Asymmetric Catalysis

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Catalytic Asymmetric Diastereodivergent Deracemization**

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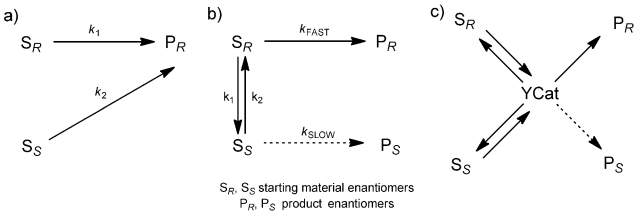
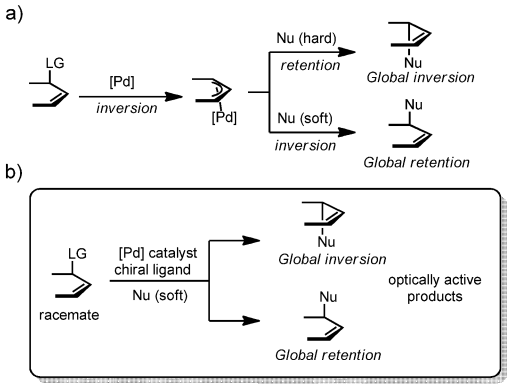
Despite the blossoming of asymmetric catalysis over the last few decades,[1] the majority of large-scale preparations of enantiopure compounds still rely on resolution techniques of racemates, wherein half of the starting material is wasted. In contrast, the catalytic "deracemization" of a racemate, leading to a theoretical 100% yield of enantiomerically pure product, is an attractive alternative strategy.[2] Enantioconvergent processes, dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DYKAT) are the most popular among catalytic deracemization methods (Scheme 1). Notably, all these state-of-the-art techniques



Scheme 1. Strategies for deracemization of a racemate. a) Enantioconvergent process. b) Dynamic kinetic resolution (DKR). c) Dynamic kinetic asymmetric transformation (DYKAT). Dashed arrows represent steps with low rate constant.

allow a maximum of two different products to be obtained (the two enantiomers of the product P).

The palladium-catalyzed allylic alkylation (also known as the Tsuji–Trost reaction) is a powerful and versatile synthetic tool for C–C bond formation that has been exhaustively studied over the past years.[3,4] Its textbook mechanism



Scheme 2. a) Conventional mechanism and stereochemical outcome of the palladium-catalyzed allylic alkylation (Tsuji–Trost reaction). b) Diastereodivergent deracemization through palladium-catalyzed asymmetric allylic alkylation.

typically involves two distinct, stereospecific steps (Scheme 2a): 1) the ionization of the allylic electrophile by the palladium catalyst, which proceeds with inversion, followed by 2) nucleophilic attack, which is nucleophile-dependent: "non-stabilized" nucleophiles (colloquially referred to as "hard") tend to attack the metal center, leading to retention through reductive elimination whereas "stabilized" carbon nucleophiles (typically referred to as "soft") lead to outer-sphere attack with inversion of configuration.[5] Since so-called "soft" nucleophiles are by far the most often employed, this led to the celebrated "double inversion = retention" textbook rule for palladium-catalyzed allylic alkylation.[3,6–11] We report herein on an unprecedented diastereodivergent ligand-controlled deracemization concept through palladium-catalyzed allylic alkylation, that offers potential access to each one of the possible stereoisomers of the product formed by deviating from the "double-inversion" rule. We propose the name "diastereodivergent deracemization" for this process (Scheme 2b).

We have already reported a racemic stereoselective synthesis of *cis*-substituted cyclobutenes **2**, in which the strained racemic lactone **1** (readily prepared from 2-pyrone in quantitative yield)[12] featured as the pivotal substrate (Scheme 3).[13] Given the high diastereoselectivities observed when triphenylphosphine (PPh_3) was employed as a ligand, we investigated the possibility of deracemization of **1** by the action of an enantiopure chiral ligand.[4]

At the onset of our ligand screening, we were surprised at obtaining both *cis*- and *trans*-disubstituted cyclobutene products in variable amounts, depending on the ligand employed (see Supporting Information). Notably, phosphoramidites

