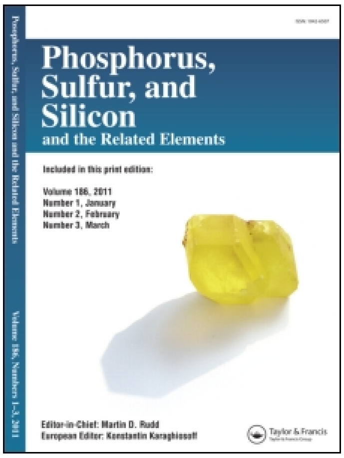

**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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**To cite this Article** Carretero, Juan C. , Arrayás, RamóN GóMez , Buezo, Nuria Diaz , Garrido, José Luis , Alonso, Inés and Adrio, Javier(1999) 'Recent Applications of Vinyl Sulfones and Vinyl Sulfoxides in Asymmetric Synthesis', Phosphorus, Sulfur, and Silicon and the Related Elements, 153: 1, 259 — 273

**To link to this Article: DOI:** 10.1080/10426509908546439

**URL:** http://dx.doi.org/10.1080/10426509908546439

*Phosphorus, Sulfur and Silicon*, 1999, Vol. 153-154, pp. 259-273
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Printed in Malaysia

# Recent Applications of Vinyl Sulfones and Vinyl Sulfoxides in Asymmetric Synthesis

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Herein we present some new synthetic applications based on the use of functionalized α,β-unsaturated sulfones and α,β-unsaturated sulfoxides. In particular, we have developed a stereodivergent approach to the synthesis of castanospermine stereoisomers from ω-amino-γ-oxygenated-α,β-unsaturated sulfones as well as a stereoselective synthesis of substituted dihydrofurans by Pd(0) catalyzed reaction of the carbonate derivatives of γ-oxygenated-α,β-unsaturated sulfones with methylene active ketones. Additionally, the use of the sulfinyl group as a novel chiral auxiliary in asymmetric Heck reactions is also described.

*Keywords:* sulfones; sulfoxides; indolizidine alkaloids; palladium

## INTRODUCTION

α,β-Unsaturated sulfones[1] and α,β-unsaturated sulfoxides[2] are having a widespread use in organic synthesis due to their easy preparation and their great chemical versatility, mainly due to their good properties as Michael and radical acceptors as well as olefinic compounds in cycloaddition reactions.

In 1990 we reported that γ-hydroxy-α,β-unsaturated sulfones can be readily prepared in one-step by condensation of sulfonyl sulfinyl methanes with enolizable aldehydes in the presence of piperidine.[3] As two recent synthetic applications based on the use of this kind of compounds in stereoselective synthesis, we have described the synthesis of polyhydroxylated indolizidine alkaloids[4] and the study of the nucleophilic allylic substitution catalyzed by Pd(0) and its application to the synthesis of dihydrofurans.[5]

Unlike Diels-Alder reactions or nucleophile additions, little is known about the behaviour of α,β-unsaturated sulfoxides in reactions catalyzed by transition metals.[6] In particular, we have recently undertaken the study of the sulfinyl group as a new potentially useful chiral auxiliary in asymmetric Heck reactions.[7]

All these studies are the subject of this article.

## RESULTS AND DISCUSSION

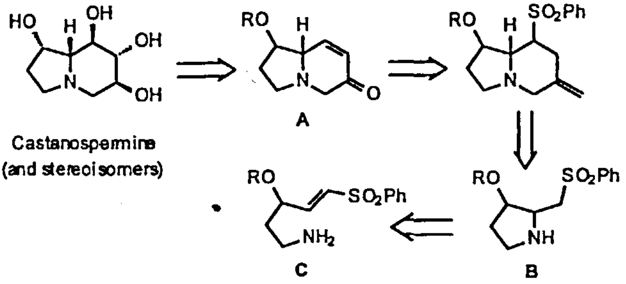
### Synthesis of Castanospermine Stereoisomers from γ-Hydroxy-α,β-unsaturated sulfones

Among naturally occurring polyhydroxylated indolizidines, castanospermine has attracted a great attention from both synthetic and biological points of view due to its excellent activity as α–glucosidase inhibitor.[8] Moreover, to find structure-activity relationships many stereoisomers and analogues should be prepared.[9] To this end, we envisaged a stereodivergent synthetic approach to the synthesis of these compounds by stereoselective reduction of the indolizidine enones **A**. In our retrosynthetic plan substrates **A** could be readily prepared from pyrrolidines **B** by double alkylation with a bis-allyl reagent, followed by further ozonolysis and basic elimination of the sulfonyl moiety. On the other hand, pyrrolidines **B** would be the result of the cyclization of the readily available amino-γ-oxygentated-α,β-unsaturated sulfones **C** (scheme 1).

