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Vinylsulfones versus alkylsulfones in the addition to chiral imines. Synthesis of *N*-(*tert*-butoxycarbonyl)-L-homophenylalanine

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Abstract—A study of the addition of vinylsulfones versus alkylsufones has been done, and applied to the synthesis of *N*-(*tert*-butoxycarbonyl)-L-homophenylalanine.

1. Introduction

The addition of organometallics to imines derived from (*R*)-2,3-diprotected-D-glyceraldehyde, has been the subject of numerous papers, in particular related to the synthesis of natural and unnatural aminoacids.[1] Recently we have published the addition of a cyclopropylvinylsulfone to the benzylimine of (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde **1**, for the synthesis of unnatural aminoacids.[2] (Fig. 1).

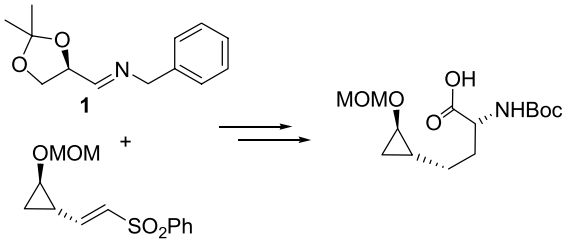

Figure 1. Addition of cyclopropylvinylsulfone to imine **1**, and transformation into an unnatural protected aminoacid.

In order to extend this approach to other systems we decided to study the addition of phenylsulfones to the chiral imine **1**. In this manner the synthesis of one of the more interesting unnatural aminoacids, L-homophenylalanine, could be achieved. This amino acid is found in several pharmaceuticals such as the angiotensin converting enzyme (ACE) inhibitors, for example, Cilazapril[3] and Enalapril[4] among others (Fig. 2). To the best of our knowledge there is no report of a synthesis applying this approach to L-homophenylalanine, although this molecule has been synthesized several times in both enantiomeric forms.[5] Initially, we decided to study the addition of sulfone **2** to the chiral imine **1** (Scheme 1).

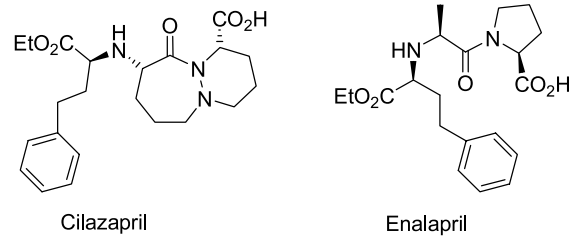

Figure 2. Some ACE inhibitors containing the L-HPA moiety.

2. Results and discussion

When sulfone **2** was treated with *n*-BuLi in THF and made to react with imine **1**, several compounds **3** (45%) **4**–**6** (21%) and **7** (30%) were obtained, which were isolated by column chromatography. Compound **3** was hydrogenated in presence of Boc_2O, giving a 48% yield of derivative **8**, which was then transformed into D-homophenylalanine using Pericàs methodology.[6] Thus, deprotection of the acetonide and oxidation with $RuCl_3$ and sodium periodate led to *N*-Boc-D-homophenylalanine[7] **10** in 59% yield from **8**, hence establishing the stereochemistry for **8**.

