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A highly enantioselective catalyst for asymmetric hydroformylation of [2.2.1]-bicyclic olefins

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Abstract—$Rh(CO)_2(acac)$/TangPhos was found to be a highly enantioselective catalyst for asymmetric hydroformylation of norbornylene under mild conditions. Application of the protocol to the desymmetrization of other [2.2.1]-bicyclic olefins gave moderate to excellent enantioselectivity (55–92% ee).

Hydroformylation of olefins represents one of the most important reactions in industry catalyzed by homogeneous catalysts. Regio- and stereoselective hydroformylation has emerged as an attractive tool in organic synthesis because optically active aldehydes are versatile intermediates for various pharmaceuticals, agrochemicals, and other fine chemicals. A large number of chiral ligands including phosphines, phosphites, P–O, P–N, and P–S ligands have been developed as rhodium and platinum catalysts for asymmetric hydroformylation.[1] The first highly enantioselective hydroformylation was reported in 1991 by Consiglio using a bisphosphine $PtCl_2/SnCl_2$ system.[2] A breakthrough in asymmetric hydroformylation was achieved in 1993 for the hydroformylation of styrene by a phosphinophosphite/Rh complex (up to 95% ee).[3] Although Rh and Pt catalyzed asymmetric hydroformylation has been extensively studied in the past three decades, practical applications of this important transformation are far less documented than asymmetric hydrogenations. Most of the studies have been focused on the development of chiral ligands.[4] As with many other asymmetric catalytic systems, a benchmark substrate, styrene, is often chosen to evaluate the effectiveness of those ligands. Ironically, it has been well recognized that no universal catalyst exists for all substrates. This situation makes catalyst screening become more and more important as more chiral ligands are commercially available. In this letter, we report our discovery of a highly enantioselective hydroformylation catalytic system (using a specific ligand family) that works for a specific family of substrates.

We chose the highly strained norbornylene (**1**) as our initial target-oriented substrate for asymmetric hydroformylation to obtain the chiral *exo*-norbornyl aldehyde (**2**). Enantioselective hydroformylation of this [2.2.1]-bicyclic olefin is interesting due to the following features: (1) desymmetrization of the olefin will generate three chiral carbon centers upon one C–C bond formation; (2) there are no regio-selectivity issues due to the symmetry of such olefins, although high enantioselectivity, *endo*- and *exo*-selectivities are important; and (3) functional groups located opposite to the C=C bond could be versatile, which may lead to interesting building blocks. In spite of these features, few studies of hydroformylation of this type of substrates have been documented and only low selectivities (20–60% ee) were reported in the case of norbornylene.[5]

On the outset, a ligand pool of more than 130 chiral phosphines, phosphites, phosphinophosphites, and phosphoramidites was screened for asymmetric hydroformylation of norbornylene. We were gratified to find that all ligands gave exclusively *exo*-product (*exo*/*endo* >99%) and, furthermore, the C_2-symmetric DuPhos-like bisphosphines (**3**–**8**, Fig. 1, Table 1) were outstanding

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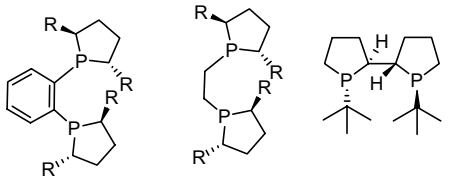
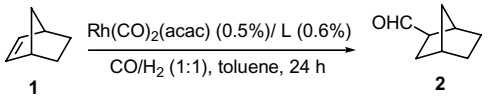


Figure 1.

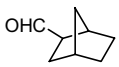
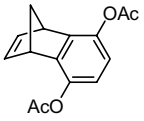
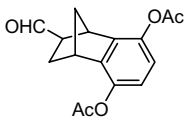
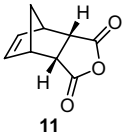
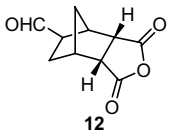
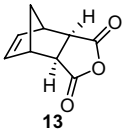
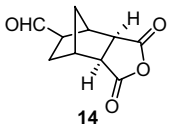
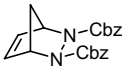
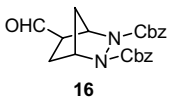
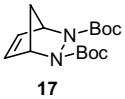
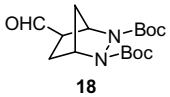
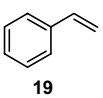
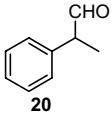
among the screened ligands for this particular substrate.[6] Among these structurally similar phosphines, a ligand structure trend had been observed: The highly rigid, sterically hindered, and electron-rich TangPhos (**8**)[7] showed the highest enantioselectivity (92–93% ee). To the best of our knowledge, this represents the highest enantioselectivity for the asymmetric hydroformylation of an unfunctionalized olefin.

