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Synthesis of γ-functionalized allyltrichlorosilanes and their application in the asymmetric allylation of aldehydes

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

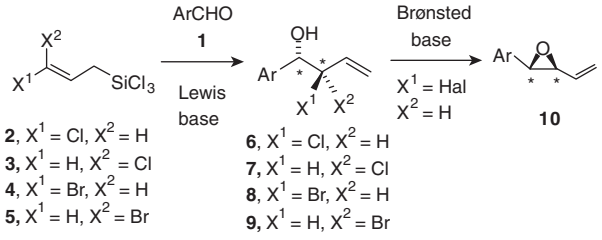
Isomerically pure *trans*- and *cis*-γ-bromoallyltrichlorosilanes **4** and **5** have been synthesized and shown to react with aromatic aldehydes **1** in the presence of Lewis-basic catalysts (e.g., DMF) to produce the corresponding *anti*- and *syn*-allylbromohydrins **8** and **9**, respectively, as single diastereoisomers. With BINAPO **25** as a chiral catalyst, promising enantioselectivity (⩽50% ee) has been attained.

1. Introduction

The addition of allymetal reagents to aldehydes constitutes a popular method for the stereocontrolled construction of a carbon–carbon bond with the concomitant formation of up to two stereogenic centers. The more recent variant, namely the asymmetric allylation of aldehydes with allyltrichlorosilanes, catalyzed by chiral Lewis bases (Scheme 1), has now evolved into an efficient and practical method for the synthesis of enantiomerically enriched homoallylic alcohols,[1] thereby providing a viable alternative to the protocols that employ stoichiometric chiral allylboranes. In general, the reaction displays an excellent diastereocontrol in the case of *trans*- and *cis*-crotylsilanes, which is believed to originate from a cyclic transition state.[1] However, the synthetic applications are currently limited to simple alkyl homologues of allyltrichlorosilanes.[1,2] We reasoned that the use of isomerically pure allylsilanes functionalized in the γ-position **2**–**5** would broaden the scope of this reaction and produce halohydrins **6**–**9** (Scheme 1), which could further undergo cyclization to afford the corresponding vinyl epoxides in a stereoselective fashion: thus, a ring closure in the case of *anti*-halohydrins **6** or **8** should result in the formation of *trans*-epoxides **10**.[3] It is noteworthy that in an analogous allylation of aldehydes employing γ-chloroallyltin reagents, the corresponding chlorohydrins could not even be isolated due to their spontaneous cyclization to afford vinylepoxides **10** directly.[4]

2. Results and discussion

In order to explore the feasibility of this approach, a mixture of 3-chloroallylsilanes **2** and **3** (*E*/*Z* ~1.3:1) was prepared by a copper(I)-catalyzed hydrosilylation of the commercially available 1,3-dichloropropene (*E*/*Z* ~1.3:1) with trichlorosilane in the presence of an equimolar amount of triethylamine.[5] The latter **2**/**3** mixture was then reacted with benzaldehyde (rt, 2 h) in DMF, which acted both as a solvent and as a Lewis-basic catalyst, to afford a 1:1 mixture of the diastereoisomeric chlorohydrins **6** and **7** in 62% yield.



Scheme 1.

With this promising result in hand, we set out to synthesize pure isomers *E*-**2**/*Z*-**3** or *E*-**4**/*Z*-**5**. Since the initial attempts of the separation of the *cis*- and *trans*-isomers of commercial 1,3-dichloropropene by fraction distillation were unsuccessful, an alternative route had to be developed; we focused on the vinyl bromides *E*-**4**/*Z*-**5**.

The synthesis of the *trans*-isomer *E*-**4** is shown in Scheme 2. Following the method of Just et al.[6] the addition of hydrobromic acid to propiolic acid **11** afforded *trans*-β-bromoacrylic acid **12** (75%), which was reduced with lithium aluminum hydride to give *E*-3-bromo-propenol **13** in 62% yield as a single stereoisomer. The subsequent conversion of the latter allylic alcohol **13** into chloride **14** is worthy of note: several methods, including the use of *N*-chloro succinimide with triphenyl phosphine, thionyl chloride, oxalyl chloride in DMF, and phosphorus trichloride in pyridine proved

