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Fischer carbene complexes. A new tool for heterocyclic synthesis*

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Abstract: This short review covers our contribution in the field of the application of group 6 Fischer carbene complexes toward the synthesis of heterocyclic compounds. Alkenyl and alkynyl carbene complexes are suitable partners in [2+2], [3+2], [4+2], and [4+3] cycloaddition reactions. Moreover, chiral alkenyl carbene complexes react in sequential processes involving an initial Michael addition of a ketone lithium enolate to afford lactones with up to five consecutive stereogenic centers. Based on this strategy, we have devised a new method for the enantioselective synthesis of eight-membered carbocycles.

INTRODUCTION

Group 6 Fischer carbene complexes have become valuable building blocks for the construction of organic molecules [1]. In particular, these organometallic compounds offer the opportunity to access carbocyclic and heterocyclic rings not easily available through conventional routes. Some recent results are herein presented, within the framework of our studies dealing with the application of Fischer carbene complexes to the synthesis of heterocyclic compounds. These examples clearly demonstrate the potential of transition-metal carbene complexes in the stereoselective synthesis of normal and medium-sized heterocycles.

RESULTS AND DISCUSSION

Synthesis of nitrogen-containing heterocycles

[3+2] Cycloadditions

We have widely used chiral, nonracemic carbene complexes derived from (–)-8-phenylmenthol in diastereoselective processes. For instance, the one-pot procedure, shown in Scheme 1, represents an expeditious, highly diastereoselective route to 4,5-dihydro-1*H*-pyrazole esters [2]. Thus, the consecutive reaction of chiral alkenyl carbene complexes with diazomethane derivatives in THF at room temperature for 2–12 h, followed by BOC protection and subsequent oxidation of the metal–carbon double bond leads to the corresponding pyrazole derivatives as single diasteroisomers in yields ranging between 55 and 79 %. It is interesting to compare these results to those obtained from the analogous reaction using the chiral *trans*- cinnamate as starting material. In this case, the reaction requires higher temperatures and longer reaction times to obtain the pyrazole derivatives with much poorer diastereoselectivity (dr = 60/40).

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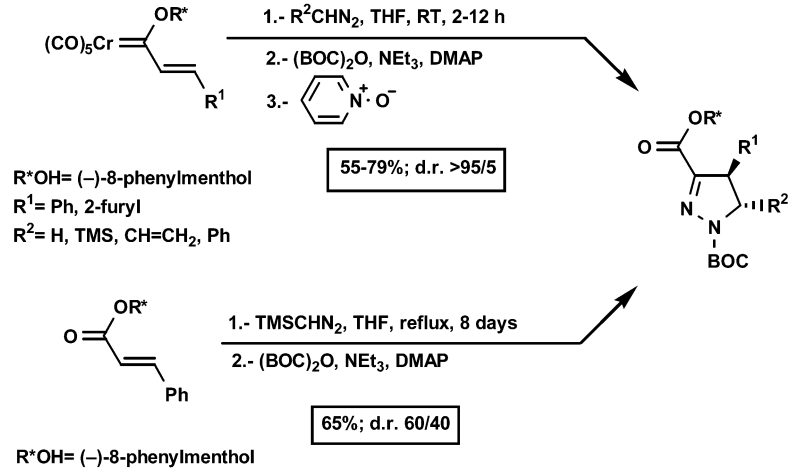
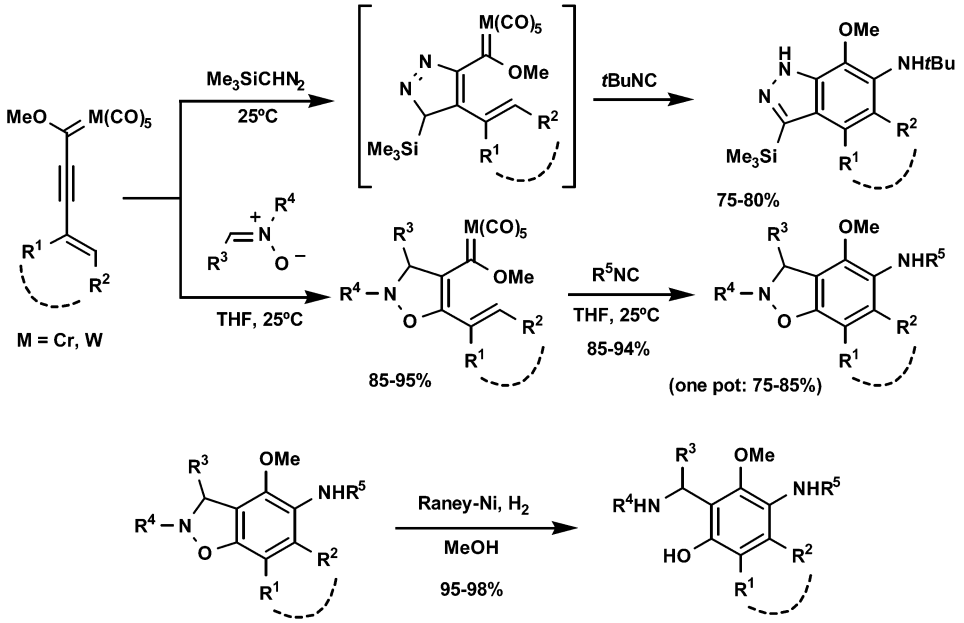


