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Deracemization of Quaternary Stereocenters by Pd-Catalyzed Enantioconvergent Decarboxylative Allylation of Racemic β -Ketoesters**

Justin T. Mohr, Douglas C. Behenna,
Andrew M. Harned, and Brian M. Stoltz*

Enantioconvergent catalysis is a powerful synthetic method that converts a racemic stereogenic substrate into an enantiomerically enriched product with a theoretical yield of 100% in a single operation.^[1] Conceptually, a catalytic system for such a reaction must achieve a stereomutation^[2] or stereoablation^[3,4] of the substrate (or an intermediate), followed by an enantioselective conversion into product (Figure 1, compare pathways I

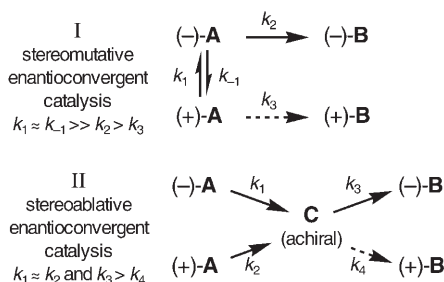
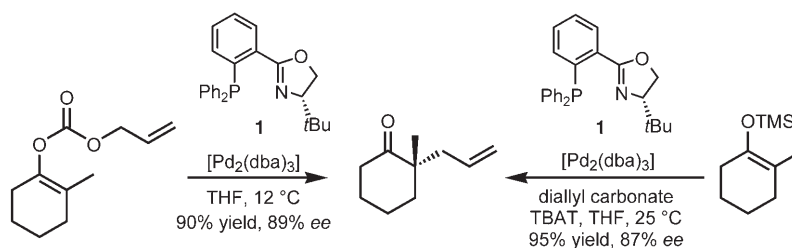


Figure 1. Stereomutative versus stereoablative enantioconvergent catalysis.

and II). A number of catalytic processes of this type have been developed, including chemical, enzymatic, and chemo-enzymatic strategies.^[1,2,4] Racemic compounds that contain quaternary carbon centers are typically unsuitable substrates for enantioconvergent catalysis because of the difficulty associated with C–C bond cleavage in the stereomutative or

stereoablative process.^[5,6] Herein, we describe the first catalytic system for the deracemization of quaternary carbon stereocenters. Our enantioconvergent method converts racemic α -substituted 2-carboxyallylcyclohexanones into highly enantioenriched cycloalkanones that bear quaternary stereocenters through catalytic asymmetric decarboxylative allylation.

We recently reported the first catalytic asymmetric allylation methods for the synthesis of 2-alkyl-2-allylcycloalkanones (Scheme 1).^[7] These reactions, based on racemic



Scheme 1. Enantioselective Tsuji allylations. dba = dibenzylideneacetone; TBAT = tetrabutylammonium difluorotriphenylsilicate; TMS = trimethylsilyl.

transformations reported in the early 1980s by Tsuji,^[8] use enol carbonates and silyl enol ethers along with various allyl carbonates and a Pd⁰ catalyst supported by a chiral phosphino-oxazoline ligand (e.g., **1**).^[9–11]

To demonstrate the utility of this methodology, we have started to employ these allylations as the key enantioselective reaction in multistep syntheses. In one such project, we required the substituted cyclohexenone **6** (Scheme 2). Unfortunately, the preparation of the allylation precursor **4** (R = CO₂allyl or SiMe₃) was hampered by nonselective enolization of **3** to form inseparable mixtures of **4** and **5**, which resulted in significant amounts of **7** after allylation.