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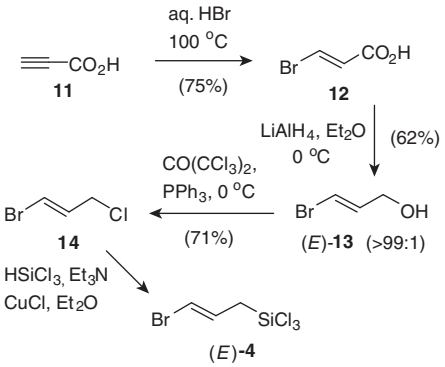
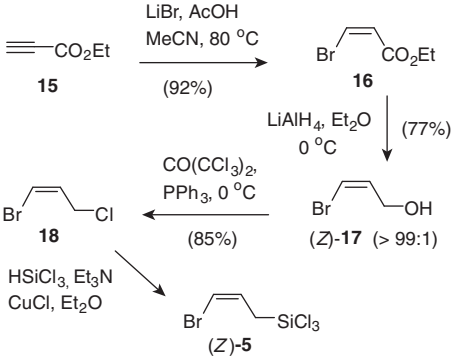


Scheme 2.

unsuccessful, with the yields of the desired product not exceeding 22%. Finally, after further experimentation, we found that the procedure employing hexachloroacetone as the source of the chloride, produced the required allylchloride **14** in 71% yield. The reaction proceeded under mild conditions with retention of the regio- and stereo-integrity. Furthermore, purification of the product can be accomplished by its distillation directly from the reaction mixture. Silane *E*-**4** was then obtained by a CuCl-catalyzed hydrosilyation of **14** with trichlorosilane in the presence of an equimolar amount of triethylamine.[5] After removing the solid residues by filtration under an inert atmosphere, an aliquot sample was analyzed by ^{1}H NMR spectroscopy, which confirmed a quantitative conversion. To avoid decomposition, the remaining material was used in the next step without further purification.

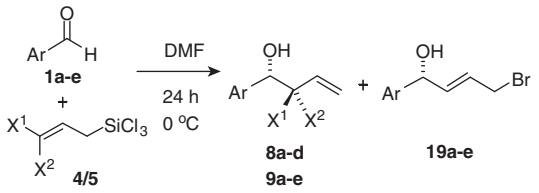
For the synthesis of *Z*-**5** (Scheme 3), ethyl propiolate **15** was readily converted into *Z*-bromoacrylate **16** (92%) by reaction with lithium bromide in acetic acid. Here, the nucleophilic addition of the halide anion to the electron-deficient carbon–carbon triple bond, stereodirected by coordination of the lithium cation to the carbonyl group, was proposed to account for the high stereoselectivity observed for this reaction.[7] Ester **16** was then reduced with lithium aluminum hydride at 0 °C to provide the *cis*-alcohol **17** in 77% yield. The last two steps toward the target *Z*-**5** were carried out in the same way as described for the synthesis of *E*-**4**.



Scheme 3.

With the geometrically pure allylsilanes **4** and **5** in hand, we first investigated a racemic variant of the allylation reaction, employing DMF as a Lewis-basic activator.[1] The results are summarized in Table 1; since silanes **4** and **5** were prepared in situ, without isolation, the yields are given over the two steps. The reaction proved highly diastereoselective: thus, silane *E*-**4** produced exclusively the *anti*-isomers **8a–d**, whereas *Z*-**5** afforded *syn*-**9a–e** contaminated with only trace amounts of the opposite diastereoisomers (⩾95:5), as revealed by the ^{1}H NMR spectra of the crude products.

Table 1
Allylation of aldehydes in DMF[a]



Entry	Aldehyde, Ar	Silane	X^1, X^2	Product[b], yield[c] (%)
1	**1a**, Ph	**4**	Br, H	**8a**, 38
2	**1b**, 2-Naphthyl	**4**	Br, H	**8b**, 36[d]
3	**1c**, 4-$CF_3C_6H_4$	**4**	Br, H	**8c**, 41
4	**1d**, 4-ClC_6H_4	**4**	Br, H	**8d**, 25
5	**1a**, Ph	**5**	H, Br	**9a**, 48
6	**1b**, 2-Naphthyl	**5**	H, Br	**9b**, 38
7	**1c**, 4-$CF_3C_6H_4$	**5**	H, Br	**9c**, 48
8	**1d**, 4-ClC_6H_4	**5**	H, Br	**9d**, 31
9	**1e**, 4-$MeOC_6H_4$	**5**	H, Br	**9e**, 32

[a] The reactions were carried out on a 2.0 mmol scale at 0 °C for 24 h, using a 1:1 aldehyde to silane ratio at 0.4 M concentration.
[b] Variable quantities (up to 30%) of the isomeric products **19a–e** were also formed. The products were isolated as almost pure diastereoisomers (⩾95:5) as shown by ^{1}H NMR spectroscopy. The relative configuration was established by ^{1}H NMR spectroscopy in analogy with other crotyl derivatives.[9,10]
[c] The yields are shown for the two-step sequence (**14**/**18**→**4**/**5**→**8**/**9**) since the silanes **4** and **5** were used without isolation.
[d] The product was difficult to purify; the diastereoisomeric ratio was ⩾9:1.

