Synthetic Methods

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[1,5]-Hydride Transfer/Cyclizations on Alkynyl Fischer Carbene Complexes: Synthesis of 1,2-Dihydroquinolinyl Carbene Complexes and Cascade Reactions**

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Cascade [1,5]-hydride transfer/cyclization reactions are synthetically powerful strategies for the construction of heterocycles involving a C–H to C–C transformation. The most typical examples of this relatively unusual reaction sequence involve the cyclization of *N*-*N*-dialkyl-2-vinylanilines,[1] which results from the *tert*-amino effect[2] (Figure 1 a). In these processes the first and rate-limiting step comprises of a hydride migration from the carbon atom, α to the hetero atom, to the electrophilic position of the vinyl group. Thus, suitable systems for the tandem reaction must feature a heteroatom, to stabilize the carbocation that develops upon hydride migration, and a strong electron-withdrawing group on the terminal position of the double bond. More recently, this strategy has been extended to functionalize the α position of ethers and carbamates, and even tertiary benzylic C–H bonds in processes promoted by Lewis acid catalysts (Figure 1 b).[3]

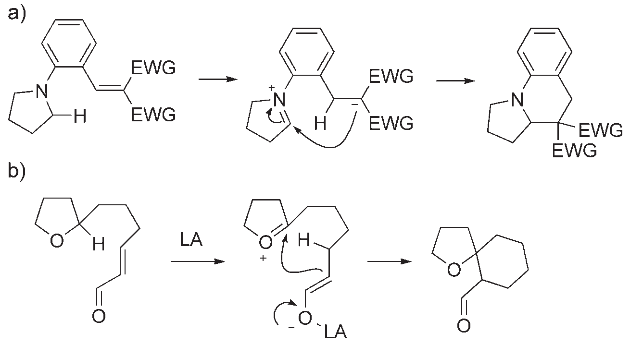
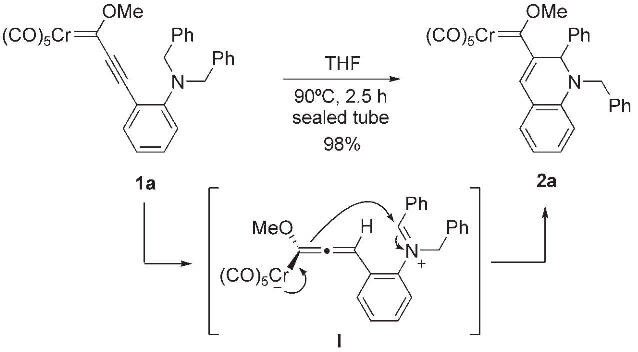


Figure 1. Examples of [1,5]-hydride transfer/cyclization cascades.

To the best of our knowledge, there is no precedent for analogous hydride-transfer-promoted cyclizations involving triple bonds, despite the synthetic power of this type of cascade isomerization. In contrast, *ortho*-alkynyl anilines undergo metal-catalyzed *5-endo-dig* cycloisomerizations leading to indole derivatives.[4]

As a part of our work on the chemistry of alkynyl Fischer carbene complexes,[5] we turned our attention to the study of chromium *ortho*-aminophenylalkynyl complexes (**1**; Scheme 1). Alkynyl carbene complex **1a** was synthesized by standard procedures,[6] and it was stable at room temperature, however, when a solution of **1a** in THF was heated at 90 °C in a sealed tube, new carbene complex **2a** was isolated in 98 % yield after the workup (Scheme 1).



Scheme 1. Synthesis of 1,2-dihydroquinolinyl carbene complex **2a**.

The formation of carbene complex **2a** can be explained by an intramolecular two-step process which involves the migration of one hydride, from the benzylic carbon center to the highly electrophilic β carbon of the triple bond of alkynyl carbene complex **1a**, to generate zwitterionic intermediate **I**. The subsequent cyclization step would then lead to new carbene complex **2a**. The presence of the strong electron-withdrawing effect of the chromium pentacarbonyl moiety is essential to provide a proper scenario for the [1,5]-hydride transfer/cyclization in which the internal sp carbon atom participates. This chemical behavior does not have any precedent in the chemistry of Fischer carbene complexes. Moreover, to the best of our knowledge, this reaction represents the first example of a hydride migration/cyclization cascade involving a triple bond.

