Letter

Decarboxylative Allylation using Sulfones as Surrogates of Alkanes

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Decarboxylative Allylation using Sulfones as Surrogates of Alkanes

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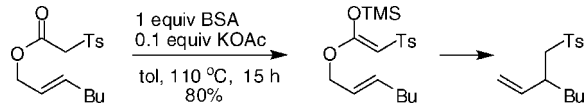
ABSTRACT

α-Sulfonyl functional groups are traceless activating groups that facilitate catalytic decarboxylative allylations in high yield yet can be cleaved to allow the synthesis of simple allylated alkanes. Substrate studies suggest that decarboxylation to form an α-sulfonyl anion is rate-limiting. Furthermore, the anion is formed regiospecifically under formally neutral conditions.

Recently, Craig reported an interesting decarboxylative sigmatropic rearrangement of allyl sulfonylacetic esters (Scheme 1).[1] For all of its utility, the need for an α-hydrogen inherently limits the substrates for this transformation to α-unsubstituted[1a] or highly activated α-sulfonyl-β-ketoesters.[1b]

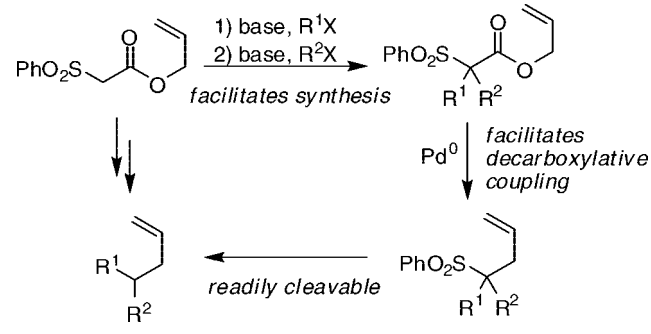
Scheme 1



Our group and others have been interested in developing related catalytic decarboxylative couplings that facilitate C−C bond formations under neutral conditions.[2,3] While a variety of nucleophilic reaction partners can be generated via decarboxylation, the generation of sp^3-hybridized carbanion equivalents is thus far limited to the generation of nucleophiles with pK_a's < 25. Thus, simple unstabilized alkane nucleophiles do not undergo facile decarboxylative coupling.

We surmised that merging the reaction chemistry of Craig with our catalytic decarboxylative coupling methodology would allow us to greatly extend the range of alkyl groups that undergo decarboxylative coupling. Specifically, we expected that the sulfone could be used to facilitate synthesis of pronucleophiles for decarboxylative coupling, accelerate decarboxylative coupling, and be readily cleaved to form allylated alkanes (Scheme 2).

Scheme 2



(1) (a) Bourgeois, D.; Craig, D.; King, N. P.; Mountford, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 618. (b) Craig, D.; Grellepois, F. *Org. Lett.* **2005**, *7*, 463.

(2) For decarboxylative couplings of β-ketoesters, see: (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, 3199. (b) Tsuda, T.; Chujo, Y.; Nishi, S.-i.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (c) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (d) Mohr, J. T.; Behenna, D. C.; Harned, A. W.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (e) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109.

(3) (a) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860. (b) Burger, E., C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002. (c) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510.

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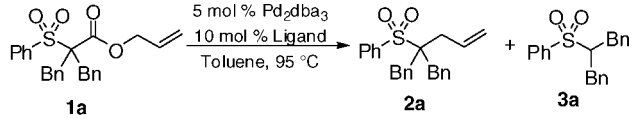
Herein, we report that palladium can be used to catalyze the decarboxylative coupling of sulfonylacetic esters and can be used for the coupling of α,α-disubstituted sulfones that are not viable reaction partners for the Carroll-like rearrangement developed by Craig.[4] Moreover, the ability to readily cleave the sulfone allows the formal decarboxylative coupling of simple alkyl nucleophiles (Scheme 2). This allows us to circumvent the limitation that the nucleophilic components in decarboxylative allylations are currently restricted to relatively stabilized nucleophiles.[2,3]

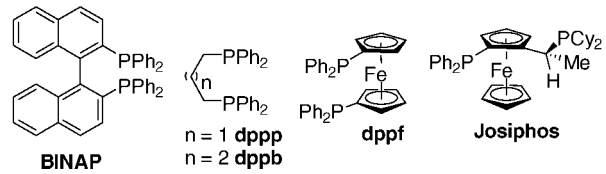
To begin, allyl (phenylsulfonyl)acetate (**1a**) was chosen as a model substrate for reaction optimization. Substrate **1a** is prepared by the straightforward dialkylation of the parent allyl (phenylsulfonyl)acetate. Initial attempts to effect the decarboxylative coupling using $Pd(PPh_3)_4$ in dry toluene resulted in successful coupling; however, the reaction mixture contained a significant amount of **3a** (Table 1). Despite

