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Mechanistic origin of the stereodivergence in decarboxylative allylation

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Abstract

A stereochemical test has been used to probe the mechanism of decarboxylative allylation. This probe suggests that the mechanism of DcA reactions can change based on the substitution pattern at the α-carbon of the nucleophile, however reaction via stabilized malonate nucleophiles is the lower energy pathway. Lastly, this mechanistic proposal has predictive power and can be used to explain chemoselectivities in decarboxylative reactions that were previously confounding.

Decarboxylative allylation reactions (DcA) have received considerable attention as methods for the asymmetric allylation of ketone enolates.[1,2] While much attention has been paid to the development of enantioselective decarboxylative allylations,[2] little attention has been paid to the investigation of the diastereoselectivity of DcA reactions.[3,4] Herein we report that the stereoselectivity of DcA reactions changes depending on the substitution of the substrate. We attribute the observed stereochemical reversal to a change in reaction mechanism.

As part of our efforts to develop chemical libraries derived from dihydrocoumarins, we became interested in the decarboxylative coupling of 3-carboxydihydrocoumarin derivatives.[5] Initial investigations showed that such substrates (**1a** and **1b**) readily undergo DcA at ambient temperature (Scheme 1). This is noteworthy since simple aliphatic diesters require high temperatures to effect decarboxylative coupling.[1f] In addition to the mildness of the reaction conditions, the high diastereoselectivities of the DcA reactions are remarkable. Since little attention has been paid to the diastereoselectivities of DcA reactions, we wanted to determine the relative stereochemistries of the coupling products. Fortunately, two analogs could be crystallized and analyzed by x-ray crystallography (Figure 1).[6] Intriguingly, the α-protio derivative **1b**, selectively produced *cis*-**2b** as the major diastereomer while the α-methyl derivative **1a**, produced *trans*-**2a** exclusively. Thus, on going from α,α-disubstituted malonic ester **1a** to an α-monosubstituted malonic ester **1b** *there was a complete reversal in stereochemical outcome of the allylation.*

One potential explanation for the reversal in stereoselectivity is that the α-protio compound **2b** simply undergoes base-catalyzed epimerization under the reaction conditions to form a more stable *cis* compound. However, simple MM2 calculations suggest that the *cis*- and

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trans-stereoisomers of **2b** are nearly equienergetic.[7] More convincingly, addition of independently synthesized *trans*-**2b** to a catalytic reaction mixture does not lead to any appreciable epimerization (Scheme 2); the small decrease in dr from 6.7:1 to 5.6:1 is attributed to the conversion of **1b** to *cis*-**2b** under the reaction conditions. Since epimerization of the α-stereocenter does not occur under the catalytic reaction conditions, the *cis*-selectivity must be kinetic in origin.

Next, a small variety of dihydrocoumarins were subjected to DcA reactions to test whether the stereochemical reversal would hold for multiple substrates (Table 1). Indeed the allylations of α-protio malonate derivatives selectively formed the *cis*-stereoisomer, while the α-alkylated derivatives produced the *trans*-products exclusively. While α-methyl dihydrocoumarins were formed with excellent diastereoselectivity, an α-benzyl derivative was formed with lower dr. Notably, a variety of functional groups (OMe, CF_3, Br, Cl, NO_2) were tolerated by the mild reaction conditions. It is also important to note that the dr of the product was independent of the stereochemistry of the reactant.[8] Such stereoconvergence is expected for reactions that proceed via planar enolate intermediates.

To explain the observed substitution-dependent stereochemical divergence, we propose that the two classes of substrates (α-protio vs. α-alkyl) react via different mechanisms. Indeed, two limiting mechanisms for decarboxylative coupling of allyl β-ketoesters have been proposed.[1d] The mechanisms differ mainly in the timing of two chemical events; mechanism A involves decarboxylation *prior to* allylation while mechanism B involves decarboxylation *after* allylation. More specifically, mechanism A involves formation of the π-allyl palladium carboxylate ion pair followed by decarboxylation to produce an allyl palladium enolate that is either directly bound to palladium or forms a tight ion pair with the cationic palladium allyl complex (Scheme 3). Allylation of the enolate provides the observed products.

