Hydroformylation

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# Rhodium-Catalyzed Desymmetrization by Hydroformylation of Cyclopentenes: Synthesis of Chiral Carbocyclic Nucleosides

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***Abstract:*** *Excellent enantioselectivities (up to 97% ee) and diastereoselectivities (up to >99:1 d.r.) have been achieved in the desymmetrization of cyclopentenes by catalytic hydroformylation. This novel methodology provides an efficient and concise synthetic route to chiral cyclopentane carboxaldehydes. The key intermediate, (1S,3S)-(3-hydroxymethyl)cyclopentanol, for the synthesis of carbocyclic-ddA was obtained in three steps.*

Carbocyclic nucleosides are nucleoside analogues whose endocyclic oxygen atom is replaced by a methylene group. These analogues usually exhibit more metabolic stability towards phosphorylases and hydrolases than natural nucleosides because of the lack of the labile glycosidic bond. More importantly, many carbocyclic nucleosides show good antiviral or antitumor activities, such as carbocyclic-ddA, carbovir, neplanocine A, and aristeromycin[1] (Figure 1). Consequently, the synthesis of carbocyclic nucleosides has attracted considerable attention. Typically, synthetic approaches include enzymatic kinetic resolution,[2] asymmetric aldol condensation with subsequent ring-closing metathesis,[3] palladium-catalyzed asymmetric allylic substitution,[4] and other transformations.[5] Tedious reaction sequences, however, are required for synthesizing the carbocycle in these cases. Thus, the development of efficient and concise synthetic routes to carbocyclic nucleosides is highly desirable.

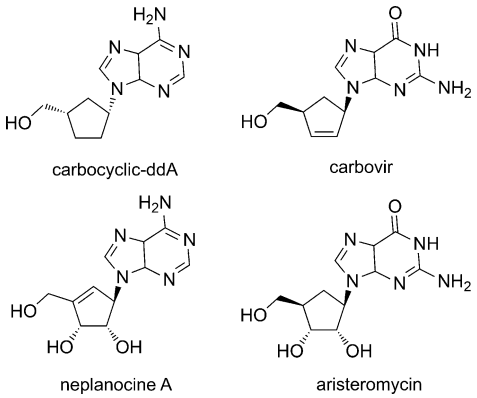
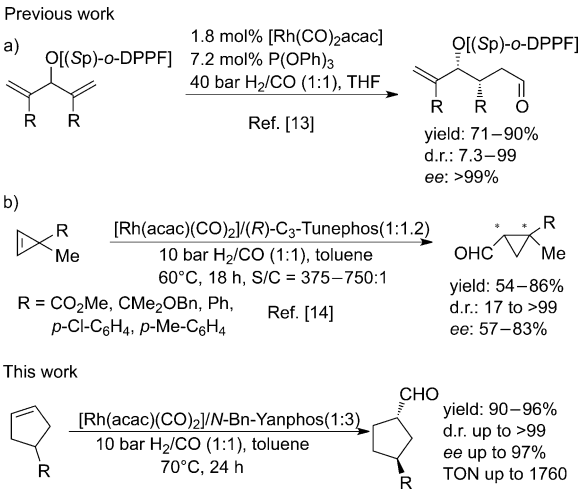



***Figure 1.*** Structures of biologically active carbocyclic nucleosides.

Asymmetric hydroformylation (AHF) is an atom-economic method to convert olefins into enantiomerically pure aldehydes, which are important intermediates for pharmaceuticals and fine chemicals.[6] Since the Rh/BINAPHOS catalyst system was reported,[7] a number of chiral phosphorus ligand systems have been developed for AHF reactions, including bis(diazaphospholane) (BDP),[8] Chiraphite,[9] Ph-BPE,[10] Yanphos,[11] and some monophosphine ligands.[12] Although good regio- and enantioselectivities have been achieved for AHF reactions of many substrates, such as monosubstituted and 1,2-disubstituted olefins, only very limited examples have been used in desymmetrization reactions by rhodium-catalyzed hydroformylation. In 2004, Breit used *o*-DPPF as a substrate-bound catalyst-directing group (CDG) in the desymmetrizing hydroformylation of prochiral bis(alkenylcarbinol)s and bis(allylcarbinol)s. Excellent enantio- and diastereoselectivities were achieved, but an equivalent of a chiral auxiliary was needed[13] (Scheme 1a). In 2008, Sherrill and Rubin reported a rhodium-catalyzed desymmetrizing hydroformylation of cyclopropenes to afford cyclopropyl carboxaldehydes with only moderate to good *ee* values (57–83%; Scheme 1b), albeit with excellent diastereoselectivities.[14] Obviously, employing a desymmetrizing hydroformylation strategy in catalytic synthesis of chiral aldehydes with high diastereo- and enantioselectivities is still




***Scheme 1.*** Examples of desymmetrizing hydroformylation. acac = acetylacetonate, DPPF = 1,1′-bis(dipheny1phosphino)ferrocene, THF = tetrahydrofuran, TON = turnover number.

