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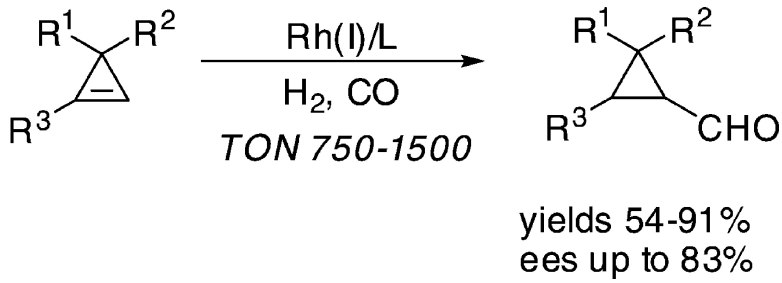

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Rhodium-Catalyzed Hydroformylation of Cyclopropenes

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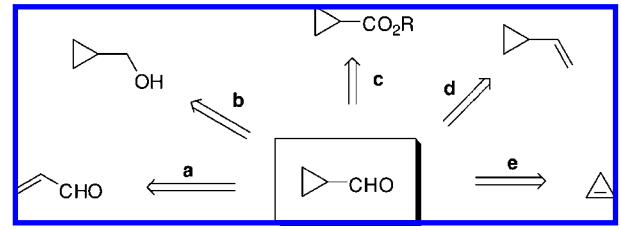
Abstract: The first catalytic diastereo- and enantioselective hydroformylation of cyclopropenes was demonstrated. The reaction proceeds efficiently under very mild conditions and low catalyst loadings providing high yields of cyclopropylcarboxaldehydes. This novel methodology represents a convenient, atom-economic approach toward optically active cyclopropylcarboxaldehydes from readily available prochiral cyclopropenes.

Introduction

Cyclopropylcarboxaldehydes are arguably some of the most sought after compounds in the chemistry of small cycles. Not only are they themselves important biologically active targets,[1] but they also are extremely versatile synthons as the aldehyde group can be readily transformed into a number of useful functionalities.[2] Established synthetic approaches toward these important targets include various modes of [2 + 1] cycloadditions (Scheme 1, path a), such as Michael-initiated ring-closure reaction (MIRC);[3] the cyclization of conjugated aldehydes with carbenoid equivalents derived from dihalomethanes,[4,5] diazo compounds,[6] nitrogen ylides,[7] sulfur ylides,[8] or arsonium ylides;[9] as well as

Scheme 1. Synthetic Approaches toward Formylcyclopropanes



functional group transformations in pre-existing cyclopropyl rings, such as oxidation of cyclopropylmethanols (Scheme 1, path b),[10] reduction of cyclopropylcarboxylic acid derivatives (Scheme 1, path c),[11] and oxidative cleavage of the double bond in vinylcyclopropanes (Scheme 1, path d).[12] In light of the recent advances in chemistry of cyclopropenes,[13,14] we envisioned an

(1) See, for example: (a) Paul, V. J.; Fenical, W *Science* **1983**, *221*, 747. (b) Zheng, G. C.; Hatano, M.; Ishitsuka, M. O.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1990**, *31*, 2617. (c) Shuto, S.; Takada, H.; Mochizuki, D.; Tsujita, R.; Hase, Y.; Ono, S.; Shibuya, N.; Matsuda, A. *J. Med. Chem.* **1995**, *38*, 2964.

(2) For recent application of cyclopropyl carboxaldehydes in synthesis, see: (a) Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781. (b) White, J. D.; Martin, W. H. C.; Lincoln, C.; Yang, J. *Org. Lett.* **2007**, *9*, 3481. (c) Al Dulayymi, J. R.; Baird, M. S.; Roberts, E.; Deysel, M.; Verschoor, J. *Tetrahedron* **2007**, *63*, 2571. (d) Chiu, C.-W.; Lai, C.-C.; Chiu, S.-H. *J. Am. Chem. Soc.* **2007**, *129*, 3500. (e) Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 6361. (f) Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560. (g) Pietruszka, J.; Wilhelm, T. *Synlett* **2003**, 1698. (h) Nicolaou, K. C.; Sasmal, P. K.; Rassias, G.; Reddy, M. V.; Altmann, K.-H.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3515.

(3) For a recent example, see: Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886.

(4) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131.

(5) For Wideqvist reaction, see: (a) Araki, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1286. (b) Chen, C.; Liao, Y.; Huang, Y. *Tetrahedron* **1989**, *45*, 3011. (c) Chen, C.; Huang, Y.; Shen, Y. *Tetrahedron Lett.* **1988**, *29*, 1033.

(6) (a) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174. (b) Branstetter, B.; Hossain, M. M. *Tetrahedron Lett.* **2005**, *47*, 221. (c) Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, *19*, 3267.

(7) (a) Kowalkowska, A.; Sucholbiak, D.; Jonczyk, A *Eur. J. Org. Chem.* **2005**, 925. (b) Shi, L.; Wang, P.; Liu, X.; Liu, W.; Liang, Y. *Synthesis* **2004**, 2342. (c) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 828. (d) Jonczyk, A.; Konarska, A. *Synlett* **1999**, 1085.