An NMR study revealed that a temperature of 70 °C is necessary for the reaction to take place, although 90 °C is a more convenient temperature as it provides the product after a shorter reaction time.

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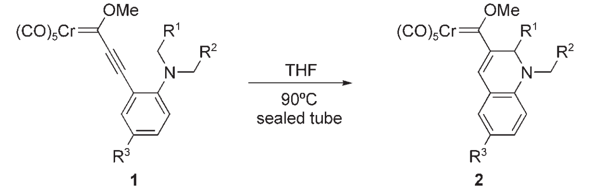
Next, we tried to determine the scope of this reaction by using different *ortho*-aminophenylalkynyl carbene complexes (**1**), in which the nitrogen atom and the phenyl ring substituents were modified.

As shown in Table 1, *N*-benzylalkynyl carbene complexes undergo this hydride transfer/cycloaddition process with moderate to very good yields. The substituents on the tertiary amine have a significant influence on the reaction time and the yield of the reaction. High yields are obtained when the initial alkynyl carbene complex has either benzyl or alkylbenzyl substituents on the nitrogen atom (Table 1, entries 1, 2, and 5). A decrease in the product yield is observed when the initial carbene complex bears an electron-withdrawing group, such as a chloro or bromo substituent, on the benzene rings (Table 1, entries 3 and 4). The decrease in the yields is associated with longer reactions times because part of the product may decompose as a result of the extended exposure to high temperatures.

Table 1: Synthesis of 1,2-dihydroquinolinyl carbene complexes (**2**) by a [1,5]-hydride transfer/cyclization process.

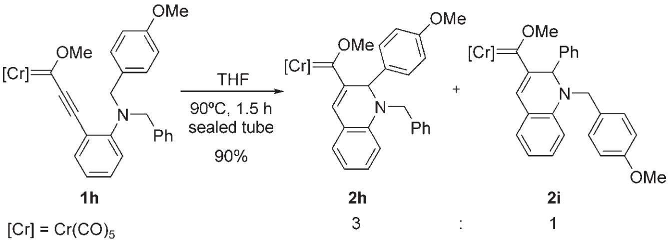


Entry	**1**	R^1	R^2	R^3	**2**	*t* [h]	Yield [%]
1	**1a**	Ph	Ph	H	**2a**	2.5	98
2	**1b**	Ph	Ph	Me	**2b**	2	95
3	**1c**	Ph	Ph	Cl	**2c**	6	72
4	**1d**	4-Br-Ph	4-Br-Ph	H	**2d**	10	63
5	**1e**	4-Tol	4-Tol	H	**2e**	2	96
6	**1f**	Ph	H	H	**2f**	9	65
7	**1g**	Ph	*t*Bu	H	**2g**	1.5	85

When the reaction was carried out with nonsymmetric carbene complex **1f** the corresponding quinolinyl carbene complex **2f** was obtained in a 65 % yield after 9 hours (Table 1, entry 6). Notably, the reaction proceeds with total chemoselectivity, as only migration of the benzylic hydrogen atom was observed. The use of a bulkier group, such as a *neo*-pentyl group, gave rise to carbene **2g** in better yield after a shorter reaction time (Table 1, entry 7). Again, only migration of the benzylic hydrogen atom was observed.

In the case of alkynyl Fischer carbene complex **1h**, which bears both a benzyl and a 4-methoxybenzyl group as substituents on the nitrogen atom (Scheme 2), the formation of two reaction products, **2h** and **2i**, in a 3:1 ratio was observed. The major product, **2h**, derives from the intramolecular addition of a hydride from the 4-methoxybenzyl group, showing that the presence of an electron-donor group in the phenyl ring favors the formation of the 1,2-dihydroquinolinyl carbene complex.

