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Rhodium-Catalyzed Stereoselective Intramolecular Tandem Reaction of Vinyl Oxiranes with Alkynes: Atom- and Step-Economic Synthesis of Multifunctional Mono-, Bi- and Tri-Cyclic Compounds

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ABSTRACT: Skeletal diversity in diversity-oriented synthesis has proven to be especially challenging. A rhodium-catalyzed intramolecular tandem reaction of vinyl oxirane-alkynes leading to four structurally distinct classes of mono-, bi- and tri-cyclic carbocycles and heterocycles was developed. $[Rh(NBD)_2]^+ BF_4^-$ is identified to be efficient catalyst for these transformations. Using this highly efficient catalyst, hetero-[5+2] cycloadditions, tandem hetero-[5+2] cycloaddition/Claisen rearrangement and subsequent cyclopropane ring opening reactions of vinylic oxiranes with mono-alkynes afford 2,5-dihydrooxepins, tetrasubstituted vinylcyclopropanes and multifunctional five-membered rings, respectively, under mild conditions with high stereoselectivity and yield. Moreover, hetero-[5+2] cycloaddition/Claisen rearrangement/[5+2] cycloaddition reaction of vinylic oxiranes with diynes for step-economic construction of linearly fused 5-7-5 tricyclic skeletons has also been developed. The complete transfer of chirality from readily available vinylic oxiranes to the corresponding products provides a highly efficient and practical access to these chiral cyclic compounds.

KEYWORDS: *Rhodium, tandem reaction, vinylic oxirane, alkyne, diversity-oriented synthesis, chirality transfer*

1. INTRODUCTION

The design or discovery of new versatile building blocks is of preeminent importance to the realization of the diversity-oriented synthesis (DOS).[1] Cyclopropanes, cyclopentenes, 2,3-dihydro-1*H*-pyrroles, 2,3-dihydrofurans, oxepines and linearly fused 5-7-5 tricyclic skeletons are ubiquitous structural motifs found in an array of natural products and pharmaceuticals with diverse biological and medicinal properties (Figure 1).[2] Therefore, the development of highly efficient synthetic methods to access these skeletons has been intensively pursued by synthetic community.[3] However, the widely applied approaches for construction of these three-, five- and seven-membered carbocycles and heterocycles require building each ring independently from different building blocks. Thus, the development of an ideal method for construction of these diverse scaffolds from a common building block in an atom- and step-economic fashion is extremely interesting and highly desirable.[4]

Modern transition metal-catalyzed cycloaddition reactions represent powerful tools enabling quick and efficient access to mono-, bi- and tricyclic structures from relatively simple starting materials.[5] In particular, using small-ring compounds as cycloaddition partners brings opportunities for developing novel reactions that complement to or surpass traditional cycloadditons.[6,7] Among them, vinylcyclopropanes (VCPs) represent an important subclass of activated cyclopropane derivatives with rich cycloaddition chemistry.[7] For example, Wender's group pioneered the development of Rh-catalyzed [5+2] cycloadditions of VCPs and π-systems for synthesis of seven-membered rings.[8] Subsequently, the research groups of

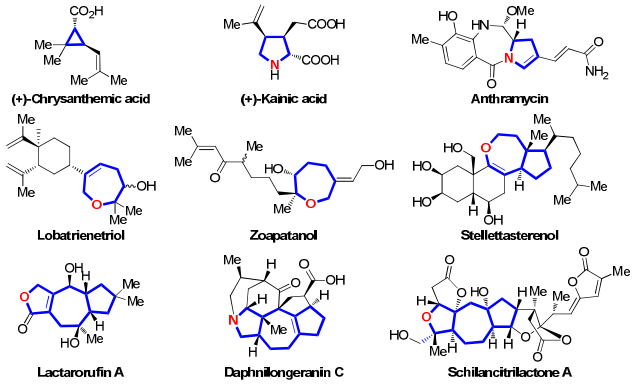


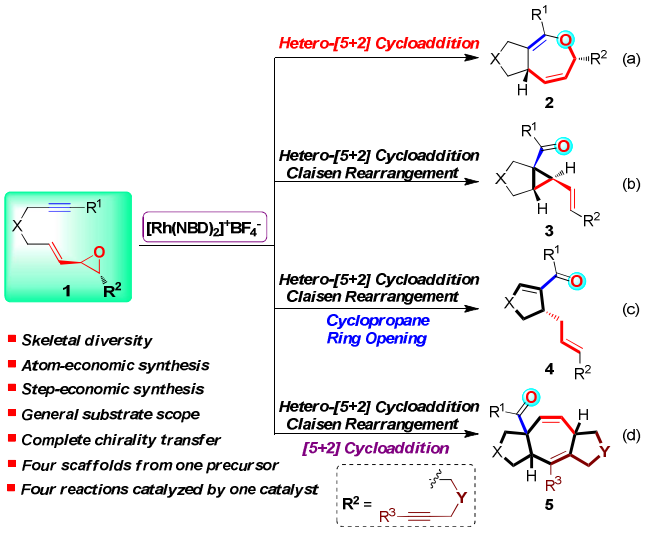
Figure 1. Representative biologically active three-, five- and seven-membered carbocycles and heterocycles.

Trost,[9] Louie,[10] Fürstner[11] have realized the [5+2] cycloadditions of VCPs and alkynes by using different transition-metal catalysts. [5+2+1],[12] [5+1],[13] [5+1+2+1][14] cycloadditions have also been developed for constructing different cyclic systems in which VCPs serving as five-carbon synthons. The VCP motif can also act as an activated cyclopropane ring (three-carbon synthon) to undergo [3+x] cycloadditions, Tsuji,[15a] Trost,[15b-c] Yu,[15d-i] and others[15j-m] have done seminal work on this kind of cycloadditions. The significance of the VCPs has been highlighted in the synthesis of several natural products by using [5+x] and [3+x] cycloadditions.[7c,16]

Due to the inherent reactivity of their constrained ring system, cyclopropane and oxirane derivatives constitute valuable building blocks for organic synthesis.[17] In contrast to VCPs, vinyl oxiranes[18], one of versatile synthons of oxirane deriva-

tives, have and continue to serve as attractive ring-expansion motifs in metal-catalyzed [3+2] cycloadditions,[19] epoxide carbonylation[20] and substitution reactions.[21] Recently, an elegant system for copper-catalyzed rearrangement of vinylic oxiranes to 2,5-dihydrofurans has been developed by Njardarson group.[22] However, there has been no report about utilizing vinyl oxiranes as a hetero five-atom partner in cycloaddition reaction until we reported an atom-economic route to multi-substituted VCPs relying upon a new synthetic application of vinylic oxiranes in a rhodium-catalyzed intramolecular hetero-[5+2] cycloaddition/Claisen rearrangement reaction.[23] Although many five-carbon components have been developed,[8m, 24] cyclopropylimines had been the only heteroatom-containing five-atom component in Rh-catalyzed hetero-[5+2] cycloaddition prior to our study.[25a,b] Considering that the product of hetero-[5+2] cycloaddition/Claisen rearrangement reaction is the multifunctional VCPs and the rich chemistry of VCPs,[7,8] we became interested in whether vinylic oxirane-alkynes **1** could be used as a common precursor to build structurally distinct compounds and tuning the selectivity by the subtle choice of catalyst and modification of the substrate.

