

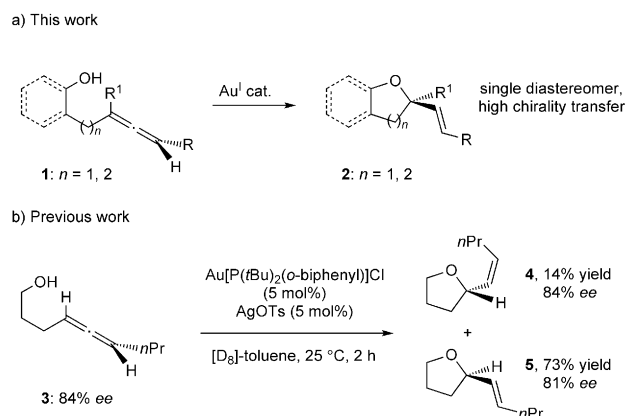
# Catalytic Asymmetric Synthesis of Cyclic Ethers Containing an $\alpha$ -Tetrasubstituted Stereocenter\*\*

Nick Cox, Mycah R. Uehling, Karl T. Haelsig, and Gojko Lalic\*

Cyclic ethers are an important class of heterocycles present in a variety of biologically active molecules. For example, tetrahydrofurans (THFs) and tetrahydropyrans (THPs) are found in several classes of natural products, including macrodiolides,<sup>[1]</sup> acetogenins,<sup>[2]</sup> ionophores,<sup>[3]</sup> lignans,<sup>[4]</sup> and macro-lides,<sup>[5]</sup> while arene-fused THPs are the major structural motif of chromans.<sup>[6]</sup> The importance of cyclic ethers as structural elements of organic molecules has led to continued interest in the development of new catalytic and stereoselective methods for their synthesis.<sup>[7,8]</sup> However, despite significant progress in the field, the asymmetric synthesis of cyclic ethers containing tetrasubstituted stereocenters<sup>[9]</sup> is still a major synthetic challenge. Herein we describe the development of a method for the catalytic, asymmetric synthesis of THFs, THPs, and chromans containing a tetrasubstituted stereocenter.

Our approach is based on a catalytic method for the synthesis of cyclic ethers developed in 2006 by Widenhoefer and co-workers,<sup>[10]</sup> who reported a gold-catalyzed *exo*-selective cyclization of allenols as an efficient method for the synthesis of THFs and THPs. This method has been applied to the asymmetric synthesis of compounds containing trisubstituted, but not tetrasubstituted stereocenters.<sup>[10,11]</sup> We reasoned that cyclic ethers containing a tetrasubstituted stereocenter could be prepared by cyclization of enantioenriched trisubstituted allenols, as outlined in Scheme 1a.

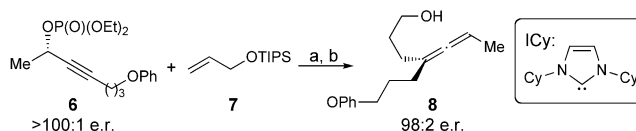
The key aspect of this transformation is transfer of chirality from the chiral axis of an allene to the tetrasubstituted stereocenter of the cyclic ether. Chirality transfer to a trisubstituted stereocenter in *exo* cyclizations of allenols is known to be compromised by the formation of a mixture of diastereoisomers with the opposite sense of chirality (Scheme 1b).<sup>[10]</sup> However, chirality transfer to a tetrasubstituted stereocenter has so far not been explored in the context of this transformation. Furthermore, chirality transfer from enantioenriched trisubstituted allenols has, in general, rarely been used in gold-catalyzed hydrofunctionalization reactions, despite its enormous potential<sup>[12]</sup> in the asymmetric synthesis of tetrasubstituted stereocenters, because of the lack of a general method for the synthesis of enantioenriched



**Scheme 1.** Gold-catalyzed *exo*-selective cyclization of allenols. a) Formation of cyclic ethers containing an  $\alpha$ -tetrasubstituted stereocenter. b) Formation of cyclic ethers containing a trisubstituted stereocenter. Ts = 4-toluenesulfonyl.

trisubstituted allenols.<sup>[14]</sup> With the exception of the synthesis of dihydrofurans by *endo*-selective hydroalkoxylation of allenols pioneered by Marshall and Pinney,<sup>[13]</sup> and further developed by Krause and co-workers,<sup>[15]</sup> there are only few isolated examples of such transformations.<sup>[16]</sup>

Our group has recently reported the synthesis of enantioenriched trisubstituted allenols by copper-catalyzed substitution of propargylic phosphates using alkyl boranes as nucleophiles.<sup>[17,18]</sup> As Scheme 2 illustrates, we were able to