Alternatively, formation of the π-allyl palladium carboxylate ion pair may be followed by a proton transfer from the α-carbon of the β-oxoester (pK_a ~ 14 in DMSO) to the carboxylate (pK_a ~ 12 in DMSO) (path B, Scheme 3).[9] This stabilized anion can undergo allylation followed by decarboxylation of the β-oxoacid to form the product.[8,10]

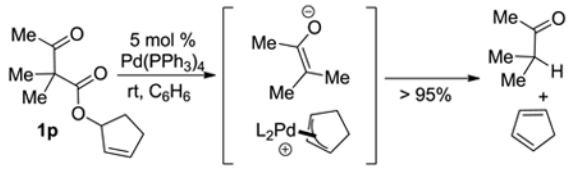
Aside from the different timing of steps, the two mechanisms differ in another critical area: the stereochemistry determining step. For mechanism A, the stereochemistry at the α-carbon is determined by allylation. For mechanism B, the stereochemistry at the α-carbon is determined by protonation. The conformation of the intermediate enolate most likely has a pseudo-axial aryl group (Scheme 4). We base this assumption on calculated conformational energies of similar half-chair dihydrocoumarin intermediates[11] as well as the fact that the crystal structure of the products **2a** and **2b** both contain pseudoaxial aryl groups (Figure 1). Thus, DcA of α,α-disubstituted malonate **1a** derivative which reacts via mechanism A is expected to proceed by addition of the allyl *anti* to the bulky aryl substituent (Scheme 4). Conversely, the reaction of the α-monosubstituted malonate derivative **1b** proceeds through mechanism B and thus the stereochemistry is determined by addition of a proton *anti* to the aryl group, producing the 3,4-*cis* product.[12,13]

If our mechanistic hypothesis is correct, we can further conclude that mechanism A is a higher energy pathway than mechanism B. This conclusion can be drawn because α-protio substrates like **1b**, which can react via either pathway A or B, react primarily via mechanism B.

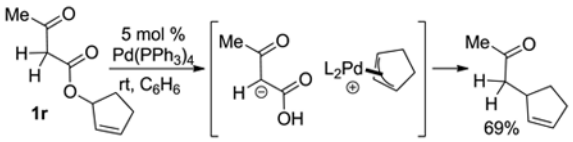
To further investigate the mechanism of decarboxylative allylation, the reactions of **1c** (α-protio) and **1d** (α-methyl) were monitored by ^{1}H NMR spectroscopy. While no intermediates were observed in the formation of **2d**, monitoring the reaction of **1c** revealed the growth and disappearance of a carboxylic acid. (Fig. 2).[8] This observation supports our

hypothesis that α-protio malonate derivatives react through path B (Scheme 3) and further suggests that decarboxylation is the rate-limiting step.

Ultimately, our observations suggest that α-protio malonate derivatives undergo DcA primarily through a mechanism that is different than that for α,α-dialkyl malonates. Such a proposal also readily explains differences in chemoselectivity exhibited in decarboxylative couplings of differently substituted β-ketoesters. For example, we predict that the dialkyl β-ketoester **1p** will react via mechanism A which goes through a basic enolate intermediate (eq. 1). Indeed, **1p** reacts exclusively by elimination when treated with $Pd(PPh_3)_4$. Alternatively, we predict that **1r** reacts via mechanism B and less basic stabilized enolate intermediates (eq. 2). In fact, the unsubstituted derivative **1r** provides high conversion to the allylated product with no observable elimination.[2l] Such a result is not easily ascribed to sterics alone since large, carbon-based nucleophiles are readily allylated by α-allyl palladium complexes.[14] However, the results are readily interpreted using our proposed mechanistic dichotomy.



(1)



(2)

