Asymmetric Synthesis

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Gold(I)-Catalyzed Desymmetrization of 1,4-Dienes by an Enantioselective Tandem Alkoxylation/Claisen Rearrangement**

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Abstract: *An enantioselective alkoxylation/Claisen rearrangement reaction was achieved by a strategic desymmetrization of 1,4-dienes under the catalysis of (S)-DTBM-Segphos(AuCl)$_2$/AgBF$_4$. This reaction system was highly selective for the formation of 3,3-rearrangement products, providing cycloheptenes with various substitutions in good yield and good to excellent enantioselectivity. This transformation was further extended to bicyclic ring substrates, providing the opportunity to easily assemble 5,6- and 6,7-fused ring systems.*

Strategies involving the rearrangement of vinyl gold intermediates generated from alkoxylation of alkynes have attracted intense research during the last decade.[1] Varied architectures including indenes, piperidines, cycloheptenes, indanones, and cyclopenta[*b*]indoles have been rapidly assembled through these transformations. In particular, our group discovered that enantioenriched benzylic ethers undergo an alkoxylation/1,3-rearrangement to give indenes with highly efficient chirality transfer (Figure 1 a).[1a,2] In a related study, Rhee and co-workers demonstrated that introducing steric hindrance at C1 resulted in an alkoxylation/Claisen rearrangement reaction giving seven-membered rings (Figure 1 b).[1d] This transformation provides a straightforward route to cycloheptane skeletons that are commonly encountered in natural products and bioactive molecules.[3] On the basis of these precedents, we anticipated that an enantioselective transformation to construct valuable multisubstituted seven-membered carbocycles would be possible.[4]

Mechanistically, the 3,3-rearrangement is thought to proceed through a concerted sigmatropic process that was expected to follow a similar chirality transfer to the previously reported 1,3-rearrangement. As depicted in Figure 2 a, we initially found that under cationic gold catalysis, chiral ether **1** gave a mixture of 3,3- and 1,3-rearrangement products (**2** and **3**) in a ratio of 1.8:1. Importantly, whereas enol ether **3** was formed with complete erosion of enantiomeric excess, we observed full chirality transfer during the formation of the 3,3-rearrangement product **2**. Although this discovery provided an exciting possibility to access chiral cycloheptene **2**, we anticipated that an enantioselective variant starting from achiral substrates would be more valuable, because it circumvents the requirement for enantioenriched starting material **1**.[5] Thus we endeavored to develop a ligand-controlled enantioselective alkoxylation/Claisen rearrangement.[6]

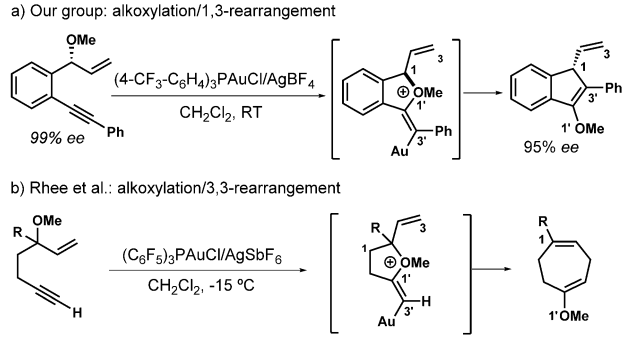

Figure 1. Gold(I)-catalyzed tandem alkoxylation/sigmatropic rearrangement.

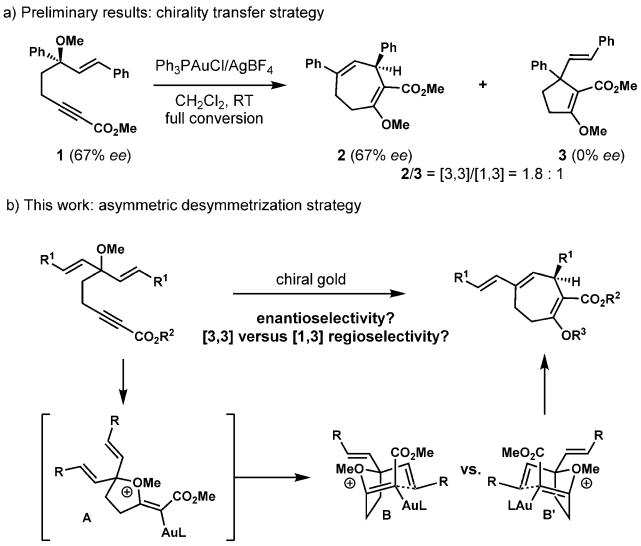

Figure 2. Strategies for asymmetric alkoxylation/Claisen rearrangement.

