DOI: 10.1002/adsc.201100023

C_2-Symmetrical Bipyridyldiols as Promising Enantioselective Catalysts in Nozaki–Hiyama Allylation

Xin-Ren Huang,[a] Xin-Hong Pan,[a] Gene-Hsian Lee,[b] and Chinpiao Chen[a,*]

[a] Department of Chemistry, National Dong Hwa University, Soufeng, Hualien 974, Taiwan, Republic of China
Fax: (+886)-3-863-3597; e-mail: chinpiao@mail.ndhu.edu.tw
[b] Instrumentation Center, College of Science, National Taiwan University, Taipei 106, Taiwan, Republic of China

Received: January 11, 2011; Revised: March 18, 2011; Published online: August 10, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100023.

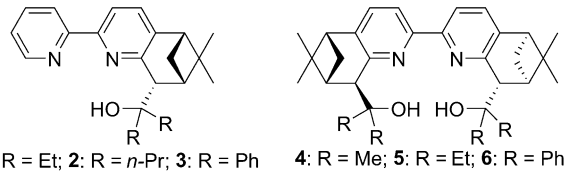
Abstract: Several new chiral bipyridyldiol ligands that promote the chromium-catalyzed enantioselective addition of allylic halides to aldehydes in up to 99% *ee* were synthesized. The chromium-catalyzed allylation of aldehydes using ligands **4** and **4a** in the presence of chromium(III) chloride and allyl chloride provided the highest enantioselectivity.

Keywords: asymmetric catalysis; bipyridyldiol; chromium catalysis; enantioselectivity; Nozaki–Hiyama allylation

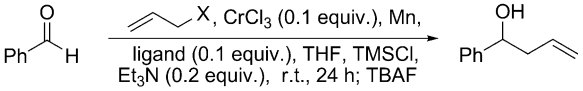
The nucleophilic addition of organochromium reagents [Nozaki–Hiyama–Kishi (NHK) reaction] to carbonyl compounds is a versatile carbon-carbon bond forming reaction that can be used with a wide range of substrates and has a diverse range of application.[1] The synthetic utility of the reaction has been significantly increased by the development of a catalytic redox process that involves the recycling of Cr(II) by the reduction of Cr(III) species.[2] These preliminary improvements have motivated numerous efforts to develop an enantioselective version of this reaction. Many structurally different chiral ligands were applied as enantioselective catalysts for the allylation of aldehydes, and have resulted in various degrees of asymmetric induction.[3] Notably, chiral salen, quinoline and oxazoline-based chromium complexes exhibit high enantioselectivities in the asymmetric allylation of aromatic and aliphatic aldehydes. In most of the catalyst systems, the use of less reactive allylic chlorides gave lower yields, while the more reactive allylic iodides worsened the stereochemical outcome of the reaction. To solve these problems, a new catalyst of the Nozaki–Hiyama allylation is desirable. This work is the first to describe a new C_2-symmetrical bipyridyldiol-based chromium catalyst that is effective in the enantioselective addition of allyl chloride to aldehydes.

Our recent study involved chiral bipyridine ligands from enantioenriched pinene which gave good enantioselectivities in several asymmetric transformations.[4] The successful application of these ligand systems motivated us to screen the Nozaki–Hiyama allylation of aromatic aldehydes. Initial evaluation of symmetrical (**4**–**6**) and non-symmetrical bipyridine ligands (**1**–**3**) in the Cr(II)-catalyzed addition of allyl halides to benzaldehyde revealed that C_2-symmetrical

Table 1. Optimization of chiral bipyridine ligand for the chromium-catalyzed addition of allyl halide to PhCHO.



1: R = Et; **2**: R = *n*-Pr; **3**: R = Ph **4**: R = Me; **5**: R = Et; **6**: R = Ph



Entry	Ligand	X	Yield [%][a]	*ee* [%][b]	Configuration
1	(*S,R,S*)-**1**	Br	81	45	*R*
2	(*S,R,S*)-**2**	Br	79	31	*R*
3	(*S,R,S*)-**3**	Cl	70	75	*R*
4	(*R,S,R,R,S,R*)-**4**	Cl	83	95	*S*
5	(*R,S,R,R,S,R*)-**5**	Cl	73	79	*S*
6	(*R,S,R,R,S,R*)-**6**	Cl	75	69	*S*

[a] Isolated yield.
[b] HPLC conditions: Chiralcel® OD-H, hexane:*i*-PrOH 9:1, flow rate 0.25 mL min^{-1}, retention times: 23.30 min (*R* isomer) and 24.90 min (*S* isomer).

