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Flexible Tetrahydropyran Synthesis from Homopropargylic Alcohols Using Sequential Pd−Au Catalysis

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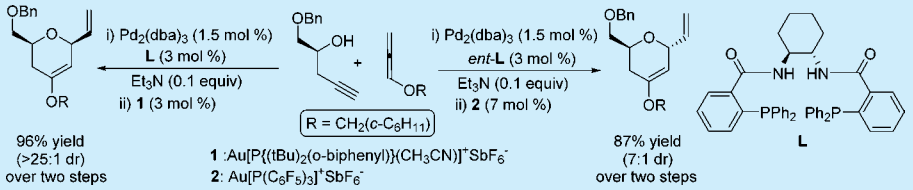
Supporting Information



ABSTRACT: A flexible synthetic method toward highly substituted tetrahydropyran is reported. The key transformation involves atom-efficient sequential metal catalysis consisting of Pd-catalyzed addition of homopropargylic alcohols to alkoxyallene and the subsequent gold(I)-catalyzed cycloisomerization. Notably, this method gives access to both 2,6-*cis*- and 2,6-*trans*-tetrahydropyrans possessing diverse substitution patterns.

Tetrahydropyran is a common structural core that can be easily found in numerous bioactive natural products and pharmaceutical candidates.[1] As illustrated by some representative examples (Figure 1), a notable feature of the tetrahydropyran

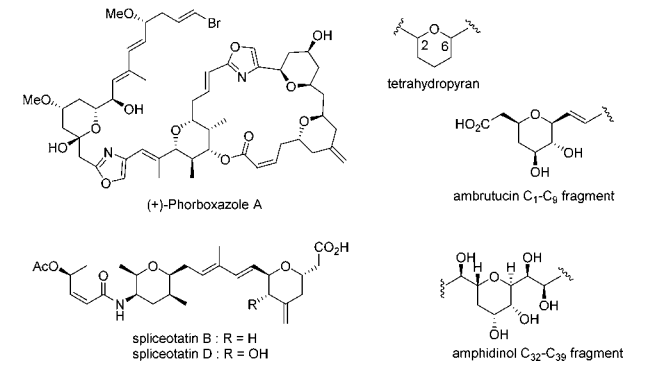
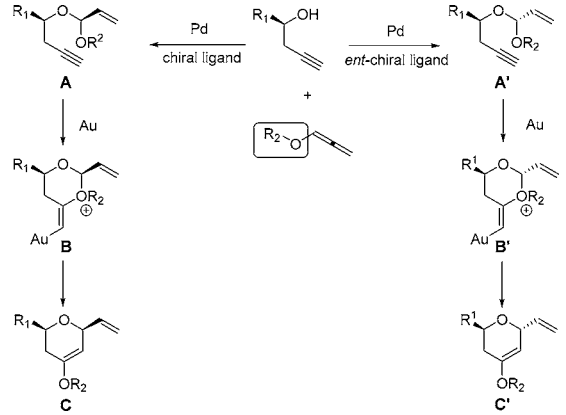


Figure 1. Tetrahydropyran-containing natural products.

core is highlighted by the stereochemical diversity with regard to the substituents at the 2,6-positions. This feature in the diversity is further enriched by the wealth of the substitution patterns in the tetrahydropyran ring. The natural products possessing tetrahydropyran core have a wide range of biological activities. Thus, a flexible synthetic approach allowing access to the diverse structure should be highly powerful. However, this challenging divergent strategy has not been easily accomplished by the well-known methods such as hetero-Diels−Alder[2] reaction, intramolecular nucleophilic addition,[3] Petasis−Ferrier rearrangement,[4] Prins cyclization,[5] and other metal-catalyzed reactions.[6]

Based upon our recent reports in the related area,[7,8] we envisioned that the Au-catalyzed stereoretentive cycloisomerization of the chiral *O*,*O*-acetals **A**/**A**′ mediated by formation of intermediate **B**/**B**′ may suggest unique solution to this challenging problem (Scheme 1).[9−11] Furthermore, the enol

Scheme 1. Basic Concept: Sequential Catalysis



ether moiety in the product **C**/**C**′ should be easily converted into numerous functional groups. The *O*,*O*-acetals **A**/**A**′ may be prepared by the ligand-driven Pd-catalyzed diastereodivergent addition of chiral homopropargylic alcohols to alkoxyallene.[12,13] Because *O*,*O*-acetals are configurationally unstable under acidic conditions, we reasoned that the key issue would be to find the optimal structure of *O*,*O*-acetal (R_2 group) that would work for both chemoselective metal catalyzed reactions.