As expected, bromohydrin **8a** was readily cyclized upon treatment with NaH in CH_2Cl_2 (0 °C, 2 h) to afford the pure *trans*-epoxide **10a** (Ar=Ph) in 82% yield.

In some cases, the allylation of aldehydes with silanes **4**/**5** was accompanied by the formation of variable quantities of the isomeric linear products **19**, presumably formed by the allylic rearrangement of halohydrins **8**/**9**, which in turn was catalyzed by traces of residual CuCl left in the reaction mixture from the previous step. The isomers can be separated by chromatography but for obtaining the epoxides this may not be necessary, since the corresponding iodo-analogues of **19** have been shown to undergo a facile cyclization into vinylepoxides **10** anyway (upon treatment with NaH).[8]

To develop an enantioselective variant of this process, several chiral Lewis bases were examined as potential catalysts (Fig. 1). First, we used our pyridine-type N-oxide catalysts METHOX **20**[2,9] and QUINOX **21**,[10] which have previously been shown by us to exhibit high catalytic activity and enantioselectivity in the addition of allyltrichlorosilane and its non-functionalized homologues to a variety of aromatic aldehydes.[9–11] However, in the case of bromoallyltrichlorosilanes **4** and **5**, both N-oxides **20** and **21** proved

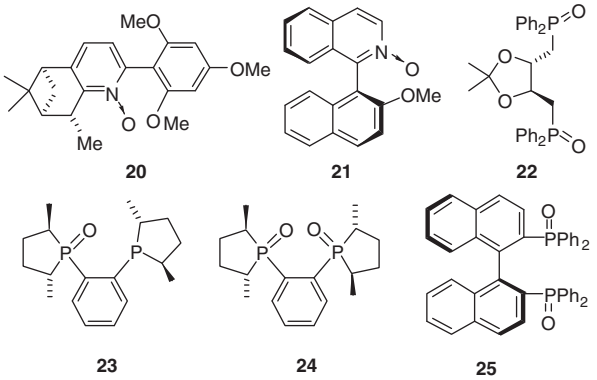


Figure 1. Chiral catalysts.

unreactive (Table 2, entries 1 and 2), suggesting that the nucleophilicity of the γ-carbon in silanes **4** and **5** is significantly reduced (compared to allyltrichlorosilane) due to the electron-withdrawing effect of the bromine. Therefore, we turned our attention to phosphine oxides as potentially more reactive catalysts.

Table 2
Asymmetric allylation of aldehydes **1** with **4** and **5**[a]

Entry	Catalyst (mol %)	Aldehyde, Ar	Silane, X^1, X^2	T (°C)	Product, yield[b] (%)	Ee[c] (%)
1	**20** (10)	**1a**, Ph	**4**, H, Br	−20	**8a**, 0	n/a
2	**21** (10)	**1c**, 4-$CF_3C_6H_4$	**5**, Br, H	−20	**9c**, 0	n/a
3	**22** (10)	**1a**, Ph	**5**, Br, H	−20	**9a**, 17	18
4	**23** (20)	**1a**, Ph	**4**, H, Br	−20	**8a**, 23	29
5	**24** (10)	**1a**, Ph	**4**, H, Br	−20	**8a**, 10	15
6	**24** (10)	**1a**, Ph	**5**, Br, H	−20	**9a**, 43	25[d]
8	**25** (10)	**1a**, Ph	**5**, Br, H	−20	**9a**, 34	50[e]
9	**25** (10)	**1c**, 4-$CF_3C_6H_4$	**5**, Br, H	−10	**9c**, 22	43

[a] For the Scheme, see Table 1. The reactions were carried out in MeCN on a 0.5 mmol scale with a 1:1.1 aldehyde/silane ratio in the presence of the catalyst overnight.

