ORGANIC LETTERS

2010
Vol. 12, No. 11
2528−2531

Rh(I)-Catalyzed [(3 + 2) + 1] Cycloaddition of 1-Yne/Ene-vinylcyclopropanes and CO: Homologous Pauson−Khand Reaction and Total Synthesis of (±)-α-Agarofuran

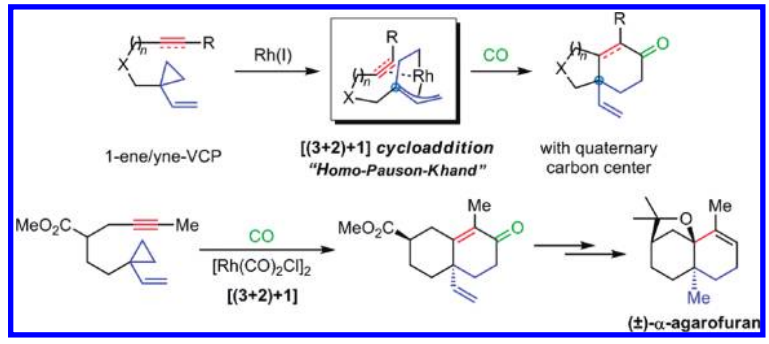
Lei Jiao, Mu Lin, Lian-Gang Zhuo, and Zhi-Xiang Yu*

Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering, College of Chemistry, Peking University, Beijing 100871, China

yuzx@pku.edu.cn

Received March 16, 2010

ABSTRACT



A novel Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition, which can be regarded as a homologous Pauson−Khand reaction, was developed to synthesize bicyclic cyclohexenones and cyclohexanones, enabling a new approach for synthesis of six-membered carbocycles ubiquitously found in natural products and pharmaceutics. The significance of the Rh-catalyzed [(3 + 2) + 1] cycloaddition has been demonstrated by the total synthesis of a furanoid sesquiterpene natural product, α-agarofuran, in which the bicyclic skeleton was constructed by the [(3 + 2) + 1] reaction of 1-yne-VCP and CO.

Six-membered rings are ubiquitous in organic molecules. Therefore, developing reactions to synthesize six-membered rings is one of the key endeavors in the science of synthesis. Today, the Diels−Alder reaction is arguably the most powerful method to construct six-membered rings.[1] However, developing new cycloaddition reactions[2] for the synthesis of six-membered rings is still in high demand due to the inquiries for functionalized six-membered rings that are impossible or very difficult to approach by existing methods. Herein we report a new Rh(I)-catalyzed [(3 + 2) + 1] reaction[3] of 1-yne/ene-vinylcyclopropanes (1-yne/ene-VCPs), a homologous Pauson−Khand reaction, to reach bicyclic cyclohexenone and cyclohexanone derivatives as a practical protocol in six-membered ring synthesis. We further demonstrate its potential application by using this reaction in the total synthesis of a furanoid sesquiterpene natural product, α-agarofuran.

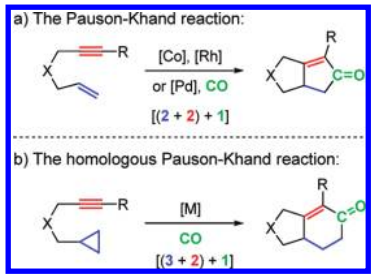
(1) Recent reviews on the Diels−Alder reaction: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (d) Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051. (e) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359. (f) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839. (g) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983.

(2) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

10.1021/ol100625e
Published on Web 05/13/2010

Our design of the [(3 + 2) + 1] reaction was inspired by the great success of the Pauson−Khand reaction, which is a powerful method to synthesize five-membered rings (cyclopentenone) using alkynes, alkenes, and CO, intramolecularly or intermolecularly (Scheme 1a).[4] This reaction has been widely

