Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition reactions of 1-ene-, 1-yne- and 1-allene-vinylcyclopropanes†

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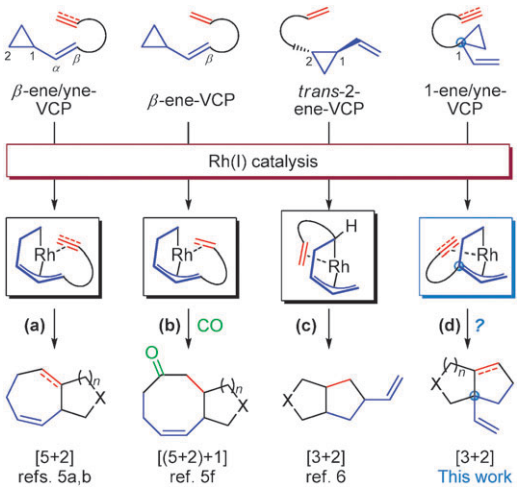
New Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition reactions of 1-ene-, 1-yne and 1-allene-vinylcyclopropanes have been developed, affording an efficient and versatile synthesis of cyclopentane- and cyclopentene-embedded bicyclic structures.

A five-membered carbocycle is an ubiquitous skeleton in organic molecules. Due to this, developing methods to synthesize five-membered carbocycles has been intensively pursued by the synthetic community.[1] To this end, many powerful synthetic methodologies have been developed (*e.g.*, the Pauson–Khand reaction,[2] the Nazarov cyclization,[3] and various [3 + 2] cycloadditions[4]). Nevertheless, even with these marvellous reactions in hand, discovering new reactions for the construction of five-membered carbocycles, especially five-membered-ring-embedded polycyclic structures, is still highly in demand.

One straightforward but challenging way was to develop new intramolecular [3 + 2] cycloadditions between unique three-carbon and two-carbon components. Vinylcyclopropane (VCP) was reported as a good intramolecular cycloaddition participant.[1c] VCP substrates bearing an olefin or alkyne functionality at the C(β)-position (named as β-ene/yne-VCP) were employed in various transition-metal catalyzed [5 + *x*] cycloadditions, where VCP moiety acts as a five-carbon component (Scheme 1, pathways a and b).[5] Recently, we discovered that *trans*-2-ene-VCP could participate in the intramolecular [3 + 2] cycloaddition, rendering the first example that VCP serves as an unconventional three-carbon component in Rh(I)-catalyzed cycloadditions (Scheme 1, pathway c).[6] However, this [3 + 2] cycloaddition suffers from the limitations that only 5,5-bicyclic skeleton could be generated, carbon-tethered substrates were not tolerated, the alkyne as the 2π-component was not compatible and the quaternary carbon center could not be established at the bridgehead.[6] Based on the knowledge that these VCP-participating cycloadditions proceeded *via* a π-allyl rhodacyclohexene intermediate (Scheme 1, intermediates in the boxes),[7] we hypothesized to derive a new type of substrate, 1-ene/yne-VCP, by tethering the 2π component to the C(1)-position of VCP to achieve the rhodacyclohexene intermediate with a new substitution pattern. We envisioned that this new intermediate could lead to a novel [3 + 2] cycloaddition mode (Scheme 1, pathway d)



Scheme 1 Reaction modes of ene/yne-VCPs under Rh(I)-catalysis and a new reaction design.

and may overcome the limitations associated with the previous [3 + 2] reaction. More attractive was that the designed [3 + 2] cycloaddition could install an all-carbon quaternary stereocenter at the bridgehead carbon of the cycloadduct. Herein, we wish to report our endeavours towards the development of this new Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition reaction.

Our test of the new design started with the tosylamide-tethered 1-ene-VCP substrate **1**. The first run was conducted under the Wender [5 + 2] cycloaddition conditions ($[Rh(CO)_2Cl]_2$ as the catalyst, toluene as the solvent, a reaction temperature of 110 °C).[5b] To our delight, the proposed bicyclic [3 + 2] cycloadduct **2** was generated as a single diastereomer, albeit accompanied by a minor amount of β-hydride elimination byproduct **3** (Table 1, entry 1). This result indicates that our designed process is operative and thus opens up a new reaction type of VCP derivatives.

With the above encouraging results, we then concentrated our efforts on finding the optimal reaction conditions that can selectively produce the [3 + 2] cycloadduct **2**. Several cationic Rh(I) catalysts proved ineffective for promoting this [3 + 2] process (Table 1, entries 2 to 4). We observed that cationic Rh(I)-bidentate phosphine complexes[8] could suppress the undesired β-hydride elimination pathway (Table 1, entries 5–7). Among them, $[Rh(dppp)]SbF_6$ gave the best selectivity (40 : 1) and the highest reaction yield (93%). Therefore, we chose this optimal reaction condition (Table 1, entry 6) to further study the scope of the [3 + 2] cycloaddition.