Table 1. Ligand Screening



entry	ligand	2a:3a[a]
1	PPh_3[b]	1:1
2	dppp	3.5:1
3	dppb	3.1:1
4	dppf	3.5:1
5	Josiphos	4.5:1
6	BINAP	11.3:1
7	Amino-BINAP	No Rxn

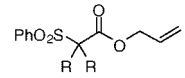
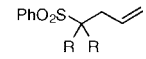
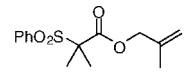
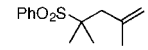
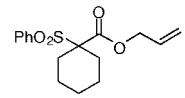
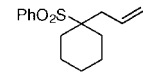
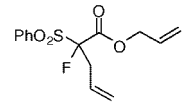
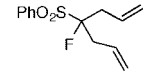
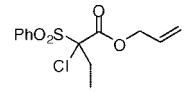
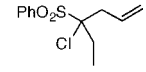
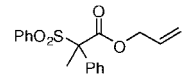
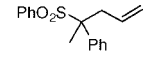
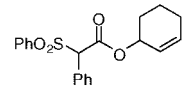
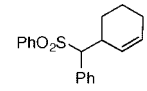
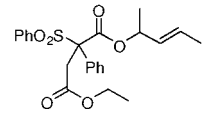
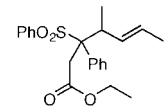
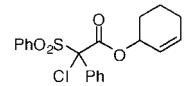
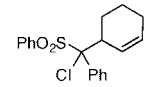
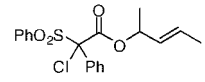
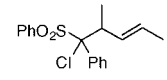
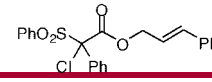
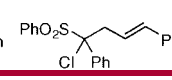
[a] Ratios determined by ^1H NMR of crude reaction mixture [b] $Pd(PPh_3)_4$



rigorous removal of water from reagents and solvent, the generation of protonation product **3a** could not be eliminated. Thus, a series of ligands were investigated for their ability to minimize the amount of product **3a**. It was gratifying to find that use of *rac*-BINAP as a ligand with $Pd_2(dba)_3$ substantially reduced the amount byproduct with a concomitant increase in the yield of desired product.

Next, we turned our attention to investigating the scope of this transformation. As can be seen in Table 2, simple α,α-dialkyl sulfones undergo coupling to give good yields of product; the couplings of α,α-dialkyl sulfones generally take 12−15 h at 95 °C for completion. While fluorination

Table 2. Decarboxylative Coupling of α-Sulfonyl Esters

entry	substrate	product	conditions[a]	yield (%)[b] (dr)
1			a	R = Bn 84
2				R = Me 74
3				R = allyl 78
4			a	81
5			a	83
6			a	45
7			a	96
8			b	96
9			b	95 (1.5:1)
10			b	98 (1.2:1)
11			b	98 (1.5:1)
12			b	84 (1.2:1)
13			b	96[c]

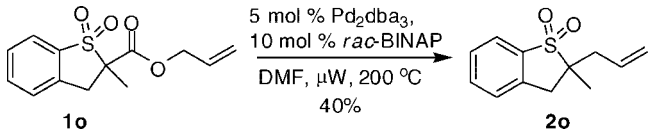
of the α-center results in a reduced yield, α-chlorination is readily tolerated (entries 6 and 7). Interestingly, it appears that oxidative addition of the allylic C−O bond is more favorable than addition of the sterically hindered quaternary C−Cl bond. Moreover, the reactions of α-chloro substrates are somewhat accelerated and require only 3−4 h for completion.

The decarboxylative couplings of substrates that contain an α-aryl group are further accelerated relative to alkyl- and chloro-substituted sulfones. This allows the reactions of α-aryl sulfones to take place in ca. 10 min at room temperature rather than at 95 °C, which is required for α,α-dialkyl sulfones. Moreover, $Pd(PPh_3)_4$ is active enough to catalyze these reactions and the loading of catalyst can be lowered to 1−2 mol %. The fact that α-aryl-substituted sulfones undergo more rapid decarboxylative coupling than alkyl analogues suggests that decarboxylation of the sulfone is rate-limiting. In such a scenario, benzylic stabilization of the incipient anion can account for the observed rate acceleration.

To further probe whether decarboxylation is rate-limiting, a conformationally constrained substrate **1o** was prepared

(4) For allylation of stabilized α-sulfonyl anions, see: Giambastiani, G.; Poli, G. *J. Org. Chem.* **1998**, *63*, 9608. (b) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 6112. (c) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. (d) Hiroi, K.; Suzuki, Y.; Kato, F.; Kyo, Y. *Tetrahedron: Asymmetry* **2001**, 37.