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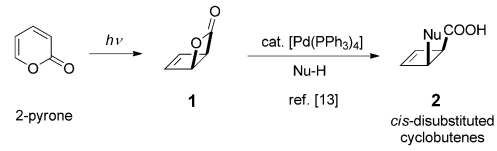
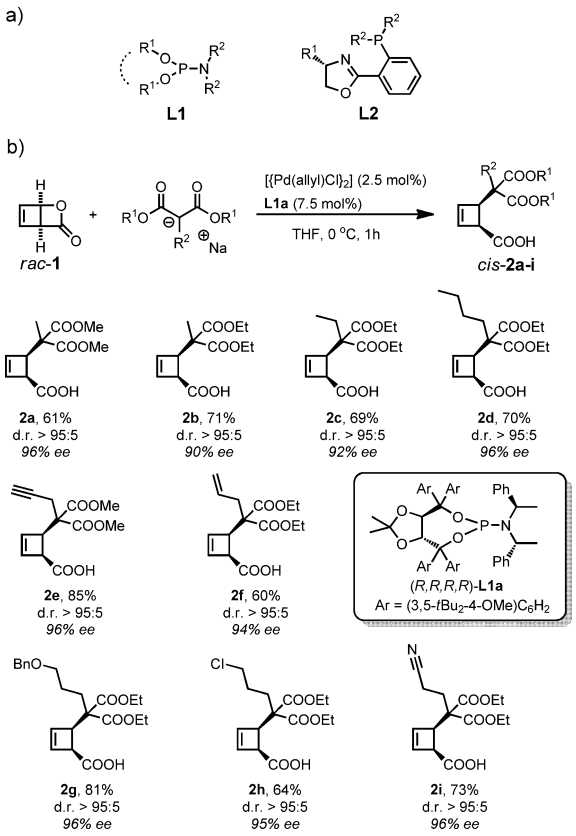


Scheme 3. Palladium-catalyzed diastereoselective synthesis of cyclobutenes.



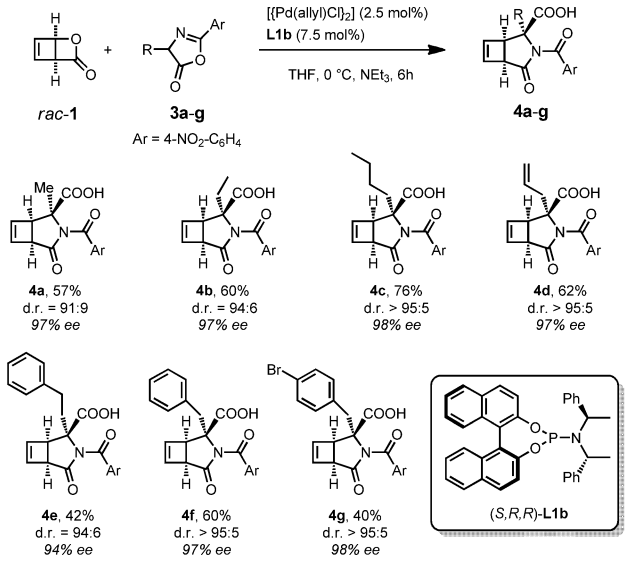
Scheme 4. a) Best-performing chiral ligands for the diastereodivergent deracemization process. b) Scope of malonate nucleophiles in the *cis*-selective diastereodivergent deracemization. Yields refer to analytically pure, isolated compounds; for compounds **2d**, **2e**, **2f**, **2h** the yields were determined by NMR spectroscopy (internal standard). The d.r. values were determined by NMR analysis of the crude mixture. The *ee* values were determined for the corresponding benzamides (see Supporting Information). For compounds **2c** and **2g** the reactions were performed using 5 mol% of [{Pd(allyl)Cl}$_2$] and 15 mol% **L1a**.

L1[14] tended to be highly *cis*-selective whereas phosphine oxazolines of the structural type **L2**[15] favored the formation of *trans* product (Scheme 4a).

As shown in Scheme 4b, use of the TADDOL-derived phosphoramidite **L1a**[16,17] afforded very high yields and enantioselectivities in the coupling of lactone **1** with malonate nucleophiles.[18] Importantly, a variety of functional groups was tolerated. The possibility of including polar moieties such as benzyloxy (**2g**), cyano (**2i**), or chloro (**2h**) also bodes well for further functionalization of the final products.[13] From a conceptual point of view, obtaining yields higher than 50% with consistently excellent enantioselectivities testifies to the process being a deracemization.

