Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2101–2104

Synthesis of chiral cyclohexane-backbone P,N-ligands derived from pyridine and their applications in asymmetric catalysis

Qi-Bin Liu and Yong-Gui Zhou*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, Liaoning 116023, PR China

Received 14 November 2006; revised 23 January 2007; accepted 24 January 2007
Available online 27 January 2007

Abstract—P,N-ligands *trans*-**4** and *cis*-**5** with a cyclohexane backbone were easily synthesized. The key step was chiral resolution of (±)-*trans*-2-pyridylcyclohexanols with DBTA. Enantiopure trans isomer was subjected to Mitsunobu reaction and deprotection to give the corresponding cis isomer. These ligands have been successfully used in asymmetric hydrogenation of arylalkenes with up to 93% ee using **5** and 90% ee using **4** and asymmetric allylic alkylations with up to 95% ee using **5** and 93% ee using **4**. Trans and cis P,N-ligands **4** and **5** all gave the product with the same configuration. It was suggested that the absolute configuration of the product was controlled by the configuration of the stereogenic pyridyl-bearing carbon of the ligands.

1. Introduction

Transition-metal-catalyzed asymmetric transformations in the presence of chiral ligands have proved to be one of the most efficient methods for the construction of enantioenriched chiral compounds.[1] Design and synthesis of novel chiral ligands have therefore been a topic of great interest in organic and organometallic chemistry in the past few decades. In late-transition-metal catalysis, the development of phosphorus- and nitrogen-based chiral ligands has been most extensively investigated.[2] Pfaltz and others have developed chiral mimics of Crabtree's catalyst,[3] and successfully used iridium complexes of P,N-ligands for the asymmetric hydrogenation of unfunctionalized olefins.[4] However, P,N-ligands derived from pyridine have been reported in only a few examples. The representative examples were ligands **1** and **2** (Fig. 1). Very recently, we[5] and Pfaltz[6] have also developed a class of bicycle P,N-ligands **3** and successfully applied in iridium-catalyzed asymmetric hydrogenation. As our work extends, herein, we wish to report the synthesis of a new class of trans and cis chiral cyclohexane-backbone P,N-ligands **4** and **5**, which form seven-member ring in their metal-complex, and their applications in Ir-catalyzed hydrogenations of arylalkenes and Pd-catalyzed allylic alkylations.

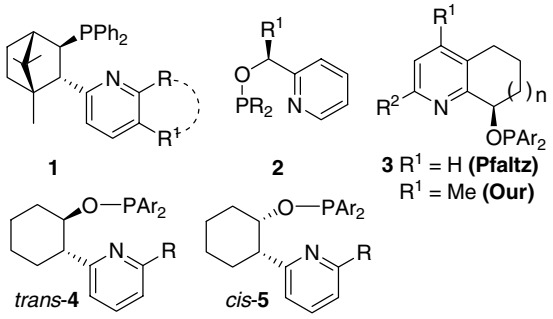
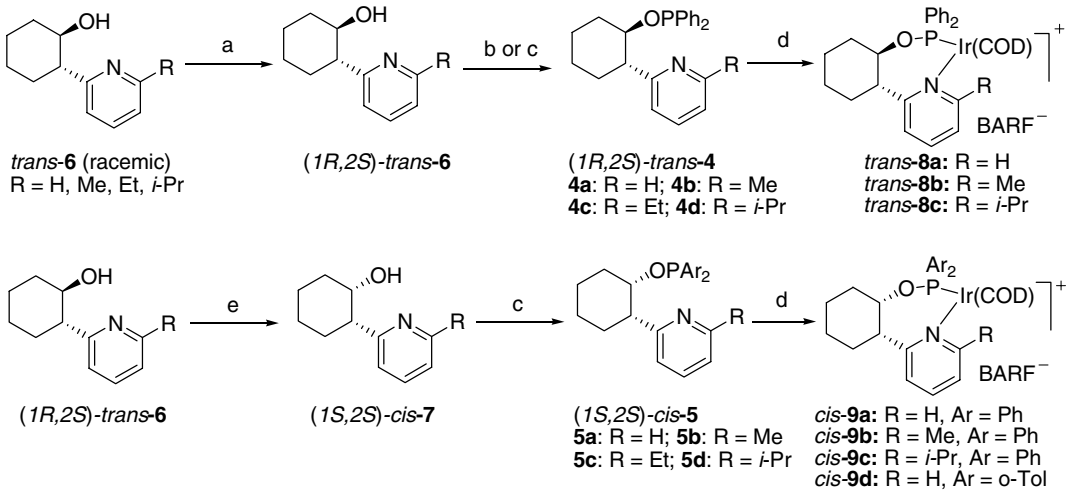


Figure 1.