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a challenge. Herein, we report an efficient access to chiral cyclopentane carboxaldehydes with high diastereoselectivities (up to > 99:1 d.r.) and excellent enantioselectivities (up to 97% *ee*) by desymmetrizing hydroformylation (Scheme 1c).

We started our investigation using methyl cyclopent-3-enecarboxylate (**1a**) as a model substrate. The AHF reactions were carried out with 20 bar $CO/H_2$ (1:1) gas at 60°C in the presence of 0.2 mol% of the catalyst, which was generated in situ by mixing $[Rh(acac)(CO)_2]$ with the ligand in toluene. Under these reaction conditions, a series of bidentate diphosphine ligands were tested (Figure 2). To our delight,

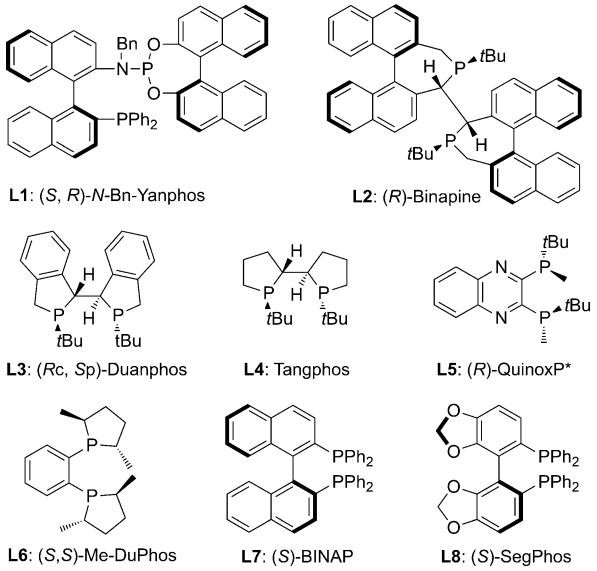
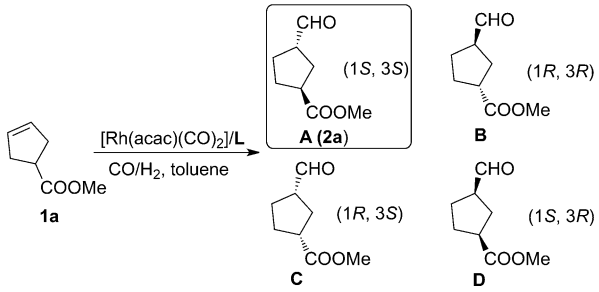



***Figure 2.*** Chiral ligands for the asymmetric hydroformylation reaction.

when (*S*,*R*)-*N*-Bn-Yanphos was used as the ligand, the desired aldehyde was achieved with 91% *ee*, 95:5 d.r., and 62% conversion (Table 1, entry 1). Further ligand screening, however, disclosed that P-chiral diphosphine ligands such as (*R*)-Binapine, (*Rc*, *Sp*)-Duanphos, Tangphos, (*S*,*S*)-Me-Duphos, and (*R*,*R*)-QuinoxP* exhibited almost no reactivity in this transformation (entries 1–6). (*S*)-BINAP and (*S*)-Segphos, having axial chirality, were also unsatisfactory ligands for this reaction (entries 7 and 8).

The success of (*S*,*R*)-*N*-Bn-Yanphos (**L1**) encouraged us to investigate the effects of reaction temperature, solvent, and syngas pressure in order to obtain optimal reaction conditions, as summarized in Table 2. We found that increasing reaction temperature beneficial for increasing the conversion, but the enantio- and diastereoselectivity were remained the same (entries 1–3). Solvent screening showed that different solvents have an influence on conversion and diastereoselectivity, but a very small effect on the enantioselectivity (entries 2 and 4–7). Among them, toluene gave the best result (91% *ee* and 95:5 d.r. with 91% conversion). Although no significant influence of the $CO/H_2$ pressure on the enantio- and diastereoselectivity was observed, the total pressure dramatically affected the reaction rate (entries 2, 8, and 9). The complete conversion was achieved in 24 hours under 10 bar of $CO/H_2$ at 70°C, affording the desired product with