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

tetradentate ligands offered excellent reactivity and enantioselectivity (Table 1). Ligand **4** with methyl groups surprisingly afforded greater reactivity and enantioselectivity than ligands with bulkier groups (Table 1, entry 4). Ligands **4**–**6** have N_2O_2 binding sites, and so resemble chiral salen ligands. They are readily obtainable from (+)-α-pinene in six steps, which include the stereoselective alkylation of chiral bipyridine with ketones as a key step.[4a] To increase the applicability of the ligand system, the enantiomer **4a** of ligand **4** was synthesized from (−)-β-pinene according to the synthetic protocol for ligand **4** (Figure 1). An X-ray crystallographic analysis of (+)-**6** (Figure 2) verified the general structure of these tetradentate N_2O_2 ligands,[5] which have features that resemble those of the well known Jacobsen salen ligand and TADDOL.

Allylation of benzaldehyde using the Cr-**4** complex was optimized by performing the reaction in various solvents and at various reaction temperatures (see Supporting Information). Reactions performed at room temperature in THF afforded better results than

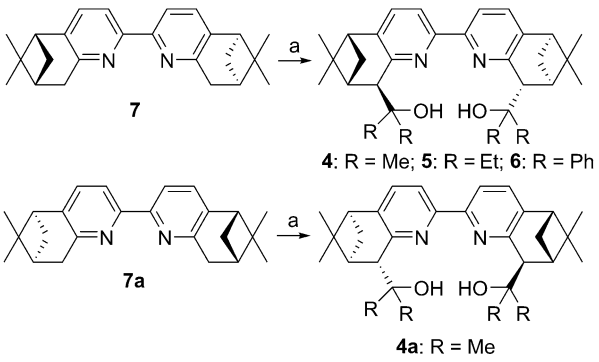


Figure 1. Ligand synthesis, a) LDA, R_2CO, THF, −50 °C.

all of the other screened conditions. Also, a 10 mol% loading of catalyst gave the best yield and enantioselectivity. The use of bases other than triethylamine gave mixed results (see Supporting Information). The optimal conditions were therefore 10 mol% of $CrCl_3$, an excess of Mn and 10 mol% of **4**, in the presence of triethylamine and THF at room temperature; followed by the successive addition of allyl chloride, aldehyde and TMSCl. The final product was isolated following a TBAF work-up.

The effects of the halide component of the allyl halide and the chromium(III) halide used in the reaction were explored by adopting various combinations of them, as shown in Table 2. Allyl chloride unexpectedly afforded better results than the usually used allyl bromide, independently of the nature of the metal salt employed (Table 1, entries 1 and 4).

The extents of enantioselection with various aldehydes using Cr-**4** were explored under the optimized reaction conditions (Table 3). Aryl aldehydes were excellent substrates for the transformation, as revealed by the 61–65% yield and the 98% *ee* of the allylation of 3-chlorobenzaldehyde (entry 9). The nature and position of the substituent on the aryl ring only weakly affects the enantioselective outcome of the reaction (entries 1–12), although 4-methoxybenzaldehyde and 4-cyanobenzaldehyde are unsuitable substrates for the transformations (entries 4 and 12). Additionally, good yields were obtained with over 96% *ee* using other aryl aldehydes (entries 13–14, 16–17). An α,β-unsaturated aldehyde was also a good substrate (entry 15). The enantioselection was excellent when aliphatic aldehydes were used, as revealed by the 80% yield and >99% *ee* for the allylation of cyclohexanecarboxaldehyde (entry 20).

The synthesis of both enantiomers of a chiral compound usually requires the use of both enantiomers of

