Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1419–1423

Catalytic asymmetric induction of planar chirality: palladium catalyzed intramolecular Mizoroki–Heck reaction of prochiral (arene)chromium complexes

Ken Kamikawa, Kenji Harada and Motokazu Uemura*

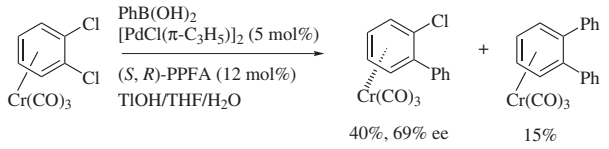
Department of Chemistry, Faculty of Integrated Arts and Sciences, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Received 20 January 2005; accepted 4 February 2005
Available online 23 March 2005

Abstract—The asymmetric intramolecular Mizoroki–Heck reaction of prochiral tricarbonyl(2,6-dibutenylchlorobenzene)chromium in the presence of a chiral phosphine–palladium catalyst gave the corresponding bicyclic chromium complex up to 73% ee.

1. Introduction

Transition metal π-complexes exist in two enantiomeric forms based on a planar chirality when the arene or Cp ring is substituted with different groups at the *ortho*- or *meta*-positions. Thus planar chiral metal complexes, such as ferrocene and (arene)chromium complexes, have been widely employed in asymmetric reactions and natural product synthesis.[1,2] For the preparation of optically active planar chiral π-complexes, resolution of the corresponding diastereomers by chromatography,[3] enzymatic resolution,[4] diastereoselective complexation[5] and diastereo- or enantioselective *ortho*-lithiation[6] utilizing chiral auxiliaries or chiral lithium amides are employed. However, these procedures require more than stoichiometric amounts of the chiral reagent. Catalytic asymmetric synthesis of the planar π-complexes is the most attractive and challenging approach. With this in mind, we reported the first catalytic asymmetric desymmetrization of a prochiral *o*-dichlorobenzene chromium complex by a Suzuki–Miyaura cross-coupling reaction in the presence of a chiral palladium catalyst (Scheme 1).[7] However, the yield and enantiomeric excess of the monocoupling products in this catalytic asymmetric desymmetrization were moderate. In order to achieve highly enantiomerically enriched monocoupling products in this reaction, it is essential to discriminate between the carbon–chlorine bonds of the prochiral dichlorobenzene chromium complex at the oxidative addition step. However, only a few examples have been reported in which both high yield and enantiomeric excess are obtained by this desymmetrization strategy.[8]



Scheme 1.

As a further extension of this asymmetric desymmetrization reaction, Schmalz reported a similar type of palladium-catalyzed methoxycarbonylation. In this methoxycarbonylation, a kinetic resolution of the initially formed monocoupling products giving dicoupling product is included.[9] An improvement of the enantiomeric excess of the monocoupling product in this catalytic system is based on different rates of the two competing catalytic cycles leading to the enantiomeric monocoupling products and subsequent dicoupling reaction. Therefore, the yield of the monocoupling product decreased in this palladium catalyzed asymmetric coupling. There is still much room for further development of efficient catalytic asymmetric synthesis of planar chiral transition metal π-complexes with satisfactory yield and enantiomeric excess.[10] To overcome these problematic features, an intramolecular asymmetric cyclization of prochiral π-complexes in which a key step is insertion after oxidative addition, is promising. Bräse reported an intramolecular Mizoroki–Heck reaction of

* Corresponding author. Tel.: +81 72 254 9698; fax: +81 72 254 9931; e-mail: uemura@ms.cias.osakafu-u.ac.jp

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.02.007

prochiral arene chromium complexes, although an asymmetric variant has not been reported.[11] We report herein a catalytic asymmetric intramolecular Mizoroki–Heck reaction of the prochiral tricarbonyl(2,6-dibutenylchlorobenzene)chromium complex **1**.

