ORGANIC LETTERS

2010
Vol. 12, No. 23
5434−5437

Asymmetric Epoxidation of α-Substituted Acroleins Catalyzed by Diphenylprolinol Silyl Ether

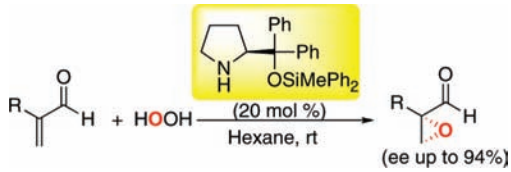
Bojan P. Bondzic, Tatsuya Urushima, Hayato Ishikawa, and Yujiro Hayashi*

Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

hayashi@ci.kagu.tus.ac.jp

Received September 21, 2010

ABSTRACT



Asymmetric epoxidation of α-substituted acroleins with hydrogen peroxide has been catalyzed by diphenylprolinol diphenylmethylsilyl ether to afford α-substituted-β,β-unsubstituted-α,β-epoxy aldehyde with excellent enantioselectivity and the generation of a chiral quaternary carbon center. The method was applied to a short synthesis of (*R*)-methyl palmoxirate.

Epoxide is a synthetically important functional group, and there are several methods for preparation of chiral epoxides from the corresponding alkene via asymmetric epoxidation reactions.[1] For instance, Katsuki−Sharpless epoxidation of allyl alcohols[2] and manganese−salen complex-mediated epoxidation reported independently by Jacobsen and Katsuki[3] are well-known methods catalyzed by organometallic reagents.

In recent years, organocatalysis has been developing very rapidly,[4] and several excellent epoxidation reactions catalyzed by organocatalysts have been developed. For electrophilic epoxidation, Shi developed a reaction using a sugar-derived organocatalyst,[5] while a pyrrolidine-based catalyst was utilized by Aggarwal.[6] Chiral iminium salt[7] and chiral tripeptide[8] were also used as efficient organocatalysts. Organocatalysts are also effective in nucleophilic epoxidation reactions. β-Substituted acrolein is enantioselectively epoxidized by diarylprolinol silyl ether,[9] chiral phosphoric amine salt,[10] and diphenylfluoromethylpyrrolidine,[11] while the

(1) (a) Johnson, R. A.; Sharpless, K. B. *Asymmetric methods of epoxidation in Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 7, pp 389−437. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (c) *Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000.

(2) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. For reviews, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 103−158. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

(3) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345. (c) For a review, see: Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 159−202.

(4) For selected reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) *Asymmetric Organocatalysis*; Berkessel, A., Groger, H., Eds.; Wiley-VCH: Weinheim, 2005. (c) Hayashi, Y. *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 464. (d) List, B. *Chem. Commun.* **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (f) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (g) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007. (h) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (i) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477. (j) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (k) Barbas, C. F. III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (l) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (m) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (n) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.

(5) (a) Wang, Z.-X.; Tu, W.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224 Review, see. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, *14*, 1979. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

(6) Adamo, M. F. A.; Aggarwal, V. A.; Sage, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 8317.

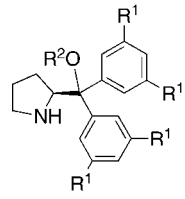
10.1021/ol102269s
Published on Web 11/04/2010

epoxidation of α,β-unsaturated ketone is catalyzed by diphenylprolinol,[12] amino alcohol,[13] and guanidine-based catalysts.[14]

Among the epoxides, α-substituted-β,β-unsubstituted-α,β-epoxyaldehyde is a synthetically useful chiral building block possessing a quaternary carbon center because β,β-unsubstituted epoxide reacts readily with several nucleophiles in a regio- and stereocontrolled manner. One of the most straightforward methods for its preparation is asymmetric epoxidation of α-substituted acroleins. In contrast to the several successful epoxidation reactions of β-substituted acroleins catalyzed by organocatalysts, asymmetric epoxidation of α-substituted acroleins is a synthetic challenge. Moreover, the asymmetric reaction of α-acroleins via organocatalyst is a difficult reaction.[15]

