Gold Catalysis

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Gold(I)-Catalyzed Enantioselective Desymmetrization of 1,3-Diols through Intramolecular Hydroalkoxylation of Allenes

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Abstract: *A gold(I)-catalyzed enantioselective desymmetrization of 1,3-diols was achieved by intramolecular hydroalkoxylation of allenes. The catalyst system 3-F-dppe$(AuCl)_2$/(R)-C_8-TRIPAg proved to be specifically efficient to promote the desymmetrizing cyclization of 2-aryl-1,3-diols, which have proven challenging substrates in previous reports. Multisubstituted tetrahydrofurans were prepared in good yield with good enantioselectivity and diastereoselectivity by this method.*

Asymmetric desymmetrization of prochiral 1,3-diols provides an indirect but powerful way to form stereogenic centers, especially for the synthesis of chiral all-carbon quaternary centers.[1] During the past decade, substantial effort has been made towards the development of methods for the enantioselective intermolecular desymmetrization of such substrates;[2,3] however, intramolecular asymmetric desymmetrization reactions of 1,3-diols to generate two or more stereogenic centers have only recently been realized by organocatalysis.[4] Sun et al. described a chiral phosphoric acid-catalyzed intramolecular transacetalization of 1,3-diols to form tetrahydrofuran skeletons with high efficiency and stereoselectivity.[4a] Yeung et al. reported enantioselective desymmetrizing bromoetherification reactions of olefinic 1,3-diols catalyzed by a quinidine derived amino-thiocarbamate[4b] or a C_2 symmetric sulfide.[4c]

In contrast, transition-metal catalyzed reactions for the intramolecular asymmetric desymmetrization of 1,3-diols have been far less explored.[5] Palladium-catalyzed asymmetric C–O bond formation, including allylic alkylation reaction[5a] and Ullmann-type coupling reaction,[5b] were designed for this purpose; however, only modest enantioselectivities were obtained. A copper-catalyzed consecutive desymmetrization and kinetic resolution sequence was designed to obtain highly enantioenriched products.[5c]

Gold-catalyzed asymmetric hydrofuctionalization of allenes has drawn extensive interest during the last decade.[6] These reactions serve as atom-economical and highly stereoselective methods to assemble commonly encountered heterocycle motifs found in natural products and bioactive molecules. Despite these achievements, no succesful method has been established to construct heterocycles incorperating more than one stereocenter via these transformations. In 2007, our group reported an enantioselective hydroalkoxylation of allenes enabled by a chiral counter anion strategy.[7] Herein we disclose our recent efforts towards a gold-catalyzed desymmetrizing hydroalkoxylation of allenes that implements this same tactic, and provides access to multisubstituted tetrahydrofurans containing two stereogenic centers with good enantioselectivity and excellent diastereoselectivity.

Previous studies have demonstrated that the chiral induction induced by a chiral counteranion can be sharply modulated by achiral ligands.[8] Thus, our exploration commenced with the examination of varying achiral phosphine ligands and their synergistic properties in combination with Ag-(*S*)-TRIP in the desymmetrization of 1,3-diols. The fact that 2-aryl-1,3-diol (R = Ar, Figure 1) derived substrates were

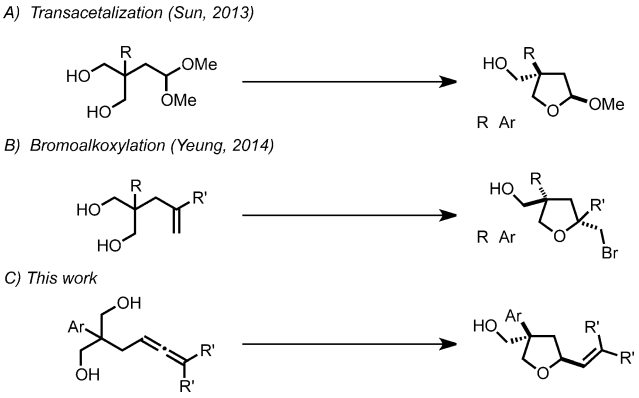

Figure 1. Strategies for enantioselective intramolecular desymmetrization of 1,3-diols.

absent in Sun and Yeung's reports,[4] prompted us to employ 2-phenyl substituted 1,3-diol **1a** as the model substrate (Table 1). Various mono- and bis-phosphines ligands for gold were first investigated. Excellent diastereoselectivity and reactivity was obtained with monophosphine ligands (Ph_3P, tBu_3P); however, the enantioselectivity was very low (entries 1 and 2). Switching to the a bisphosphine ligand, diphenylphosphinomethane (dppm), produced an improvement in the enantioselectivity of the reaction, but with a slight loss of diastereoselectivity (d.r. = 15:1, 50% *ee*). Other bisphosphine ligands were subsequently examined (entries 4 and 5).[9] Among them, diphenylphosphinoethane (dppe) proved optimal not only in enantioselectivity but also in diastereoselectivity (> 25:1 d.r., 57% *ee*).