2. Results and discussion

We began our study by surveying chiral ligands for the asymmetric intramolecular Mizoroki–Heck reaction of tricarbonyl(2,6-dibutenylchlorobenzene)chromium **1**. The results are summarized in Table 1. Reaction of **1** catalyzed by palladium(0) with a variety of chiral ligands including BINAP **4**, PPFA **5** and DIOP **6** gave good to moderate yields of bicyclic products **2** and **3**, although in a racemic form (entries 1–3). Since bidentate phosphine ligands were not effective for this reaction, we next turned our attention to chiral monophosphine ligands, developed by Feringa and co-workers (Fig. 1).[12] However, P–N ligands **7** and **8** derived from TADDOL also gave the product in a racemic form. We were pleased to find that P–N ligand **9** possessing a binaphthyl backbone afforded enantiomerically enriched Heck product **2** in 46% ee.[13] Other types of P–N ligands **10**–**12**, **14** and P–O ligand **13** possessing a binaphthyl backbone resulted in lower enantioselectivities (entries 7–11).

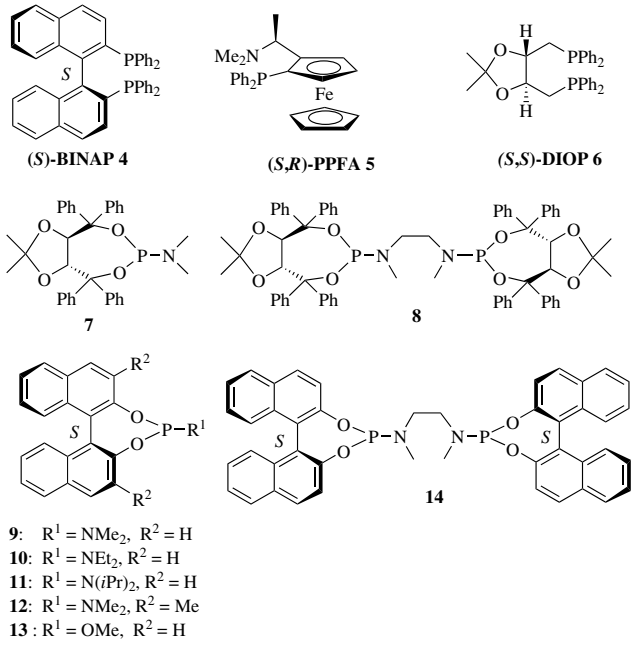
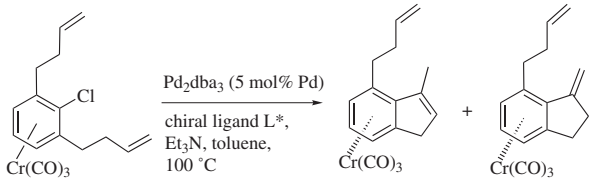


Figure 1. Chiral ligand L*.

We next optimized the reaction conditions and examined other substrates using chiral ligand **9** (Table 2). It is generally believed that in the asymmetric Mizoroki–Heck reaction, Ag(I) salts act as halide scavengers and enhance reactivity and enantioselectivity.[14] However, the addition of silver ions decreases the yield and enantioselectivity in this reaction (entry 2). Tertiary amine organic bases such as a proton-sponge® are also detrimental to the reaction (entry 3). In the presence of amine bases, the major product was **2**, which has an *endo*-cyclic double bond, along with a small amount of *exo*-cyclic double bond product **3**. When using the inorganic base K_2CO_3, the *exo*-cyclic double bond chromium complex **3** was obtained as the sole product with 64% ee (entry 4). We also studied the effect of solvent. While methanol led to a racemic product, employment of nonpolar solvents such as toluene or 1,2-dichloroethane, increased the enantioselectivity of the product. Increasing the amount of chiral ligand **9** and decreasing the temperature improved the yield and enantioselectivity. The best conditions were found to be 20 mol % of Pd and 40 mol % of the chiral ligand in dichloroethane, leading to an enantiomeric excess of 73% ee (entry 7).[15] Prochiral chromium complex **15** ($n = 3$) with a longer side chain was also examined, however in this case, the enantioselectivity of Heck product **17** dropped to 40% ee (entry 10).