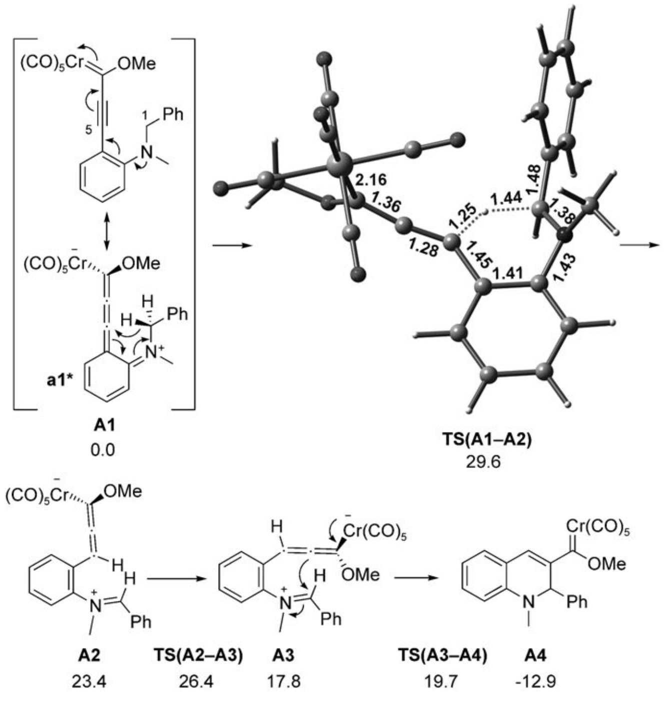
The results presented above with respect to the influence of the substituents, can be explained by considering the hydride migration that gives rise to zwitterionic intermediate **I** as the rate-limiting step in the mechanism depicted in Scheme 1. Thus, the reaction will be favored in the presence of substituents that can stabilize the positive charge that develops upon hydride migration.



Scheme 2. Competition reaction of alkynyl carbene complex **1h**.

This mechanistic proposal is also consistent with DFT computations carried out on model system **A**.[7,8] We found that the transformation of **A1** into **A4** takes place through the stepwise mechanism depicted in Scheme 3.

As expected by the experimental observations, the key step of the sequence is the hydrogen atom migration that leads to zwitterionic species **A2**. We obtained an activation free energy of 29.6 kcal mol^{-1} for this step,[9] which is a reasonable barrier for a process that takes place at 90 °C. The hydrogen atom migration occurs in an asynchronous concerted manner through a late transition state, as shown by the shorter distance found for the newly formed C–H bond (C5–H = 1.25 Å) compared to the C–H bond that is being broken (C1–H = 1.44 Å). The structure obtained for **TS(A1–A2)** (TS = transition state)resembles the transition state of a [1,5]-sigmatropic rearrangement. Indeed, taking into account the



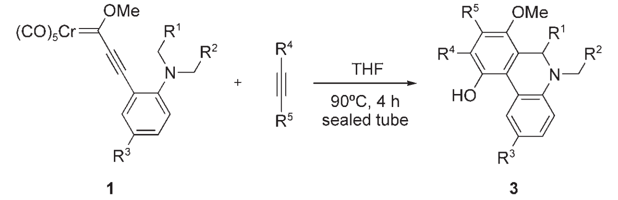
Scheme 3. Calculated energies for the formation of dihydropyridine **A4**. The values are the relative Gibbs free energies (kcal mol^{-1}) obtained at the B3LYP/6-311++G**+LANL2DZ//B3LYP/6-31G*+LANL2DZ level.

push/pull nature of **A1**, the canonical form (**a1***) must have an important contribution in the resonance hybrid, and thus, the hydrogen atom migration could be envisioned as a sigmatropic rearrangement. This step is endergonic ($\Delta G_{\text{A2-A1}} = 23.4\ \text{kcal mol}^{-1}$), and gives rise to highly unstable zwitterionic intermediate **A2**. Then, after a conformational interconversion into **A3**, cyclization through an almost barrierless process ($\Delta G_{\text{act}} = 2.1\ \text{kcal mol}^{-1}$) gives rise to dihydroquinoline **A4** with regeneration of the Fischer carbene complex moiety. The overall process is exergonic ($\Delta G_{\text{A4-A1}} = -12.9\ \text{kcal mol}^{-1}$).

