

Catalytic Enantioselective Cr-Mediated Propargylation: Application to Halichondrin Synthesis

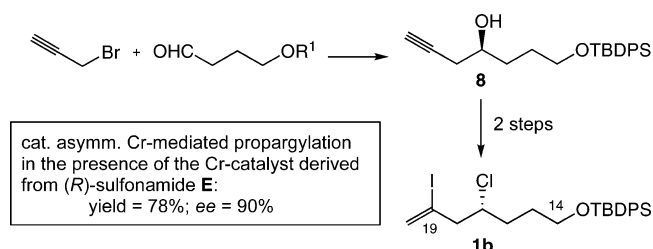
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ABSTRACT



A catalytic enantioselective propargylation in the presence of 10 mol % of Cr catalyst prepared from Cr(III) bromide and (*R*)-sulfonamide **E** furnishes homopropargyl alcohol **8** in 78% yield with 90% ee. Coupled with the workup based on Amano-lipase, this method provides a practical synthesis of optically pure **8** on a multigram scale. With maintenance of its optical purity, **8** has been converted to **1b**, the C14–C19 building block of halichondrins and E7389, in two steps.

In the first-generation synthesis of halichondrin B, we synthesized the C14–C26 building block from 2-deoxy-L-arabinose diethyl thioacetal 4,5-acetonide in 17 steps in approximately 20% overall yield (Scheme 1).^{1,2} This synthesis used three C–C bond-forming reactions highlighted in Scheme 1. Although lengthy, it served well for not only the first-generation total synthesis of the halichondrins but also the discovery and development of E7389.^{1,3} For the past several years, we have been exploring a new synthetic route, resulting in a concise and stereoselective synthesis of the same building block. The new synthesis relied on three catalytic asymmetric Cr-mediated couplings in a consecutive manner (Scheme 1).⁴ With one chromatographic separation, the new synthesis provides us with a stereochemically

homogeneous C14–C26 building block in six steps from (*t*-Bu)(Ph)₂SiO(CH₂)₃CHO.

We were pleased with the new synthesis in terms of the overall yield and stereoselectivity, except for the catalyst loading for the C19–C20 coupling (Scheme 2). This bond was formed via a catalytic asymmetric Ni/Cr-mediated coupling of **1a** with **2** in the presence of the Cr catalyst derived from (*R*)-sulfonamide **A**, with a useful level of stereoselectivity (dr = 22:1). However, this

(3) For discovery and development of E7389, see ref 5 in ref 2.

(4) For reviews on Cr-mediated carbon–carbon bond-forming reactions, see: (a) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 173. (b) Fürstner, A. *Chem. Rev.* **1999**, 99, 991. (c) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (d) Takai, K.; Nozaki, H. *Proc. Jpn. Acad. Ser. B* **2000**, 76, 123. (e) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, 349, 2407.

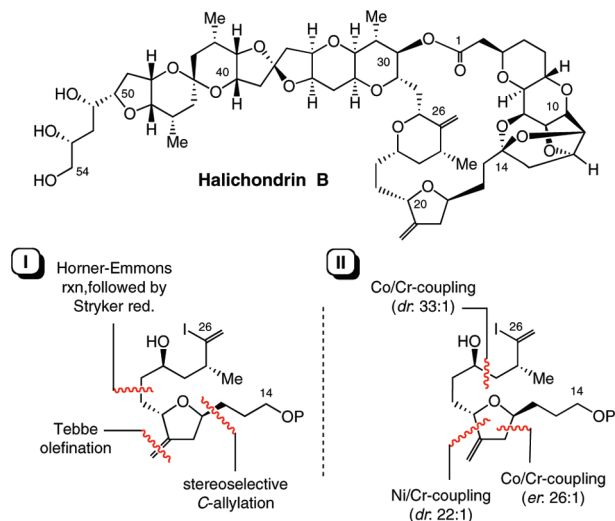
(5) Kim, D.-S.; Dong, C.-G.; Kim, J. T.; Guo, H.; Huang, J.; Tisener, P. S.; Kishi, Y. Submitted for publication.

(6) (a) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, 126, 12248. (b) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, 10, 3073.

(1) 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.