Diarylprolinol silyl ether, developed independently by our group[16] and Jørgensen's group,[17] is an effective organocatalyst,[18] while Jørgensen and co-workers developed the epoxidation of β-substituted acroleins catalyzed by diarylprolinol silyl ether substituted with trifluoromethyl groups.[9a,b] Pihko and co-workers applied the same catalyst to epoxidation of α-benzylacrolein and observed no reaction.[19] However, our continuous interest in diphenylprolinol silyl ether led us to the successful asymmetric epoxidation reaction of α-substituted acroleins, which will be described in this communication. While this manuscript was in preparation, List and co-workers reported an excellent asymmetric epoxidation of α-substituted acroleins with a wide generality, in which a cinchona alkaloid-derived primary ammonium salt in combination with a chiral phosphoric acid counterion is an effective catalyst.[20]

We chose 2-methylenenonanal as a model α-substituted acrolein and investigated the reaction in the presence of 10 mol % of various organocatalysts (Figure 1) using aqueous

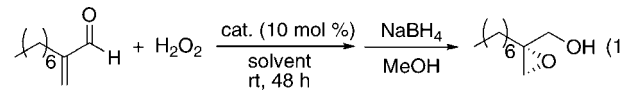


catalyst	R^1	R^2
1	H	H
2	H	TMS
3	H	TBS
4	H	$SiPh_2Me$
5	H	Me
6	CF_3	H
7	CF_3	TMS

Figure 1. Organocatalysts examined in this study.

H_2O_2 (30%) as an oxidant (Table 1). Although diphenylprolinol **1** and diarylprolinol **6** did not promote the reaction (entries 1 and 6), their silyl ethers showed catalytic activity.

Table 1. Effects of Organocatalysts and Solvents in Epoxidation Reactions[a]



entry	catalyst	solvent	conv/%[b]	yield/%[c]	ee/%[d]
1	**1**	CH_2Cl_2	2	nd	nd
2	**2**	CH_2Cl_2	55	35	67
3	**3**	CH_2Cl_2	53	32	76
4	**4**	CH_2Cl_2	53	34	80
5	**5**	CH_2Cl_2	26	23	40
6	**6**	CH_2Cl_2	<10	nd	nd
7	**7**	CH_2Cl_2	36	32	78
8	**4**	$CHCl_3$	58	55	87
9	**4**	THF	21	nd	nd
10	**4**	CH_3CN	<10	nd	nd
11	**4**	Et_2O	57	45	84
12	**4**	MeOH	47	37	80
13	**4**	toluene	63	44	86
14	**4**	hexane	85	65	94
15[e]	**4**	neat	90	70	88
16[f]	**4**	hexane	>90	72	94

[a] Reaction conditions: 2-methylenenonanal (0.5 mmol), H_2O_2 (30% in water, 1.5 mmol), catalyst (0.05 mmol), and solvent (0.5 mL) at room temperature for 48 h. See the Supporting Information for details. nd = not determined. [b] Determined by ^1H NMR spectroscopy. [c] Isolated yield after column chromatography. [d] ee was determined by chiral phase HPLC analysis. [e] Reaction run without organic solvent. [f] The catalyst **4** was employed in 20 mol % and the reaction time is 6 h. Product is isolated as aldehyde.

When trimethylsilyl ether was employed, moderate enantioselectivity (67% ee) was obtained (entry 2). The presence of bulkier *tert*-butyldimethylsilyl (TBS) ether in catalyst **3** led to greater enantioselectivity, while similar reactivity was maintained. Further increasing the bulkiness of the silyl ether moiety increased the enantioselectivity, and good selectivity was obtained when diphenylmethylsilyl ether catalyst **4** was employed.[21] In contrast to silyl ethers, methyl ether gave low enantioselectivity (entry 5). Trifluoromethyl-substituted diarylprolinol trimethylsilyl ether gave good enantioselec-

(7) (a) Page, P. C. B.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2004**, *6*, 1543. (b) Page, P. C. B.; Buckley, B. R.; Farah, M. M.; Blacker, A. J. *Eur. J. Org. Chem.* **2009**, 3413.

