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# Diastereoselective Hydroformylation of 2,5-Cyclohexadienyl-1-carbinols with Catalytic Amounts of a Reversibly Bound Directing Group

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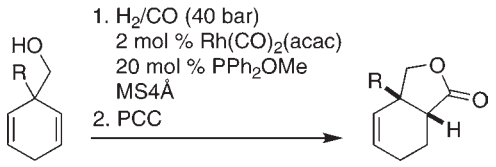
## ABSTRACT




**A phosphinite plays a role as a reversibly bound directing group for the regio- and diastereoselective hydroformylation of 2,5-cyclohexadienyl-1-carbinols. Of the two alkene functions only one was functionalized through hydroformylation to form a synthetically attractive quaternary carbon center leaving the second alkene function for potential further functionalization.**

Hydroformylation of alkenes has contributed to industrial chemistry and academic research for several decades.[1] In spite of its utility, the control of regio- and stereoselectivity is still a challenging problem. The selectivity can be controlled by a substrate and/or a ligand. Due to an electronic effect or a directing effect, branched aldehydes are provided selectively from some families of monosubstituted olefins regardless of a choice of ligand.[2] However, simple alkenes generally provide a mixture of linear and branched aldehydes. We have investigated methods to change the selectivity by employing a catalyst-directing group (CDG). Employing *o*-diphenylphosphinobenzoic acid (*o*-DPPBA) as a stoichiometric CDG connected to allylic alcohols and homoallylic alcohols via an ester linkage, the double bond was functionalized in a regio- and diastereoselective manner under hydroformylation conditions.[3] With the chiral derivative *o*-DPPFA, we have studied hydroformylative desymmetrization of bisalkenyl carbinols and bishomoallylic carbinols.[4] The methodology

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(2) (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. (b) Nozaki, K.; Takaya, H.; Hiyama, T. *Top. Catal.* **1997**, *4*, 175. (c) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251 and references cited therein. (d) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.

(3) (a) Breit, B. *Angew. Chem.* **1996**, *108*, 3021; *Angew. Chem., Int. Ed.* **1996**, *35*, 2835. (b) Breit, B. *Liebigs Ann.* **1997**, 1841. (c) Breit, B. *Eur. J. Org. Chem.* **1998**, 1123. (d) Breit, B.; Heckmann, G.; Zahn, S. K. *Chem.—Eur. J.* **2003**, *9*, 425. (e) Breit, B.; Grünanger, C. U.; Abillard, O. *Eur. J. Org. Chem.* **2007**, 2497. (f) Rein, C.; Demel, P.; Outten, R. A.; Netscher, T.; Breit, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 8670. (g) Bruch, A.; Breit, B. *Synthesis* **2008**, 2169. (h) Laemmerhold, K.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 2367.

(4) (a) Breit, B.; Breuninger, D. *J. Am. Chem. Soc.* **2004**, *126*, 10244. (b) Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, 3916. (c) Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, 3930. (d) Breit, B.; Bigot, A. *Chem. Commun* **2008**, 6498. (e) Bigot, A.; Breuninger, D.; Breit, B. *Org. Lett.* **2008**, *10*, 5321.

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was successfully applied in total synthesis.[3f,h,4d] An obvious drawback of this approach is the requirement of a stoichiometric amount of the directing group and additional steps for its connection and removal.

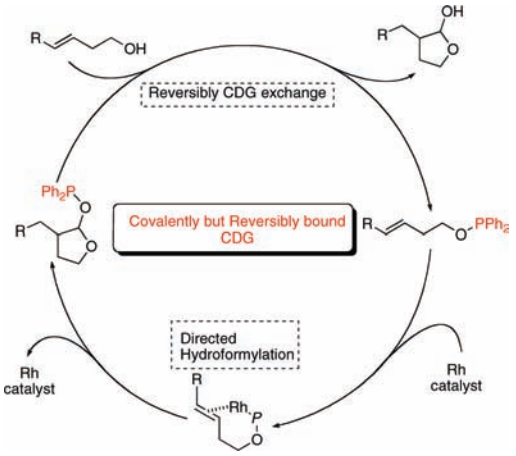
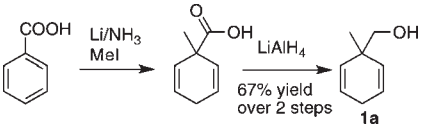



**Figure 1.** Hydroformylation with a catalyst-directing group (CDG) needed only in catalytic amounts through reversible covalent substrate binding.

Recently, Tan's group[5] and we[6] independently reported the study of catalytic amounts of covalently but reversibly bound catalyst-directing groups for hydroformylation reactions (Figure 1). These studies proved that the employed ligands are required in catalytic amounts and enable us to perform hydroformylation of homoallylic and bishomoallylic alcohols under mild conditions to afford branched aldehydes selectively through a chelated transition state in an intramolecular manner. Herein, we report the diastereoselective hydroformylation of cyclic dienes,[7] known as challenging substrates for hydroformylation, employing a phosphinite ligand bound covalently but reversibly on the substrates.