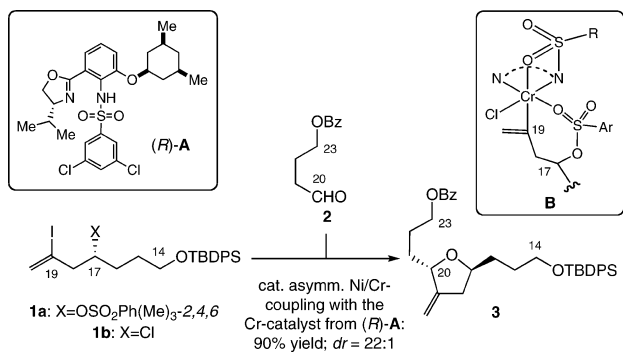
(2) For isolation and synthesis on the halichondrins, see refs 1–3 in the preceding paper: Yang, Y.-R.; Kim, D.-S.; Kishi, Y. *Org. Lett.* **2009**, 11, (DOI 10.1021/ol9016589).

Scheme 1. Structure of Halichondrin B and C–C Bond-Forming Sites in the Synthesis of C14–C26 Building Block. Panel I: First-Generation Synthesis Using Three C–C Bond-Forming Reactions Indicated.¹ Panel II: New Synthesis Using Three Catalytic Asymmetric Cr-Mediated Coupling Reactions Indicated⁵



process required 20 mol % of the catalyst to maintain an acceptable level of coupling rate. We speculated that the poor catalyst loading might be attributed to the fact that one of the O=S bonds of the sulfate group present in the nucleophile **1a** could coordinate to the Cr metal, cf. **B** in Scheme 2, thereby slowing or shutting down the coupling.

Scheme 2. New Synthesis of C14–C23 Building Block **3**^a

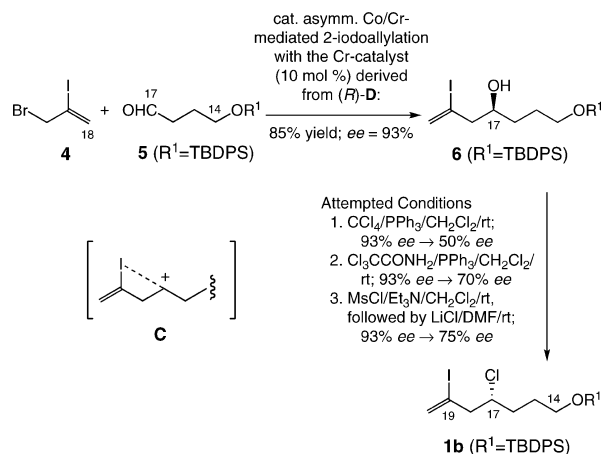


^a Note that the S_N2-cyclization of the C20–OH to the C17 carbon takes place in situ.

This notion encouraged us to study the Ni/Cr-mediated coupling with the nucleophile bearing no O=S or O=C bond, such as the chloride **1b**. Experimentally, it was found that the efficiency of Cr-mediated coupling, i.e., coupling rate and catalyst loading, was noticeably improved in the **1b** series (catalyst loading: ≤10 mol %) over the **1a** series (catalyst loading: ≥20 mol %), while the same level of the asymmetric induction was maintained.⁵

Originally, we planned to synthesize **1b** from the vinyl iodide alcohol **6**, readily available via a catalytic enantioselective Co/Cr-mediated 2-haloallylation (Scheme 3).⁶

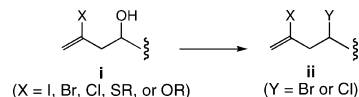
Scheme 3. Attempted S_N2 OH → Cl Substitution



However, we soon realized that the S_N2 OH → Cl substitution is accompanied with partial racemization under various conditions tested (Scheme 3). No literature precedent related to the observed partial racemization was found.⁷ However, because the corresponding homoallyl alcohols are known to maintain the optical purity in the S_N2 OH → Cl substitution,⁷ we speculated that the observed partial racemization might be due to formation of the (partial) carbocation **C** stabilized via participation of the lone pair electron of iodine. For this reason, we modified the original plan to perform the S_N2 OH → Cl substitution on homopropargyl alcohol **8** (Scheme 4).

