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Reaction of α-Ene-Vinylcyclopropanes: Type II Intramolecular [5+2] Cycloaddition or [3+2] Cycloaddition?

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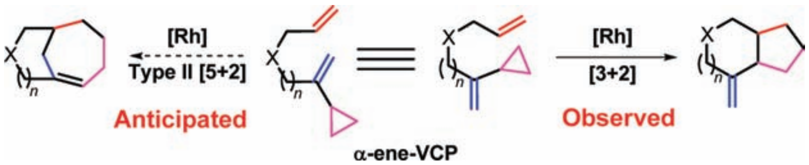
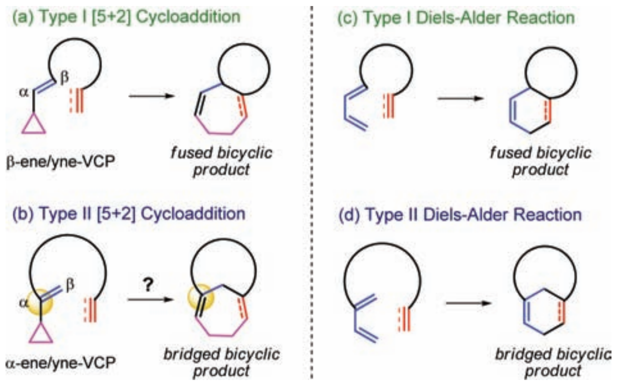
ABSTRACT



Exposure of α-ene-VCPs to catalytic [Rh(dppm)]SbF_6 led to the discovery of a novel Rh(I)-catalyzed [3+2] reaction, which was shown to be efficient for the construction of 5/6- and 5/7-bicyclic compounds rather than the anticipated type II [5+2] products.

Transition metal-catalyzed cycloadditions provide efficient tools for the synthesis of complex molecules from simple starting acyclic materials. In particular, they provide access to medium-sized ring systems, which are difficult to achieve by alternative approaches, such as intramolecular substitution reactions. Impressive examples in this field are the transition metal-catalyzed [5+2] cycloadditions, pioneered by Wender and co-workers.[1] Both inter- and intramolecular [5+2] reactions have been developed and have great potential in synthesis. For instance, the intramolecular [5+2] cycloadditions of β-ene/yne-vinylcyclopropanes (β-ene/yne-VCPs) enable rapid access to 5/7- and 6/7-bicyclic systems (Scheme 1, reaction a) and have had a significant impact on synthetic endeavors.[2]

Scheme 1. Type I and II [5+2] and Diels−Alder Reactions



Inspired by type I and type II Diels−Alder reactions,[3] which form fused and bridged bicyclic six-membered-ring

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[1] [5+2] cycloadditions of VCPs: (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940. (c) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348. (d) Wender, P. A.; Williams, T. *Angew. Chem., Int. Ed.* **2001**, *41*, 4550. (e) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379. (f) Trost, B. M.; Shen, H. C.; Horne, D. B.; Toste, F. D.; Steinmetz, B. G.; Koradin, C. *Chem.—Eur. J.* **2005**, *11*, 2577. (g) Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5798. (h) Fürstner, A.; Majima, K.; Martín, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

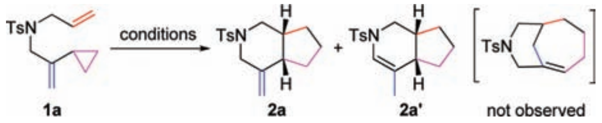
[2] Total synthesis :(a) Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137. (b) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323. (c) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105. (d) Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781. (e) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2007**, *129*, 14556. (f) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424. (g) Ashfeld, B. L.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4535.

10.1021/ol100237h

systems, respectively (Scheme 1, reactions c and d), we wondered whether a type II [5+2] cycloaddition could be realized from a new type of substrate, an α-ene-VCP (Scheme 1, reaction b). Here we name the original Wender [5+2] reaction of *β*-ene/yne-VCPs as the type I [5+2] reaction, by analogy to type I and type II Diels−Alder reactions. If the proposed type II [5+2] reaction succeeded, it would provide a direct way to construct bridged cycloheptane bicycles, which are found in a variety of natural products such as cyclocitvinol.[4]

