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C–H Insertion Processes on Stabilized Indolyl and *ortho*-Aminophenyl Fischer Carbene Complexes: Synthesis of Azepino[3,2,1-*hi*] indole, Benzazepine and Indole Derivatives

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Fischer carbene complexes have become very useful materials in organic synthesis. Since their discovery in 1964,[1] their chemistry has been extensively studied, and at the present, there are a large number of useful transformations involving Fischer carbene complexes that find application in synthetic organic chemistry,[2] mostly oriented to the preparation of carbo- and heterocycles.[3] In fact, a particularly interesting feature of the chemistry of Fischer carbene complexes is their ability to provide complex polycyclic structures from simple starting materials in cascade processes that usually involve the formation of several C–C bonds.[4]

On the other hand, a very versatile methodology for the formation of C–C bonds is the C–H carbene insertion. These type of processes are commonly observed in reactions involving metal carbenoids.[5] However, they are rare for stabilized Fischer carbene complexes. The more electrophilic character of the carbene carbon atom of the former, which requires the presence of at least one electron-withdrawing group,[5e] could be the reason for this difference behavior in C–H insertion reaction. In fact few examples of C–H insertion are known for stabilized Fischer carbene complexes. We have previously described the formation of oxaborolane or oxazaborolidine derivatives from boroxy Fischer carbene complexes via an intramolecular C–H insertion process.[6] Takeda reported that the reaction of acetoxyalkenylcarbene complexes with electron-rich butadienes afforded bicycloheptane derivatives, along with other compounds, derived from an intramolecular C–H insertion product of the initially formed Diels–Alder adduct.[7] Wienand and Reissig reported the formal insertion of the carbene ligand of pentacarbonyl(benzylidenemethoxy)chromium complex into the β-C–H bond of (*E*)- and (*Z*)-crotonitrile which involves a β-elimination and a reductive elimination reaction.[8] However, as far as we know, only one example of a direct C–H insertion process, in which a typical methoxycarbene chromium complex is involved, has been described thus far.[9]

As a part of our work based on the study of cycloaddition-promoted cascade processes of alkynyl Fischer carbene complexes,[10] we have recently turned our attention to the development of cascade reactions of indolylalkynyl carbene complexes[11] which are interesting starting materials for the synthesis of complex polycyclic systems containing the indole core, a prominent structural unit frequently found in numerous natural products and pharmaceutically active compounds.[12]

In the present paper, we report a new sequential reaction of alkoxy indolyl and *ortho*-aminophenyl alkynyl Fischer carbene complexes that lead to azepino[3,2,1-*hi*]indoles and benzazepines. These unusual transformations involve an initial cycloaddition step followed by an intramolecular C–H insertion process. Based on this transformation we have also extended the C–H insertion reaction to simpler *ortho*-aminophenyl Fischer carbene complexes, in a process that leads to the formation of indoles.

First, we focused on indolylalkynylcarbene complex **1a**, which bears an allyl group at the nitrogen atom (Scheme 1). In order to break the linear arrangement of the triple bond enabling a subsequent intramolecular reaction we chose, as a first approach, the well-known [2+2]-cycloaddition reaction.[10c–d,11a,13] Thus, when we treated carbene complex **1a** with 2,3-dihydrofuran in THF at room temperature and the reaction mixture was subsequently warmed at 90 °C in a sealed tube, we obtained a separable mixture of compounds **2a** and **3** in 57 % combined yield and in a 4.2:1 ratio. Both products were obtained as unique diastereoisomers (Scheme 1). Structural assignments of these new compounds were based on a series of NMR studies. Additionally, the relative configuration of the new stereogenic centres of both compounds was determined by NOESY experiments.

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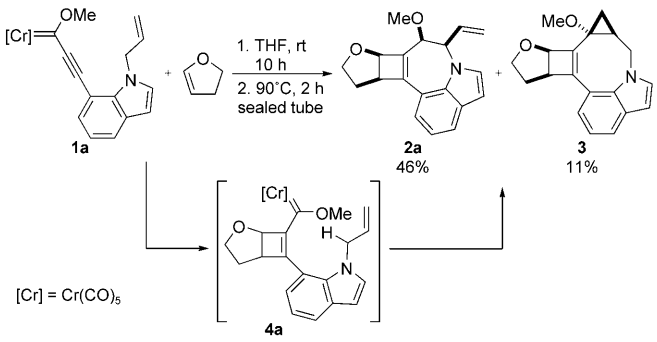
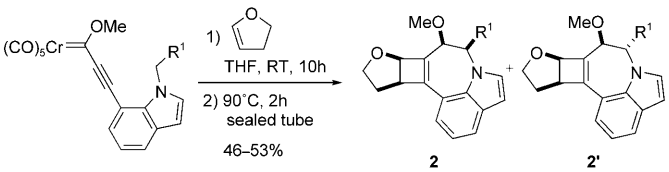