Various 1-ene/yne-VCP substrates were submitted to the optimized reaction conditions (Table 2). It was found that the

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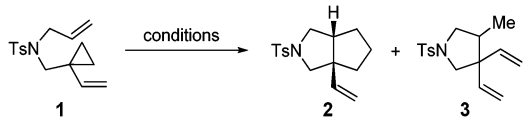
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds. See DOI: 10.1039/b922417c

Table 1 Optimization studies on the new [3 + 2] cycloaddition[a]



Entry	Catalyst	T/°C	Time	Ratio **2**:**3**[b]	Yield (%)[c]
1	$[Rh(CO)_2Cl]_2$	110[d]	4.5 h	4:1	57
2	$[Rh(PPh_3)_3]OTf$[e]	110[d]	3 h	—[f]	—[f]
3	$[Rh(CO)_2]SbF_6$[e]	80	1 h	1:1	15
4	[Rh(NBD)]SbF_6[e]	80	2 h	5:1	38
5	[Rh(dppe)]SbF_6[e]	80	2 h	15:1	93
6	[Rh(dppp)]SbF_6[e]	80	2 h	40:1	93
7	[Rh(dppb)]SbF_6[e]	80	2.5 h	8:1	88

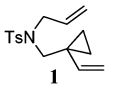
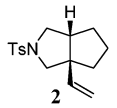
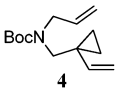
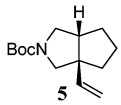
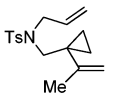
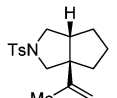
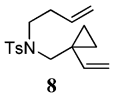
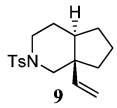
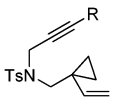
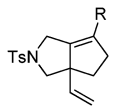
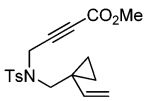
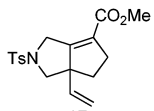
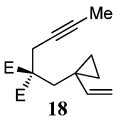
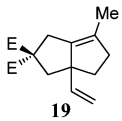
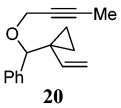
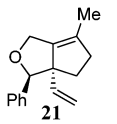
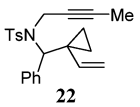
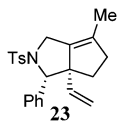
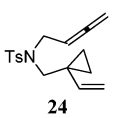
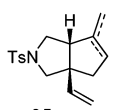
[a] Reaction conditions: 5 mol% Rh(I) catalyst, anhydrous dichloroethane (DCE) as solvent (substrate concentration 0.05 M), argon atmosphere. [b] Determined by ^{1}H NMR. [c] Combined isolated yield of inseparable product mixture of **2** and **3**. [d] Toluene as solvent. [e] See ESI† for experimental details. [f] No [3 + 2] cycloadduct **2** was generated.

yields were generally moderate to excellent and no β-hydride elimination byproduct was observed. Nitrogen-, oxygen- and *gem*-diester-tethered substrates could be employed to construct hetero- and carbo-bicyclic skeletons. In addition to a tosyl group, this [3 + 2] reaction also tolerates a *N*-Boc protecting group (entry 2). For 1-ene-VCPs, the formation of a 5,5-bicyclic skeleton favors a *cis* ring-fusion (entries 1–3); while the formation of a 6,5-ring system prefers a *trans* ring-fusion (entry 4). Except for 1-ene-VCPs, both terminal and internal 1-yne-VCPs serve as good substrates, giving rise to the corresponding [3 + 2] cycloadducts in good yields (entries 5–11). Two 1-yne-VCPs with a stereocenter neighbouring C(1), **20** and **22**, were tested to examine the stereoinduction in this new [3 + 2] cycloaddition process (entries 10 and 11). A good level of stereoinduction was achieved, albeit the stereochemical outcomes of oxygen-tethered 1-yne-VCP **20** and tosylamide-tethered substrate **22** are opposite (cycloadduct **21** *versus* **23**). This [3 + 2] reaction can also be extended to 1-allene-substituted VCP (entry 12). Under the optimized conditions, 1-allene-VCP **24** produced a mixture of cycloadducts **25a** and **25b** with *exo* and *endo* C=C bond, respectively. An identical reaction using $[Rh(CO)_2Cl]_2$ as the catalyst afforded **25a** as the major product.

The 1-ene-VCP substrates **26** and **28** bearing a disubstituted ene-moiety were also tested to further explore the substrate scope (Scheme 2). Under the standard conditions, the reaction of **26** gave no desired [3 + 2] cycloadduct but a monocyclic byproduct **27**, which is assumed to be generated *via* β-hydride elimination on the methyl group. The reaction of **28** to construct a bicyclic structure with two quaternary bridgehead carbons was feasible, but the reaction was sluggish and only a minor amount of the desired cycloadduct **29** was obtained.