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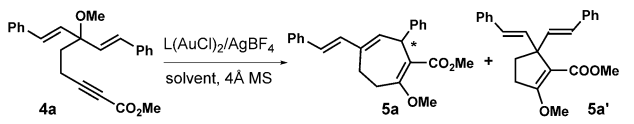
We envisioned that an enantioselective variant might be available through a desymmetrization reaction[7,8] of 1,4-dienes. Recently, gold-catalyzed enantioselective desymmetrization by nucleophilic addition to alkynes has been reported either through differentiation of enantiotopic alkynes[9] or nucleophiles.[10] In contrast, successful implementation of a desymmetrization strategy to the tandem alkoxylation/3,3-sigmatropic rearrangement reaction does not rely on enantiocontrol of the nucleophilic addition because this step forms achiral intermediate **A**. Rather, the proposed mechanism and the chirality transfer experiment suggest that the catalysts must exert influence over the sigmatropic rearrangement[11,12] event and thus differentiate between enantiotopic transition states **B** and **B′** (Figure 2b) On the basis of this intriguing possibility, herein we describe our efforts to develop a gold(I)-catalyzed asymmetric tandem alkoxylation/Claisen rearrangement reaction enabled by a strategic desymmetrization of 1,4-dienes (Figure 2b).

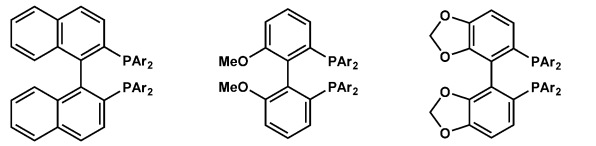
The 1,4-diene **4a** was chosen as the model substrate (Table 1). Sterically demanding ligands with various chiral backbones were examined (entries 1–5).[13] Among them, DTBM-Segphos (**L4**) gave the best performance, not only in enantioselectivity but also in regioselectivity. Although the less sterically hindered DM-Segphos ligand (**L5**) dramatically diminished the formation of the undesired 1,3-rearrangement product, it also resulted in decreased enantioselectivity (entries 4 and 5). Thus, DTBM-Segphos (**L4**) was chosen as the ligand for further optimization. Various solvents were screened (entries 6–9), revealing that nonpolar solvents such as benzene gave the best results (1,3/3,3 = 17:1, >95% conversion, 85% *ee*).[14] Interestingly, when the reaction was conducted in DCM, the opposite sense of enantioinduction was obtained (entry 6). Other silver salts besides $AgBF_4$ were investigated and showed no improvement; however, we found that an increased loading of $AgBF_4$ (0.2 equiv) led to improved regio- and enantioselectivity (entry 10). Additionally, decreasing the reaction temperature and employing a solvent mixture of toluene/benzene (4:1) afforded improved enantioselectivity without loss of regioselectivity (entry 11). Finally, when the reaction was run at −20 °C, the desired 3,3-rearrangement product **5a** was isolated in 89% yield and 93% *ee* (entry 12).

With the optimized conditions in hand, we next examined the substrate scope of this reaction (Table 2). Phenyl groups (R^1 = Ar) with various substituents were investigated first. Electron donating groups (Me, MeO) at *para*-, *meta*-, or *ortho*-positions of the phenyl ring are well tolerated, affording the desired products in good yield with high enantioselectivity

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



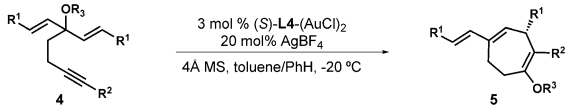
Entry	L	Solvent	**5a**/**5a′**[b]	Conv. [%][b]	*ee* [%][c]
1	(*R*)-**L1**	toluene	9:1	60	−27
2	(*S*)-**L2**	toluene	6:1	>95	48
3	(*R*)-**L3**	toluene	3:1	>95	−33
4	(*S*)-**L4**	toluene	13:1	>95	82
5	(*S*)-**L5**	toluene	>20:1	>95	70
6	(*S*)-**L4**	CH_2Cl_2	3:1	>95	−61
7	(*S*)-**L4**	CCl_4	6:1	>95	73
8	(*S*)-**L4**	Et_2O	8:1	>95	81
9	(*S*)-**L4**	PhH	17:1	>95	85
10[d]	(*S*)-**L4**	PhH	19:1	>95	88
11[d,e]	(*S*)-**L4**	PhH/toluene (5:1)	20:1	>95	91
12[d,f]	*(S)-L4*	*PhH/toluene (1:2)*	*14:1*	*>95(89)*[g]	*93*