The desire to probe the generality of this asymmetric process with other "soft" nucleophiles prompted us to explore the reaction of electrophile **1** with azlactones **3**.[13] This transformation appeared to be more challenging in terms of overall stereocontrol, as it involves the merger of two prochiral entities leading to a product containing a total of three contiguous stereocenters.

Commercially available phosphoramidite ligand **L1b** proved to be the ligand of choice for the asymmetric synthesis of azabicycles **4a–g** (Scheme 5).[18] No decrease in the enantioselectivity was observed upon modification of the

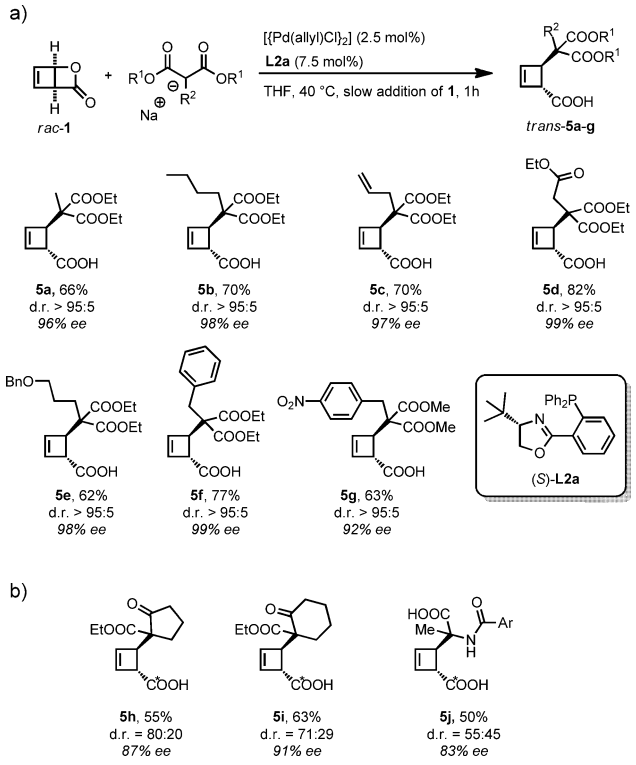


Scheme 5. Scope of azlactone nucleophiles in the *cis*-selective diastereodivergent deracemization. Yields refer to analytically pure, isolated compounds. The d.r. values were determined by NMR analysis of the crude mixture, and refer to the additional stereocenter.

substituent borne by the azlactone moiety. Remarkably, this transformation brings together two racemic substances (electrophile **1** and pronucleophile **3**) to generate one out of four possible stereoisomeric products **4a–g** with high levels of selectivity—a combination of catalyst-controlled enantioselection and powerful double diastereoselection.[13]

In striking contrast to the results described above, changing to the ligand **L2a** enabled the enantioselective preparation of the corresponding *trans*-stereoisomers. Thus, this ligand mediated the reaction of diverse nucleophiles with lactone **1** to produce *trans*-disubstituted cyclobutenes **5** (Scheme 6). Note that to obtain high yields and enantioselectivities, slightly modified reaction conditions were required. In particular, the slow addition of the electrophile to a warm (40°C) solution of palladium catalyst and nucleophile was found to be crucial.

Once again, the substrate scope proved to be quite broad (Scheme 6a) and common functional groups, such as esters, protected alcohols, olefins as well as nitro groups were well tolerated. As before, the yields well above 50% combined

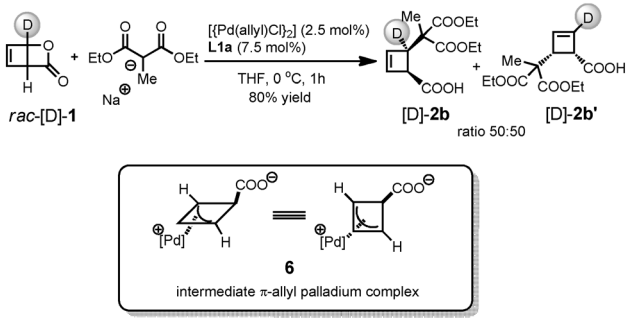


Scheme 6. a) Scope of malonate nucleophiles in the *trans*-selective diastereodivergent deracemization. The *ee* values were measured on the corresponding benzamides. The d.r. values were determined by NMR analysis of the crude mixture. b) Scope of additional nucleophiles for the *trans*-selective process. Yields refer to analytically pure, isolated compounds. The yield of **5j** was determined by NMR spectroscopy (internal standard). For **5** and **5i** the *ee* values were determined for the corresponding benzamides, and for **5j** on the dimethylester; these values refer to the major diastereoisomer. The d.r. values were determined by NMR analysis of the crude mixture. For **5h**, **5l**, and **5j**, exclusively *trans*-disubstituted cyclobutenes were obtained, the d.r. values refer to the center marked with *. See Supporting Information.