Among a number of methods reported for synthesis of chiral homopropargyl alcohols,^{8,9} we were interested in a catalytic enantioselective Cr-mediated propargylation of an aldehyde with a propargyl halide, primarily because of the directness of preparation. The work by Inoue and Nakada is most relevant to the proposed catalytic enantioselective Cr-

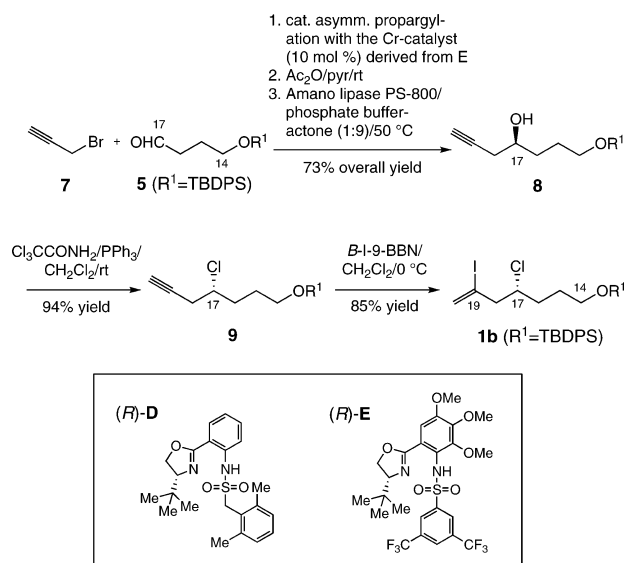
(7) No literature example was found for the **i** → **ii** transformation where X is I, Br, Cl, SR, and OR. To the contrary, examples are known to demonstrate no racemization where X is H; for example, see: Clapp, C. H.; Grandizio, A. M.; Yang, Y.; Kagey, M.; Turner, D.; Bicker, A.; Muskardin, D. *Biochemistry* **2002**, *41*, 11504.



(8) Carbonyl propargylations with allenylmetal reagents are well established to synthesize chiral homopropargyl alcohols. For general reviews, see, for example: (a) Denmark, S. D.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Marshall, J. A.; Gung, B. W.; Grachan, M. L. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, p 493. (c) Gung, B. W. *Org. React.* **2004**, *64*, 1. (d) Marshall, J. A. J. *Org. Chem.* **2007**, *72*, 8153. Also see: Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220, and references cited therein.

(9) For enantioselective propargylations with a propargyl halide in the presence of low-valent metal, see: (a) Bandini, M.; Cozzi, P. G.; Umami-Ronchi, A. *Polyhedron* **2000**, *19*, 537. (b) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Tino, R.; Umami-Ronchi, A. *Tetrahedron Asymmetry* **2001**, *12*, 1063. (c) Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 507.

Scheme 4. New Synthesis of C14–C19 Building Block



mediated propargylation; with use of carbazole-based ligands, they demonstrated that the catalytic enantioselective Cr-mediated propargylation is a valuable synthetic method.¹⁰ We were encouraged with their propargylation of hexanal because of its structural similarity to the aldehyde **5**. However, we wished to improve its overall efficiency (55% yield; 58% ee). In particular, considering a possible mechanistic similarity between Cr-mediated propargylation and allylation/2-haloallylation, we were anxious to test the sulfonamide ligand developed for catalytic enantioselective Cr-mediated 2-haloallylation and allylation in this laboratory.^{6b}

In the presence of the Cr catalyst prepared from CrBr_3 and the (*R*)-sulfonamide **D** (Scheme 4),^{6b} catalytic enantioselective propargylation of **5** with propargyl bromide (**7**) proceeded smoothly to furnish **8** in 83% yield with 87% ee. The optical purity of **8** was estimated from a ^1H NMR analysis of its Mosher ester, and on the basis of the previous examples,⁶ the absolute configuration was predicted as indicated and then confirmed by a chemical correlation with the authentic sample prepared via a different route.¹¹

As shown for the allylation/2-haloallylation, this reaction was easy to scale up. Unlike the allylation/2-haloallylation, however, the asymmetric induction of this process varied between 80% and 87%. Despite extensive efforts, we were unable to establish an experimental protocol to reproducibly perform the coupling at the level of 87% ee. Under this circumstance, we shifted our focus to search for a new sulfonamide ligand.