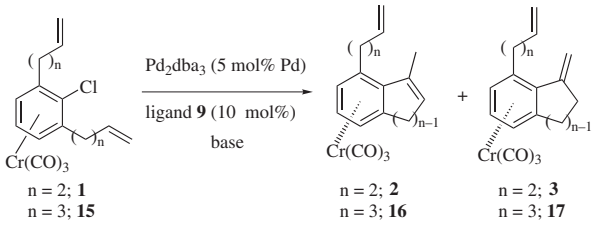
Table 1. Asymmetric intramolecular Mizoroki–Heck reaction of prochiral arene chromium complexes



1 2 3

Entry	Chiral ligand L* (mol %)	Time (h)	Yield (%) **2**	Yield (%) **3**	% Ee of **2**
1	**4** (5)	1.5	73	1	0
2	**5** (5)	16	20	11	0
3	**6** (5)	0.5	53	12	0
4	**7** (10)	0.5	60	—	3
5	**8** (5)	0.5	68	—	1
6	**9** (10)	10	44	5	46
7	**10** (10)	1	53	7	31
8	**11** (10)	22	32	6	9
9	**12** (10)	18	20	11	30
10	**13** (10)	1	53	7	31
11	**14** (5)	16	20	4	10

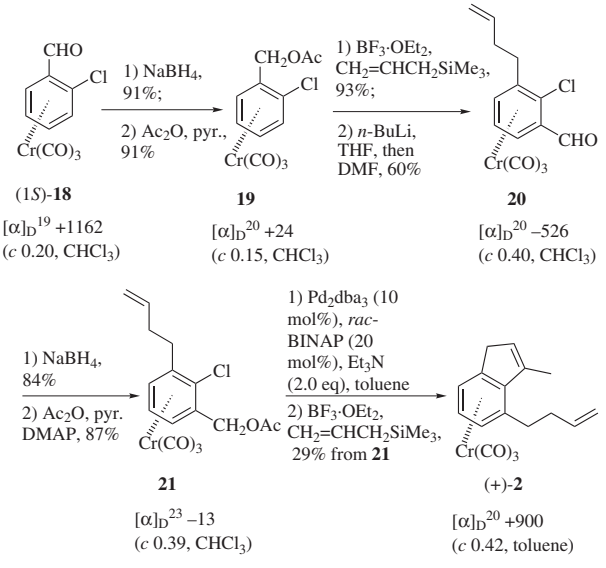
Table 2.



Entry	Compound	Solvent	Temp (°C)	Yield (%) **2** or **16**	Yield (%) **3** or **17**	% Ee[f]
1[a]	**1**	Toluene	100	44	5	46
2[a,d]	**1**	Toluene	100	27	22	36
3[b]	**1**	$(ClCH_2)_2$	60	38	7	20
4[c]	**1**	Toluene	60	—	93	64
5[c]	**1**	Toluene	40	—	89	70
6[c]	**1**	$(ClCH_2)_2$	60	—	92	67
7[c,e]	**1**	$(ClCH_2)_2$	40	—	78	73
8[c]	**1**	MeCN	60	—	59	57
9[c]	**1**	MeOH	60	—	54	3
10[c]	**15**	$(ClCH_2)_2$	60	—	38	40

[a] Triethylamine was used as base.
[b] Proton-sponge® was used as base.
[c] Potassium carbonate was used as base.
[d] In the presence of AgOTf.
[e] 20 mol % of Pd and 40 mol % chiral ligand were used.
[f] % Ee of the major product.

The absolute configuration of the cyclization product was determined as follows (Scheme 2). Enantiomerically pure (+)-(1*S*)-*o*-chlorobenzaldehyde chromium complex **18** $\{[\alpha]_D^{19} = +1162$ (*c* 0.20, $CHCl_3)\}$[16] was reduced and subsequently acetylated to give complex **19** $\{[\alpha]_D^{20} = +24$ (*c* 0.15, $CHCl_3)\}$. Reaction of **19** with allyl trimethylsilane[17] in the presence of $BF_3{\cdot}OEt_2$ followed by the introduction of a formyl group gave 2-chloro-3-butenylbenzaldehyde chromium complex **20** $\{[\alpha]_D^{20} = -526$ (*c* 0.40, $CHCl_3)\}$. Reduction and acetylation gave complex **21** $\{[\alpha]_D^{21} = -13$ (*c* 0.39, $CHCl_3)\}$, which was converted to (+)-complex **2** $\{[\alpha]_D^{20} = +900$ (*c* 0.42, toluene)} by an intramolecular Heck reaction and following the introduction of an allyl group at the benzylic position. Thus, the absolute configuration of the major product **2** $\{[\alpha]_D^{18} = -365$ (*c* 0.39, toluene)} obtained using chiral ligand **9**–palladium catalyst system was the antipode of the authentic (+)-complex **2** derived from (+)-(1*S*)-*o*-chlorobenzaldehyde chromium complex **18**. We further extended the asymmetric desymmetrization of the prochiral chromium complex **1** to the in situ trapping of the palladium intermediate with phenyl- or vinylboronic acids for cascade processes. Thus, the palladium catalyzed reaction of (arene)chromium complex **1** was performed in the presence of *p*-methoxyphenyl boronic acid under the optimized conditions for an asymmetric Mizoroki–Heck reaction using ligand **9**. Fortunately, an intramolecular Heck reaction followed by a Suzuki–Miyaura cross-coupling reaction occurred to give the desired *exo*-benzyl substituted indan derivative **22** as a single diastereomer in 54% yield with 68% ee[18] (Table 3, entry 1). Other phenyl or vinyl boronic acid derivatives were also examined to give the desired products in the optically enriched forms (entries 2–4).