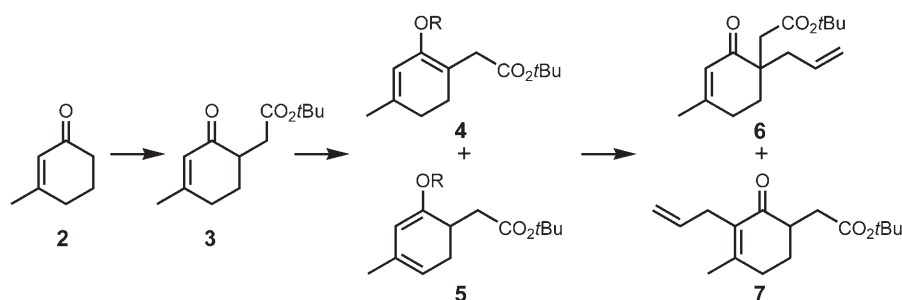
Prompted by the need for better position control in these synthetic sequences, we sought mechanistically guided alternatives to the reactions depicted in Scheme 1. To this end, we synthesized dideuterated carbonate **8** and trideuterated carbonate **9**. When **8** was subjected to our standard conditions for allylation, the deuterium label was almost evenly scrambled between the termini of the allyl fragment in the product (Scheme 3a).^[12] In a separate crossover experiment, the reaction of equimolar amounts of carbonates **8** and **9** was performed under our standard allylation conditions. As expected, NMR spectroscopic analysis of the product showed deuterium scrambling between the allyl termini, but interestingly, mass spectrometric analysis of the product showed an almost perfect statistical distribution of enolate and allyl fragment pairs with four possible masses (Scheme 3b).^[12] Thus, all six possible products were formed in the reaction including those derived from crossover reactions. Although the specific details associated with the enantiodiscrimination remain unclear, we hypothesized that a discrete achiral ketone enolate (namely, **10**) must exist in solution for some period to explain our observations.^[13]

We took this mechanistic insight into account, and so reasoned that the putative prochiral enolate needed for the

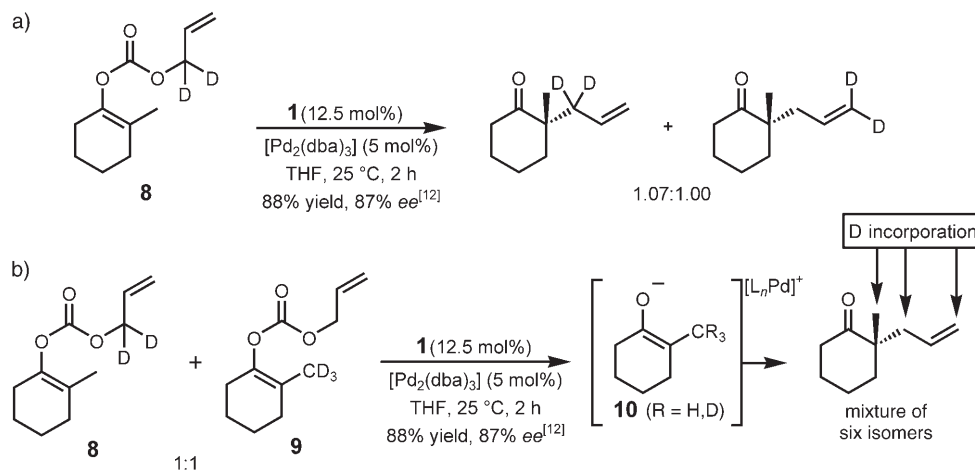
[*] J. T. Mohr, D. C. Behenna, Dr. A. M. Harned, Prof. B. M. Stoltz
The Arnold and Mabel Beckman Laboratories of Chemical Synthesis
Division of Chemistry and Chemical Engineering
California Institute of Technology
1200 E. California Boulevard
MC 164-30, Pasadena, CA 91125 (USA)
Fax: (+1) 626-564-9297
E-mail: stoltz@caltech.edu

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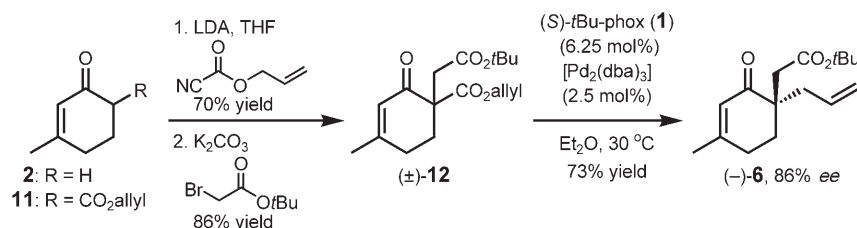
Scheme 2. Nonselective enol formation. R = anion.