Scheme 1. (a) Pauson−Khand Reaction and (b) Designed Homologous Pauson−Khand Reaction



used in total syntheses of natural products. We envisioned that there is an opportunity to transform this Pauson−Khand [(2 + 2) + 1] cycloaddition to a homologous [(3 + 2) + 1] counterpart by replacing the alkene with a cyclopropane unit (Scheme 1b), which has been well documented as an equivalent of a 2-π component in many organic and organometallic reactions.[5] In principle, we regard this design as a homologous Pauson−Khand reaction. Narasaka and co-workers have previously reported the [(3 + 2) + 1] cycloaddition of yne-cyclopropanes (yne-CP), but unfortunately, the preliminary result was acquired under harsh conditions (reaction temperature 160 °C, 4 atm CO, >48 h) that inevitably led to side reactions and severely limited its synthetic utility (Scheme 2a).[6]

Previously we have reported that vinylcyclopropane can act as a three-carbon synthon to achieve intramolecular [3 + 2] cycloadditions.[7] The vinyl group was found to act as an activating group that facilitates the ring opening of cyclopropane under much milder conditions.[7,8] We hope to apply this activation strategy[9] to the development of a synthetically practical [(3 + 2) + 1] process using 1-yne-VCP as the potential substrate (Scheme 2b).

Our test of the above design started with the vinylcyclopropane substrate **1** with a terminal alkyne substitution. We first

(3) We suggest here a new nomenclature for the two-component cycloaddition of an ene/yne-VCP substrate and CO. It is referred to as [(3 + 2) + 1] cycloaddition, where the "3 + 2" part comes from one molecule, the "1" part comes from another molecule.

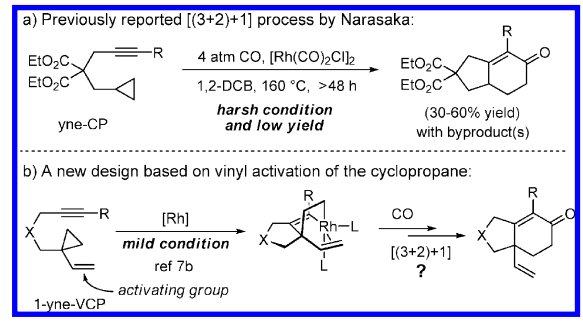
(4) Selected reviews on the Pauson−Khand reaction: (a) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297. (b) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (c) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800. (d) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328.

(5) Selected recent reports on cyclopropane participating cycloaddition reactions: (a) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918. (b) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 1107. (c) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. (d) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642. (e) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689. (f) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.

(6) Koga, Y.; Narasaka, K. *Chem. Lett.* **1999**, *7*, 705.

(7) (a) Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 7178. (b) Jiao, L.; Lin, M.; Yu, Z.-X. *Chem. Commun.* **2010**, *46*, 1059. (c) Li, Q.; Jiang, G.-J.; Jiao, L.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 1332.

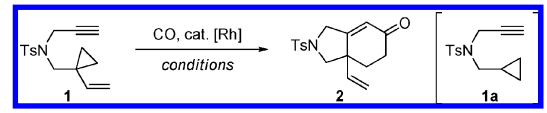
Scheme 2. (a) Previously Reported Prototype [(3 + 2) + 1] Reaction and (b) New Activation Strategy[a]



[a] 1,2-DCB = 1,2-dichlorobenzene.

applied the previous [3 + 2] reaction conditions,[7b] together with a low pressure of CO (Table 1, entry 1). Gratifyingly, we

Table 1. Reaction Conditions for the [(3 + 2) + 1] Cycloaddition[a]



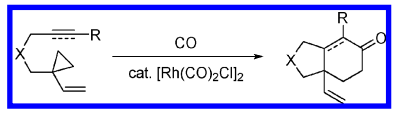
entry	catalyst	CO (atm)	solvent[b]	temp (°C)	time (h)	yield (%)[c]
1	[Rh(dppp)]SbF_6	0.2	DCE	80	8	25[d]
2	$[Rh(CO)_2Cl]_2$	0.2	dioxane	80	4	64
3	$[Rh(CO)_2Cl]_2$	0.2	toluene	80	1.5	81
4	$[Rh(CO)_2Cl]_2$	1	toluene	80	6	39
5	$[Rh(CO)_2Cl]_2$	0.2	toluene	70	4	78