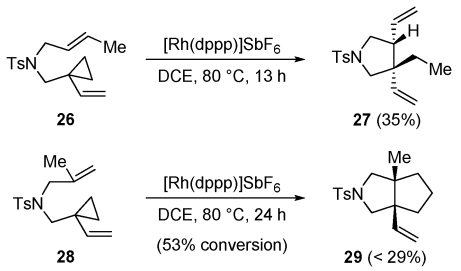
Control experiments were conducted by submitting ene-cyclopropane **1a** and yne-cyclopropane **1b** to the cycloaddition reaction to probe the mechanism of this [3 + 2] cycloaddition. It was found that under identical reaction conditions, no corresponding [3 + 2] cycloadduct was observed and both substrates remained intact (Scheme 3). This result clearly identified the crucial function of the vinyl group in this transformation.

Table 2 Rh(I)-catalyzed [3 + 2] cycloaddition reactions[a]

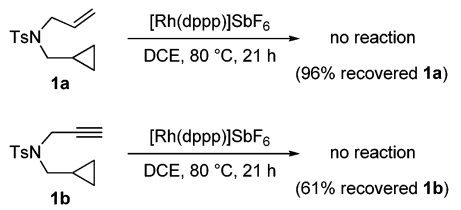
Entry	Substrate	Cycloadduct[b]	Conditions	Yield[c]
1	 **1**	 **2**	80 °C, 2 h	93%
2	 **4**	 **5**	80 °C, 13 h	66%
3	 **6**	 **7**	90 °C, 3.5 h	53%
4	 **8**	 **9**	80 °C, 12 h	98%
				
5	**10** R = H	**11**	80 °C, 5 h	82%
6	**12** R = Me	**13**	80 °C, 23 h	78%
7	**14** R = *i*-Pr	**15**	80 °C, 48 h	35%[d]
8	 **16**	 **17**	80 °C, 13 h	66%
9	 **18**	 **19**	80 °C, 39 h	59%
10	 **20**	 **21**	80 °C, 11.5 h	74% dr 19:1[e]
11	 **22**	 **23**	80 °C, 5 h	>99% dr 6:1[e]
12	 **24**	 **25a** *exo* **25b** *endo*	80 °C, 13 h 110 °C, 2 h[f]	48% a:b 3.6:1[e] 41% a:b 10:1[e]

[a] Reaction conditions: 5 mol% [Rh(dppp)]SbF_6 as catalyst, DCE as solvent, unless otherwise indicated. Ts = tosyl, Boc = *tert*-butoxycarbonyl, Ph = phenyl, E = COOMe. [b] The cycloadducts were obtained as racemic compounds. [c] Isolated yields after column chromatography. [d] Recovered 32% of **14**. [e] Determined by ^{1}H NMR. [f] Use 4 mol% $[Rh(CO)_2Cl]_2$ as catalyst, toluene as solvent.

A proposed mechanism of this [3 + 2] process was shown in Fig. 1. The catalytic cycle commences on the binding of the cationic catalytic species $Rh(dppp)^+$ to the alkene moiety of VCP to give intermediate **A**, followed by cyclopropane ring



Scheme 2 Further exploration of the substrate scope.



Scheme 3 Control experiments.

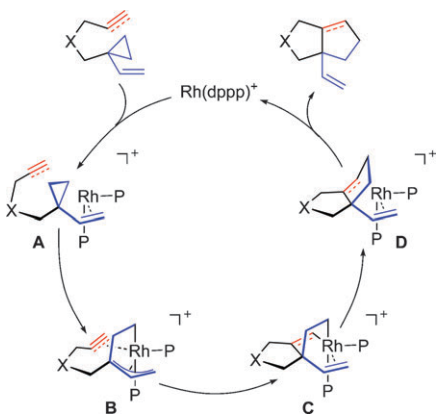


Fig. 1 Plausible catalytic cycle of the [3 + 2] reaction.

cleavage to generate the key π-allyl rhodacyclo-hexene intermediate **B**.[7] Then insertion of a C=C or C≡C bond to the C(1)–Rh bond occurs to form the intermediate **C**, which undergoes reductive elimination to furnish the bicyclic [3 + 2] cycloadduct, with the concomitant generation of the catalytic species for the next catalytic cycle. A minor amount of the observed byproduct **3** is probably generated through *β*-hydride elimination of intermediate **C**. In the reaction process, the vinyl group plays an important role as a "spectator" binding group to facilitate the ring-opening of a cyclopropane ring, well explaining the lack of activity for ene/yne-cyclopropanes.

In conclusion, we have developed a new type of Rh(I)-catalyzed intramolecular [3 + 2] cycloaddition of 1-ene-, 1-yne- and 1-allene-VCP substrates. The experimental findings represent the second example where VCP serves as a three-carbon component in Rh(I)-catalyzed cycloadditions. The present methodology provides an efficient, versatile and diastereoselective approach to carbo- and hetero-bicyclic compounds. The formation of a vinyl substituted quaternary stereocenter in this process enables further access to functionalized quaternary-stereocenter-containing cycloadducts. Further studies on the reaction mechanism, origins of the stereoinduction and the application of these cycloaddition reactions are ongoing.

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