Scheme 1. Diversity-Oriented Synthesis of Three-, Five and Seven-Membered Rings from Vinyl Oxirane-Alkynes



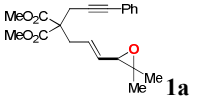
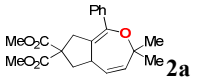
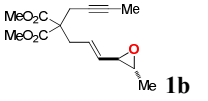
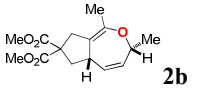
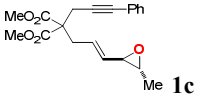
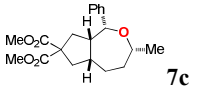
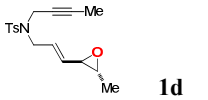
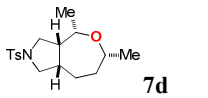
In previous examples,[23] we found that RhCl(IPr)(COD) /$AgSbF_6$ bearing a strong σ-donating IPr ligand can catalyze the hetero-[5+2] cycloaddition/Claisen rearrangement reaction at 60-84 °C. Because the Claisen rearrangement of **2** to **3** is a rapid process under thermal conditions, it is very hard to obtain the hetero-[5+2] cycloadducts **2**. With respect to substrate scope, the alkyne moiety of **1** was limited to internal alkyne. In this article, we demonstrate the details of the development of this hetero-[5+2] cycloaddition/Claisen rearrangement reaction and expansion of its substrate scope to both trimethylsilyl alkyne and terminal alkynes by using $[Rh(NBD)_2]^+BF_4^-$ as the catalyst (Scheme 1b). Furthermore, We also found that $[Rh(NBD)_2]^+BF_4^-$ is an efficient catalyst for catalyzing this reaction at room temperature, which give an opportunity to obtain the hetero-[5+2] cycloaddition product, *i.e.* 2,5-dihydrooxepin **2** (Scheme 1a). We also disclose two new $[Rh(NBD)_2]^+BF_4^-$ catalyzed cascade reactions: 1) hetero-[5+2] cycloaddition/Claisen rearrangement/cyclopropane ring opening reaction of vinyl oxiranes with mono-alkynes leading to multifunctional five membered rings (Scheme 1c); 2) hetero-[5+2]cycloaddition/Claisen rearrangement/[5+2] cycloaddition reaction of vinyl oxiranes with diynes for construction of 5-7-5 tricyclic compounds in one step (Scheme 1d). In addition, enantioselective synthesis of these compounds from optically pure vinyl oxiranes via a chirality transfer process was achieved and mechanistic studies have also been investigated. Of note, while other catalyst-selective synthesis systems are known,[26] we know few being capable of delivering the level of skeletal diversity by simply varying the reaction temperature and using a single catalyst.

2. RESULTS AND DISCUSSION

2.1 $[Rh(NBD)_2]^+BF_4^-$ catalyzed hetero-[5+2] cycloaddition and tandem hetero-[5+2] cycloaddition/Claisen rearrangement reaction of vinyl oxiranes with mono-alkynes

Oxepine derivatives represent a ubiquitous class of oxygen-containing heterocycles with wide occurrence in numerous biologically active natural products and pharmaceuticals, such as *Lobatrienetriol, Zoapatanol, and Stellettasterenol* (Figure 1).[2] However, relative to reactions that establish five- and six-membered oxygen-heterocycles, the development of efficient methodology for construction of oxepine skeletons is often much more difficult because of the unfavorable entropic factors and transannular interactions.[27]

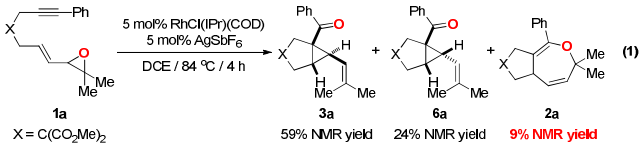
Table 1. $[Rh(NBD)_2]^+BF_4^-$-Catalyzed Hetero-[5+2] Cycloaddition Reaction[a]

entry	substrate	product	yield (%)[b]
1[c]	 **1a**	 **2a**	72
2[c]	 **1b**	 **2b**	75
3[d]	 **1c**	 **7c**	56
4[d]	 **1d**	 **7d**	65

[a] Conditions A: **1** (0.2 mmol), $[Rh(NBD)_2]^+BF_4^-$ (5 mol%), in CH_2Cl_2 (0.08 M) at 0 °C. [b] Isolated yield. [c] The reaction was run at 20 °C. [d] the corresponding hetero-[5+2] cycloadduct was treated with 10 % Pd/C and H_2 (1atm).

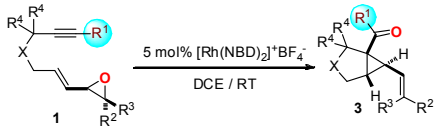
During our investigation of Rh(I)-catalyzed cycloadditions of vinylaziridines with π-systems,[28] we found that the cationic rhodium(I) complex $[Rh(NBD)_2]^+BF_4^-$ is a convenient and highly effective catalyst for the intramolecular hetero-[5+2] cycloaddition of vinylaziridines and a wide range of terminal and internal alkynes. Atom analogy suggests that vinyl oxirane-alkynes could be analogously activated by $[Rh(NBD)_2]^+BF_4^-$ to generate fused oxepine derivatives. Although this assumption was first validated by us in 2011, the use of first-generation catalyst (RhCl(IPr)(COD)/$AgSbF_6$) makes it very hard to intercept of hetero-[5+2] cycloadducts **2**, due to the rapid Claisen rearrangement of **2** to vinylcyclopropane derivative **3** under thermal conditions. For example, sub-

strate **1a** in presence of 5 mol% of RhCl(IPr)(COD)/$AgSbF_6$ in DCE for 4 h at 84 °C, gave only 9% NMR yield of the hetero-[5+2] cycloadduct **2a** with the further Claisen rearrangement products **3a** and **6a** in 83% total NMR yield (eq 1).[23] Moreover, the previous tandem hetero-[5+2] cycloaddition/Claisen rearrangement reaction of vinyl oxiranes with mono-alkynes under the catalysis of RhCl(IPr)(COD)/$AgSbF_6$ is limited to internal alkynes. Thus, the development of the second-generation catalyst to broaden the substrate scope under mild reaction conditions and intercept the hetero-[5+2] cycloadduct is highly desirable.



To our delight, as depicted in Table 1, subjection of **1a** and **1b** to the mixture of 5 mol% $[Rh(NBD)_2]^+BF_4^-$ in CH_2Cl_2 at 20 °C afforded the desired products **2a** and **2b** in 72% and 75% yields, respectively (Table 1, entries 1 and 2). It was found that 2,5-dihydrooxepin products were not stable at room temperature for prolonged reaction time, because of the enol ether moiety. To facilitate easy characterization, the hetero-[5+2] cycloadducts **2c** and **2d** were further treated with 10 % Pd/C and H_2, delivering the fully saturated oxepanes **7c** and **7d** in acceptable yield over two steps (Table 1, entries 3 and 4).