Scheme 1

Another interesting transformation involving a similar [3+2] cycloaddition is shown in Scheme 2. The reaction of alkenylethynyl carbene complexes with diazoalkanes or nitrones gives rise to novel 1,3,5-metallahexatrienes, which are stable and sometimes isolable compounds [3]. The benzannulation reaction of these intermediates with isocyanides affords 2,3-dihydro-1,2-benzisoxazoles or indazoles. Both reactions proceed under mild conditions, in a completely regioselective fashion and with high yields. Interestingly, the final benzene-fused heterocycles can be easily obtained in a one-pot process starting from the alkynyl carbene complex.

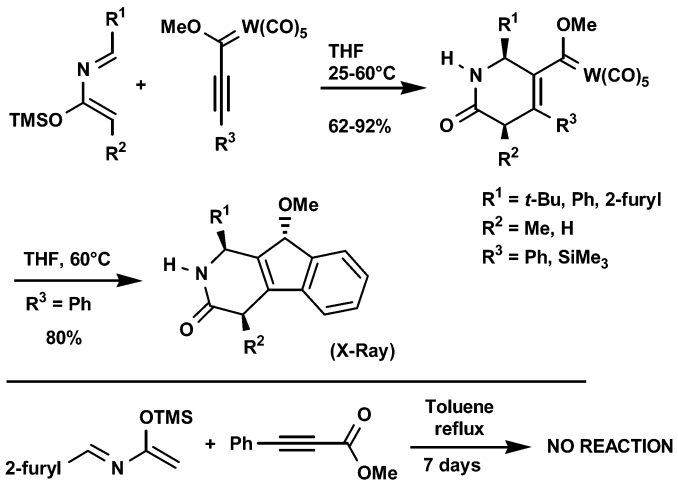


Scheme 2

A particular synthetic utility of the reaction sequence above described is clearly demonstrated by the transformation of the 2,3-dihydro-1,2-benzisoxazoles into *p*-aminophenols (Scheme 2). The isoxazole ring is reductively cleaved by reaction with Raney nickel in methanol under a hydrogen atmosphere to provide the corresponding polysubstituted aminophenols in almost quantitative yield.