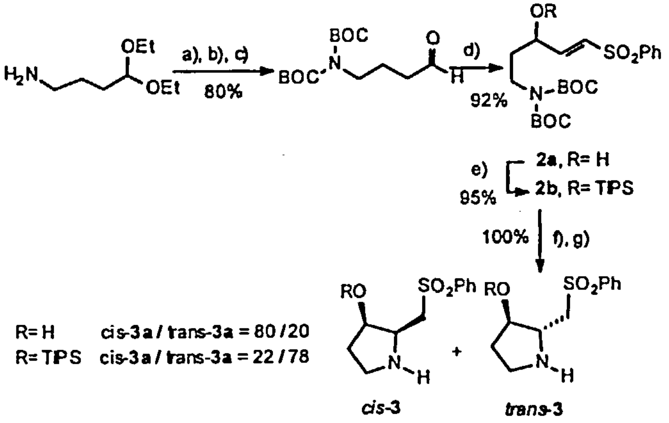
The preparation of pyrrolidines **3** is outlined in the scheme 2. The protected 4-aminobutyraldehyde **1** was prepared in a straightforward manner from commercially available 4-aminobutyraldehyde diethyl acetal. Its condensation with (±) phenylsulfonyl p-tolylsulfinyl methane[3] in the presence of piperidine ($CH_3CN$, 0°C) afforded the expected (±) γ-hydroxy-α,β-unsaturated sulfone **2a** in excellent yield (94%). To determine if the size of the oxygenated substitution at γ-position had a significant effect on the stereoselectivity of the intramolecular conjugate addition, the hydroxyl group was protected as the bulky TIPS group (TIPSOTf, 2,6-lutidine, $CH_2Cl_2$). Deprotection of the BOC moiety with TFA at room temperature afforded the corresponding ammonium salts, which were isolated, redissolved (THF or toluene) and treated with $Et_3N$ (10 equiv) at -78°C. In these conditions the cyclizations took place quantitatively in less than 30 min affording a *cis+trans* mixture of pyrrolidines **3**. Interestingly, substrates **2a** and **2b** showed opposite stereoselectivities: whereas the cyclization of **2a** was *cis*-stereoselective (*cis*-**3a**/*trans*-**3a**= 80/20) **2b** evolved in a *trans* stereoselective manner (*cis*-**3b**/*trans*-**3b**= 22/78).[10]

After some experimentation we found that an appropriate way to accomplish the construction of the indolizidine skeleton was the two-step alkylation of pyrrolidines **3** with 3-chloro-2-chloromethyl-1-propene (scheme 3). Thus, *trans*-**3b** was transformed into indolizidine **4** (89% yield) by initial N-alkylation in the presence of a soft base ($K_2CO_3$)

scheme 1



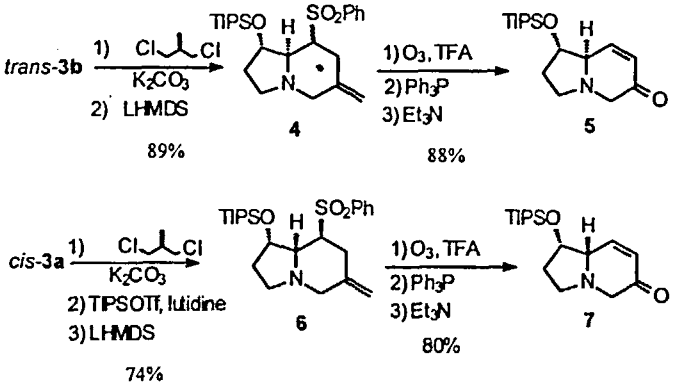
scheme 2



a) (BOC)$_2$O; b) *n*-BuLi, (BOC)$_2$O; c) AcOH, H$_2$O; d) PhSO$_2$ SOTol
e) TPSOTf, 2,6-lutidine, CH$_2$Cl$_2$; f) CF$_3$CO$_2$H, CH$_2$Cl$_2$; g) Et$_3$N