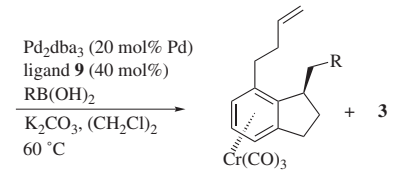


Scheme 2.

3. Conclusion

In conclusion, we have developed a valuable catalytic asymmetric synthesis of planar-chiral (arene)chromium complexes by the asymmetric intramolecular Mizoroki–Heck reaction of tricarbonyl(2,6-dibutenylchlorobenzene)chromium in the presence of a chiral phosphine–palladium catalyst in good yield with moderate enantioselectivity. We have also further developed the asymmetric cascade Mizoroki–Heck reaction/Suzuki–Miyaura cross-coupling reaction. Further

Table 3. Asymmetric cascade reaction of intramolecular Mizoroki–Heck reaction followed by Suzuki–Miyaura cross-coupling



22

Entry	$RB(OH)_2$	Yield **22**	Yield **3**	% Ee **22**
1	4-$MeOC_6H_4B(OH)_2$	54	13	68
2	3,4-Di-$MeOC_6H_3B(OH)_2$	66	10	67
3	CH_2=CHB(OH)$_2$	51	10	64
4	PhCH=CHB(OH)$_2$	65	12	67

investigations directed towards developing an efficient catalytic asymmetric synthesis of these planar chiral transition metal π-complexes are in progress.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

