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One-Pot Desymmetrizing Hydroformylation/Carbonyl Ene Cyclization Process: Straightforward Access to Highly Functionalized Cyclohexanols

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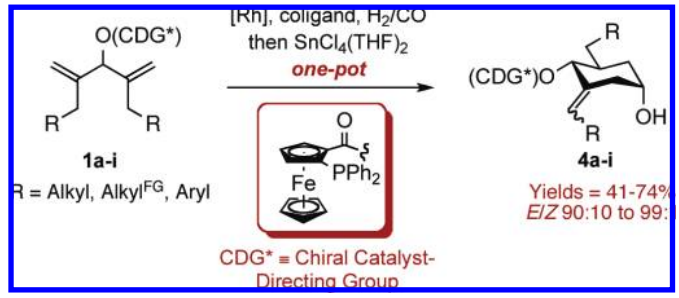
ABSTRACT



Rapid access to highly functionalized alkylidene cyclohexanols through a one-pot desymmetrizing hydroformylation/carbonyl ene cyclization starting from simple bisalkenylcarbinols is reported. Mechanistic insight into the carbonyl ene reaction is given, highlighting the importance of hyperconjugative substituent effects.

Densely functionalized cyclohexanes are structural elements that are ubiquitous in natural and synthetic bioactive molecules.[1] The variety of functionality and substitution patterns found continues to drive efforts toward the development of new synthetic methods. Particularly attractive is the access to this class of compounds from simple acyclic precursors through atom economic procedures with control of all levels of selectivity.[2] In this context, recent advances have been made relying on transition metal catalysis[3] or organocatalysis.[4] We recently disclosed the stereoselective synthesis of important carbahexoses based on a desymmetrizing hydroformylation and subsequent carbonyl ene cyclization in a one-pot process.[5] The planar-chiral catalyst-directing group, the *o*-(diphenylphosphanyl)ferrocenylcarbonyl (*o*-DPPF)[6]moiety (Scheme 1), attached to the symmetrical bis-2-propenyl-methanol allowed for diastereotopic alkene group and face discrimination in the hydro-

(1) Bayón, P.; Marjanet, G.; Toribio, G.; Ramon, A.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 3486.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(3) See, for example: (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) Aubert, O.; Buisine, M.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) Plumet, J.; Gomez, A. M.; Lopez, J. C. *Mini-Rev. Org. Chem.* **2007**, *4*, 201.

(4) See, for example: (a) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 9202. (c) Cabrera, S.; Alemán; an, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *47*, 121. (d) Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *10*, 2437.

(5) Bigot, A.; Breit, B. *Chem. Commun.* **2008**, DOI: 10.1039/8817786D.

(6) Breit, B.; Breuninger, D. *Synthesis* **2005**, *16*, 2782.

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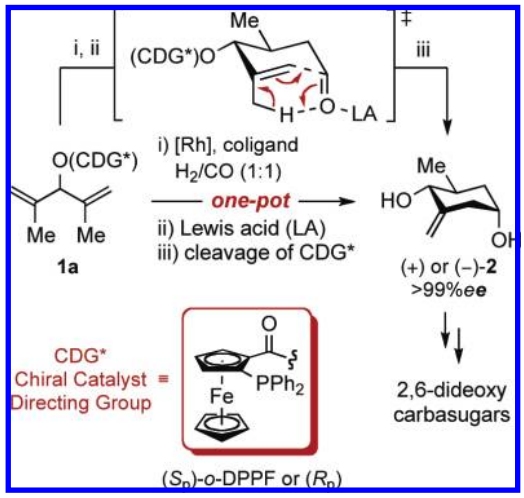
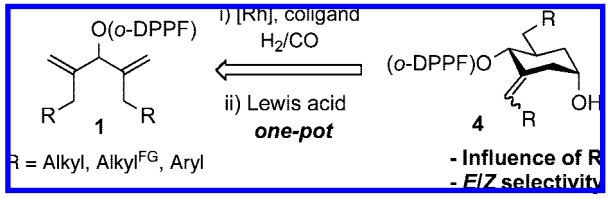
Scheme 1. One-Pot Desymmetrizing Hydroformylation/Carbonyl Ene Cyclization Process



formylation of **1a** to furnish selectively the *syn*-aldehyde intermediate.[7] Subsequent carbonyl ene cyclization and cleavage of the directing group in the same pot gave gave both optical antipodes of **2**, either starting from (S_p)-*o*-DPPF ester or its (R_p) enantiomer. Further selective and protecting group-free transformations provided the carbocyclic analogues of four important 2,6-dideoxysugars in a straightforward manner.

