J|A|C|S COMMUNICATIONS

Published on Web 10/28/2010

Enantioselective Desymmetrization of Cyclopropenes by Hydroacylation

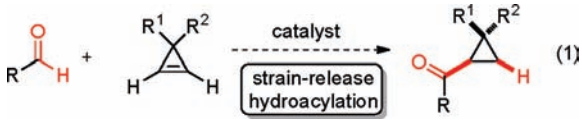
Diem H. T. Phan, Kevin G. M. Kou, and Vy M. Dong*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

Received August 27, 2010; E-mail: vdong@chem.utoronto.ca

Abstract: We report an enantioselective desymmetrization of cyclopropenes by intermolecular Rh-catalyzed hydroacylation. Cyclopropylketones, bearing quaternary stereocenters, are produced with diastereocontrol (up to >20:1) and excellent enantiomeric excess (up to >99 *ee*).

Cyclopropanes are relevant structures in physical organic, natural product, and medicinal chemistry.[1] As a result, this three-membered motif has inspired various methods for its synthesis.[1,2] Our laboratory aims to design atom-economical and stereoselective methods for synthesis,[3] particularly by catalytic hydroacylation.[4] To make cyclopropanes bearing vicinal stereocenters, we imagined a novel intermolecular hydroacylation of cyclopropenes (eq 1).[5] In general, intermolecular hydroacylation is difficult to achieve due to competing pathways, namely decarbonylation and catalyst decomposition.[4] However, we reasoned the strain energy released by reducing the cyclopropene would favor hydroacylation over these pathways.[6]



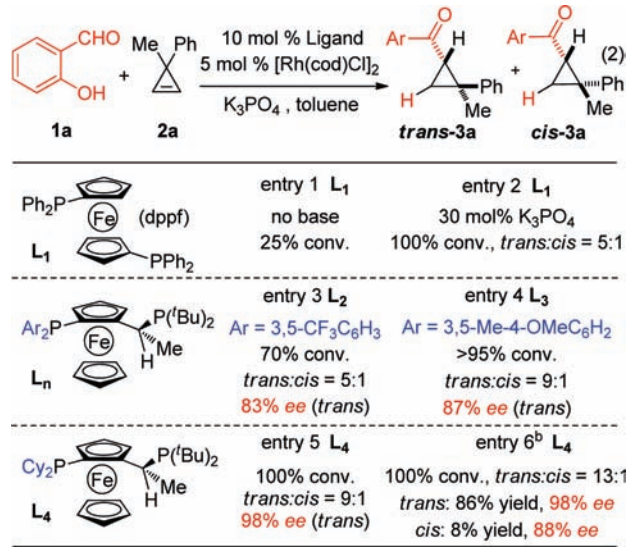
(1)

To date, only three other highly enantioselective intermolecular hydroacylations have been published, featuring allenes,[7a] acrylamides,[7b] and homoallylic sulfides.[7c] Norbornenes,[7d] norbornadienes,[7d] and 1,5-hexadiene[7e] also undergo hydroacylation, but with moderate enantioselectivity. Encouraged by these studies, we searched for a Rh-complex to catalyze hydroacylation of achiral cyclopropene **2a** using salicylaldehyde **1a** (Table 1). We chose **1a** because its phenolic oxygen is known to coordinate to Rh and promote hydroacylation.[7d−g] In the absence of catalyst, no transformation was observed.

We evaluated various catalysts, prepared *in situ* by adding different ligands to $[Rh(cod)Cl]_2$. A family of ferrocene-based phosphines proved promising. Using dppf as a ligand resulted in 25% conversion of aldehyde **1a** to the cyclopropylketone **3a** (entry 1). Previous reports suggest that inorganic bases promote hydroacylation,[7d−g] possibly by deprotonating phenol to form phenolate, a better coordinating substrate. Indeed, a catalytic amount of K_3PO_4 completely transformed **1a** to **3a** with 5:1 *dr* (entry 2). To achieve asymmetric induction, we tested various chiral Josiphos ligands.[8] Among those tested, the more electron-rich *and* sterically bulky ligands gave better yields and enantioselectivity (cf entries 3−5). With further optimization using Josiphos ligand $\mathbf{L_4}$, cyclopropylketones **3a** were produced with 13:1 *dr* in favor of the *trans*-diastereomer, as determined by NMR analysis (5 mol % Rh, entry 6). The observed diastereoselectivity suggests that Rh-hydride insertion (and subsequent C−C bond reductive elimination) preferentially occurs on the cyclopropene face opposite the *larger* substituent (i.e., the phenyl group). The major diastereomer was produced in 98% *ee*, and the minor in 88% *ee* (Table 2, entry 1).