(8) (a) Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Tang, Y. J. *Org. Chem.* **2007**, *72*, 1335. (b) Hartikka, A.; Slosarczyk, A. T.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2007**, *18*, 1403. (c) Hartikka, A.; Arvidsson, P. I. *J. Org. Chem.* **2007**, *72*, 5874. (d) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240. (e) Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113. (f) Le Stanc, Y.; Le Corre, M *Can. J. Chem.* **1985**, *63*, 2958.

(9) Zhao, Y.-H; Zhao, G.; Cao, W.-G. *Tetrahedron: Asymmetry* **2007**, *18*, 2462.

(10) (a) Arasappan, A.; Venkatraman, S.; Padilla, A. I.; Wu, W.; Meng, T.; Jin, Y.; Wong, J.; Prongay, A.; Girijavallabhan, V.; Njoroge, F. G. *Tetrahedron Lett.* **2007**, *48*, 6343. (b) Zhao, Q.; Wong, H. N. C. *Tetrahedron* **2007**, *63*, 6296. (c) Miura, T.; Murakami, Y.; Imai, N. *Tetrahedron: Asymmetry* **2006**, *17*, 3067. (d) Al-Dulayymi, J. R.; Baird, M. S.; Mohammed, H.; Roberts, E.; Clegg, W. *Tetrahedron* **2006**, *62*, 4851. (e) Mattson, R. J.; Catt, J. D.; Denhart, D. J.; Deskus, J. A.; Ditta, J. L.; Higgins, M. A.; Marcin, L. R.; Sloan, C. P.; Beno, B. R.; Gao, Q.; Cunningham, M. A.; Mattson, G. K.; Molski, T. F.; Taber, M. T.; Lodge, N. J. *J. Med. Chem.* **2005**, *48*, 6023. (f) Kazuta, Y.; Tsujita, R.; Yamashita, K.; Uchino, S.; Kohsaka, S.; Matsuda, A.; Shuto, S. *Bioorg. Med. Chem.* **2002**, *10*, 3829. (g) Brana, M. F.; Guisado, C.; Fernando Alguacil, L.; Garrido, E.; Perez-Garcia, C.; Ruiz-Gayo, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3561.

(11) (a) Borthwick, A. D.; Davies, D. E.; Ertl, P. F.; Exall, A. M.; Haley, T. M.; Hart, G. J.; Jackson, D. L.; Parry, N. R.; Patikis, A.; Trivedi, N.; Weingarten, G. G.; Woolven, J. M. *J. Med. Chem.* **2003**, *46*, 4428. (b) Johansson, A.; Poliakov, A.; Akerblom, E.; Wiklund, K.; Lindeberg, G.; Winiwarter, S.; Danielson, U. H.; Samuelsson, B.; Hallberg, A. *Bioorg. Med. Chem.* **2003**, *11*, 2551. (c) Baldwin, J. E.; Cianciosi, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 9401. (d) Dalton, K. H.; et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5647.

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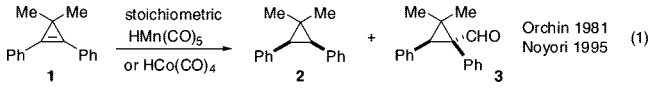
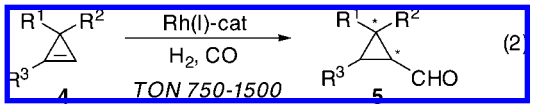
alternative approach to cyclopropylcarboxaldehydes via catalytic hydroformylation[15] of the cyclopropene double bond (Scheme 1, path e). We hoped to develop a mild, practical, and atom economic protocol for the stereoselective installation of a new carbon−carbon bond in the three-membered cycle, while avoiding the use of reactive organometallic reagents invoked in most C−C bond forming reactions involving cyclopropenes.[12,16,17]

To date, hydroformylation of cyclopropenes is represented by a few stoichiometric reactions mediated by $HMn(CO)_5$ or $HCo(CO)_4$, reported by Orchin and Noyori.[18,19] Orchin first demonstrated that 1,2-substituted cyclopropenes undergo hydroformylation in the presence of Mn- and Co-complexes to afford low yields of aldehyde **3**, accompanied by large amounts of the reduction product **2** (eq 1). Application of micellar catalysis allowed for improved yields of aldehydes (up to 93%); however, this reaction produced mixtures of *syn*- and *anti*-addition products.[16c] Later, Noyori investigated the hydroformylation reaction using a stoichiometric $HMn(CO)_5$ complex in various solvents, including $scCO_2$, yet was unsuccessful in obtaining an aldehyde yield above 40%.[17]



(1)

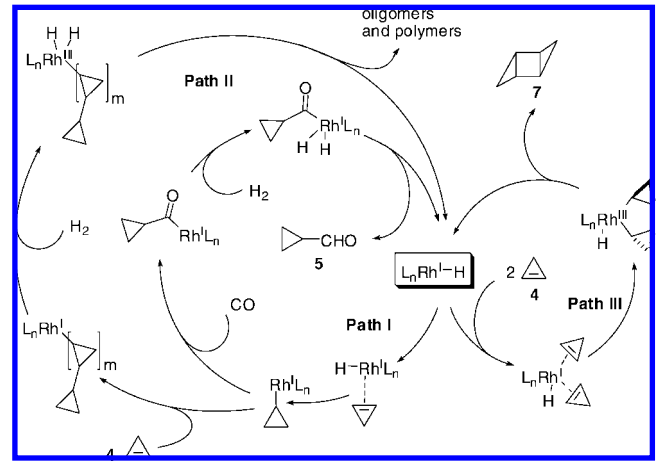
Herein we report the first examples of catalytic diastereo- and enantioselective hydroformylation of prochiral cyclopropenes to produce tri- and tetrasubstituted cyclopropylcarboxaldehydes, proceeding under mild conditions and very low catalyst loading (eq 2).



