Asymmetric Catalysis

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Diastereodivergent De-epimerization in Catalytic Asymmetric Allylic Alkylation**

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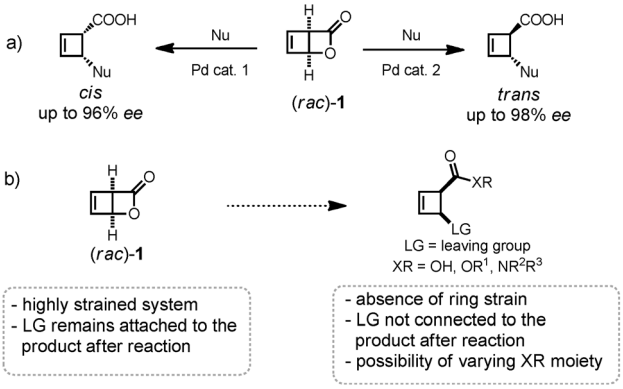
The deracemization of a racemic mixture has become a powerful alternative to classical resolution techniques, and dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DYKAT) represent the cutting-edge technologies in this field.[1] The ability to overcome the main drawback of simple kinetic resolutions (namely the maximum yield of enantiopure product of 50%) by directly transforming a racemic mixture into a single enantiopure product in 100% theoretical yield justifies the popularity of DKR and DYKAT. Despite impressive advances in this area, the deracemization of epimers or "de-epimerization"—in other words, the enantioselective and quantitative conversion of racemic mixtures of diastereomers—still presents a formidable challenge, and only rare examples are known. All prior reports in this field allow access to only one of the possible diastereoisomers of the product.[1d,2]

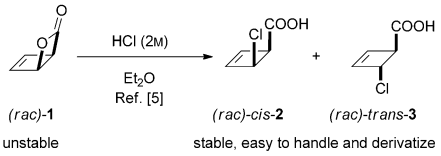
We have recently developed an unprecedented, palladium-catalyzed ligand-controlled diastereodivergent deracemization, with which the racemic lactone **1**[3] can be converted into any one out of four stereoisomeric products, in high selectivity (Scheme 1a).[4] At the outset, we wondered whether the diastereodivergent deracemization was a substrate-specific phenomenon or extendable to other systems. To address this issue, it was critical to evaluate two aspects: 1) the role played by internal coordination from the pendant carboxylate in the putative allyl–palladium intermediate; 2) the contribution of strain-release intrinsic to the bicyclic framework of lactone **1** (Scheme 1b).

Herein we present our results on these investigations and mechanistic insight into this phenomenon, as well as the discovery of a unique and hitherto unknown case of de-epimerization, termed diastereodivergent de-epimerization, wherein a racemic mixture of diastereoisomers is converted into each and every one of four possible stereoisomers of the product.



Scheme 1. a) Previous results on the diastereodivergent deracemization of (*rac*)-**1**. b) Design of a new system suitable for further investigation.

The *cis*-4-chlorocyclobut-2-ene carboxylic acid **2**[5] emerged as an ideal candidate for our studies (Scheme 2), since it possesses the same stereochemical pattern as **1** (*cis* configuration) and exhibits no marked release of ring strain associated with the departure of the leaving group, and the latter is not expressed in the final product. Compound *cis*-**2** would also provide the opportunity to manipulate the carboxylate moiety and study the reactivity of derivatives (Scheme 1b).



Scheme 2. Preparation of cyclobutenes *cis*-**2** and *trans*-**3**.

An efficient stereoselective synthesis of pure racemic *cis*-**2** and *trans*-**3** chloro carboxylic acid precursors was developed (Scheme 2).[5–7] Compounds **2** and **3** proved reasonably stable, in contrast to the highly labile nature of **1**. Moreover, whereas *cis*-**2**[7] might be seen as a surrogate of lactone **1**, the *trans* diastereomer **3** would represent a new system that might advance our understanding of this process.