Scheme 1. Synthesis of **2a** and **3** from indolylalkynylcarbene complex **1a**.

The formation of both products can be explained considering first the formation of the intermediate carbene complex **4a**, generated by a formal [2+2]-cycloaddition reaction between the alkynyl Fischer carbene **1a** complex and the 2,3-dihydrofuran. Benzazocine derivative **3**, which could be initially considered as the expected product, would come from the intramolecular cyclopropanation of the double bond of the allylic moiety in carbene complex **4a**. On the other hand, the major product, the azepinoindole derivative **2a** could be explained by the intramolecular C–H insertion reaction of the carbene carbon atom into a C–H bond in α position to the nitrogen atom in **4a**. As far as we know this is the first example in which a seven-membered ring is formed in a C–H carbene insertion process.[14]

In order to examine the scope of this new C–H insertion reaction, a set of experiments were carried out with different *N*-substituted indolylalkynylcarbene complexes **1** (Scheme 2 and Table 1).



Scheme 2. Synthesis of azepino[3,2,1-*hi*]indoles **2** through a sequential [2+2]-cycloaddition/C–H insertion reaction of indolylalkynylcarbene complexes **1**.

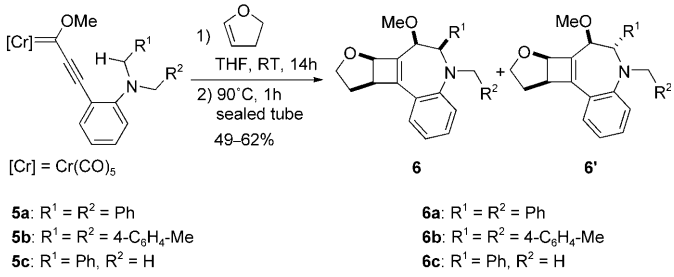
Thus, when the reaction was conducted with the *N*-crotyl carbene complex **1b** (Table 1, entry 2) and 2,3-dihydrofuran under the same reaction conditions described above, the azepinoindole derivative **2b** was exclusively formed in 53% yield and as a single diastereoisomer. This sequential [2+2]-cyclization/C–H insertion reaction could also be successfully carried out with alkynyl carbene complexes **1c** and **1d**, which bear a benzyl and a methoxymethyl group at the nitrogen atom, respectively, leading to azepinoindole derivatives **2c** and **2d** in moderate yields (Table 1, entries 3 and 4). While compound **2c** was formed with complete diastereoselectivity, the azepinoindole **2d** was generated as a 1.3:1 mixture of diastereoisomers. Conversely, when the reaction was carried out with alkynyl carbene complexes **1e** and **1f**, which present a methyl and a propyl group respectively at the nitrogen atom (Table 1, entries 5 and 6), the corresponding azepinoindole derivatives could not be obtained. Taking into account these results, it seems that the presence of an additional activating group is necessary to give rise to the C–H insertion products.

Table 1. Synthesis of azepino[3,2,1-*hi*]indoles **2** and benzazepines **6** by a sequential [2+2] cycloaddition/C–H insertion reaction of Fischer carbene complexes **1** and **5**.

Entry	**1**/**5**	R^1	R^2	Product	Yield [%][a]	dr **2**:**2′**/**6**:**6′**
1	**1a**	$CH=CH_2$	–	**2a**	46[b]	1:0
2	**1b**	(*E*)-CH=CHMe	–	**2b**	53	1:0
3	**1c**	Ph	–	**2c**	49	1:0
4	**1d**	OEt	–	**2d**	50[c]	1.3:1
5	**1e**	H	–	–	–	
6	**1f**	Et	–	–	–	
7	**5a**	Ph	Ph	**6a**	59[d]	3.5:1
8	**5b**	4-Me-C_6H_4	4-Me-C_6H_4	**6b**	62[d]	3.4:1
9	**5c**	Ph	H	**6c**	54[d]	3.1:1

