

Stereospecific Decarboxylative Allylation of Sulfones

Jimmie D. Weaver, Being J. Ka, David K. Morris, Ward Thompson, and Jon A. Tunge*

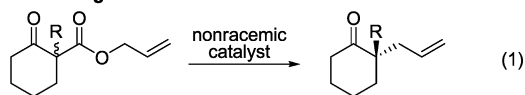
Department of Chemistry, The University of Kansas, 2010 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045

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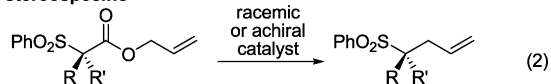
Abstract: Allyl sulfonylacetate esters undergo highly stereospecific, palladium-catalyzed decarboxylative allylation. The reaction allows the stereospecific formation of tertiary homoallylic sulfones in high yield. In contrast to related reactions that proceed at $-100\text{ }^{\circ}\text{C}$ and require highly basic preformed organometallics, the decarboxylative coupling described herein occurs under mild nonbasic conditions and requires no stoichiometric additives. Allylation of the intermediate α -sulfonyl anion is more rapid than racemization, leading to a highly enantiospecific process. Density functional theory calculations indicate that the barrier for racemization is 9.9 kcal/mol, so the barrier for allylation must be <9.9 kcal/mol.

Catalytic decarboxylative coupling is a powerful method for C–C bond formation that avoids the use of strong bases and/or preformed organometallics that are typically required for cross-coupling reactions. In 2004, we reported the first asymmetric decarboxylative allylation of enolates.¹ This was followed by several reports of decarboxylative enolate allylations that allow enantioselective formation of quaternary carbon centers α to ketones.² Since these reactions proceed through achiral enolate intermediates, the reactions are stereoconvergent, allowing racemic starting materials to form highly enantioenriched products (eq 1). Stereoconvergence is a common reaction profile in carbanion chemistry, where resonance-stabilized carbanions often exist as planar achiral intermediates and unstabilized carbanions rapidly racemize by inversion.³ Herein we report that optically active sulfonylacetate esters undergo enantiospecific decarboxylative coupling in which the original stereochemistry is maintained in the product (eq 2). Furthermore, density functional theory (DFT) calculations are used to examine the origin of the enantiospecificity.

stereoconvergent

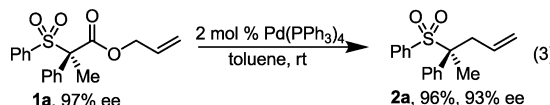


stereospecific



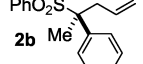
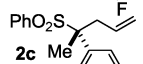
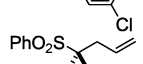
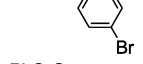
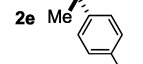
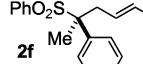
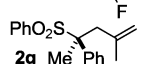
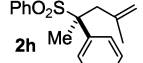
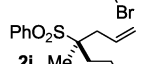
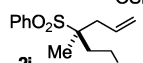
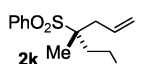
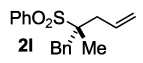
From the elegant work of Corey and Cram in the early 1960s, it has been known that the decarboxylative protonation of sulfonylacetate esters is stereospecific.⁴ While there are several examples of stereospecific decarboxylative protonations,^{4,5} none has been extended to C–C bond-forming reactions. With this in mind, we set out to develop a stereospecific decarboxylative C–C bond-forming reaction.

To begin, sulfone **1a** was synthesized and treated with 2 mol % $\text{Pd}(\text{PPh}_3)_4$ in toluene at room temperature (eq 3).⁶ It was gratifying to find that the decarboxylative allylation was highly stereospecific, with a conservation of enantiomeric excess (cee) of 96% [cee = $100 \times (\text{product ee})/(\text{reactant ee})$].



