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Catalytic Asymmetric Synthesis of Hexahydro-furofuran-3-ol and Its Pyran Derivatives

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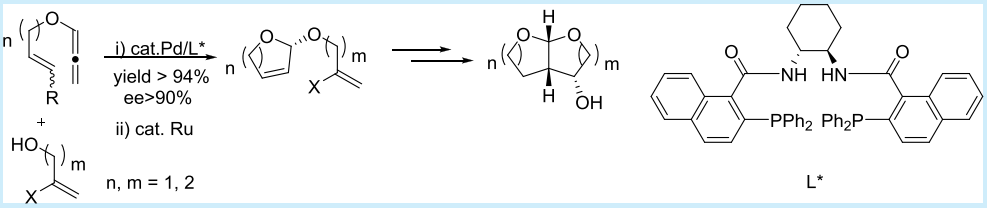

ABSTRACT: The catalytic asymmetric synthesis of hexahydro-furofuran-3-ol, a key fragment of HIV protease inhibitors, is reported. A signature event is represented by the sequential metal catalysis that combines the Pd-catalyzed asymmetric hydroalkoxylation of ene-alkoxyallene and ring-closing metathesis (RCM). Notably, this unprecedented and highly chemoselective approach allows for a unified access to pyranofuranol and furopyranol derivatives.

HIV-1 protease inhibitors (PIs) block viral replication by inhibiting viral enzymes.[1] Moreover, the combination of HIV-1 PIs with reverse transcriptase inhibitors proved to be an effective treatment against AIDS. However, the emergence of drug-resistant HIV-1 variants cause serious concerns for HIV-1-infectious patients. Therefore, the development of various novel PIs that show activity against drug-resistant HIV-1 strains is critical. A number of multidrug-resistant PIs, such as Darunavir, a new front-line therapy for HIV/AIDS, possess a unique (3*R*,3a*S*,6a*R*)-hexahydro-furo-[2,3-*b*]furan-3-ol (*bis*-THF) fragment (structure A, Figure 1).[2] SAR (Structure–activity relationship) studies revealed that synthetic analogs possessing THF-THP (structure B, Figure 1) or a THP-THF bicyclic ring (structure C, Figure 1) also exhibited interesting inhibitory effects.[3]

The unique structure of these bicyclic compounds and their excellent biological activities have drawn significant attention from the synthetic community. Most studies aimed at the synthesis of the *bis*-THF ring rely on chiral pool approaches, which generally require lengthy sequences and the extensive use of protective groups.[4] In addition, the preparation of analogs often requires a redesign of the synthetic scheme. Alternative approaches starting from achiral substrates mostly proceed in a racemic manner and thus require enzymatic kinetic resolution for the synthesis of enantioenriched products.[5] Here, we report a catalytic asymmetric synthesis of hexahydro-furofuranol (Scheme 1). In this new approach, enantioenriched cyclic acetal generated in an early stage is exploited as the directing group for all the other stereocenters. This unique strategy enables the development of a protective group-free protocol with minimal functional group transformations and thus provides the target compounds in a highly efficient manner. The key cyclic allylic acetal moiety can be prepared by the chemoselective Pd-catalyzed asymmetric coupling reaction of commercial bromo-olefinic alcohols and readily available ene-alkoxyallene in combination with the ring-closing-metathesis (RCM) reaction.[6−9] This approach also gives access to derivatives containing a tetrahydropyran ring with a comparable efficiency to that of *bis*-THF simply by changing the structure of the commercial achiral starting materials.

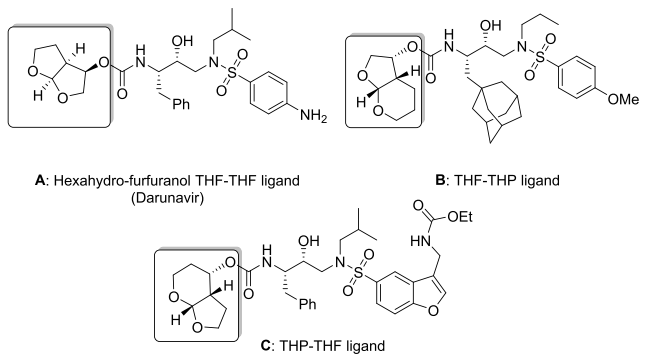

Figure 1. Structures of HIV protease inhibitors.