Table 2. $[Rh(NBD)_2]^+BF_4^-$-Catalyzed Tandem Hetero-[5+2] Cycloaddition/Claisen Rearrangement Reaction[a]

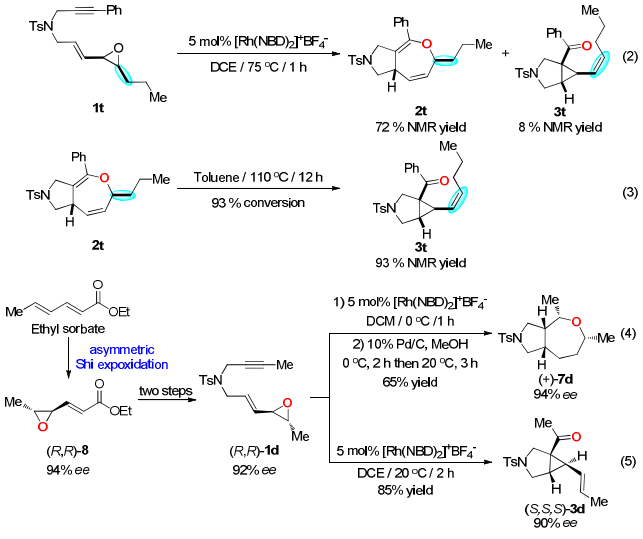


entry	X	$R^1/R^2/R^3/R^4$ (**1**)	t (h)	yield (%)[b]
1	$C(CO_2Me)_2$	Ph/Ph/H/H (**1e**)	5	**3e** (92)
2	$C(CO_2Me)_2$	4-$MeOC_6H_4$/Ph/H/H(**1f**)	7	**3f** (89)
3	$C(CO_2Me)_2$	4-ClC_6H_4/Ph/H/H (**1g**)	7	**3g** (72)
4[c]	$C(CO_2Me)_2$	4-ClC_6H_4/Ph/H/H (**1g**)	5	**3g** (50)
5	$C(CO_2Me)_2$	TMS/Ph/H/H (**1h**)	2	**3h** (64)
6[c]	$C(CO_2Me)_2$	TMS/Ph/H/H (**1h**)	5	**3h** (<5)
7	NNs	Ph/Ph/H/H (**1i**)	7	**3i** (82)
8	NTs	Ph/CH_2OTBS/H/H (**1j**)	1.5	**3j** (80)
9	NTs	Me/Ph/H/H (**1k**)	1	**3k** (88)
10	NTs	Me/Me/H/H (**1d**)	2	**3d** (86)
11[d]	NTs	H/Ph/H/H (**1l**)	2	**3l** (60)
12[c,d]	NTs	H/Ph/H/H (**1l**)	4	**3l** (<5)
13[d]	NTs	H/Ph/H/Me (**1m**)	4	**3m** (45)
14	O	Ph/Ph/H (**1n**)	5	**3n** (83)

[a] Conditions B: **1** (0.2 mmol), 5 mol% $[Rh(NBD)_2]^+BF_4^-$, DCE (0.08 M), 20 °C. [b] isolated product. [c] Conditions C: 5 mol% RhCl(IPr)(COD)/$AgSbF_6$ (1:1), DCE (0.08 M), 75 °C; [d] 10 mol% catalyst was used.

Unfortunately, the interception of hetero-[5+2] cycloadduct **2** is still quite challenging even using the second-generation catalyst $[Rh(NBD)_2]^+$ BF_4^- and the subsequent Claisen rearrangement reaction could occur even at room temperature (Table 2). Both internal (entries 1-10, 14) and terminal alkynes (entries 11-13) were compatible to afford the corresponding vinylcyclopropane products **3**, which have demonstrated a broad substrate scope in current reaction (entry 11 *versus* 12). Dramatic improvements were also observed for other substrates, when using $[Rh(NBD)_2]^+BF_4^-$ as the catalyst. For example, moderate yield was obtained for substrate **1g** under conditions C (RhCl(IPr)(COD)/$AgSbF_6$). By contrast, product **3g** was isolated in 72% yield under conditions B (entry 3 *versus* 4). What's more, the treatment of **1h** (R^1 = TMS) with $[Rh(NBD)_2]^+BF_4^-$ can also furnish the corresponding product in 64% yield. Whereas, **1h** decomposed quickly under the catalysis of RhCl(IPr)(COD)/$AgSbF_6$ (entry 5 *versus* 6). Substrate **1s** was prepared to test the limitation of the present reaction. Under conditions B, no reaction occurred, and the starting material was recovered (Figure 2).

In order to gain insight into above transformations, *cis*-oxirane substrate **1t** was also prepared. It is noteworthy that substrate **1t** in presence of 5 mol% $[Rh(NBD)_2]^+BF_4^-$ in DCE for 1 h at 75 °C gave a more stable hetero-[5+2] cycloadduct **2t** in 72% NMR yield together with a 8% NMR yield of **3t** (eq 2). Moreover, **2t** could rearrange to **3t** as a single diastereomer upon heating in the absence of the Rh catalyst (eq 3). Besides these, enantioenriched substrate (*R*,*R*)-**1d** (92% *ee*) was prepared from the corresponding chiral epoxide **8**, which was easily accessed by asymmetric Shi expoxidation of ethyl sorbate.[29] Surprisingly, both *di*- and *tetra*-substituted alkene moieties of the corresponding hetero-[5+2] cycloadducts could be hydrogenated under the Pd/C, H_2 conditions, affording the corresponding (+)-**7d**, possessing four chiral stereocenters, with 94% *ee* as a single diastereomer (eq 4). The absolute configuration of (+)-**7d** was determined by X-ray analysis (Figure 2).[30] Complete transfer of chirality in hetero-[5+2] cycloaddition/Claisen rearrangement reaction of **1d** under conditions B to access multi-substituted VCPs was also observed (eq 5).



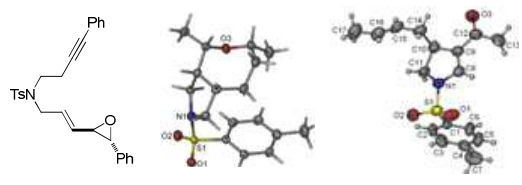
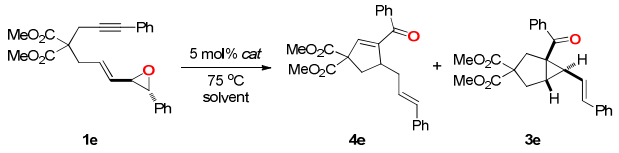


Figure 2. Substrate **1s** and crystal structure of compound (+)-**7d** and **4d**.