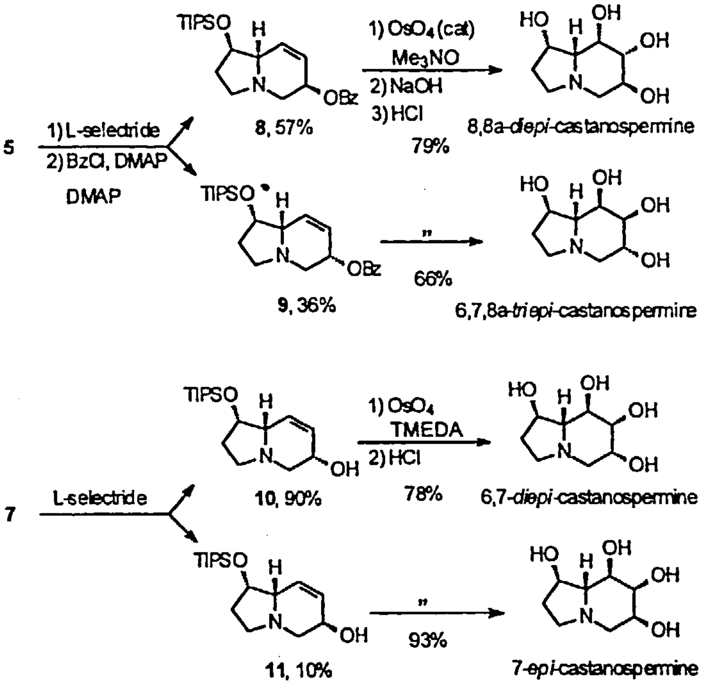
followed by intramolecular C-alkylation with a strong base (LHMDS). It should be pointed out that the ozonolysis of **4** only occurred cleanly when pure TFA was used as solvent, likely due to the competitive amine oxidation in the presence of the usual nonacidic solvents. Subsequent reductive workup (PPh$_3$) and addition of triethylamine (to promote the basic elimination of the sulfone) afforded the enone **5** in 88% yield after silica gel purification. In a similar manner, *cis*-**3a** was transformed first to the methylene indolizidine **6** and then to the diastereoisomeric enone **7** (59% overall yield from *cis*-**3a**).

scheme 3



Due at least in part to the relative unstability of compounds **5** and **7** at room temperature, all attempts to dihydroxylate them were unfruitful, giving complex mixtures of products. In contrast, a quantitative and fast reaction occurred in the reduction of these compounds with L-Selectride (or DIBALH) in THF at -78°C. However, while the reduction of **5** was hardly stereoselective in favour of **8** (separated as its benzoate derivative) that of **7** afforded with high stereocontrol the alcohol **10** in agreement with the approach of the hydride from the face opposite to the OTIPS group at C-1 (scheme 4). Remarkably, the dihydroxylation ($OsO_4$) of the four olefins (**8-11**) gave in all cases a single isomer, which after hydrolysis of the protecting groups led to the corresponding racemic castanospermine stereoisomers (8,8a-*diepi*-castanospermine, 6,7,8a-*triepi*-castanospermine, 6,7-*diepi*-castanospermine and 7-*epi*-castanospermine).

scheme 4



At present, we are preparing the enantiomerically pure alkaloids from enantiopure γ-hydroxy-α,β-unsaturated sulfones, as well as other castanospermine epimers by straightforward functional group transformations.

## Palladium-catalyzed nucleophilic substitution in γ-oxygenated-α,β-unsaturated sulfones

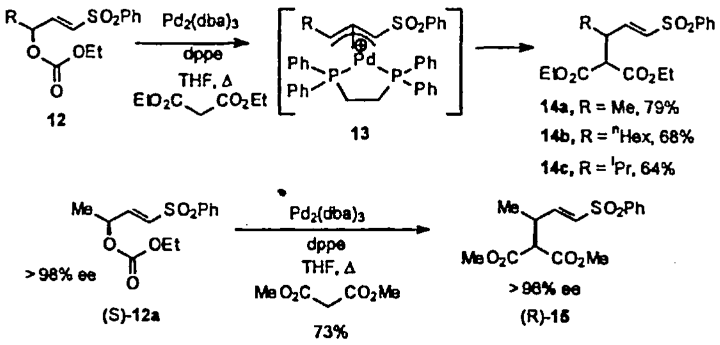
During the last two decades the palladium-catalyzed nucleophilic substitution of allylic oxygenated compounds, mainly esters, carbonates and epoxides, has become a crucial method for the formation of carbon-

carbon and carbon-heteroatom bonds.[11] However, unlike allylic systems substituted with alkyl, aryl or donating substituents those substituted with electron-withdrawing groups at the double bond (ester, carbonyl or cyano groups) have been much less studied because of their lower reactivity toward the palladium catalysts and their tendency to undergo either conjugate addition of the nucleophile or β-elimination on the π-allylpalladium intermediate to give 1,3-dienes.[12]

As it has been shown before γ-hydroxy-α,β-unsaturated sulfones are readily available compounds and exhibit excellent properties as Michael acceptors, allowing an efficient functionalization at β and α positions. This kind of vinyl sulfones would be even more versatile in organic synthesis if it was possible the substitution of the oxygenated function at γ-position by nucleophiles, to afford a new vinyl sulfone suitable for further functionalization at β and α positions.