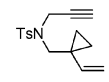
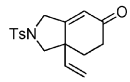
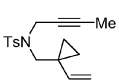
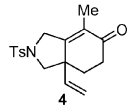
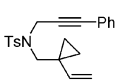
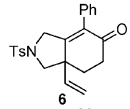
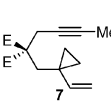
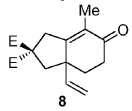
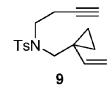
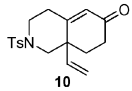
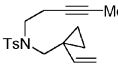
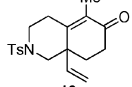
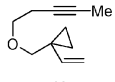
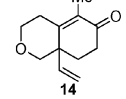
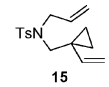
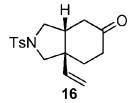
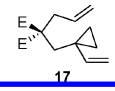
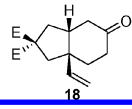
[a] Conditions: 5 mol % of the catalyst, substrate concentration 0.05 M. [b] DCE = 1,2-dichloroethane. [c] Isolated yield after column chromatography. [d] Together with a 59% yield of the [3 + 2] cycloadduct.[7b]

observed the formation of 25% of the bicyclic cyclohexenone cycloadduct **2**, albeit the major part of 1-yne-VCP **1** underwent the [3 + 2] cycloaddition.[7b] We then tested the reaction conditions for the [(5 + 2) + 1] cycloaddition[10] ($[Rh(CO)_2Cl]_2$ as catalyst, employing 0.2 atm CO + 0.8 atm N_2[11]). To our delight, the [(3 + 2) + 1] cycloadduct **2** was obtained in a greatly improved yield (Table 1, entry 2). Toluene was found to be an optimal solvent, giving rise to an 81% yield of **2**. Higher CO pressure (1 atm) and decreased temperature (70 °C) were both found to diminish the efficiency of the reaction (Table 1, entries 4 and 5). A control experiment employing yne-cyclopropane **1a** was also conducted under optimal conditions (Table 1). We found that no corresponding [(3 + 2) + 1] cycloadduct was generated under such mild conditions. This indicated that the vinyl unit is crucial for the observed reactivity of cyclopropane. Thus, by introducing a vinyl group to the cyclopropane unit, we successfully achieved the [(3 + 2) + 1] process under much more operable and milder conditions, which greatly improved its synthetic utility as compared with the previous method.

Various 1-yne-VCP substrates were submitted to the optimized reaction conditions to explore the scope and limitation of this homologous Pauson−Khand reaction (Table 2). It was found that both terminal and internal alkynes were compatible to afford bicyclic cyclohexenone cycloadducts, and the alkyne substitution could be either an alkyl (entries 2, 4, 6, and 7) or phenyl (entry 3) group. The tether length could allow the formation of 5,6- (entries 1−4) and 6,6-bicyclic systems (entries 5−7), and a variety of tethers (nitrogen-, oxygen-, and *gem*-diester) could be employed to construct hetero- and carbobicyclic skeletons. The reaction yields were generally good to excellent, well demonstrating the efficiency and synthetic potential of this [(3 + 2) + 1] process. The products of this homo-Pauson−Khand reaction possess a functionalized six-membered ring bearing an α,β-unsaturated ketone functional group and a vinyl-substituted quarternary carbon, which will provide access to further functionalization and operation.

Table 2. Rh(I)-Catalyzed [(3 + 2) + 1] Cycloaddition Reactions[a]



entry	substrate	cycloadduct[b]	conditions	yield[c]
1	 1	 2	80 °C, 1.5 h	81%
2	 3	 4	80 °C, 7 h[d]	85%
3	 5	 6	80 °C, 1 h	89%
4	 7	 8	80 °C, 3 h[d]	60%
5	 9	 10	70 °C, 2 h	92%
6	 11	 12	80 °C, 12 h	78%
7	 13	 14	80 °C, 5 h	68%
8	 15	 16	80 °C, 168 h[e]	50%[f]
9	 17	 18	80 °C, 18 h[e]	70%

[a] Reaction conditions: 5 mol % $[Rh(CO)_2Cl]_2$ as catalyst, 0.2 atm CO, toluene as solvent, substrate concentration 0.05 M, unless otherwise indicated. Ts = tosyl, Ph = phenyl, E = COOMe. [b] The cycloadducts were obtained as racemic compounds. [c] Isolated yields after column chromatography. [d] 1 atm CO was used. [e] 1,4-Dioxane as solvent. [f] Together with 19% yield of the [3 + 2] cycloadduct.[7b]