In conclusion, the divergent stereoselectivity of DcA reactions with differently substituted β-oxo esters is readily explained by the operation of two competing mechanisms. Furthermore, the results reported herein indicate that DcA reactions that proceed via stabilized malonate nucleophiles is the lower energy pathway. Lastly, this mechanistic proposal has predictive power and can be used to rationalize chemoselectivities in decarboxylative reactions that were previously unexplained.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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4. Single examples suggest that 1,3 and 1,4-diastereocontrol in double decarboxylative allylations is not high. See footnote 2d and Enquist JA Jr, Stoltz BM. Nature. 2008; 453:1228. [PubMed: 18580947]
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6. Attempts to crystallize the direct analog of **2a** failed, so **2b** was used for confirmation of stereochemistry by crystallography.
7. Using the MM2 force field of ChemBio 3D indicates that *cis*-**2b** is more stable than *trans*-**2b** by 0.1 kcal/mol.
8. See supporting information for details.
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13. Asymmetric decarboxylative protonation reactions deliver protons to the same prochiral enolate face that is allylated in decarboxylative allylations. Compare footnote 2d with Mohr JT, Nishimata T, Behenna DC, Stoltz BM. J Am Chem Soc. 2006; 128:11348. [PubMed: 16939246]
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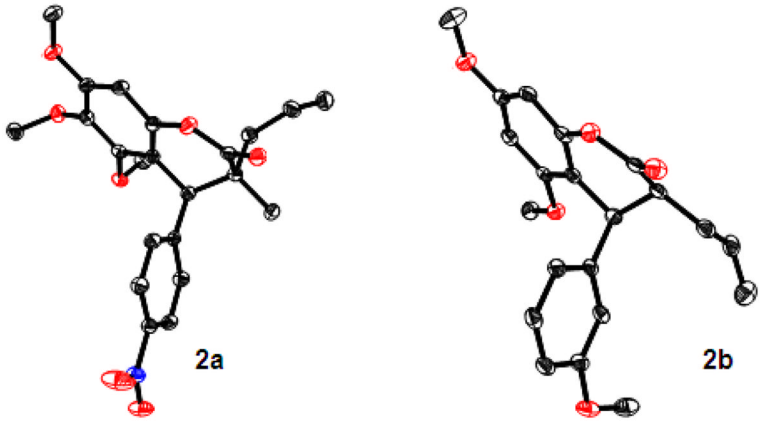


Figure 1.
Crystal structures of **2a** and **2b**

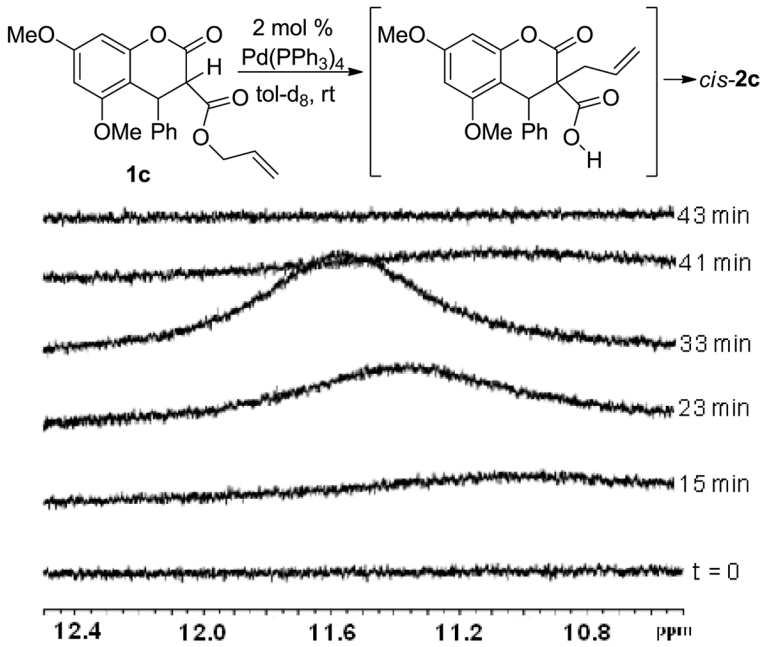
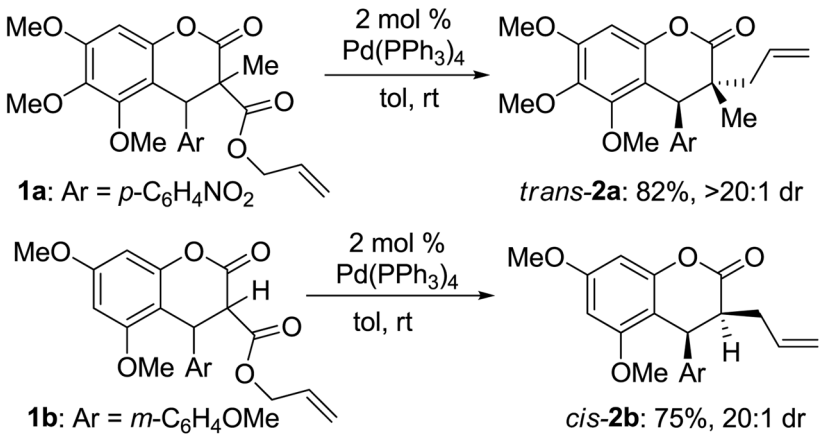
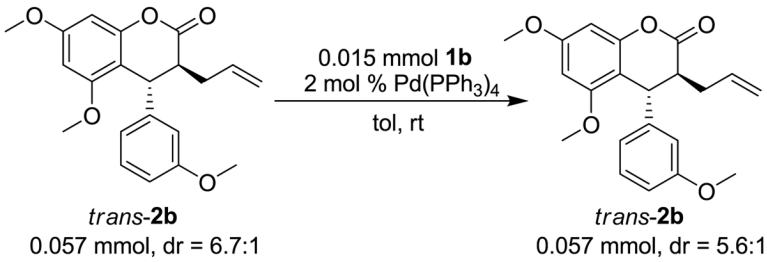