2.2 Tandem hetero-[5+2] cycloaddition/Claisen rearrangement/cyclopropane ring opening reaction.

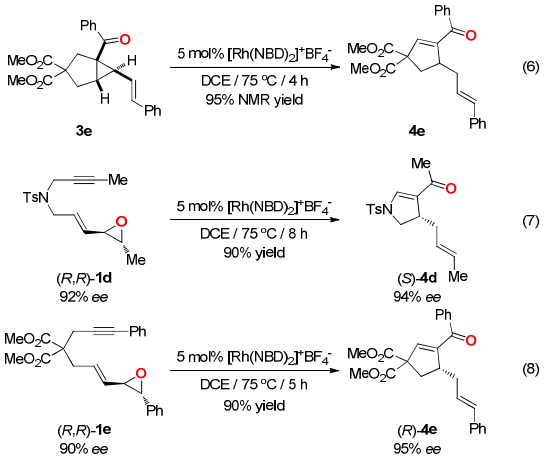
After running the reaction of **1e** at rt for 21 hours under the catalysis of $[Rh(NBD)_2]^+BF_4^-$, 6% NMR yield of cyclopentene derivative **4e** was observed, which was derived from the ring-opening of **3e** in the presence of rhodium catalyst (Table 3, entry 1 and eq 6). Given that five membered rings are ubiquitous in organic molecules and tandem reactions involved VCPs are relatively rare,[8k,l] a systemic screening of the catalysts and conditions for realizing the tandem hetero-[5+2] cycloaddition/Claisen rearrangement/cyclopropane ring opening reaction was carried out. Under the conditions C described in Table 2, no any five membered ring product **4e** was detected (Table 3, entry 3). In contrast, the treatment of **1e** with 5 mol% $[Rh(NBD)_2]^+BF_4^-$ in DCE at 75 °C for 5 h furnished **4e** in 91% NMR yield. Other cationic rhodium catalysts were also examined, but did not give better result (entries 4-5). Different solvents (entries 6-8) were tested and 1,4-dioxane was also found to be a suitable solvent.

Table 3. Optimization of Reaction Conditions[a]



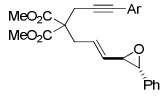
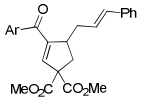
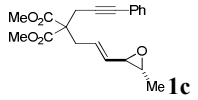
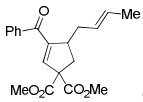
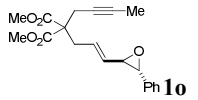
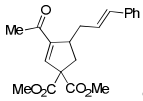
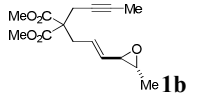
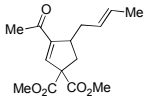
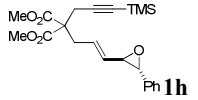
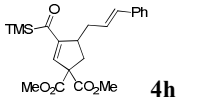
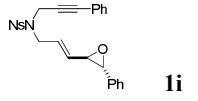
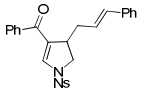
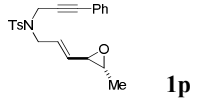
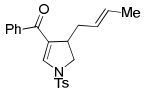
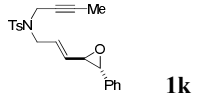
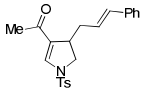
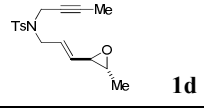
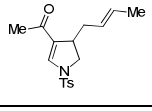
entry	catalyst (mol%)	solvent	time (h)	yield(%)[d] 4e	3e
1[b]	$[Rh(NBD)_2]^+BF_4^-$	DCE	21	6	85
2	$[Rh(NBD)_2]^+BF_4^-$	DCE	5.0	91	0
3[c]	RhCl(IPr)(COD)/$AgSbF_6$	DCE	2.0	0	94
4	$[Rh(\eta^6\text{-}C_{10}H_8)(COD)]^+SbF_6^-$	DCE	8.0	80	0
5	$[Rh(COD)_2]^+BF_4^-$	DCE	5.0	52	24
6[e]	$[Rh(NBD)_2]^+BF_4^-$	Toluene	5.0	0	67
7	$[Rh(NBD)_2]^+BF_4^-$	Dioxane	5.0	91	0
8	$[Rh(NBD)_2]^+BF_4^-$	MeOH[f]	5.0	69	13

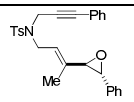
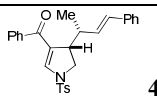
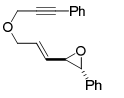
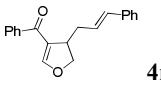
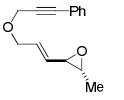
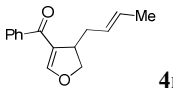
[a] Unless otherwise noted, the reaction was performed with 0.2 mmol of **1e** and 5 mol% of catalyst in 2.5 mL DCE at 75 °C. [b] Reaction was run at RT. [c] Rh to $AgSbF_6$ = 1:1. [d] NMR yield with CH_2Br_2 as an internal standard. [e] 30% **1a** was recovered. [f] 0.1 mL MeOH in 2.5 mL DCE.



With the optimal reaction conditions in hand, we next examined the scope of this tandem reaction by variation of the substitution patterns on alkyne and epoxide moieties (Table 4).

Table 4. Rh(I)-Catalyzed Tandem Hetero-[5+2] Cycloaddition/Claisen Rearrangement/Cyclopropane Ring-Opening Reaction[a]

entry	substrate	product	yield(%)[b]
			
1	**1e**, R = Ph	**4e**, R = Ph	90
2	**1f**, R = 4-$MeOC_6H_4$	**4f**, R = 4-$MeOC_6H_4$	86
3	**1g**, R = 4-ClC_6H_4	**4g**, R = 4-ClC_6H_4	77
4	 **1c**	 **4c**	93
5[c]	 **1o**	 **4o**	86
6	 **1b**	 **4b**	71
7	 **1h**	 **4h**	41
8	 **1i**	 **4i**	85
9	 **1p**	 **4p**	81
10	 **1k**	 **4k**	92
11	 **1d**	 **4d**	93

12		**1q**		**4q**	94
13[c]		**1n**		**4n**	61
14[c]		**1r**		**4r**	40

[a] Reaction conditions: **1** (0.2 mmol), $[Rh(NBD)_2]^+BF_4^-$ (5 mol%) in DCE (2.5 mL) at 75 °C. [b] Isolated yield. [c] the reaction was carried out as follow: $RhCl(IPr)(COD)/AgSbF_6$ (5 mol%), 60 or 75 °C, 3 h then $[Rh(NBD)_2]^+BF_4^-$ (5 mol%), 75 °C, 6 h, DCE (3 mL).

