Rh(I)-Catalyzed [5 + 1] Cycloaddition of Vinylcyclopropanes and CO for the Synthesis of α,β- and β,γ-Cyclohexenones
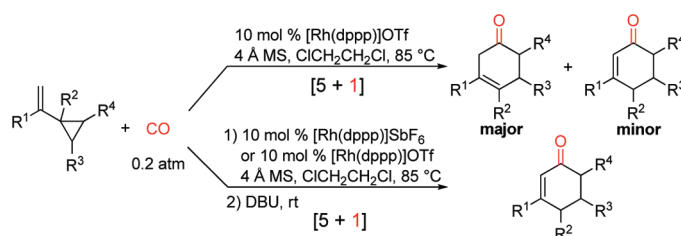
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ABSTRACT

A cationic Rh(I)-catalyzed [5 + 1] cycloaddition of vinylcyclopropanes and CO has been developed, affording either β,γ-cyclohexenones as major products or α,β-cyclohexenones exclusively, under different reaction conditions.

Transition-metal-catalyzed cycloadditions (annulations) via coordination, oxidative addition, insertion, and reductive elimination processes[1] provide powerful approaches to synthesize various sized ring compounds, which range from three- to nine-membered carbocycles. Despite this, developing new transition-metal-catalyzed cycloadditions that can expand, complement, or even surpass the reported ones is still highly demanded, considering the possible different skeletons, substitutions, and stereochemistry of the target molecules. Among them, developing metal-catalyzed cycloadditions to synthesize six-membered nonbenzenoid carbocycles is one of the most actively pursued research fields, because six-membered nonbenzenoid carbocycles are the most ubiquitous ring compounds in organic chemistry. Until now, some

(1) Selected reviews of transition-metal-catalyzed cycloaddition reactions: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (d) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (e) Yu, Z.-X.; Wang, Y.; Wang, Y. *Chem.—Asian J.* **2010**, *5*, 1072.

(2) (a) Huang, Y.; Lu, X. *Tetrahedron Lett.* **1988**, *29*, 5663. (b) He, X.-C.; Wang, B.; Bai, D. *Tetrahedron Lett.* **1998**, *39*, 411.

(3) (a) See refs in 1a and 3b−3g. For selected examples, see: (b) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. (c) O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Org. Biomol. Chem.* **2003**, *1*, 2038. (d) Aikawa, K.; Akutagawa, S.; Mikami, K. *J. Am. Chem. Soc.* **2006**, *128*, 12648. (e) Fürstner, A.; Stimson, C. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8845. (f) Kusama, H.; Karibe, Y.; Onizawa, Y.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4269. (g) Kim, S. M.; Park, J. H.; Chung, Y. K. *Chem. Commun.* **2011**, *47*, 6719.

(4) [5 + 1] cycloadditions of vinylcyclopropanes: (a) Ben-Shoshan, R.; Sarel, S. *J. Chem. Soc., Chem. Commun.* **1969**, 883. (b) Victor, R.; Ben-Shoshan, R.; Sarel, S. *Tetrahedron Lett.* **1970**, 4253. (c) Sarel, S. *Acc. Chem. Res.* **1978**, *11*, 204. (d) Aumann, R. *J. Am. Chem. Soc.* **1974**, *96*, 2631. (e) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, *122*, 6807. (f) Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem.* **2004**, *69*, 2268. (g) Kurahashi, T.; de Meijere, A. *Synlett* **2005**, 2619.

(5) [5 + 1] cycloadditions of allenylcyclopropanes: (a) Iwasawa, N.; Owada, Y.; Matsuo, T. *Chem. Lett.* **1995**, 115. (b) Owada, Y.; Matsuo, T.; Iwasawa, N. *Tetrahedron* **1997**, *53*, 11069. (c) Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4. (d) Shu, D.; Li, X.; Zhang, M.; Robichaux, P. J.; Tang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 1346.

(6) Rh-catalyzed [5 + 1] steps are also involved in the following reactions of dienylcyclopropanes and 1-yne−vinylcyclopropanes: (a) Yao, Z.-K.; Li, J.; Yu, Z.-X. *Org. Lett.* **2011**, *13*, 134. (b) Lin, M.; Li, F.; Jiao, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 1690.

(7) [5 + 1] cycloadditions of vinylcyclopropenes: (a) Grabowski, N. A.; Hughes, R. P.; Jaynes, B. S.; Rheingold, A. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1694. (b) Cho, S. H.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2631. (c) Semmelhack, M. F.; Ho, S.; Steigerwald, M.; Lee, M. C. *J. Am. Chem. Soc.* **1987**, *109*, 4397.