1. (a) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659–667; (b) Togni, A.; Bieler, N.; Burckhardt, U.; Knöllner, C.; Pioda, G.; Schneider, R.; Schnyder, A. *Pure Appl. Chem.* **1999**, *71*, 1531–1537; (c) Togni, A. In *Metallocenes*; Togni, A., Halterman, R. L., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 2, Chapter 11; (d) Hayashi, T. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, Germany, 1995, Chapter 2; (e) Semmelhack, M. F. In Comprehensive Organometallic Chemistry II; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science: Oxford, 1995; Vol. 12, pp 979–1015, 1017–1038; (f) Davies, S. G.; McCarthy, T. D. In Comprehensive Organometallic Chemistry II; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science: Oxford, 1995; Vol. 12, pp 1039–1070; (g) Schmalz, H.-G.; Siegel, S. In Transition Metals for Fine Chemicals and Organic Synthesis; Bolm, C., Beller, M., Eds.; VCH: Weinheim, 1998; Vol. 1; (h) Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917–2940; (i) *Transition Metal Arene p-Complexes in Organic Synthesis and Catalysis*; Kündig, E. P., Ed.; Topics in Organometallic Chemistry; Springer: Berlin, 2004; Vol. 7.
2. (a) Some representative references: Uemura, M.; Daimon, A.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1943–1944; (b) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375–1384; (c) Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938–949; (d) Monovich, L. G.; Le Huerou, Y.; Ronn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52–57; (e) Ratni, H.; Kündig, E. P. *Org. Lett.* **1999**, *1*, 1997–1999; (f) Schellhaas, K.; Schmaltz, H.-G.; Bats, J. W. *Chem. Eur. J.* **1998**, *4*, 57–66; (g) Tanaka, Y.; Taniguchi, N.; Kimura, T.; Uemura, M. *J. Org. Chem.* **2002**, *67*, 9227–9237; (h) Watanabe, T.; Tanaka, Y.; Shoda, R.; Sakamoto, R.; Kamikawa, K.; Uemura, M. *J. Org. Chem.* **2004**, *69*, 4152–4158.
3. (a) Solladié-Cavallo, A.; Solladié, G.; Tsamo, E. *J. Org. Chem.* **1979**, *44*, 4189–4191; (b) Broomly, L. A.; Davies, S. G.; Goodfellow, C. L. *Synlett* **1989**, 59–62; (c) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 192–194.
4. (a) Top, S.; Jaouen, G.; Gillois, J.; Baldoli, C.; Maiorana, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1284–1285; (b) Gillois, J.; Jaouen, G.; Buisson, D.; Azerad, R. *J. Organomet. Chem.* **1989**, *367*, 85–93; (c) Maléziex, B.; Jaouen, G.; Salatin, J.; Howell, J. A. S.; Palin, M. G.; McArdle, P.; O'Gara, M.; Cunningham, D. *Tetrahedron: Asymmetry* **1992**, *3*, 375–376; (d) Yamazaki, Y.; Hosono, K. *Tetrahedron Lett.* **1989**, 5313–5314; (e) Nakamura, K.; Ishihara, K.; Uemura, M.; Nishimura, H.; Hayashi, Y. *Tetrahedron Lett.* **1990**, *31*, 3603–3604; (f) Yamazaki, Y.; Hosono, K. *Tetrahedron Lett.* **1990**, *31*, 3895–3896.
5. (a) Kamikawa, K.; Norimura, K.; Furusho, M.; Uno, T.; Sato, Y.; Konoo, A.; Bringmann, G.; Uemura, M. *Organometallics* **2003**, *22*, 1038–1046; (b) Jones, G. B.; Mustafa, G. *Tetrahedron: Asymmetry* **1998**, *9*, 2023–2026; (c) Uemura, M.; Minami, T.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* **1992**, *57*, 5590–5596; (d) Schmalz, H.-G.; Millies, B.; Bats, J. W.; Duerner, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 631–633; (e) Kündig, E. P.; Leresche, J.; Saudan, L.; Bernardinelli, G. *Tetrahedron* **1996**, *52*, 7363–7378; (f) Jones, G. B.; Heaton, S. B.; Chapman, B. J.; Guzel, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3625–3636; (g) Alexakis, A.; Mangeney, P.; Marek, I.; Rose-Munch, F.; Rose, E.; Semra, A.; Robert, F. *J. Am. Chem. Soc.* **1992**, *114*, 8288–8290.
6. (a) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835–5836; (b) Rebière, F.; Riant, O.; Richard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568–570; (c) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1991**, *56*, 7199–7201; (d) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1993**, *58*, 6182–6189; (e) Aubé, J.; Heppert, J. A.; Milligan, M. L.; Smith, M. J.; Zenk, P. *J. Org. Chem.* **1992**, *57*, 3563–3570; (f) Price, D. A.; Simpkins, N. S.; MacLeod, A. M.; Watt, A. P. *J. Org. Chem.* **1994**, *59*, 1961–1962; (g) Dickens, P. J.; Gilday, J. P.; Negri, J. T.; Widdowson, D. A. *Pure Appl. Chem.* **1990**, *62*, 575–581; (h) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1427–1430; (i) Kündig, E. P.; Quattropani, A. *Tetrahedron Lett.* **1994**, *35*, 3497–3500.
7. (a) Uemura, M.; Nishimura, H.; Hayashi, T. *J. Organomet. Chem.* **1994**, *473*, 129–137; (b) Uemura, M.; Nishimura, H.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 107–110.
8. An exceptional example for achievement of high enantiomeric excess in good yield by oxidation step at the discriminate position: Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101–9102.
9. (a) Gotov, B.; Schmalz, H.-G. *Org. Lett.* **2001**, *3*, 1753–1756; (b) Schumann, H.; Kaufmann, J.; Schmalz, H.-G.; Boettcher, A.; Gotov, B. *Synlett* **2003**, 1595–1598.
10. Catalytic asymmetric complexation of 1,3-diene was achieved for planar chiral (diene)$Fe(CO)_3$ complexes: Knölker, H.-J. *Chem. Rev.* **2000**, *100*, 2941.
11. Bräse, S. *Tetrahedron Lett.* **1999**, *40*, 6757–6759.
12. (a) Imos, R.; Minnaard, A. L.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184–185; (b) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409–2413; (c) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374–2376.