We began our investigation by exploring the reaction of α-ene-VCP substrate **1a** with a variety of Rh catalysts. Interestingly, both neutral [Rh(CO)$_2$Cl]$_2$ and cationic [Rh(CO)$_2$]SbF$_6$ failed to promote the desired cycloaddition (Table 1, entries 1 and 2). We then employed a cationic rhodium−bidentate phosphine complex as the catalyst, generated in situ by treating [Rh(CO)$_2$Cl]$_2$ with AgSbF$_6$ and the dppm ligand. Interestingly, we obtained a bicyclo[4.3.0]nonane cycloadduct **2a** as the major product, together with an isomerization product **2a′** (Table 1, entry 3). Here the vinylcyclopropane was participating in a [3+2] cycloaddition rather than the expected [5+2] pathway. This is the third example of an unactivated vinylcyclopropane acting as a three-carbon synthon instead of a five-carbon synthon.[5,6] We then screened various ligands to see whether the reaction could be tuned to produce the type II [5+2] product or improve the yield of the [3+2] cycloadduct. When diphosphine ligands with longer tethers were used, the reaction became messy (entries 4−6). For example, employing [Rh(dppb)]SbF$_6$ as the catalyst led to a complex mixture. More bulky and more electron-rich ligands also failed to give improved results (entries 7−9). We then turned back to using dppm as the ligand and optimized other reaction parameters. To our delight, when 4 Å molecular sieves (MS) were used as an additive in this reaction system, cycloadduct **2a** was obtained in 94% isolated yield without contamination of the isomerization product (entry 10). Presumably, 4 Å MS functioned as a water scavenger to prevent the generation of acid, which was responsible for the alkene isomerization. The structure of product **2a** was unambiguously determined by X-ray crystallography. Interestingly, none of the above conditions led to the anticipated [5+2] cycloadduct.

Table 1. Screening of the Reaction Conditions[a]

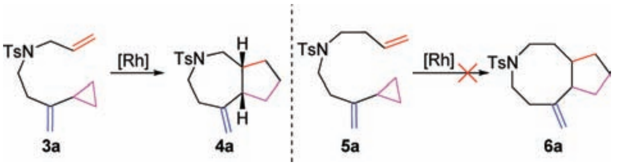


entry	catalyst	*t* (h)	additive	yield (**2a**, **2a′**)[b]
1	[Rh(CO)$_2$Cl]$_2$	24		<5%, <5%
2	[Rh(CO)$_2$]SbF$_6$[c]	24		<5%, <5%
3	[Rh(dppm)]SbF$_6$[d]	24		61%, 10%
4	[Rh(dppe)]SbF$_6$[d]	24		46%, 5%
5	[Rh(dppp)]SbF$_6$[d]	24		12%, <5%
6	[Rh(dppb)]SbF$_6$[d]	24		<5%, <5%[e]
7	[Rh(BINAP)]SbF$_6$[d]	24		<5%, <5%[e]
8	[Rh(dppf)]SbF$_6$[d]	24		–[f]
9	[Rh(dppCy)]SbF$_6$[d]	24		–[f]
10	[Rh(dppm)]SbF$_6$[d]	6	4 Å MS	94%, 0%

[a] Conditions: 5 mol % of Rh(I) catalyst, DCE as solvent (0.05 M), 85 °C. [b] Isolated yields after flash column chromatography. [c] Prepared by treatment of [Rh(CO)$_2$Cl]$_2$ with AgSbF$_6$. [d] Prepared by treatment of [Rh(CO)$_2$Cl]$_2$ with AgSbF$_6$ and corresponding bidentate phosphine ligand. [e] The substrate was consumed, but a complex mixture was obtained. [f] No reaction.

We hypothesized that the tether between the alkene and the VCP unit in α-ene-VCP **1a** might be too short for the type II [5+2] reaction. To test this hypothesis, substrates **3a** and **5a** with longer tethers were synthesized and subjected to the optimized conditions. Interestingly, the Rh(I)-catalyzed reaction of **3a** still gave a [3+2] cycloadduct bearing a 5/7-bicyclic skeleton, whereas for **5a**, neither a [5+2] nor a [3+2] reaction occurred (Scheme 2).

Scheme 2. Substrates with Longer Tethers



Considering the importance of the synthesis of five-membered carbocycles in chemistry, and the facts that bicyclo[4.3.0]nonane and bicyclo[5.3.0]decane skeletons are widely found in many biologically active natural products, we were excited to explore the versatility of the [3+2] cycloaddition. Especially, we expected that this [3+2] reaction would provide a new approach for the synthesis of

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(3) For a recent review, see: Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820.

(4) Sheikh, S. E.; Greffen, A. M.; Lex, J.; Neudörfl, J.; Schmalz, H.-G. *Synlett* **2007**, 1881.

(5) For representative [5+*x*] cycloadditions employing VCP as a five-carbon unit, see refs 1 and 2 and the following: Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10060.

