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Further Improvement on Sulfonamide-Based Ligand for Catalytic Asymmetric 2-Haloallylation and Allylation

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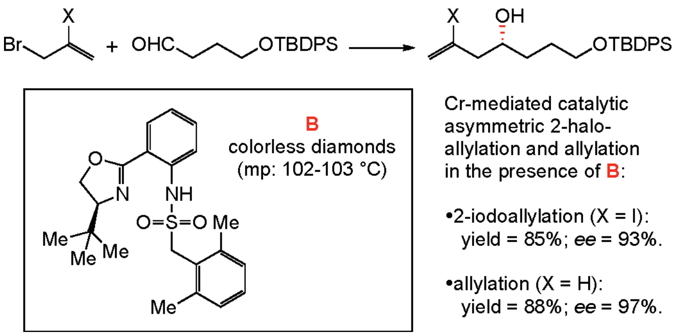
ABSTRACT



Cr-mediated catalytic asymmetric 2-haloallylation and allylation in the presence of **B**:

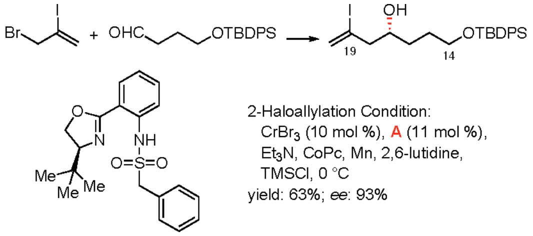
- 2-iodoallylation (X = I): yield = 85%; *ee* = 93%.
- allylation (X = H): yield = 88%; *ee* = 97%.

The sulfonamide-based ligand B was found to exhibit an outstanding crystallinity and perform well as a ligand for Cr-mediated catalytic asymmetric 2-haloallylation and allylation. The new ligand has an appealing advantage over the first generation ligand; its high crystallinity allows effective recovery of the ligand from a reaction in a pure form.

We have recently reported a Co/Cr-mediated catalytic asymmetric 2-haloallylation of aldehydes with 2-haloallyl halides.[1–4] This method gives direct access to valuable synthetic intermediates with a useful level of enantiomeric excess. The value of this method can be seen from the example shown in Scheme 1; the Co/Cr-mediated 2-iodoallylation allows us to obtain the C14−C19 building block for the synthesis of the marine natural product halichondrin B and its analogues in a single step.[5–8]

Considering the synthetic utility of 3-halohomoallylic alcohols,[9] we wished to make further improvement on the sulfonamide-based ligand **A** (Scheme 1). In particular, **A** exists as an amorphous solid thus far, but we recognized that a crystalline ligand should offer appealing advantages,

Scheme 1. Cr-Mediated Catalytic Asymmetric 2-Iodoallylation in the Presence of Ligand **A**[1]



Ligand **A**

2-Haloallylation Condition:
$CrBr_3$ (10 mol %), **A** (11 mol %),
Et_3N, CoPc, Mn, 2,6-lutidine,
TMSCl, 0 °C
yield: 63%; *ee*: 93%

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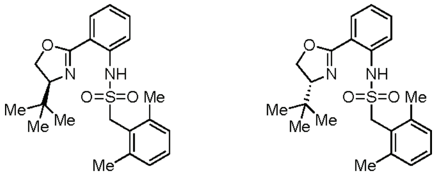
(1) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248.

(2) For reviews on Cr-mediated carbon−carbon bond-forming reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Takai, K.; Nozaki, H. *Proc. Japan Acad. Ser. B* **2000**, *76*, 123. (d) Saccomano, N. A. *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Eds. Pergamon, Oxford, 1991, Vol. 1, 173.

10.1021/ol801093p CCC: $40.75

including the purification and recovery of ligand and the reproducibility and scalability of coupling reactions.

For this reason, we initiated a search for a crystalline sulfonamide-based ligand, which should act as an effective (i.e., equal to or better than **A**) catalyst for catalytic asymmetric 2-haloallylation and allylation. We began with a structure modification on the benzylsufonyl moiety. Through this effort, sulfonamide ligand **B** and its enantiomer ***ent*-B** (Figure 1), prepared from natural and unnatural *tert*-leucinols, respectively, in 20−30 g,[10] were found to exhibit an outstanding crystallinity.[11]



B
colorless diamonds
(mp: 102-103 °C)
$[\alpha]_D$ -15.3° ($CHCl_3$)

***ent*-B**
colorless diamonds
(mp: 102-103 °C)
$[\alpha]_D$ +15.0° ($CHCl_3$)

Figure 1. New crystalline sulfonamide ligands **B** and ***ent*-B**.