Notably, the 1,2-dihydroquinolines (**2**) obtained through the hydride transfer/cyclization processes are new alkenyl Fischer carbene complexes. Taking into account the synthetic versatility of Fischer carbene complexes, which can be transformed through a myriad of different reactions,[10] this cascade cyclization offers the opportunity to manipulate the 1,2-dihydroquinolines to introduce different functionalities or incorporate more complex cyclic systems.

We explored the possibility of developing more sophisticated cascade processes starting from the initial alkynyl carbene complex. Thus, the isomerization of the Fischer carbene complexes (**1**) was promoted in the presence of alkynes. When a solution of alkynyl carbene complex **1b** in THF was heated at 90 °C in the presence of 4 equivalents of 1-hexyne, the reaction gave rise to 5,6-dihydrophenantridine derivative **3a** (Table 2). The structure of **3a** was determined by NMR techniques and confirmed by X-ray crystallographic analysis.[11] These conditions were used for other carbene complexes and both terminal and internal alkynes (Table 2).

Table 2: Synthesis of 5,6-dihydrophenantridines (**3**) by a hydride transfer/cyclization/Dötz benzannulation cascade process.



Entry	1	R1	R2	R3	R4	R5	3	Yield [%]
1	**1b**	Ph	Ph	Me	Bu	H	**3a**	72
2	**1b**	Ph	Ph	Me	TMS	H	**3b**	63
3	**1e**	4-Tol	4-Tol	H	CH_2OMe	H	**3c**	42
4	**1e**	4-Tol	4-Tol	H	Et	Et	**3d**	60

TMS = trimethylsilyl.

The formation of the 5,6-dihydrophenantridines (**3**) can be explained by a sequential process in which quinolinyl carbene complex **2**, formed in the hydride transfer/cyclization reaction, participates in a subsequent Dötz benzannulation[12] reaction with the alkyne. From a synthetic point of view, this is a remarkable transformation that provides complex heterocyclic structures from readily available materials in a single step.

In conclusion, we have described a novel [1,5]-hydride transfer/cyclization process of alkynyl Fischer carbene complexes which leads to 1,2-dihydroquinolynyl carbene complexes. This reaction represents the first example of this type of processes involving triple bonds. Moreover, the reactivity of newly formed carbene complexes can be exploited in the development of more complex cascade reactions to expand the synthetic potential of this transformation. Herein we have presented preliminary examples of a hydride transfer/cyclization/Dötz benzannulation cascade which leads to 5,6-dihydrophenantridine derivatives.

Experimental Section

General procedure for the synthesis of 1,2-dihydroquinolinyl carbene complexes **2**: A solution of alkynyl carbene complex **1** (0.5 mmol) in THF (8 mL) was heated to 90 °C in a sealed tube under an argon atmosphere until the TLC analysis showed the completion of the reaction (the solution becomes dark violet). The mixture was then cooled to room temperature after which it was diluted with hexanes (10 mL) and filtered through a pad of Celite. Removal of the solvent under reduced pressure afforded carbene complex **2** as a violet solid. The crude complex was purified by column chromatography on silica gel.

General procedure for the synthesis of 5,6-dihydrophenantridines **3**: The procedure is identical to that described above but in the presence of alkyne (2 mmol) in THF (10 mL). The crude mixture was purified by column chromatography on silica gel.

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[6] Experimental details on the syntheses of the carbenes (**1**) are provided on the Supporting Information.

[7] DFT computational calculations were carried out by employing the B3LYP functional. Geometry optimizations were carried out by employing the 6-31G* basis set for C, H, N, and O, and the

LANL2DZ ECP for Cr. Single-point energy calculations on the optimized structures were conducted by employing the 6-31++G** basis set for the C, H, N, and O and LANL2DZ for Cr. See the Supporting Information for details.

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[9] Four different conformers, very close in energy, were found for the transition state of the migration of a benzylic hydrogen atom. Only the lowest energy structure, **TS(A1–A2)**, was considered. Moreover, the transition state for the migration of a hydrogen atom from the methyl group, not observed experimentally, featured a Gibbs free energy value that was 3.4 kcal mol^{-1} higher than that for **TS(A1–A2)**.

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[11] CCDC 687236 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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