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Iterative Cr-Mediated Catalytic Asymmetric Allylation To Synthesize *syn/syn*- and *anti/anti*-1,3,5-Triols

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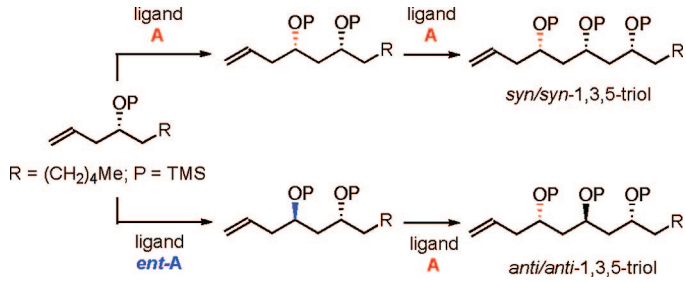
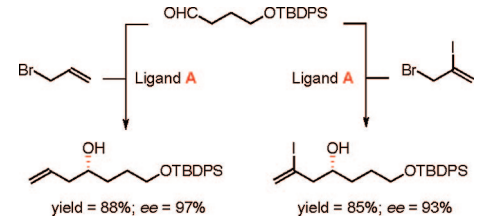
ABSTRACT



Iterative use of Cr-mediated catalytic asymmetric allylation could give a simple access to 1,3-polyols. Using *syn/syn*- and *anti/anti*-1,3,5-triols as representative examples, the feasibility of this approach is studied, thereby demonstrating that (1) the pre-existing TMS-protected alcohol at the *β*-position does not give a significant effect on the Cr-mediated catalytic asymmetric allylation and (2) this synthetic route furnishes the expected *syn/syn*- and *anti/anti*-1,3,5-triols at the useful level of asymmetric induction and yield.

In the preceding paper,[1] we reported Cr-mediated catalytic asymmetric 2-haloallylation and allylation in the presence of sulfonamide-based ligand **A** (Scheme 1). Many natural products are known to contain a 1,3-polyol as a structure cluster. Interestingly, this structure cluster is found in a wide range of natural products, with a great diversity of stereochemistry arrangement.[2] In addition, some natural products are known to possess the permethylated form of 1,3-polyol.[3] We notice that an iterative use of the Cr-mediated catalytic asymmetric allylation might give us a stereocontrolled synthetic access to this structure cluster. In this letter, using *syn/syn*- and *anti/anti*-1,3,5-triols as representative examples, we demonstrate the feasibility of this approach.

Scheme 1. Co/Cr-Mediated Catalytic Asymmetric 2-Iodoallylation and Cr-Mediated Catalytic Asymmetric Allylation in the Presence of Sulfonamide Ligand **A**[a]



[a]For the structure of **A**, see Scheme 2.

(1) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073.

(2) The 1,3-polyol structure cluster is present in numerous natural products ranging from antibiotics to marine natural products. A substructure search with SciFinder gave 87 and 35 natural products bearing one or more of 1,3,5,7,9-pentaol(s) and 1,3,5,7,9,11,13-heptaol(s), respectively.

(3) For example, see: (a) Mynderse, J. S.; Moore, R. E *Phytochemistry* **1979**, *18*, 1181. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Mori, Y.; Suzuki, M *J. Org. Chem.* **1990**, *55*, 4431. (c) Mori, Y.; Kawajiri, N.; Furukawa, H.; Moore, R. E *Tetrahedron* **1994**, *50*, 11133, and references cited therein. (d) Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T *Tetrahedron Lett.* **1989**, *30*, 6529 and the preceding paper. (e) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559. (f) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 1201.

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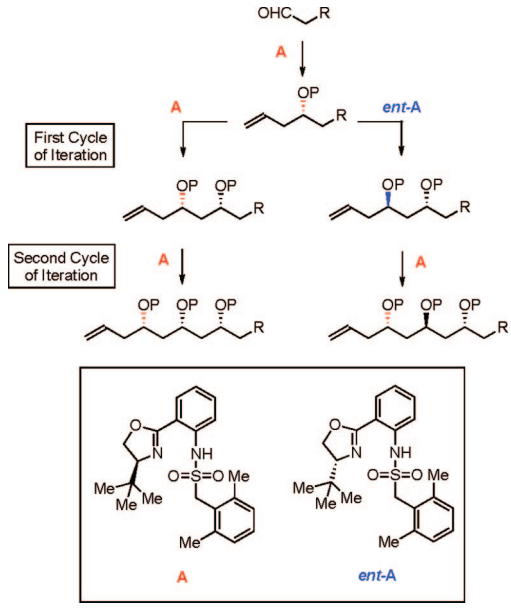
Scheme 2. Iterative Synthesis of *syn/syn*- and *anti/anti*-1,3,5-Triols via Cr-Mediated Catalytic Asymmetric Allylation in the Presence of Ligands **A** and ***ent*-A**[a]



[a]One cycle of iteration is composed of oxidative cleavage of the olefin to form an aldehyde, catalytic asymmetric allylation, and protection of the resultant alcohol.