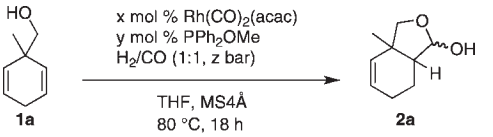
**Scheme 1.** Synthesis of 1-Methyl-2,5-cyclohexadienyl-1-methanol **1a**




1,4-Cyclohexadienes have been employed for several desymmetrization reactions.[8] The substrate, 1-methyl-2,5-cyclohexadienyl-1-methanol **1a** bearing a hydroxy group in an appropriate homoallylic position, was easily prepared from benzoic acid and methyl iodide via Birch alkylation and followed by lithium aluminum hydride (LAH) reduction to provide **1a** in 67% yield over 2 steps (Scheme 1).

First, the reaction conditions were optimized with 1-methyl-2,5-cyclohexadienyl-1-methanol **1a** as a standard

**Table 1.** Optimization of Reaction Conditions




| entry | *x* mol % | *y* mol % | *z* bar | convn[a] |
|---|---|---|---|---|
| 1[b] | 1 | 10 | 40 | 0[c] |
| 2 | 1 | 10 | 20 | 25 |
| 3 | 1 | 10 | 40 | 50 |
| 4 | **2** | **20** | **40** | **100** |
| 5 | 2 | 20 | 40 | 100[d] |
| 6 | 2 | 20 | 40 | 23[e] |

[a] The conversions were determined by $^1$H NMR. [b] The reaction was carried out without distillation of the substrate. [c] The starting material was recovered completely. [d] Overreaction proceeded, and **2a** was not obtained, 72 h reaction time. [e] Three aldehydes and **2a** was observed.

substrate (Table 1). Surprisingly, employing **1a** without prior distillative purification, and treating it with a catalyst prepared from $Rh(CO)_2$acac (1 mol %) and $Ph_2POMe$ (10 mol %), in the presence of molecular sieves 4 Å (MS4 Å) under 40 bar of $CO/H_2$ gas at 80 °C for 18 h resulted in the complete recovery of the starting material (entry 1). This proved the necessity of predistillation to remove traces of water or peroxide which could deactivate the catalyst. Although the reaction with the distilled substrate **1a** under 20 bar gave the desired lactol **2a**, the conversion was only 25% (entry 2). The conversion was improved to 50% at 40 bar (entry 3). The reaction with 2 mol % Rh catalyst and 20 mol % ligand at 40 bar provided **2a** in 100% conversion (entry 4). When the reaction was performed under the same conditions for 72 h, overreaction also proceeded, and **2a** was not observed (entry 5). A catalyst prepared from 1 mol % of $Rh(CO)_2$(acac) and 10 mol % of $PPh_3$ provided a mixture of **2a** and the other three diastereomers in a stereorandom fashion in 23% conversion, proving the directing role of the phosphinite system.

In comparison to the previous result obtained with a simple homoallylic alcohol,[6] this substrate needs harsher conditions (higher amount of catalyst, higher pressure, and higher temperature). Generally, cyclic alkenes are less reactive to hydroformylation catalysts than both *trans*- and *cis*-1,2-disubstituted alkenes. Additionally, formation of a covalent bond between the ligand and **1a** bearing

(5) (a) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (b) Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764. (c) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841. (d) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757.

(6) (a) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 967–970. (b) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346.

(7) Spencer, A. *J. Organomet. Chem.* **1977**, *124*, 85.

(8) (a) Studer, A.; Schleth, F. *Synlett* **2005**, *20*, 3033. (b) Nakahara, K.; Fujioka, H. *Symmetry* **2010**, *2*, 437 and references therein.

a sterically hindered quaternary center adjacent to the hydroxy group might be difficult. Moreover, rhodium could coordinate too tightly with the substrate having two coordinative moieties, phosphinite and diene. To dissociate the coordination after the desired reaction, a higher temperature could be required.