We herein report on the development, limitation, and scope of this one-pot desymmetrizing hydroformylation/carbonyl ene cyclization reaction of various dialkenyl-carbinol *o*-DPPF esters (**1**, Scheme 2), which provides a rapid access to a variety of

Scheme 2. Concept of This Study



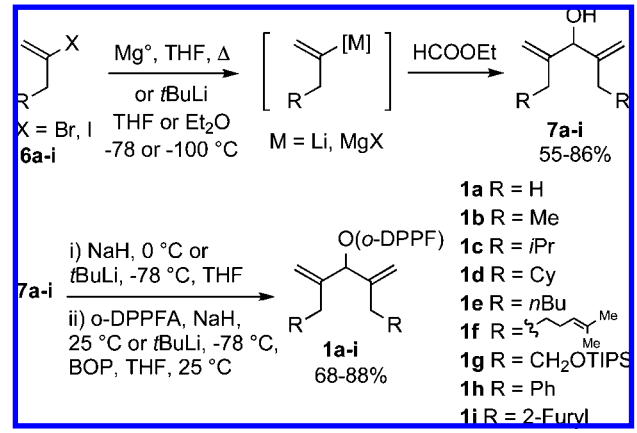
functionalized alkylidene substituted cyclohexanols, particularly interesting for further design of carbohydrate mimetics.[8] In particular, the role of the substituent R at the allylic position was probed in the course of this study and revealed interesting stereoelectronic effects on the ene cyclization step.

For the synthesis of dialkenylcarbinols of type **7** we adopted the route formerly developed[7b] of double addition of alkenylmetal species to ethylformate (Scheme 3). Carbinols **7a–i** were obtained in satisfactory to good yields.

(7) (a) Breit, B.; Breuninger, D. *J. Am. Chem. Soc.* **2004**, *126*, 10244. (b) Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, *18*, 3916.

(8) (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (b) Arjona, O.; Gomez, A. M.; Lopez, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919.

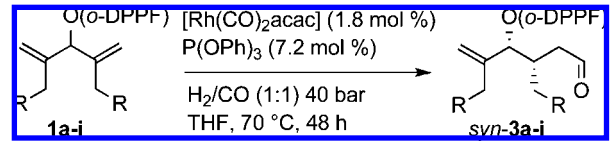
Scheme 3. Preparation of Dialkenylcarbinol *o*-DPPF Esters **1a–i**[a]

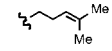


[a] See Supporting Information for detailed procedures.

Subsequent esterification with the *o*-(diphenylphosphanyl-)ferrocene carboxylic acid (*o*-DPPFA) under a dual activation protocol and BOP as coupling reagent[7b] furnished the desired esters **1a–i** in good yields. Desymmetrizing hydroformylation conditions applied to **1a–i** provided *syn*-aldehydes **3a–i** in high yields and with good to excellent diastereoselectivities as a function of the steric demand of the substituent R (Table 1).[9]

Table 1. Desymmetrizing Hydroformylation of **1a–i**

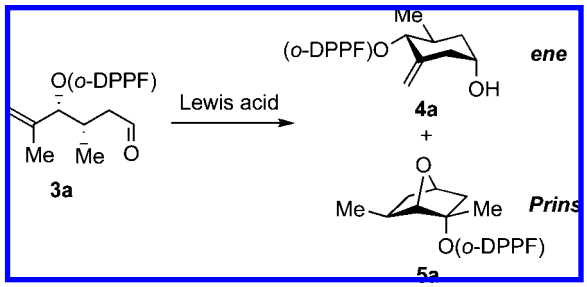


entry	R	product	dr (*syn*/*anti*)[a]	yields (%)[b]
1	H	**3a**	88 12	92
2	Me	**3b**	92:8	84
3	*i*Pr	**3c**	95:5	85
4	Cy	**3d**	91:9	85
5	*n*Bu	**3e**	95:5	78
6[c]		**3f**	99:1[d]	78
7	CH_2OTIPS	**3g**	99:1	82
8	Ph	**3h**	91:9	82
9	2-Furyl	**3i**	93:7	85