Table 1. Asymmetric hydroformylation of norbornylene (**1**) under various conditions



Ligand	120 psi/rt ee (conv., %)	500 psi/60 °C ee (conv., %)	1000 psi/60 °C ee (conv., %)
3	75 (64)	61 (>99)	75 (>99)
4	81 (81)	77 (>99)	77 (>99)
5	85 (86)	77 (>99)	72 (>99)
6	69 (55)	46 (>99)	69 (>99)
7	78 (57)	73 (>99)	75 (>99)
8	**92 (90)**	**91 (>99)**	**87 (>99)**

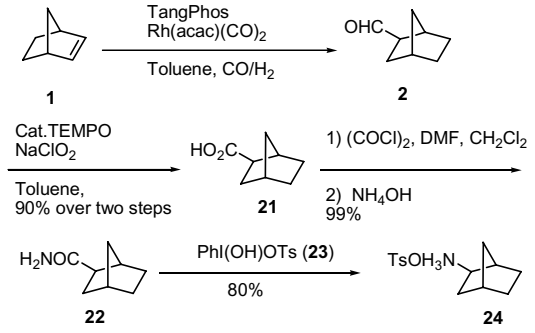
Table 2. Asymmetric hydroformylation of olefins under various conditions[a]

Olefin	Product	Ligand	Time	Conv. (%)	ee (%)
 **1**	 **2**	**8**	48	>99	**92**[b]
		7	48	>99	85[b]
		5	48	>99	78[b]
 **9**	 **10**	**8**	48	>99	**92**[b]
		8	24	>99	83[c]
		7	24	>99	72[c]
		5	24	>99	28[c]
 **11**	 **12**	**8**	48	>99	**93**[b]
		8	24	>99	91[c]
		7	24	>99	82[c]
		5	24	>99	27[c]
 **13**	 **14**	**8**	48	>99 (25/75)[e]	**92/91**[c]
		7	48	>99 (27/73)[e]	88/76[c]
		5	48	>99 (25/75)[e]	29/8[c]
 **15**	 **16**	**8**	48	>99	**60**[c]
		7	48	>99	44[c]
		5	48	>99	3[c]
 **17**	 **18**	**8**	48	>99	**56**[c]
		7	48	>99	19[c]
		5	48	>99	8[c]
 **19**	 **20**	**8**	120	44 (94/6)[f]	**76**[d]
		7	120	44 (93/7)[f]	74[d]
		5	120	20 (79/21)[f]	5[d]

[a] All reactions were performed in pressure reactors with $Rh(CO)_2$ (acac) (0.5%)/L (0.6%) in toluene, the reaction time was not optimized; Conversions and ee's were analyzed by GC or HPLC.
[b] 120 psi ($CO/H_2 = 1/1$), room temperature.
[c] 500 psi ($CO/H_2 = 1/1$), 60 °C.
[d] 600 psi ($CO/H_2 = 1/1$), 70 °C.
[e] *exo*/*endo* ratio were determined by GC and assignment was arbitrary.
[f] Branch/linear ratio were determined by GC.

Further investigation of the reaction using ligands **3**–**8** showed that pressure and temperature only slightly affect the enantioselectivity in most cases, although the reaction rates varied (Table 1). For example, when TangPhos (**8**) was used, the ee's decreased from 92%, 90%, and 87% as temperature/pressure increased from 120 psi/23 °C, 500 psi/50 °C, and 100 psi/60 °C, respectively. The rest of the ligands behaved irregularly toward the changes of temperature and pressure. When TangPhos (**8**) was used at room temperature, the ee's were consistently 92–93% for experiments where the pressures were varied from 30 psi up to 500 psi. Among several solvents tested, all gave the same ee of the product, but the less polar toluene was superior in terms of reaction rate. This solvent effect is probably due to the competitive association to the active catalytic site of Rh complex between the substrate and the more polar solvents. In practice, the catalyst precursor was generated in situ and used directly.[8] It was found that the ratio of Rh/L from anywhere 1 to 2 did not change the outcome of the reaction.

A variety of olefins were tested with the current catalytic protocol utilizing three ligands (**5**, **7**, and **8**). Interestingly, this series of C_2-symmetric ligands seemed to only favor the [2.2.1]-bicyclic olefins under relatively mild conditions. For example, [2.2.1]-bicyclic olefins (Table 2) gave quantitative formation of the corresponding aldehyde in moderate to excellent ee's (55–92% ee) and *exo*-selectivity.[9] For compounds, which have no functionality, a flat aryl ring or an *endo* moiety gave exclusively *exo*-products. One exception is the hydroformylation of the *exo*-anhydride (**13**), which gave approximately 25/75 *exo*/*endo* selectivity.[10] Moderate ee's for *meso* bicyclic hydrazine (Cbz- (**15**) and Boc- (**17**) derivatives) are probably due to the interference of the flexible protective groups. The current results are very attractive because these hydrazine products can be useful building blocks after reductive cleavage of the N–N bond.[11] It is worth noting that asymmetric hydroformylation of the benchmark styrene was very slow and showed lower enantioselectivities under the same conditions. Much harsher conditions (e.g., 800 psi/70 °C, 120 h) were employed for styrene but still no satisfactory results were obtained (44% conversion and 76% ee). Also, the product was not detected for the closely related [2.2.2]-bicyclic system under the current conditions.