(2)

The long-standing challenge associated with the use of coordinatively unsaturated electron-deficient transition metal catalysts derived from metal carbonyl complexes in cyclopropene chemistry lies in the significantly more facile migratory insertion of cyclopropene into a metal−carbon bond (Scheme 2, Path II) as compared to the CO insertion step (Path I). Another commonly encountered problem is a very fast formal [2 + 2]

Scheme 2. Mechanistic Pathways for Different Processes Occurring in the Rh(I)-Catalyzed Hydroformylation of Cyclopropenes



dimerization of cyclopropenes occurring in the presence of electron-poor transition metal reagents (Scheme 2, Path III).[20,21] These two dominating side processes do not allow efficient incorporation of the carbonyl function into the final product, leading instead to the formation of polymers and mixtures of oligocarbocyclic hydrocarbons and ketones.[22] To date, only one highly selective carbonylative transformation involving cyclopropenes, the Pauson-Khand reaction, has been reported; however, this process requires use of at least stoichiometric amounts of metal carbonyl complexes.[23]

In line with the reasoning mentioned above, our initial experiments demonstrated that treatment of 3-methyl-3-phenylcyclopropene (**4a**) with syngas in the presence of standard hydroformylation catalyst, $Rh(acac)(CO)_2$, afforded quantita-

(12) (a) Pellicciari, R.; Marinozzi, M.; Macchiarulo, A.; Fulco, M. C.; Gafarova, J.; Serpi, M.; Giorgi, G.; Nielsen, S.; Thomsen, C. *J. Med. Chem.* **2007**, *50*, 4630. (b) Pandey, R. K.; Lindeman, S.; Donaldson, W. A. *Eur. J. Org. Chem.* **2007**, 3829. (c) Melancon, B. J.; Perl, N. R.; Taylor, R. E. *Org. Lett.* **2007**, *9*, 1425. (d) Barluenga, J.; de Prado, A.; Santamaria, J.; Tomas, M. *Chem.−Eur. J.* **2007**, *13*, 1326. (e) Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W.; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006**, *128*, 9730. (f) Racouchot, S.; Sylvestre, I.; Ollivier, J.; Kozyrkov, Y. Y.; Pukin, A.; Kulinkovich, O. G.; Salaün, J. *Eur. J. Org. Chem.* **2002**, 2160. (g) Fujita, M.; Hiyama, T.; Kondo, K. *Tetrahedron Lett.* **1986**, *27*, 2139. (h) Halazy, S.; Krief, A. *Tetrahedron Lett.* **1981**, *22*, 4341. (i) Monpert, A.; Martelli, J.; Gree, R.; Carrie, R. *Tetrahedron Lett.* **1981**, *22*, 1961. (j) Holm, K. H.; Lee, D. G.; Skattebøl, L. *Acta Chem. Scand., Ser. B: Org. Chem. Biochem.* **1978**, *B32*, 693.

(13) For recent reviews, see: (a) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Rubin, M; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (d) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719.

(14) For recent examples, see: (a) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563. (b) Rubina, M.; Woodward, E. W.; Rubin, M. *Org. Lett.* **2007**, *9*, 5501. (c) Simaan, S.; Marek, I. *Org. Lett.* **2007**, *9*, 2569. (d) Chuprakov, S.; Malyshev, D. A.; Trofimov, A.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 14868. (e) Marasawa, A.; Sranger, A.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 8039.

(15) For recent reviews on catalytic hydroformylation of olefins, see: (a) Nozaki, K. In *New Frontiers in Asymmetric Catalysis*; Koichi, M., Lautens, M, Eds.; Wiley: New York, 2007; pp 101−127. (b) Claver, C.; Dieguez, M.; Pamies, O.; Castillon, S. *Top. Organomet. Chem.* **2006**, *18*, 35. (c) Leighton, J. L. In *Modern Rhodium-Catalyzed Organic Reactions*; EvansP. A., Ed.; Wiley: New York, 2005; pp 93−110. (d) Dieguez, M.; Pamies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. (e) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264. (f) Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

(16) For recent examples on additions of Grignard reagents to cyclopropenes, see: (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (b) Liao, L.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322. (c) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3960. (d) Simaan, S.; Marasawa, A.; Bertus, P.; Marek, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3963. See also ref 13a,c.

(17) For the Pd-catalyzed addition of terminal alkynes to cyclopropenes proceeding under mild and neutral conditions, see: Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632.

(18) (a) Nalesnik, T. E.; Orchin, M. *J. Organomet. Chem.* **1981**, *222*, C5. (b) Nalesnik, T. E.; Freudenberger, J. H.; Orchin, M. *J. Organomet. Chem.* **1982**, *236*, 95. (c) Matsui, Y.; Orchin, M. *J. Organomet. Chem.* **1983**, *244*, 369.