[a] Ratio was determined by integration of ^{1}H NMR spectrum of the crude. [b] Isolated yields of the *syn*/*anti* mixture. [c] Temperature was 50 °C, and the reaction stopped after 40 h. [d] 14% of five other aldehydes were detected.

In a first set of experiments, we examined the ene cyclization[10,11] of aldehyde **3a** in the presence of various Lewis acid promoters (Table 2). Interestingly, when employing $Sc(OTf)_3$

Table 2. Cyclization of **3a** under Lewis Acidic Activation



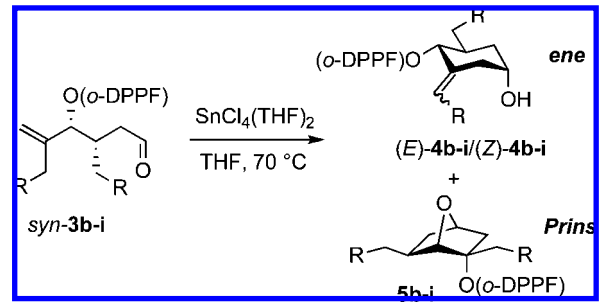
entry[a]	Lewis acid	equiv (mol %)	time (h)[b]	ene/Prins **4a**:**5a**[c]
1	$Sc(OTf)_3$	20	1	79:21
2	BF_3·THF	20	2	85:15
3	$B(C_6F_5)_3$	20	2	89:11
4	Me_2AlCl	100	1	92:8
5	Me_2AlCl	50	6[d]	94:6
6	$SnCl_4(THF)_2$	20	<0.5	91:9

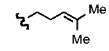
[a] All reactions were performed in THF at 70 °C except for entries 4 and 5, which were run at 25 °C. [b] At quantitative conversion. [c] Ratio was determined by integration of ^{1}H NMR spectrum of the crude mixture. [d] Conversion was incomplete (90%).

(entry 1), a mixture of two products was formed composed of the ene cyclization product **4a** and a bridged bicyclic ether **5a** (Prins product, vide infra) in a ratio of 79:21. BF_3·THF complex and $B(C_6F_5)_3$ (entries 2 and 3) gave better selectivities in favor of the ene product, but the reaction proceeded slower. A much better result was obtained with Me_2AlCl; however, stoichiometric amounts of Lewis acid were required (entries 4 and 5). Finally $SnCl_4(THF)_2$ (entry 6) was found to be the best compromise in terms of reactivity and selectivity since a substoichiometric amount (20 mol %) promoted the cyclization smoothly in less than 30 min with high selectivity (91:9 ene/Prins ratio).

Thus, $SnCl_4(THF)_2$ also catalyzed the cyclization of *syn*-aldehydes **3b**−**h** to furnish ene products **4** with good chemoselectivity and excellent stereoselectivity (Table 3). In all cases the exocyclic alkene function possesses the *E*-configuration, and the newly formed secondary alcohol stereocenter had in all cases the axial configuration as proven by NOESY experiments. Notably, when R was an alkyl substituent, aldehydes **3b**−**f** underwent a fast ene cyclization (entries 1−5) with excellent control of *E*/*Z*-configuration, regardless of the size of R. With an oxygen-substituted alkyl substituent R (entry 6), the reaction proceeded significantly more slowly and with decreased ene/Prins selectivity. For the phenyl-substituted derivative (entry 7), the cyclization