Scheme 3. a) Deuterium-labeling experiment with enol carbonate **8**. b) Crossover experiment with deuterium-labeled enol carbonates **8** and **9**.

synthesis of **6** (namely, **4**; R = anion) could be derived through decarboxylation of a racemic β -ketoester precursor, such as (\pm) -**12** (Scheme 4).^[14] Moreover, this route would solve the enolization problem outlined above because the position-

In addition to changes at the α position, variation of the cyclic and allylic portions of the quaternary β -ketoester is tolerated (Table 2). Examples in which the cyclohexane ring has been substituted (entries 1–4), unsaturated (entry 5),



Scheme 4. β -Ketoester synthesis and enantioconvergent decarboxylative allylation. LDA = lithium diisopropylamide.

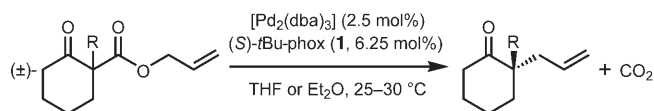
selective α -alkylation of ketoester **11** would be facile. We prepared β -ketoester (\pm) -**12** by acylation and alkylation of enone **2** to test the reaction (Scheme 4).^[15] To our delight, treatment of (\pm) -**12** with the complex derived from $[\text{Pd}_2(\text{dba})_3]$ and (S) -*t*Bu-phox ligand **1** in Et_2O exclusively produced allyl ketone **(-)-6** in 73% yield and with 86% *ee*. Importantly, β -ketoester **12** remained racemic throughout the course of the reaction, thus indicating that significant kinetic resolution of the starting material had not occurred. This

appended (entry 6), or enlarged (entry 7) proceed to products in high yield and enantioselectivity. Finally, substrates with internal allylic substitution (entries 8 and 9) and a racemic heterocycle (entry 10) also afford products in excellent yield and enantioselectivity.

With a general procedure for enantioconvergent decarboxylative allylation in hand and given our interest in tandem reactions and catalysis,^[16] we designed a substrate that could undergo a double allylation cascade to afford a product that possesses two all-carbon quaternary stereocenters. Thus, we prepared (\pm) -**13**, a substrate that contains a reactive enol carbonate and a latent β -ketoester moiety (Scheme 5).^[12] Treatment of (\pm) -**13** under our catalytic asymmetric conditions provided the double alkylation product in 76% yield as a 4:1 mixture of C_2 /*meso* diastereomers.^[17] Gratifyingly, the major diaster-

information, coupled with the product yield of over 50% and high enantiomeric excess, clearly demonstrates the enantioconvergent nature of the system (Figure 1, pathway II).

With the enantioconvergent decarboxylative allylation of (\pm) -**12** established, we investigated the scope of this unusual asymmetric transformation. In general, the system is highly tolerant to an array of functionalities and substitution patterns (Tables 1 and 2). A variety of α -substituted 2-carboxyallylcyclohexanones can be converted into products with high enantiopurity in excellent yields under the conditions for decarboxylative allylation (Table 1). The presence of enolizable functional groups (entries 4 and 5) and β -heteroatom substitution (entry 9) is of particular note. Furthermore, the 2-fluoro derivative (entry 10) allows for the high-yielding synthesis of stereodefined tertiary fluorides.

Table 1: Catalytic enantioconvergent decarboxylative allylation of α -substituted 2-carboxyallylcyclohexanones.


