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Ambient-Pressure Asymmetric Preparation of *S,S*-DICHED, a C_2-Symmetrical Director for Matteson Reactions

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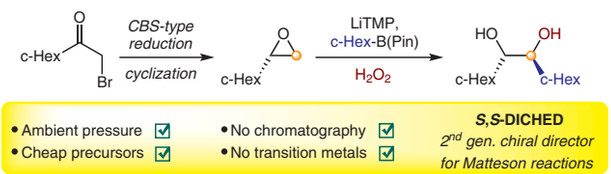

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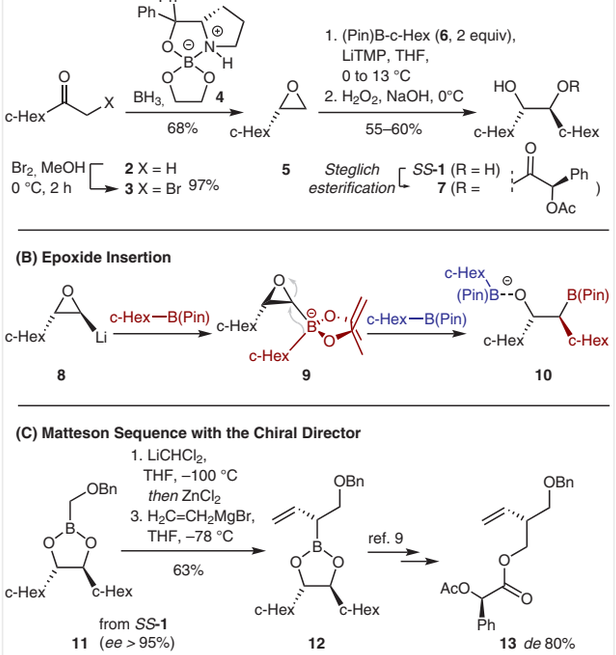
Abstract A synthesis of *S,S*-DICHED (dicyclohexylethane-1,2-diol), a C_2-symmetrical chiral director for Matteson homologations, is described. It relies on the insertion of lithiated *S*-2-cyclohexyloxirane into cyclohexylboronic acid pinacol ester and proceeds in three linear steps from readily available starting materials. No step requires chromatography or any specialized equipment.

Key words DICHED, DIPED, Matteson reaction, lithiated epoxide, chiral director

DICHED (dicyclohexylethane-1,2-diol, **1**) and DIPED (diisopropylethane-1,2-diol) are C_2-symmetrical, highly effective chiral directors for Matteson's diastereoselective homologation of corresponding boronic esters.[1] *S,S*-DICHED (*SS*-**1**) is commercially available in enantiomerically pure form but rather expensive. Preparation of scalemic DICHED was first described by Hoffmann and co-workers.[2] It requires Sharpless bishydroxylation of *trans*-stilbene and subsequent hydrogenation, which was achieved with Rh/Al_2O_3 at 60–70 atm H_2. Matteson *et al.* developed a reduction protocol that proceeds via a concentrated solution of the corresponding methoxy borate, which only requires 10–11 atm H_2.[3] The high cost of $RhCl_3$, as well as the inconvenience of the high-pressure hydrogenation procedures[4] led us to explore alternative routes, the best of which is shown in Scheme 1. It was based on the work of Aggarwal *et al.*, who first described the insertion of lithiated epoxides (similar to **8**) into pinacol boronates.[5]

For our synthesis of *S,S*-DICHED (*SS*-**1**), enantiomerically pure cyclohexyloxirane **5** was prepared as reported by Ortiz-Marciales *et al.*[6] by brominating ketone **2** and submitting the crude product **3** to a CBS-type reduction and cyclization using catalyst **4**. Scale up of the procedure to multigram levels was straightforward, as bromide **3** could be used directly after aqueous workup and oxirane **5** was distilled at 56–65 °C at 14 mbar.



Scheme 1 (A) Synthesis of *S,S*-DICHED (*SS*-**1**). (B) Mechanism of Aggarwal homologation with lithiated epoxides and suggested explanation for the need for two equivalents of **6**.[7] (C) Application of *SS*-**1** in a short Matteson sequence showed no double stereodifferentiation, but confirmed the absolute configuration of *SS*-**1**.

To convert oxirane **5** into DICHED, lithiation with LiTMP in the presence of two equivalents of cyclohexylpinacol boronate **6** had to be carried out at 0 °C for two hours. The

chiral carbenoid **8** and boronate **6** form ate complex **9** that undergoes a 1,2-rearrangement to α-alkoxyboronate **10**. Aggarwal's original procedure for this type of reaction[5] employed –30 °C, but **5** did not react with LiTMP under these conditions (as confirmed by *in situ* quench with TMSCl). Initially we allowed the reaction mixture to reach room temperature to facilitate the 1,2-rearrangement. However, on warmer days competing β-elimination (of **10** to 1,2-dicyclohexylethylene) was observed. This problem was completely avoided by using a p-xylene/solid CO_2 cooling bath (13 °C). The reaction was then completed by H_2O_2/NaOH oxidation at 0 °C. Attempts to reduce the required amount of boronate **6** led to significant losses in yield.[7] However, as **6** can be readily made on a large scale (see Supporting Information), the need for two equivalents of **6** is of little preparative concern.