We first examined the reactivity of racemic *cis*-**2**. Pleasingly, it was observed that a palladium-catalyzed diastereodivergent deracemization was operative. Under optimized conditions,[6,8] phosphoramidites[9] **L1a** and **L1b** were highly *cis*-selective, affording substituted cyclobutenes with excel-

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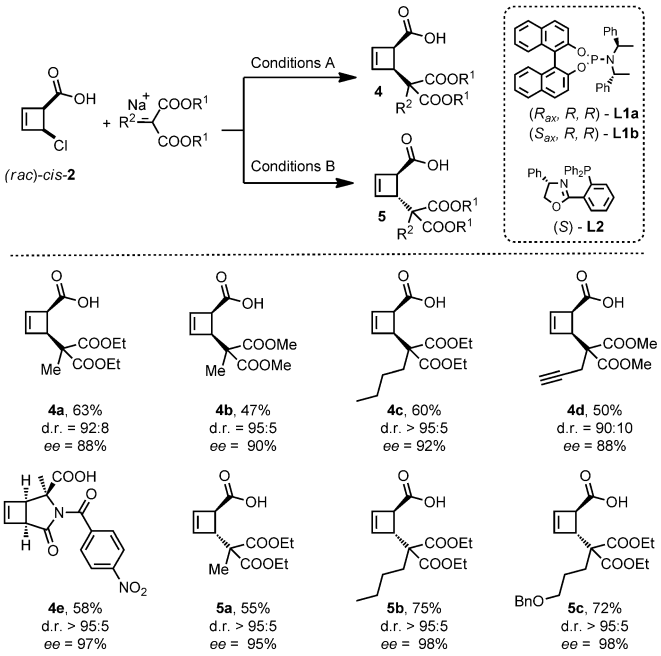
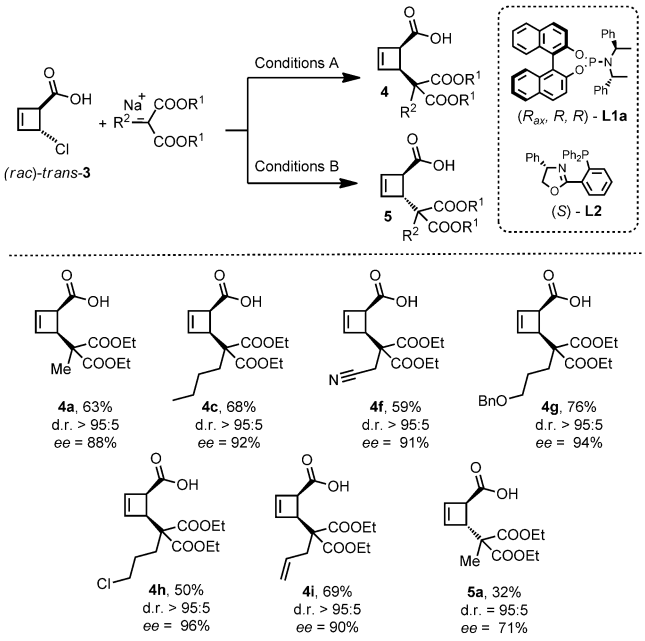


Scheme 3. Scope of the diastereodivergent process from the *cis*-**2**. Conditions A: 2.5 mol% [{Pd(allyl)Cl}$_2$], 7.5 mol% ligand **L1a**, CH_3CN, 0 °C. Conditions B: 2.5 mol% [{Pd(allyl)Cl}$_2$], 15 mol% ligand **L2**, THF, 40 °C, slow addition of (*rac*)-*cis*-**2**. The reaction that led to **4e** was performed with **L1b** in THF.



Scheme 4. Scope of the diastereodivergent process from the *trans*-**3**. Conditions A: 2.5 mol% [{Pd(allyl)Cl}$_2$], 7.5 mol% ligand **L1a**, CH_3CN, 0 °C. Conditions B: 5 mol% [{Pd(allyl)Cl}$_2$], 30 mol% ligand **L2**, THF, 30 °C.