Further optimization of the ligand focused on the adjustment of its electronic properties. Neither strongly electron-donating groups (4-MeO) nor strongly electron-withdrawing groups (4-CF_3) were beneficial to the reaction (entries 4, 6

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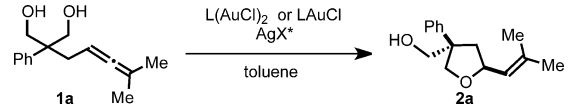
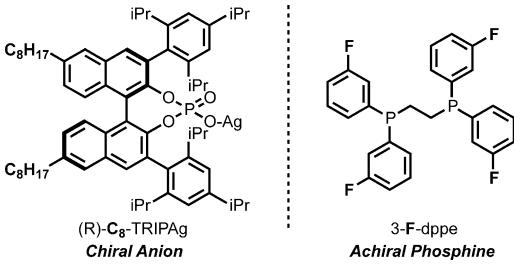
Table 1: Optimization of the reaction conditions.[a]



Entry[a]	Ligand	Anion	d.r.[b]	Yield [%][c]	*ee* [%][d]
1	Ph_3P	(*S*)-TRIP	>25:1	90	−28
2	$tBuP_3$	(*S*)-TRIP	>25:1	>95	−4
3	dppm	(*S*)-TRIP	15:1	87	−50
4	dppe	(*S*)-TRIP	>25:1	93	−57
5	dppp	(*S*)-TRIP	18:1	>95	−41
6	4-MeO-dppe	(*S*)-TRIP	>25:1	>95	−39
7	4-CF_3-dppe	(*S*)-TRIP	14:1	84	−28
8	4-F-dppe	(*S*)-TRIP	>25:1	>95	−66
9	3-F-dppe	(*S*)-TRIP	>25:1	>95	−70
10	3-F-dppe	(*R*)-H_8-TRIP	18:1	>95	81
11[e]	3-F-dppe	(*R*)-C_8-TCYP	>25:1	>95	83
12	3-F-dppe	(*R*)-C_8-TRIP	>25:1	94	87
13[f]	3-F-dppe	(*R*)-C_8-TRIP	>25:1	92	91
14[f,g]	3-F-dppe	(*R*)-C_8-TRIP	>25:1	>95	93

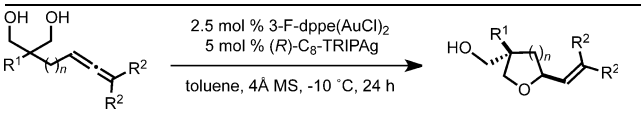
[a] Reaction conditions: 2.5 mol% $L(AuCl)_2$ or 5.0 mol% LAuCl, 5 mol% AgX*, 0.05 mmol substrate in 0.5 mL toluene (C = 0.1 M), room temperature, 2 h. [b] d.r. was determined by ^{1}H NMR analysis of the crude product. [c] ^{1}H NMR yield based on internal standard. [d] Determined by chiral HPLC. [e] Full conversion after 12 h. [f] C = 0.01 M. [g] Reaction was run at −10 °C with 20 mg 4 Å molecular sieve as additive.