(8) Peris, G. C. E.; Jakobsche, S.; Miller, J. *J. Am. Chem. Soc.* **2007**, *129*, 8710.

(9) (a) Marigo, M.; Franzen, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. (b) Zhuang, W.; Marigo, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3883. (c) Sunden, H.; Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 99. (d) Zhao, G.-L.; Ibrahem, I.; Sunden, H.; Cordova, A. *Adv. Synth. Catal.* **2007**, *349*, 1210.

(10) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119.

(11) Sparr, C.; Schweizer, W. B.; Senn, H. M.; Gilmour, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 3065.

(12) (a) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579. (b) Lattanzi, A. *Chem Commun.* **2009**, 1452. (c) Russo, A.; Lattanzi, A. *Synthesis* **2009**, *9*, 1551.

(13) Lu, J.; Xu, Y.-H.; Liu, F.; Loh, T.-P. *Tetrahedron Lett.* **2008**, *49*, 6007.

(14) Tanaka, S.; Nagasawa, K. *Synthesis* **2009**, *4*, 667.

(15) (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (b) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930. (c) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892.

(16) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(17) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjasgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703.

(18) For reviews, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed* **2006**, *45*, 7876. (b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.

(19) Erkkila, A.; Pihko, P. M.; Clarke, M.-R. *Adv. Synth. Catal.* **2007**, *349*, 802.

(20) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227.

tivity but was slightly less reactive compared with diphenylprolinol catalysts (entry 7).

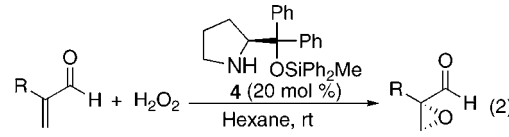
Next, the effect of the solvent was investigated, and the results are summarized in Table 1. In polar aprotic solvents such as THF and CH_3CN, the reaction scarcely proceeded even though the reaction is homogeneous. In other solvents such as CH_2Cl_2, $CHCl_3$, MeOH, and toluene, the reaction proceeded in all cases, affording the desired epoxide with good enantioselectivity, although yields were dependent on the solvent. Among the solvents examined, the best selectivity was obtained when the reaction was performed in hexane, a highly nonpolar solvent, affording the product in 65% yield and 94% ee (entry 14). The reaction proceeds in neat conditions as well, but a slight decrease in enantioselectivity was observed (entry 15). When 20 mol % of catalyst **4** was employed, the reaction was completed within 6 h, and a good yield (72%) was obtained with excellent enantioselectivity. The reaction proceeds in a two-phase system. The α,*β*-unsaturated iminium ion, which possesses both hydrophilic and hydrophobic properties, would exist on the interface of organic and water phases, where it reacts with H_2O_2 efficiently to afford the product in good yield.

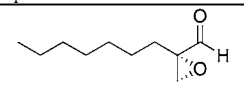
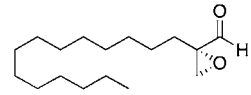
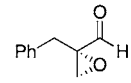
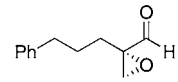
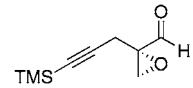
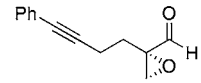
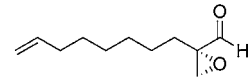
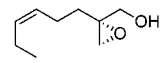
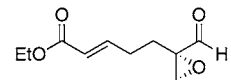
The effect of additives was also tested, as additives can beneficially influence rate, selectivity, and yield in some diarylprolinol-catalyzed reactions.[22] However, we could not observe any positive effect of either acid or base additives such as $PhCO_2H$, *p*-NO_2PhCO_2H, $ClCH_2CO_2H$, *p*-NO_2PhOH, and $NaHCO_3$.