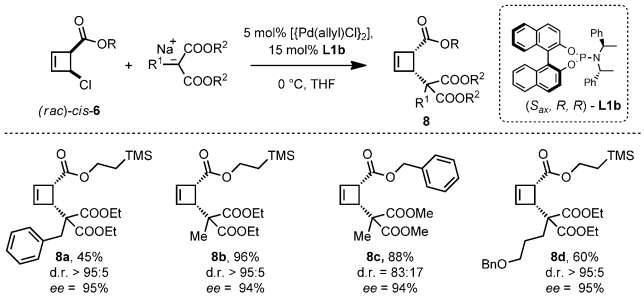
lent diastereo- and enantioselectivity for stabilized nucleophiles such as malonates and azlactones (Scheme 3). On the other hand, when phosphine-oxazoline[10] **L2** was employed, the *trans* isomer could be prepared with a high degree of efficiency (Scheme 3). From a theoretical point of view, yields higher than 50% along with high enantioselectivities suggest that a dynamic deracemization is operative.[11] Therefore, ring strain is not a prerequisite for this process, though we believe that its significant attenuation in *cis*-**2** might be responsible for the increased reaction times when **L2** is employed.

We subsequently investigated the reactivity of the diastereoisomeric, racemic *trans*-**3** (Scheme 4). To our surprise, under similar conditions **L1a** proved again to be *cis*-selective and products **4a–i** were isolated in very good to excellent levels of selectivity. This outcome was unexpected as we originally assumed that **L1a** mediated stereoretentive allylic alkylation by palladium catalysis.[12] As before, the substrate scope was broad and common functional groups were tolerated.[13]

When **L2** was employed, the reaction proved to be sluggish. Nevertheless, the *trans*-cyclobutene **5a** was obtained in modest yield as the major diastereomer (d.r. = 95/5) with reasonable enantioselectivity (Scheme 4).[14] The absence of detectable epimerization to *cis*-**2** or formation of lactone **1** during background experiments[6] supports the notion that *trans*-**3** is indeed the real substrate of the transformation.

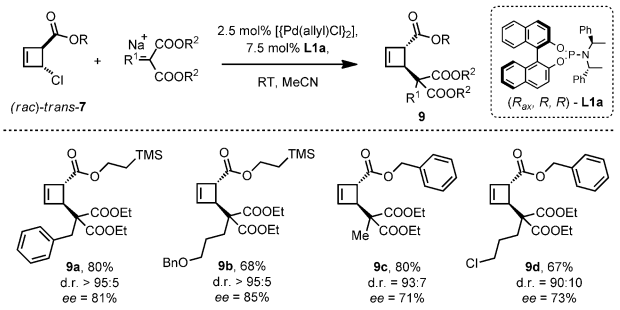
From these results, it appears that it is the stereochemical identity of the final product (i.e. *cis* or *trans*) and not the stereochemical outcome of the reaction (i.e. overall retention or inversion) which is controlled by the ligand. Strikingly, each ligand leads to a preferred product regardless of the stereochemical information of the starting material, and both ligands can mediate either overall retention or overall inversion (depending on the electrophile considered).

In order to probe the influence of the internal carboxylate moiety in this ligand-dependent process, esters **6** and **7** were prepared.[6] In the presence of **L1b**, the *cis* esters **6** were transformed into *cis*-disubstituted cyclobutenes **8a–d** in good yields and selectivities (Scheme 5). Surprisingly, **L2** was not a competent ligand for this transformation (the outcome of this reaction did not differ from the corresponding background reaction in the absence of catalyst).[6]



Scheme 5. Catalytic deracemization of esters (*rac*)-*cis*-**6**.

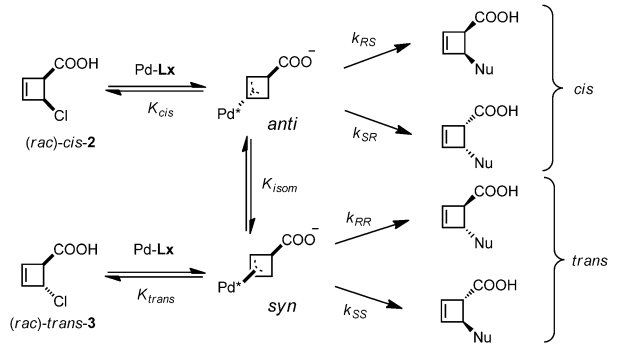
In sharp contrast to the results obtained with *trans* acid **3**, **L1a** smoothly mediated the conversion of *trans* esters **7** into *trans*-cyclobutenes **9a–d** (Scheme 6). Once more, ligand **L2** led only to trace amounts of racemic background products **9**.[6]



Scheme 6. Catalytic deracemization of esters (*rac*)-*trans*-**7**.