Table 3. Cyclization of **3b**−**i** under Lewis Acidic Conditions



entry[a]	aldehyde	R	time (h)	conversion (%)[b]	composition (products) (%)[b] *Ene* (*E*/*Z*) **4**	*Prins* **5**
1	**3b**	Me	0.5	100	91 (98:2)	9
2	**3c**	*i*Pr	0.25	100	92 (94:6)	8
3	**3d**	Cy	0.25	100	92 (95:5)	8
4	**3e**	*n*Bu	0.25	100	92 (91:9)	8
5	**3f**		0.25	100	92 (91:9)	8
6	**3g**	CH_2OTIPS	2	100	81 (99:1)	19
7	**3h**	Ph	4	97	81 (97:3)	19
8	**3i**	2-Furyl	8	0	-	-

[a] All reactions were performed with 20 mol % $SnCl_4(THF)_2$ except for entry 1, which was run with 5 mol %, and entry 8, which was run with 40 mol %. BF_3·THF (20 mol %) was used in entry 7. [b] Conversion determined by integration of ^{1}H NMR spectrum of the crude mixture.

was even slower, and the furyl derivative *syn*-**3i** did not react at all (entry 8). These observations indicated that the ene cyclization is strongly affected by the electronic properties of the allylic substituent R, the better σ-electron-donating groups leading to higher reactivity and selectivity, irrespective of their steric demand.

For synthetic purpose, these optimized conditions of cyclization could be combined with the hydroformylation in a one-pot process (Table 4). Simple addition of the Lewis acid to the crude mixture of the hydroformylation reaction led directly from **1a**−**h** to ene products **4a**−**h**, respectively, in fair to good yields and excellent selectivity.

A rational accounting for the formation of the reaction products and the stereochemical outcome of the cyclization reaction is depicted in Scheme 4. Thus, assuming a bicyclic transition state with minimization of *syn*-pentane interactions would account for the formation of both the *E*-configured alkene function and the axial hydroxy group.

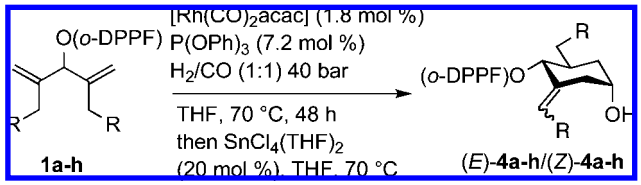
Furthermore, such a bicyclic transition state places the allylic substituent R in an ideal position to allow hyperconjugative stabilization of the positive charge developing at C2 in the course of the cyclization.[12] This would account for the observed higher reactivity of the alkyl-substituted derivatives **3b**−**f** (Table 3, entries 1−5) and the lower

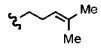
(9) For determination of relative and absolute configuration, see: Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, *18*, 3916.

(10) (a) For a review on the ene reaction, see: Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) For recent advances on intramolecular carbonyl ene reaction, see: Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1469.

(11) For mechanistic aspects of the type II carbonyl ene cyclization, see: (a) Johnston, M. I.; Kwass, J. A.; Beal, R. B.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 5419. (b) Braddock, D. C.; Hii, K. K.; Brown, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1720. (c) Mondal, N.; Mandal, C. S.; Das, G. K. *J. Mol. Struct.* **2004**, *680*, 73.

Table 4. One-Pot Desymmetrizing Hydroformylation/Carbonyl Ene Cyclization Process