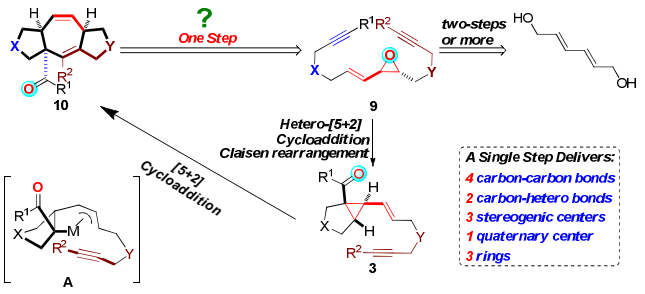
Variation of the substituent with different electron nature of the aryl ring on the alkyne moiety showed that the electron rich ones would give higher yields than those with electron-deficient ones (Table 4, entries 1-3). Besides the substituted phenyl, methyl- and trimethylsilyl alkyne could be compatible with this reaction (entries 4-7). The present transformation is tolerant of tether incorporating sulfonamide functionality to afford 81-94% yield of the corresponding 2,3-dihydropyrroles that commonly appear in natural alkaloids and biologically relevant compounds (entries 8-12). The structure of the 2,3-dihydropyrrole **4d** was unambiguously assigned by the X-ray analysis (Figure 2).[30] Moreover, it should be noted that **1q** with trisubstituted alkene reacts cleanly to afford the desired product **4q** as a single diastereomer (entry 12). However, Substrates **1n** or **1r** with an oxygen linker yielded the corresponding product **4** in poor yield using $[Rh(NBD)_2]^+BF_4^-$ as catalyst. But it can be improved to moderate to good yield by one-pot operation and a stepwise addition of $RhCl(IPr)(COD)/AgSbF_6$ and $[Rh(NBD)_2]^+BF_4^-$ (entries 13 and 14).

Importantly, a complete chirality transfer was observed in the present tandem process, providing a new and rapid method for the synthesis of multifunctional five-membered carbocycles and heterocycles in an enantioselective manner (eq 7 and 8).

2.3 Tandem hetero-[5+2] cycloaddition/Claisen rearrangement/[5+2] cycloaddition reaction of vinyl oxiranes with diynes.

Tricyclic and polycyclic carbocycles and heterocycles are widely found in biologically active natural and unnatural products, such as the linearly fused 5-7-5 tricyclic skeletons of the *Calyciphylline A* class alkaloids (Figure 1).[2f] Owing to the diversity of biological functions and pharmacological activities coupled with complex structural features, these multifunctional 5-7-5 tricyclic compounds have attracted much attention as targets for total synthesis. Previous approaches for construction of these challenging 5-7-5 tricyclic scaffolds have focused on building each ring step by step[2e] or building one ring first and then the other two rings in one step.[9a-c] The design of new cycloaddition reactions and reaction sequences that enable the construction these 5-7-5 tricyclic skeletons in one step offer decisive advantages in developing step- and atom-economical synthesis.

Scheme 2. Constructions of the Linearly Fused 5-7-5 Tricyclic Systems



The plausible mechanism for the formation of five membered ring **4** was presumably originated from the oxidative addition of **3** affords the Rh(III) intermediate followed by β-H elimination and reductive elimination. With this in mind, we wondered whether we can intercept this Rh(III) intermediate **A** by another alkyne or not. If it works, one step construction of multifunctional fused 5-7-5 tricyclic skeleton **10** from a readily available linear starting materials could be realized (Scheme 2). This step-,[31a,b] atom-[32] and time-[31c] economical approach precludes the challenging synthesis of multisubstituted vinylcyclopropanes with high diastereoselectivities and enantioselectivities. The major challenge for this route is to identify the

Scheme 3. [5+2] Cycloaddition of 3u

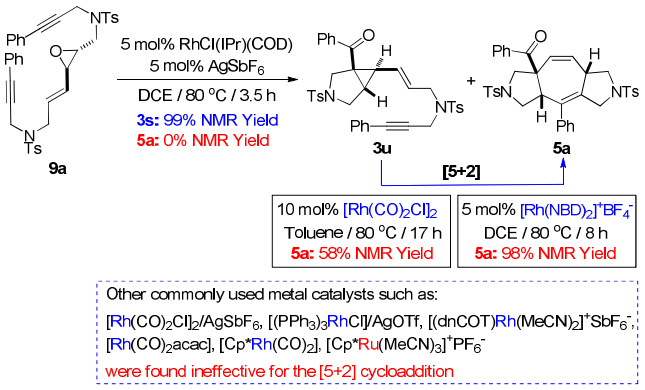
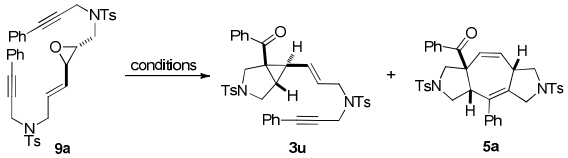


Table 5. Optimization of Reaction Conditions[a]

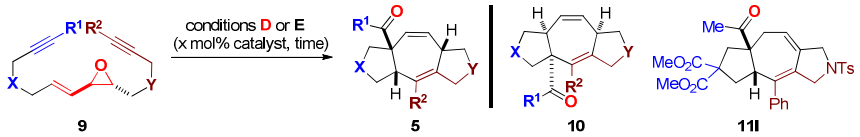


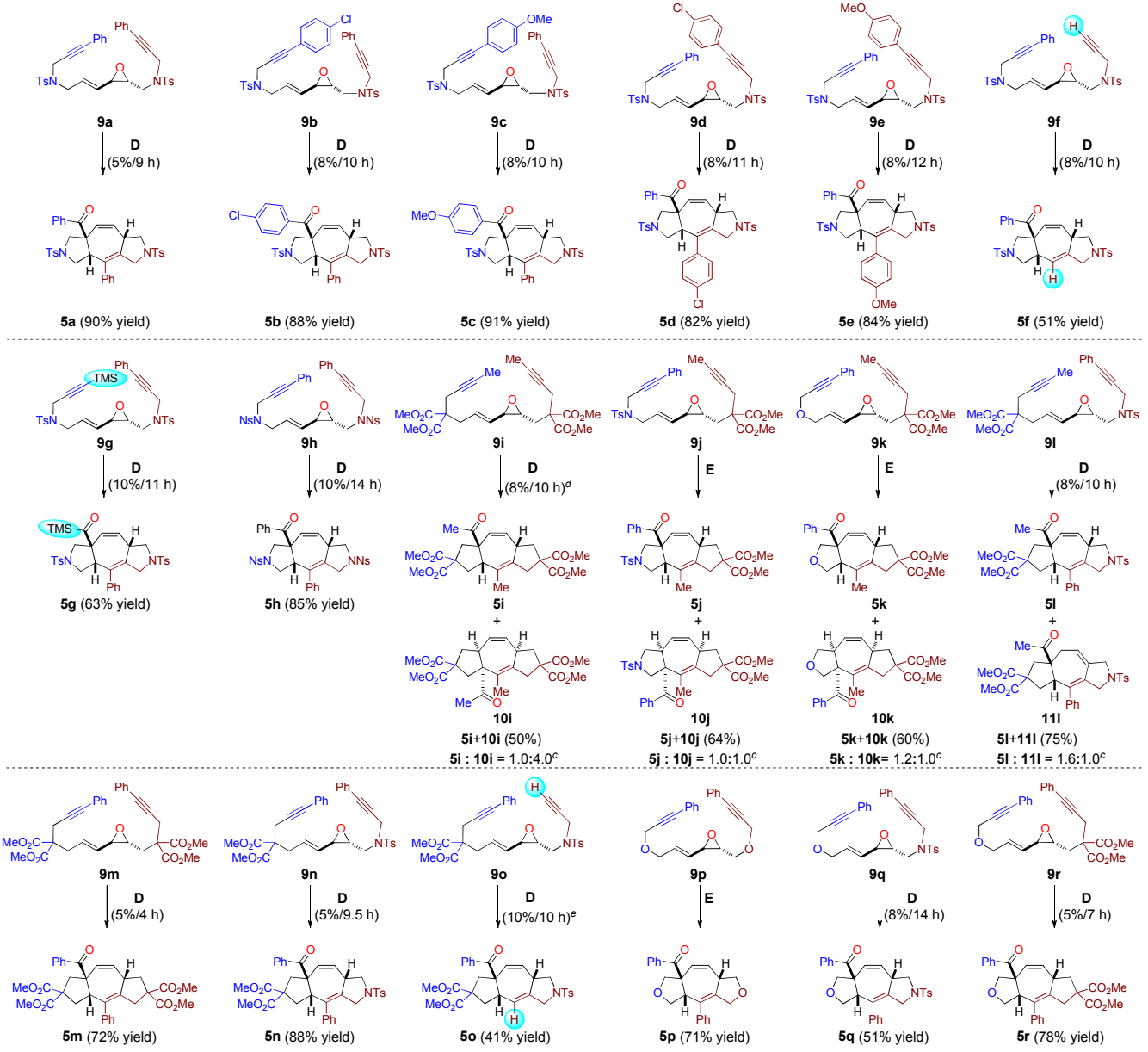
entry	catalyst (5 mol%)	T(°C)	*t* (h)	yield(%)[d] 3u	5a
1[b]	$RhCl(IPr)(COD)/AgSbF_6$	80	3.5	99	0
2[b]	$RhCl(IMes)(COD)/AgSbF_6$	80	3.5	95	0
3[b,f]	$NHCRh/AgSbF_6$	80	5.0	43	0
4[c]	$[Rh(CO)_2Cl]_2$	80	7.0	-[e]	0
5[b,c]	$(PPh_3)_3RhCl/AgSbF_6$	80	7.0	37	0
6	$[Rh(\eta^6\text{-}C_{10}H_8)(COD)]^+SbF_6^-$	30	4.0	99	0
7	$[Rh(dnCOT)(MeCN)_2]^+ SbF_6^-$	30	4.0	25	0
8[c]	$[Cp^*Ru(MeCN)_3]^+PF_6^-$	50	7.0	29	0
9[b]	$[Rh(COD)Cl]_2/AgSbF_6$	30	1.0	99	0