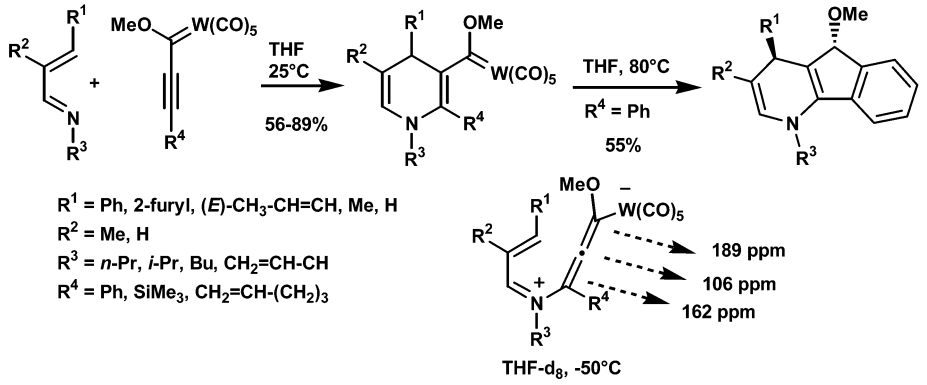
[4+2] Cycloadditions

Alkynyl Fischer carbene complexes are excellent dienophile partners in the classic Diels–Alder reaction. Thus, they react with 2-azadienes to afford, after column chromatography, the corresponding pyridone derivatives in high yield (Scheme 3) [4]. Moreover, when the (phenylethynyl)carbene complex is used as starting material, a double cyclization process takes place, resulting in the stereoselective formation of the 2-azafluorene ring in good yields. This transformation likely involves a selective electrocyclic ring closure of the [4+2] cycloadduct leading to a new metallacycle, which after a suprafacial [1,5]-hydrogen shift and reductive elimination, gives the final 2-azafluorene. We also found that the metal carbene-substituted alkynes are much more reactive toward azadienes than the acetylenic ester analogs, since the attempted cycloaddition between methyl phenylpropionate and an azadiene of this sort in refluxing toluene for seven days resulted in the recovery of the starting materials.



Scheme 3

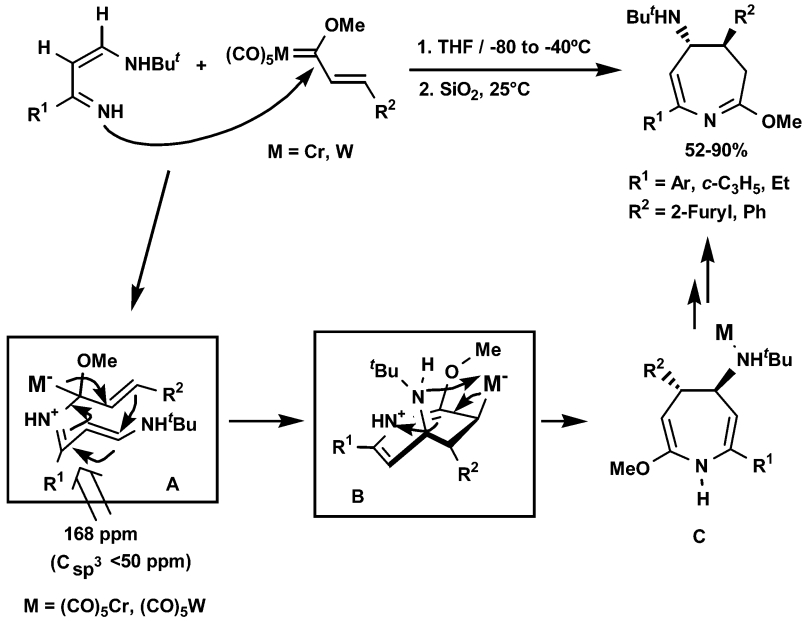
In a similar way, 1-azadienes react with tungsten Fischer alkynyl carbene complexes to regioselectively afford 1,4-dihydropyridines (Scheme 4) [5]. The reaction initiates through a Michael addition of the nitrogen lone pair to the conjugated triple bond of the complex with the formation of an allenic intermediate [5]. This reaction pathway was confirmed by an NMR experiment in THF-d_8 at −50 °C. Under these conditions, the allenic intermediate could be unequivocally characterized by its spectroscopic data ($\delta_{C=C=C}$: 189, 162, 106 ppm). Furthermore, when the reaction was carried out at 80 °C in THF and starting from (phenylethynyl)carbene complex, the corresponding fluorene was obtained (Scheme 4).