Indeed, the structure of the alkoxy moiety in the allene proved critical for the metal catalyzed reactions (Table 1). Based upon our recent studies on the Pd-catalyzed asymmetric hydro-

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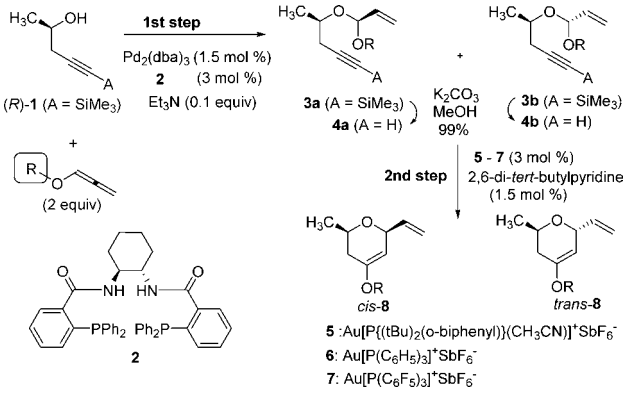
Table 1. Optimization



Entry	R	1st step Yield[a] (**3a**:**3b**[b])	2nd step cat.	Yield[c] **8** (cis:trans)[b]
1	*c*-C_6H_{11}	99% (>25:1)	**5** (3 mol %)	trace (N.D[d])
2	*n*-C_5H_{11}	99% (8:1)	-	------
3	CH_2Ph	83% (7:1)	-	-------
4	CH_2(*c*-C_6H_{11})	99% (20:1)	**5** (3 mol %)	94% (>25:1)
5	CH_2(*c*-C_6H_{11})	99% (1:23)[e]	**5** (3 mol %)	trace (N.D[d])
6			**6** (3 mol %)	trace (N.D[d])
7			**7** (3 mol %)	22% (1:2)
8			**7** (7 mol %)[f]	81% (1:6.4)

[a]Isolated yield of mixture. [b]dr was determined by integration of the crude NMR. [c]Isolated yield of the major diastereomer. [d]Not determined. [e]*ent*-**2** was used as the ligand. [f]In this case, 1.8 mol % of 2,6-di-*tert*-butylpyridine was used along with 4 Å molecular sieve.

alkoxylation reaction,[7a] we first examined the cyclohexyl-substituted oxyallene. The reaction of this allene (2.0 equiv) with alcohol **1** in the presence of $Pd_2(dba)_3$ (1.5 mol %), ligand **2** (3 mol %), and triethylamine (0.1 equiv) proceeded in near-quantitative yield to produce the product **3a** virtually as single diastereomer.[14] However, the gold(I)-catalyzed cycloisomerization reaction of desilylated alcohol **4a** gave the product *cis*-**8** only in trace yield when gold complex **5** was used (entry 1), presumably because the large alkoxy moiety slowed the formation of the intermediate **B** (Scheme 1).[15] Varying the gold complexes and other reaction conditions little improved the results. Using the smaller *n*-pentyloxyallene, however, significantly lowers the selectivity of the Pd-catalyzed hydroalkoxylation reactions (entry 2). In light of these disappointing results, we reasoned that the size of the alkoxy moiety should be elaborately modified to maintain the high stereoselectivity in the Pd-catalyzed reaction without too much slowing of the gold catalysis. Based upon this analysis, we then tested benzyloxyallene. However, the dr was still low for the Pd-catalyzed reaction (entry 3). A notable improvement arises when cyclohexylmethyl-substituted allene[16] was used (R = CH_2(*c*-C_6H_{11}), entries 4−8). For example, the Pd-catalyzed reaction for this allene gave the corresponding *O*,*O*-acetals in 99% yield with high (~20:1) selectivity. In addition, the gold-catalyzed cycloisomerization of **4a** using complex **5** gave the corresponding cyclic ether *cis*-**8** in 94% yield with no indication of formation of *trans*-**8** (entry 4). Thus, the stereochemical information on the acetal **4a** is completely retained in the cycloisomerization reaction. As shown in entry 5, synthesis of diastereomeric *O*,*O*-acetal **4b** again proceeded in high yield and selectivity when the ligand *ent*-**2** was used. Interestingly, the gold(I)-catalyzed cycloisomerization reaction turned out to be significantly slower than the that of *syn*-diastereomer **4a**.[17] In this case, using complex **5** as well as **6** gave the dihydropyran product *trans*-**8** in much lower yield and selectivity (entries 5 and 6). After extensive variation of the reaction condition, we discovered that the use of electron poorer gold complex **7** (3 mol %) gave *trans*-**8** in moderate yield with low selectivity *cis*-**8** (entry 7).[18−20] Using higher catalyst loading along with the molecular sieve (4 Å) significantly improved both the yield and the selectivity of the cycloisomerization reaction (entry 8). In this case, the *trans*-**8** was obtained in 81% isolated yield along with small amount of *cis*-**8**.