The synthesis of chiral cyclohexane-backbone P,N-ligands **4** and **5** starts from the known racemic compounds **6**[7,8] (Scheme 1), which can be obtained by $NaBH_4$ reduction (mixture of trans and cis isomer, trans/cis: ~2/1) of the corresponding ketones. The preparation of the optical pure of trans and cis isomers was the key step. Kita reported a simple method of separation by extraction.[8,9a] The (±)-*trans*-2-pyridylcyclohexanols reacted with chiral 3β-acetoxyetienic acid chloride to give the corresponding diastereomeric esters, which were separated by extraction using achiral-organic solvent and acid solution based on a difference in p*K*a values of the diastereomers. Reduction of the corresponding diastereomeric esters gave optically active pyridyl alcohols. Subsequently, Kita also reported kinetic resolution of (±)-*trans*-2-pyridylcyclohexanols using chiral 3β-acetoxyetienic acid, DCC and DMAP.[9b] Due

* Corresponding author. Tel./fax: +86 411 84379220; e-mail: ygzhou@dicp.ac.cn

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.123



Scheme 1. Reagents and conditions: (a) (L)-DBTA, MeOH (*trans*-**6a**), EtOH (*trans*-**6b**), acetone/EtOH (*trans*-**6c** and *cis*-**7c**), petroleum/EtOH (*trans*-**6d** and *cis*-**7d**); then KOH, CH_2Cl_2, 40% (**6a**), 56% (**6b**), 7% (**6c**), 12% (**6d**) (two steps); (b) *n*-BuLi, THF, Ph_2PCl; (c) Ar_2PNEt_2, Et_3N, 4,5-dichloroimidazole, DCM or $ClCH_2CH_2Cl$, reflux; (d) for *trans* series: $[Ir(COD)Cl]_2$ (0.5 equiv), CH_2Cl_2, reflux, then NaBARF (1.0 equiv), H_2O, rt, 10 min; for *cis* series: $[Ir(COD)Cl]_2$ (0.5 equiv), CH_2Cl_2, reflux, 1.5 h, then NaBARF (1.5 equiv), H_2O, 50 °C, 30 min. BARF = (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate); (e) *p*-$NO_2C_6H_4COOH$, PPh_3, DIAD, benzene, rt, then K_2CO_3/MeOH, reflux, 67–91% (two steps).

to the difficulty in obtaining the enantiopure pyridylhexanols for the above methods, therefore, developing a convenient method to enantiopure *trans*- and *cis*-pyridyl cyclohexanols was still required. Encouraged by the successful use of crystallization procedures of diastereomeric salts of tartaric acid with secondary alcohols containing the pyridyl group,[10] we focused on the development of a resolution protocol of pyridyl alcohols **6** with inexpensive tartaric acid derivatives.

In our attempts for (±)-*trans*-2-pyridylcyclohexanols resolution, we found the di-benzyl tartaric acid (DBTA) be an efficient resolving agent. When (±)-*trans*-pyridylcyclohexanols **6a** was reacted with 1.0 equiv (L)-DBTA·H_2O in methanol, the collected diastereomeric salts of (L)-DBTA·H_2O by filtration can be upgraded to >99% ee via three recrystallization in MeOH. The absolute stereochemistry of *trans*-**6a** was determined by comparison of the sign of the optical rotation with reported data.[8] The cis isomer could not form the diastereomeric salt with (L)-DBTA·H_2O due to the intramolecular hydrogen bonding between pyridine nitrogen and hydroxyl group. So, we can resolve directly the trans and cis mixtures to give only chiral trans isomer **6a**. *trans*-**6b** was also resolved with (L)-DBTA in ethanol. For the mixture of *trans*-**6c–d** and *cis*-**7c–d**, no single solvent was suitable, but when the mixture solvents were used, the enantiopure *trans*-**6c** or **6d** could be easily obtained (see Supplementary data).

A key transformation in our synthetic approach toward the enantiopure cis isomer **7** was configuration inversion of the secondary alcohol moiety of *trans*-**6**. After surveying a variety of modifications of the Mitsunobu reaction for more sterically congested substrates, we found that using *p*-nitrobenzoic acid in benzene resulted in almost quantitative yield with perfect inversion of stereochemistry with secondary alcohols by S_N2 replacement (by HPLC, (1*S*,2*S*)-*cis*-**7a**: >99% ee).[11] The yields for other substance *trans*-**6b–d** were slightly low due to the increasing bulk of the R group. Hydrolysis of the corresponding esters with K_2CO_3/methanol at reflux afforded the corresponding enantiopure *cis*-**7a–d** in high yields.