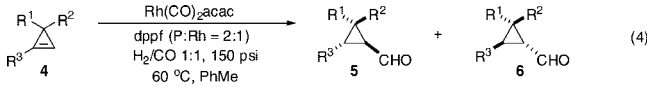
(19) Jessop, P. G.; Ikariya, T; Noyori, R *Organometallics* **1995**, *14*, 1510.

(20) For transition metal-catalyzed formal [2 + 2] cycloaddition of cyclopropenes, see for example: (a) Lukin, K. A.; Zefirov, N. S. *Zh. Org. Khim.* **1990**, *26*, 289.

(21) For the formation of metallacycles from cyclopropenes, see: (a) Hashmi, A. S. K.; Grundl, M. A.; Bats, J. W.; Bolte, M *Eur. J. Org. Chem.* **2002**, *7*, 1263, and refs cited therein. On oligomerization of cyclopropenes in the presence of Rh(I), see: (b) Cetinkaya, B.; Binger, P. *Chem. Ber.* **1982**, *115*, 3414.

(22) (a) Grobovenko, S. Ya.; Zlobina, V. A.; Surmina, L. S.; Bolesov, I. G.; Lapidus, A. L.; Beletskaya, I. P. *Metalloorg. Khim* **1990**, *3*, 697. (b) Binger, P.; Biedenbach, B. *Chem. Ber.* **1987**, *120*, 601. (c) Kireev, S. L.; Smit, V. A.; Ugrak, B. I.; Nefedov, O. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1991**, 2565.

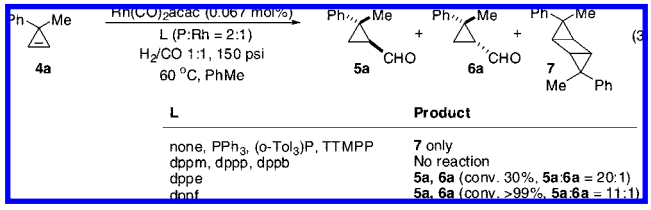
Table 1. Rh(I)-Catalyzed Hydroformylation of 3,3-Disubstituted Cyclopropenes



	R^1	R^2	R^3		Rxn time, hrs (**4**:Rh ratio)[a]	[c]	Yield of **5**, %	dr (**5**:**6**)[b]
1	Ph	Me	H	**4a**	18 (1500:1)	**5a**	87	11:1
2	*p*−Cl-C_6H_4	Me	H	**4b**	18 (1500:1)	**5b**	71[d]	8:1
3	*p*−F-C_6H_4	Me	H	**4c**	18 (100:1)	**5c**	91[d]	12:1
4	Ph	CH_2OMOM	H	**4d**	36 (1500:1)	**5d**	72	10:1
5	Ph	CH_2OAc	H	**4e**	36 (1500:1)	**5e**	75	7:1
6	Ph	CO_2Me	H	**4f**	18 (1500:1)	**5f**	90[d]	1:1
7	CO_2Me	Me	H	**4g**	36 (1500:1)	**5g**	64	24:1
8	CMe_2OBn	Me	H	**4h**	72 (1500:1)	**5h**	91	−[e]
9	Ph	Me	Me	**4i**	18 (100:1)	**5i**	80[d]	7:1[f]

[a] dppf:Rh molar ratio of 2:1 was employed. [b] Determined by ^{1}H NMR analysis of crude reaction mixtures. [c] Isolated yields of a major diastereomer [d] Combined isolated yields of two diastereomers. [e] A single diastereomer **5h** was obtained. [f] Regioselectivity of >10:1 was observed.

tively dimeric product **7** (eq 3). Attempts to suppress the unwanted cyclization by saturating the coordination sphere of the transition metal with monodentate phosphine ligands[24a,22b] were unsuccessful (eq 3). Next, we tested several bidentate diphosphine ligands[24c,d] anticipating their chelating effect would help stabilize the catalytically active Rh(I) species in a more saturated form. It was found that employment of dppm, dppp, and dppb in combination with $Rh(acac)(CO)_2$ allowed for suppressing of the redundant cyclization; however, it did not promote the hydroformylation reaction, leading instead to complete recovery of cyclopropene **4a** (eq 3). In contrast, the $Rh(acac)(CO)_2$/dppe combination produced the desired product **5a** in low yield, whereas the analogous complex with a more rigid ferrocenyl backbone (dppf) provided complete conversion of **4a** into formylcyclopropanes **5a** and **6a** (eq 3). The hydroformylation reaction proceeded very diastereoselectively affording less sterically hindered aldehyde **5a** as a major product. Remarkably, no products of ring-opening were detected in this reaction. On the basis of the ligand effect observed, it would be reasonable to propose that the reaction is very sensitive to the ligand bite angle; however, the enhanced catalytic activity of the dppf complex might also be explained by the increased electronic density provided by the ferrocenyl backbone.