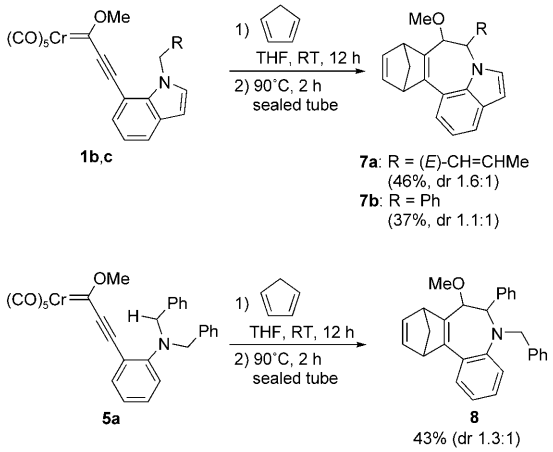
[a] Isolated yield based on starting alkynylcarbene complex. [b] The cyclopropanation product **3** was also obtained with an 11% yield. [c] The product was obtained as a mixture of diastereoisomers which could not be separated. [d] The product was obtained as a mixture of diastereoisomers which could be separated by column chromatography.

This sequential [2+2]-cyclization/C–H insertion reaction could also be accomplished with *ortho*-aminophenylalkynyl Fischer carbene complexes **5**[15] which can be considered structural analogues of carbene complexes **1**. So, when carbene complexes **5** was treated with 2,3-dihydrofuran under the conditions described above, benzazepine derivatives **6** were obtained as a mixture of two diastereoisomers which could be separated by column chromatography (Scheme 3 and Table 1, entries 7–9). The structure of these compounds was determined by NMR analysis and the relative configuration of the new stereogenic centres could be confirmed by X-ray analysis of the major diastereoisomer of benzazepine **6a**.[16]



Scheme 3. Synthesis of benzazepine derivatives **6** from a sequential [2+2] cycloaddition/C–H insertion reaction of alkynylcarbene complexes **5**.

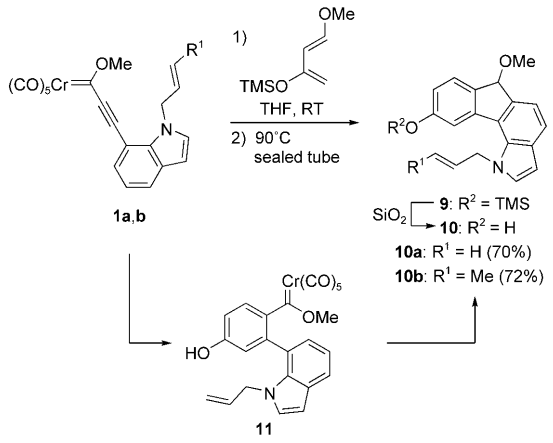
The scope of this sequential process was evaluated by changing the nature of the triggering cycloaddition reaction. The cascade process can be promoted by a [4+2] cycloaddition[17] when cyclopentadiene is employed as diene component. Thus, the reaction of alkynylcarbene complexes **1b**,**c** and **5a** with cyclopentadiene led exclusively to the formation of the C–H insertion products **7** and **8** as a mixture of two out of four possible diastereoisomers with moderate yields (Scheme 4).



Scheme 4. Synthesis of azepino[3,2,1-*hi*]indoles **7** and benzazepine derivative **8** by a sequential [4+2]-cycloaddition/C–H insertion reaction of Fischer carbene complexes **1** and **5**.

However, when the reaction was carried out with 1-methoxy-3-trimethylsililoxy-1,3-butadiene (Danishefsky's diene) was used as the diene component the corresponding C–H insertion products were not obtained. In this case, the reaction of carbene complexes **1a**,**b** gave rise exclusively to indenoindoles **10** as a result of a sequential [4+2]-cycloaddition/cyclopentannulation[18] process (Scheme 5).