(8) [5 + 1] cycloaddition of 3-acyloxy-1,4-enynes: Brancour, C.; Fukuyama, T.; Ohta, Y.; Ryu, I.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Chem. Commun.* **2010**, *46*, 5470.

(9) For reports of hetero-[5 + 1] reactions, see: (a) Kamitani, A.; Chatani, N.; Morimoto, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 9230. (b) ref 4g.

elegant transition-metal-catalyzed cycloadditions, for example, the metal-catalyzed [3 + 3],[2] [4 + 2],[3] [5 + 1],[4−9] [2 + 2 + 2],[10] [3 + 2 + 1],[11] and [4 + 1 + 1][12] reactions, have been developed for the synthesis of six-membered carbocycles. In particular, the metal-mediated or -catalyzed [5 + 1] reactions of vinylcyclopropanes (VCPs)[4] or allenylcyclopropanes[5] with CO are of synthetic significance, due to the easy preparation of the substrates and generation of various functionalized cyclohexenones. The [5 + 1] reactions of vinylcyclopropanes and CO can be mediated by Fe(CO)$_5$ under photoirradiation (developed by Sarel,[4a−c] Aumann,[4d] and Taber[4e,f]) or catalyzed by Co$_2$(CO)$_8$ or [Rh(CO)$_2$Cl]$_2$ (developed by de Meijere[4g]). The [5 + 1] cycloadditions of allenylcyclopropanes and CO can be catalyzed by either Co catalyst (developed by Iwasawa[5a,b]) or Ir complex (developed by Murakami and Ito[5c]). Very recently, Tang and co-workers developed a Rh-catalyzed tandem 1,3-acyloxy migration/[5 + 1] cycloaddition reaction to produce highly functionalized cyclohexenones.[5d] In Tang's reaction, the key step is the Rh-catalyzed 1,3-acyloxy migration of propargyl esters to give allenylcyclopropanes, which then produce the [5 + 1] cycloadducts under the same catalytic condition. The importance of the [5 + 1] reaction of vinylcyclopropanes and CO has been demonstrated by its application in total synthesis by Taber's group.[13] Even though the Rh-catalyzed [5 + 1] reaction of in situ generated allenylcyclopropanes and CO by Tang and co-workers has broad scope, the [5 + 1] reaction of VCPs and CO catalyzed by Rh has not been developed into a general one. In the reported [5 + 1] reaction of VCPs and CO catalyzed by [Rh(CO)$_2$Cl]$_2$ from de Meijere's group, only very special VCP substrates can give good results. Here we report our development of a general cationic Rh(I) complex-catalyzed [5 + 1] reaction of VCPs and CO to synthesize both α,β- and β,γ-cyclohexenones.

We discovered the [5 + 1] reaction of VCP and CO serendipitously during our study of the [3 + 2] reaction of α-ene−VCPs and α-yne−VCPs.[14] Previously we found that, under the Rh catalysis, α-ene−VCPs underwent intramolecular [3 + 2] cycloadditions[15] to give 5/6- and 5/7-bicyclic compounds (Scheme 1a). When an α-yne-VCP was used, a cycloisomerization happened instead. Inspired by many [$m + n + o$] cycloadditions,[1] we wondered whether a [(3 + 2) + 1] reaction could also be developed if CO was introduced to the reaction system.

(10) For recent reviews on transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (b) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (c) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307.

(11) (a) Koga, Y.; Narasaka, K. *Chem. Lett.* **1999**, 705. (b) Lee, S. I.; Park, J. H.; Chung, Y. K.; Lee, S.-G. *J. Am. Chem. Soc.* **2004**, *126*, 2714. (c) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528. (d) Li, C.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 3082.

(12) Taber, D. F.; Guo, P.; Guo, N. *J. Am. Chem. Soc.* **2010**, *132*, 11179.

(13) Taber, D. F.; Sheth, R. B.; Tian, W. *J. Org. Chem.* **2009**, *74*, 2433.

(14) Li, Q.; Jiang, G.-J.; Jiao, L.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 1332.