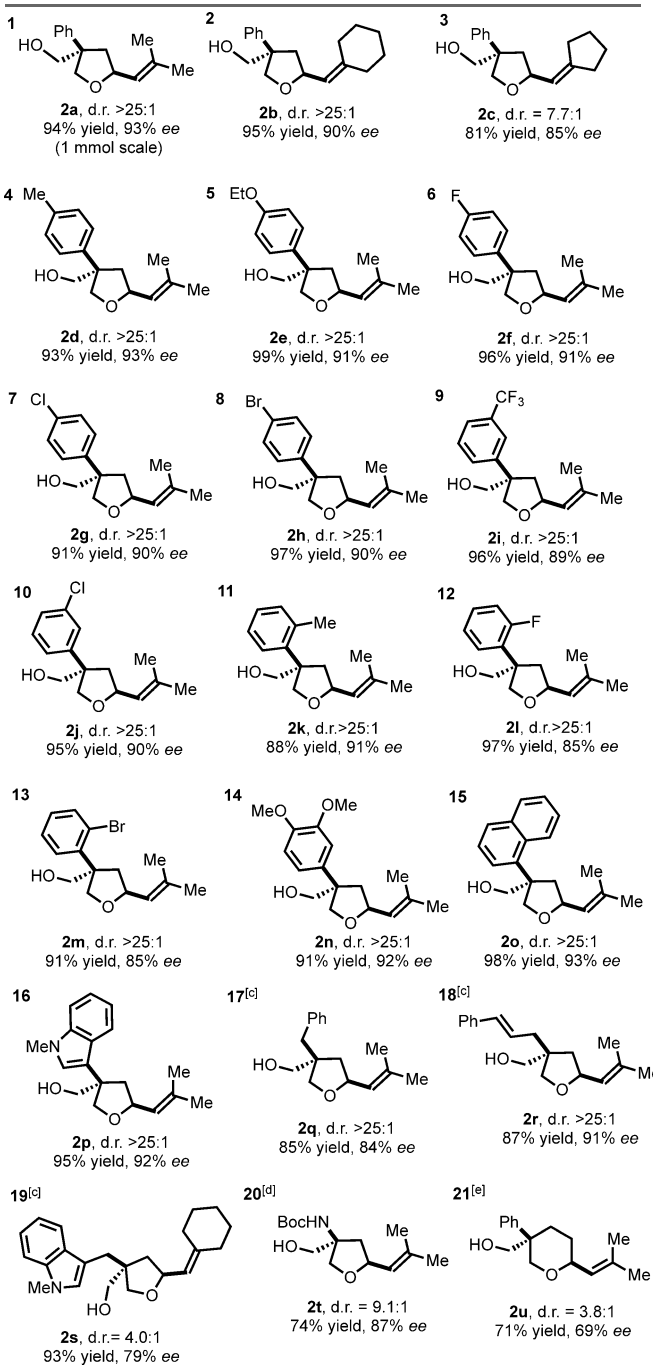


and 7). However, a mild electron withdrawing group (4-F) increased the *ee* to 66% (entry 8). Additional enhancement of the enantioselectivity was observed by employing 3-F-dppe as the ligand instead of 4-F-dppe (70% *ee*, entry 9). The structure of the counter anion was also examined, with (*R*)-C_8-TRIP providing the desired product **2a** in 94% yield with 87% *ee* as a single diastereoisomer (entry 12). Finally, performing the reaction at increased dilution and low temperature resulted in further improvements to the enantioselectivity (entries 13, 14).

With the optimal reaction conditions in hand, we next examined the substrate scope of this reaction (Table 2). The allene moiety (R^2) was investigated, with six-membered ring substituent on the allene affording the desired product **2b** in 95% yield with 90% *ee* (entry 2). By contrast, slightly poorer results were obtained for the five-membered ring containing substrate (entry 3). Substrates with an electron-withdrawing group (F, Cl, Br, CF_3), an electron-donating group (EtO, Me), or two substituents on the aryl ring all were well-tolerated (entries 4 to 14). Additionally, reactions for substrates bearing a naphthalene or indole proceeded smoothly under the standard reaction conditions (entries 15 and 16).

Table 2: Scope of substrates.[a,b]





[a] Reaction conditions: 2.5 mol% 3-F-dppe$(AuCl)_2$, 5 mol% (*R*)-C_8-TRIPAg, 0.1 mmol substrate in 10 mL toluene (C = 0.01 M), 40 mg 4 Å molecular sieve, −10 °C for 24 h. See Supporting Information for details. [b] d.r. was determined by ^{1}H NMR analysis of the crude product and *ee* was determined by chiral HPLC. Isolated yield. [c] −35 °C for 60 h. [d] −10 °C for 72 h. [e] 20 °C for 24 h.

We next turned our attention to substrates varying at the nascent desymmetrized quaternary carbon. When a benzyl

group was introduced, modified conditions (−35 °C, 60 h) were needed to maintain good enantioselectivity (entry 17). A substrate with a cinnamyl group was also tested, giving the hydroalkoxylation product **2r** in 87 % yield, without formation of any [2+2] adduct (entry 18).[10] Similarly, no hydroarylation of allene was observed during the preparation of **2s** by this method (entry 19).[11] These results further demonstrate counterion-controlled reactivity in homogeneous gold catalysis.[12] Finally, the reaction was easily extended to a substrate incorporating a protected amine functionality at the C2 position. While prolonged reaction time was required, the desired tetrahydrofuran with a protected amine moiety was isolated in 74 % yield with 87 % enantioselectivity (entry 20). Attempts to prepare tetrahydropyran product **2u** by this desymmetrization method under the standard conditions (−10 °C for 24 h) resulted in low conversion (< 10 %). Elevated reaction temperature expedited the transformation, however, modest diastereoselectivity and enantioselectivity was obtained (d.r. = 3.8:1, 69 % *ee*, entry 21).[13]

The absolute stereochemistry of the hydroalkoxylation product **1a** was determined by transformation to its sulfonylated derivative **3** (Figure 2). X-ray crystallographic analysis

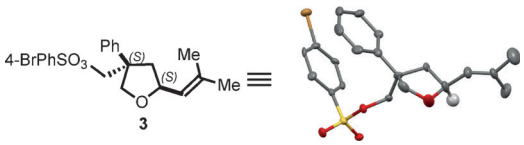
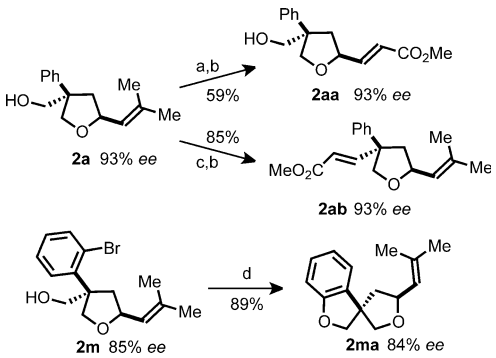


Figure 2. Absolute stereochemistry of **3** determined by X-ray crystallography.