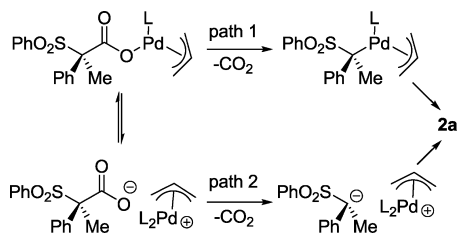
Next, a variety of different enantioenriched sulfones were similarly subjected to the conditions for palladium-catalyzed

Table 1. Stereospecificities of Decarboxylative Allylation

entry	reactant ee(%) ^c	product	procedure ^a	yield (%) ^b	ee (%) ^c	cee (%) ^c
1	46		A	96	43	91
2	89		A	99	87	98
3	97		A	99	96	99
4	61		A	99	61	99 ^d
5	73		A	99	69	96 ^d
6	97		A	99	93	96
7	80		A	99	80	99
8	94		B	82	92	99
9	94		B	95	92	98
10	>99		B	97	>99	>99
11	98		B	85	95	97
12	98		B	93	95	97

^a Conditions A: 2 mol % $\text{Pd}(\text{PPh}_3)_4$, 0.2 M toluene, $23\text{ }^{\circ}\text{C}$, 0.25–2 h. Conditions B: 5 mol % Pd_2dba_3 , 10 mol % ($\pm$)-binap, 0.2 M toluene, $95\text{ }^{\circ}\text{C}$, 11–15 h. ^b Isolated yields. ^c Determined via chiral stationary phase HPLC analysis. ^d Linear/branched = 8:1.

Scheme 1



decarboxylative coupling. As can be seen from the data in Table 1, a variety of α -aryl and α,α -dialkyl sulfones all undergo decarboxylative allylation with a high degree of stereospecificity. It is noteworthy that high *ee*'s were obtained even at elevated temperatures (95 °C). Moreover, our reaction proceeds under formally neutral conditions, in contrast to more classical alkylations of sulfones, which typically require stoichiometric, highly basic organolithium reagents.⁷ Lastly, the X-ray crystal structure of a derivative of **2k** confirmed that the allylation proceeds with overall retention of configuration.⁸

The overall retention of stereochemistry in the decarboxylative allylation can be explained if the decarboxylation directly produces either a configurationally stable alkylpalladium complex that undergoes reductive elimination (path 1 in Scheme 1) or if decarboxylation produces a configurationally stable α -sulfonyl anion that attacks the palladium π -allyl complex (path 2 in Scheme 1).⁹

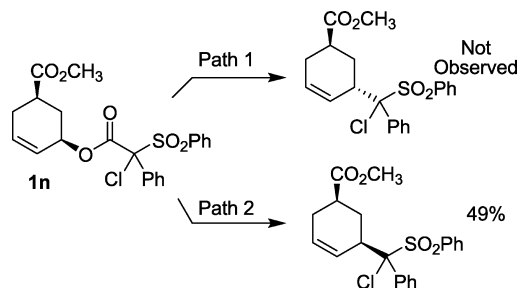
To begin to address whether path 1 or 2 (Scheme 1) is operative, we investigated the effect of palladium on the rates of decarboxylation of several α -sulfonylacetates. Control studies showed that the rate of decarboxylation is relatively unaffected by the addition of a variety of palladium sources (Table 2).⁸ For example, the cesium or triethylammonium salts of α -sulfonylacetic acids readily decarboxylate under our reaction conditions. Addition of $\text{Pd}(\text{OAc})_2$ or $(\text{Ph}_3\text{P})_2\text{Pd}(\text{allyl})\text{Cl}$ to these reaction mixtures does not substantially affect the rate of decarboxylation.¹⁰ When palladium is directly involved in the decarboxylation, such experiments usually show a dramatic acceleration of the decarboxylation.¹¹ Ultimately, Corey and Cram have detailed thermal decarboxylations of α -sulfonylacetates under conditions similar to those used by us,⁴ and we failed to observe catalysis of decarboxylation by palladium. Thus, the simplest conclusion is that decarboxylation of the α -sulfonylcarboxylates is a thermal process that proceeds via path 2.