After determining the best reaction conditions, the generality of the reaction was investigated, and the results are summarized in Table 2. In addition to 2-methylenenonanal, 2-methylenehexadecanal is also an effective substrate to afford the epoxide with good yield and excellent enantioselectivity (entries 1 and 2). α-Benzyl and α-(3-phenylpropyl) acroleins react with H_2O_2 to provide the epoxide in 86 and 87% ee, respectively (entries 3 and 4). Acroleins with alkynyl substituents at the α-position are also suitable substrates, affording the product with excellent enantioselectivity, in which the base-sensitive trimethylsilyl acetylene moiety remains intact under the present reaction conditions (entries 5 and 6). When substrates possessing two alkenes, such as one substituted with the formyl group and the other with the terminal or internal double bond, are employed, the reaction only proceeds efficiently with the formyl-substituted alkene, providing the α,*β*-epoxy aldehyde with excellent enantioselectivity (entries 7 and 8). For substrates possessing both α-substituted acrolein and α,*β*-unsaturated ester moieties, only the former moiety reacts to afford the monoepoxide with good enantioselectivity (entry 9).

The present epoxidation was applied to enantioselective synthesis of (*R*)-methyl palmoxirate (Scheme 1), a potent oral hypoglycemic and antiketogenic agent in mammals including humans.[23,24] 2-Methylenehexadecanal was treated with H_2O_2 in the presence of (*R*)-diphenylprolinol silyl ether **ent-4**, derived from unnatural D-proline, to afford the desired

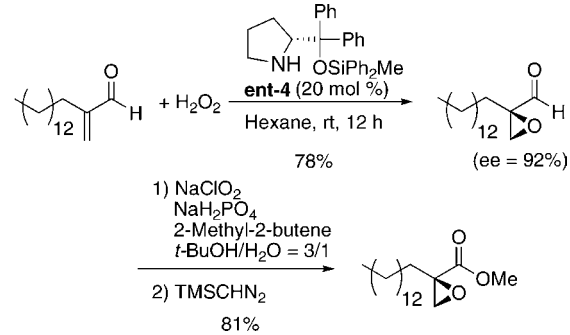
Table 2. Generality of the Asymmetric Epoxidation Reaction of α-Substituted Acroleins[a]



entry	product	time/h	yield/%[b]	ee/%[c]
1		6	72	94
2		10	80	92 (*S*)
3		12	65	86 (*S*)[e]
4		20	62	87
5		8	70	84
6		24	61	82
7		3	73	93
8[d]		12	64	91
9[f]		48	75	74

[a] Unless otherwise shown, reaction conditions: α-substituted acrolein (0.5 mmol), H_2O_2 (30% in water, 1.5 mmol), catalyst **4** (0.1 mmol), hexane (0.5 mL) at room temperature for a designated time. [b] Isolated yield of the product. [c] ee was determined by chiral phase HPLC analysis. See the Supporting Information for details. [d] Isolated as alcohol after $NaBH_4$ reduction (2 steps). [e] The determination of the absolute configuration. See the Supporting Information. [f] Catalyst **4** was employed in 10 mol %.

Scheme 1. Enantioselective Synthesis of (*R*)-Methyl Palmoxirate



(21) Groselj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. *Helv. Chim. Acta* **2009**, *92*, 1225.

(22) See for instance: (a) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (b) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053. (c) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854.

epoxide in 78% yield with excellent enantioselectivity (92% ee). Kraus oxidation followed by treatment with $TMSCHN_2$ gave (*R*)-methyl palmoxirate in 81% yield over two steps.

The absolute configuration can be explained by the following reaction mechanism (Figure 2). There are two conformers, A and B, in the imine generated from α-substituted acrolein and catalyst **4**. Conformer B would be more stable than conformer A because of steric repulsion between the vinylidene C−H and methylene C−H at the 5-position of pyrrolidine. Nucleophilic attack by H_2O_2 occurs from the less hindered face of the iminium ion to generate C and D. The ring-closing reaction for formation of the epoxide proceeds from D to afford the desired epoxide.