Scheme 4

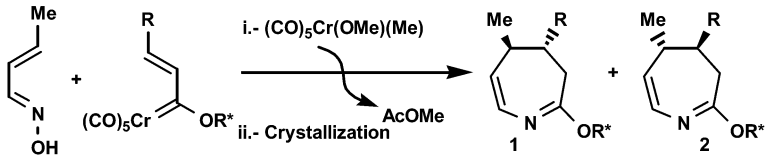
[4+3] Cycloadditions

[4+3] Heterocyclizations have been successfully effected in our laboratory starting from 4-amino-1-azadiene derivatives. The cycloaddition of reactive 4-amino-1-aza-1,3-butadienes toward alkenyl carbene complexes goes to completion in THF at a temperature as low as –40 °C to produce substituted 4,5-dihydro-3*H*-azepines in 52–91 % yield (Scheme 5) [6]. Monitoring the reaction by NMR allowed us to determine various intermediates and to establish the reaction course outlined in Scheme 5. This mechanism features the following points in the chemistry of Fischer carbene complexes: (i) the reaction initiates at –78 °C by nucleophilic 1,2-addition, (ii) the key step cyclization is triggered by a novel [1,2]-$W(CO)_5$ shift.



Scheme 5

A chiral version of this [4+3] heterocyclization was achieved using chiral, nonracemic carbene complexes derived from menthol and oximes as depicted in Scheme 6 [6]. This reaction requires the use of one equivalent of another simple carbene complex in order to remove the oxygen of the oxime functionality at some point during the reaction process. Significantly, the major diastereoisomer crystallizes readily from methanol, allowing the isolation of the azepine in enantiomerically pure form.

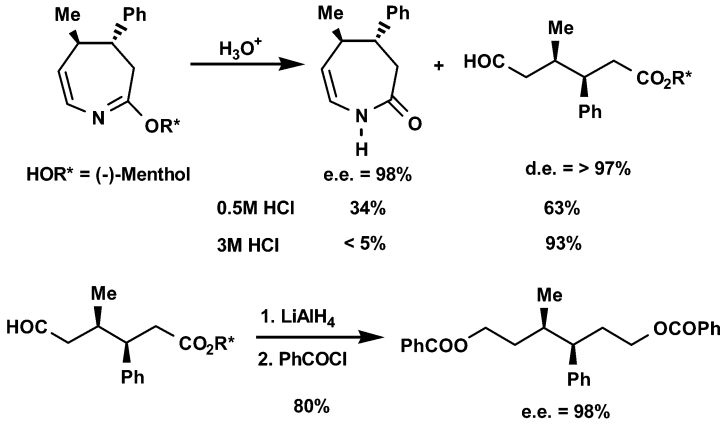


	HOR*	R	Yield	1 + 2 Ratio	Isolated Product	Isolated Yield (d.e.)	
a	(-)-Menthol	Ph	87	70:30	1a	50% (>97%)	(X-Ray)
b	(-)-Menthol	2-Furyl	90	72:28	1b	48% (>97%)	
c	(+)-Menthol	Ph	80	30:70	2c	46% (>97%)	

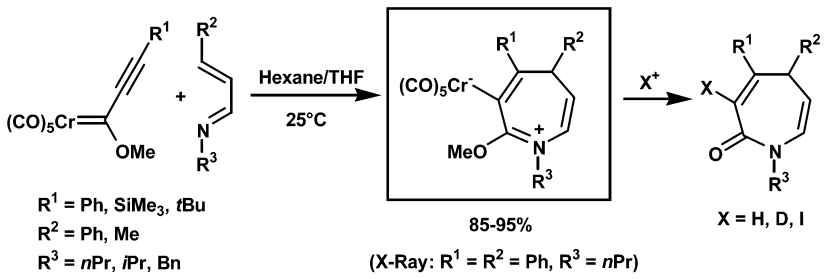
Scheme 6

The chiral azepines are easily transformed into the corresponding formyl esters by treatment with 3M HCl. Thus, the entire protocol formally represents the enantioselective Michael addition of ester homoenolates to α,β-unsaturated aldehydes, in which two chiral centers are created [6]. Finally, the chiral auxiliary is removed by reducion with $LiAlH_4$ to give a chiral diol in very high yield (Scheme 7).