Table 2

$\text{PhO}_2\text{S}-\text{C}(\text{R})(\text{R}')-\text{CO}_2\text{H} \xrightarrow[\text{toluene-d}_8]{\text{conditions}} \left[\text{PhO}_2\text{S}-\text{C}(\text{R})(\text{R}')-\text{CO}_2^- \right] \rightarrow \text{PhO}_2\text{S}-\text{C}(\text{R})(\text{R}')-\text{H}$						
R	R'	conditions	Pd source	time	% conv.	
H	H	95 °C, Et_3N	none	5 min	17	
H	H	95 °C, Et_3N	100 mol % $\text{Pd}(\text{allyl})\text{Cl}(\text{PPh}_3)_2$	5 min	23	
Me	Bn	95 °C, Et_3N	none	45 min	25	
Me	Bn	95 °C, Et_3N	10 mol % $\text{Pd}(\text{OAc})_2$	45 min	27	
Me	H	23 °C, Cs_2CO_3	none	36 h	59	
Me	H	23 °C, Cs_2CO_3	10 mol % $\text{Pd}(\text{OAc})_2$	36 h	59	

Reaction via path 1 or path 2 can also be distinguished via the observed diastereoselectivity in nucleophilic attack of a stereochemically labeled allyl ester substrate (Scheme 2).¹² In such a reaction, nucleophiles that are bound to palladium prior to reductive elimination, as in path 1, would react with overall inversion of configuration. Alternatively, if the free nucleophile directly attacks the allyl ligand, as in path 2, then one would observe retention of stereochemistry by way of the standard double-inversion mecha-

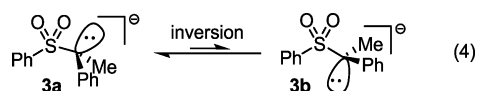
Scheme 2



nism.¹² Toward this end, substrate **1n** was prepared and allowed to react under our standard reaction conditions (Scheme 2).¹³ The reaction produced the 1,3-*cis* diastereomer as the only C–C bond-forming product in 49% yield,¹⁴ suggesting that the decarboxylative coupling proceeds via attack of an α -sulfonyl anion on the back side of the palladium π -allyl complex (path 2 in Scheme 2). While we could not generate the α -chloro- α -sulfonyl ester in enantioenriched form in order to test the enantiospecificity of the coupling, the product was formed as a 1:1 mixture of diastereomers at the sulfonyl stereocenter. Thus, the stereochemistry at the α -position did not change during the reaction, which is consistent with a stereospecific process.

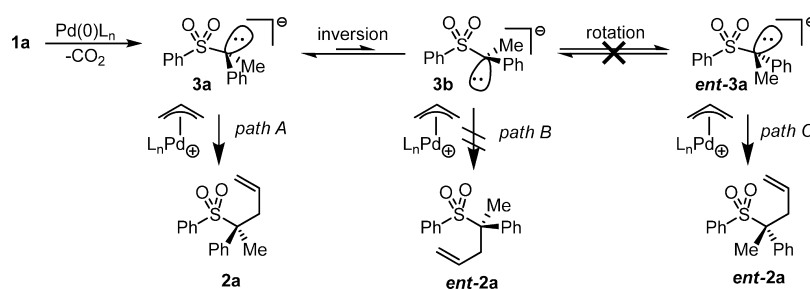
Our control studies and stereochemical studies both suggest that α -sulfonyl anions are formed, and react, outside the coordination sphere of palladium. In order to form highly enantioenriched products, these intermediate α -sulfonyl anions must be configurationally stable. While it is known that α -sulfonyl anions are more configurationally stable than typical carbanions, Gais has reported the rapid racemization of anion **3a** at –80 °C.¹⁵ Thus, we became curious about why our reaction was highly stereospecific even at elevated temperatures.