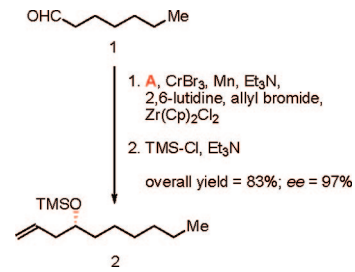
Various methods are known effectively to synthesize 1,3-polyols.[4] Among them, the method by Cossy and co-workers[5] is most relevant to the current work; they iteratively utilized enantioselective allyltitanation with (*R,R*)- or (*S,S*)-cyclopentadienyldialkoxy allyltitanium complex developed by Hafner, Duthaler, and co-workers.[6] An impressive level of stereochemistry control was achieved, although it utilized a stoichiometric amount of (*R,R*)- or (*S,S*)-titanium complex.

Scheme 2 outlines our iterative approach for a synthesis of *syn/syn*- and *anti/anti*-1,3,5-triols. One cycle of iteration is composed of a three-step operation, i.e., oxidative cleavage of the olefin to form an aldehyde, catalytic asymmetric allylation, and protection of the resultant alcohol. Conceptually, this iterative approach is the same as the method used by Cossy, with two exceptions. First, Cossy utilized the Ti-based asymmetric allylation, whereas we intend to utilize the Cr-based asymmetric allylation. Second, Cossy used a stoichiometric amount of the chiral Ti reagent, whereas we attempt to employ a catalytic amount of the chiral Cr reagent.

Clearly, the central issue concerned with this iterative approach is how to eliminate, or reduce, the effect from the pre-existing alcohol, or its protected form, at the β-position on the catalytic asymmetric allylation.[7] As reported in the preceding paper, a significant effect from a methyl group at the β-position was detected for allylation of (*R*)-(+)-citronellal with allyl and methallyl bromides, whereas only an insignificant effect was detected for allylation with γ,γ-dimethylallyl and 2-haloallyl bromides.[1] Despite these somewhat confusing results, we decided to study the feasibility of this approach, with the hope that a suitable protecting group could be found, to override the pre-existing alcohol at the β-position on the Cr-mediated catalytic asymmetric allylation.

To avoid the technical difficulty associated with high volatility of substrates, we chose to use heptanal (**1**) for this demonstration. Thus, **1** was subjected to the Cr-mediated catalytic asymmetric allylation in the presence of sulfonamide ligand **A**, followed by TMS protection, to furnish the anticipated, protected allylic alcohol **2** in 83% yield (Scheme 3).[8] The enantiomeric excess (ee) of **2** was estimated to be

Scheme 3. The First Cr-Mediated Catalytic Asymmetric Allylation



97% from the ^{1}H NMR spectra of (*R*)- and (*S*)-Mosher esters of the allylic alcohol.[9]

We then conducted a preliminary study on the protecting-group effect on the next round of catalytic asymmetric allylation. Among three types of protecting groups tested: (1) silyl ethers (TMS, TES, and TBS), (2) ether (PMB), and (3) esters (Ac and MeOAc), sterically least demanding TMS was found to give the most satisfactory result on both asymmetric induction and yield.[10]

With this result in hand, we subjected the TMS-protected allylic alcohol **2** to the first cycle of iteration (Scheme 4).

(4) For reviews on this subject, see: (a) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557. (b) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375. (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (d) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (e) Hoveyda, A. M.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (f) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (g) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(5) (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501. (b) BouzBouz, S.; Cossy, J *Tetrahedron Lett.* **2000**, *41*, 3361. (c) BouzBouz, S.; Cossy, J *Org. Lett.* **2000**, *2*, 3975. (d) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S *J. Org. Chem.* **2002**, *67*, 1982. (e) Amans, D.; Bellosta, V.; Cossy, J. *Org. Lett* **2007**, *9*, 1453. (f) Ferrié, L.; Boulard, L.; Pradaux, F.; Bouzbouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864.