Unexpectedly, chromium Fischer alkynyl carbene complexes react with simple 1-azadienes in the same way as the 4-amino-1-azadienes leading to 2-azepinones after acid workup [7]. Interestingly, we were able to crystallize the metallated zwiterionic intermediate shown in Scheme 8 and determine unambiguously its structure by X-ray analysis.



Scheme 7

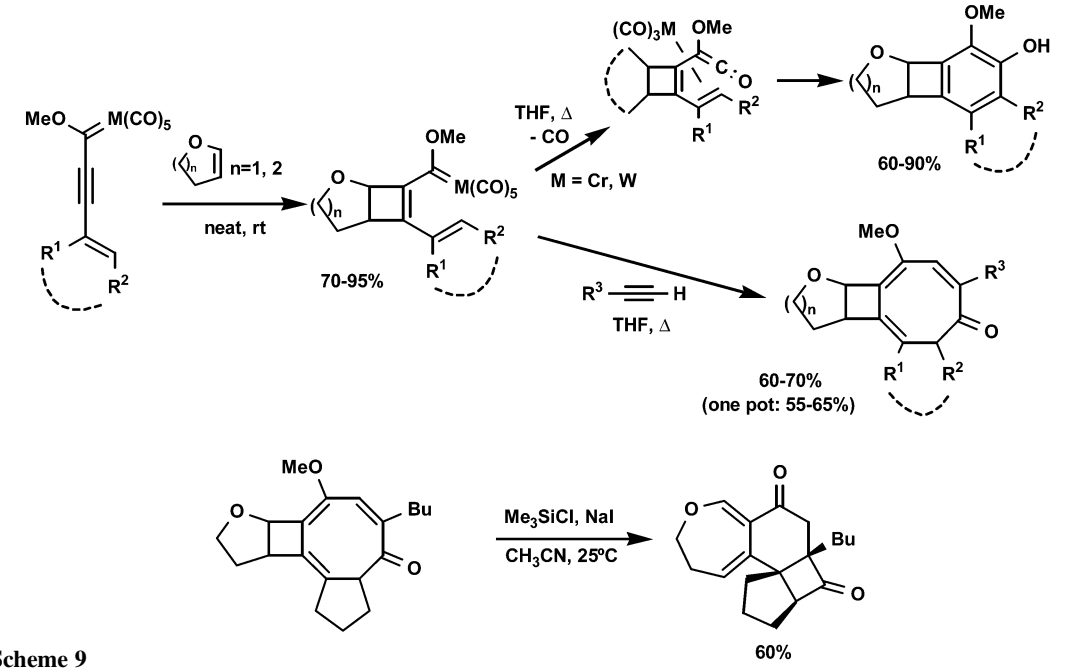


Scheme 8

Synthesis of oxygen-containing heterocycles

Reactions initiated by [2+2] cycloadditions

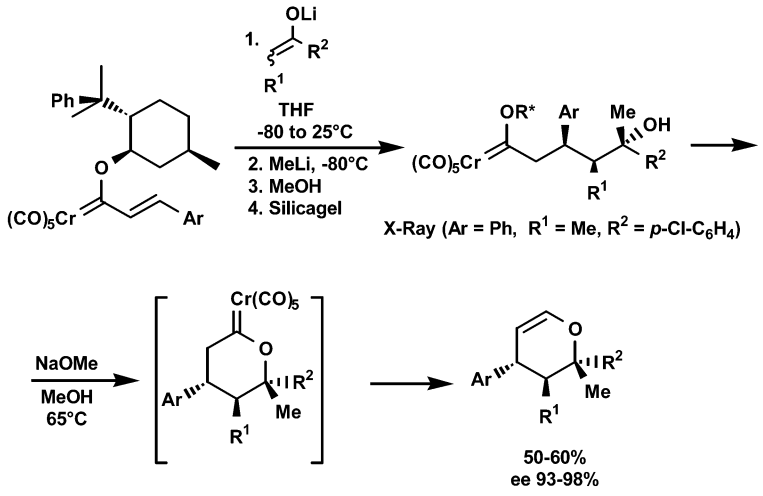
One of the current interests in our research group focuses on the preparation and synthetic applications of 1-metalla-1,3,5-hexatrienes. These dienyl complexes can be easily obtained by a [2+2] cycloaddition reaction between enol ethers and alkenylethynyl carbene complexes (Scheme 9). This methodology allows the synthesis of cyclobutene-containing 1,3,5-metallatrienes, which undergo thermal benzannulation instead of the expected cyclopentannulation reaction [8]. In a more detailed study about the behavior of the cyclobutene-containing metallatrienes, we performed the reaction between