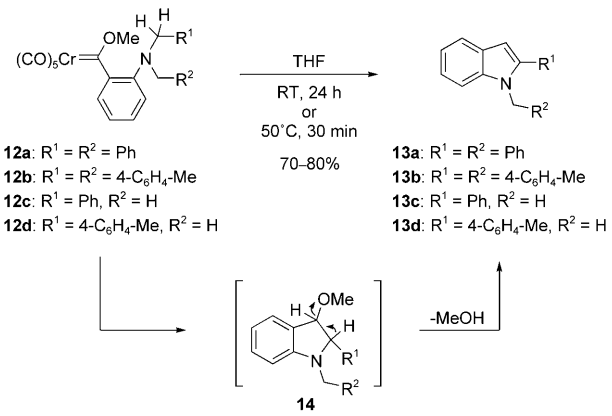
This different behavior could be explained taking into account the geometry of the carbene complex intermediate **11**.



Scheme 5. Formation of indenoindoles **10** through a sequential [4+2] cycloaddition/cyclopentannulation reaction

Due to the aromatization of the Diels–Alder cycloadduct promoted by the elimination of one molecule of methanol, the complete planar arrangement in **11** would probably place the carbene carbon atom away from the methylene group in α position to the nitrogen atom, disfavoring the C–H insertion reaction. This fact would on the contrary favor the cyclopentannulation reaction.

Taking into account the chemical behavior shown by alkynylcarbene complexes **1** and **5**, we decided to further investigate the possibility of carrying out a C–H insertion process with the simpler methoxy *ortho*-aminophenyl Fischer carbene complexes **12** (Scheme 6). Thus, Fischer carbene complexes **12** were synthesized from 2-bromoanilines following standard procedures (see Supporting Information). Interestingly, although complexes **12** could be efficiently synthesized, a little amount of compound **13** was obtained during the reaction work-up. Moreover, in a single experiment, we observed that carbene complexes **12** was fully transformed into indoles **13** through an intramolecular C–H insertion reaction at room temperature in 24 h.[19] The same transformation takes place in 30 min at 50 °C (Scheme 6).



Scheme 6. Transformation of *o*-aminophenyl carbene complexes **12** into indoles **13** by an intramolecular C–H insertion reaction.

The formation of 1,2-disubstituted indoles **13** could be explained through an intramolecular insertion reaction of the carbene carbon into the C–H bond of the benzylic carbon of Fischer carbene complex **12**. The resulting intermediate **14** of this C–H insertion would experiment a spontaneous aromatization through the loss of a molecule of methanol affording indole **13**. As it was observed for alkynylcarbene complexes **1** and **5**, the C–H insertion only took place in the benzylic positions and no product from an insertion in the methyl group was obtained when the reaction was carried out with *N*-methyl substituted complexes **12c** and **12d**.

In conclusion, we have described a new sequential [*n*+2] cycloaddition/C–H insertion reaction of stabilized indolyl and *ortho*-aminophenyl alkynyl Fischer chromium carbene complexes which leads to the formation of azepino[3,2,1-*hi*]indoles and benzazepines, respectively. It is also remarkable that for the best of our knowledge this is the first time

that a seven-membered ring has been generated in a C–H carbene insertion process. On the other hand, azepino[3,2,1-*hi*]indole moiety have a high synthetic interest because it is present in compounds with important and specific biological activities.[20] As an application of this chemical behavior we have also describe the transformation of *ortho*-aminophenyl carbene complexes into 1,2-disubstituted indoles.

Experimental Section

General procedure for preparation of azepino[3,2,1-*hi*]indoles 2 or benzazepine derivatives 6: 2,3-Dihydrofuran (2 mmol) was added to a solution of Fischer carbene complex **1** or **5** (0.5 mmol) in THF (10 mL), and the mixture was stirred at room temperature under argon atmosphere until the TLC analysis showed the disappearance of **1** or **5**. Then the tube was sealed and the solution was heated at 90 °C during two hours. The mixture was diluted with hexane (30 mL) and was exposed to air and light. Finally, the mixture was filtered through a pad of Celite, solvents were removed under reduced pressure and the crude product was purified by column chromatography to afford **2** or **6**.

General procedure for preparation of 1,2-disubstituted indoles 13: A solution of Fischer carbene complex **12** (0.5 mmol) in THF (10 mL) was stirred under argon atmosphere at room temperature during 24 h or at 50 °C during 30 min. Then the mixture diluted with hexane (30 mL) and was exposed to air and light. Finally, the mixture was filtered through a pad of celite, solvents were removed under reduced pressure and the crude indole **13** was purified by column chromatography.

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Keywords: benzazepines · carbenes · cascades · C–H insertion · heterocycles

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