The *de* of the reaction was excellent and no formation of the undesired *meso*-diol was observed by ^{1}H NMR analysis of the crude product. The enantiomeric purity of the product was assessed after derivatization with (*S*)-OAc-mandelic acid (*SS*-**1** → **7**) and was usually >95% *ee*. On occasions when slightly less pure batches of catalyst **4** were used, the *ee* dropped to 89–91%. Such material could, however, be enantiomerically enriched afterwards by recrystallization from EtOH (0.75 g/mL) or by column chromatography after conversion into **7** (see Supporting Information). The absolute configuration of *SS*-**1**was confirmed after using its boronic ester derivative **11**[8] in a short homologation sequence to yield **12** (Scheme 1, C). Conversion into **13** delivered a product of which both diastereomers are known.[9] Interestingly **13** had a *de* of only 80%, although the sequence started with highly pure material (>95% *ee*). This could indicate that the double stereodifferentiation discovered by Matteson[1] did not occur in this case, probably due to the high migration tendency of the newly introduced vinyl group.[10]

In the context of this work, we also looked at Matteson's synthesis of DIPED from tartaric acid,[11] which we were able to modify, so that the use of a pyrolysis oven was avoided and the expensive rhodium catalyst could be replaced by Raney nickel (see Supporting Information). Nevertheless the enantioselective synthesis of *S*,*S*-DICHED[12] (Scheme 1), emerged as advantageous, as it creates a nonvolatile product (unlike DIPED), does not require expensive transition metals or chromatography and can be conducted without the use of high pressure or other specialized equipment. Its disadvantage is the need for the potentially toxic intermediates **3** and **5**, for which we recommend careful handling. Accordingly annotated procedures are given in the Supporting Information.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591530.

References and Notes

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(3) Hiscox, W. C.; Matteson, D. S. *J. Org. Chem.* **1996**, *61*, 8315.

(4) Ref. 3 reports problems with overreduction when using the procedure described in ref. 2. Our attempts to run the procedure in ref. 3 on 0.5–2 g scales required some dilution, leading to mixtures of starting material and (partially) hydrogenated product. Ref. (3) also describes $RhCl_3$ recovery.

(5) (a) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165. Also see: (b) Alwedi, E.; Zakharov, L. N.; Blakemore, P. R. *Eur. J. Org. Chem.* **2014**, 6643.

(6) Huang, K.; Wang, H.; Stepanenko, V.; De Jesús, M.; Torruellas, C.; Correa, W.; Ortiz-Marciales, M. *J. Org. Chem.* **2011**, *76*, 1883.

(7) We initially thought that the 1,2-rearrangement/epoxide opening had to be facilitated by a Lewis acid, the role of which could be fulfilled by excess boronate. However, attempts to replace it with $ZnCl_2$ or TMSCl (added after LiTMP) resulted in lower conversions of **5** and thus lower yields. The formation of an ate complex of type **10** after the 1,2-rearrangement would explain this observation if the rearrangement occurs as fast/faster than the formation of **9**.

(8) Singh, R. P.; Matteson, D. S. *J. Org. Chem.* **2000**, *65*, 6650.

(9) Struth, F. R.; Hirschhäuser, C. *Eur. J. Org. Chem.* **2016**, 958.

(10) Based on our previous studies (ref. 9) we expected a *de* of 80% for the homologation of **11** with $LiCHX_2$ under the employed conditions. However, we did expect the *de* to increase again after substitution with vinyl Grignard (→ **12**) due to the double stereodifferentiation discovered by Matteson for this type of chiral director (ref. 1e). See Supporting Information for further discussion.

(11) Matteson, D. S.; Beedle, E. C.; Kandil, A. A. *J. Org. Chem.* **1987**, *52*, 5034.

(12) **Procedure for the Preparation of *SS*-1**
Immediately before the reaction, LiTMP was prepared in a separate flask by addition of n-BuLi (2 equiv, 1.6 M in hexanes) to a solution of dry tetramethylpiperidine (2 equiv) in dry THF (1 L/mol of LiTMP) at 0 °C. The LiTMP solution was stirred for 0.5 h at r.t., transferred into a dropping funnel and added dropwise to a solution of epoxide **5** (1 equiv) and boronate **6** (2 equiv) in THF (1 L/mol of **6**) with cooling in an ice bath (0 °C). Afterwards the reaction mixture was stirred for 0.5 h at 0 °C and 1.5 h at 13–14 °C (p-xylene/dry ice bath). The reaction mixture was cooled to 0 °C before aq. NaOH (2 M, 3.5 equiv) and aq. H_2O_2 (30%, 10 equiv) were added simultaneously. After stirring for 30 min aq. $Na_2S_2O_5$ (2 M) was added over the course of 15 min at the same temperature. Stirring was continued for 5 min before Et_2O and H_2O were added and the phases were separated. The aqueous

layer was re-extracted with Et_2O, and the combined organic layers were washed with sat. aq. NH_4Cl, brine and aq. NaOH (1 M). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to yield a yellow solid. Recrystallization from EtOH or chromatography on silica (CyHex/EtOAc, 9:1) yielded *SS*-**1** in 55–60% yield. R_f = 0.28 (CyHex/EtOAc, 4:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45–3.25 (m, 2 H), 1.95–1.42 (m, 12 H), 1.34–0.95 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.1, 40.4, 29.6, 28.2, 26.4, 26.2, 26.1. ^{1}H NMR and ^{13}C NMR data were consistent with those previously reported by: Scott, M. S.; Lucas, A. C.; Luckhurst, C. A.; Prodger, J. C.; Dixon, D. J. *Org. Biomol. Chem.* **2006**, *4*, 1313.