with remarkable enantioselectivities strongly suggest that a true deracemization process is operative. To our knowledge, there are no precedents of palladium-catalyzed asymmetric allylic alkylation with global inversion of configuration for "soft" nucleophiles, let alone processes that lend themselves to both inversion and retention of configuration, at will.

Following these results, we were intrigued by the ability of ligand **L2a** to bias the Tsuji–Trost reaction of lactone **1** towards formation of the *trans* product diastereoisomer with "soft" nucleophiles. Indeed, other classes of nucleophiles, such as β-ketoesters and azlactones also led to selective generation of the corresponding *trans* products (Scheme 6b). As depicted, β-ketoesters led to good levels of diastereoselection with excellent enantioselection for the major isomer. In the case of azlactones, the intramolecular cyclization that allows formation of an azabicyclic product in the case of the *cis*-selective process is geometrically impossible.[13] The *trans* cylobutene aminodiacid **5j** was therefore the product of this reaction.

Concerning the mechanistic details of this ligand-controlled diastereodivergent deracemization of lactone **1**, we assume that the expected *cis* products **2** and **4** arise from the well-established double inversion mechanism for Tsuji–Trost reactions, involving formation of a π-allyl complex on the face opposite to the leaving group followed by attack of the nucleophile *anti* to palladium (global retention, Scheme 2 and Scheme 3). It is anticipated that such a reaction would proceed through a symmetric π-allyl palladium complex **6** (Scheme 7), implying that the enantioselectivity of the process directly reflects the ability of the chiral ligand to



Scheme 7. *cis*-Selective deuterium labeling experiment employing substrate [D]-**1**. The yield was determined by NMR spectroscopy (internal standard). See Supporting Information.

direct the incoming nucleophile to only one of the two enantiotopic faces of the complex **6**. Clear evidence in support of this mechanism was obtained by treating deuterio-lactone [D]-**1** with a malonate salt in the presence of phosphoramidite ligand **L1b**, whereupon complete deuterium scrambling was found in the final product (see Supporting Information).

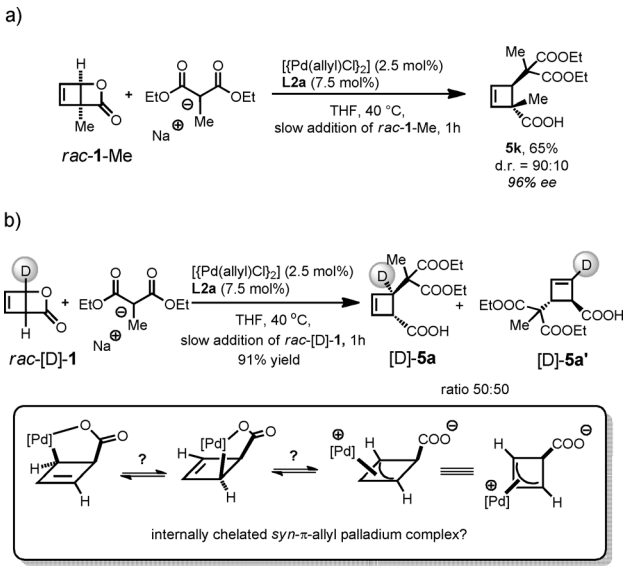
Concerning the unprecedented enantioselective *trans*-selective process mediated by ligand **L2a**, it is clear that a stereo-anomalous step must be involved. Four scenarios can in principle be envisaged: 1) *syn*-addition of the catalyst (i.e., retention upon oxidative addition), 2) isomerization of the complexed intermediate, 3) nucleophilic addition onto palladium followed by reductive elimination (analogous to what is observed for "hard" nucleophiles, see Scheme 2), or 4) quantitative epimerization of an intermediate *cis*-product.