Using the ligand-optimization strategy recently developed,¹² we searched for an alternative ligand within the pool of chiral sulfonamides, whose performance is better than,

or comparable with, that of (*R*)-sulfonamide **D**.¹³ Among them, (*R*)-sulfonamide **E** was found to be the best ligand in terms of the asymmetric induction, although the coupling yield was modest (65%). In order to improve the coupling efficiency, we then attempted various modifications on the coupling conditions used for allylation/2-haloallylation and eventually found that addition of LiCl significantly improves the coupling yield. The mechanistic explanation for the LiCl effect is not clear at this time. However, we should note that addition of LiCl slightly slows down the coupling rate.

With this modification, it is now possible to prepare **8** in approximately 80% yield with 90% ee in a multigram scale with excellent reproducibility (Scheme 4).¹⁴ It is worthwhile adding that sulfonamide **E** can be recovered in at least 50% yield (80% before recrystallization) by simple operation.

To reveal the scope and limitation, we studied the catalytic asymmetric propargylation on representative aliphatic and aromatic aldehydes in the presence of the Cr catalysts (10 mol %) derived from two sulfonamides **D** and **E** (Table 1). Not surprisingly, it was found that the Cr catalyst derived from **E** performs well for aliphatic aldehydes with no α -substituent (see entries 1–3). Interestingly, unlike the 2-haloallylations,^{6b} the Cr catalysts derived from both **E** and **D** recognize the chirality of the β -methyl group present in (*S*)- and (*R*)-citronellals (entries 4a,b and 5a,b). For α -substituted aliphatic aldehydes, the Cr catalyst derived from **D** gives a better result than the catalyst from **E** (entries 6 and 7). Overall, the Cr catalysts derived from **E** and **D** match well with aliphatic aldehydes. However, their performance on benzaldehyde and *trans*-cinnamaldehyde is slightly lower than, or comparable with, that by Nakada's catalyst (entries 8 and 9).¹⁰

In order to use the reported catalytic asymmetric reaction for the preparative purposes, it is important to have a practical means to enrich the optical purity of **8**. To achieve this goal, we took two different approaches. First, we attempted to convert **8** into a crystalline derivative suitable for fractional recrystallization, but with no significant success.¹⁵ Second, we tested use of Amano lipase to discriminate **8** from its enantiomer at either esterification or saponification. Eventually, it was found that the acetate derived from only (*S*)-**8** is hydrolyzed by Amano lipase PS-800 to furnish optically pure (*S*)-**8**, readily separable from the remaining acetate via filtration through a silica gel plug. Amano lipase PS-800 was found to be equally effective for the crude acetate directly prepared from the crude product obtained in the catalytic enantioselective Cr-mediated propargylation. Thus, the step of lipase-based optical purity enrichment was coupled with the workup of the catalytic enantioselective Cr-mediated

(12) Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. Submitted for publication.

(13) These included the following sulfonamides: $\text{R}_1 = t\text{-Bu}/\text{R}_2 = 3,5\text{-(CF}_3)_2\text{Ph}/\text{R}_3 = (\text{OMe})_3$ (er = 20:1, 65% yield); $\text{R}_1 = t\text{-Bu}/\text{R}_2 = 3,5\text{-(CF}_3)_2\text{Ph}/\text{R}_3 = \text{OPh}$ (er = 17:1, 68% yield); $\text{R}_1 = t\text{-Bu}/\text{R}_2 = 3,5\text{-(CF}_3)_2\text{Ph}/\text{R}_3 = \text{OMe}$ (er = 15:1, 65% yield); $\text{R}_1 = t\text{-Bu}/\text{R}_2 = 3,5\text{-(Cl)}_2\text{Ph}/\text{R}_3 = (\text{OMe})_3$ (er = 15:1, 73% yield); $\text{R}_1 = t\text{-Bu}/\text{R}_2 = 3,5\text{-(Cl)}_2\text{Ph}/\text{R}_3 = \text{F}$ (er = 11:1, 80% yield); $\text{R}_1 = t\text{-Bu}/\text{R}_2 = 3,5\text{-(CF}_3)_2\text{Ph}/\text{R}_3 = \text{F}$ (er = 11:1, 80% yield).

(14) For details, see the Supporting Information.