To address the reasons for the apparently lower rate of racemization than coupling of the α -sulfonyl anion and the Pd π -allyl complex, DFT calculations were performed to determine the inversion barrier for the free α -sulfonyl carbanion. The calculations revealed that the most stable conformation is **3a**, which has the major lobe of the lone pair oriented antiperiplanar to the S–Ph bond (eq 4). A definitive number for the inversion barrier could not be determined because all attempts to minimize the energy of conformation **3b** led to convergence to the minimum-energy structure **3a**. While we could not obtain a specific energy for structure **3b**, this result does support the conclusion that the barrier to inversion is small (<2 kcal/mol). The small inversion barrier is supported by other studies, as is the slightly pyramidal structure of the carbanion.^{15–17}

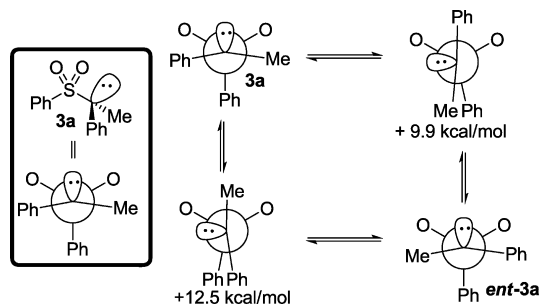


Taking into account the small barrier to inversion, our mechanistic hypothesis is as follows. Ionization and decarboxylation of **1a** generates sulfonyl anion **3a**, which is likely ion-paired with the Pd π -allyl complex (Scheme 3). The C–C bond formation proceeds via path A, where the carbanion can react through the low-energy, staggered transition state to form the product with retention of stereochemistry. Coupling through the inverted conformer **3b** (path B) to form the enantiomeric product not only requires the anion to react through a higher-energy conformer but also requires a higher-energy transition state to form the eclipsed product.⁴ Alternatively, the enantiomer *ent*-**2a** could be formed by allylation of the anion

Scheme 3



Scheme 4



that has undergone inversion and rotation (path C). Thus, we hypothesize that the reaction is stereospecific because rotation about the C–S bond of the sulfone (path C) is slower than reaction of α -sulfonyl anion **3a** with the palladium π -allyl complex through path A.

DFT calculations carried out at the B3LYP/6-31+G* level of theory revealed that the lowest barrier to rotation about the α -C–S bond is 9.9 kcal/mol, which is consistent with experimental measurements in related systems (Scheme 4).^{15–17} Thus, the barrier for allylation of the α -sulfonyl anion must be <9.9 kcal/mol or rotation would lead to racemization. Such a low barrier is consistent with the reaction between an ion pair of a highly nucleophilic α -sulfonyl anion and a palladium π -allyl complex.^{8,18} Thus, the stark contrast between our observations and those of Gais can be attributed to the fact that our reaction generates the reactive α -sulfonyl anion intermediates in the presence of highly electrophilic π -allyl palladium electrophiles, allowing it to effect the C–C bond formation faster than rotation.

In conclusion, we have developed a stereospecific decarboxylative coupling reaction that provides access to enantioenriched homoallylic sulfones. The enantiospecific nature of this reaction is unique among, yet complementary to, existing decarboxylative allylation methodologies. The stereospecificity is made possible by the relatively high barrier for racemization of axially chiral α -sulfonyl anions and the low barrier for their reaction with palladium π -allyl complexes.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and a CIF file. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) See the Supporting Information for more details.
- (9) Complete crossover was observed when two sulfonyl esters were allowed to undergo coupling in the same flask. The interpretation of complete crossover is ambiguous since crossover can likely occur via either the intermediate π -allylpalladium carboxylates or the π -allylpalladium α -sulfonyl anion complexes.
- (10) The presence of acidic protons from the carboxylic acid resulted in the formation of the protonation product rather than the allylation product that may be expected from (allyl)PdCl(PPh₃)₂.
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- (13) Unfortunately, the α -methyl- α -phenylsulfonylacetic ester of cyclohexen-3-ol gave 78% elimination product. Thus, it could not be used for the stereochemical test. Elimination is less problematic with an α -chloro substituent (see ref 6b).
- (14) Analysis of the crude reaction mixture by ¹H NMR spectroscopy indicated that the mass balance of the decarboxylative allylation of **1n** was made up of elimination products.
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