Preparative scale hydroformylation of **4a** also proceeded smoothly under these conditions providing aldehyde **5a** in high isolated yield. It was found that as little as 0.067 mol% of Rh(I) was enough to drive this reaction to completion under very mild conditions (Table 1, entry 1). Efficient isolation of products could be achieved either by column chromatography or by direct vacuum distillation of the reaction mixtures. The scope of this novel transformation was examined on a series of 3,3-disubstituted cyclopropenes (Table 1). Cyclopropenes **4b**-**c** bearing substituted aryl groups at C3 reacted uneventfully to provide the corresponding aldehydes **5b**−**c** (entries 2−3). Both acetal (entry 4) and ester (entry 5) protecting groups for a primary alcohol function were perfectly compatible with the reaction conditions: the corresponding aldehydes **5d** and **5e** were obtained in high yield and good selectivity. The diastereoselectivity of this transformation is largely controlled by steric factors. Thus, the reaction of electron-deficient cyclopropene **4f** provided a nearly equimolar mixture of two diastereomeric cyclopropylcarboxaldehydes **5f** and **6f** due to the similar effective size of the substituents at C3 (entry 6). At the same time, the analogous ester derivative bearing a small Me-group at C3 (**4g**) reacted very selectively (entry 7). Finally, the substrate possessing a very bulky Bn-protected tertiary alcohol function (**4h**) provided a single diastereomer of formylcyclopropane **5h** (entry 8). We also tested the hydroformylation reaction of 1,3,3-trisubstituted cyclopropene **4i**, which represents a more challenging model, as it can potentially produce four different products in the *syn*-specific addition and, therefore, requires simulataneous control of facial and regioselectivity. It was found that standard reaction conditions using 0.067 mol% of Rh-catalyst did not produce any reaction with **4i**, presumably, due to the increased steric demand in the substrate. However, increasing catalyst loading to 1 mol% provided tetrasubstituted cyclopropane **5i** in good yield and high regio- and diastereoselectivity (entry 9).

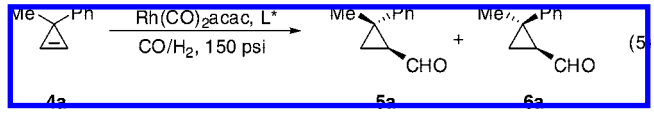
Naturally, having in hand efficient conditions for the diastereoselective hydroformylation, we were very intrigued by the possibility of performing an asymmetric hydroformylation of prochiral cyclopropenes (eq a). We began our optimization[25] by testing several commercially available ligands, which were shown to produce high enantioselectivities in the asymmetric hydroformylation (AHF) of styrene.[26] However, all of these ligands provided unsatisfactory results in the hydroformylation of cyclopropene **4a**. Thus, Ph-BPE (**L1**),[25] reported by Klosin as one of the best-performing ligands for the AHF of terminal

(23) (a) Kireev, S. L.; Smit, V. A.; Ugrak, B. I.; Nefedov, O. M. *Bull. Acad. Sci. USSR (Engl. Transl.)* **1991**, 2240. (b) Witulski, B.; Gössmann, M. *Synlett* **2000**, 1793. (c) Marchueta, I.; Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2001**, *3*, 3193. (d) Pericas, M. A.; Balsells, J.; Castro, J.; Marchueta, I.; Moyano, A.; Riera, A.; Vazquez, J.; Verdaguer, X. *Pure Appl. Chem.* **2002**, *74*, 167. (e) Nüske, H.; Bräse, S.; de Meijere, A. *Synlett* **2000**, 1467. (f) Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2005**, *7*, 3593.

(24) For use of these ligands in low-p ressure hydroformylation of olefins, see for example: (a) Hjortkjaer, J.; Toromanova-Petrova, P *J. Mol. Catal.* **1989**, *50*, 203. (b) Choukroun, R.; Gervais, D.; Kalck, P.; Senocq, F. *J. Organomet. Chem.* **1987**, *335*, C9. (c) Rajurkar, K. B.; Tonde, S. S.; Didgikar, M. R.; Joshi, S. S.; Chaudhari, R. V. *Ind. Eng. Chem. Res.* **2007**, *46*, 8480. (d) Rosales, M.; Gonzalez, A.; Guerrero, Y.; Pacheco, I.; Sanchez-Delgado, R. A. *J. Mol. Cat. A* **2007**, *270*, 241.

(25) Typical procedure described on page SI9 (Supporting Information) was used for optimization of the asymmetric hydroformylation, except that dppf was substituted with an equimolar amount of the corresponding chiral ligand.

Table 2. 2. Ligand Screening in the Asymmetric Hydroformylation of 3-Methyl-3-phenylcyclopropene (**4a**)