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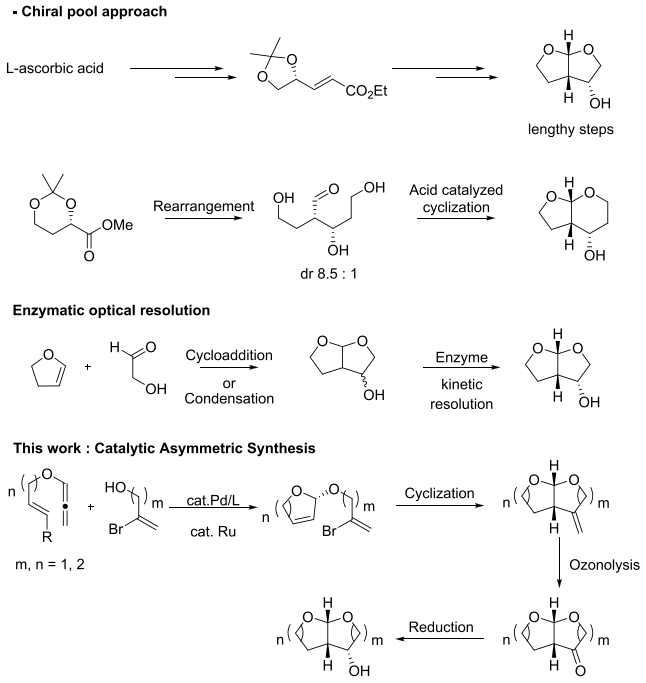
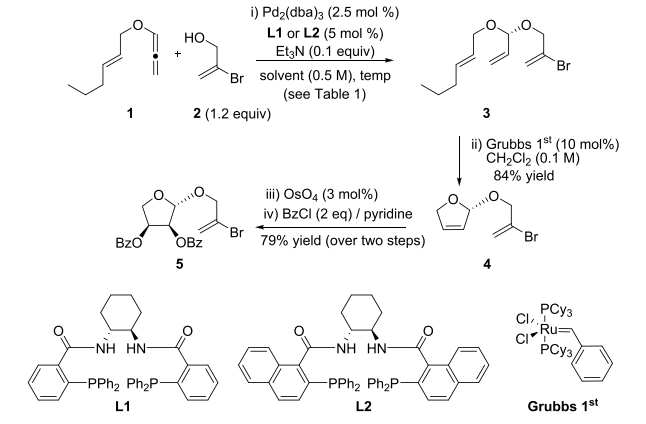
Scheme 1. Synthetic Strategies Towards Hexahydro-furfuranol and Its Pyran Derivatives



At the outset of the study, we examined the Pd-catalyzed coupling reaction of readily available allene **1**[10] with commercially available 2-bromo allylic alcohol **2**. As shown in Table 1, the reaction employing $Pd_2(dba)_3$ (2.5 mol %), chiral ligand **L1** (5 mol %), and triethylamine (0.1 equiv) in toluene immediately generated the adduct **3** in a 89% yield. The subsequent RCM reaction using 10 mol % first generation Grubbs catalyst proceeded smoothly to give the cyclic acetal product **4** in an 84% yield.[11] It should be noted that the vinyl bromide moiety proved to be compatible with the sequential metal catalysis. Because the measurement of the ee of **4** was troublesome, we converted this compound to bis-benzoate **5**, whose ee was determined to be a moderate 62% by the HPLC measurement. Notably, switching to the ligand **L2** significantly improved the enantioselectivity (88% ee) of **3** without harming the yield of the reaction (Table 1, entry 2). Little change of the result occurred when using CH_2Cl_2 as the solvent (Table 1, entry 3). In this case, lowering the temperature to 0 °C led to a further increase of the ee to 96% (Table 1, entry 4).

Table 1. Optimization of the Monocyclic Acetal Synthesis



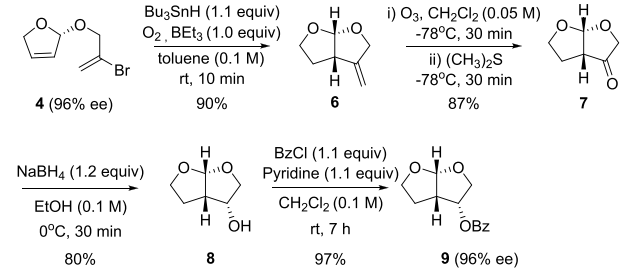
entry	ligand	solvent	temperature	time	yield (%)[a]	ee (%)[b]
1	**L1**	toluene	rt	5 min	89	62
2	**L2**	toluene	rt	5 min	94	88
3	**L2**	CH_2Cl_2	rt	5 min	95	88
4	**L2**	CH_2Cl_2	0 °C	2 h	94	96

[a]Isolated yield. [b]The ee of compound **5**.

At the outset of the study, we examined the Pd-catalyzed coupling reaction of readily available allene **1**[10] with commercially available 2-bromo allylic alcohol **2**. As shown in Table 1, the reaction employing $Pd_2(dba)_3$ (2.5 mol %),

