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**New Synthetic Approaches to  
Alk-1-enyl Sulfones and  
Sulfoxides**

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# Abstract

This thesis is mainly devoted to the study of new synthetic approaches to alk-1-enyl sulfoxides and sulfones, important intermediates in organic synthesis. New reactions were found that allowed the synthesis of these substances in excellent yields under simple and practical conditions. Dialkyl alk-1-enyl aluminum reagents, both uncomplexed or complexed with pyridine, were effective in the formation of *a)* alk-1-enyl sulfoxides; *b)* alk-1-enyl sulfones; *c)* N-acyl-2-alkenyl-2H-dihydropyridine derivatives, depending on the reaction conditions.

More specifically, this work describes the following results:

- a)* Uncomplexed organoaluminum reagents reacted smoothly with aluminum sulfinates, produced *in situ* from sulfonyl chlorides and Et<sub>3</sub>Al, to afford alk-1-enyl sulfoxides in good yields (72-75%). Reaction of sulfonyl chlorides with pyridine-complexed alanes, in the presence of triphenylphosphine as reducing agent, afforded the sulfoxides in up to 94% yield; a reasonable mechanism is proposed. It was also found that sulfinyl chlorides react with alkynyl aluminum reagents only with a partial conversion to give alkynyl sulfoxides in modest yields (43-57%).
- b)* Reaction of pyridine-complexed alanes with sulfonyl chlorides, in the presence of Ph<sub>3</sub>PO, afforded the corresponding sulfones in good yields (75%). The more reactive uncomplexed alanes effectively alkenylated sulfonyl chloride-pyridine complexes albeit in very variable (40-90%) yields; CuCl was found to improve the yields of these reactions.
- c)* Finally, a new approach was developed to the synthesis of N-acyl-2-alkenyl-2H-dihydropyridine and dihydroisoquinoline derivatives *via* reaction of alkenyl aluminum reagents complexed with pyridine or isoquinoline and acid halides.

# Publications

The following results obtained in the context of this thesis work have been so far published in the form of poster presentations at international conferences or scientific articles:

## Articles

1. Signore, G.; Samaritani, S.; Malanga, C.; Menicagli, R. "Reinheckel Protocol Revisited: Synthesis of (E)- $\alpha,\beta$ -unsaturated Sulfoxides" *Synthesis* 762-764 (2006)
2. Signore, G.; Calderisi, M.; Malanga, C.; Menicagli, R. "Alkenylalane-pyridine complexes in a new synthesis of aryl alk-1-enyl sulfoxides" *Tetrahedron* **63**(1), 177-182 (2007)

## Poster presentations

1. Signore, G.; Samaritani, S.; Malanga, C.; Menicagli, R. "The Reinheckel protocol revisited: a useful approach to  $\alpha,\beta$ -unsaturated sulfoxides" *pre-OMCOS13 "Recent advances in organometallic chemistry and applied catalysis"*, Paris, 15-16 July 2005, Abstract Book, **P35**
2. Signore, G.; Menicagli, R.; Samaritani, S.; Calderisi, M. "Alk-1-enyl alanes in the synthesis of unsaturated aryl sulfoxides". *OMCOS13 "13th IUPAC international symposium on organometallic chemistry directed towards organic synthesis"*, Geneva, 17-21 July 2005, Abstract Book **P169**
3. Signore, G.; Malanga, C.; Menicagli, R. "Unsaturated organoalanes in the synthesis of (2H) dihydropyridines and (2H) dihydroquinolines" *ICOMC-XXII, "International conference in organometallic chemistry"* Zaragoza, 23-28 July 2006, Abstract book **P 442**

## Table of acronyms and abbreviations

<b>AcO</b>	Acetate	<b>LiHDMS</b>	lithium hexamethyl disilazide
<b>AIBN</b>	4,4'-azobisisobutyronitrile	<b>MCPBA</b>	<i>m</i> -Chloroperbenzoic acid
<b>Ar</b>	Aryl	<b>Me</b>	Methyl
<b>Alk</b>	Alkyl	<b>Ment</b>	Mentyl
<b>Bn</b>	Benzyl	<b>MMPP</b>	Magnesium mono peroxy phthalate
<b>Bu</b>	Butyl	<b>Ms</b>	Methanesulfonyl
<b>BuLi</b>	Butyllithium	<b>NBS</b>	N-Bromo succinimide
<b>CAN</b>	Cerium ammonium nitrate	<b>NIS</b>	N-iodo succinimide
<b>Cp</b>	Cyclopentadienyl	<b>PCC</b>	pyridine chloro chromate
<b>Dbp</b>	dibenzylidene acetone	<b>Ph</b>	Phenyl
<b>DIBAL-H</b>	di- <i>i</i> -butyl aluminum hydride	<b>Pr</b>	Propyl
<b>DMAD</b>	dimethylamino dicarboxylate	<b>Py</b>	Pyridine
<b>DMAP</b>	4-(N,N-dimethylamino)-pyridine	<b>r.t.</b>	room temperature
<b>DMF</b>	dimethylformamide	<b>TBA</b>	Tetrabutylammonium
<b>Et</b>	Ethyl	<b>TBSO</b>	<i>t</i> -Butyldimethylsilyloxy
<b>F<sub>20</sub>TPPFe</b>	iron tetrakis (pentafluorophenyl) porphyrine	<b>TfO</b>	Trifluoro methanesulfonate
<b>Fur</b>	Furyl	<b>THF</b>	tetrahydrofuran
<b>Hex</b>	Hexyl	<b>TMSO</b>	Trimethylsilyloxy
<b>LDA</b>	Lithium di <i>i</i> -propyl amide	<b>Tol</b>	Tolyl
		<b>Ts</b>	<i>p</i> -Toluenesulfonyl