#	Ligand	conv, % (NMR)	dr[c] (**5a**:**6a**)	ee[d] (**5a**), %	ee (**6a**), %	ee[e](b:l) in the AHF of styrene
1	(*R,R,R,R*)-Ph-BPE (**L1**)	100	12:1	−42	−3	**−94 (44.6:1)**[27]
2	(*R*)-BINAPINE (**L2**)	49	13:1	+18	+1	**+94 (9.5:1)**[27]
3	(*R,R,S,S*)-Tangphos (**L3**)	100	2.9:1	+31	−24	**+65 (14.9:1)**[27a]
4	(*R,R,S,S*)-DUANPHOS (**L4**)	100	14:1	+8	−3	**−79 (13:1)**[28]
5	(*S,S,S,S*)-Me-DUPHOS (**L5**)	6	4:1	−10	N/D	+44 (16:1)[29b]
6	(*R,R,R,R*)-*i*Pr-DUPHOS (**L6**)	100	13:1	−18	+43	**−83 (12:1)**[29b]
7	CatASium m(R) (**L7**)	0	–	–	–	−61(15.4:1)[26]
8	Josiphos J001−1 (**L8**)	82	14:1	+14	−6	−39 (11.9:1)[27]
9	Josiphos J002−1 (**L9**)	80	10.6:1	+56	−41	−43 (5.4:1)[27]
10	Josiphos J003−1 (**L10**)	95	18.5:1	+24	−7	+47 (7.1:1)[27]
11	Josiphos- J008−1 (**L11**)	100	14:1	+16	−20	+55 (24.2:1)[27]
12	Josiphos- J010−1 (**L12**)	23	27:1	−19	−4	
13	Walphos W001−1 (**L13**)	100	5.4:1	+50	+33	+44 (2.4:1)[27]
14	Walphos W002−1 (**L14**)	100	10.3:1	+42	+28	
15	Taniaphos T001−1 (**L15**)	96	7:1	−43	−34	
16	Taniaphos T003−1 (**L16**)	100	12:1	−47	−36	
17	Taniaphos T021−1 (**L17**)	<1	–	N/D	N/D	
18	Mandyphos M001−1 (**L18**)	<1	–	N/D	N/D	+24 (5.6:1)[27]
19	Mandyphos M004−1 (**L19**)	**100**	27:1	−73	+23	+10 (6.6:1)[27]
20	(*R*)-BINAP (**L20**)	84	12:1	−13	+28	+28(10.2:1)[27]
21	(*R*)-Tol-BINAP (**L21**)	72	13:1	−1	+19	
22	(*R*)-Xyl-BINAP (**L22**)	52	20:1	+14	−10	
23	CTH-(*R*)-BINAM (**L23**)	0	–	–	–	−2 (2.1:1)[27]
24	(R)-SYNPHOS (**L24**)	86	15:1	−64	+77	
25	(R)-SOLPHOS (**L25**)	70	22:1	−68	+78	
26	(R)-Xyl-SOLPHOS (**L26**)	50	31:1	−53	N/D	
27	(R)-C_3**-TUNEPHOS** (**L27**)	**100**	25:1	−74	+78	+19 (11:1)[27]
28	(R)-DIFLUOROPHOS (**L28**)	86	12:1	−36	+64	
29	BIPHEP SL-A101 (**L29**)	4	13:1	−8	−3	
30	BIPHEP SL-A109 (**L30**)	36	34:1	−45	+10	
31	(*R*)-Cl-MeO-BIPHEP (**L31**)	64	13:1	−41	+47	
32	CTH-R-P-PHOS (**L32**)	100	15:1	−27	+55	
33	CTH-R-Xyl-P-PHOS (**L33**)	100	36:1	−13	+22	
34	(*R,R*)-NORPHOS (**L34**)	2	9:1	N/D	N/D	+17 (15.7:1)[27]
35	(*R,R*)-DIOP (**L35**)	100	10:1	−16	+27	+13 (1.5:1)[27b]
36	(*S,S*)-CHIRAPHOS (**L36**)	91	16:1	−5	+10	−2 (16.8:1)[4,30]
37	(*S*)-PHANEPHOS (**L37**)	0	–	–	–	
38	(*S*)-Xyl-PHANEPHOS (**L38**)	0	–	–	–	+8 (8.8:1)[27]
39	CARBOPHOS (**L39**)	30	11:1	+13	0	+6 (6:1)[27]
40	(*R,R*)-BINAPHANE (**L40**)	8	6:1	+2	+20	−34 (8.2:1)[27]
41	(*R*)-SDP (**L41**)	0	–	–	–	
42	CTH-R-SpiroP (**L42**)	90	5:1	+36	−50	+14 (2:1)[27]
43	CatASium I (**L43**)	<1		N/D	N/D	+29 (4.2:1)[27]
44	CatASium T2 (**L44**)	7	4.4:1	+2	0	+26 (8.7:1)[27]
45	CatASium DR (**L45**)	50	13:1	+12	−6	+10 (18.5:1)[27]
46	Rhophos P001−2 (**L46**)	0	–	–	–	

[a] A Rh:L ratio of 1:1.2 was employed. See ref 27. [b] In the cited literature the opposite enantiomers of these ligands were employed; accordingly, the opposite enantiomers of the products were obtained. [c] Determined by ^{1}H NMR analysis of crude reaction mixtures. [d] Negative values of ee are provided when the levorotatory (*R,R*)-enantiomer was obtained as major product. Positive values of ee indicate the predominant formation of the dextrorotatory (*S,S*)-product. [e] Negative and positive values of ee indicate the predominant formation of (−)-R and (+)-S enantiomer, respectively.

olefins, provided **5a** with 42% ee only (Table 2, entry 1). Another highly reputed AHF ligand BINAPINE (**L2**) afforded 18% ee in the reaction with **4a** (entry 2). Further optimization demonstrated that, generally, all C_2-symmetric phospholane ligands provided significantly lower enantioselectivities than those observed in the AHF of styrenes (entries 3−7). Next, we screened a series of C_1-symmetric ligands with planarly chiral ferrocene backbone (**L8-L19**). This family of ligands,[31] possesses great structural diversity and a wide spectrum of electronic properties. Here again, it was found that several ligands showing respectable selectivities in hydroformylation of styrenes, demonstrated less than satisfying results in the reaction with **4a** (entries 10,11). And *vice versa*, the "obvious outsiders" unexpectedly produced promising enantioselectivities (entry 19). While not comprehensive, this screening clearly demonstrated that the existing immense experience in ligand optimization acquired through the AHF of terminal olefins cannot be directly applied to the hydroformylation of small cycles. Such a discrepancy is not surprising, considering the significant difference in geometry, electronic properties, and reactivity of the two types of substrates.