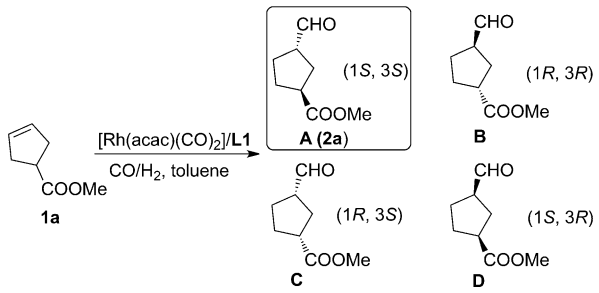
***Table 1:*** Ligand screening in the asymmetric hydroformylation of methyl cyclopent-3-ene-1-carboxylate (**1a**).[a]




| Entry | Ligand | Conv. [%][b] | d.r.[b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **L1** | 62 | 95:5 | 91 (1*S*,3*S*) |
| 2 | **L2** | 2 | 90:10 | 88 (1*S*,3*S*) |
| 3 | **L3** | 2 | 89:11 | 88 (1*S*,3*S*) |
| 4 | **L4** | 1 | 88:12 | 92 (1*S*,3*S*) |
| 5 | **L5** | trace | – | – |
| 6 | **L6** | trace | – | – |
| 7 | **L7** | trace | – | – |
| 8 | **L8** | trace | – | – |

[a] Reactions were performed on a 0.5 mmol scale at 60°C in 1 mL toluene with substrate/Rh = 500:1, L/Rh = 3:1, 20 bar $CO/H_2$ (1:1), and a reaction time of 24 hours. [b] Determined by $^1$H NMR analysis of crude reaction mixtures. d.r. = (**A** + **B**)/(**C** + **D**). [c] Refers to major diastereomer. Determined by GC analysis using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation of the derivative, 3-(hydroxymethyl)cyclopentanol, with that reported in the literature; see Ref. [5c].

***Table 2:*** Asymmetric hydroformylation of **1a**.[a]




| Entry | Solvent | *T* [°C] | $CO/H_2$ [bar] | Conv. [%][b] | d.r.[b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | toluene | 60 | 10:10 | 62 | 95:5 | 91 |
| 2 | toluene | 70 | 10:10 | 91 | 95:5 | 91 |
| 3 | toluene | 80 | 10:10 | 99 | 95:5 | 90 |
| 4 | $CH_2Cl_2$ | 70 | 10:10 | 20 | 93:7 | 92 |
| 5 | THF | 70 | 10:10 | 12 | 93:7 | 91 |
| 6 | EtOAc | 70 | 10:10 | 16 | 77:23 | 90 |
| 7 | $CH_3CN$ | 70 | 10:10 | 16 | 94:6 | 92 |
| 8 | toluene | 70 | 5:5 | 99 | 95:5 | 91 |
| 9 | toluene | 70 | 20:20 | 13 | 95:5 | 92 |
| 10[d] | toluene | 70 | 5:5 | 88 | 95:5 | 91 |

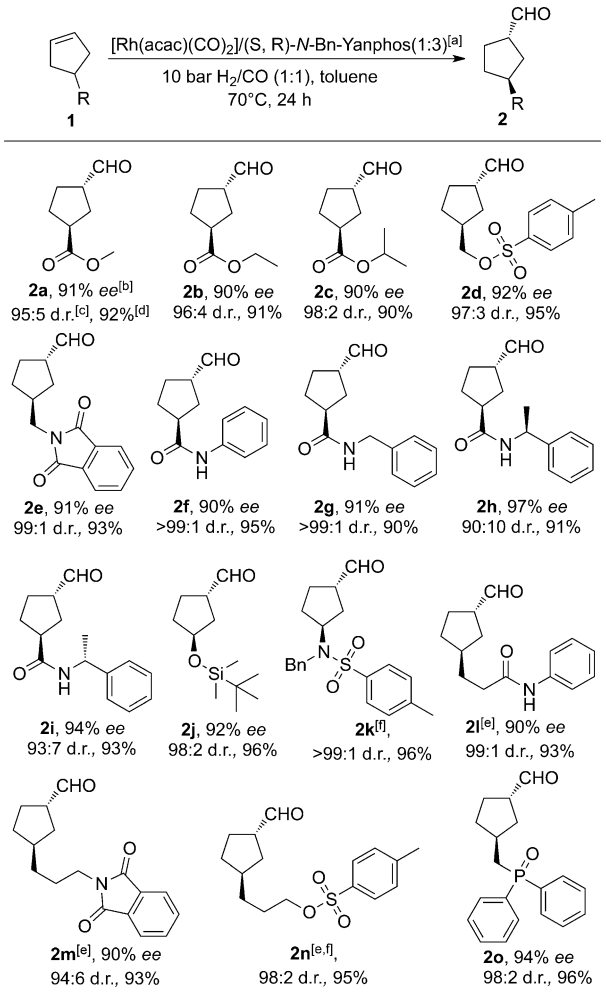
[a] Reactions were performed on a 0.5 mmol scale in 1 mL toluene with substrate/Rh = 500:1, **L1**/Rh = 3:1, and a reaction time of 24 hours. [b] Determined by $^1$H NMR analysis of crude reaction mixtures. d.r. = (**A** + **B**)/(**C** + **D**). [c] Refers to major diastereomer. Determined by GC analysis using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation of the derivative, 3-(hydroxymethyl)cyclopentanol, with that reported in the literature; see Ref. [5c]. [d] S/C = 2000.