(15) For other intramolecular [3 + 2] cycloadditions employing VCP as a three-carbon unit, see: (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.
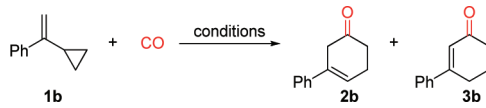
Scheme 1. (a) Our Previous Report of α-Ene/Yne-VCP and (b) Observed [5 + 1] Cycloaddition[a]
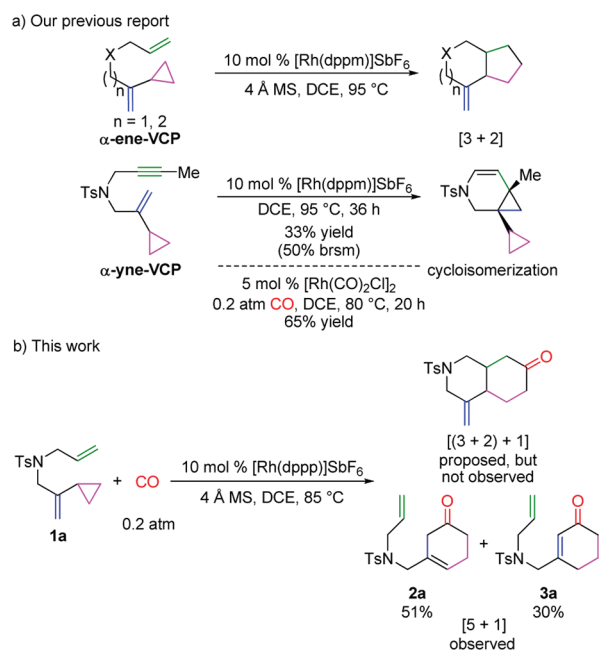
[a] DCE = 1,2-dichloroethane.

We first used an α-yne−VCP substrate to test this proposal. However, cycloisomerization still took place instead of the designed [(3 + 2) + 1] cycloaddition (Scheme 1a). To our surprise, when the standard α-ene-VCP substrate **1a** was tested in the presence of CO, [5 + 1] cycloaddition occurred, affording both β,γ- and α,β-cyclohexenones (**2a** and **3a**, Scheme 1b) in 51% and 30% yields, respectively. The tethered alkene part in the α-ene−VCP substrate was not involved in the cycloaddition. Considering the [5 + 1] cycloaddition reaction is very useful in the six-membered ring synthesis, we began to investigate whether the Rh-catalyzed [5 + 1] reaction of more general VCP substrates and CO is possible.

To improve the [5 + 1] reaction yield and the selectivity between α,β- and β,γ-cyclohexenones, we further screened the reaction conditions, using the more easily accessible substrate **1b** (Table 1). To our delight, under the catalysis of [Rh(dppp)]SbF$_6$, the total yield was high, even though the selectivity was not very good. In this case, 41% of the β,γ-cyclohexenone **2b** and 34% of the α,β-unsaturated product **3b** were generated (entry 1). Both neutral [Rh(CO)$_2$Cl]$_2$ (this is effective in some special substrates shown by de Meijere and Kurahashi[4g]) and cationic [Rh(CO)$_2$]SbF$_6$ failed to promote the desired cycloaddition (entries 2 and 3). We then tested a few other bidentate phosphine ligands and found that the yields became lower (entries 4−6). In particular, the standard reaction condition of the [3 + 2] cycloaddition was not suitable for the [5 + 1] reaction at all, giving no product (entry 4). We found that the presence of 4 Å molecular sieves (MS) was essential to this reaction because the yield was much lower
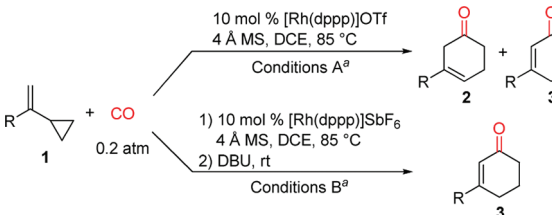
Table 1. Screening of the Reaction Conditions[a]

entry	catalyst[b]	solvent[c]	t (°C)	CO (atm)	additive	yields (**2b**, **3b**)[d] (%)
1	[Rh(dppp)]SbF$_6$	DCE	85	0.2	4 Å MS	41, 34
2	[Rh(CO)$_2$Cl]$_2$	DCE	85	0.2	4 Å MS	NR[e]
3	[Rh(CO)$_2$]SbF$_6$	DCE	85	0.2	4 Å MS	dec[f]
4	[Rh(dppm)]SbF$_6$	DCE	85	0.2	4 Å MS	NR[e]
5	[Rh(dppe)]SbF$_6$	DCE	85	0.2	4 Å MS	20, 15
6	[Rh(dppb)]SbF$_6$	DCE	85	0.2	4 Å MS	19, 24
7	[Rh(dppp)]SbF$_6$	DCE	85	0.2	no	0, 44
8	[Rh(dppp)]SbF$_6$	DCE	95	0.2	4 Å MS	dec[f]
9	[Rh(dppp)]SbF$_6$	DCE	75	0.2	4 Å MS	NR[e]
10	[Rh(dppp)]SbF$_6$	DCE	85	1	4 Å MS	dec[f]
11	[Rh(dppp)]SbF$_6$	DCE	85	0.1	4 Å MS	27, 39
12	[Rh(dppp)]OTf	DCE	85	0.2	4 Å MS	66, 12
13	[Rh(dppp)]OTf	DME	85	0.2	4 Å MS	16, 0
14	[Rh(dppp)]OTf	dioxane	85	0.2	4 Å MS	dec[f]
15[g]	[Rh(dppp)]SbF$_6$	DCE	85	0.2	4 Å MS	0, 73
16[h]	[Rh(dppp)]OTf	DCE	85	0.2	4 Å MS	22, 2