This contrast between the behavior of the free carboxylic acids (**2** and **3**) and their esters (**6** and **7**) is a salient feature of this system and highlights the crucial role of the carboxylate in enabling the diastereodivergent phenomena. Thus, the reactions of esters *cis*-**6** and *trans*-**7** proceed with overall retention of configuration, while still representing notable examples of DYKAT. The peculiar behavior observed with **L2**, for which the absence of the carboxylate moiety completely shuts down reactivity, shows that the -COOH moiety is actually a mandatory feature for activation of the Pd–**L2** complex (and eventual *trans* selectivity).

Comparison of data reported in Scheme 3 and Scheme 4 reveals that, for each nucleophile, the same enantiomer of the *cis* product is obtained with equal enantioselectivity (compare **4a** and **4c** in Scheme 3 and Scheme 4). This suggests that the key intermediate involved in the enantiodetermining step is the same when **L1a** is employed. We therefore propose a rationale through which the two π-allyl complexes originally formed from each starting material interconvert in a dynamic equilibrium (Scheme 7). This would correspond to a scenario

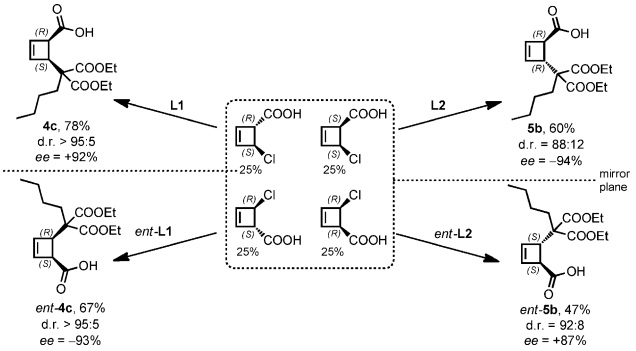


Scheme 7. Proposed mechanism for diastereodivergent de-epimerization.

characteristic of DYKAT,[1d] which is supported by the monitoring of *ee* values during the reaction.[6] The loss of the stereochemical integrity of the intermediate π-allyl complexes in allylic alkylation is a well-known phenomenon previously attributed to a number of factors, most commonly the direct nucleophilic displacement of palladium from a metal–allyl complex by a second, incoming palladium(0) center.[15]

In the case of ligand **L1a**, the observed preference for the *anti* π-allyl isomer (and therefore the *cis* product) is consistent with the minimization of charge repulsion between the negatively charged carboxylate and a neutral [LPd(Cl)(η^3-allyl)] intermediate. As a consequence, when the corresponding esters are employed this Coulombic interaction is absent and the aforementioned dynamic behavior is suppressed. The role played by the free carboxylate is even more crucial when the reactivity in the presence of ligand **L2** is considered.[16] Since **L2** is a bidentate nonsymmetrical P,N ligand,[17] the weaker σ-donation of the imino fragment to the metal may result in a more significant contribution of cyclometalated η^1-allyl intermediates, in which the carboxylate moiety of *cis*-**2** and *trans*-**3** can act as an additional ligand.[4] Without this internal chelation (as in the case of esters *cis*-**6** and *trans*-**7**), the reactivity of **L2** is therefore shut down, also suggesting that internal return[18] can become faster than outer-sphere nucleophilic attack.[19]

A remarkable consequence of the reactions reported herein is expressed in the following key experiment: A 1:1 mixture of diastereomers *cis*-**2** and *trans*-**3** (each one as a racemic mixture of enantiomers) was subjected to the optimized conditions. The corresponding *cis*- and *trans*-cyclobutene products were obtained in excellent yields and stereoselectivities (Scheme 8). In the event, a mixture containing a total of four different stereoisomers of the starting material was converted into each one of four stereoisomers of the product at will, with high selectivities, upon simple choice of the appropriate chiral ligand (Scheme 8).



Scheme 8. Diastereodivergent de-epimerization of a complex racemic mixture containing four stereoisomeric substances.

This represents a unique and, to the best of our knowledge, unprecedented example of the diastereodivergent de-epimerization of a mixture of two diastereomeric racemates. The remarkable ability of **L1a** and **L2** to control the stereochemical outcome of the reaction regardless of the stereochemistry of the starting material is noteworthy and unprecedented in palladium-catalyzed asymmetric allylic alkylation.