Our next task was to demonstrate the effectiveness of **B** for catalytic asymmetric 2-haloallylation. We were delighted to observe that, under the previously used conditions (ligand/CrBr$_3$/cobalt phthalocyanine (CoPc)/Mn/ Et$_3$N/THF/rt, followed by addition of 2,6-lutidine, two coupling partners, and TMS-Cl),[1] the new ligand **B** performed at least as well as the first-generation ligand **A**.

With this result in hand, we then conducted the study to identify the optimum conditions for Cr-mediated catalytic asymmetric 2-haloallylation, thereby revealing the following. First, the complexation of CrBr$_3$ with **B** is best achieved under the condition of **B**/CrBr$_3$/CoPc/Mn/Et$_3$N/THF/42 °C/1.5 h.[1,12] Second, CoPc is a better activator than Fe(TMHD)$_3$ (iron tris(2,2,6,6-tetramethyl-3,5-heptanedione)).[1] Third, although both Zr(Cp)$_2$Cl$_2$ and TMS-Cl are effective dissociation agents, a higher yield is generally observed in the presence of the former.[13,14] Fourth, the optimum concentration of reaction is 0.2 M. Fifth, 2-haloallylation is effectively achieved in the presence of 5 mol % of CrBr$_3$ and 5.5 mol % of **B**.[15]

Under the optimized conditions, 2-haloallylations were conducted (Table 1). 2-Iodoallyl, 2-bromoallyl, and 2-chloroallyl bromides were coupled with aldehydes **4a** and **4b**.

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(3) For Cr-mediated enantioselective allylation, see: (a) Cazes, B.; Vernière, C.; Goré, J. *Synth. Commun.* **1983**, *13*, 73. (b) Chen, C.; Tagami, K.; Kishi, Y *J. Org. Chem.* **1995**, *60*, 5386. (c) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031, ref 1 and references cited therein. (d) Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322. (e) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3357. (f) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Chem. Commun.* **2002**, 919, and references cited therein. (g) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140. (h) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252, and references cited therein. (i) Berkessel, A.; Menche, D.; Sklörtz, C. A.; Schroder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032. (j) Lee, J.-Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S *Org. Lett.* **2005**, *7*, 1837. (k) Miller, J. J.; Sigman, M. S *J. Am. Chem. Soc.* **2007**, *129*, 2752. (l) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554. (m) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 496.

(4) For reviews on metal-mediated enantioselective allylation, for example, see: (a) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (b) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

(5) For the isolation of the halichondrins from a marine sponge *Halichondria okadai* Kadota, see: (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y *J. Am. Chem. Soc.* **1985**, *107*, 4796. (b) Hirata, Y.; Uemura, D *Pure Appl. Chem.* **1986**, *58*, 701. For isolation of the halichondrins from different species of sponges, see: (c) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rutzler, K. C *J. Med. Chem.* **1991**, *34*, 3339. (d) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J. C.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P *J. Org. Chem.* **1993**, *58*, 2538. (e) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H; G, *Tetrahedron Lett.* **1994**, *35*, 9435. (f) Litaudon, M.; Hickford, S. J. H.; Lill, R. E.; Lake, R. J.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1997**, *62*, 1868.

(6) For the synthetic work on the marine natural product halichondrins from this laboratory, see: (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (b) Choi, H.-w.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C *Pure Appl. Chem.* **2003**, *75*, 1. (c) Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770. (d) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382. (e) Kaburagi, Y.; Kishi, Y *Org. Lett.* **2007**, *9*, 723, and references cited therein.

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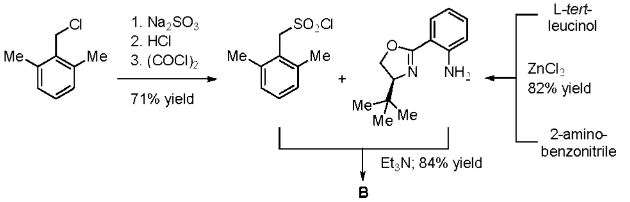
(8) (a) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551. (b) Yu, M. J.; Kishi, Y.; Littlefield, B. A. In *Anticancer Agents from Natural Products*, Eds. Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC Press: Boca Raton, FL, 2005; pp 241−265. (c) Littlefield, B. A.; Palme, M. H.; Seletsky, B. M.; Towle, M. J.; Yu, M. J.; Zheng, W. U.S. Patents 6214865 and 6365759 and International Patent WO99/65894.