[a] Conditions: 10 mol % of Rh(I) catalyst, substrate concentration 0.05 M, 24 h. [b] dppp = 1,3-bis(diphenylphosphino)propane, dppm = bis(diphenylphosphino)methane, dppe = 1,2-bis(diphenylphosphino)ethane, dppb = 1,4-bis(diphenylphosphino)butane. [c] DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane. [d] Isolated yield after column chromatography. [e] No reaction occurred. [f] The substrate decomposed. [g] After the reaction was finished, 1 equiv of DBU was added and the mixture was stirred at room temperature for 1 h. [h] 5 mol % of Rh(I) catalyst was used.

without this additive (entry 7). Screening of the reaction temperature and the pressure of CO gave no better results (entries 8−11). Notably, 1 atm of CO is not beneficial to the [5 + 1] reaction (entry 10). To our delight, using AgOTf instead of AgSbF$_6$ can improve the selectivity of the β,γ-unsaturated product **2b** (66% yield), together with 12% of the α,β-unsaturated product **3b** (entry 12). When the solvent was changed to DME or dioxane, the result became worse (entries 13 and 14). To obtain the α,β-cyclohexenone exclusively, DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) was added to the reaction system at room temperature after the accomplishment of the [5 + 1] cycloaddition. After 1 h, only a single product **3b** was obtained in 73% yield through the isomerization procedure (entry 15). If the catalyst loading was reduced to 5 mol %, the reaction yield decreased sharply (entry 16).

We selected two conditions as the optimal conditions to explore the substrate scope of the [5 + 1] reaction: conditions A (using [Rh(dppp)]OTf as the catalyst to obtain the β,γ-unsaturated product **2** as the major product) and conditions B (using [Rh(dppp)]SbF$_6$ (for VCPs without substituents on the cyclopropyl rings) or [Rh(dppp)]OTf (for VCPs with substituents on the cyclopropyl rings) as the catalyst, and then treating the [5 + 1] system with DBU to obtain the α,β-unsaturated product **3** exclusively. See the Supporting Information for a

Table 2. Scope of the [5 + 1] Reaction

entry	substrate	Conditions A yields of **2**, **3**[b]	Conditions B yield of **3**[b]
1	TsN, **1a**	61%, 16%	80%
2	**1b**	66%, 12%	73%
3	MeO, **1c**	53%, 22%	76%
4	OMe, **1d**	53%, 10%	63%
5	F, **1e**	58%, 7%	64%
6	S, **1f**	46%, trace	43%
7	**1g**	74%, 13%	85%
8	Ph, **1h**	41%, 43%	85%
9	Me, TsN, **1i**	65%, 15%	78%
10	TsHN, **1j**	68%, 14%	51%[c]

[a] Conditions A: 10 mol % of [Rh(dppp)]OTf, 4 Å MS (100 mg), 0.2 atm of CO, DCE as solvent (0.05 M), 85 °C, 24 h. Conditions B: 10 mol % of [Rh(dppp)]SbF$_6$ (for VCPs without substituents on the cyclopropyl rings), 4 Å MS (100 mg), 0.2 atm of CO, DCE as solvent (0.05 M), 85 °C, 24 h; then DBU (1 equiv), rt, 1 h. DCE = 1,2-dichloroethane. [b] Isolated yield after column chromatography. [c] Because of the instability of the product to DBU and the presence of 4 Å MS, 5 equiv of TsOH·H$_2$O was used instead of DBU, and the mixture reacted at rt for 2 h.

detailed discussion) (Tables 2 and 3). Besides the neutral phenyl group, both electron-donating and electron-withdrawing substituents can be tolerated in the cycloaddition (entries 2, 3 and 5, Table 2). The more hindered substrates **1d** and **1g** also afforded the desired products in good yields (entries 4 and 7). In addition, a heterocyclic aryl-substituted substrate can also give a moderate yield (entry 6). Moreover, the R group could be alkyl substituents (entries 1 and 8−10). The [5 + 1] cycloaddition was not affected even if there was an alkene substituent or an acidic hydrogen in the substrates (entries 1 and 10). The addition of DBU made the [5 + 1] product of substrate **1j** decompose; therefore, TsOH·H$_2$O was used instead to give a good yield of the isomerized product (entry 10).