these complexes and terminal alkynes in refluxing THF [9]. This reaction leads to the formation of the corresponding cyclooctatrienones. This process can be viewed as a variation of the Dötz reaction, since both an alkyne and CO are inserted. Most of the cyclooctatrienes are unstable in solution, leading in a few hours to complex and unidentifiable mixtures of products. However, treatment of the compound shown in Scheme 9 with trimethylsilyl iodide in acetonitrile at room temperature leads to the formation of a new tetracyclic compound through the sequential six-electron electrocyclization, enol ether hydrolysis, and opening of one of the four-membered rings.



Scheme 9

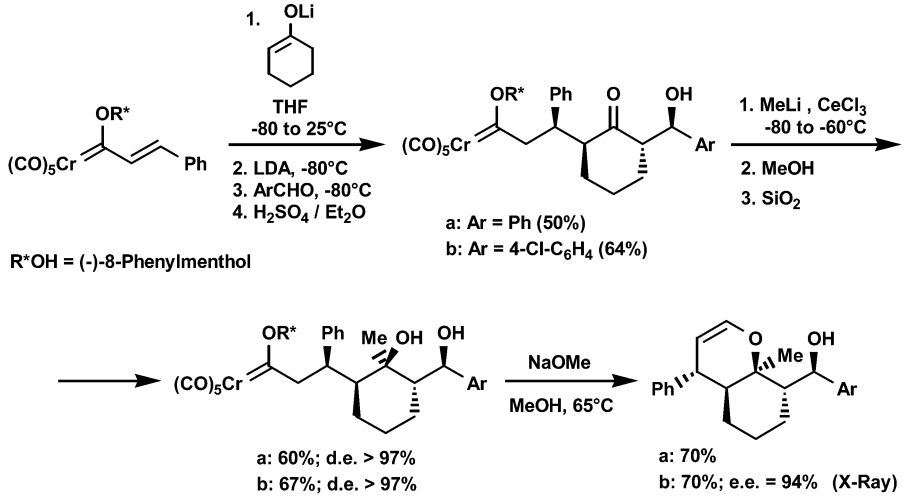
Reactions initiated by Michael additions

Lithium ketone enolates react with chiral, alkenylcarbene complexes derived from (−)-8-phenylmenthol in a Michael fashion, leading to the corresponding functionalized adducts as a sole diastereoisomer in most cases [10]. The sequence shown in Scheme 10 illustrates the sequential Michael addition, methyllithium-to-carbonyl addition, and lactone formation.