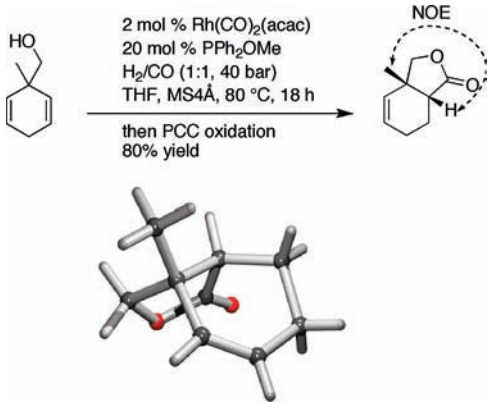
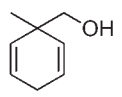
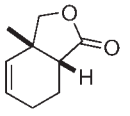
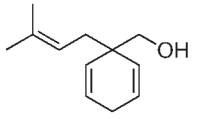
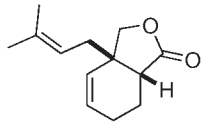
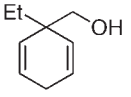
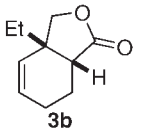
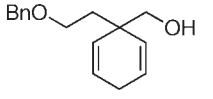
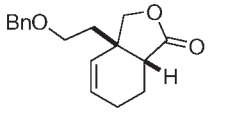
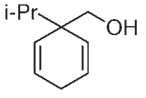
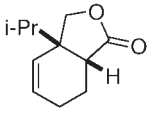
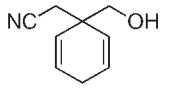
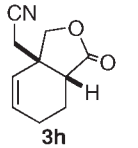
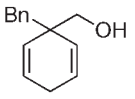
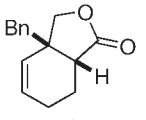
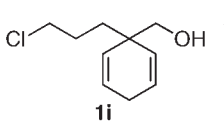
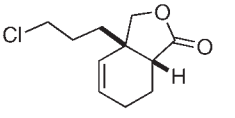
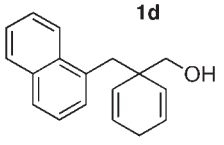
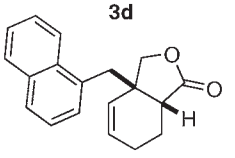
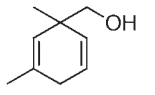
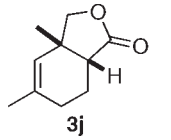



**Figure 2.** Determination of relative configuration; PLATON plot of the molecular structure of lactone **3a** in the crystal state.

After the hydroformylation, the resulting lactol **2a** was oxidized to lactone **3a** for the ease of characterization. The relative configuration of **3a** was confirmed by an NOE experiment and an X-ray structure analysis (see Figure 2). The relationship between the α-proton and methyl group of lactone **3a** was a *cis* configuration. As expected, *syn*-hydrorhodation took place to provide the lactol **2a** as a single diastereomer and PCC oxidation afforded bicyclic lactone **3a** without epimerization. The product has an attractive carbon quaternary center and a double bond which can be functionalized at a later stage.

In order to determine the generality of the reaction, we employed various substrates **1** under the optimized conditions (Table 2). These substrates could be prepared easily over two steps by Birch alkylation and LAH reduction in good to moderate yield. Employing substrates with alkyl substituents, the reaction furnished desired products as a single diastereomer in good yield except one with an isopropyl group (entry 1−5). Employing **1c** as a substrate, higher temperature and higher pressure did not improve conversion at all. Presumably, the secondary alkyl group is

**Table 2.** Scope of Substrates[a]

| entry | substrate | product | yield[b] (%) | entry | substrate | product | yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **1a** |  **3a** | 80 | 6 |  **1f** |  **3f** | 79 |
| 2 |  **1b** |  **3b** | 87 | 7 |  **1g** |  **3g** | 83 |
| 3 |  **1c** |  **3c** | 30 | 8 |  **1h** |  **3h** | 66 |
| 4 |  **1d** |  **3d** | 79 | 9 |  **1i** |  **3i** | 80 |
| 5 |  **1e** |  **3e** | 66 | 10 |  **1j** |  **3j** | 92 |

[a] The solution of diene **1** (0.6 mmol) with MS4 Å in THF (3 mL) was stirred in the presence of 2 mol % $Rh(CO)_2(acac)$ and 20 mol % $PPh_2OMe$ at 80 °C at 40 bar for 18 h. [b] The lactone **3** was isolated after hydroformylation followed by PCC oxidation.

too sterically hindered to allow exchange of the directing group from the product to the next substrate. A substrate with three alkene functions furnished the desired product without touching the other two double bonds (entry 6). Several heteroatoms were tolerated under the reaction conditions. A substrate bearing a protected hydroxy group provided the product in good yield without deprotection of a benzyl ether (entry 7). A nitrile group is known to direct a rhodium catalyst in hydroformylation reactions, though the phosphinite ligand bound to the alcohol overruled this effect (entry 8).[9] An alkyl chloride moiety was not dehalogenated under the reaction conditions, and the desired product was obtained (entry 9). An additional methyl group on one of the double bonds led to hydroformylation of the less substituted double bond (entry 10).[10]

In summary, we have demonstrated diastereoselective hydroformylation of 2,5-cyclohexadienyl-1-methanol employing a catalytic amount of a directing group. The obtained bicyclic lactones are interesting building blocks with an attractive carbon quaternary center and an additional alkene functions which can be subsequently functionalized. Investigation of a chiral phosphorus ligand leading to hydroformylative desymetrization reaction with the substrates is ongoing.[4d]

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

(9) Lambers-Verstappen, M.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 478.

(10) Relative configuration of some products was determined by NOE experiments. See Supporting Information.