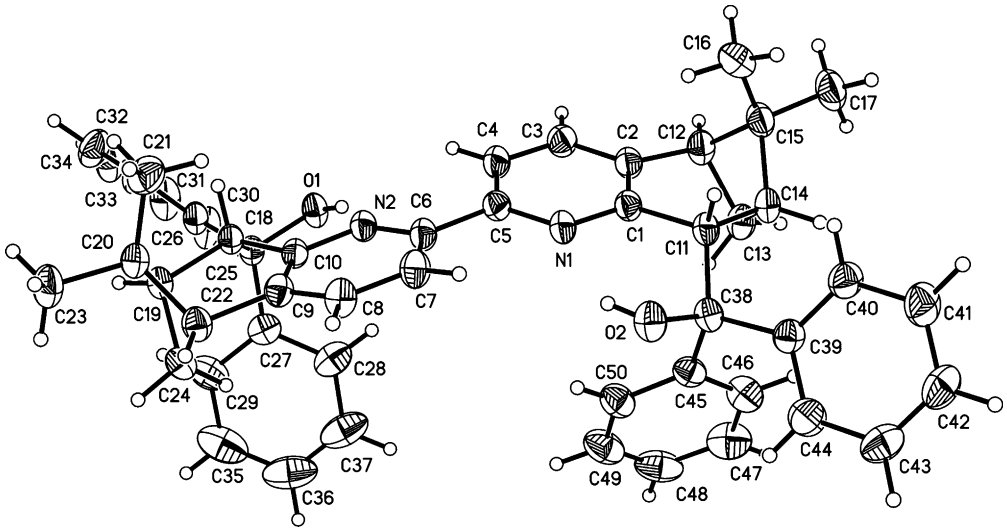
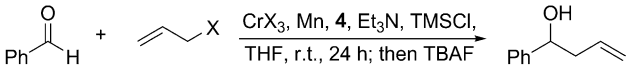


Figure 2. X-ray crystallographic structures of bipyridyldiol **6** (CCDC 757403).

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 2. Influence of nature of allyl halide and metal halide in the enantioselective allylation of benzaldehyde.



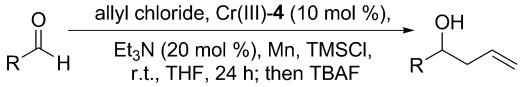
Entry	CrX_3	X	Yield [%][a]	*ee* [%][b]	Configuration
1	Cl	Cl	83	95	*S*
2	Cl	Br	62	37	*S*
3	Cl	I	44	73	*S*
4	Br	Cl	83	91	*S*
5	Br	Br	79	73	*S*
6	Br	I	21	23	*S*

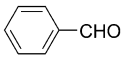
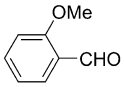
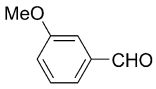
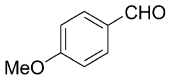
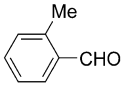
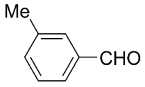
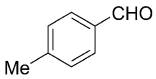
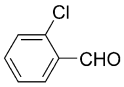
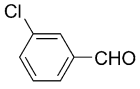
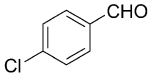
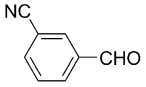
[a] Isolated yields.
[b] HPLC conditions: Chiralcel® OD-H, hexane:*i*-PrOH 9:1, flow rate 0.25 mL min^{-1}, retention times: 23.30 min (*R* isomer) and 24.90 min (*S* isomer).

a chiral catalyst.[6] Many of the generally used chiral ligands are naturally available in only one enantiomer; the other enantiomer often requires a labor-intensive preparation. The importance of enantioselective catalysis has increased in this regard, as it allows easy access to both enantiomers of a product without any complex modification of the structure of the chiral promoter. In this work, very similar enantioselectivities of both products were obtained, by means of of ligands **4** and **4a**.

The highly enantioselective catalysts were explored to determine whether any of them showed promise as an enantioselective catalyst of the Nozaki–Hiyama reaction. A natural product, (+)-spirolaxine methyl ether, was synthesized through asymmetric allylation. Phillips et al. synthesized lactone **28** in 39% yield (4 steps) using (+)-IPC$_2$BOMe as a chiral allylboron re-

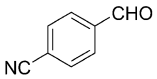
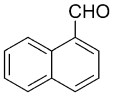
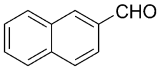
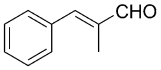
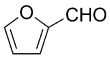
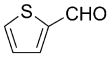
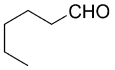
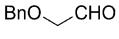
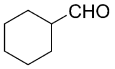
Table 3. Nozaki–Hiyama allylation reactions of aldehydes catalyzed by Cr-**4** complexes.