We were pleased to find that the reaction of the carbonates **12**[13] (prepared by reaction the alcohols with ethyl chloroformate in the presence of pyridine and DMAP) with diethyl malonate in the presence of $Pd_2(dba)_3$ (5 mol %), dppe (20 mol %) as bidentate phosphine ligand and molecular sieves, in THF at reflux, afforded exclusively the γ-substituted products **14** in good yields, by regioselective attack of the nucleophile to the γ-position of the intermediate π-allylpalladium intermediates **13** (scheme 5). As expected, this palladium catalyzed process took place with complete retention of configuration. Thus, reaction of (S)-**12a** (prepared from the enantiomerically pure alcohol) with dimethyl malonate, under the above mentioned conditions, afforded the previously reported compound (R)-**15** in enantiomerically pure form.

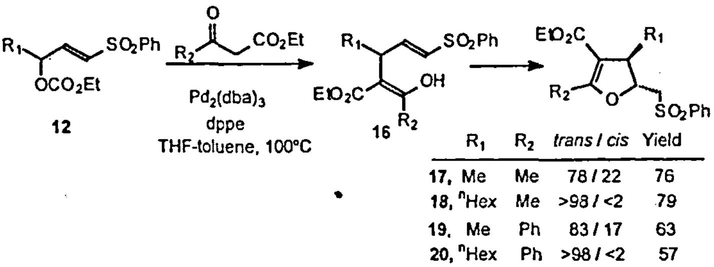
Scheme 5



Surprisingly, under the same experimental conditions the reaction of carbonates **12** with β-ketoesters afforded tetrasubstituted dihydrofurans (compounds **17-20**) in good yields (57-79%) instead of the γ-substituted acyclic compounds **16** (scheme 6). These results showed that a tandem process, based on an initial γ-allylic substitution followed by *in situ* intramolecular conjugate addition of the enol to the vinyl sulfone moiety had taken place.[14]

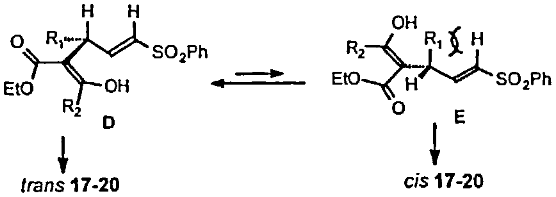
Concerning the stereoselectivity of the cyclization, that occurred in all cases with a remarkable *trans* stereoselectivity, especially in the case of substrates with $R_1$ chains bulkier than Me ($R_1$= Hex or i-Pr). This high *trans* stereocontrol might be explained on the basis of the ground state confomation of the acyclic intermediates **16** (scheme 7). Conformer **D**, that leads to the *trans* isomer, should be more stable than **E** because minimizes the allylic 1,3-strain between α and γ positions, whereas the cyclization of the less stable conformer **E** (owing a $R_1$/Hα 1,3-allylic interaction) would led to the minor *cis*-dihydrofuran.[15]

Scheme 6

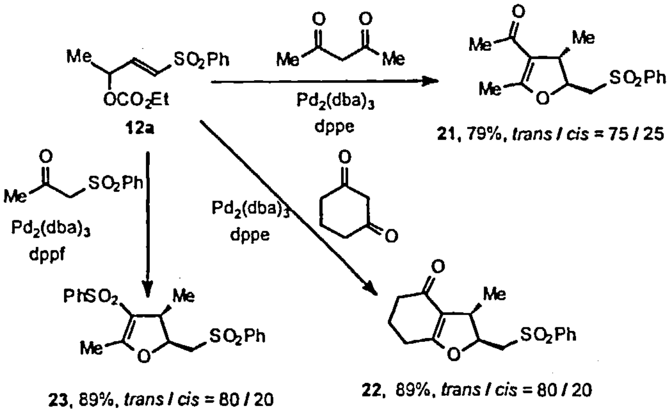


| | $R_1$ | $R_2$ | *trans / cis* | Yield |
|---|---|---|---|---|
| **17**, | Me | Me | 78 / 22 | 76 |
| **18**, | $^n$Hex | Me | >98 / <2 | 79 |
| **19**, | Me | Ph | 83 / 17 | 63 |
| **20**, | $^n$Hex | Ph | >98 / <2 | 57 |