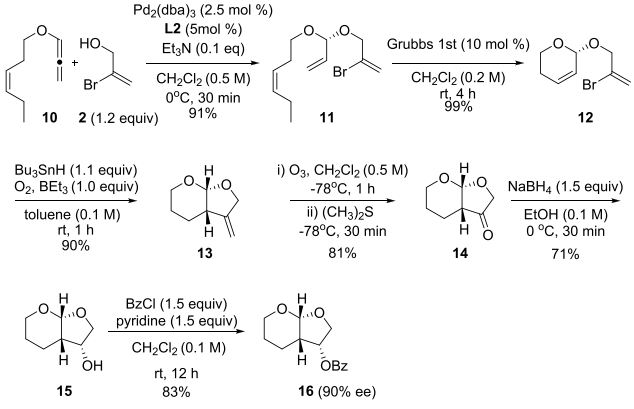
Having obtained the key intermediate **4** in an enantioenriched manner, we then investigated the synthesis of the target compound **8**. We first anticipated that the radical-mediated 5-exo cyclization of **4** should generate the intermediate **6** in a straightforward manner. However, initial attempts to employ Bu_3SnH under thermal conditions led to the extensive decomposition of **4**.[12] Using triethylborane as the initiator at rt minimized this undesired event, affording **6** in a 90% yield.[13] The subsequent ozonolysis of this compound generated the bicyclic ketone **7** in an 87% yield, which was reduced with $NaBH_4$ to the target alcohol **8** in an 80% yield with complete diastereoselectivity. The optical purity of this compound was determined to be 96% by the conversion into the corresponding benzoate **9**. This result confirms that the enantiopurity of **4** does not erode significantly during the sequence described in Scheme 2.

Scheme 2. Synthesis of *bis*-Hexahydro-furofuranol 8



As described in Scheme 3, the synthetic scheme developed above was successfully expanded to the synthesis of the THP-

Scheme 3. Synthetic Route to the THF-THP Ligand



THF derivative depicted in Figure 1.[14] Performing the Pd-catalyzed hydroalkoxylation reaction of **2** with allene **10**[10] under the optimized conditions in Table 1 gave the desired acetal intermediate **11** in a 91% yield, which was smoothly converted into the cyclic acetal intermediate **12** by the RCM reaction in a 99% yield. The subsequent radical-mediated cyclization, combined with ozonolysis, gave the bicyclic ketone

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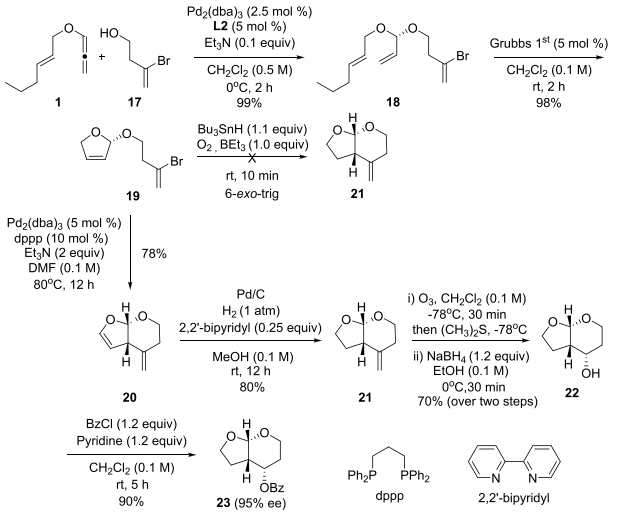
14 in a 72% combined yield over two steps. The reduction of this ketone **14** with $NaBH_4$ provided the target molecule **15** in a 71% yield, again with complete diastereoselectivity. The enantiopurity of this compound was determined to be 90% by the conversion into the benzoate derivate **16**.

Our final efforts were directed at the synthesis of the THP-THF core using an analogous strategy.[15] Compared with the previous examples, this route turned out to be more troublesome because of the poor outcome of the 6-exo radical cyclization of the vinyl halide **19**. As depicted in Scheme 4, the

Scheme 4. Synthetic Route to THP-THF Ligand



synthesis of **19** proceeded uneventfully from the homoallylic alcohol **17** in a near-quantitative yield over two steps by way of the key sequential metal catalysis. However, the reductive cyclization of **19** using Bu_3SnH failed to produce the product **21**.[16] Varying the initiators and hydrogen donors did little to improve the yield of the reaction. Because of this disappointing result, we turned our attention to the Pd-catalyzed cyclization reaction of **19**. Indeed, using $Pd_2(dba)_3$ (5 mol %) with dppp (10 mol %) generated the diene **20** in a 78% yield. The chemoselective hydrogenation of this compound provided the exo-olefin **21** in an 80% yield,[17] which was converted to the target compound **22** in a 70% combined yield (over two steps) by way of a two-step sequence combining ozonolysis and reduction with $NaBH_4$. The ee of this compound was determined to be 95%, again by the conversion into the benzoate **23**.

In conclusion, we reported a versatile synthetic method toward hexahydro-furfuranol and its derivatives, a key fragment in HIV-1 protease inhibitors.[18] This work illustrates well the utility of the Pd-catalyzed asymmetric hydroalkoxylation. In combination with a chemoselective radical-mediated or Pd-catalyzed cyclization reaction, structurally diverse analogues could also be accessed. Currently, we are working on expanding the scope to the synthesis of new derivatives in addition to exploring their biological activities. The results of this study will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00981.

Experimental details, spectral data, and ^1H and ^{13}C NMR spectra of all new compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **3**−**9**, **11**−**16**, and **18**−**23** (ZIP)

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Notes

The authors declare no competing financial interest.

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