Entry	Aldehyde	Catalyst	Product	Yield [%][a]	*ee* [%][b]	Configuration[c]
1		Cr-**4**	**8**	83	95	*S*
2		Cr-**4**	**9**	89	87	*S*
3		Cr-**4**	**10**	75	91	*S*
4		Cr-**4**	**11**	86	60	*S*
5		Cr-**4**	**12**	53	96	*S*
6		Cr-**4**	**13**	44	90	*S*
7		Cr-**4**	**14**	73	94	*S*
8		Cr-**4**	**15**	77	88	*S*
9		Cr-**4**	**16**	65	98	–
10		Cr-**4**	**17**	76	93	*S*
11		Cr-**4**	**18**	70	92	–

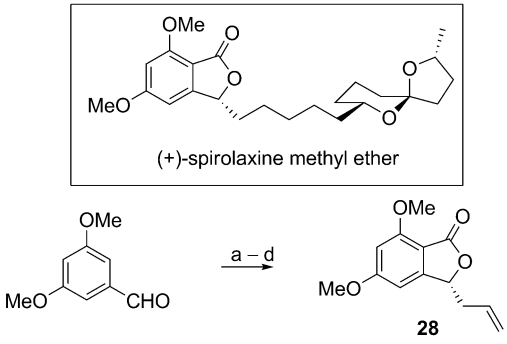
 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 3. (Continued)

Entry	Aldehyde	Catalyst	Product	Yield [%][a]	*ee* [%][b]	Configuration[c]
12		Cr-**4**	**19**	25	65	–
13		Cr-**4**	**20**	85	90	*S*
14		Cr-**4**	**21**	87	94	*S*
15		Cr-**4**	**22**	90	92	*S*
16		Cr-**4**	**23**	87	96	*S*
17		Cr-**4**	**24**	79	92	*S*
18		Cr-**4**	**25**	85	92	*S*
19		Cr-**4**	**26**	85	91	*S*
20		Cr-**4**	**27**	80	>99[d]	*S*

[a] Isolated yields.
[b] Enantiomeric ratio determined by HPLC equipped with a chiral stationary phase.
[c] Assigned by comparison of the sign of optical rotation with reported value.
[d] Enantiomeric ratio determined by H NMR of Mosher's ester.

agent.[7] Brimble et al. used TiF_4, (+)-BINOL and allyltrimethylsilane as asymmetric allylation reagents to produce lactone **28** in 43% yield (4 steps) and 86% ee.[8] Therefore, the asymmetric Nozaki–Hiyama reaction was used as an efficient allylation reaction using ligand **4a** as the enantioselective catalyst, to afford the corresponding homoallylic alcohol and simultaneously form lactone **28** in a high enantiomeric excess (90% *ee*)[9] and 58% yield (4 steps) (Scheme 1).



Scheme 1. *Reaction conditions:* a) Br_2, AcOH; b) $HOCH_2CH_2OH$, *p*-TSA, benzene; c) *n*-BuLi, EtOCOCl; HCl; d) ligand **4a**, NH allylation.

In summary, Cr-bipyridinediol efficiently catalyzed the asymmetric NH allylation reactions of both aromatic and aliphatic aldehydes. Excellent enantioselectivities (of up to 99% *ee*) for the NH allylation reaction of aldehydes were obtained using both enantiomers of bipyridyldiols. Moreover, the use of bipyridinediol in other instances of asymmetric catalysis will be reported upon in due course.

Experimental Section

Synthesis of Bipyridine Ligand 4

To a solution of diisopropylamine (146 μL, 1.04 mmol) in THF (10 mL) was added *n*-butyllithium (0.65 mL, 1.04 mmol, 1.6 M in hexane) and the misture was stirred at 0 °C for 30 min. The thus produced LDA solution was cooled to −50 °C, and added to a solution of compound **7** (350 mg, 1.02 mmol) in THF (10 mL), and stirred at −50 °C for 2 h. A solution of acetone (87 μL, 1.2 mmol) in THF (2 mL) was added at −50 °C, after which the reaction temperature was raised to room temperature, and the solution was stirred for 30 min. The reaction temperature was decreased to −50 °C, and a prepared LDA (1.04 mmol) solution was added. After stirring at −50 °C for 4 h, a solution of acetone (87 μL, 1.2 mmol) in THF (2 mL) was added, and the mixture was stirred at room temperature overnight until