We also wondered whether this vinyl activation strategy is potent enough to promote the cycloaddition between an olefin, cyclopropane, and CO, which was never achieved before. For this purpose, the reactions of 1-ene-VCP substrates **15** and **17** were conducted (entries 8 and 9). To our delight, these reactions proceeded smoothly to give *cis*-fused bicyclic cyclohexanone products in moderate yields.[12] This further showcases the success of the vinyl activation protocol for promoting the cyclopropane-participating cycloaddition reactions.

The results represent the first synthetically practical homo-Pauson−Khand reaction under mild and easy-to-operate conditions to synthesize multifunctional bicyclic cyclohexenones and cyclohexanones. We hope to demonstrate its synthetic potential further by using this reaction as a key step in natural product synthesis. Our attention was drawn to the unique tricyclic structure of the furanoid sesquiterpene natural products.[13] It was envisioned that, the tricyclic core of agarofuran could be constructed from a 6,6-bicyclic structure, which is easily accessible by our homo-Pauson−Khand approach (Figure 1).

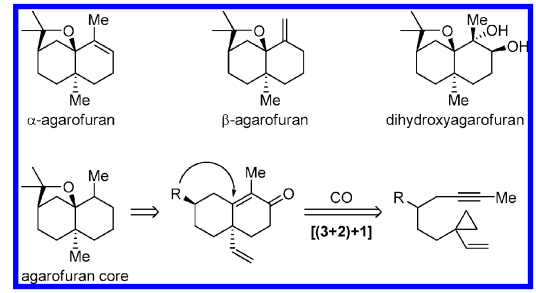
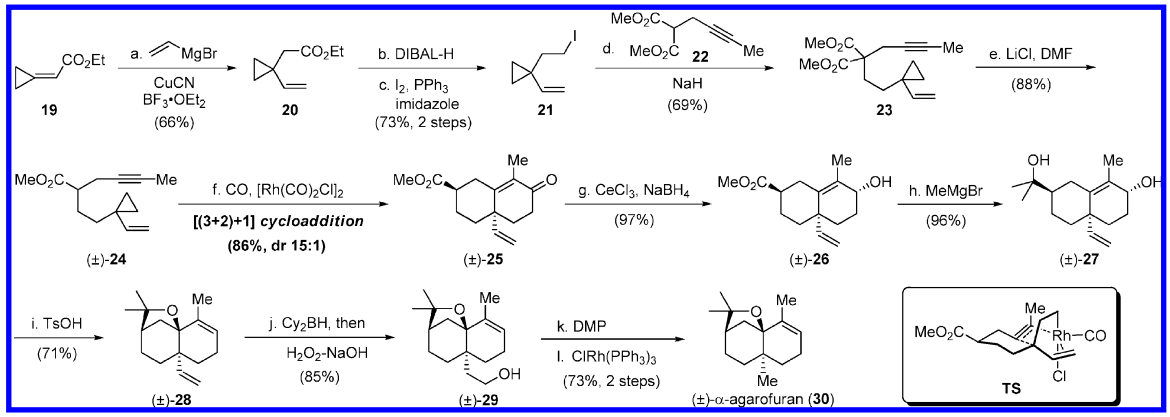


Figure 1. Agarofuran sesquiterpene natural products and retrosynthetic analysis utilizing the [(3 + 2) + 1] reaction.

We selected α-agarofuran as our target molecule, and the detailed synthetic route is depicted in Scheme 3. Starting from the known cyclopropylidene ester **19**,[14] we prepared vinylcyclopropane iodide **21** using traditional transformations. Then compound **21** was coupled with propargyl diester **22** to give the *gem*-diester-tethered 1-yne-VCP **23**. Krapcho decarboxylation[15] afforded monoester-substituted 1-yne-VCP **24**, which serves as the definitive cycloaddition precursor for our homo-Pauson−Khand reaction. Gratifyingly, the key [(3 + 2) + 1] reaction proceeded very well under the previously optimized conditions, affording bicyclic cyclohexenone **25** in 86% isolated yield with a good diastereoselectivity (*trans*:*cis* 15:1, the structure of **25** was confirmed by X-ray crystal analysis of its 2,4-dinitrophenylhydrazone derivative, see the Supporting Information).[16] The observed *trans* selectivity could be rationalized by a postulated alkyne insertion transition state **TS** (Scheme 3). This alkyne insertion transition state is expected to adopt a chair conformation and has its ester and vinyl groups, both of