(6) For Pd(0)-catalyzed nucleophilic-addition-type [3+2] cycloaddition between activated VCPs and electron-deficient alkenes, see: (a) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825. For free-radical-mediated [3+2] cycloaddition of activated VCPs and alkenes, see: (b) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091, and references cited therein. (c) Bertrand, M. P.; Nouguier, R.; Archavlis, A.; Carriere, A. *Synlett* **1994**, 736. (d) Jung, M. E.; Rayle, H. L. *J. Org. Chem.* **1997**, *62*, 4601. For Rh(I)-catalyzed [3+2] cycloaddition of unactivated VCPs and alkenes, see: (e) Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 7178. (f) Jiao, L.; Lin, M.; Yu, Z.-X *Chem. Commun.* **2010**, *46*, 1059. For Lewis acid-catalyzed [3+2] cycloaddition of activated vinylcyclopropanes, see: (g) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541.

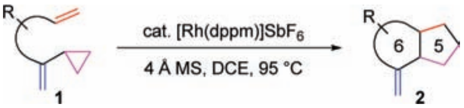
(7) Rare examples to construct 5/7 bicyclic system were the intramolecular Pauson−Khand reaction and the Pd-catalyzed [3+2] cycloaddition of methylenecyclopropanes. Moreover, specific substrates or activated multiple bonds were obligatory in these cases. See refs 8 and 9.

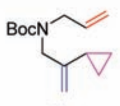
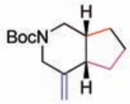
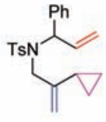
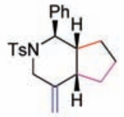
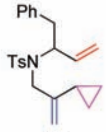
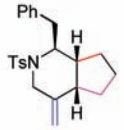
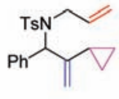
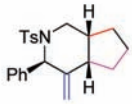
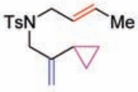
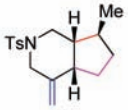
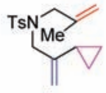
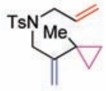
(8) (a) Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350. (b) Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1992**, *57*, 686. For a recent highlight of transition metal-catalyzed [3+2] cycloadditions to synthesize five-membered carbocycles, see: (c) Marquand, P. L.; Tam, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 2976.

the bicyclo[5.3.0]decane skeleton, which is a challenging problem in synthesis and can be accessed by only a limited number of methods.[7−9]

Exploration of the substrate scope was performed by using the optimal conditions (Table 2). To our delight, the *N*-Boc protected amine tether was also found to be compatible, affording a satisfactory yield of the bicyclic product **2b** (entry 1). To access substituted bicyclo[4.3.0]nonane products, a series of α-ene-VCP substitution patterns were tested. The [3+2] cycloaddition reaction tolerated both phenyl and alkyl substituents on the tether and in all cases excellent diastereoselectivity was observed (entries 2−4). Diastereomeric ratios of >19:1, together with moderate to good yields, were observed for cycloadducts **2c**, **2d**, and **2e**. Introduction of a methyl group to the terminal position of the ene part of the substrate was also tolerated, albeit in decreased yield (entry 5). Attempts to construct a bridgehead quaternary carbon failed: substitution on the internal carbon of the ene moiety or the C(1) of the VCP unit resulted in loss of reactivity (entries 6 and 7, **1g** and **1h**), which is likely due to increased steric repulsion.

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

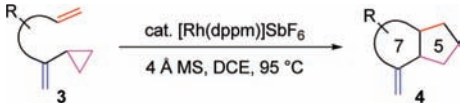


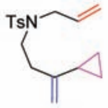
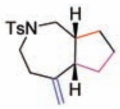
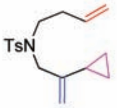
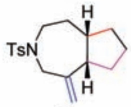
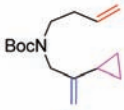
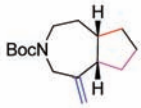
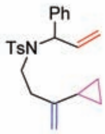
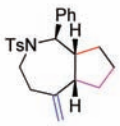
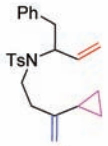
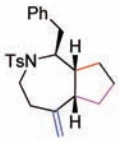
entry	substrate	time	yield	product
1	 **1b**	24 h	69%	 **2b**
2	 **1c**	36 h	88% dr > 19:1[b]	 **2c**
3	 **1d**	36 h	72% dr > 19:1[b]	 **2d**
4	 **1e**	40 h	30% (55%)[c] dr > 19:1[b]	 **2e**
5	 **1f**	48 h	25% (52%)[c]	 **2f**
6	 **1g**		*no reaction*[d]	
7	 **1h**		*no reaction*[d]	

[a] Conditions: 5 mol % of [Rh(dppm)]SbF$_6$, DCE as solvent (0.05 M), 95 °C, 4 Å MS. Isolated yields are reported. [b] Determined by ^{1}H NMR. [c] The number in parentheses is the yield based on recovered starting material. [d] No reaction occurred and the starting material remained intact.

