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

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Received (in College Park, MD, USA) 26th October 2009, Accepted 18th November 2009 First published as an Advance Article on the web 14th December 2009 DOI: 10.1039/b922417c

New Rh(1)-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 fivemembered 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] cycloadditions⁴). 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)



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(1)-catalyzed intramolecular [3 + 2] cycloaddition reaction.

Our test of the new design started with the tosylamidetethered 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(1) catalysts proved ineffective for promoting this [3 + 2] process (Table 1, entries 2 to 4). We observed that cationic Rh(1)-bidentate phosphine complexes⁸ could suppress the undesired β -hydride elimination pathway (Table 1, entries 5–7). Among them, [Rh(dppp)]SbF₆ 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 1Optimization studies on the new [3 + 2] cycloaddition^a



^{*a*} Reaction conditions: 5 mol% Rh(1) catalyst, anhydrous dichloroethane (DCE) as solvent (substrate concentration 0.05 M), argon atmosphere. ^{*b*} Determined by ¹H 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-, oxygenand 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 enecyclopropane **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

Table 2	Rh(1)-catalyzed [3 +	21 cycloaddition	reactions ^a
I abic L	Itin(i) catalyzed [.	5	2 cycloadantion	reactions

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

^{*a*} Reaction conditions: 5 mol% [Rh(dppp)]SbF₆ 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 ¹H NMR. ^{*f*} Use 4 mol% [Rh(CO)₂Cl]₂ as catalyst, toluene as solvent.

identified the crucial function of the vinyl group in this transformation.

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.





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(1)-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.

We thank Peking University, the Natural Science Foundation of China (20825205-National Science Fund for Distinguished Young Scholars and 20672005) and the Ministry of Education of China (108001) for financial support.

Notes and references

- (a) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, 96, 49;
 (b) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, 103, 1151;
 (c) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, 107, 3117.
- 2 J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez and J. Perez-Castells, *Chem. Soc. Rev.*, 2004, **33**, 32.
- 3 (a) C. Santelli-Rouvier and M. Santelli, *Synthesis*, 1983, 429; (b) H. Pellissier, *Tetrahedron*, 2005, **61**, 6479.
- 4 Selected recent reports on [3 + 2] cycloadditions: (a) J. E. Wilson and G. C. Fu, Angew. Chem., Int. Ed., 2006, 45, 1426; (b) M. Gulías, R. García, A. Delgado, L. Castedo and J. L. Mascarenas, J. Am. Chem. Soc., 2006, 128, 384; (c) L. Liu and J. Montgomery, J. Am. Chem. Soc., 2006, 128, 5348; (d) S. Ogoshi, M. Nagata and H. Kurosawa, J. Am. Chem. Soc., 2006, 128, 5350; (e) B. M. Trost, J. P. Stambuli, S. M. Silverman and U. Schwörer, J. Am. Chem. Soc., 2006, 128, 13328; (f) P. A. Wender, T. J. Paxton and T. J. Williams, J. Am. Chem. Soc., 2006, 128, 14814; (g) H.-T. Chang, T. T. Jayanth and C.-H. Cheng, J. Am. Chem. Soc., 2007, 129, 4166; (h) X. Huang and L. Zhang, J. Am. Chem. Soc., 2007, 129, 6398; (i) T. Nishimura, Y. Yasuhara and T. Hayashi, J. Am. Chem. Soc., 2007, 129, 7506; (j) B. M. Trost, N. Cramer and S. Silverman, J. Am. Chem. Soc., 2007, 129, 12396; (k) S. S. Yudha, Y. Kuninobu and K. Takai, Angew. Chem., Int. Ed., 2008, 47, 9318.
- 5 For representative [5 + x] cycloadditions employing VCP as five-carbon unit, see: (a) P. A. Wender, H. Takahashi and B. Witulski, J. Am. Chem. Soc., 1995, 117, 4720; (b) P. A. Wender and D. Sperandio, J. Org. Chem., 1998, 63, 4164; (c) B. M. Trost, F. D. Toste and H. Shen, J. Am. Chem. Soc., 2000, 122, 2379; (d) P. A. Wender, G. G. Gamber, R. D. Hubbard and L. Zhang, J. Am. Chem. Soc., 2002, 124, 2876; (e) P. A. Wender, G. G. Gamber, R. D. Hubbard, S. M. Pham and L. Zhang, J. Am. Chem. Soc., 2005, 127, 2836; (f) Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender and Z.-X. Yu, J. Am. Chem. Soc., 2007, 129, 10060.
- 6 L. Jiao, S. Ye and Z.-X. Yu, J. Am. Chem. Soc., 2008, 130, 7178.
- 7 Z.-X. Yu, P. A. Wender and K. N. Houk, J. Am. Chem. Soc., 2004, 126, 9154.
- 8 Cationic Rh(I)-phosphine complexes were employed as efficient catalysts in intramolecular cycloaddition reactions, see: B. Wang, P. Cao and X. Zhang, *Tetrahedron Lett.*, 2000, 41, 8041.