Scenario 4 can be ruled out as we found the *cis*-products **5** to be perfectly stable under these reaction conditions and, in addition, the enantiomeric excess of the trace amounts of *cis*-isomer **2** formed using ligand **L2a** was always much lower than that observed for the *trans* analogue **5** (See Supporting Information). A direct nucleophilic addition of a malonate anion to palladium (Scenario 3) would be difficult to rationalize on electronic grounds. Scenarios 1 and 2 are, therefore, the most plausible ones.

Considering possible isomerization mechanisms for palladium allyl complexes (Scenario 2), Bäckvall and others have proposed[6d,7b,9] the direct displacement of palladium from a metal allyl complex by another palladium center. Such a mechanism, however, requires a strong dependence of the reaction outcome on the concentration of metal (i.e., the catalyst loading). In control experiments, we did not detect any significant change in enantio- or diastereoselectivity upon

modifying the catalyst loading across a three-fold range (see Supporting Information).

An alternative isomerization mechanism could involve loss of stereochemical information during the reaction (or upon workup) at the carboxylate-bearing stereocenter. Nevertheless, the formation of cyclobutene **5k** from substituted lactone **1-Me** in good yield and excellent diastereo- and enantioselectivity (featuring the diastereo- and enantiocontrolled generation of a quaternary stereocenter) precludes such a possibility (Scheme 8a). It is interesting that this transformation, along with the scrambling of deuterium in the



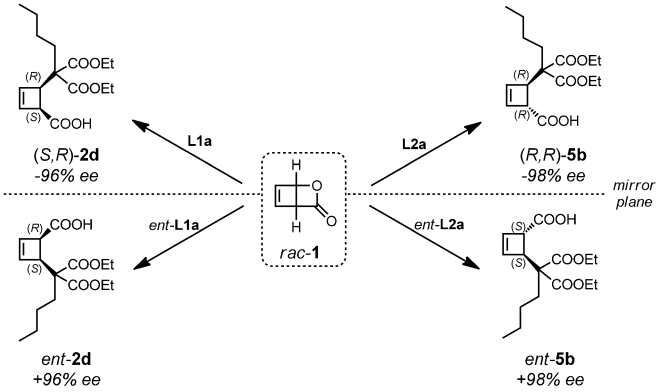
Scheme 8. a) Preparation of a cyclobutyl quaternary center through *trans*-selective diastereodivergent deracemization. b) *trans*-selective deuterium labeling experiment employing substrate [D]-**1**. The yield was determined by NMR spectroscopy (internal standard).

labeling experiment shown in Scheme 8b, strongly suggests that the *trans*-selective allylic alkylation mediated by ligand **L2a** also involves a transient symmetrization event.

The most likely pathway appears to be Scenario 1: a stereoretentive π-allyl generation in the presence of **L2a**, followed by "classical" nucleophilic attack on the opposite side of palladium. Although the reasons for this intriguing behavior are not clear, it is tempting to speculate that internal coordination from the pendant carboxylate may play a crucial role, as suggested in Scheme 8b.[7,8]

The method disclosed represents a deracemization process (i.e., the full conversion of a chiral racemic starting material into a single, enantioenriched product) in which the product has more than one stereogenic element (therefore allowing the existence of different diastereoisomers). The ability to selectively prepare each one of the possible stereoisomers of the final product simply by tuning of the reaction conditions leads us to propose the name "diastereodivergent deracemization". Although this definition includes several examples already reported,[19] we are not aware of any case in which n stereocenters of the racemic starting material (with $n \geq 2$) are manipulated to afford each one of the possible 2^m products (where m is the total number of stereogenic centers of the final product) in high levels of efficiency and selectivity.

The corollary of this postulate is shown in Scheme 9, where each and every one of the four different products (for diethyl(butyl)malonate as the nucleophile) could be prepared



Scheme 9. Preparation of four different products starting from racemic lactone **1** through diastereodivergent deracemization. See the Supporting Information.

in high selectivities by employing the enantiomers of ligands **L1a** and **L2a** (*ent*-**L1a**, *ent*-**L2a**).[20] Note the exceptional level of atom economy of these reactions combined with their stereoselectivity.[21]

Deracemization techniques that are amenable to structural but also stereochemical diversification clearly represent exciting avenues for further development in asymmetric catalysis, and we anticipate that the concepts presented herein will have a major impact on the field. Further experiments to fully understand, control, and ultimately design such processes are underway.

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