Accordingly, we performed an independent search for the best catalytic system. To this end, we performed screening of a few more sets of commercially available chiral diphosphine ligands, which included a group of C_2-symmetric ligands with a flexible axially chiral backbone (**L20**−**L33**, entries 20−33), and several other types of chiral ligands featuring both flexible and rigid scaffolds (**L34**−**L46**, entries 34−46). Although no

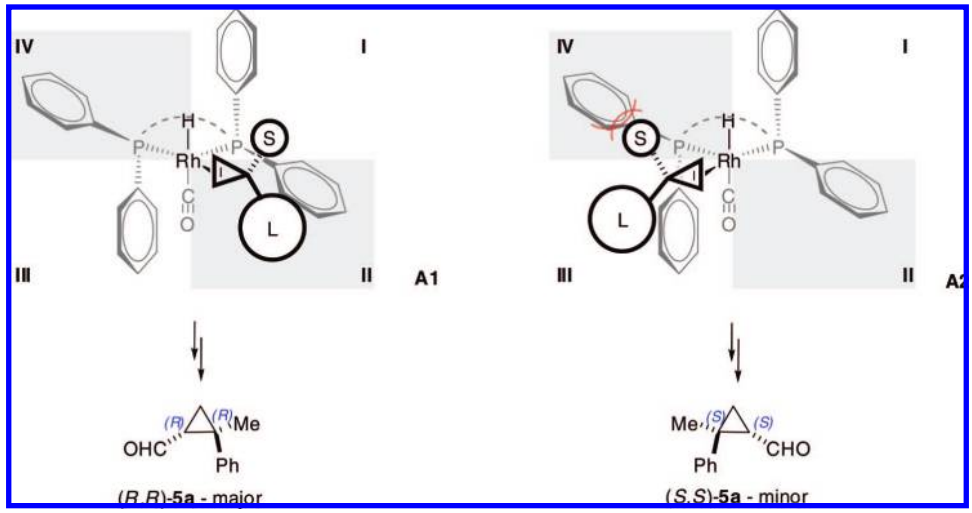
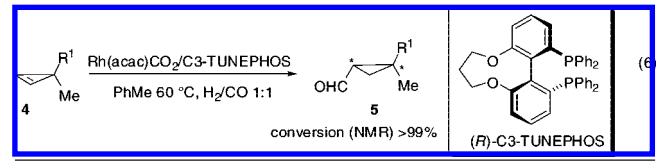


Figure 1. Proposed stereomodels for the Rh/(*R*)-C3-TUNEPHOS-catalyzed hydroformylation.

promising results were obtained in the latter case, the screening of the former group appeared to be more rewarding. Thus, promising results were obtained for SYNPHOS (**L24**, entry 24), SOLPHOS (**L25**, entry 25), and DIFLUOROPHOS (**L28,** entry 28), while the best conversion and enantioselectivity were attained in the presence of C3-TUNEPHOS (**L27**, entry 27). Notably, C3-TUNEPHOS was previously reported to be a marginal ligand for the AHF of styrene.[27]

The following rationale, based on molecular mechanics modeling (UUF), was used to account for the origins of diastereo- and enantioselectivity in the asymmetric hydroformylation reaction (stereomodels **A1** and **A2**, Figure 1).[32] As mentioned above, the facial selectivity of the reaction is controlled by sterics, as the approach of the rhodium hydride species predominantly occurs from the less hindered face of the cyclopropene (i.e., *syn*- to a smaller substituent, Figure 1). The absolute stereochemistry of the process is determined by the relative orientation of the cyclopropene in the resulting rhodium complex (**A1** vs **A2**). Molecular modeling suggests the two pseudoequatorial phenyl rings at the phosphorus atoms of (*R*)-C3-TUNEPHOS obstruct quadrants **II** and **IV** (shaded in gray in Figure 1), while quadrants **I** and **III**, with the pseudoaxial phenyl groups slightly tilted back, remain relatively unhindered.[33] Accordingly, the orientation of the cyclopropene in the trigonal bipyramidal rhodium complex **A1** is such that it minimizes the unfavorable interaction of the small substituent "S" with the phenyl groups of the ligand, favoring complex **A1** vs **A2**, which explains the absolute stereochemistry of the obtained products **5a** (Figure 1).[34]

Table 3. Rh-Catalyzed Asymmetric Hydroformylation of 3,3-Disubstituted Cyclopropenes