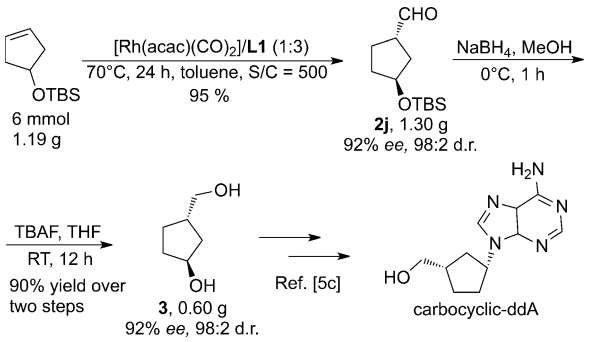
91 % *ee* and 95:5 d.r. Upon decreasing the catalyst loading to 0.05 mol %, the diastereo- and enantioselectivity were unchanged, and there was a slight decrease in conversion (entry 10).

The substrate scope of this reaction was explored under the optimized reaction conditions (Scheme 2). As the *trans* products were obtained, we thought that enhancement of the steric hindrance of the ester would improve the diastereoselectivity. Our predictions were demonstrated by the experimental results. When the substituents were changed from methyl to isopropyl, the diastereomeric ratio increased from 95:5 to 98:2, but with the similar enantioselectivities (**2a–c**). The *p*-toluenesulfonyl protected cyclopentenylmethanol was used, and excellent results were obtained (**2d**). When the OTs group was replaced by a phthaloyl group, the enantioselectivity slightly decreased, but excellent diastereoselectivity was obtained (**2e**). Next, cyclopentenes with different amide groups were evaluated. When either phenyl or benzyl was used as the protecting group for the amide, excellent distereo- and enantioselectivities were achieved (**2f,g**). Interestingly, the chiral center on the substrate had no effect on the enantioselectivity, but somewhat decreased the diastereoselectivity, whether the chiral center was either *S* or *R* (**2h,i**). Notably, substrates with the heteroatoms directly linked to the rings were tested, and the reaction went smoothly with excellent results (**2j**,**k**). By prolonging the chain length of the substituent, no effect on the reactivity was observed and excellent enantio- and diastereoselectivities remained (**2l–n**). The diphenylphosphine-oxide-containing substrate is also tolerated for this reaction, thus affording the product **2o**, which could be used in the synthesis of some chiral phosphine ligands, with 96 % *ee* and 98:2 d.r.

To demonstrate the synthetic utility of the current methodology, (1*S*,3*S*)-3-(hydroxymethyl)cyclopentanol (**3**), a key intermediate of carbocyclic-ddA, was synthesized by a concise synthetic route (Scheme 3). The asymmetric hydroformylation product **2j** was reduced by $NaBH_4$ in MeOH and afforded the corresponding alcohol. Then, by treating the alcohol with tetrabutylammonium fluoride (TBAF) in THF, **3** was obtained in good yield. Starting from the key intermediate **3**, carbocyclic-ddA can be readily synthesized following the literature procedure.[5c]




***Scheme 2.*** Rhodium-catalyzed desymmetrizing hydroformylation of cyclopentene. [a] Reactions were performed on a 0.5 mmol scale at 70 °C in toluene with substrate/Rh = 500:1, **L1**/Rh = 3:1, 10 bar $CO/H_2$ (1:1), and a reaction time of 24 hours. [b] Determined by GC or HPLC analysis using a chiral stationary phase. [c] Determined by $^1H$ NMR spectroscopy. [d] Yield of the isolated product. [e] S/C = 200. [f] The *ee* values were not determined. [g] Because of the solubility, $CH_2Cl_2$ was used as the solvent for **2f–i** and **2l**.




***Scheme 3.*** Synthesis of (1*S*,3*S*)-3-(hydroxymethyl)cyclopentanol (**3**). TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

In conclusion, we developed an efficient approach for synthesizing chiral cyclopentane carboxaldehydes by a catalytic desymmetrizing hydroformylation of cyclopentenes. This transformation exhibits excellent enantioselectivities and high diastereoselectivities under mild reaction conditions with low catalyst loading. More importantly, this method provides a concise route to the synthesis of chiral carbocyclic nucleosides and has potential applications in the synthesis of bioactive molecules. Further studies on the applications of the desymmetrizing hydroformylation strategy in organic synthesis are in progress in our lab.

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