[b] The absolute configuration of the products was inferred from the known absolute configuration of the (*S*,*S*)-(−)-bromohydrin **9a** (as shown in the Schemes) and the corresponding chlorohydrin[18] and extrapolated to the rest of the series. This configuration corresponds to that of the laevorotatory product obtained from the reaction of PhCHO with *Z*-crotyltrichlorosilane catalyzed by (*S*)-**25**.[17] The crude products were almost pure diastereoisomers (⩾95:5) as shown by ^{1}H NMR spectroscopy. The relative configuration was established by ^{1}H NMR spectroscopy in analogy with other crotyl-derived products;[9,10] **8a** and **9a** are known compounds.[18]

[c] Established by chiral HPLC.

[d] $[\alpha]_D^{20} = -8.1$ (*c* 0.5, CH_2Cl_2); lit (Ref. 18) gives $[\alpha]_D = -34.7$ (*c* 2.1, $CHCl_3$) for the highly enantiomerically enriched (1*S*,2*S*)-**9a**.

[e] $[\alpha]_D^{20} = -19.8$ (*c* 0.5, CH_2Cl_2).

Indeed, the allylation of benzaldehyde with *Z*-**5** in the presence of the phosphine dioxide **22** (10 mol %),[12] derived from Kagan's DIOP,[13] produced *syn*-**9a**, though in low yield (17%) and with only 18% ee (entry 3). Monoxide[14] **23** and dioxide[15] **24** exhibited similar levels of reactivity and enantioselectivity (entries 4–6). The most promising results were obtained with (*S*)-BINAPO[16,17] **25** (10 mol %), which catalyzed the formation of *syn*-**9a** in 50% ee (entry 7) and *syn*-**9c** in 43% ee (entry 8).[18] High diastereoselectivities (⩾95:5) were again observed.[19]

3. Conclusion

In conclusion, we have synthesized isomerically pure *trans*- and *cis*-γ-bromoallyltrichlorosilanes **4** and **5**, which in the Lewis base-catalyzed addition to aromatic aldehydes **1** produced the corresponding allylbromohydrins **8** and **9**, respectively, as highly pure diastereoisomers (⩾95:5). In the enantioselective variant, promising enantioselectivity (50% ee) was obtained with BINAPO **25** as a catalyst. It is noteworthy that all these reactions proceed solely via the γ-attack of the allylic moiety; the formation of the products corresponding to the α-attack was not observed within the limits of the ^{1}H NMR spectroscopy.[20]