(9) For the synthetic value of this functional group, for example, see Scheme 1 in: (a) Corey, E. J.; Yu, C-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

(10) This ligand was synthesized as depicted below. For the details, see the Supporting Information.



(11) In addition to 2,6-dimethylbenzylsulfonamide **B**, 2-methylbenzyl-, 2,4-dimethylbenzyl-, and 2,5-dimethylbenzylsulfonamides were tested, but all of them existed as oils. Using the procedure shown in ref,[10] we attempted to synthesize 2,4,6-trimethylbenzylsulfonyl chloride, but unsuccessfully.

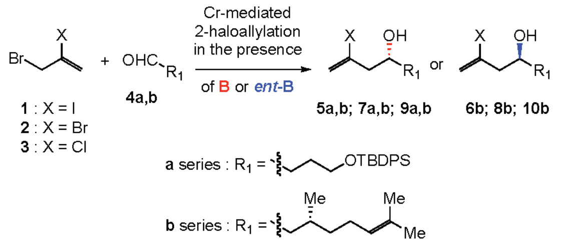
(12) The tested conditions included: complexation at rt for 45 min, 1.5 h, and 2.5 h; complexation at 42 °C for 45 min, 1.5 h, and 2.5 h. We attempted to follow the complexation event by react IR spectroscopy, but the result was not conclusive. Therefore, we relied on the overall performance (asymmetric induction and yield) of 2-haloallylation to draw this conclusion. We should note that, with this optimized complexation protocol, the reproducibility of 2-haloallylation was also improved.

(13) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.

(14) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031.

(15) The catalyst loading was tested for the case of **2** + **4a** → **7a**; the following results were obtained: 10 mol % (yield = 85%, ee = 93%), 5 mol % (yield = 76%, ee = 92%), and 2.5 mol % (yield = 60%, ee = 91%).

Table 1. Cr-Mediated Catalytic Asymmetric 2-Haloallylations[a]



entry	**1 ~ 3** +	**4a,b** /	ligand ⟶	**5 ~ 10**	yield (%)[b]	*ee* or *de* (%)[d]
1	**1**	**4a**	B	**5a** (X = I)	85	93
2	**1**	**4b**	B	**5b** (X = I)	70	94
3	**1**	**4b**	*ent*-B	**6b** (X = I)	71	94
4	**2**	**4a**	B	**7a** (X = Br)	82	93
5	**2**	**4b**	B	**7b** (X = Br)	85	99
6	**2**	**4b**	*ent*-B	**8b** (X = Br)	73	97
7	**3**	**4a**	B	**9a** (X = Cl)	71	92
8	**3**	**4b**	B	**9b** (X = Cl)	75[c]	93
9	**3**	**4b**	*ent*-B	**10b** (X = Cl)	72[c]	91

[a] All reactions were performed with $CrBr_3$ (10 mol %), **B**, or ***ent*-B** (11 mol %) and CoPc (0.2 mol %) at 0 °C. [b] Yields based on chromatographically isolated products. [c] Yields based on chromatographically isolated TMS ethers. [d] Enantiomeric excess (ee) was estimated by ^1H NMR analysis of its Mosher ester, whereas diastereomeric excess (de) was estimated directly from its ^1H NMR spectrum. For details, see the Supporting Information.

Aldehyde **4a** was chosen because the product **5a** is a building block in the halichondrin synthesis. On the other hand, (*R*)-(+)-citronellal (**4b**)[16] was selected to examine the effect on the asymmetric induction from a substituent at the *β*-position.

As seen from entries 1, 4, and 7 in Table 1, new ligand **B** gave an excellent result for 2-haloallylation of **4a**; the level of asymmetric induction with **B** was virtually the same as that observed with **A**, whereas the chemical yields with **B** were higher than those with **A**.[17,18] With the study with (*R*)-(+)-citronellal (**4b**), the methyl group at the *β*-position was found to give no significant effect on the asymmetric induction, i.e., entry 2 vs entry 3, entry 5 vs entry 6, and entry 8 vs entry 9.