Using the optimized conditions established in Table 1, we tested an array of homopropargylic alcohols for the stereodivergent synthesis of dihydropyran cyclic ethers (Table 2). In general, the homopropargylic alcohol substrates gave the corresponding *O*,*O*-acetal with high ligand-driven diastereoselectivity as with the optimization studies.[21] In addition, *cis*-enol ether products were obtained in excellent yield with near-complete chirality transfer from the *O*,*O*-acetals; whereas the *trans*-enol ethers were obtained with formation of small amount of the *cis*-diastereomer. The reaction was compatible with benzyl ether **9** (entries 1 and 2) and silyl ether **11** (entries 3 and 4). In addition, substrate possessing benzyl group **13** also worked smoothly to give the cyclic ether products **14** (entries 5 and 6). The unique chemoselectivity of the reaction was also illustrated by the benzylic alcohol substrate **15** (entries 7 and 8).

Both Pd-catalyzed and gold-catalyzed reaction worked smoothly to give the diastereomeric products **16** in good to excellent yield. In addition to the terminal alkynes discussed above, internal alkyne **17** also proved efficient for the sequential catalysis to give the products **18** in high yield (entries 9 and 10). Also, the allylic ether substrate **19** gave the dihydropyran compound **20** in high yields with no interference from the gold(I)-catalyzed enyne cyclization. These examples further address the chemoselectivity of the proposed gold(I)-catalyzed cycloisomerization reaction.

Having established the generality of the sequential metal catalysis, we then investigated the synthetic transformation of the enol ether products. As described in Scheme 2, *cis*-**10** was successfully converted into the cyclic ketal **21** in 85% yield upon treatment with excess TMSCl and ethylene glycol. Under the analogous condition, the *trans*-**10** was also converted into the *trans*-ketal **22**[22] in 91% yield with no formation of the *cis*-diastereomer **21**.

In addition to the simple ketal formation described above, highly electron rich enol ether moiety in the product should allow for introduction of more dense functional groups into the tetrahydropyran ring. As an illustrative example, we examined the Os-catalyzed dihydroxylation of compound *cis*-**8**. As depicted in Scheme 2, the reaction proceeded smoothly. However, the hydroxyketone product **23** could not be easily isolated due to the undesired dimerization.[23] This problem was successfully avoided by the acetate formation from the crude **23** to generate **24** in 58% yield (over two steps).[24] Notably, complete chemoselectivity in the dihydroxylation was observed; the terminal olefin remained intact in the dihydroxylation. Unlike *cis*-**8**, the *trans*-**10** gave the desired hydroxyketone **25** only in low yield because of the poor chemoselectivity. To our delight, alternative epoxidation with DMDO followed by *in situ* treatment with catalytic CSA produced **25** in 76% yield with high stereoselectivity (~10:1) and

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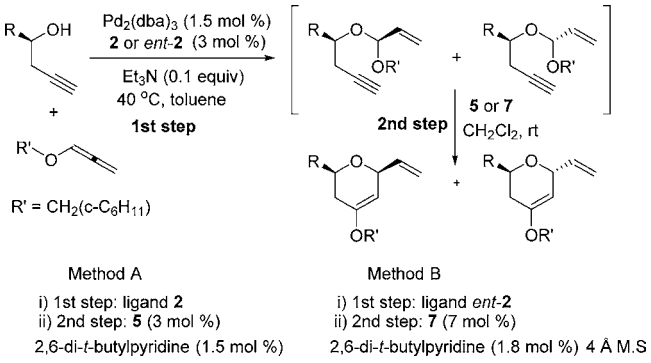
Table 2. Scope of Stereodivergent Dihyropyran Synthesis