(6) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

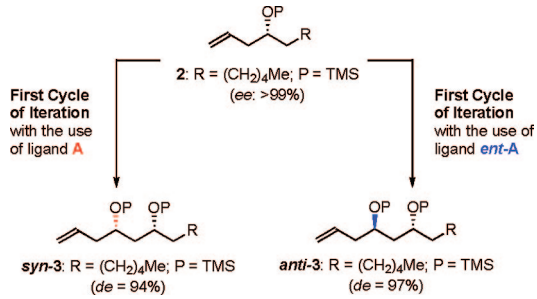
(7) For a review on this subject, see: (a) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(8) With use of TMS-Cl as the dissociating agent, the transformation of **1** into **2** could be achieved in a single step. Under this condition, however, the rate of coupling was significantly slower and the yield was lower.

(9) For the determination of absolute configuration, see the Supporting Information for (a) Kurosu, M.; Lin, M.-H.; Kishi, Y *J. Am. Chem. Soc.* **2004**, *126*, 12248.

(10) Protection with an ether (PMB) or silyl ether (TES and TBS) group made the rate of allylation to be significantly slower. Protection with an acyl (Ac and MeOAc) group gave an excellent result in terms of asymmetric induction, but products were often accompanied with the corresponding elimination by-products. In addition, the rate of allylation with an aldehyde bearing a free alcohol was found to be very slow.

Scheme 4. First Cycle of Iterative Synthesis in the Presence of Ligand **A** or Its Enantiomer ***ent*-A**[a]



[a] One cycle of iteration is composed of a three-step sequence: (1) OsO_4/NMO, followed by $Pb(OAc)_4$ treatment (85% yield); (2) Cr-mediated catalytic asymmetric allylation in the presence of ligand **A** or ***ent*-A**; (3) TMS-Cl/Et_3N (81% yield for two steps). These transformations were also performed with **2** (ee = 97%) to furnish ***syn*-3** (de = 92%) and ***anti*-3** (de = 95%), respectively.

After oxidative cleavage of the olefin, **2** was subjected to the Cr-mediated catalytic asymmetric allylation in the presence of sulfonamide ligand **A** or its enantiomer ***ent*-A**, followed by TMS protection and product isolation by passing through a short silica gel column.[11] The ^{1}H NMR analysis revealed that the diastereomeric purity of resultant ***syn*-3** and ***anti*-3** was de = 92% and de = 95%, respectively, thereby showing that the pre-existing TMS ether group at the β-position gave a small match/mismatch effect for this transformation.

We should note that the optical purity of **2** used for this study was ee = 97%. Taking account of the optical purity of **2** and assuming that the aldehyde derived from **2** and contaminated enantiomer reacted with allyl bromide in the same rate, we could estimate the degree of asymmetric induction for **2**→***syn*-3** and **2**→***anti*-3** to be de → 95% and de → 98%, respectively.

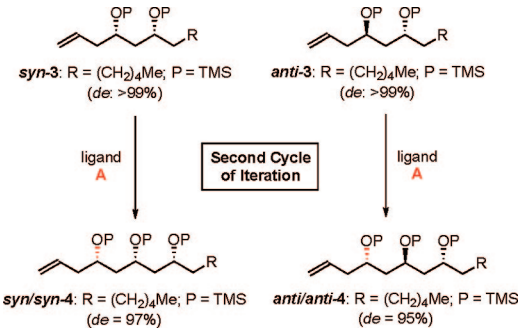
We naturally wished to confirm this estimation experimentally. For this reason, we looked for a method to enrich the optical purity of **2** and eventually found that the optical purity of **2** can be enriched via a 3-step operation, i.e., (1) preparation of crystalline *p*-acetylphenylcarbamate, (2) recrystallization, and (3) NaOH/MeOH.[12] With use of the optically pure **2** (ee >99%), the anticipated degree of asymmetric induction was experimentally verified (Scheme 4).[12]

It is also worthwhile commenting on the optical purity of ***syn*-3** and ***anti*-3**. Even for the case where **2** with ee = 97% was used, we expected that the optical purity of products should be enhanced in this process; based on the same considerations, we anticipated the optical purity of both ***syn*-3** and ***anti*-3** should exceed 99%. Because of the low polarity, chromatographic separation of ***syn*-3** and ***anti*-3** was not practical. However, after TMS-deprotection, separation of *syn*- and *anti*-diols was readily achieved by silica gel chromatography. The optical purity of *syn*- and *anti*-diols was then examined by ^{1}H NMR spectroscopy of their Mosher esters, thereby confirming the predicted optical purity.[12]

Overall, these experiments demonstrated that the pre-existing TMS-protected β-alcohol does not give a significant effect on the Cr-mediated catalytic asymmetric allylation in the terms of asymmetric induction.