Scheme 1.

To demonstrate the application of the asymmetric hydroformylation, the synthesis of *R*-*exo*-norbornylamine was carried out: The crude hydroformylated product of norbornylene in toluene was directly oxidized to the carboxylic acid (**21**). Amide (**22**) was formed via acid chloride and quenching with ammonia. Hofmann reaction of **22** gave the corresponding *exo*-norbornylamine tosylate (**24**) using Koser's reagent (PhI(OH)OTs, **23**)[12] in high chemical yield (overall 71% from norbornylene) with full retention of enantiomeric purity. This process provides a convenient and scalable access to the highly enantiomerically pure *exo*-norbornylamine that is otherwise difficult to obtain (Scheme 1).[13]

In summary, a catalytic system for highly enantioselective hydroformylation of [2.2.1]-bicyclic olefins was discovered based on ligand screening. When TangPhos was used, ee's in the range of 56–93% were observed. Further mechanistic studies are planned and insights gained will be used to guide the design of more efficient catalysts.[14]

References and notes

1. (a) Agbossou, F.; Carpentier, J.-F.; Mortreux, X. *Chem. Rev.* **1995**, *95*, 2485; (b) Gladiali, S.; Bayon, J. C.; Claver, C. *Tetrahedron: Asymmetry* **1995**, *6*, 1453; (c) Nozaki, K.; Ojima, I. In *Catalytic Asymmetric Catalysis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 429.
2. Consiglio, G.; Nefkens, S. C. A.; Borer, A. *Organometallics* **1991**, *10*, 2046.
3. (a) Sakai, S.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033; (b) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 3313; (c) Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 4051; (d) Nozaki, K.; Matsuo, T.; Shibahara, F.; Hiyama, T. *Adv. Synth. Catal.* **2001**, *343*, 61.
4. In the process of preparation of this manuscript, a communication on asymmetric hydroformylation of olefins appeared using newly designed ligands: Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040.
5. (a) Parrinello, G.; Deschenaux, R.; Stille, J. K. *J. Org. Chem.* **1986**, *51*, 4189; (b) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122; (c) Lu, S.; Li, X.; Wang, A. *Catal. Today* **2000**, *63*, 531.
6. BINAPHOS,[1c] the well-known chiral ligand for asymmetric hydroformylation, gave only 70% ee under the same conditions.
7. Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612.
8. ^{31}P NMR studies showed instant substitution of phosphine for CO in benzene-d_6.
9. The absolute structure of **2** was determined by the comparison of optical rotation of the corresponding acid with the literature.[5b] The structure of **10** was determined by X-ray analysis of single crystal. The structures of the rest of the aldehydes were proposed by analogy of **2** and **10**.
10. Even when PCy_3 was used to prepare the racemic reference, the same *exo*/*endo* distribution was observed. The assignments are arbitrary.
11. Asymmetric hydroboration of such substrates was reported recently: (a) Luna, A. P.; Bonin, M.; Micouin,

L.; Husson, H.-P. *J. Am. Chem. Soc.* **2002**, *124*, 12098; (b) Luna, A. P.; Ceschi, M.-A.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2002**, *67*, 3522.

12. (a) Koser, G. F.; Wettach, R. H. *J. Org. Chem.* **1977**, *42*, 1476; For a review, see: (b) Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89, and references cited therein.
13. Typical procedure for the asymmetric hydroformylation of norbornylene: Under an inert atmosphere, solutions of norbornylene (**1**, 753 g), and TangPhos (**8**, 12.9 g) in toluene and $Rh(CO)_2(acac)$ (10.3 g) in toluene (total volume of 4 L) were successively charged into a Büchi (5 L) reactor. After purging with argon, the reactor was pressurized to 60 psi with CO/H_2 (1:1) and the mixture was vigorously stirred. The reaction was complete in 36–48 h as indicated by GC analysis (>99% conversion, 92% ee).
14. High enantioselectivities were recently reported for asymmetric hydroformylation of styrene, vinyl acetate, and cyanopropene using new ligands with similar but more complicated skeleton,[4] however, very low ee's (20–30%) were found for hydroformylation of norbornylene when two of the most promising ligands were tested in our laboratory.