Encouraged by our initial success in creating a 5/7 ring system, we made further efforts to generate seven-membered-ring-containing products (Table 3). Isomeric substrate **3b** gave a new cycloadduct (**4b**) in good yield (entry 2). Employing Boc as the nitrogen protecting group also worked well to generate product **4c** (entry 3). Introducing aryl and

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



entry	substrate	time	yield	product
1	 **3a**	10 h	91%	 **4a**
2	 **3b**	36 h	71% (79%)[b]	 **4b**
3	 **3c**	36 h	82%	 **4c**
4	 **3d**	60 h	56% (90%)[b] dr > 19:1[c]	 **4d**
5	 **3e**	20 h	90% dr > 19:1[c]	 **4e**[d]

[a] Conditions: 5 mol % of [Rh(dppm)]SbF$_6$, DCE as solvent (0.05 M), 95 °C, 4 Å MS. Isolated yields are reported. [b] The number in parentheses is the yield based on recovered starting material. [c] Determined by ^{1}H NMR. [d] The structure of cycloadduct **4e** was determined by X-ray crystallography.

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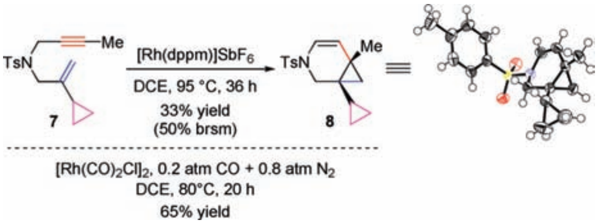
(9) (a) Inagaki, F.; Narita, S.; Hasegawa, T.; Kitagaki, S; Mukai, C. *Angew Chem., Int. Ed.* **2009**, *48*, 2007 and references cited therein. (b) Inagaki, F.; Mukai, C. *Org. Lett.* **2006**, *8*, 1217 and references cited therein. (c) Brummond, K. M.; Chen, D. *Org. Lett.* **2008**, *10*, 705, and references cited therein. (d) Brummond, K. M.; Chen, D.; Davis, M. M. *J. Org. Chem.* **2008**, *73*, 5064, and references cited therein.

alkyl substitutents at the allylic position of the olefin afforded excellent diastereoselectivity (dr >19:1), providing the bicyclic products **4d** and **4e** in good yields (entries 4 and 5). The results shown in Tables 2 and 3 demonstrate that the present [3+2] cycloaddition can construct both 5/6- and 5/7-bicyclic skeletons, a notable extension of VCP chemistry. Unfortunately, substrates containing a carbon or oxygen tether did not give the desired products (see the Supporting Information for details). This is in contrast to previously reported [3+2] reactions of 1-ene/yne/allene-VCPs, which can incorporate C, N, and O tethers.[6f]

We synthesized α-yne-VCP **7** to test whether an alkyne is also a good 2π component in the developed [3+2] cycloaddition (Scheme 3). Surprisingly, under the standard reaction conditions for α-ene-VCPs, no [3+2] cycloadduct was observed, but instead, cycloisomerization product **8** was obtained in low yield.[10] A higher yield of **8** was obtained when this reaction was carried out with [Rh(CO)$_2$Cl]$_2$ as the catalyst, under a low pressure of CO.

Scheme 3. Reaction of α-Yne-VCP **7**



In conclusion, a novel [3+2] cycloaddition to give cyclopentane-containing bicycles has been developed. The VCP moiety of the α-ene-VCP acts as a three-carbon synthon instead of as the initially anticipated five-carbon synthon.[6e,f,11] This unexpected [3+2] reaction provides a new approach for the synthesis of five-membered carbocycles with attractive features: not only the bicyclo[4.3.0]nonane skeleton but also the challenging bicyclo[5.3.0]decane skeleton can be realized through this transformation. Further studies of the reaction mechanism, stereochemistry, ligand effects, and origin of the preference for the [3+2] reaction over the type II [5+2] reaction are ongoing.

Acknowledgment. We dedicate this paper to Prof. Paul A. Wender of Stanford University for his pioneering research of Rh(I)-catalyzed [5+2] reactions. We thank the Natural Science Foundation of China (20825205-National Science Fund for Distinguished Young Scholars, 20772007 and 20672005) and the National Basic Research Program of China-973 Program (2010CB833203) for financial support. Dr. Andrew Leach of AstraZeneca and Dr. Cheyenne S. Brindle of Harvard University are highly appreciated for polishing the language.

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

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[10] (a) Ota, K.; Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203. (b) Kim, S. Y.; Chung, Y. K. *J. Org. Chem.* **2010**, *75*, 1281.

[11] For a recent review of the applications of activated cyclopropanes, see: Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.