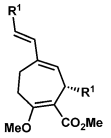
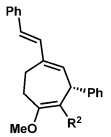
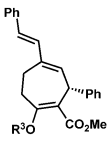


L1: Ar=3,5-(*t*Bu)$_2$-4-(MeO)C$_6$H$_2$ **L2**: Ar=3,5-(*t*Bu)$_2$C$_6$H$_2$ **L3**: Ar=3,5-(*t*Bu)$_2$-4-(MeO)C$_6$H$_2$ **L4**: Ar=3,5-(*t*Bu)$_2$-4-(MeO)C$_6$H$_2$ **L5**: Ar=3,5-(CH$_3$)$_2$C$_6$H$_2$

[a] Reaction conditions: 3 mol% gold catalyst, 6 mol% $AgBF_4$, 0.05 mmol **4a**, 20 mg 4 Å molecular sieves, 1 mL toluene, RT. [b] Ratio of **5a**/**5a′** and the conversion of **4a** were determined by ^{1}H NMR analysis of the crude product. [c] Determined by chiral HPLC, the minus sign indicates reversed absolute stereochemistry relative to optimized results. [d] 20 mol% $AgBF_4$ was used. [e] The reaction was conducted at 0 °C. [f] The reaction was conducted at −20 °C for 4 h. [g] Isolated yield is given in parentheses.

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

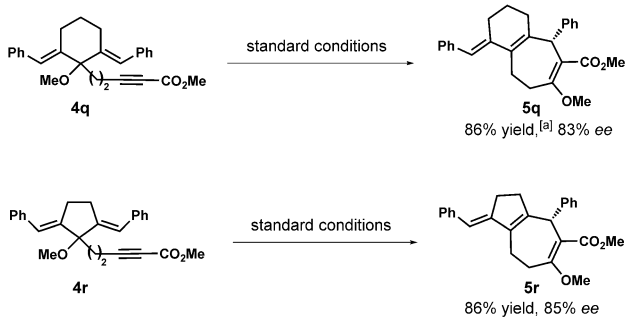


Entry	Product **5**		Yield [%][c]	*ee* [%][d]
1		**5a** (R^1 = Ph)	89	93
2		**5b** (R^1 = 2-MeC$_6$H$_4$)	90	95
3		**5c** (R^1 = 4-MeC$_6$H$_4$)	92	90
4		**5d** (R^1 = 3-MeOC$_6$H$_4$)	87	92
5		**5e** (R^1 = 2-MeOC$_6$H$_4$)	94	95
6		**5f** (R^1 = 4-MeOC$_6$H$_4$)	88	96
7		**5g** (R^1 = 2-FC$_6$H$_4$)	89	86
8		**5h** (R^1 = 2-ClC$_6$H$_4$)	81	84
9		**5i** (R^1 = 4-FC$_6$H$_4$)	90	93
10		**5j** (R^1 = 1-naphthyl)	90	93
11		**5k** (R^1 = 2-furyl)	89	80
12		**5l** (R^1 = Me)	86	60
13[e]		**5m** (R^1 = *t*Bu)	60	93
14		**5n** (R^2 = CO$_2$Bn)	85	86
15		**5o** (R^2 = CO$_2$Allyl)	90	91
16		**5p** (R^3 = Allyl)	89	88

[a] Reaction conditions: 3 mol% (*S*)-**L4**-(AuCl)$_2$ catalyst, 20 mol% $AgBF_4$, 0.05 mmol substrate, 20 mg 4 Å molecular sieves, 1 mL toluene and 0.5 mL benzene, at −20 °C for 4 h. [b] Unless noted, the regioselectivity of [3,3]/[1,3] > 12:1. [c] Yield of the isolated product. [d] Determined by chiral HPLC. [e] [1,3]-rearrangement product was also isolated in 35% yield.