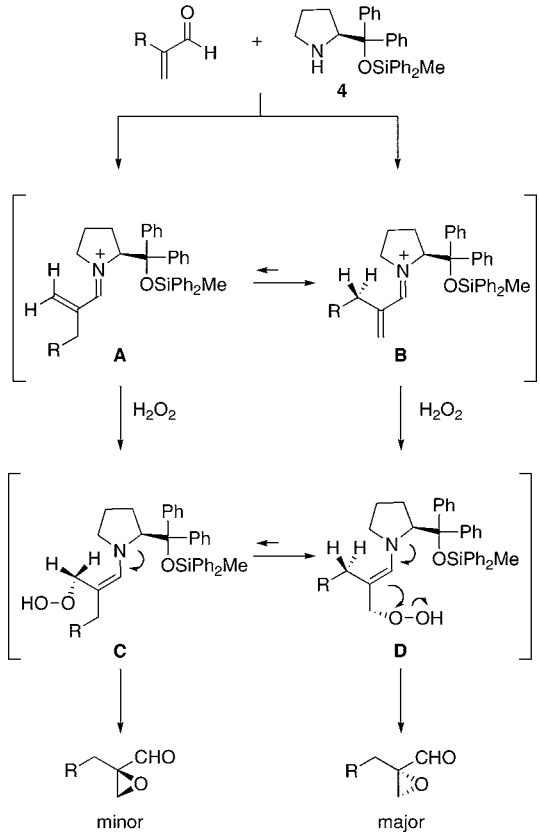


Figure 2. Reaction mechanism of epoxidation of α-substituted acroleins.

Another possible explanation is as follows. There would be an equilibrium between *s-cis* (C) and *s-trans* (D) conformers of enamine, and conformer D would be more stable than C. The ring-closing reaction for the formation of epoxide proceeds from D to afford the desired epoxide.

The enantio-differential step for the formation of chiral epoxide is the transformation from intermediates C and D to the epoxide. There is no clear evidence at this stage whether kinetically generated D or thermodynamically stable D would be converted into the epoxide.

In summary, an asymmetric epoxidation of α-substituted acroleins was catalyzed by diphenylprolinol silyl ether **4** using H_2O_2 as an oxidant. There are several noteworthy features in this epoxidation: (1) This is the first successful application of a secondary amine catalyst for epoxidation of α-substituted acroleins; (2) excellent enantioselectivity has been realized; and (3) chiral quaternary carbon centers can be constructed with excellent enantioselectivity. As α-substituted-*β*,*β*-unsubstituted-α,*β*-epoxyaldehyde is a very valuable chiral building block, the present method would be synthetically useful for asymmetric synthesis, and an application was shown in the short-step synthesis of (*R*)-methyl palmoxirate.

Supporting Information Available: Detailed experimental procedures, full characterization, copies of ^1H, ^{13}C NMR, and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102269S

(23) (a) Tutwiler, G. F.; Kirsch, T.; Mohrbacher, R. J.; Ho, W. *Metabolism* **1978**, *27*, 1539. (b) Verhagen, J.; Leempoels, J.; Brugmans, J.; Tutwiler, G. F. *Diabetes Suppl. 1* **1984**, *33*, 688. (c) Mandarino, L.; Tsalikian, E.; Bartold, S.; Marsh, H.; Carney, A.; Buerklin, E.; Tutwiler, G.; Haymond, M.; Rizza, R. *J. Clin. Endocrinol. Metab.* **1984**, *59*, 658.

(24) For the enantioselective synthesis of methyl palmoxirate, see: (a) Ho, W.; Tarhan, O.; Kiorpes, T. C.; Tutwiler, G. F.; Mohrbacher, R. J. *J. Med. Chem.* **1987**, *30*, 1094. (b) Garcia, R. J. L.; Martin, C. A. M.; Rodriguez, J. H. *J. Org. Chem.* **1994**, *59*, 533. (c) Jimenez, O.; Bosch, M. P.; Guerrero, A. *J. Org. Chem.* **1997**, *62*, 3496.