Table 3. Scope of the [5 + 1] Reaction

entry	substrate	Conditions A yield of **2**[b]	Conditions B yield of **3**[b]

[a] Conditions A: 10 mol % of [Rh(dppp)]OTf, 4 Å MS (100 mg), 0.2 atm of CO, DCE as solvent (0.05 M), 85 °C, 24 h. Conditions B: 10 mol % of [Rh(dppp)]OTf (for VCPs with substituents on the cyclo-propyl rings), 4 Å MS (100 mg), 0.2 atm of CO, DCE as solvent (0.05 M), 85 °C, 24 h; then DBU (1 equiv), rt, 1 h. DCE = 1,2-dichloroethane. [b] Isolated yield after column chromatography. [c] The β,γ-cyclohexenone **2** could not isomerize to α,β-cyclohexenone **3** after some attempts. [d] The reaction time was 36 h. [e] 3% of **2l** was also isolated. [f] 75 °C was used, and the reaction time was 48 h. [g] The reaction time was 48 h. [h] 6% of **3q** was also isolated. [i] Because of the instability of the product to DBU, and the presence of 4 Å MS, 5 equiv of TsOH·H$_2$O was used instead of DBU, and the mixture reacted at 50 °C for 4 h.

The substrates could have other different substitution patterns (Table 3). Both 1-phenyl- and benzyloxymethyl-VCP (**1k**, **1l**) could afford the β,γ-unsaturated products
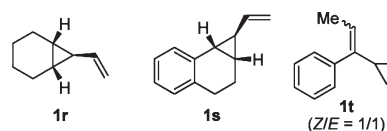
Figure 1. Unsuccessful substrates for the [5 + 1] reaction.

exclusively under conditions A, in moderate to good yields (entries 1 and 2). At the same time, *cis*-2-benzyloxy-methyl-VCP (**1m**) can also be subjected to the [5 + 1] reaction (entry 3). The benzyl protecting group in **1m** can be changed to a TBS (*tert*-butyldimethylsilyl) group, and even unprotected alcohols can be tolerated in the cycloaddition (entries 4–6). In the reactions of substrates **1m**–**o**, the cyclopropanes were cleaved on the less hindered monosubstituted C−C bonds; therefore, only one kind of [5 + 1] cycloaddition product was observed. Compared with substrate **1o**, the [5 + 1] reaction of its *trans*-isomer **1o'** gave two cyclopropane cleavage products **2o** and **2o'** with a total yield higher than that in the reaction of **1o**. The reaction of the substrate **1p**, which has a six-membered ring fused with the VCP and has the vinyl group at the bridgehead position, can also take place, affording a functionalized nonconjugated 6/6-bicyclic compound (entry 7). However, if the vinyl group is not at the bridge-head position (**1r** and **1s**, Figure 1), the formation of the 6/6-cycloadducts was not observed and the reasons for this are not clear at this stage. We were pleased to find that for substrates **1q** and **1q'**, which have a five-membered ring fused with the VCP and have the vinyl group at the nonbridgehead position, the expected [5 + 1] reaction can happen via two cyclopropane cleavage modes, giving two [5 + 1] cycloadducts **2q** and **2q'** (the skeleton of the natural products of Taiwaniaquinoids[16]) in moderate yields (entries 8 and 9, Table 3). Most β,γ-unsaturated products could isomerize to the α,β-unsaturated ones quantitatively under reaction conditions B, except for **2k** and **2p** (Table 3). To our disappointment, the β-substituted VCPs (for example, **1t**, Figure 1) were not suitable substrates for this [5 + 1] cycloaddition reaction.

In conclusion, we have developed a useful Rh(I)-catalyzed [5 + 1] cycloaddition of vinylcyclopropanes (VCPs) and CO. This reaction provides a new strategy for the assembly of six-membered carbocycles. Application of this reaction in synthesis is ongoing in our laboratory.

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

(16) Majetich, G.; Shimkus, J. M. *J. Nat. Prod.* **2010**, *73*, 284.