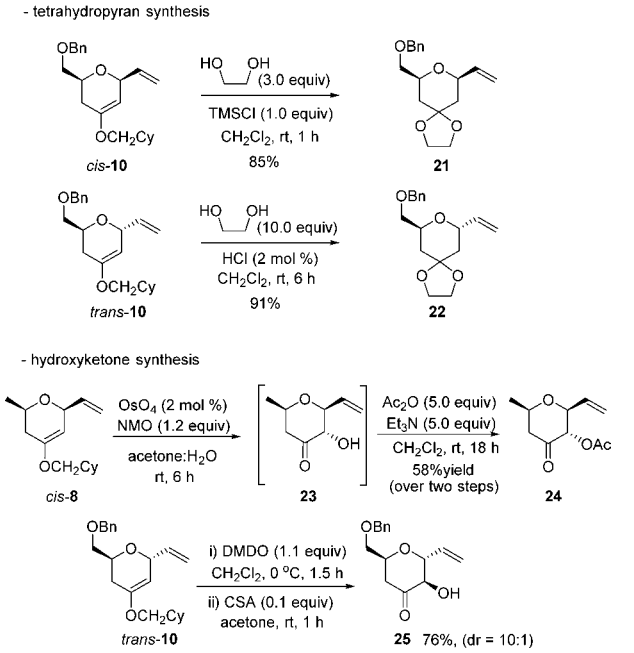
Entry	S.M	Method	Yield (%) (1^{st}[a],2^{nd}[b])	Product	ratio[c] (*cis*:*trans*)
1	**9** (R = CH_2OBn	A	(99, 96)	**10**	>25:1
2		B	(99, 77)		1:7
3	**11** (R = $(CH_2)_3OTBS$	A[d]	(84, 95)	**12**	25:1
4		B[d]	(89, 78)		1:6
5	**13** (R = CH_2Ph)	A[e]	(99, 93)	**14**	>25:1
6		B[d]	(99, 83)		1:8
7	**15** (R = Ph)	A	(99, 70)	**16**	12:1
8		B[e]	(99, 49)		1:4
9	**17**	A[d]	(98, 98)	**18**	18:1
10	**17**	B[d]	(96, 88)		1:6
11	**19**	A	(93, 95)	**20**	25:1[f]
12	**19**	A	(89, 99)		1:8[f]

[a]Isolated yield of mixture. [b]Isolated yield of the major diastereomer. [c]Determined by the integration of the crude NMR after the second step (Au catalysis). In all cases, the diastereomeric ratio of the first step (Pd catalysis) was determined to be >20:1. [d]5 mol % of Pd/10 mol % of ligand was used. [e]14 mol % of 7 was used. [f]The ratio was determined after purification using column chromatography.

chemoselectivity.[25] The transformations depicted in Scheme 2 illustrates the potential utility of the proposed method in the divergent synthesis of tetrahydropyran natural products.

In summary, we reported a new and highly flexible synthesis of tetrahydropyran structure based upon the use of sterodefined *O*,*O*-acetals as the key moiety. Notably, a variety of tetrahydropyran structure could be accessed by the chemoselective sequential Pd/Au metal catalysis. This new reaction significantly broadens the synthetic scope of the sterodefined *O*,*O*-acetals. Currently, we are working on the total synthesis of bioactive tetrahydropyran natural products as well as further expansion of the utility of the sterodefined *O*,*O*-acetals based on chemoselective metal catalysis.

Scheme 2. Synthetic Transformation of Enol Ether Products



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03532.

Experimental details and spectral data; ^1H and ^{13}C scan of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Alkynyl alcohol substrates were generally prepared by BF_3-promoted addition of lithium acetylide to epoxides; see Supporting Information for details.
(15) In this case, extensive formation of alcohol **1** by way of the cleavage of the acetal was observed as the major event.
(16) Alkoxyallenes were prepared by potassium *tert*-butoxide catalyzed isomerization of the corresponding alkyl propargyl ethers; see Supporting Information for details.
(17) This rate difference may be explained by the increased steric hindrance in formation of the oxonium ion intermediate **B**/**B′** chiral acetal **A**/**A′**.
(18) For detailed list of optimization, see the SI.
(19) Partial epimerization was observed for the slower-reacting *trans*-acetals such as **4b**, when the reaction was stopped before full conversion. Thus, the lower selectivity can be explained by the competing epimerization.
(20) The high degree of stereochemical transfer observed in this reaction may be explained by the attack of the vinylgold moiety to the acetal carbon in intermediate B (Scheme 1). For a related study, see: Pawar, S. K.; Wang, C.-D.; Bhunia, S.; Jadhav, A. M.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559.
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