Acknowledgments

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References

1. For leading reviews, see: (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432–440; (b) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167–170; (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793; (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732–4739; (e) Oestreich, M.; Rendler, S. *Synthesis* **2005**, 1727–1747; (f) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391–1401; (g) Benaglia, M.; Guizzetti, S.; Pignataro, L. *Coord. Chem. Rev.* **2007**, *252*, 492–512; (h) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29–36; (i) Kočovský, P.; Malkov, A. V. Chiral Lewis Bases as Catalysts. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; p 255; (j) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.
2. Malkov, A. V.; Kabeshov, M. A.; Bařłóg, M.; Kočovský, P. *Chem. Eur. J.* **2009**, *15*, 1570–1573.
3. For asymmetric synthesis of vinylepoxides, see: (a) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513–7520; (b) Solladie-Cavallo, A.; Bouerat, L.; Roje, M. *Tetrahedron Lett.* **2000**, *41*, 7309–7312; (c) Bandini, M.; Cozzi, P.; Melchiorre, P.; Morganti, S.; Umani-Ronchi, A. *Org. Lett.* **2001**, *3*, 1153–1155; (d) Zanardi, J.; Lamazure, D.; Miniere, S.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2002**, *67*, 9083–9086; (e) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J.-L.; Winn, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 10926–10940; (f) Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274–3278.
4. Shibata, I.; Fukuoka, S.; Baba, A. *Chem. Lett.* **1998**, 533–534.
5. (a) Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1–C3; (b) Nishiyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1981**, *22*, 5289–5292.
6. Just, G.; Ouellet, R. *Can. J. Chem.* **1976**, *54*, 2925–2934.
7. (a) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643–1644; (b) Ma, S.; Lu, X. *Org. Synth.* **1999**, *Coll. Vol. 9*, 415–417.
8. Kazmaier, U.; Lucas, S.; Klein, M. *J. Org. Chem.* **2006**, *71*, 2429–2433.
9. Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219–3222.
10. (a) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew, Chem., Int. Ed.* **2003**, *42*, 3674–3677; (b) Malkov, A. V.; Ramírez-López, P.; Biedermannová, L.; Rulíšek, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kočovský, P. *J. Am. Chem. Soc.* **2008**, *130*, 5341–5348.
11. For other chiral N-oxide catalysts, see Refs. 1h–j and the following: (a) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047–1049; (b) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A: Chem.* **2003**, *196*, 179–186; (c) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659–9668; (d) Malkov, A. V.; Westwater, M.-M.; Kadlčíková, A.; Gutnov, A.; Hodačová, J.; Rankovic, Z.; Kotora, M.; Kočovský, P. *Tetrahedron* **2008**, *64*, 11335–11348; (e) Malkov, A. V.; Gordon, M. R.; Stončius, S.; Hussain, J.; Kočovský, P. *Org. Lett.* **2009**, *11*, 5390–5393; (f) Hrdina, R.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. *Adv. Synth. Catal.* **2007**, *349*, 822–826; (g) Hrdina, R.; Kadlčíková, A.; Valterová, I.; Hodačová, J. *Tetrahedron: Asymmetry* **2007**, *17*, 3185–3191; (h) Hrdina, R.; Boyd, T.; Valterová, I.; Hodačová, J.; Kotora, M. *Synlett* **2008**, 3141–3144; (i) Hrdina, R.; Dračinský, M.; Valterová, I.; Hodačová, J.; Císařová, I.; Kotora, M. *Adv. Synth. Catal.* **2008**, *350*, 1449–1456; (j) Kadlčíková, A.; Hrdina, R.; Valterová, I.; Kotora, M. *Adv. Synth. Catal.* **2009**, *351*, 1279–1283; (k) Hrdina, R.; Opekar, F.; Roithová, J.; Kotora, M. *Chem. Commun.* **2009**, 2314–2316; For chiral sulfoxide-type catalysts, see: (l) Massa, A.; Malkov, A. V.; Kočovský, P.; Scettri, A. *Tetrahedron Lett.* **2003**, *44*, 7179–7181.
12. Hashmi, A. S. K.; Naumann, F.; Probst, R.; Bats, J. W. *Angew. Chem., Int. Ed.* **1997**, *36*, 104–106.
13. Dang, T. P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* **1971**, 481–482.
14. Cote, A.; Desrosiers, J.-N.; Boezio, A. A.; Charette, A. B. *Org. Synth.* **2006**, *83*, 1–4.
15. Cote, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6525–6528.
16. (a) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629–635; (b) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20–32; (c) Gladiali, S.; Pulacchini, S.; Fabbri, D.; Manassero, M.; Sansoni, M. *Tetrahedron: Asymmetry* **1998**, *9*, 391–395; (d) Berthod, M.; Saluzzo, C.; Mignani, G.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 639–645; (e) Nakajima, M.; Sugiura, M.; Kotani, S.; Tando, T.; Shimoda, Y. *Tetrahedron: Asymmetry* **2009**, *20*, 1369–1370.
17. The related allylation of aldehydes with *E*- and *Z*-crotyl-trichlorosilane, catalyzed by BINAPO, exhibited 46% and 4% ee, respectively: Kotani, S.; Hashimoto, S.; Nakajima, M. *Tetrahedron* **2007**, *63*, 3122–3132.
18. The (1*R*,2*R*)-(+)- and (1*S*,2*S*)-(−)-bormohydrin **9a** was previously obtained via the BF_3-catalyzed stoichiometric addition of the enantiomeric [*Z*-γ-bromoallyl]B(Ipc)$_2$ to PhCHO in 74% ee (at −78 °C) and 86% ee (at −90 °C); the *syn*:*anti* ratio was 90:10 and 94:6, respectively.[3a]
19. Silane **5** (0.55 mmol) was added to a solution of **25** (0.05 mmol), *i*-$PrEt_2N$ (2.5 mmol), and PhCH=O (0.50 mmol) in MeCN (2 mL) under argon at −20 °C and the mixture was stirred at −20 °C overnight. The reaction was quenched with aq. $NaHCO_3$ (1 mL) and the mixture was extracted with ether (3 × 10 mL). The extract was washed with brine (2 × 10 mL), dried (Na_2SO_4), and evaporated. Purification by flash chromatography on silica gel (15×1 cm) with petroleum ether/AcOEt (6:1) afforded (−)-**9a** (34%). HPLC (Chiracel IB, flow rate: 0.5 mL/min, hexane/*i*-PrOH 99:1; t_{minor} = 40.30 min, t_{major} = 42.84 min) showed 50% ee.
20. Formation of small amounts of the products of α-attack (⩽10%) was observed for the stoichiometric allylation of aldehydes with γ-haloallylboranes.[18]