13. Enantiomeric excesses of compounds **2**, **3** and **17** were determined by conversion to the corresponding 1-*endo* methyl indan or tetralin chromium complexes by reduction of the conjugated double bond with SmI_2. Schmalz, H.-G.; Siegel, S.; Bernicke, D. *Tetrahedron Lett.* **1998**, *39*, 6683–6686. HPLC conditions: Chiralcel OD, hexane/2-propanol = 200/1, 1.0 mL/min, 30 °C.
14. Review: Shibasaki, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1996; Vol. 5, pp 119–151.
15. Typical experiment: A mixture of chromium complex **1** (100 mg, 0.28 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (28.8 mg, 10 mol %), chiral ligand **9** (40.8 mg, 40 mol %), base (0.56 mmol) in solvent (10 mL) was degassed by three freeze/vacuum/thaw cycles and heated at 100 °C under nitrogen. The reaction mixture was extracted with EtOAc, washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane–benzene = 4:1) and chromium complexes **2** and **3** were isolated as a pure form, respectively. Complex **2**: $[\alpha]_D^{20} = -365$ (*c* 0.39, toluene); 46% ee; ^{1}H NMR (500 MHz, C_6D_6) δ 1.82 (3H, d, J = 1.7 Hz), 1.92–2.05 (2H, m), 2.18 (1H, ddd, J = 8.0, 9.2, 15.2 Hz), 2.64 (1H, dt, J = 1.7, 23.4 Hz), 2.82–2.90 (2H, m), 4.23 (1H, d, J = 6.4 Hz), 4.63 (1H, t, J = 6.4 Hz), 4.84 (1H, d, J = 6.4 Hz), 4.86–4.91 (2H, m), 5.52–5.59 (2H, m); ^{13}C NMR (126 MHz, C_6D_6) δ 16.2, 31.5, 36.3, 36.9, 88.2, 91.6, 91.9, 108.6, 112.8, 115.7, 128.1, 132.3, 136.4, 138.9, 234.3; IR ($CHCl_3$) 1960, 1882, 1225 cm^{-1}; MS (relative intensity) *m*/*z*, 320 (M^+, 27), 264 (10), 236 (100), 234 (49), 149 (94); HRMS calcd for $C_{17}H_{16}O_3Cr$, 320.0505. found: 320.0490. Complex **3**: $[\alpha]_D^{18} = +272$ (*c* 0.70, toluene); 73% ee; ^{1}H NMR (500 MHz, C_6D_6) δ 1.94–2.31 (6H, m), 2.56–2.64 (1H, m), 2.82–2.86 (1H, m), 4.23 (1H, d, J = 6.1 Hz), 4.44 (1H, d, J = 6.1 Hz), 4.63 (1H, t, J = 6.1 Hz), 4.84–4.85 (1H, m), 4.91 (1H, d, J = 6.1 Hz), 4.94 (1H, s), 5.11 (1H, d, J = 2.3 Hz), 5.55–5.63 (1H, m); ^{13}C NMR (126 MHz, C_6D_6) δ 29.3, 32.3, 32.5, 34.4, 87.2, 90.7, 94.5, 105.6, 108.9, 110.3, 115.9, 118.6, 136.7, 147.4, 233.4; IR ($CHCl_3$) 3082, 2963, 2444, 1962, 1890, 1642, 1447, 1271 cm^{-1}; MS (relative intensity) *m*/*z*, 320 (M^+, 24), 279 (6), 256 (6), 236 (100), 194 (43), 167 (19); HRMS calcd for $C_{17}H_{16}O_3Cr$, 320.0505. found: 320.0503.
16. Kündig, E. P.; Ratni, H.; Crousse, B.; Bernardinelli, G. *J. Org. Chem.* **2001**, *66*, 1852–1860.
17. Reviews: (a) Uemura, M. In Advances in Metal-Organic Chemistry; Liebeskind, L. S., Ed.; JAI: Greenwich, 1991; Vol. 2, pp 195–245; (b) Davies, S. G.; Donohoe, T. J. *Synlett* **1993**, 323–332.
18. HPLC conditions: Chiralcel OD, hexane/2-propanol = 200/1, 30 °C. Stereochemistry of the complex **22** (R = CH_2=$CHCH_2$) was determined by comparison with the authentic sample prepared from the enantiomerically pure (1-indanol)chromium complex.