Entry	R	Solvent	T [°C]	t [h]	Yield [%] ^[a]	ee [%] ^[b]
1	CH ₃	THF	25	7.5	85	88
2	CH ₃	Et ₂ O	25	4.75	89	88
3	prenyl	Et ₂ O	30	6	97	91
4	CH ₂ CH ₂ CN	Et ₂ O	25	6.5	97	88
5 ^[c]	CH ₂ CH ₂ CO ₂ Et	Et ₂ O	25	6	96	90
6	CH ₂ C ₆ H ₅	THF	25	0.5	99	85
7	CH ₂ (4-CH ₃ OC ₆ H ₄)	THF	25	10	80	86
8	CH ₂ (4-CF ₃ C ₆ H ₄)	THF	25	0.5	99	82
9 ^[c]	CH ₂ OTBDPS	THF	25	5	86	81
10	F	Et ₂ O	30	3.5	80	91

[a] Yield of isolated product from reaction of 1.0 mmol substrate at 0.033 M in solvent, unless otherwise noted. [b] Determined by chiral GC or HPLC.^[12]

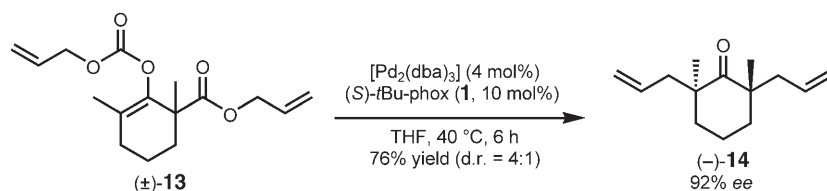
[c] Conditions: 4 mol % [Pd₂(dba)₃], 10 mol % (S)-tBu-phox (1), 0.021 M. phox = phosphinooxazoline; TBDPS = *tert*-butyldiphenylsilyl.

Table 2: Enantioconvergent decarboxylative allylation of β -ketoesters.

Entry	Substrate	Product	T [°C]	t [h]	Yield [%] ^[a]	ee [%] ^[b]
1			25	1.5	94	85
2 ^[c]			25	24	94	86
3			30	9	89	90
4			25	5	90	85
5 ^[d,e]			30	4	77	90
6 ^[d]			25	10	97	92
7			25	9.5	83	87
8 ^[d]			35	6.5	87	92
9 ^[d,e]			35	2.5	87	91
10			25	2.5	91	92

[a] Yield of isolated product from reaction of 1.0 mmol substrate, 2.5 mol % [Pd₂(dba)₃], and 6.25 mol % (S)-tBu-phox (1) at 0.033 M in THF, unless otherwise noted. [b] Determined by chiral GC or HPLC.^[12] [c] Conditions: 25 mmol substrate, 1.5 mol % [Pd₂(dba)₃], and 3.75 mol % (S)-tBu-phox (1).

[d] Performed in Et₂O. [e] Conditions: 4 mol % [Pd₂(dba)₃] and 10 mol % (S)-tBu-phox (1) at 0.021 M. Bn = benzyl.



Scheme 5. Enantioselective allylation cascade generating two quaternary carbon stereocenters.

omer (–)-**14** was obtained with 92% ee and bears two quaternary stereocenters set by a single catalytic asymmetric transformation.

In conclusion, we have developed the first example of a catalytic enantioconvergent synthesis of quaternary stereocenters from racemates with quaternary stereocenters. The decarboxylative allylation reaction described herein is an example of an enantioconvergent process in which the same catalyst is intimately involved in both the stereoablative (C–C bond-breaking) and stereoselective (C–C bond-forming) steps. The availability of racemic β -ketoesters of the type employed in this study greatly increases the practical value of these Pd-catalyzed allylations for the enantioselective synthesis of cyclic ketones with one or more quaternary stereocenters. The utility of this methodology for enantioselective synthesis of complex targets is currently under investigation.

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