Scheme 3. Total Synthesis of (±)-α-Agarofuran[a]



[a] DIBAL-H = diisobutylaluminum hydride, DMF = dimethylformamide, DMP = Dess−Martin periodinane.

which are in the equatorial positions, in a *trans* configuration. This single reaction established the basic skeleton of agarofuran efficiently, with the correct placement of a quaternary stereocenter and an enone moiety for further elaboration. The key intermediate **25** was converted to allylic alcohol **26** by Luche reduction, and then the 2-hydroxyisopropyl unit was installed by reaction with methylmagnesium bromide.[17] Acid-catalyzed intramolecular S_N2' reaction of diol **27** constructed the tetrahydrofuran framework of agaroguran,[18] affording compound **28**. Finally, the vinyl unit was converted to the angular methyl group by a hydroboration−oxidation−decarbonylation sequence, completing the synthesis of (±)-α-agarofuran **30**.[19] The homo-Pauson−Khand [(3 + 2) + 1] reaction is the crucial step in the synthesis, which allowed the concomitant generation of the enone functional group and a quaternary carbon stereocenter diastereoselectively. The enone functional group was well utilized in the subsequent structure-building steps, nicely showcasing the synthetic utility of the [(3 + 2) + 1] process.

In conclusion, we have developed a new type of Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition of 1-yne/ene-vinylcyclopropanes and CO using the vinyl activation strategy. The reaction features the use of both alkynes and alkenes as two-carbon synthons, efficient production of multifunctional bicyclic cyclohexenone and cyclohexanone derivatives, and mild reaction conditions. These discoveries represent the first synthetically practical homo-Pauson−Khand-type [(3 + 2) + 1] cycloaddition utilizing VCP as a three-carbon component. The formation of a vinyl-substituted quaternary stereocenter and the carbonyl functional group in this process enables further access to more complex structures, as demonstrated by the synthesis of α-agarofuran.

Acknowledgment. We thank the Natural Science Foundation of China (20825205-National Science Fund for Distinguished Young Scholars, and 20672005), the Ministry of Education of China (108001), and the National Basic Research Program of China-973 Program (2010CB833203) for financial support.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The vinyl group activation strategy was also demonstrated by Wender's group in [2 + 2+ 1] cycloaddition reactions; see: (a) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 5948. (b) Wender, P. A.; Deschamps, N. M.; Williams, T. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3076. (c) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2459. (d) Pitcock Jr, W. H.; Lord, R. L.; Baik, M.-H. *J. Am. Chem. Soc.* **2008**, *130*, 5821. For a review, see: (e) Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, 19.

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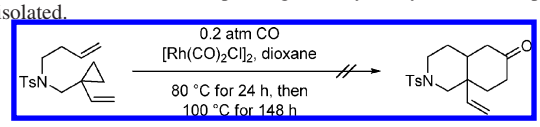
(11) $[Rh(CO)_2Cl]_2$-catalyzed Pauson−Khand reaction was also found to be optimal under low CO pressure, see: Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73.

(12) We also attempted the [(3 + 2) + 1] reaction of a 1-ene-VCP substrate with elongated tether. Unfortunetely, the reaction afforded a complex mixture, and no corresponding 6,6-bicyclic cyclohexanone product was isolated.



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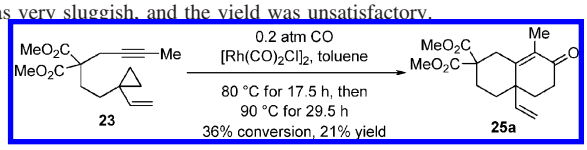
(16) The [(3 + 2) + 1] cycloaddition of *gem*-diester-tethered substrate **23** was also conducted under identical conditions. However, the reaction was very sluggish, and the yield was unsatisfactory.



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