10	$[Rh(COD)Cl]_2$	80	13	-[g]	0
11[c]	$[Rh(COD)_2]^+BF_4^-$	80	9.0	97	0
12	$[Rh(NBD)dppe]^+BF_4^-$	30	2.5	-[g]	-[g]
13	$[Rh(NBD)_2]^+BF_4^-$	30	3.5	99	0
14	$[Rh(NBD)_2]^+BF_4^-$	60	28.0	17	77
15[c]	$[Rh(NBD)_2]^+BF_4^-$	60	4.5	0	94
16	$[Rh(NBD)_2]^+BF_4^-$	80	9.0	0	94

[a] Unless otherwise noted, the reaction was performed with 0.12 mmol of **9a** and 5 mol% of catalyst in 3.0 mL DCE. [b] Rh to $AgSbF_6$ = 1:1. [c] Using 10 mol% catalyst. [d] Determined by ^1H NMR analysis using CH_2Br_2 as the internal reference. [e]Complex mixture. [f] NHCRh = Bromo(cyclooctadiene)[1-(benzyloxy)-3-benzyl-4,5-dimethylimidazolylidene]rhodium. [g] no reaction.

Table 6. Exploration of Substrate Scope[a,b]





[a] Conditions D: **9** (0.12 mmol), $[Rh(NBD)^2]^+BF_4^-$ (5-10 mol%), DCE (0.04 M), 80 °C; Conditions E: **9** (0.12 mmol), RhCl(IPr)(COD)/$AgSbF_6$ (5 mol%), 60 or 80 °C, 4-10 h then $[Rh(NBD)_2]^+BF_4^-$ (5 mol%), 80 °C, 10 h, DCE. [b] Yield of the isolated product. [c] Determined by ^1H NMR analysis of the crude product. [d] The reaction was run at RT for 4 h then at 75 °C for 10 h. [e] The reaction

was run at 65 °C

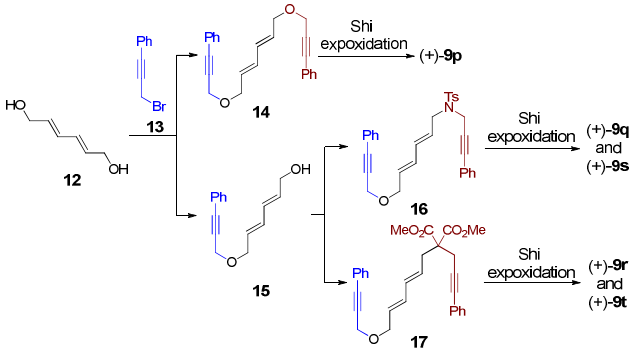
catalyst system which must be compatible with substrates, intermediates and also exhibit reaction sequence selectivity to avoid the competing isomerization of the vinyl oxiranes,[22,33] [2 + 2 + 2] cycloadditions of alkynes[34] and the reaction described in section **2.2** of this article. Furthermore, the [5+2] cycloaddition of tetrasubstituted vinylcyclopropane-alkynes **3** in which the cyclopropane bearing a carbonyl group have rarely been studied with Rh catalysts and are unreactive substrates for Ru-catalyzed [5+2] cycloaddition.[9b,c] Thus, a variety of catalysts were examined to achieve the [5+2] cycloaddition of **3u** (see SI-Table 1 in the Supporting Information). However, no [5+2] cycloadduct was detected in presence of commonly used rhodium and ruthenium catalysts in literatures (Scheme 3). Gratifyingly, treatment of **3u** with 10 mol% $[Rh(CO)_2Cl]_2$ in toluene for 17 h at 80 °C gave 5-7-5 tricyclic product **5a** in 58% NMR yield favoring regioselective cleavage of the less substituted cyclopropane bond of **3u**, rather than the product **10** described in Scheme 2. Notably, the NMR yield of the [5+2] cycloaddition of **3u** could be improved to 98% using $[Rh(NBD)_2]^+BF_4^-$.

To simplify the procedure, an ideal way to build the tricyclic skeleton that would be to mediate both hetero-[5+2] cycloaddition/Claisen rearrangement reaction and [5+2] cycloaddition by a cascade catalyst system. A series of Rh and Ru catalysts was tested but failed to realize this idea (Table 5, entries 1-12). When we carried out the reaction in the presence of 5 mol% $[Rh(\mathbf{NBD})_2]^+BF_4^-$ at 30 °C, **3u** was also obtained in 99% NMR yield (entry 13). To our delight, elevating the temperature to 60 °C provided **5a** as a single stereoisomer in 77% NMR yield together with a 17% NMR yield of **3u** (Table 5, entry 14). Both increasing the catalyst loading and raising the temperature significantly improved the yield of **5a** to 94% (Table 5, entries 15 and 16). Interestingly, $[Rh(\mathbf{COD})_2]^+BF_4^-$ containing a **COD** ligand failed to catalyze this reaction (Table 5, entry 11).