We then proceeded to the second cycle of iteration. As before, after oxidative cleavage of the olefin, ***syn*-3** (*de* > 99%) and ***anti*-3** (*de* > 99%) were subjected to catalytic asymmetric allylation in the presence of sulfonamide ligand **A**. After the resultant alcohol protected as a TMS ether, the products were isolated by passing through a short silica gel column to furnish ***syn/syn*-4** and ***anti/anti*-4**, respectively (Scheme 5). The diastereomeric purity of ***syn/syn*-4** (de = 97%) and ***anti/anti*-4** (de = 95%) was estimated from their ^{1}H NMR spectra. Like the first cycle of iteration, we once again detected only a small match/mismatch effect from the pre-existing TMS ether groups. Interestingly, contrary to the first cycle, a better asymmetric induction was observed for the path leading to *syn*-product than the path to *anti*-product for this cycle.[13]

Scheme 5. Second Cycle of Iterative Synthesis in the Presence of Ligand **A**[a]



[a] One cycle of iteration is composed of a three-step sequence: (1) OsO_4/NMO, followed by $Pb(OAc)_4$ treatment (85% yield); (2) Cr-mediated catalytic asymmetric allylation in the presence of ligand **A**; (3) TMS-Cl/Et_3N (two-step yield: 64% in the *syn/syn*-series and 70% in the *anti/anti*-series).[11]

Overall, the second cycle of iteration once again demonstrated that the pre-existing TMS-protected alcohol does not give a significant effect on the Cr-mediated catalytic asymmetric allylation in the terms of asymmetric induction and chemical yield.

Up to this stage, we assigned the stereochemistry of allylation product, based on the sulfonamide-based ligand **A** or ***ent*-A** employed for a given allylation.[9] In this connection, we should mention our NMR database relevant to the current case; the central carbon of an acyclic 1,3,5-triol exhibits a distinctive chemical shift *dependent* on its

(11) The oxidative cleavage could be done in one step (O_3, followed by PPh_3 treatment or OsO_4/$NaIO_4$) or two steps (OsO_4/NMO, followed by $NaIO_4$ treatment or by $Pb(OAc)_4$ treatment). Among them, the procedure of OsO_4/NMO, followed by $Pb(OAc)_4$ treatment, gave the best yield.

(12) For details, see the Supporting Information.

(13) These transformations were first studied with ***syn*-3** (de = 92%) and ***anti*-3** (de = 95%). The diastereomeric purity of resultant ***syn/syn*-4** and ***anti/anti*-4** was estimated to be de = 93% and 91%, respectively.

relative stereochemistry, but *independent* of the functionalities present outside of the structure cluster.[14] In practice, the central carbon of *anti/anti*-, *anti/syn*- or *syn/anti*-, and *syn/syn*-1,3,5-triols gives a ^{13}C NMR resonance in CD_3OD at 66.3 ± 0.5 ppm, 68.6 ± 0.5 ppm, and 70.7 ± 0.5 ppm, respectively.[15] In the case of 1,3,5-triols derived from ***syn/syn*-4** and ***anti/anti*-4**, the chemical shift of central carbon was observed at 70.5 and 66.3 ppm, respectively, thereby confirming the stereochemistry assigned based on the sulfonamide-based ligands **A** or ***ent*-A** employed for a given allylation.

In summary, iterative Cr-mediated catalytic asymmetric allylation has been shown to give a simple access to *syn*- and *anti/anti*-1,3,5-triols. This study has demonstrated that (1) the pre-existing TMS-protected alcohol at the β-position does not give a significant effect on the Cr-mediated catalytic asymmetric allylation and (2) this synthetic approach furnishes the expected *syn/syn*- and *anti/anti*-1,3,5-triols at the useful level of asymmetric induction and yield.

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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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(14) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562.

(15) In DMSO-d_6, *anti/anti*-, *anti/syn*-, and *syn/syn*-1,3,5-triols give the characteristic chemical shift at 63.9 ± 0.5 ppm, 66.2 ± 0.5 ppm, and 68.2 ± 0.5 ppm, respectively.