(15) Propargyl alcohol derivatives, including 4-acetylphenylurethane, were tested.

(10) Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977.

(11) Chiral homopropargyl alcohol **8** was synthesized via addition of TMS-acetylene anion to chiral epoxide obtained through Jacobsen's hydrolytic kinetic resolution of racemic epoxide: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

Table 1. Catalytic Asymmetric Cr-Mediated Propargylations^a

entry	R ₁	sulfonamide	yield ^b (%)	ee or de ^c (%)
1a	–CH ₂ CH ₂ CH ₂ OTBDPS	E	78	90
1b		D	85	83
2a	–CH ₂ CH ₂ CH ₂ CH ₂ Me	E	82	81
2b		D	81	67
3a	–CH ₂ CH ₂ C ₆ H ₅	E	91	89
3b		D	94	72
4a	–CH ₂ CH(Me)CH ₂ CH ₂ CH=C(Me) ₂ -S	E	70	93
4b		D	81	93
5a	–CH ₂ CH(Me)CH ₂ CH ₂ CH=C(Me) ₂ -R	E	73	80
5b		D	86	84
6a	–(CH ₂) ₆ -c	E	67	78
6b		D	88	90
7a	–C(Me) ₃	E	55	92
7b		D	75	73
8a	–C ₆ H ₅	E	80	46
8b		D	92	73
9a	–CH=CHC ₆ H ₅ -E	E	84	51
9b		D	89	70

^a All reactions were performed with CrBr₃ (10 mol %) and **D** or **E** (11 mol %) at 0 °C. On the basis of the previous examples,⁶ the absolute configuration of the major product was predicted as indicated and confirmed from the ¹H NMR analysis of Mosher esters. ^b Yields based on chromatographically isolated products. ^c Ee and de were estimated by ¹H NMR analysis of its Mosher ester. For details, see the Supporting Information.

propargylation to furnish optically pure (*S*)-**8** in 73% overall yield from **5** (5 g scale).¹⁶ Overall, the catalytic enantioselective Cr-mediated propargylation provides us with a practical and scalable synthesis of (*S*)-**8**.¹⁴

With optically pure homopropargyl alcohol (*S*)-**8** in hand, we studied the S_N2 OH → Cl substitution, which was uneventfully achieved on treatment with trichloroacetamide and triphenylphosphine.¹⁷ Upon treatment with 9-iodo-9-borabicyclo[3.3.1]nonane (*B*-iodo-9-BBN),¹⁸ the terminal acetylene in **9** was cleanly converted to the corresponding vinyl iodide **1b**. As mentioned previously, our concern was the optical purity of **1b** obtained from (*S*)-**8**. Among several methods studied, HPLC analyses on a chiral column of the 4-acetylphenyl urethane of **1b** gave the most reliable result.¹⁹ With this method, we demonstrated no detectable loss of the optical purity in the process of **8** → **9** → **1b**.

(16) Amano lipase PS-800 was found effective to obtain the optically pure (*S*)-**8** (42% isolated yield) from the racemic homopropargyl acetate,¹⁴ prepared via propargylation of **5** in the presence of 1 mol % of 3,3'-dimethyl-2,2'-dipyridyl-Cr(III) complex, followed by acetylation: Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421.

(17) Pluemanupat, W.; Chavasiri, W. *Tetrahedron Lett.* **2006**, *47*, 6821.

(18) (a) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. For a review, see: Suzuki, A. *Rev. Heteroatom Chem.* **1997**, *17*, 271.

In summary, we have reported a catalytic enantioselective Cr-mediated propargylation in the presence of 10 mol % of Cr catalyst prepared from Cr(III) bromide and (*R*)-sulfonamide **E** to furnish homopropargyl alcohol **8** in 78% isolated yield with 90% ee. Coupled with the workup based on Amano lipase, this method provides us with a practical route to obtain optically pure (*S*)-**8** in 73% overall yield from **5** in a multigram scale. (*S*)-**8** is then transformed to optically pure **1b**, the C14–C19 building block of halichondrins and E7389.

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

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(19) The optical purity of **1b** was determined via HPLC analysis (OJ-H chiral column) of 4-acetylphenylurethane **iii** prepared from **1b**. For details, see the Supporting Information.