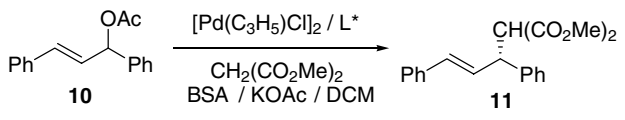
Trans-**6a–d** were deprotonated with *n*-BuLi at 0 °C, then treated with chlorodiphenylphosphine to afford the desired *trans*-**4a–d** in 34–82% yields. Cis isomer **7a–d** cannot afford the desirable products under the above condition, the reason might be the strong intramolecular hydrogen bonding of *cis*-**7a–d**. Using Pfaltz's condition, Ar_2PNEt_2/Et_3N/4,5-dichloroimidazole/reflux, the desired phosphinites *cis*-**5a–d** can be obtained in 56–77% yields.[4l,6b] Although the resulting ligands are acid-labile, they can be purified by rapid flash chromatography on silica gel.

2. Pd-catalyzed asymmetric allylic alkylation

Ligands *trans*-**4** and *cis*-**5** were evaluated in the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**10**) with dimethyl malonate as shown in Table 1. The reaction was carried out in the presence of 2.5 mol% $[Pd(C_3H_5)Cl]_2$, 5 mol% of ligand **4** or **5** and a mixture of *N*,*O*-bis(trimethylsilyl) acetamide (BSA) and 5 mol% of KOAc. All reactions were complete in 2 h at 20 °C. For ligands *trans*-**4** series, the enantioselectivity increased from 53% to 93% when R group of the ligand increased from hydrogen to isopropyl group (entries 1–4). Ligand *trans*-**4d** afforded the highest enantiomeric excess of up to 93% (entry 4).

Very interestingly, *cis*-**5a–d** ligands gave slightly higher activity and enantioselectivity than the corresponding trans isomer except for ligand **5d**. The enantioselectivity increased from 79% to 95% when the bulk of R group in the ligand increased from hydrogen to methyl group (entries 5–6). However, when R group was isopropyl

Table 1. Palladium-catalyzed asymmetric allylic substitution reactions[a]



Entry	Ligand	Yield[b] (%)	ee (%)/Conf.
1	*trans*-**4a**	98	53 (*R*)
2	*trans*-**4b**	94	84 (*R*)
3	*trans*-**4c**	98	89 (*R*)
4	*trans*-**4d**	92	93 (*R*)
5	*cis*-**5a**	95	79 (*R*)
6	*cis*-**5b**	92	95 (*R*)
7	*cis*-**5c**	91	94 (*R*)
8	*cis*-**5d**	92	92 (*R*)

[a] Reaction conditions: 2.5 mol% $[Pd(C_3H_5)Cl]_2$ and 5 mol% ligand was stirred for 1 h and subsequently 5 mol% KOAc and **10** was added, after 1 h, dimethylmalonate and BSA was added to the reaction solution.
[b] Isolated yield.

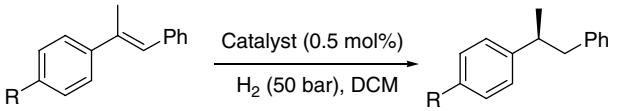
group, slightly lower enantioselectivity (92%) was observed (entry 8). Among all *cis*-**5** series, ligand *cis*-**5b** afforded the highest enantiomeric excess of up to 95% (entry 6). In the above experiments, P,N ligands *trans*-**4** and *cis*-**5** gave the products with the same absolute configuration, so, the absolute configuration of the product was controlled by the configuration of the stereogenic pyridyl-bearing carbon of the ligands.

3. Ir-catalyzed asymmetric hydrogenations

Chiral P,N-ligands have showed high activity and excellent enantioselectivity in Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins. To evaluate the catalytic properties of ligands **4** and **5** in asymmetric hydrogenation, their Ir-complexes were prepared according to the known literature procedure,[4d,l,5,6] in which a weakly coordinating group BARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was used as the counter ion (Scheme 1).