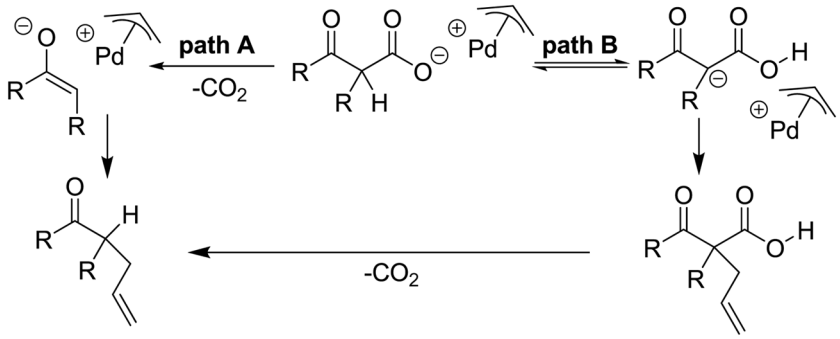
Figure 2.
Observation of intermediate carboxylic acid.



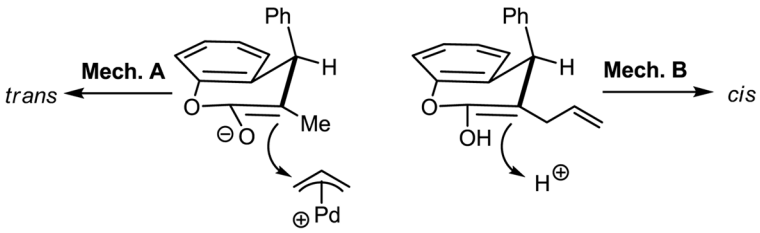
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

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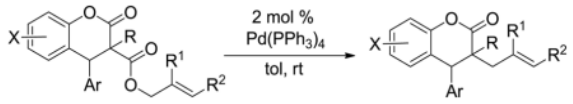
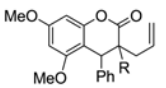
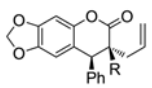
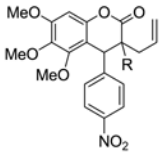
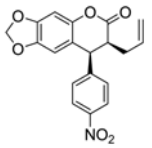
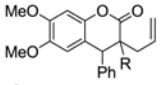
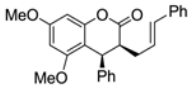
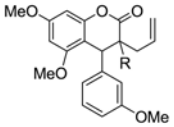
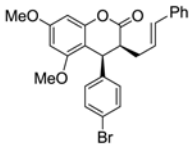
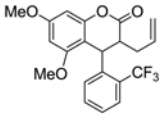
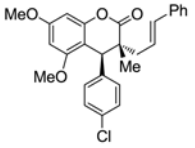
Table 1

Diastereoselective allylation



product	R	yield (*trans:cis*)	product		yield (*trans:cis*)
 **2c** **2d**	H	72% (1:18)	 **2j** **2k**	Me	92% (>20:1)
	Me	90% (>20:1)		Bn	92% (2.8:1)
 **2e** **2a**	H	60% (1:10)	 **2l**		60% (1:5.6)
	Me	82% (>20:1)			
 **2f** **2g**	H	80% (1:10)	 **2m**		70% (1:18)
	Me	88% (>20:1)			
 **2b** **2h**	H	75% (1:20)	 **2n**		72% (1:18)
	Me	90% (>20:1)			
 **2i**		90% (1:13)	 **2o**		80% (10:1)[a]

[a] 10:1 linear: branched, branched dr= 1:1