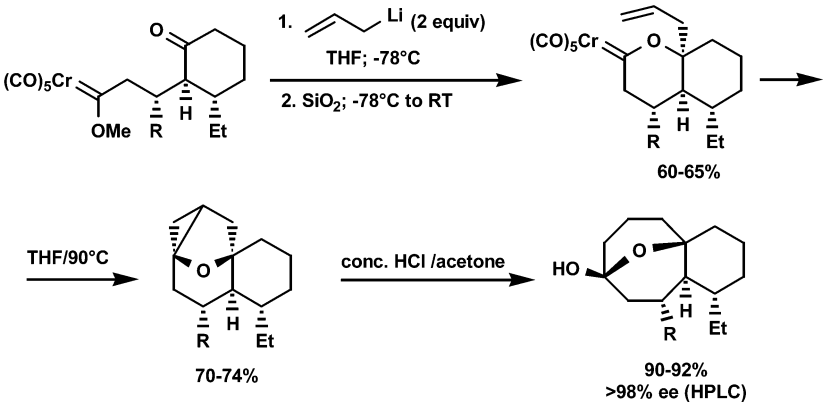
Scheme 10

Even more functionalized lactones with up to five contiguous stereogenic centers could be obtained following the transformations shown in Scheme 11. The configuration of all new stereocenters was unequivocally established by X-ray analysis of the final lactone [10].



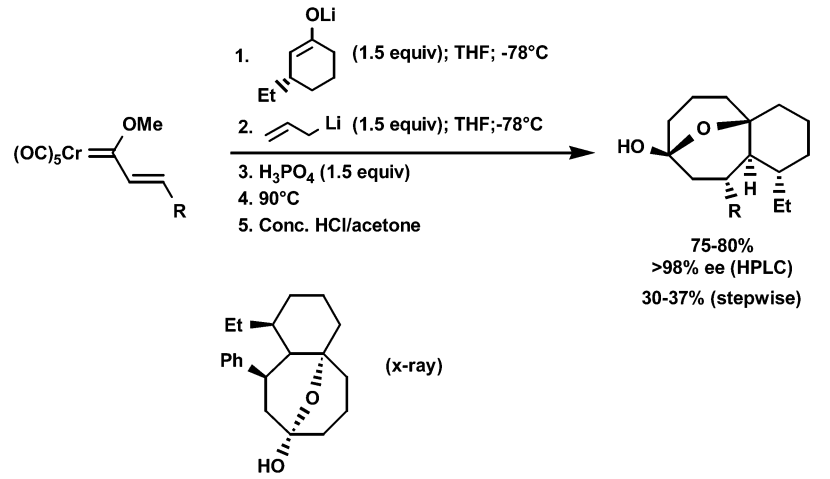
Scheme 11

Taking into account the studies described above, we devised a method for obtaining eight-membered carbocycles following the sequence of reactions shown in Scheme 12 [11]. Thus, the 1,4-addition of a chiral ketone enolate to an alkenyl Fischer carbene complex gives rise to a new carbene complex as a single diastereoisomer. Further reaction with allyllithium diastereoselectively leads to a cyclic carbene. Warming of this complex in THF at 90 °C resulted in the intramolecular cyclopropanation of the allylic moiety to afford the corresponding tetracyclic compound as a single diastereoisomer. Finally, treatment of the cyclopropyl derivative with hydrochloric acid in acetone gives the eight-membered hemiketal as a single stereoisomer (98 % ee).



Scheme 12

Attracted by the possibility of performing all of the reactions described above following a "one-pot" procedure, we carried out all the sequences without the isolation of any intermediate as depicted in Scheme 13. As a result, this strategy was much more efficient (76 % yield) than the multistep process (37 % overall yield). The structure of the final eight-membered carbocycle was unequivocally determined by X-ray structure analysis (Scheme 13).



Scheme 13

ACKNOWLEDGMENTS

The contribution of the members of my group whose names appear throughout the references is greatly acknowledged. This research was supported by the Ministerio de Ciencia y Tecnología of Spain (DGICYT, Grants PB94-1313, PB97-1271). Thanks are also given to MECD, FICYT, and the European Community for a number of doctoral and postdoctoral fellowships.

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