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[2] For examples of DYKAT type III, see: a) M. Edin, J. Steinreiber, J. E. Bäckvall, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5761–5766; b) A. B. L. Fransson, Y. M. Xu, K. Leijondahl, J. E. Bäckvall, *J. Org. Chem.* **2006**, *71*, 6309–6316; c) B. Martín-Matute, J. E. Bäckvall, *J. Org. Chem.* **2004**, *69*, 9191–9195. See also page S58 of the Supporting Information.

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[5] W. H. Pirkle, L. H. Mckendry, *J. Am. Chem. Soc.* **1969**, *91*, 1179–1186.

[6] See the Supporting Information for details and additional experiments.

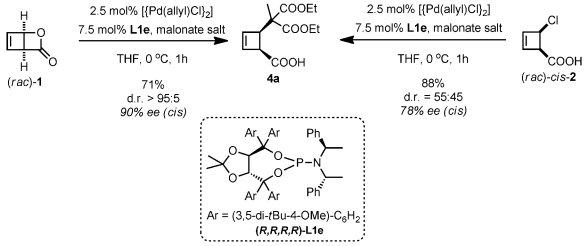
[7] The structure of *(rac)-cis* **2** was confirmed by X-ray analysis. CCDC 854277 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[8] An additional equivalent of nucleophile was added since in situ deprotonation of the carboxylic acid moiety of *cis*-**2** and *trans*-**3** consumes a similar amount.

[9] a) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353; b) J. F. Teichert, B. L. Feringa, *Angew. Chem.* **2010**, *122*, 2538–2582; *Angew. Chem. Int. Ed.* **2010**, *49*, 2486–2528.

[10] G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345.

[11] Two key experimental observations disprove the intermediacy of lactone **1** as a possible substrate of the transformation: 1) in background experiments in the absence of either palladium/ligand or nucleophile neither **1** nor products derived from it were detected; 2) when the best performing ligand (**L1e**) for **1** was employed, markedly inferior levels of diastereo- and enantioselectivity were obtained:



Similarly, *trans* products **5a**–**c** appear to arise directly from *cis*-**2**, since we never observed epimerization of *cis*-**2** to *trans*-**3** in control experiments (see the Supporting Information).

[12] a) B. M. Trost, D. L. VanVranken, *Chem. Rev.* **1996**, *96*, 395–422; b) Z. Lu, S. M. Ma, *Angew. Chem.* **2008**, *120*, 264–303; *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; c) B. M. Trost, T. Zhang, J. D. Sieber, *Chem. Sci.* **2010**, *1*, 427–440; d) G. Helmchen, U. Kazmaier, S. Förster in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 3rd ed., Wiley, Hoboken, **2010**, pp. 497–641; e) J. C. Fiaud, J. Y. Legros, *J. Org. Chem.* **1987**, *52*, 1907–1911.

[13] When azlactones served as the nucleophiles, no reaction occurred (unreacted starting *trans*-**3** was recovered when **L1b** was employed).

[14] After 48 h, conversion was not complete (48%) and the recovered starting material showed only a very modest enantioenrichment (6% *ee*); this ruled out a kinetic resolution process.

[15] Relevant literature on this topic (p. S58) as well as an outline of relevant experiments (p. S48 and Ref. [4]) can be found in the Supporting Information.

[16] Though *trans*-**3** is a less competent substrate than *cis*-**2**, it is noteworthy that both processes lead to the same major enantiomer of the product (compare product **5a** in Schemes 3 and 4).

[17] A. Pfaltz, W. Drury, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5723–5726.

[18] L. A. Evans, N. Fey, J. N. Harvey, D. Hose, G. C. Lloyd-Jones, P. Murray, A. G. Orpen, R. Osborne, G. J. J. Owen-Smith, M. Purdie, *J. Am. Chem. Soc.* **2008**, *130*, 14471–14473. When conditions for attenuation of ion-pair return were employed, only low yield and selectivity were observed for the product (see the Supporting Information for details).

[19] Additional experiments further support the proposal that bidentate coordination plays a key role in the *trans* diastereoselectivity. See the Supporting Information for details.