(entries 2–6). Electron-withdrawing groups such as F and Cl at the *ortho*-position showed some deleterious effects on enantioselectivity (entries 7 and 8), but the substrate with *para*-fluoro substitution still performed well (entry 9). A 1-naphthyl group was compatible with our reaction conditions, affording **5j** in 90% yield with 93% *ee* (entry 10). A substrate with a more electron-rich furan substituent reacted smoothly to give **5k** in 89% yield, albeit with diminished enantioselectivity (entry 11). Aliphatic R^1 groups were also investigated and an apparent steric effect was observed. When R^1 was methyl group, the enantioselectivity dropped dramatically, although good yield was retained (entry 12). However, when a more sterically hindered *tert*-butyl group was introduced, the enantioselectivity was restored (93% *ee*), but the yield decreased as a result of formation of a significant amount of [1,3]-rearrangement product (entry 13). Switching the R^2 group from methyl ester to Cbz or Alloc resulted in a slightly decreased enantioselectivity (entries 14 and 15).[15] An allylic ether substrate was also tested under these conditions, and gave **5p** in 89% yield with 88% *ee* (entry 16).

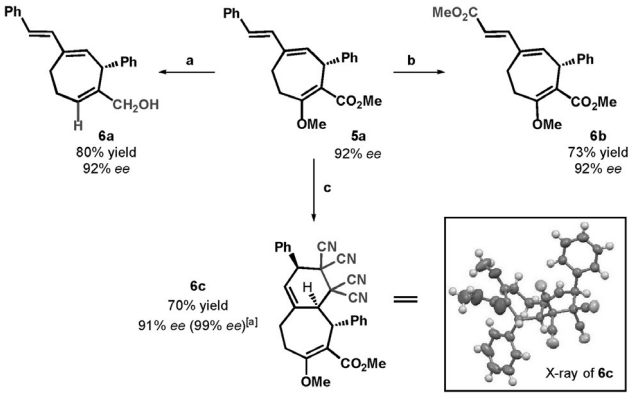
The success in preparing cycloheptenes prompted us to extend this methodology to more complex systems. 5,7- or 6,7-fused bicyclic systems are common skeletons in natural products.[16] We examined the possibility of assembling these carbon skeletons by the gold-catalyzed enantioselective tandem alkoxylation/Claisen rearrangement reaction. The desired bicyclic compounds **5q** and **5r** were obtained in high yield with good enantioselectivity under the standard conditions (Scheme 1).



Scheme 1. Synthesis of 5,7- and 6,7-fused ring systems. [a] The purity of starting material **4q** was 76% by ^{1}H NMR analysis. Adjusted yield was given based on the purity of **4q** (See the Supporting Information).

The diverse functional group generated from the gold-catalyzed rearrangement allow for rapid generation of molecular complexity by further transformations (Scheme 2). The enol ether moiety of **5a** was subjected to DIBAL-H reduction to give allylic alcohol **6a** in 80% yield by a cascade 1,4-reduction/elimination and 1,2-reduction. Regioselective alkene cross-metathesis of **5a** with ethyl acrylate, catalyzed by second generation Hoveyda–Grubbs catalyst, gave α,β-unsaturated ester **6b**. Additionally, the diene moiety was reacted with a dienophile to give the 6,7-fused cycloadduct **6c**.[17]

In summary, a gold(I)-catalyzed asymmetric tandem alkoxylation/Claisen reaction has been developed. The transformation provides the opportunity to assemble multisubstituted cycloheptenes efficiently and with high enantioselectivity. The reaction is believed to proceed through an enantiodetermining sigmatropic rearrangement of a vinylgold intermediate and, therefore, extends the types of processes amenable to enantioselective gold catalysis. More generally, the desymmetrization reaction illustrates a strategy for developing enantioselective catalyst-controlled reactions from transition-metal-catalyzed processes that have previously been shown to proceed with chirality transfer.



Scheme 2. Synthetic transformation of the products. Reaction conditions: a) DIBAL-H, toluene, RT; b) methyl acrylate, Hoveyda–Grubbs catalyst II, DCM, 50°C; c) Tetracyanoethylene, toluene, 80°C. [a] *ee* value in parentheses obtained after purification, see details in the Supporting Information.

Keywords: alkoxylation · Claisen rearrangement · desymmetrization · enantioselectivity · gold

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