Methylstilbene **12a**, a typical substrate for Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins, was initially tested with complexes *trans*-**8a-c** under 50 bar of H_2 pressure at room temperature in CH_2Cl_2. As shown in Table 2, catalyst *trans*-**8a** gave complete conversions and 88% ee, however, catalysts *trans*-**8b–c** exhibited no reactivity (entries 2–3). Substitution of pyridine ring in ligands remarkably lowered the catalyst activities. The product of 90% ee can be obtained for substrate **12b** in the presence of catalyst *trans*-**8a** (entry 4). For the catalyst *cis*-**9a**, the conversion of 98% and 90% ee were obtained under the standard conditions. Consistently, for *cis*-**9** series, substitution of pyridine ring in ligands remarkably lowered the catalyst activities (entries 6–7). The product of 91% ee and full conversion were obtained for substrate **12b** in the presence of catalyst *cis*-**9a** (entry 9). The enantioselecitivities and activities of catalyst *cis*-**9d** with steric $(o\text{-Tol})_2P$ group were slightly superior to that of the corresponding catalyst

Table 2. Iridium-catalyzed asymmetric hydrogenations of arylalkenes[a]



12a: R = H
12b: R = OMe
13a: R = H
13b: R = OMe

Entry	Sub.	Catalyst	Convn.[b] (%)	ee[c] (%)
1	**12a**	*trans*-**8a**	>99	88 (*S*)
2	**12a**	*trans*-**8b**	<5	—
3	**12a**	*trans*-**8c**	<5	—
4	**12b**	*trans*-**8a**	>99	90 (*S*)
5	**12a**	*cis*-**9a**	98	90 (*S*)
6	**12a**	*cis*-**9b**	<5	—
7	**12a**	*cis*-**9c**	<5	—
8	**12a**	*cis*-**9d**	>99	90 (*S*)
9	**12b**	*cis*-**9a**	>99	91 (*S*)
10	**12b**	*cis*-**9d**	>99	93 (*S*)

[a] Reaction conditions: all reactions were performed using 0.5 mmol of substrate and 2 mL of dichloromethane in the pressure of 50 bar hydrogen.
[b] Conversion was determined by ^1H NMR.
[c] Determination by HPLC with a chiral column.

cis-**9a** with Ph_2P group (entry 8 vs entry 5, entry 10 vs entry 9).

In comparison to the configuration of the product observed in palladium-catalyzed asymmetric allylic alkylation, catalyst **8** and **9** also afforded a similar result giving product with the same configuration in asymmetric hydrogenations of aryl alkenes. This fact, again strongly suggests that the absolute configuration of the product was controlled by the configuration of the stereogenic pyridyl-bearing carbon of the ligands.

In summary, a new type of P,N-ligands, *trans*-**4** and *cis*-**5** containing a cyclohexane backbone, was easily synthesized. The key steps were chiral resolution of (±)-*trans*-2-pyridylcyclohexanols and Mitsunobu inversion. These ligands have been successfully used in asymmetric hydrogenation of arylalkenes with up to 93% ee using **5** and 90% ee using **4** and asymmetric allylic alkylations with up to 95% ee using **5** and 93% ee using **4**. Trans and cis P,N-ligands **4** and **5** all gave the product with the same configuration. Further studies on application to other asymmetric reactions are underway.

Acknowledgment

We are grateful for the financial support from National Science Foundation of China (20672112).

References and notes

1. (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.,

Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. I, pp 121–182.
2. For recent reviews on chiral P,N-ligands, see: (a) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497–537; (b) Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471–9515; (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.
3. Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331–338.
4. For reviews, see: (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2002**, *344*, 33–44; (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296; (c) Källström, K.; Munslow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194–3200; For selected examples, see: (d) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897–2899; (e) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445–4447; (f) Menges, F.; Pfaltz, A. *Adv. Synth. Catal.* **2002**, *344*, 40–44; (g) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713–4716; (h) Bunlaksananurson, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941–3943; (i) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943–946; (j) Xu, G.; Gilberston, S. R. *Tetrahedron Lett.* **2003**, *44*, 953–955; (k) Cozzi, P. G.; Menges, S.; Kaiser, S. *Synlett* **2003**, 833–836; (l) Durry, W. J., III; Zimmerman, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 70–74; (m) Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023–2026; (n) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308–14309; (o) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513–516; (p) Trifonava, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825–3827; (q) Focken, T.; Raabe, G.; Blom, C. *Tetrahedron: Asymmetry* **2004**, *15*, 1693–1706; (r) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61–77; (s) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995–3001.
5. Liu, Q.-B.; Yu, C.-B.; Zhou, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 4733–4736.
6. (a) Bell, S.; Wustenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642–644; (b) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194–5197.
7. The detailed procedures see Supplementary data.
8. Matsugi, M.; Itoh, K.; Norjima, M.; Hagimoto, Y.; Kito, Y. *Chem. Eur. J.* **2002**, *8*, 5551–5564.
9. (a) Matsugi, M.; Hagimoto, Y.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 8039–8042; (b) Matsugi, M.; Hagimoto, Y.; Nojima, M.; Kita, Y. *Org. Process Res. Dev.* **2003**, *7*, 583–584.
10. Davies, A. G.; Kenyon, J.; Thaker, K. *J. Chem. Soc.* **1956**, 3394–3397.
11. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.