Under the optimal reaction conditions, a series of vinyl oxirane-diyne substrates **9** were tested under the optimized reaction conditions D (Table 6). It was found that a variety of tethers (nitrogen-, oxygen-, and *gem*-diester) could be compatible, delivering 5-7-5 hetero- and carbotricyclic skeletons (substrates **9a**, **9h**, **9m**, **9n**, **9q** and **9r**). Both internal and terminal alkynes were compatible to afford 5-7-5 tricyclic scaffolds (**9f** and **9o**). The alkyne substitution could be either an aromatic (**9a-9e**) or alkyl group (**9i**). A substrate (**9g**) bearing a trimethylsilyl alkyne was also successfully converted to the desired product. Notably, when R^1 and R^2 substituents of **9** are aromatic group, the reactions provided **5** as a single regioisomer and diastereoisomer favoring regioselective cleavage of the less substituted cyclopropane bond of **3**, suggesting that the steric effect is the dominant factor. Compound **9i** bearing methyl group on R^1 and R^2 gave **5i** and **10i** in a ratio of 1:4, whereas substrate **9l** with methyl group on R^1 and phenyl group on R^2 afforded **5l** in reasonable 45% yield and 30% yield of **11l** which arises from the isomerization of the olefin to form a more stable 1,3-diene. For substrates **9j**, **9k**, and **9p** either some complex mixture or only trace amount of the 5-7-5 tricyclic products was observed under conditions D probably owing to the cationic and Lewis acidic rhodium catalyst induced isomerization of the epoxide. In order to address this issue, an alternative strategy was developed. Coupling the hetero-[5+2] cycloaddition/Claisen rearrangement and [5+2] cycloaddition reaction into a sequential, one-pot process by using conditions E smoothly produced the corresponding products in moderate yields.

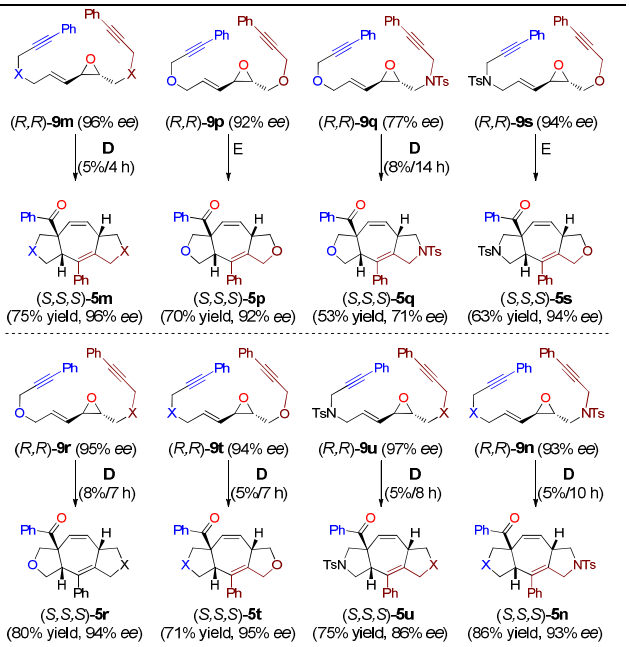
After the successful transfer of chirality in the above reaction (section **2.1** and **2.2)**, we then investigate chirality transfer in the more challenging tandem hetero-[5+2] cycloaddition/Claisen rearrangement/[5+2] cycloaddition reaction of vinyl oxiranes with diynes. This transformation delivers the formation of four new carbon-carbon bonds, two new carbon-hetero bonds, three chiral stereogenic centers containing one quaternary center and three rings in one single step. In order to be able to synthesize chiral fused 5-7-5 tricyclic products stereospecifically in a step-economic fashion, it is mandatory to develop a general route of the enantioenriched vinyl oxirane-diyne substrates. The Shi asymmetric monoexpoxidation of conjugated dienes could successfully deliver optically pure

Scheme 4. Converting One Common Precursor to Five Enantioenriched Vinylic Oxiranes-Diynes



vinyloxiranes-diynes **9**.[29] Enantioenriched substrates **9m, 9n** and **9p-9u** were rapidly prepared from readily available (2*E*,4*E*)-hexa-2,4-diene-1,6-diol **12** or (2*E*,4*E*)-1,6-dibromohexa-2,4-diene in just two or three steps (please see Supporting Information for details). For example, as depicted in Scheme 4, Compounds **14** and **15** were synthesized by Williamson etherification reaction of **12** with **13**, then **15** reacted with the corresponding functionalized alkynes to generate diynes **16** or **17**. Shi asymmetric monoexpoxidation of **14**, **16** and **17** finally gave the enantioenriched vinyl oxirane-diynes **9p, 9q, 9s, 9r** and **9t**. According to this synthetic route, strating from one common precursor **12**, five optically pure vinyl oxirane-diynes were efficiently synthesized.

Table 7. Stereospecific Tandem Hetero-[5+2] Cycloaddition/Claisen Rearrangement/[5+2] Cycloaddition[a,b]

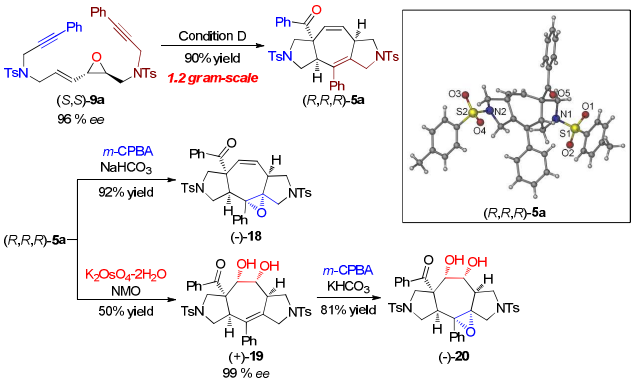


[a] The reaction was carried out under the conditions D or E as those described in Table 6. [b] Yield of the isolated product. **X** = $C(CO_2Me)_2$

With the optically pure substrates **9** in hand, a series of tandem hetero-[5+2] cycloaddition/Claisen rearrangement/[5+2] cycloaddition reaction were carried out. Under conditions D, $[Rh(NBD)^2]^+BF_4^-$ catalyzed tandem reaction of enantioenriched **9m**, **9r**, **9t**, **9n** delivered 5-7-5 tricyclic products with excellent chirality transfer. Under condition E, a complete transfer of chirality was obtained for **9p** and **9s**. By contrast, the efficiency of the chirality transfer was found to be lower for substrates **9q** and **9u**.