Scheme 7



Scheme 8



As it is depicted in scheme 8 this cyclization process can be also applied to other methylene acid ketones such as 1,3-diketones (both acyclic and cyclic) and α–sulfonyl ketones. Thus, the reaction of **12a** with 2,4-pentanodione, 1,3-cyclohexanodione and phenylsulfonylacetone under the usual palladium catalyzed conditions ($Pd_2(dba)_3$ 5 mol %, dppe 20 mol %, THF-toluene, 100°C) afforded the dihydrofurans **21**, **22** and **23**, respectively.

## Vinyl Sulfoxides in Asymmetric Heck Reactions

At present, the palladium-catalyzed arylation and alkenylation of olefins (Heck reaction) is one of the most versatile catalytic methods for C-C bond formation.[16] However, only very recently have been described successful examples of the asymmetric version of this reaction, mainly using enantiopure chelating diphosphines such as BINAP or (phosphinoaryl)oxazolines as chiral ligands.[17]

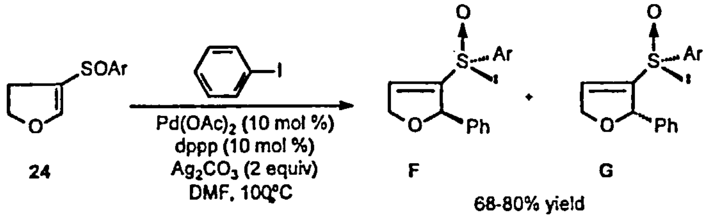
Although the sulfinyl group has proved to be an efficient and widely used chiral auxiliary in many classical reactions little is known about their use in processes catalyzed by transition metals. In particular no precedents of its use in asymmetric Heck reactions were known. As 2,3-dihydrofuran has been the most frequently substrate in this kind of reaction we undertake the study of Heck reactions of racemic and enantiomerically pure 4-arylsulfinyl-2,3-dihydrofurans (**24**) with iodobenzene (table 1).[18]

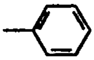
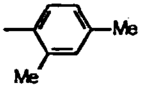
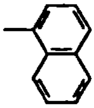
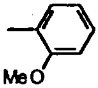
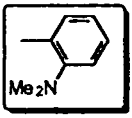
After some experimentation we found that the best conditions required $Ag_2CO_3$ as base. Typical experimental conditions are as follows: PhI (3 equiv), $Pd(OAc)_2$ 10 mol %, and $Ag_2CO_3$ (2 equiv) in DMF at 100°C for a few hours. The reactions can be performed both in absence and presence of phosphine ligands ($PPh_3$, dppp or dppf) although in the latter case the processes are faster. In these conditions a mixture of 2-phenyl-3-arylsulfinyl-2,5-dihydrofurans stereoisomers **F** and **G** were obtained in good yields, but the most interesting result concerns the dependence of the stereoselectivity with the substitution at the sulfoxide. Thus, whereas the arylsulfoxides **24a-d** evolved in a similar manner to give predominantly the isomers **F** (products **25-28**) with poor stereocontrol (**F**:**G**= ~3:1) the o-dimethylaminosulfoxide **24e** led to the isomer **G** with high stereoselectivity (product **29**, **F**:**G**= 1:15).

It is worth noting that a similar opposite stereochemical behaviour from **24a-d** and **24e** was observed in the Heck reactions with other aryl iodides. As it is shown in table 2, regardless the electronic character of the substitution at the aryl iodide, sulfoxide **24a** gave predominantly the isomer **F** while sulfoxide **24e** afforded with high stereoselectivity the isomer **G** (compounds **31**, **33**, **35** and **37**)