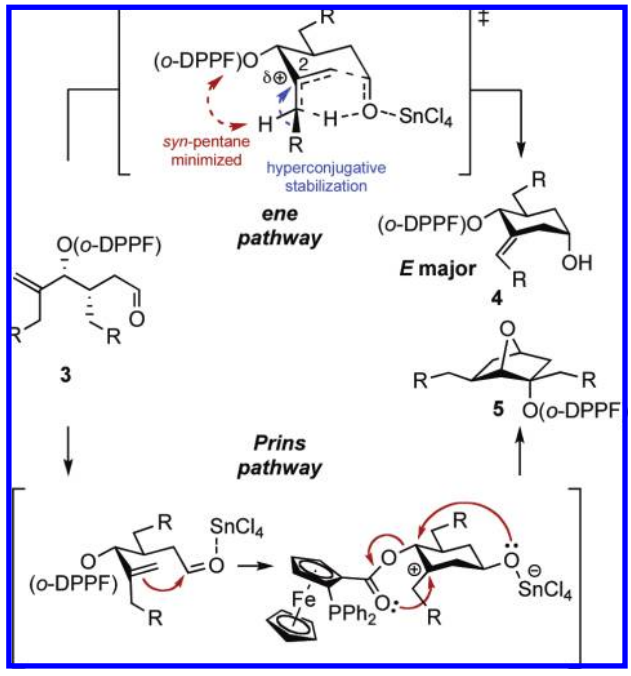
entry	R	time (h)	product	yields (%)[a]	E/Z[b]
1	H	2.5	**4a**	61%	-
2	Me	0.5	**4b**	73%	93:7
3	*i*Pr	0.5	**4c**	72%	95:5
4	Cy	0.5	**4d**	74%	95:5
5	*n*Bu	0.5	**4e**	65%	96:4
6[c]		0.5	**4f**	60%	96:4
7	CH_2OTIPS	3	**4g**	61%	99:1
8[d]	Ph	5	**4h**	47%	90:10

[a] Combined yields after chromatography. [b] Ratio was determined by integration of ^1H NMR spectrum of the isolated products. [c] Hydroformylation was carried out at 50 °C. [d] BF_3·THF (20 mol %) was used.

reactivity for substituents with a reduced σ-donor character (Table 3, entries 7 and 8).

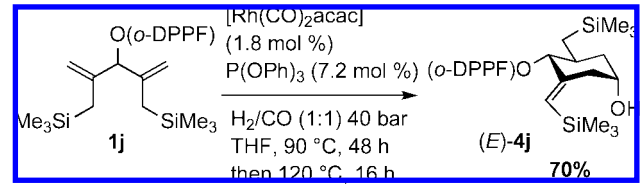
As a rationale for the formation of the bridged bicyclic ether **5**, we propose a Prins-type attack to the activated aldehyde furnishing the cationic intermediate depicted in Scheme 4. Subsequent 1,2-migration of the *o*-DPPF ester through anchimeric assistance and ring closure by alkoxide nucleophilic displacement yields bicyclic ether **5**.[13]

Scheme 4. Proposed Mechanism



Further support for our mechanistic rationale was provided by the experiment with the silyl-substituted derivative **1j**.[14] The C−Si bond is known as one of the best hyperconjugative donors.[15] Thus, cyclization of the corresponding *syn*-aldehyde obtained through directed hydroformylation occurred *without the need for Lewis acid catalysis* by simple heating. The ene cyclization product **4j** was obtained in a clean reaction as a single diastereomer (Scheme 5).

Scheme 5. Silicon Effect: No Need of Lewis Acid



In summary, starting from simple acyclic bisalkenyl carbinols a set of highly functionalized cyclohexanols could be obtained through a practical two-step, one-pot protocol. In the course of the hydroformylation excellent control of diastereoselectivity is provided by our chiral catalyst-directing *o*-DPPF group. The subsequent ene-cyclization occurred also with excellent levels of diastereocontrol. Both enantiomers are formally accessible starting from the corresponding enantiopure *o*-DPPF esters. Furthermore, our experiments gave mechanistic insights into the influence of hyperconjugative interactions of the allylic substituent R on the rate of the carbonyl ene cyclization.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The hyperconjugative stabilizing effect in the ene cyclization has been reported for allylsilanes: (a) Monti, H.; Laval, G.; Féraud, M. *Eur. J. Org. Chem.* **1999**, *8*, 1825. (b) Barbero, A.; Castreno, P.; García, C.; Pulido, F. J. *J. Org. Chem.* **2001**, *66*, 7723. (c) Barbero, A.; Castreno, P.; Fernandez, G.; Pulido, F. J. *J. Org. Chem.* **2005**, *70*, 10747.

(13) For examples of intramolecular trapping of the intermediate carbocation in the course of Prins reactions, see: (a) Mullen, C. A.; Gagne, M. *Org. Lett.* **2006**, *8*, 665. (b) Mikami, K.; Shimizu, M. *Tetrahedron* **1996**, *52*, 7287.

(14) For preparation of **1j**, see ref 7.

(15) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.