With one protocol, we prepared cyclopropylketones from 12 readily available arylaldehydes (Table 2). Salicylaldehydes, with substituents

Table 1. Rh-Catalyzed Cyclopropene Hydroacylation: Ligand Impact on Stereoselectivity[a]



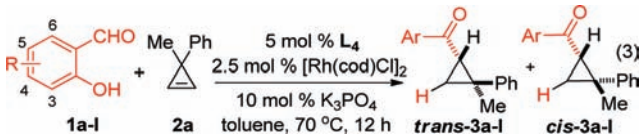
[a] Conditions: 0.1 mmol of **1a**, 0.12 mmol of **2a**, 30 mol % K_3PO_4, 60 °C, 48 h. [b] 0.2 mmol of **1a**, 0.3 mmol of **2a**, 5 mol % Rh, 5 mol % ligand, 10 mol % K_3PO_4, 70 °C, 12 h. *dr*'s based on ^{1}H NMR integration of reaction mixture; *ee*'s determined by chiral HPLC analysis.

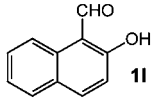
at the *ortho*-, *meta*-, or *para*-positions, were efficiently oxidized to aryl ketones (entries 2−11). Steric bulk at the 3- or 6-position on the aryl ring was accommodated by the catalyst (92 to >99% yields, 98 to >99% *ee*'s, entries 2−4, 11). Substrates with electron-donating (e.g., Me−, ^{t}Bu−, MeO−) or electron-withdrawing (e.g., −COOMe, −F, −Cl) groups were transformed to their corresponding cyclopropylketones (entries 6−10). Likewise, hydroacylation between 2-naphthaldehyde **1l** and cyclopropene **2a** gave cyclopropane **3l** (90% yield, 13:1 *dr*). The major diastereomer was produced in 95% *ee*. By single crystal X-ray analysis, the absolute configuration of the major diastereomer was found to be the (1*S*,2*S*)-isomer whereas the minor diastereomer was the (1*S*,2*R*)-isomer.[8]

Next, we subjected cyclopropenes bearing different quaternary carbon centers to hydroacylation (Table 3). Cyclopropenes **2b** and **2c** having electron-deficient aryl groups underwent hydroacylation with similar efficiency to model **2a** (93−94% yields, 98 to >99% *ee*, entries 1−2) but slightly lower diastereoselectivity (10:1 and 6:1, respectively). Cyclopropenes bearing more electron-rich aromatic rings appear to undergo hydroacylation with higher diastereoselectivity. Indeed, hydroacylation of cyclopropenes bearing *hetero*aromatic rings (**2d** and **2e**) result in >20:1 *dr*'s and 99% *ee*'s (entries 3 and 4). Cyclopropene **2f**, bearing a Lewis basic group (CH_2OMe), was transformed to the major product, *trans* isomer **3f** (76% yield, 98% *ee*, entry 5). A naphthalene-substituted cyclopropene **2g** resulted in the corresponding cyclopropylketone **3g** in excellent yield and enantiomeric excess (>99% yield, 99% *ee* for the *trans*-isomer, 10:1 *dr*, entry 6). Lastly, we

10.1021/ja107738a

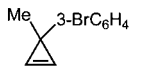
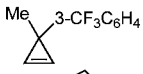
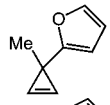
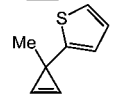
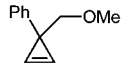
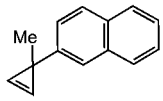
Table 2. Hydroacylation with Various Salicylaldehydes[a]



Entry	R		*dr*[b] (*trans*: *cis*)	% Total Yield	% *trans* (*ee*)[c]	% *cis* (*ee*)[c]
1	H	**1a**	13:1	94	86 (98)	8 (88)
2	3-Cl	**1b**	13:1	95	85 (>99)	10 (>99)
3	3-Me	**1c**	10:1	93	85 (99)	8 (98)
4	3-OMe	**1d**	14:1	>99	92 (>99)	8 (91)
5	4-Me	**1e**	10:1	97	89 (98)	8 (>99)
6	5-^{t}Bu	**1f**	12:1	94	86 (99)	8 (99)
7	5-OMe	**1g**	11:1	97	88 (99)	9 (97)
8	5-COOMe	**1h**	10:1	94	86 (99)	8 (96)
9	5-Cl	**1i**	11:1	93	84 (97)	9 (88)
10	5-F	**1j**	12:1	90	79 (97)	11 (93)
11	6-Me	**1k**	12:1	92	84 (99)	8 (99)
12		**1l**	13:1	90	82 (95)	8 (94)

[a] Conditions: 0.2 mmol of **1**, 0.3 mmol of **2a**. [b] Based on ^{1}H NMR integration of the crude reaction mixture. [c] Isolated yields, *ee*'s were determined by chiral HPLC analysis.