As a possible mechanistic explanation, we speculate that the different stereochemical behaviour of **24a-d** and **24e** could be the result of either a steric or a chelation control in the insertion step, respectively (scheme 9). The coordination of the cationic arylpalladium species $[ArPdL_2]^+$ (proposed as the reactive palladium intermediate after oxidative addition in the presence of $Ag_2CO_3$) to the least hindered face of the double bond of α,β-unsaturated sulfoxides **24a-d** (face opposite to the bulky $Ar^1$ group) in their *s-trans* conformations[19] would led to complex **H** that would evolve by intertion and β-hydrogen elimination to give the isomer **F**. On the contrary, due to the high affinity of the palladium atom to coordinate amino groups, it can be assumed that the complexation of $[ArPdL_2]^+$ to the $NMe_2$ moiety unit of **24e** would lead to the amino complex **I**, which would direct intramolecularly the insertion of the aryl group from the opposite face, to give finally isomer **G** after insertion and β-hydrogen elimination.[20]

Table 1



| Dihydrofuran | Ar | Product | F : G |
|---|---|---|---|
| **24a** |  | **25** | 77 : 23 |
| **24b** |  | **26** | 78 : 22 |
| **24c** |  | **27** | 71 : 29 |
| **24d** |  | **28** | 75 : 25 |
| **24e** |  | **29** | 6 : 94 |

Scheme 9

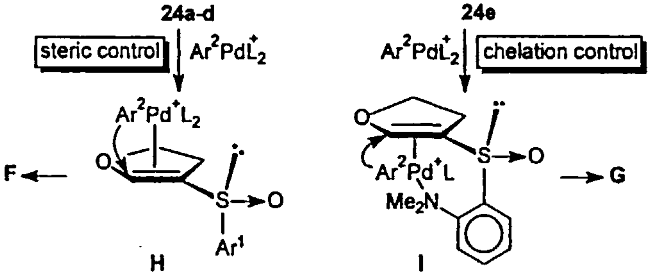
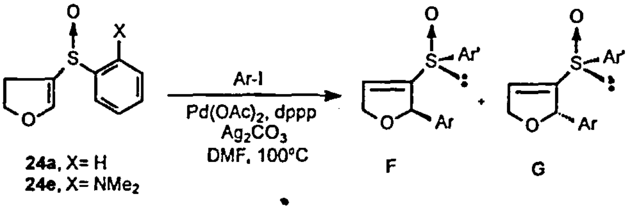
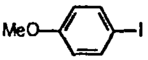
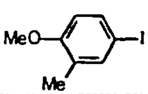
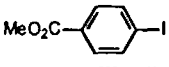
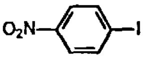


Table 2



| Substrate | Ar-I | X | Product | F : G |
|---|---|---|---|---|
| **24a** |  | H | 30 | 69 : 31 |
| **24e** | | $NMe_2$ | 31 | 14 : 86 |
| **24a** |  | H | 32 | 75 : 25 |
| **24e** | | $NMe_2$ | 33 | 15 : 85 |
| **24a** |  | H | 34 | 71 : 29 |
| **24e** | | $NMe_2$ | 35 | 7 : 93 |
| **24a** |  | H | 36 | 67 : 33 |
| **24e** | | $NMe_2$ | 37 | 6 : 94 |

## CONCLUSIONS

(a) A new stereoselective approach to the synthesis of a variety of 1,6,7,8-tetrahydroxylated indolizidines (castanospermine stereoisomers) has been described. The bicyclic skeleton has been constructed by intramolecular conjugate addition of the nitrogen moiety of the readily available acyclic ω-amino-γ-oxygenated-α,β-unsaturated sulfones (to give pyrrolidines), followed by double alkylation with 3-chloro-2-chloromethyl-1-propene.

(b) The carbonate derivatives of γ-hydroxy-α,β-unsaturated sulfones undergo a Pd-catalyzed nucleophilic substitution at γ-position under appropriate conditions. In the case of using β-ketoesters, 1,3-diketones or α-sulfonyl ketones as nucleophiles, tetrasubstituted dihydrofurans were obtained in good yields as a result of a cascade reaction based on an initial γ-substitution followed by intramolecular conjugate addition to the α,β-unsaturated sulfone.

(c) The Heck reaction of racemic and enantiomerically pure 3-arylsulfinyl-2,3-dihydrofurans with aryl iodides and its application to the enantioselective synthesis of substituted tetrahydrofurans has been studied. The stereoselectivity of the Heck reaction is highly dependent on the substitution at the arylsulfoxide. The best results have been obtained using o-(N,N-dimethylamino)phenyl sulfoxides, in which the presumed coordination of the Pd atom with the nitrogen determines a high stereocontrol.

**Acknowledgment.**
Financial support from *Ministerio de Educación y Cultura* (*Subdirección General de Formación y Promoción del Conocimiento*; project PB96-0021) is gratefully acknowledged.

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