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

the solution turned orange. The reaction was quenched by adding water, and the reaction mixture was extracted three times with ethyl acetate. The combined extracts then were dried over anhydrous magnesium sulfate. After filtering and concentration, the residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (1:49, 1:19) as the mobile phase, thus producing compound **32** [yield: 310 mg (0.77 mmol 75.5%)], and compound **4** [yield: 65.0 mg (0.14 mmol, 13.8%)]; $[\alpha]_D^{22}$: +41.5° (*c* 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s 2H, OH), 7.94 (d, *J* = 7.8 Hz, 2H, ArH), 7.37 (d, *J* = 7.9 Hz, 2H, ArH), 2.88–2.76 (m, 2H, -CH-), 3.28 (s, 2H, -CH-), 2.82–2.79 (t, *J* = 5.6 Hz, 2H, -CH-), 2.65–2.60 (m, 2H, -CH-), 2.37 (td, J_1 = 5.9 Hz, J_2 = 1.7 Hz, 2H, -CH_2-), 1.45 (s, 6H, CH_3), 1.43 (d, *J* = 7.8 Hz, 2H, -CH-), 1.35 (s, 6H, CH_3), 18H), 1.13 (s, 6H, CH_3), 0.71 (s, 6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 158.1, 151.4, 143.3, 134.7, 118.2, 74.5, 52.8, 46.5, 42.5, 42.1, 29.5, 29.0, 27.6, 26.3, 21.0; IR (KBr): ν = 3403, 2973, 2940, 2867, 1635, 1558, 1419, 1166, 734, 611 cm^{-1}; LR-MS (EI): *m/z* = 460 (M^+, 24), 403 (29), 402 (100), 387 (12), 383 (21), 369 (27), 343 (20), 341 (29), 299 (21), 59 (16); HR-MS (EI): *m/z* = 460.3094, calcd. for $C_{30}H_{40}N_2O_2$ $[M]^+$: 460.3090.

Typical Procedure for Catalytic Enantioselective Nozaki–Hiyama Allylation

Anhydrous THF (1 mL) was added to $CrCl_3$ (8.0 mg, 50.0 μmol) and Mn (83.0 mg, 1.5 mmol, 325 mesh) in an inert box, and the mixture was stirred for 1 h at room temperature. After ligand **4** (50.0 μmol) and anhydrous NEt_3 (14.0 μL, 10.0 mg, 100 μmol) were added, the suspension was stirred for 1 h at room temperature. Finally, allyl chloride (58.0 μL, 750 μmol) was added. After 1 h at room temperature, aldehyde (0.5 mmol) and Me_3SiCl (95.0 μL, 750 μmol) were added, and the suspension was stirred at room temperature for 24 h. Saturated aqueous $NaHCO_3$ was added. Following filtration and evaporation, the aqueous phase was extracted with EtOAc. After the combined organic phases had been evaporated, the residue was dissolved in THF (2 mL). A TBAF solution (1.5 mL, 1.5 mmol, 1 M in THF) was added and the mixture was stirred until desilylation was complete (as verified by TLC). Water was added; the solution was extracted using ethyl acetate, and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (EtOAc/hexane 1:19) gave the products. The enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralcel OD-H or OJ column, flow rate 0.25 mL min^{-1}).

Acknowledgements

The authors thank Ms. L. M. Hsu, at the Instruments Center, National Chung Hsing University, for her help in obtaining HR-MS, and the National Science Council of the Republic of China for financially supporting this research under Contract NSC 97-2113 M-259-002-MY3.

References

[1] For reviews, see: a) A. S. K. Hashmi, *J. Prakt. Chem.* **1996**, *338*, 491–495; b) L. A. Wessjohann, G. Scheid, *Synthesis* **1999**, 1–36; c) A. Fürstner, *Chem. Rev.* **1999**, *99*, 991–1045; d) A. Fürstner, *Chem. Eur. J.* **1998**, *4*, 567–570; e) K. Takai, H. Nozaki, *Proc. Jpn. Acad. Ser. B* **2000**, *76*, 123–131; f) M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios, *Chem. Soc. Rev.* **1999**, *28*, 169–177; g) G. C. Hargaden, P. J. Guiry, *Adv. Synth. Catal.* **2007**, *349*, 2407–2424.

[2] a) A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357; b) A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 2533–2536.