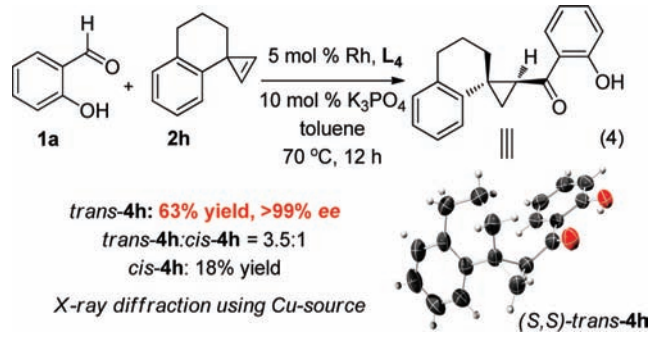
Table 3. Hydroacylation of Various Cyclopropenes[a]

Entry	Cyclopropene		*dr*[c] (*trans*:*cis*)	% Total Yield	% *trans*-**4** (*ee*)[d]	% *cis*-**4** (*ee*)[d]
1		**2b**	10:1	94	80 (99)	13 (99)
2		**2c**	6:1	95	78 (98)	17 (97)
3		**2d**	>20:1	81	81 (99)	--
4		**2e**	>20:1	88	88 (99)	--
5[b]		**2f**	6.5:1	88	76 (98)	13 (60)
6		**2g**	10:1	>99	91 (99)	9 (99)

[a] Conditions: 5 mol % catalyst, 10 mol % K_3PO_4, 70 °C, 12 h, 0.2 mmol of **1a**, 0.3 mmol of **2**. [b] 30 mol % K_3PO_4, 24 h. [c] Based on ^{1}H NMR integration of crude reaction mixture. [d] Isolated yields, *ee*'s were determined by chiral HPLC analysis.

performed hydroacylation on cyclopropene **2h** to afford **4h** featuring a *spiro*-quaternary carbon center in >99% *ee* and 3.5:1 *dr* (eq 4). Through X-ray crystallography with copper irradiation, the absolute configuration of the *trans*-**4h** product was found to be the (1*S*,2*S*)-isomer.[8]

To conclude, intermolecular Rh-catalyzed hydroacylation yields enantioenriched cyclopropylketones with vicinal tertiary and quaternary chiral centers. Our catalytic method complements the few existing ways to make quaternary carbon-substituted cyclopropanes[5] and represents a rare asymmetric cyclopropene reaction.[5f,9] These findings highlight the use of strain energy for enantioselective catalytic transformations of C−H bonds.



Acknowledgment. University of Toronto, CFI, ORF, NSERC, and Boehringer Ingelheim (Canada) Ltd. for funding. VMD is a Sloan Fellow, and KGMK a Walter and Warren OGSST scholar. We thank Matthew Coulter for helpful suggestions, Dr. Alan Lough (U of Toronto) and Dr. Thierry Maris (U de Montréal) for X-ray structure analyses, and Solvias for the donation of diphosphine ligands.

Supporting Information Available: Experimental procedures, X-ray crystallographic data, characterization data for new compounds, and chiral chromatographic analyses (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (c) Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473. (d) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625. (e) Brackmann, F.; De Meijere, A. *Chem. Rev.* **2007**, *107*, 4493.
(2) (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Kalkofen, R.; Brandau, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6667. (c) Kunz, R. K.; MacMillan, D W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240. (d) Johansson, C. C. C.; Bremeyer, N.; Ley, S. V.; Owen, D. R.; Smith, S. C.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6024. (e) Rios, R.; Sunden, H.; Vesely, J.; Zhao, G.-L.; Dziedzic, P.; Cordova, A. *Adv. Synth. Catal.* **2007**, *349*, 1028.
(3) Trost, B. M. *Science* **1991**, *254*, 1471.
(4) For reviews on olefin hydroacylation, see: (a) Fu, G. C. In *Modern Rhodium-Catalyzed Reactions*; Evan, P. A., Ed.; Wiley-VCH: New York, 2005; pp 79−91. (b) Willis, M. *Chem. Rev.* **2010**, *110*, 725. For a recent contribution from our lab, see: (c) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932.
(5) For selected enantioselective synthesis of cyclopropanes with quaternary stereocenters, see: (a) Shibata, Y.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.* **2010**, *132*, 7896. (b) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155. (c) Companyo, X.; Alba, A.-N.; Cardenas, F.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2009**, 3075. (d) Marini, F.; Sternativo, S.; Del Verme, F.; Testaferri, L.; Tiecco, M. *Adv. Synth. Catal.* **2009**, *351*, 1801. (e) Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2009**, *11*, 787. (f) Sherill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804.
(6) For a review on cyclopropene chemistry, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117, and references therein.
(7) (a) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 17232. (b) Shibata, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2009**, *131*, 12552. (c) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* In press, doi: 10.1021/ja107198e. (d) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 1185. (e) Inui, Y.; Tanaka, M.; Imai, M.; Tanaka, K.; Suemune, H. *Chem. Pharm. Bull.* **2009**, *57*, 1160. (f) Tanaka, K.; Tanaka, M.; Suemune, H. *Tetrahedron Lett.* **2005**, *46*, 6053. (g) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144.
(8) See Supporting Information for details on optimization of the catalyst and other parameters. The absolute configurations of *trans*-**3b**, *cis*-**3c**, *trans*-**3l**, *trans*-**4g** and *trans*-**4h** were assigned from single crystal X-ray crystallography results. Absolute configurations of other products are assigned by analogy.
(9) (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (b) Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600. (c) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566. (d) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (e) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824.

JA107738A