#	R^1		4:[Rh] ratio	dr (5:6)	ee (5), %	yield, %	$[\alpha]_D$ (conc., CH_2Cl_2)
1	CO_2Me	**4g**	750:1	22:1	74	63	−109.8 (c 1.17)
2	CMe_2OBn	**4h**	375:1	**5** only	57	82	−24.6 (c 1.25)
3	Ph	**4a**	750:1	25:1	74	86	−114.3 (c 1.42)
4	*p*−Cl-C_6H_4	**4b**	375:1	17:1	83	54	−137.8 (c 0.64)
5	*p*-Me-C_6H_4	**4j**	750:1	17:1	68	78	−128.1 (c 1.56)

To investigate the scope of the asymmetric hydroformylation reaction, we tested a series of cyclopropenes possessing different substituents at C3 in the presence of Rh/C3-TUNEPHOS catalyst (Table 3). It was found that the enantioselectivity of this reaction depended significantly on the substrate nature. Thus, phenyl- and ester-substituted cyclopropenes **4g** and **4a** provided the corresponding formylcyclopropanes with 74% ee (entries 1,3), while hydroformylation of cyclopropene **4h** possessing a

(26) For a review, see: (a) Agbossou, F.; Carpentier, J.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485 See, also. (b) van der Vlugt, J I.; Paulusse, J. M. J.; Zijp, E. J; Tijmensen, J. A.; Mills, A. M.; Spek, A. L.; Claver, C.; Vogt, D. *Eur. J. Inorg. Chem.* **2004**, 4193. (c) Ewalds, R.; Eggeling, E. B.; Hewat, A. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Chem.−Eur. J.* **2000**, *6*, 1496. (d) Dieguez, M.; Pereira, M. M.; Masdeu-Bulto, A. M.; Claver, C.; Bayon, J. C. *J. Mol. Cat. A* **1999**, *143*, 111. (e) Deng, C.; Ou, G.; She, J.; Yuan, Y. *J. Mol. Cat. A* **2007**, *270*, 76. (f) Clarkson, G. J.; Ansell, J. R.; Cole-Hamilton, D. J.; Pogorzelec, P. J.; Whittell, J.; Wills, M. *Tetrahedron: Asymmetry* **2004**, *14*, 1787. (g) Reetz, M. T.; Oka, H.; Goddard, R. *Synthesis* **2003**, *12*, 1809. (h) Pamies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 3441. (i) Deerenberg, S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **2000**, *19*, 2065. (j) Solinas, M.; Gladiali, S.; Marchetti, M. *J. Mol. Cat. A* **2005**, *226*, 141. (k) Shibahara, F.; Nozaki, K.; Hiyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8555. (l) Bonafoux, D.; Hua, Z.; Wang, B.; Ojima, I. *J. Flourine Chem.* **2001**, *112*, 101. (m) Dieguez, M.; Ruiz, A.; Claver, C. *TA Tetrahedron: Asymmetry* **2001**, *12*, 2827. (n) Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T. *Org. Lett.* **2004**, *19*, 3277.

(27) See, for example: Axtell, A. T.; Klosin, J; Abboud, K. A *Organometallics* **2006**, *25*, 5003.

(28) Sherrill, W. M.; Rubin, M. Unpublished results.

(29) Axtell, A.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834.

(30) Dieduez, M.; Pereira, M.; Claver, C.; Bayon, J. C. *J. Mol Cat A.* **1999**, *143*, 111.

(31) Merchandized by Solvias Inc.

(32) Analogous systems were successfully employed for predicting the stereochemical outcome in the Rh-catalyzed asymmetric hydroformylation of styrenes. Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A *J. Am. Chem. Soc.* **2005**, *127*, 5040.

(33) The steric environment in these stereomodels resembles that described by a Halpern for the mechanism of the Rh-catalyzed asymmetric hydrogenation in the presence of a structurally related (*R*)-BINAP ligand. See: Halpern, J *Science* **1982**, *217*, 401.

(34) Assignment of absolute configuration for non-racemic compound **5a** was performed by chemical transformation of this product into 2-methyl-2-phenylcyclopropylmethanol with known absolute configuration. Absolute configurations of all other compounds were assigned by analogy to **5a**. See Supporting Information for details.

benzyl-protected tertiary alcohol function afforded aldehyde **5h** with only moderate ee of 57% (entry 2). Remarkably, in the hydroformylation of the 3-arylcyclopropene series (Table 3, entries 3−5), introduction of an electron-withdrawing substituent in the *para*-position of the aryl ring led to a notable improvement of enantioselectivity (entry 4), whereas installation of an electron-donating group resulted in deterioration of ee (entry 5). The reasons for this unusual electronic effect are not yet completely understood. Further work to improve the enantioselectivity of this asymmetric transformation, and to understand the origins of the observed significant electronic effect on the enantioinduction of hydroformylation, is currently underway in our laboratories.

In conclusion, we demonstrated the first catalytic diastereo- and enantioselective hydroformylation of prochiral cyclopropenes proceeding under very mild conditions and low loadings of the Rh(I)-catalyst. Optimization of the reaction protocol allowed for complete suppression of the dominating side processes, and permitted design of a novel, efficient catalytic carbonylative transformation amenable for scale-up production. This methodology opens new avenues toward efficient preparation of optically active cyclopropylcarboxaldehydes, valuable building blocks for synthetic chemistry.

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Supporting Information Available: Experimental details. Complete ref 11d. This material is available free of charge via the Internet at http://pubs.acs.org.

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