We then proceeded to allylation in the presence of ligand **B** and its enantiomer ***ent*-B**. It is worthwhile to note that, unlike 2-haloallyl halides, allyl halides are known to react with aldehydes in the presence of only Cr(II) salt and also that $CrCl_3$•3THF, instead of $CrBr_3$, was used as the chromium source for catalytic asymmetric *allylation* in the previous study.[1,2,19] We were curious to examine if the condition optimized for 2-haloallylation might also be effective for catalytic asymmetric allylation. Therefore, the effectiveness of $CrBr_3$ in the *absence* of the activator CoPc was tested for allylation of (*R*)-(+)-citronellal (**4b**) with allyl bromide, thereby demonstrating that $CrBr_3$ is a chromium source superior to $CrCl_3$•3THF in terms of reaction rate, chemical yield, asymmetric induction, and cost.[20] Thus, both 2-haloallylation and allylation are now conducted under the same optimized condition, with one difference, i.e., *with* or *without* the activator CoPc. Table 2 summarizes the Cr-mediated catalytic asymmetric allylation of **4a** and **4b** with allyl, *γ*,*γ*-dimethylallyl, and methallyl bromides in the presence of ligand **B** or ***ent*-B**.[18]

The performance of new ligand **B** was excellent for allylation of **4a**; an excellent level of asymmetric induction was achieved for its allylation with allyl bromide (97% ee) and *γ*,*γ*-dimethylallyl bromide (98% ee), but a slightly lower level was observed with methallyl bromide (91% ee).

Unlike 2-haloallylation, the effect from the methyl group at the *β*-position was clearly detected for allylation of (*R*)-(+)-citronellal (**4b**) with allyl and methallyl bromides, i.e., entry 2 (99% ee) vs entry 3 (75% ee) and entry 8 (99% ee) vs entry 9 (83% ee). Interestingly, however, the match/mismatch effect[21] was negligibly small for allylation with *γ*,*γ*-dimethylally bromide, i.e., entry 5 (95% ee) vs entry 6 (93% ee).

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(16) The optical purity of **4b** used was better than 99%.

(17) The difference in yields could, at least partly, be attributed to the difference in the dissociating agent, i.e., $Zr(Cp)_2Cl_2$ vs TMS-Cl.[14]

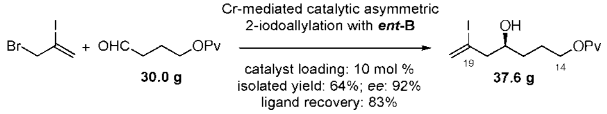
(18) For the determination of absolute configuration, see Supporting Information of reference 1.

(19) In the catalytic system, Cr(III) is reduced to Cr(II) by Mn in situ.

(20) For this combination of substrates, the time to completion, yield, and de were 15 h, 81%, and 99%, respectively, with $CrBr_3$, whereas they were 40 h, 73%, and 92%, respectively, with $CrCl_3$•3THF.

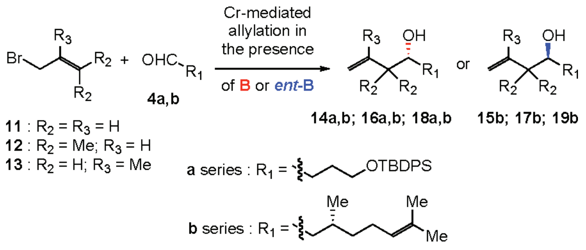
(21) For a review on this subject, see: (a) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(22) A 30-g scale 2-iodoallylation was carried out as below.