It is noteworthy that this stereospecific tandem reaction is easy to scale-up. A gram-scale reaction of 1.2 g of (*S*,*S*)-**9a** (96% *ee*) was subjected to the current reaction conditions, affording the corresponding (*R*,*R*,*R*)-**5a** in 90% yield. The absolute configuration of product (*R*,*R*,*R*)-**5a** was determined by X-ray analysis (the stereochemistry of the other 5-7-5 tricyclic products was then assigned accordingly).[30] To demonstrate the potential synthetic utility of this protocol, the diastereoselective epoxidation of the tetrasubstituted double bond in (*R*, *R*, *R*)-**5a** was accomplished with *m*-CPBA. Alternatively, the selective functionalization of the disubstituted double bond was realized by dihydroxylation with K_2OsO_4-$2H_2O$/NMO, providing the corresponding **19** in 50% yield with 98% *ee*. The preservation of the enantiomeric excess in **19** demonstrated complete chirality transfer in the present tandem hetero-[5+2] cycloaddition/Claisen rearrangement/[5 + 2] cycloaddition reaction (Scheme 5).

Scheme 5. Scale Up Reaction and Functionalization of (*R*,*R*,*R*)-5a



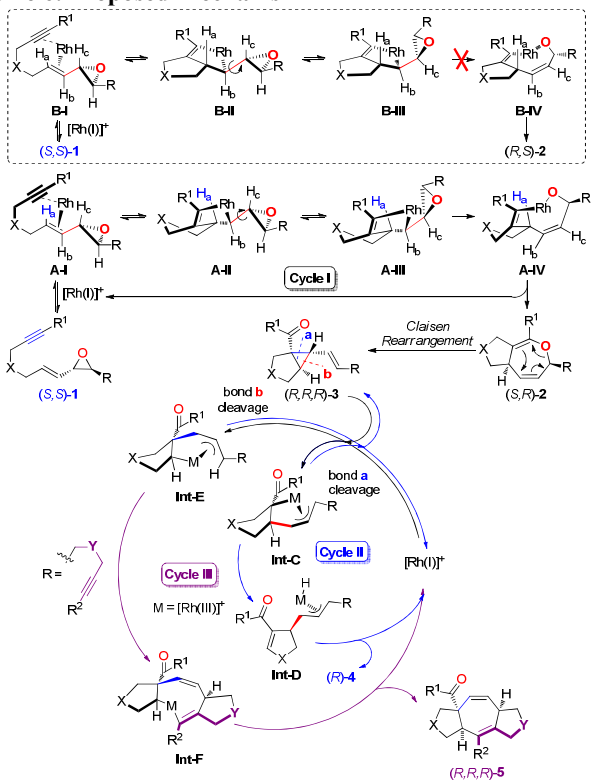
2.5 Mechanistic consideration.

With the aid of DFT calculation, two general mechanisms of transition metal-catalyzed [5+2] cycloadditions of VCPs and π-system have been proposed. Houk and Wender showed that Rh(I)-catalyzed [5+2] reactions usually involve the formation of a metallacyclohexene intermediate, which can then be intercepted by various cycloaddition components.[35] Recently Houk and Trost found that the mechanism involving an initial ene-yne oxidative cyclization to form a metallacyclopentene intermediate followed by cyclopropane cleavage and reductive elimination is favored in Ru(II) catalytic system.[9d]

Based on the above suggestion and the chirality transfer experiment, we proposed the mechanism shown in Scheme 6 for the rhodium-catalyzed tandem reaction involving hetero-[5+2] cycloaddition of vinyl oxiranes with alkynes. In cycle I, the rhodium complex π-facial selectivity coordination to ene-yne moieties of the optically pure (*S*,*S*)-**1** would give diastereomeric metallacyclopentenes **A-II** or **B-II** formed by oxidative cyclometalation of the 1,6-enyne moiety. The subsequent formation of a *Z*-olefin in **A-IV** and **B-IV** requires a *syn* alignment of the protons H_b and H_c along the C-C bond, which is achieved through rotation around the H_b-C-C-H_c bond to give **A-III** and **B-III**. However, only the conformation of **A-III** allows the C-O bond in the epoxide moiety to properly overlap with the C-Rh bond as required for concerted ring expansion to afford the rhodium species **A-IV**. Then, reductive elimination of C(sp^2)-Rh-O bond[25f] from **A-IV** produces the 2,5-dihydrooxepin (*S*,*R*)-**2** and regenerates the rhodium catalyst. The observed highly efficient chirality transfer is thus a consequence of the reversibility of the initial mechanistic steps and the influence of the substituent on a later step, putatively involving irreversible cleavage of the C-O bond. Finally, the 2,5-dihydrooxepins **2** undergo a subsequent stereospecific Claisen rearrangement to afford the VCPs (*R*,*R*,*R*)-**3**. In cycle II, metallacyclohexene intermediate **Int-C** could be derived from the cleavage of bond **a** in (*R*,*R*,*R*)-**3**, then it underwent *β*-H elimination and reductive elimination to afford product (*R*)-**4**. By contrast, in cycle III, **Int-E** could be originated from regioselective cleavage of the less substituted cyclopropane bond **b** in (*R*,*R*,*R*)-**3** owing to the steric effect. Then it was intercepted by an alkyne to generate **Int-F**. Finally, reductive elimination would afford the desired 5-7-5 tricyclic products and regenerate the rhodium (I) catalyst. It is noteworthy that the cleavage of the more substituted cyclopropane bond **a** is also possible. Compound **9r** and **9u** in Table 7 bearing phenyl group on R^2 gave **5r** and **5u** respectively as a single diastereomer, whereas substrate **9k** and **9j** in Table 6 with methyl group on R^2 afforded the desired product (**5k** and **5j**) and the

regioisomer (**10k** and **10j**), respectively. Based on the above experiments and eq 1, we believe that the cleavage of the cyclopropane bond **a** or **b** is a reversible process. Although the exact reason for the regioselective C-C cleavage remains unclear at this stage, both the another alkyne ($YCH_2C{\equiv}CR^2$) in **9** and the steric hindrance of the cyclopropane moiety play a central role on the regioselectvity of the current reaction.[8d-e]

Scheme 6. Proposed Mechanism



3. CONCLUSION

In summary, relying upon a new synthetic application of a vinyl oxirane as a heteroatom-containing five-atom component in Rh(I)-catalyzed cycloaddition reactions, four catalytic systems were developed: hetero-[5+2] cycloaddition, hetero-[5+2] cycloaddition/Claisen rearrangement reaction and hetero-[5+2] cycloaddition/Claisen rearrangement/cyclopropane ring opening reaction of vinylic oxiranes with mono-alkynes leading to multifunctional seven-, three- and five membered rings respectively; hetero-[5+2] cycloaddition/Claisen rearrangement/[5+2] cycloaddition reaction of vinyl oxirane-diynes for the construction of the linearly fused 5-7-5 tricyclic skeletons in a step-, atom-economical fashion from readily available starting materials has also been demonstrated. In most cases, the catalyst $[Rh(NBD)_2]^+BF_4^-$ is more efficient than the previous catalyst RhCl(IPr)(COD)/$AgSbF_6$. All the reactions were highly regioselective and diastereoselective, affording the corresponding product under mild conditions over a broad range of substrates with excellent functional group tolerance. In addition, the complete chirality transfer was observed for all the above reactions. Functionalization of the products and mechanistic consideration have also been investigated. Of note, the well-designed tandem reactions to form four structurally diverse products from a common vinyl oxirane-alkyne precursor give rapid access of molecular diversity.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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