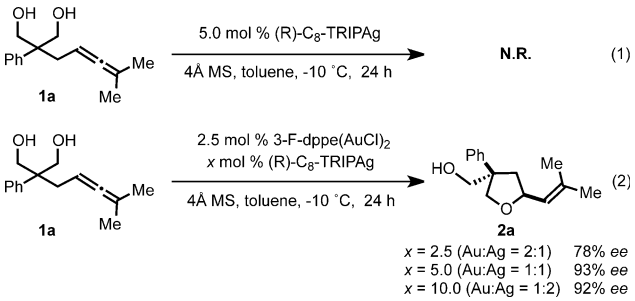
of **3** confirmed its structure and disclosed the absolute configuration as 2*S*, 4*S*.[14] Synthetic transformation of the desymmetrization products are illustrated in Scheme 1. The alkene moiety in **2a** was readily converted to the corresponding aldehyde, which was transformed to α,β-unsaturated ester using the Hornor–Wadsworth–Emmons olefination reaction. Moreover, the hydroxy in **2a** was extended to an ester by oxidation/olefination sequence. Additionally, spirocyclic ether **2ma** was prepred through an Ullmann-type C–O



Scheme 1. Synthetic transformation of the products. Reaction conditions: a) O_3, CH_2Cl_2, −78 °C then Me_2S from −78 °C to room temperature. b) $(EtO)_2P(O)CH_2CO_2Me$, NaH, THF. c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2. d) CuI, NaH, toluene, 120 °C. See the Supporting Information for details.

bond formation reaction of the adduct (**2m**) bearing a halogen group at ortho position on the phenyl ring.

To gain insight into the mechanism, some control experiments were conducted. First, when the gold catalyst was omitted, no reaction occurred, excluding a chiral silver-catalyzed hydroalkoxylation as the operative mechanism [Scheme 2, Eq. (1)].[15] Second, the ratio of Au/Ag was



Scheme 2. Control experiments.

investigated. Although excess (*R*)-C_8-TRIPAg had no obvious effect to the enantioselectivity, when a 2:1 ratio of Au/Ag was employed, the enantiomeric excess dropped dramatically to 78 % [Scheme 2, Eq. (2)].[16] These observations raise the possibility that both gold centers in the catalyst play an important role in enantioinduction. While it is tempting to invoke a mechanism involving dual activation of the allene leading to a *gem*-diaurated intermediate, these species are generally believed to be less reactive towards protodeauration and, therefore, lie off the catalytic cycle.[17] Moreover, we observed a clear linear relationship[18] ($r^2 = 0.996$) between the enantiomeric excess of the phosphate catalyst and that of the product (Figure 3). Therefore, it seems most plausible that

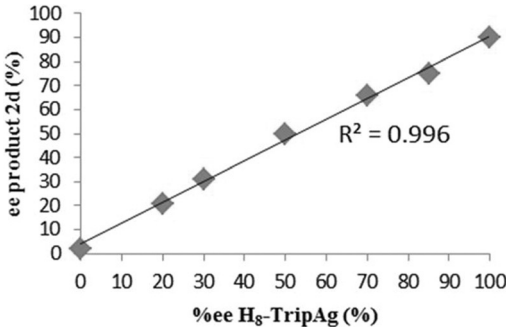


Figure 3. Relationship between the optical purity of product **2d** and catalyst using 3-F-dppe$(AuCl)_2$/H_8-TripAg in toluene.

the second gold phosphate center in the dinuclear catalyst is providing a structural or steric effect[19] rather than dual chiral induction.

In summary, we have achieved the first gold(I)-catalyzed enantioselective desymmetrization of 1,3-diols by intramolecular hydroalkoxylation of allenes. With this method, multisubstituted oxygen heterocycles, bearing all-carbon

quaternary stereogenic centers are accessed in good yield with high enantioselectivity and diastereoselectivity. Notably, in addition to selecting the appropriate chiral anion, tuning of the steric and electronic properties of the achiral phosphine supporting ligand proved crucial to identifying the ideal catalyst system. This reaction represents an important further example of power of the chiral anion strategy for transition metal catalysis.[20]

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