A 2-L three-neck, round-bottomed flask equipped with a magnetic stir bar was charged with CoPc (0.18 g, 0.296 mmol), ***ent*-B** (7.68 g, 18.0 mmol), $CrBr_3$ (Cerac, 5.08 g, 16.4 mmol), and Mn powder (Aldrich, 29.0 g, 523 mmol). The flask was capped with rubber septa. The inner atmosphere was replaced with N_2 via gentle evacuation (oil pump) and purged with N_2 three times. Anhydrous THF (Baker, ultra low water, no preservative, 700 mL) and then a THF solution of Et_3N (2.73 mL, 19.2 mmol; THF: 30 mL) were cannulated into the flask. The reaction mixture was stirred at 42 °C for 1.5 h with a slight positive pressure of N_2 and then cooled to rt. A THF solution of 2,6-lutidine (2.50 mL, 20.9 mmol; THF: 30 mL) was cannulated into the reaction flask. The reaction mixture was stirred at rt for 15 min and cooled to 0 °C. A THF solution of 2-iodoallyl bromide (99.0 g, 401 mmol; THF: 40 mL) and a THF solution of aldehyde (30.0 g, 174 mmol; THF: 40 mL) were cannulated into the reaction flask. Under a positive flow of argon, the reaction flask was charged with $Zr(Cp)_2Cl_2$ (Alfa, 50.9 g, 174 mmol). The reaction flask was capped with rubber septa, placed in a 0 °C bath, and stirred with a magnetic stirrer. Upon completion of the reaction (15 h, monitored by TLC), the reaction mixture was diluted with EtOAc (900 mL). After addition of Florisil (66 g), the mixture was stirred for 30 min and passed through a silica gel plug (130 g) with EtOAc (2.7 L). The filtrate was washed with water (3 × 300 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (400 mL), dried over Na_2SO_4 (250 g), and evaporated to dryness under reduced pressure. The residue was applied on a silica gel column (450 g), which was eluted with hexanes, hexanes/EtOAc (30:1), and then hexanes/EtOAc (20 → 10:1). On evaporation of the eluent of hexanes/EtOAc (30:1), the recovered ligand was obtained as a crystalline solid, recrystallization (EtOAc/hexanes) of which gave recovered ligand ***ent*-B** (6.02 g, 83% recovery) as colorless diamonds.[23] An evaporation of the eluent of hexanes/EtOAc (20 → 10:1) furnished the vinyl iodide (37.6 g, 64% yield) as viscous oil. The purity of product was confirmed by ^1H NMR and TLC analyses. The enantiomeric excess (92%) was estimated from ^1H NMR analysis of its (+)-Mosher ester. **Note**: Large-scale 2-iodoallylation was carried out with the Pv- and TBDPS-protected aldehydes. The observed asymmetric induction was practically identical in the two series, but the yield in the TBDPS-series was 15~20% higher than that in the Pv series. In the TBDPS series, because of their similar polarity, the product and ligand B were separated after the alcohol was transformed into its 2,4,6-trimethylbenzenesulfonate. For the details, see the Supporting Information.

Table 2. Cr-Mediated Catalytic Asymmetric Allylations[a]



entry	11 ~ 13 + 4a,b / ligand			⟶ 14 ~ 19	yield (%)[b]	*ee* or *de* (%)[c]
1	**11**	**4a**	**B**	**14a** ($R_2 = R_3 = H$)	88	97
2	**11**	**4b**	**B**	**14b** ($R_2 = R_3 = H$)	81	99
3	**11**	**4b**	*ent*-**B**	**15b** ($R_2 = R_3 = H$)	79	75
4	**12**	**4a**	**B**	**16a** (R_2 = Me; R_3 = H)	79	98
5	**12**	**4b**	**B**	**16b** (R_2 = Me; R_3 = H)	79	95
6	**12**	**4b**	*ent*-**B**	**17b** (R_2 = Me; R_3 = H)	77	93
7	**13**	**4a**	**B**	**18a** (R_2 = H; R_3 = Me)	70	91
8	**13**	**4b**	**B**	**18b** (R_2 = H; R_3 = Me)	85	99
9	**13**	**4b**	*ent*-**B**	**19b** (R_2 = H; R_3 = Me)	81	83

[a] All reactions were performed with $CrBr_3$ (10 mol %) and **B** or ***ent*-B** (11 mol %) at 0 °C. [b] Yields based on the chromatographically isolated products. [c] Enantiomeric excess (ee) was estimated by ^1H NMR analysis of its Mosher ester, whereas diastereomeric excess (de) was estimated directly from its ^1H NMR spectrum. For the details, see the Supporting Information.

In summary, the overall performance of new ligand **B** is at least equal to that of the first generation ligand **A**. We should point out the advantages that **B** offers. In our view, the most significant advantage is the fact that **B** exhibits an exceptional crystallinity. Therefore, it is practical to recover the used ligand from a reaction in a pure form, thereby allowing us to carry out a large-scale synthesis in an economical manner. In order to illustrate this advantage, we conducted 2-iodoallylation to prepare the C14−C19 segment of halichondrins on a 30-g scale with the use of commonly used laboratory glassware/equipment. From this coupling reaction, the ligand **B** was recovered in 83% (after recrystallization) for reuse.[22]

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Supporting Information Available: Experimental details and ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) This recovered ligand was shown to be as effective (asymmetric induction, yield, and reproducibility) as the original ligand.