Scheme 3



(Scheme 3). It is known that the most stable conformation of the α-sulfonyl anion has the lone pair situated antiperiplanar to the sulfonyl phenyl group (Figure 1).[5] Since the cyclic

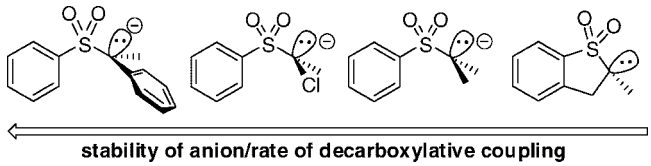


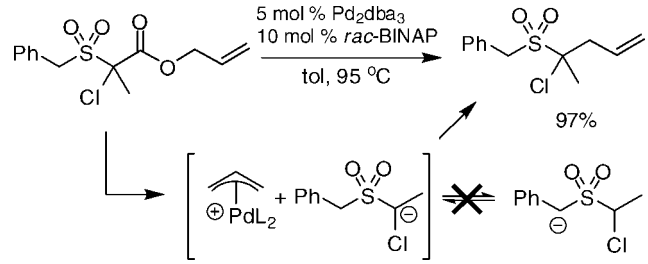
Figure 1. Qualitative correlation of rate and stability.

nature of the anion derived from **1o** cannot achieve this ideal conformation, decarboxylation is predicted to be very sluggish. Indeed, **1o** does not undergo reaction under our standard conditions. However, heating the catalytic mixture in a microwave at 200 °C for 30 min did allow the isolation of a modest yield of coupled product **2o** (Scheme 3). We believe that this result further supports our hypothesis that decarboxylation is rate-limiting.[6]

A variety of allyl groups are also compatible with the decarboxylative coupling (Table 2). For example, a monosubstituted allyl substrate reacts to give product with the standard preference for the linear product (entry 13). Reaction of disubstituted allyl alcohol derivatives also proceed in excellent yield, but occur with poor diastereoselectivity (entries 9−12). Lastly, dialkyl sulfones undergo decarboxylative coupling in high yield without any allylation at the activated benzylic position (Scheme 4). The fact that regioisomerization of the α-sulfonyl anion to the more stable anion does not take place indicates that the coupling is regiospecific with respect to the sulfone. Similar regiospecificity is exhibited in the decarboxylative allylations of ketone enolates.[2]

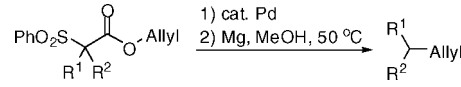
Finally, we wanted to demonstrate the ability to remove the sulfone after using it to facilitate coupling. Toward this end, several substrates were subjected to decarboxylative coupling followed by reduction using Mg in methanol.[7] In each case, clean reduction of the sulfone was achieved and

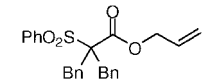
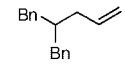
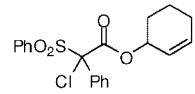
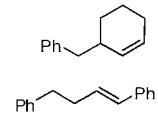
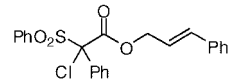
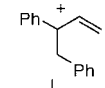
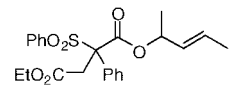
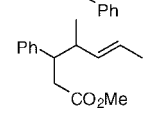
Scheme 4



the two-step decarboxylative coupling-reduction yields are good (Table 3). While reduction the α,α-dialkyl substrates

Table 3. Decarboxylative Coupling−Reduction

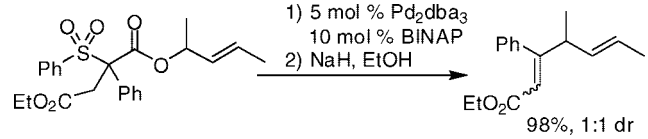


entry	substrate	product	yield (%)[a]
1			74
2			83
3			69 (10:1 l:b)
4			79 (1:1 dr)

expectedly gives rise to a tertiary carbon center, the α-chloro compounds undergo double reduction to provide the secondary carbon.

In addition to reductive cleavage, one can take advantage of the ability to eliminate the sulfinate,[8] leading to skipped dienes (Scheme 5).

Scheme 5



In conclusion, palladium-catalyzed decarboxylative coupling allows the synthesis of γ,δ-unsaturated sulfones. The

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sulfone facilitates (i) alkylation reactions to construct a nucleophile for coupling and (ii) the generation of α-sulfonyl anions under neutral conditions using decarboxylation as a driving force. Here there is a significant advantage to our method as compared to more traditional allylations of sulfones that take place under strongly basic conditions and often require toxic additives such as HMPA to achieve formation of quaternary C−C bonds.[9,10] Finally, the sulfone can be reductively cleaved, making it a "traceless" activating group.[11] Alternatively, the sulfone can facilitate many other reactions; in particular, the ability to couple α-chlorosulfones suggests our reaction as a precursor to Ramberg−Backlund olefin synthesis.

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

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(9) Our method compares favorably with the allylation of a sulfone under strongly basic conditions. See the Supporting Information for details.

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