**Scheme 2.** Synthesis of enantioenriched trisubstituted allenols. [a] **7** (1.5 equiv), 9-BBN (1.5 equiv), 1,4-dioxane, 60 °C, 12 h, then **6** (1.0 equiv), ICyCuCl (10 mol %), LiOtBu (1.0 equiv), *n*-pentane, 35 °C. [b] Bu<sub>4</sub>NF, THF, 80% yield over two steps. 9-BBN = 9-borabicyclo-[3.3.1]nonane, THF = tetrahydrofuran, TIPS = triisopropylsilyl.

prepare the enantioenriched trisubstituted allenol **8** from the readily available propargylic phosphate **6** and protected allylic alcohol **7**. Practical access to enantioenriched trisubstituted allenols gave us an opportunity to investigate chirality transfer in the hydroalkoxylation reaction, and ensured that the overall synthesis of cyclic ethers containing a tetrasubstituted stereocenter would be convergent and practical.

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**Table 1:** Chirality transfer in *exo*-selective cyclization of allenols.

Entry	L	X	t [h]	Yield [%] <sup>[a]</sup>	CT [%] <sup>[b]</sup>
1	<i>t</i> Bu <sub>2</sub> P( <i>o</i> -biphenyl)	OTs	1	73 <sup>[c]</sup>	75
2	Ph <sub>3</sub> P	ClO <sub>4</sub>	1	> 95	0
3	Ph <sub>3</sub> P	BF <sub>4</sub>	1	> 95	2
4	Ph <sub>3</sub> P	OTs	1	> 95	95
5 <sup>d</sup>	Ph <sub>3</sub> P	OAc	100	70	87
6	(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> P	OTs	1	> 95	83
7	Cy <sub>3</sub> P	OTs	1	> 95	98
8	<i>t</i> Bu <sub>3</sub> P	OTs	1	> 95	99
9 <sup>e</sup>	<i>t</i> Bu <sub>3</sub> P	OTs	1	> 95	99

[a] Yields of the product as determined by GC. [b] CT = chirality transfer. [c] Mixture of diastereomers was obtained. [d] Reaction was performed at 60 °C. [e] 1 mol % of the catalyst was used.

In the initial cyclization experiments with the allenol **8**, we explored the reactivity of Au[P(*t*Bu)<sub>2</sub>(*o*-biphenyl)]OTs, which was previously identified as effective in the *exo* cyclization of allenols.<sup>[10]</sup> We observed the formation of *E* and *Z* isomers of the *exo*-cyclization products, which is consistent with the results previously obtained (Scheme 1 b). However, the major *E* isomer of the cyclization product was formed with low chirality transfer (CT)<sup>[19]</sup> (Table 1, entry 1). This result is surprising in light of a recent study, which suggests that CT from trisubstituted allenes in gold-catalyzed reactions can be expected to be higher than in those reactions with disubstituted allenes.<sup>[12]</sup> However, low CT could be a result of a difference in rates of racemization of the trisubstituted and disubstituted allenes previously observed in related transformations.<sup>[20]</sup> Indeed, a control experiment showed that racemization of the allene was responsible for the low CT observed.<sup>[21]</sup>

Considering this result, we decided to explore the reactivity of other gold complexes supported by monodentate phosphine ligands. Surprisingly, we found that with a variety of phosphine gold complexes, the *E* isomer of *exo* cyclization is the exclusive product of the reaction (Table 1, entries 2–9). Furthermore, in reactions promoted by triphenylphosphine gold complexes, higher CT is obtained using more-coordinating counter ions. At a certain point however, the cyclization becomes prohibitively slow and CT decreases (entry 5). Overall, the best CT is obtained using a gold tosylate catalyst supported by hindered, electron-rich phosphine ligands, such as *t*Bu<sub>3</sub>P. Surprisingly, excellent yield of the desired product can be obtained within an hour with as little as 1 mol % of the gold catalyst.

Using the optimal reaction conditions, a variety of highly enantioenriched THFs and THPs containing tetrasubstituted stereocenters were prepared (Table 2). As the synthesis of compounds **9–12** demonstrates, substrates bearing various substituents perform well in the reaction, and the selectivity of the cyclization does not seem to depend on the size of the R<sup>2</sup> substituents. Similarly, both methyl and larger alkyl substituents at the tetrasubstituted stereocenter are tolerated.

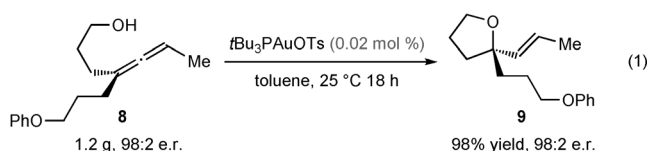
**Table 2:** Asymmetric synthesis of THFs and THPs.

Product	n	Yield [%]	e.r.
<b>9</b>	1	97%	98:2 e.r.
<b>10</b>	2	89%	97:3 e.r.
<b>11</b>	1	94%	97:3 e.r. <sup>[b]</sup>
<b>12</b>	2	75%	98:2 e.r. <sup>[b]</sup>
<b>13</b>	1	85%	96:4 e.r. <sup>[b]</sup>
<b>14</b>	2	92%	95:5 e.r. <sup>[b]</sup>
<b>15</b>		96%	95:5 e.r.
<b>16</b>		77%	93:7 e.r.
<b>17</b>		92%	96:4 e.r.
<b>18</b>		92%	98:2 e.r.
<b>19</b>		88%	99:1 e.r.
<b>20</b>		99%	95:5 e.r. <sup>[b]</sup>
<b>21</b>		91%	95:5 d.r.
<b>22</b>		97%	85:15 d.r.
<b>23</b>		95%	99:1 e.r. <sup>[b]</sup>

[a] Yields of isolated products are reported. [b] An allene with the opposite sense of chirality was used.

The cyclization can also be accomplished in the presence of a variety of functional groups including nitro, cyano, pivaloyl, azido, formyl, and silyloxy groups (**15–20**). We found that the presence of an additional stereocenter in the allenol affects the selectivity of the cyclization reaction (**21** and **22**). However, reasonable selectivity (85:15 d.r.) is obtained even in the mismatched case (**22**). Considering the results described in Scheme 1 b, we were surprised to find that our catalyst also provides excellent results in a reaction with a disubstituted allenol. The cyclization product **23** was obtained in 95 % yield, as a single diastereoisomer, and with excellent CT. Overall, in most examples, THFs and THPs were obtained in excellent yields (> 85 %) and enantiomeric ratios greater than 95:5.<sup>[22]</sup> Furthermore, in all reactions only the *E* isomer of the product was obtained.

To demonstrate the utility of the new method in a large-scale synthesis of cyclic ethers, we performed the cyclization of **8** on a 5 mmol scale (1.2 g) using 0.02 mol % of the catalyst [Eq. (1)]. The cyclization product was obtained as a single

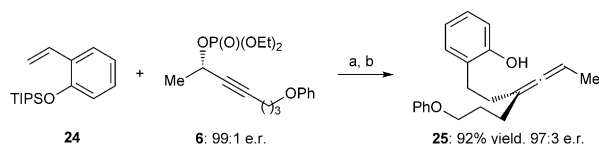


diastereoisomer, in excellent yield and with 98:2 e.r. The low catalyst loading used in this transformation is particularly noteworthy considering that in closely related reactions two-hundred-fifty-fold higher catalyst loading (5 mol %) is commonly used.<sup>[23]</sup>

Following the exploration of the synthesis of THFs and THPs we decided to explore the asymmetric synthesis of

closely related chromans, which are found in numerous biologically active compounds.<sup>[6,24]</sup> This transformation was particularly appealing considering that we found no previous reports of chroman synthesis by phenol addition to allenes. Furthermore, chromans containing a tetrasubstituted stereocenter are found in a wide range of biologically relevant molecules, and their asymmetric synthesis is still a major challenge.<sup>[25]</sup>

The synthesis of the requisite phenol-containing allenes was accomplished by an efficient two-step procedure shown in Scheme 3. The coupling of a readily available propargylic

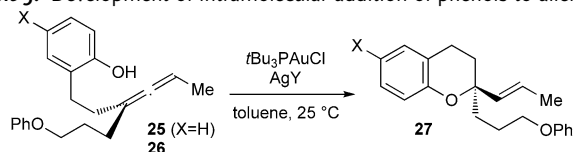


**Scheme 3.** Representative synthesis of phenol-functionalized allene. [a] **24** (1.2 mmol), 9-BBN (1.2 equiv), 1,4-dioxane, 60 °C, 12 h, then **6** (1.0 equiv), ICyCuCl (10 mol %), LiOtBu (1.0 equiv), *n*-pentane, 35 °C, 24 h. [b] TBAF (1.1 equiv), THF, 25 °C, 1 h.

phosphate with a protected phenol and subsequent deprotection provides the substrate for the cyclization reaction in excellent yield and with high e.r. value.

Initial experiments with the allene **25** using reaction conditions developed for the cyclization of allenols provided the desired chromane in excellent yield and diastereoselectivity, but with an 87 % CT (Table 3, entry 1). Significantly

**Table 3:** Development of intramolecular addition of phenols to allenes.

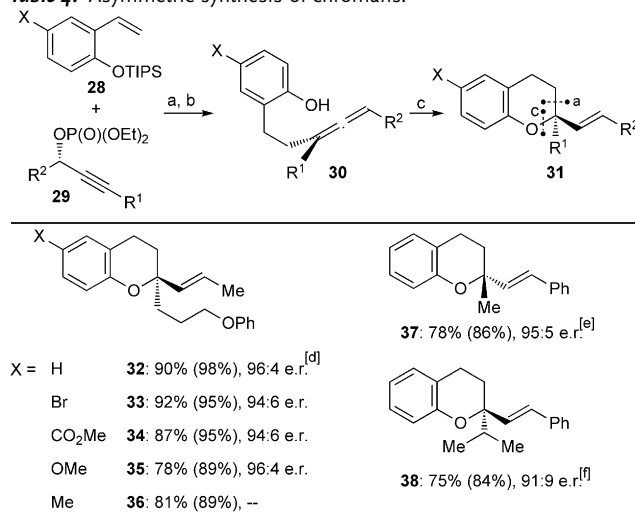


Entry	X	Cat. loading <sup>[a]</sup>	Y	Yield [%] <sup>[b]</sup>	CT [%]
1	H	10 mol %	TsO	92	87
2	H	10 mol %	PhCO <sub>2</sub>	92	98
3	OMe	10 mol %	PhCO <sub>2</sub>	58 <sup>[c]</sup>	98
4	OMe	5 mol %	4-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub>	> 95	93
5	OMe	5 mol %	4-(MeO <sub>2</sub> C)C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub>	> 95	94
6 <sup>[d]</sup>	OMe	2 mol %	4-(MeO <sub>2</sub> C)C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub>	89 <sup>[e]</sup>	94

[a] Equimolar amount of the gold precatalyst and a silver salt was used in all experiments. [b] Yield of the product as determined by GC analysis. [c] 60 % conversion after 48 h. [d] [allene] = 1 M. [e] Yield of the isolated product.

better results were obtained using a gold(I) benzoate catalyst (entry 2). Unfortunately, the reaction with a less reactive substrate **26** provided the desired product in only 58 % yield after 48 hours (entry 3). A faster reaction was observed using *p*-nitro and *p*-carbomethoxy benzoate catalysts, and the CT remained high (entries 4 and 5). Finally, we were able to achieve complete conversion with just 2 mol % of the catalyst within 48 hours by increasing the concentration of the substrate from 0.1 M to 1 M (entry 6).

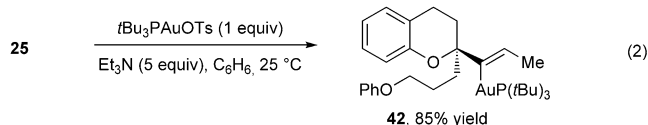
**Table 4:** Asymmetric synthesis of chromans.



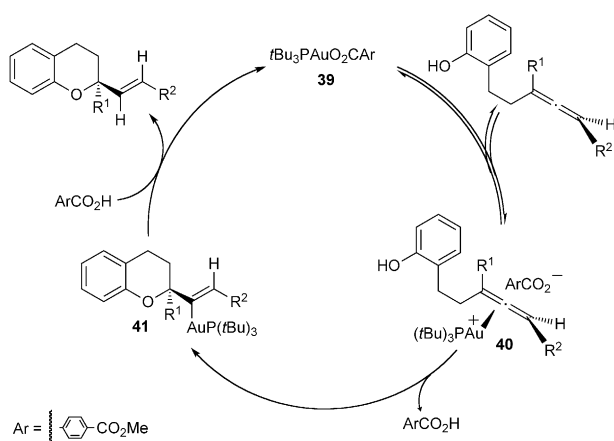
[a] **28** (1.2 equiv), 9-BBN (1.2 equiv), 1,4-dioxane, 60 °C, 12 h, then **29** (1.0 equiv), ICyCuCl (10 mol %), LiOtBu (1.0 equiv), *n*-pentane, 35 °C, 18 h. [b] TBAF (1.1 equiv), THF, 1 h, 25 °C. [c] *t*Bu<sub>3</sub>PAuCl (2 mol %), AgO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>(4-CO<sub>2</sub>Me) (2 mol %), toluene. [d] Yield of isolated product after three steps is reported. Yield of the cyclization shown in parentheses. [e] A phosphate with the opposite absolute configuration was used. [f] Propargylic phosphate with 96:4 e.r. was used.

