e** (entry 5). When the reaction was run to 80% conversion, NMR yields of 47% for **2e** and 27% for **4e** were obtained, whereas **3e** was not observed (entry 6). Treatment of **4e** with 5 mol % RhCl(IPr)(COD)/$AgSbF_6$ in DCE for 4 h at 84 °C gave **2e** in 73% NMR yield together with **3e** in 16% NMR yield (eq 1), while **2e** was obtained as a single diastereomer upon heating in the absence of the Rh(NHC) catalyst (eq 2). These results indicate that the Claisen rearrangement of the [5 + 2] cycloadducts may take place without the catalyst. To test whether **3e** arose from isomerization of **2e**, we subjected **2e** to the reaction conditions in the presence of the Rh(NHC) catalyst. Surprisingly, NMR yields of 7% for **4e** and 26% for **3e** were obtained (eq 3), while treatment of **2e** in DCE at 84 °C afforded an 8% NMR yield of **4e** (eq 4).[28] These results indicate that the Claisen rearrangement of **4e** to **2e** is a reversible process under

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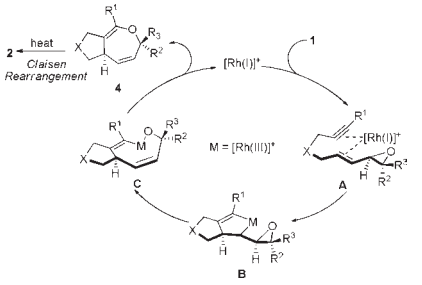
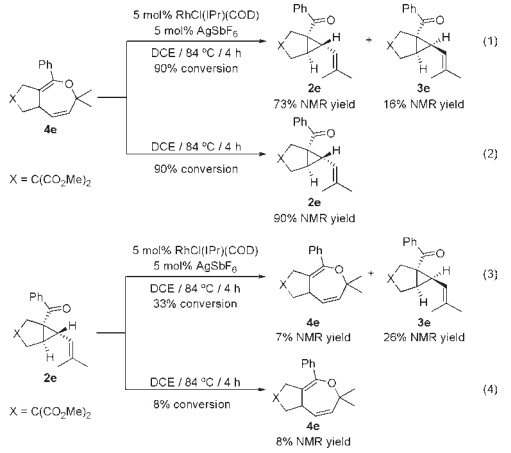
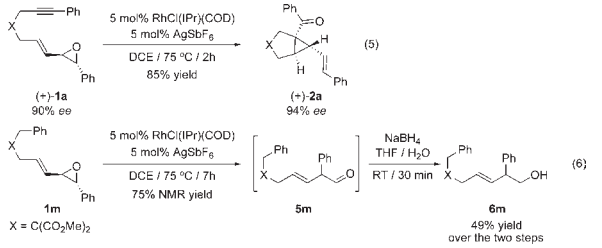
Scheme 2



thermal conditions and that **3e** may come from isomerization of **2e** in the presence of the Rh(NHC) catalyst.



In order to gain insight into this transformation, enantiomerically enriched (+)-**1a** (90% ee) was easily prepared and subjected to the current reaction conditions, affording the corresponding product (+)-**2a** in 85% yield with 94% ee (eq 5). The preservation of the enantiomeric excess in the product demonstrated complete chirality transfer in the present tandem hetero-[5 + 2] cycloaddition/Claisen rearrangement reaction. Vinylic oxirane **1m** lacking an alkyne moiety gave unstable aldehyde derivative **5m** in 75% NMR yield under the current conditions.[15b] After reduction, the corresponding alcohol **6m** was isolated in 49% yield (eq 6). These results suggest that the cycloaddition proceeds through a mechanism different from that for the vinylcyclopropane analogues.[2f]



On the basis of the above observations, one proposed mechanism is depicted in Scheme 2.The coordinated intermediate **A** is formed by the coordination of enyne **1** with a cationic Rh(I) species generated in situ. Oxidative cyclometalation of the enyne affords rhodacyclopentane **B**. Subsequent β-O elimination from **B** yields the C−Rh−O species **C**.[29] Reductive elimination from this species produces 2,5-dihydrooxepin **4** and regenerates the rhodium catalyst. Finally, **4** undergoes subsequent Claisen rearrangement to afford the [3.1.0] bicycle **2**.

In summary, an atom-economic route to bicyclo[3.1.0]-hexanes relying upon a new synthetic application of vinylic oxiranes in a rhodium-catalyzed intramolecular hetero-[5 + 2] cycloaddition/Claisen rearrangement reaction has been described. Complete chirality transfer in the present tandem process was also observed, providing a novel and rapid method for the synthesis of [3.1.0] bicycles in an enantioselective manner. Further studies of the scope, mechanism, and synthetic applications of this new process are underway.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data for the substrates and products, and crystallographic data (CIF) for **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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