[3] a) M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem.* **1999**, *111*, 3558–3561; *Angew. Chem. Int. Ed.* **1999**, *38*, 3357–3359; b) M. Bandini, P. G. Cozzi, A. Umani-Ronchi, *Polyhedron* **2000**, *19*, 537–539; c) M. Bandini, P. G. Cozzi, A. Umani-Ronchi, *Chem. Commun.* **2002**, 919–927; d) H. Choi, K. Nakajima, D. Demeke, F. Kang, H. Jun, Z. Wan, Y. Kishi, *Org. Lett.* **2002**, *4*, 4435–4438; e) M. Lombardo, S. Licciulli, S. Morganti, C. Trombini, *Chem. Commun.* **2003**, 1762–1763; f) A. Berkessel, D. Menche, C. A. Sklorz, M. Schrõder, I. Paterson, *Angew. Chem.* **2003**, *115*, 1062–1065; *Angew. Chem. Int. Ed.* **2003**, *42*, 1032–1035; g) M. Inoue, T. Suzuki, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141; h) T. Suzuki, A. Kinoshita, H. Kawada, M. Nakada, *Synlett* **2003**, 570–572; i) A. Berkessel, M. Schrõder, C. A. Sklorz, S. Tabanella, N. Vogl, J. Lex, J. M. Neudõrfl, *J. Org. Chem.* **2004**, *69*, 3050–3056; j) K. Namba, Y. Kishi, *Org. Lett.* **2004**, *6*, 5031–5033; k) M. Inoue, M. Nakada, *Org. Lett.* **2004**, *6*, 2977–2980; l) M. Kurosu, M. Lin, Y. Kishi, *J. Am. Chem. Soc.* **2004**, *126*, 12248–12249; m) J. Lee, J. J. Miller, S. S. Hamilton, S. S. Sigman, *Org. Lett.* **2005**, *7*, 1837–1839; n) B. Cazes, C. Verniere, J. Goré, *Synth. Commun.* **1983**, *13*, 73–79; o) C. Chen, K. Tagami, Y. Kishi, *J. Org. Chem.* **1995**, *60*, 5386–5387; p) K. Sugimoto, S. Aoyagi, C. Kibayashi, *J. Org. Chem.* **1997**, *62*, 2322–2323; q) N. Takenaka, G. Xia, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 13198–13199; r) G. Xia, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 2554–2555; s) M. Inoue, M. Nakada, *Angew. Chem.* **2006**, *118*, 258–261; *Angew. Chem. Int. Ed.* **2006**, *45*, 252–255; t) H. S. Schrekker, K. Micskei, C. Hajdu, T. Patonay, M. W. G. de Bolster, L. A. Wessjohann, *Adv. Synth. Catal.* **2004**, *346*, 731–736; u) H. A. McManus, P. G. Cozzi, P. J. Guiry, *Adv. Synth. Catal.* **2006**, *348*, 551–558; v) J. J. Miller, M. S. Sigman, *J. Am. Chem. Soc.* **2007**, *129*, 2752–2753; w) G. C. Hargaden, T. P. O'Sullivan, P. J. Guiry, *Org. Biomol. Chem.* **2008**, *6*, 562–566; x) R. Baati, V. Gouverneur, C. Mioskowski, *J. Org. Chem.* **2000**, *65*, 1235–1238; y) M. Inoue, M. Nakada, *Org. Lett.* **2004**, *6*, 2977–2980; z) X.-R. Huang, C. Chen, G.-H. Lee, S.-M. Peng, *Adv. Synth. Catal.* **2009**, *351*, 3089–3095.

[4] a) Y.-J. Chen, R.-X. Lin, C. Chen, *Tetrahedron: Asymmetry* **2004**, *15*, 3561–3571; b) P.-T. Lee, C. Chen, *Tetrahedron: Asymmetry* **2005**, *16*, 2704–2710; c) Y.-J. Chen, C. Chen, *Tetrahedron: Asymmetry* **2007**, *18*, 1313–1319; d) T.-C. Chang, C. Chen, *J. Chin. Chem. Soc.* **2008**, *55*, 606–615; e) Y.-J. Chen, C. Chen, *Tetrahedron: Asymme-*

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

try **2008**, *19*, 2201–2209; f) X.-R. Huang, C. Chen, *Tetrahedron: Asymmetry* **2010**, *21*, 2999–3004.
[5] The X-ray crystallographic structure of ligand **6** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 757403). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[6] G. Zanoni, F. Castronovo, M. Franzini, G. Vidari, E. Giannini, *Chem. Soc. Rev.* **2003**, *32*, 115–129.
[7] a) K. A. Keaton, A. J. Phillips, *Org. Lett.* **2007**, *9*, 2717–2719; b) R. Nannei, S. Dallavalle, L. Merlini, A. Bava, G. Nasini, *J. Org. Chem.* **2006**, *71*, 6277–6280.
[8] J. E. Robinson, M. A. Brimble, *Chem. Commun.* **2005**, 1560–1562.
[9] Ref.[7], the specific rotation of compound **28** is $[\alpha]_D$: +67.55 (*c* 1.2, $CHCl_3$), and by using NH allylation is $[\alpha]_D^{24.5}$: +68.7 (*c* 0.9, $CHCl_3$), enantiomeric excess 90% (see Supporting Information).

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim