Enantioselective Synthesis

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Dimeric TADDOL Phosphoramidites in Asymmetric Catalysis: Domino Deracemization and Cyclopropanation of Sulfonium Ylides**

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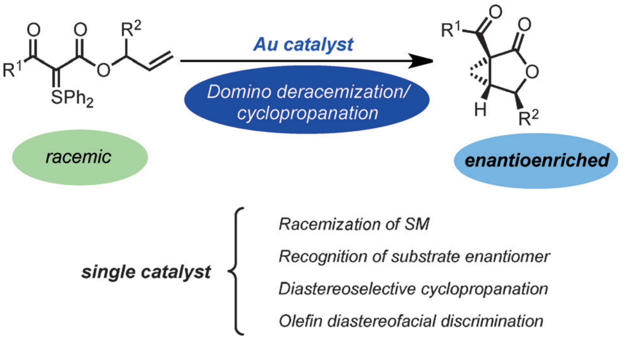
Abstract: *A gold-catalyzed asymmetric cyclopropanation of unactivated olefins with sulfonium ylides in the presence of a bimetallic catalyst with a novel dimeric TADDOL-phosphoramidite ligand is reported. This transformation allows a rare gold-catalyzed dynamic deracemization of chiral racemic substrates, where the same catalyst is responsible for several synergistic tasks in solution. The products are useful building blocks in synthesis and enable expeditious access to natural products.*

The deracemization of chiral and racemic starting materials by a given asymmetric reaction is one of the most valuable transformations in enantioselective organic synthesis. This is evident by the rise to prominence of kinetic resolutions and their powerful dynamic variants (DKR and DYKAT). The latter alternatives offer the possibility of quantitatively transforming both enantiomers of a racemic mixture into a new, optically pure product, effectively lifting the 50% theoretical yield limitation of the former.[1–4] Recently, much interest has been devoted to synergistic asymmetric catalysis, where two catalysts (and two catalytic cycles) work in concert to create new bonds in an enantioselective fashion. Several examples are known to operate according to this principle, such as dihydrofolate reductase,[5] dual transition-metal catalysis,[6] or the combination of a transition metal and organocatalyst.[7] A conceptual alternative would involve a finely tuned "super-ligand" able to accompany and assist the same metal during two (or more) different, asymmetric transformations.[8]

Recently, our group described a gold(I)-catalyzed intramolecular cyclopropanation of unactivated olefins with sulfonium ylides that proceeds through alkene activation.[9,10] Herein, we report an enantioselective intramolecular cyclopropanation of allylic esters through a synergistic effect in a bimetallic, dimeric catalyst framework.[11] In this process, an unusual and highly efficient deracemization takes place, whereby the same catalyst engages in two distinct, cooperative catalytic cycles and which results in a domino catalytic asymmetric transformation (Scheme 1).



Scheme 1. Gold-catalyzed deracemization of allylic esters.

Scheme 2 depicts a survey of various chiral gold(I) complexes used for the asymmetric cyclopropanation of substrate **1a** (for a detailed screening, see the Supporting Information). As shown, the class of TADDOL-derived phosphoramidites **L13–L16**, first employed in gold catalysis by Fürstner and co-workers,[12] gave the highest reactivity (enabling full conversion within a few hours) and good enantiomeric ratios.[13] Interestingly, other phosphoramidites such as SIPHOS-PE **L6** or the well-known BINOL derivatives **L7** and **L8**[14] showed only sluggish conversion along with poor enantioselectivity. In this initial survey, the best enantiomeric ratio of 81:19 was observed when 4-(*tert*-butyl)-phenyl was employed as the aryl substituent in the TADDOL backbone (cf. **L15**). Further manipulations of the backbone did not lead to any increase in enantioselectivity, and attempts involving chiral counterion strategies[15] led to a shutdown of reactivity (see the Supporting Information for further details).

In sharp contrast, the new dimeric ligand **L17** afforded the desired bicyclopropane **2** in an excellent enantiomeric ratio of 90:10 with a catalyst loading of only 2.5 mol%.

Particularly appealing from the outset was the prospect of employing substrates that carry branched allyl groups. We were aware that several substrates, such as methyl-substituted **3a**, were themselves chiral (racemic) compounds. Much to our surprise, subjecting *rac*-**3a** to the asymmetric cyclopropanation conditions with the dimeric ligand **L17** led to the

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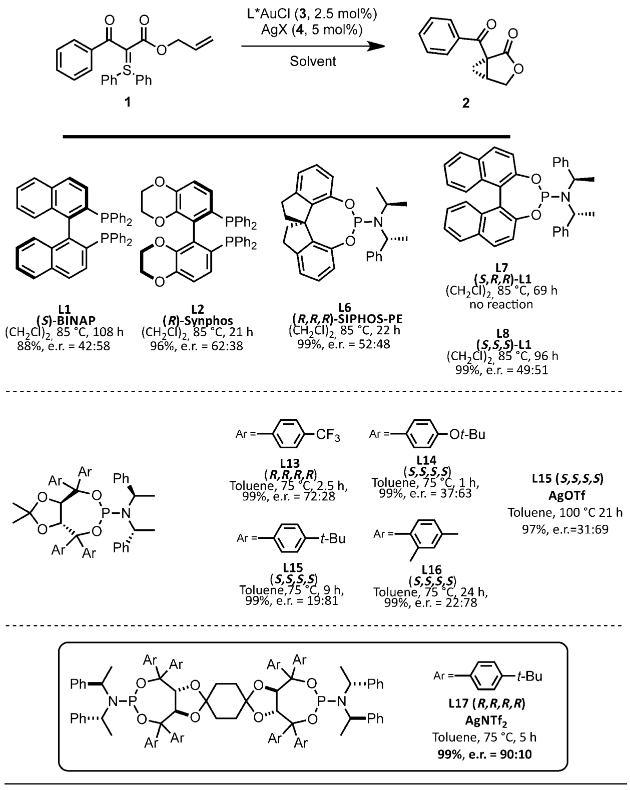
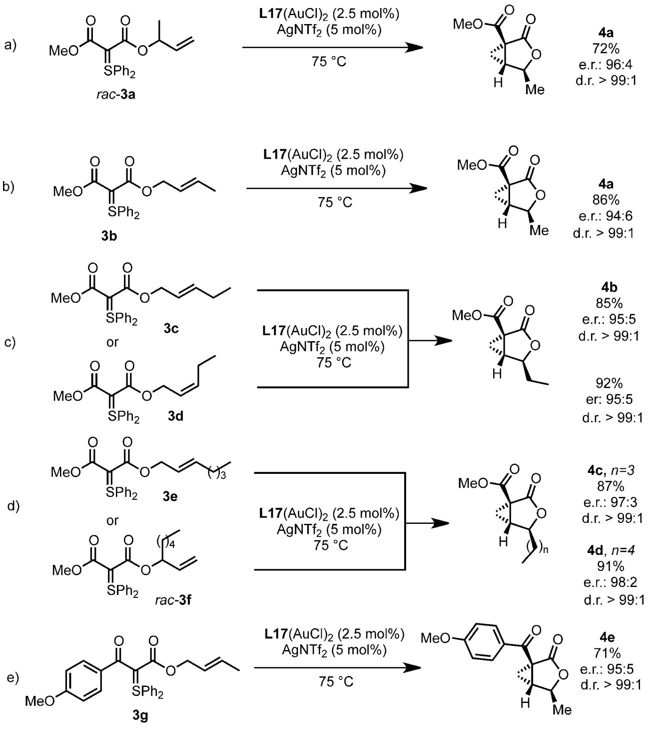


Scheme 2. Ligand screening for the asymmetric cyclopropanation of **1a**. Unless specified, AgX = AgSbF$_6$.



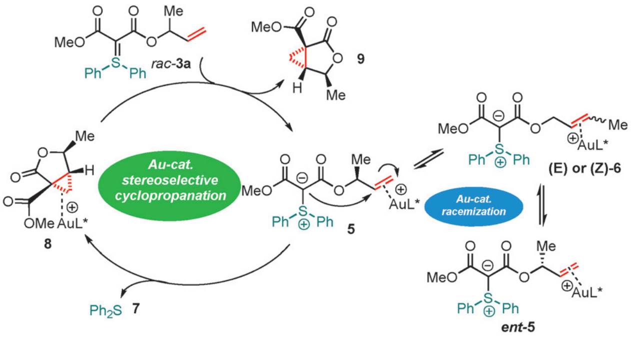
Scheme 3. Dynamic deracemization reactions promoted by **L17**.

cyclopropane product **4a** as a single diastereoisomer with an enantiomeric ratio of 96:4 (Scheme 3a). This result is all the more striking as the product is obtained in a 72 % yield, which clearly suggests a dynamic deracemization (rather than a simple kinetic resolution) process. Furthermore, the use of "linear" isomer **3b** (which is not a chiral compound; Scheme 3b) delivers the same cyclopropane **4a**, with levels of stereoselectivity nearly identical to those observed for the "branched" isomer *rac*-**3a**.

The results depicted in Scheme 3c further show how the double-bond geometry of the substrate is inconsequential (cf. the *E* and *Z* isomers **3c** and **3d**). Thus, it is possible to use starting materials with low geometrical purity (or even regioisomer mixtures) to produce diastereomerically pure, enantioenriched cyclopropanes, a significant synthetic advantage of this method. Variation in the length of the side chain is well tolerated in terminal or internal positions of the allylic tether (cf. **3e** and *rac*-**3f**, Scheme 3d). Ketoester-derived sulfonium ylide **3g** also delivers the desired bicyclopropane product **4e** in excellent selectivity.

The highly enantioselective transformations portrayed in Scheme 3 are remarkable as they constitute, to the best of our knowledge, unique examples of deracemizations promoted by gold catalysis.

The unique regio-, diastereo-, and enantioconvergence of this cyclopropanation reaction suggest the transient existence of a common intermediate and motivate us to propose the mechanism depicted in Scheme 4.[10] We believe that the substrate isomers must interconvert at a rate higher than that of the cyclopropanation reaction. The racemization of chiral racemic starting materials such as *rac*-**3a** is ensured by their dynamic conversion into the achiral, linear allylic isomers (cf. the equilibrium **5**⇌**6**⇌***ent*-5**).[16] Such an equilibrium would also account for the observed possibility of employing both isomeric forms (**5** or **6**), including double-bond isomers (i.e. (*E*)- or (*Z*)-**6**), of the starting material at will, and constitutes an interesting racemization mechanism with potential for further applications.

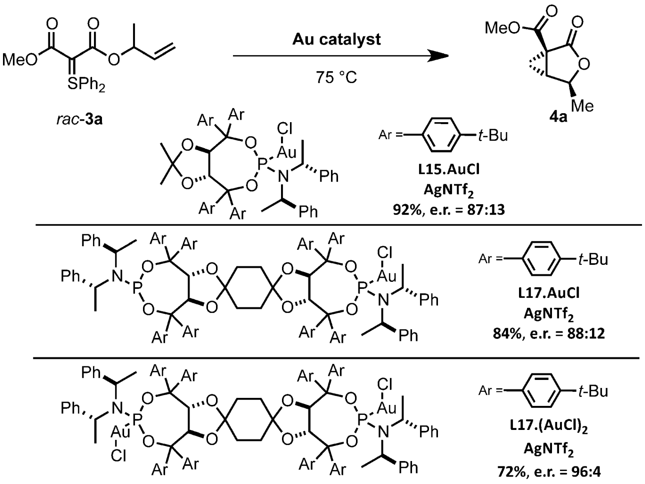


Scheme 4. Proposed mechanism of the dynamic deracemizing cyclopropanation.

We propose that the catalyst subsequently selects for those isomers carrying a terminal olefin appendage and effectively achieves highly enantioselective chiral recognition of only one enantiomer within the pair **5**/*ent*-**5**, thereby cyclopropanating that stereoisomer with very high diastereoselection.[17–19]

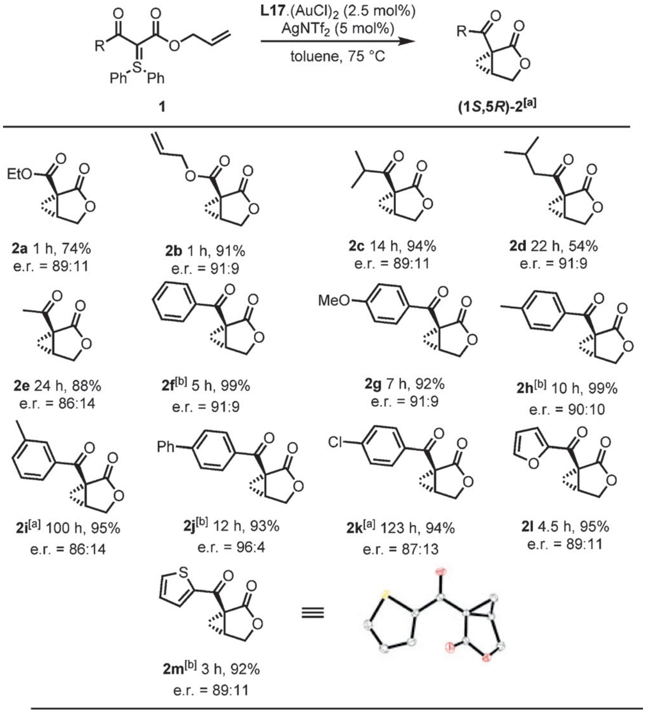
Here, the ability of the same gold catalyst to catalyze both a domino allylic isomerization and cyclopropanation sequence in high cooperativity with high regio-, diastereo-, and enantioselectivity is unprecedented.

A key structural feature of ligand **L17** is the presence of two phosphorus donor atoms. Under the reaction conditions each phosphorus atoms coordinates to one gold center in what is, effectively, a bimetallic species. This raises the question of whether the second metallic center has any noteworthy beneficial effect on the cyclopropanation reaction. The monomeric catalyst containing **L15** leads to a reduced enantioselectivity (e.r. 87:13) in the cyclopropanation of *rac*-**3a** (Scheme 5). Strikingly, monometallic **L17·AuCl**, bearing only one gold center for the dinuclear phosphoramidite ligand, performs in a virtually identical fashion towards substrate *rac*-**3a** (e.r. 88:12). Instead, the dinuclear gold catalyst **L17**·(AuCl)$_2$ is singularly able to promote the cyclopropanation with the highest enantioselection (e.r. 94:6), clearly demonstrating that a synergistic effect is imparted by the second metal center.[20]



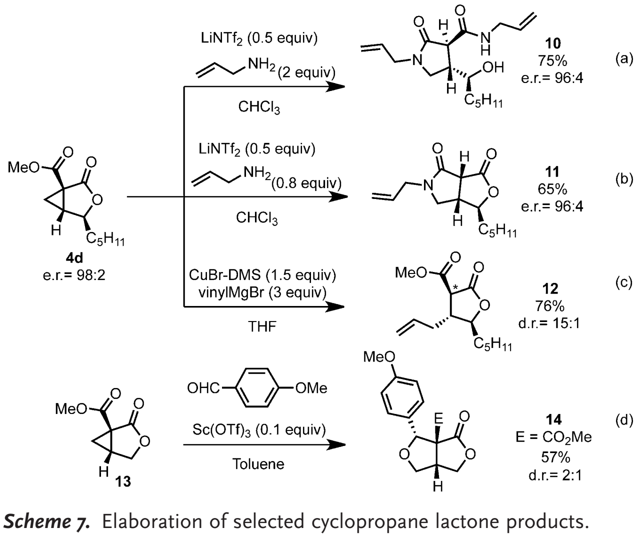
Scheme 5. Demonstration of the synergistic effect of the metal centers in the dynamic deracemization of *rac*-**3a**.

At this juncture, we further delineated the scope and limitations of this reaction (Scheme 6). Sulfonium ylides derived from malonates underwent cyclopropanation smoothly in short reaction times (Scheme 6, **2a** and **2b**). Furthermore, several ketoester-derived sulfonium ylides delivered the corresponding cyclopropanes in good to excellent yields, as did sulfonium ylides carrying aliphatic substituents (Scheme 6, **2c**–**2e**) or electron-rich aromatic groups (**2f**–**h** and **2j**). Heterocycle-bearing sulfonium ylides underwent cyclopropanation and afforded the corresponding cyclopropanes in excellent yields with high enantioselectivities (**2l** and **2m**). Several cyclopropanes readily crystallized to afford nearly enantiomerically pure substances (**2f**,**h**,**j**,**m**). For example, compound **2m** was obtained in a 98:2 enantiomeric ratio after crystallization, and the absolute configuration of the product was determined by X-ray crystallography to be (1*S*,5*R*). The cyclopropanation reaction could also be performed on a gram scale and the catalyst loading further decreased to 0.62 mol% with no loss in yield or enantioselectivity (see the Supporting Information for details).



Scheme 6. Substrate scope of the Au-catalyzed asymmetric cyclopropanation of sulfonium ylides. All the reported yields and e.r. values refer to pure isolated material. [a] Reaction performed with **L17**·(AuCl)$_2$ (5 mol%) and AgNTf$_2$ (10 mol%). [b] Recrystallization afforded the compound as enantiopure crystals, see the Supporting Information.

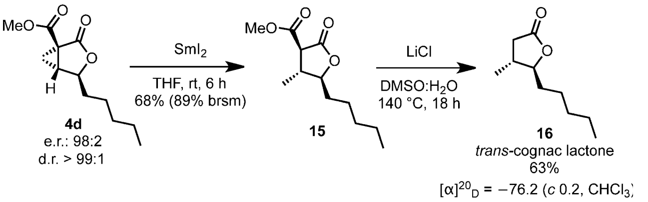
The cyclopropane products reported herein are useful synthetic intermediates in their own right (Scheme 7). For example, derivative **4d** could be subjected to ring opening with an amine nucleophile in the presence of the mild Lewis acid LiNTf$_2$. An excess (2 equiv) of amine leads to the highly functionalized lactam **10**. The use of only 0.8 equiv of the nucleophilic amine delivers the bicyclic product **11**.[21] The



Scheme 7. Elaboration of selected cyclopropane lactone products.

Michael acceptor nature of **4d** can be harnessed in a direct cuprate addition that generates lactone **12**.[22a] Furthermore, the strongly activated cyclopropane dicarboxylate moiety of the products results in a direct [3+2] cycloaddition to aldehydes being possible, thereby leading to furofuranones such as **14**.[22b–d]

The method reported herein also enables entry to the asymmetric synthesis of butenolide natural products. For example, *trans*-(−)-cognac lactone **16** could be easily prepared in two steps from cyclopropanation product **4d** (Scheme 8). SmI_2-mediated reductive cleavage of the cyclopropane followed by a Krapcho decarboxylation delivers the enantioenriched natural product **16** in good yield.[23]



Scheme 8. Asymmetric synthesis of *trans*-(−)-cognac lactone **16**.

In summary, we have developed a gold-catalyzed asymmetric cyclopropanation that delivers useful synthetic building blocks. Central to the realization of this endeavor was the design of a dimeric TADDOL-phosphoramidite ligand in a bimetallic gold catalyst, where the two metal centers work synergistically to enhance the enantioselectivity. Notably, this process is capable of achieving the dynamic deracemization of chiral racemic substrates by means of a domino allylic isomerization and enantio- as well as diastereoselective cyclopropanation. The same catalyst is responsible for several tasks in a process which, to the best of our knowledge, constitutes a rare dynamic deracemization phenomenon in gold catalysis.

Keywords: cyclopropanation · deracemization · enantioselective synthesis · lactones · total synthesis

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[16] For a related rearrangement, see N. Marion, R. Gealageas, S. P. Nolan, *Org. Lett.* **2007**, *9*, 2653. In control experiments, we have established that allylic isomerization requires the presence of the gold catalyst and is independent of the ylide appendage. See the Supporting Information for details.

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