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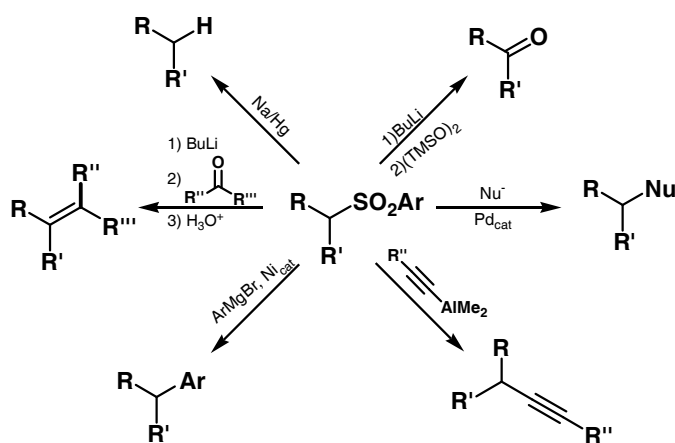




# Introduction

Sulfone and sulfoxide functional groups are useful auxiliaries in organic synthesis, even though they are seldom present in the target products; their use in synthesis could at a first sight seem to be plagued by low atom economy, since these groups are usually removed at some intermediate stage. However, their utility in synthesis is enough to overcome this limitation in many cases.

$\alpha,\beta$ -Unsaturated sulfones are widely employed as key intermediates in organic chemistry, due to the excellent stereoelectronic control on proximal and remote reaction centers. Although the sulfone functional group is seldom found in the target molecule, synthetic pathways can often be simplified by its use; for a few selected examples one may cite the synthesis of L(-)-Prostaglandin E<sub>2</sub><sup>1</sup> and of some other natural products.<sup>2</sup> In addition to their directing effects, sulfones can be easily converted to other functional groups. This important feature of the chemistry of sulfones has been extensively reviewed,<sup>3</sup> and only a few among the most useful transformations are mentioned here. It is worth citing the substitution reaction with aryl Grignard reagents,<sup>4</sup> lithium acetylides or nucleophiles in the presence of palladium catalysts,<sup>5,6</sup> conversion into  $\alpha$ -ketols,<sup>7</sup> reduction to hydrocarbons, addition of their  $\alpha$ -carbanions to carbonyl compounds and subsequent elimination (Julia reaction),<sup>8,9</sup> reduction with lithium-naphthalenide and trapping with carbonyl compounds,<sup>10</sup> olefination,<sup>11</sup> reduction to sulfides<sup>12</sup> (Scheme 1).



**Scheme 1:** Some reactions performed with the sulfone functional group

The reactivity of sulfoxides resembles under many aspects that of sulfones, and it is possible to easily remove this functional group also, when necessary. Among the transformations that the sulfoxide functional group can undergo, some of the most important ones are the modified Julia<sup>13</sup> and Julia-Lythgoe<sup>11</sup> olefinations, the Pummerer reaction,<sup>14,15</sup> reduction with Al/Hg,<sup>16</sup> and thermal fragmentation.<sup>17</sup>

The most interesting feature of sulfoxides, however, is constituted by the stereogenicity of the sulfur center, which makes them an important tool in asymmetric synthesis.<sup>18,19,20</sup> The stereogenic sulfur center can exercise a great level of stereoelectronic control.<sup>21,22</sup> The above mentioned features of stereogenic sulfur prompted the development of new synthetic routes to these derivatives, in order to further expand their role as auxiliaries in diastereo- and enantioselective reactions.

Many methodologies to prepare unsaturated sulfur derivatives have been reported in the literature; a general overview of the most important approaches is reported in Chapter 1. However, there is always room for new approaches possessing the requisites of being simple to execute, high-yielding, and of general applicability.

The aim of this work was to develop new approaches which could afford unsaturated sulfones and sulfoxides through a practical procedure. In this context, the peculiar reactivity of dialkyl alkenyl alanes was of great interest; it has been in fact shown that these reagents efficiently and often selectively transfer the unsaturated moiety, preferentially over the two alkyl residues. This fact rendered interesting to study their applicability to the synthesis of sulfoxides and sulfones; the results obtained in this study are reported in Chapters 2 and 3.