The other three compounds **4**, **5** and **6** were debenzylated

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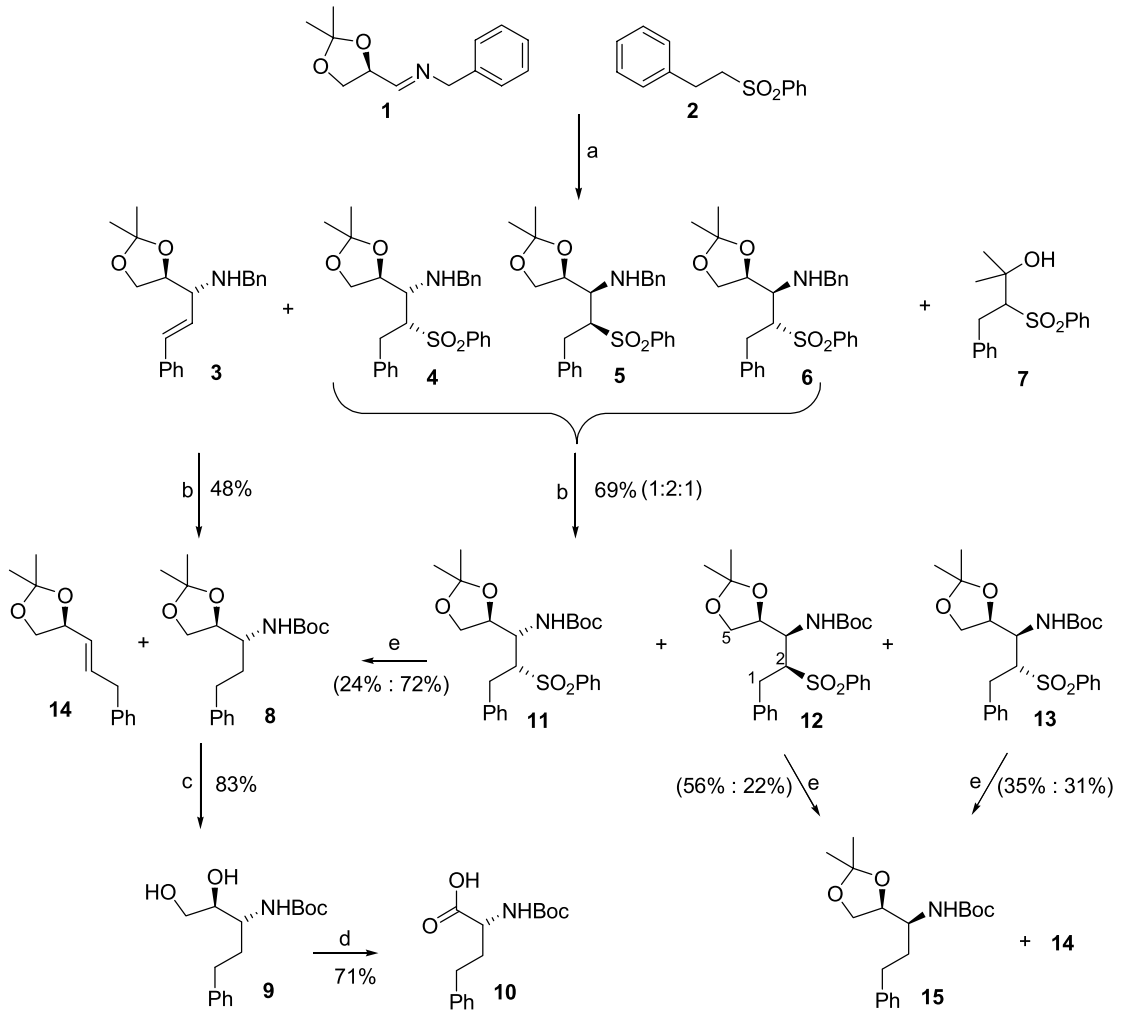

Scheme 1. Reagents: (a) *n*-BuLi, THF, −78→0 °C, 5 h (**3**:45%, **4**–**6**:21%, **7**:30%); (b) H_2, Boc_2O, $Pd(OH)_2$, EtOAc, rt, 24 h; (c) CF_3COOH, $MeOH/H_2O$ 3:1, rt, 7 h; (d) $RuCl_3$–H_2O, $NaIO_4$, $MeCN/CCl_4/H_2O$ 2:2:3, rt, 1 h; (e) Na–Hg, MeOH, 1–2 h.

under the same conditions as **3**, and *N*-Boc derivatives **11**, **12**, and **13** were obtained in 69% yield in a 1:2:1 ratio. In order to establish the stereochemistry of these compounds, they were desulfonylated with sodium amalgam. Derivative **11** gave a 3:7 mixture of the olefin **14**, via a Julia type reaction,[8] and the *N*-Boc compound **8**, in nearly quantitative yield. Compounds **12** and **13**, when similarly treated, separately gave the same desulfonylated compound **15** in quantitative yield, along with **14**. This compound **15** has already been described and the spectroscopic properties and rotation were coincident with those taken from the literature.[9] The stereochemistry of the sulfone carbon C-2 was tentatively determined for **11**, **12** and **13** by extensive NOE and comparative NMR studies. We felt sufficiently confident of this assignment for the purposes of this study, particularly since this stereocentre was in any event going to be removed.

Thus, in this case, the addition of an anion stabilised by an alkyl sulfone to the imine proceeded with moderate stereoselectivity (3:1 ratio), following a course similar to that found by Díaz-de-Villegas and Galvez et al for the addition of benzylmagnesium chloride to imine **1**,[10] and in contrast to the addition of other organometalics to the same imine observed by these authors.[11]

In order to further study the stereoselectivity of the sulfone addition, we decided to examine the behaviour of the more rigid phenylstyrylsulfone **16** in a similar manner, in the expectation that we might find changes in the stereoselectivity that would help determine the causes of that selectivity. The reaction of the anion of **16** (generated by treatment with *n*-BuLi in THF) with imine **1** gave compounds **17**, **18**, **19** and **20** in an excellent 93% yield and with complete stereoselectivity, as will be demonstrated below (Scheme 2).

The stereoselectivity obtained has been explained for analogous systems in terms of α-chelate controlled addition[1b,12] but, while the Cram, Cram-chelate, and Felkin-Anh models have all been applied to the addition of nucleophiles to imines,[1c] the substrate **1** provides a particularly complex case. As mentioned above, the stereochemical outcome of additions to **1** is known to depend upon the nucleophile used, with a complete reversal of the (nearly complete) stereoselectivity on changing, for example, from PhMgBr to $PhCH_2MgCl$[11]—this has been postulated to be due to changes in the preferred chelate formed (with the α or β oxygen of the acetonide unit). In any event, this means that the classical models provide no guidance in this context as to possible outcomes prior to