As the results in Table 4 demonstrate, using the reaction conditions developed for intramolecular addition of phenols to allenes, the three-step synthesis of chromans can be accomplished with phenols containing both an electron-donating and an electron-withdrawing substituent (**32–36**). Furthermore, both large and small substituents at the tetrasubstituted stereocenter are tolerated (**32**, **37**, and **38**). Most importantly, the overall process is efficient, stereoselective, highly convergent, and relies on readily available starting materials. As a result, this process is a valuable addition to the existing methods for the asymmetric synthesis of chromans containing tetrasubstituted stereocenters.

The mechanism of the intramolecular *exo* hydroalkoxylation of allenes catalyzed by gold has been explored in detail by Widenhoefer and co-workers.<sup>[10,26b]</sup> Considering these and other investigations of the mechanism of the addition of nucleophiles to allenes<sup>[26]</sup> we anticipated that the reaction would proceed according to a mechanism resembling the one outlined in Scheme 4. In an effort to gain a more detailed understanding of the reaction mechanism, we isolated and characterized the proposed intermediate **42** [Eq. (2)]. When



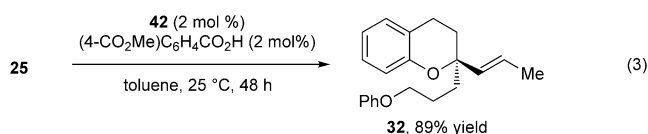
we monitored a catalytic reaction by in situ <sup>31</sup>P NMR spectroscopy we observed the gold(I) alkenyl intermediate **42** and complex **39** as the resting states of the catalyst.<sup>[21]</sup> This finding is in contrast to previous reports on closely related gold-catalyzed reactions of allenes wherein a digold(I) alkenyl complex is the resting state of the catalyst.<sup>[26b,c]</sup> We



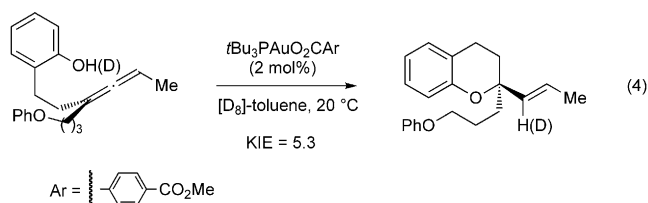
**Scheme 4.** Proposed mechanism.

speculate that a digold(I) alkenyl complex is not the resting state in our reaction because of the weakly electrophilic character of our catalyst and because of the presence of a highly coordinating counter ion.<sup>[27]</sup>

In further support of the idea that **42** is the intermediate in the catalytic reaction we have shown that in the presence of a catalytic amount of mono-methylterephthalic acid the isolated gold(I) alkenyl complex **42** is a competent catalyst for the cyclization of **25** [Eq. (3)].<sup>[28]</sup> We also found that when



**42** was treated with 1.5 equivalents of mono-methylterephthalic acid, the chroman **32** was obtained in 95% yield within 24 hours.<sup>[21]</sup> Interestingly, during the conversion of **42** into **32** we were not able to detect the formation of the allene **25**.<sup>[21]</sup> This observation, together with the <sup>31</sup>P NMR experiment which identified the resting state of the catalyst, suggests irreversible C–O bond formation.<sup>[29]</sup> Finally, a kinetic isotope effect (KIE) of 5.3, measured using deuterium-labeled phenol [Eq. (4)],<sup>[30]</sup> together with the observed resting states of the



catalyst, is consistent with the idea that protonation of the alkenyl gold intermediate is, at least partially, turnover limiting.

In conclusion, we have developed a catalytic method for asymmetric synthesis of cyclic ethers containing a tetrasubstituted stereocenter through the *exo*-selective cyclization of enantioenriched trisubstituted allenols. We demonstrated that the *exo*-selective cyclization is highly efficient and proceeds

with excellent diastereoselectivity and chirality transfer. We have also shown that in combination with the method for the synthesis of enantioenriched trisubstituted allenols recently developed by our group, the *exo*-selective cyclization of allenols constitutes a practical and convergent approach to the synthesis of THFs, THPs, and chromans containing a tetrasubstituted stereocenter.

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- [28] A control experiment in which **42** is omitted did not result in the formation of the cyclization product.
- [29] We thank one of the reviewers for suggesting this experiment.
- [30] The cyclization of the deuterium-labeled phenol ( $\geq 90\%$  *d*) afforded the deuterium-substituted chroman shown in Equation (4) in 96% yield with 89% deuterium incorporation. See the Supporting Information for details.