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Intermolecular and Regioselective Access to Polysubstituted Benzo- and Dihydrobenzo[*c*]azepine Derivatives: Modulating the Reactivity of Group 6 Non-Heteroatom-Stabilized Alkynyl Carbene Complexes

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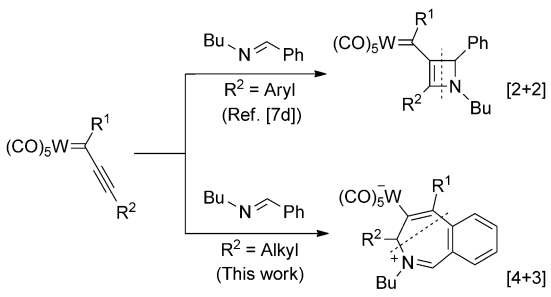
Abstract: We highlight the versatility of non-heteroatom-stabilized tungsten–carbene complexes **3** synthesized in situ, which have been used in a modular approach to access 2-benzazepinium isolable intermediates **5**. By employing very mild conditions, benzazepinium derivatives **5** have been obtained in high yield from simple compounds, such as acetylides **2**, Fischer-type alkoxycarbenes **1**, and phenylimines **4**. The process, involving a formal [4+3] heterocycloaddition, occurs in a totally regioselective manner, which differs from the approach previously observed in similar procedures for other carbene analogues. This work, which involves three components, reveals a control of the reactivity of non-heteroatom-stabilized carbene complexes **3** ([4+3] vs. [2+2]-heterocycloaddition reactions) depending on the acetylide substitution pattern. The influence of the substitution pattern in the behavior of the complexes has been computationally analyzed and rationalized. Finally, elaboration of the 2-benzazepinium intermediates allows access to 3*H*-benzo[*c*]azepines **6** and 3*H*-1,2-dihydrobenzo[*c*]azepines **7**–**9** with high control of the substitution of the nine positions of the heterocycle.

Introduction

Benzazepines are a family of heterocycles that have received special attention due to pharmacological properties exhibited by several compounds of this family. These compounds have shown activity against leukemia,[1] HIV,[2] high blood pressure,[3] and Alzheimer disease[4] among others. As the result of this activity, the synthesis of these nitrogenated heterocycles has attracted high interest in recent years. However, although many intramolecular methodologies have been described, reports of intermolecular examples of benzazepine synthesis are very scarce, especially for 2-benzazepine derivatives.[5]

On the other hand, our group has recently moved to non-heteroatom-stabilized carbenes as a synthetic alternative to Group 6 Fischer-type carbene complexes[6] due to significant differences observed in their reactivity.[7] Accordingly, we recently described a formal [2+2] heterocycloaddition in their reaction with imines,[7d] a process unknown for heteroatom-stabilized analogues. In the course of this study, we observed, as an unexpected result, a new reaction behavior promoted by a change in the alkynyl substitution of the non-heteroatom-stabilized carbene complexes.

Herein, we report an efficient synthesis of stable benzo[*c*]azepinium intermediates through a regioselective formal [4+3] heterocycloaddition of non-heteroatom-stabilized alkynyl(pentacarbonyl)tungsten–carbenes and phenylimines. From this work, there is an emergence of a remarkable differential reactivity of the alkynyl non-heteroatom-stabilized carbenes that depends on the aryl[7d] or alkyl substitution at the C_β position (Scheme 1). The influence of this substitution pattern on the carbene behavior could be explained and rationalized through



Scheme 1. Synthesis of azetinyl carbenes or benzo[*c*]azepinium derivatives from "in situ" generated non-heteroatom-stabilized carbene complexes and phenylimines.

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the accomplishment of several computational studies. Moreover, the isolation of azepinium derivatives and further transformation permits access to a family of polysubstituted benzo- and dihydrobenzo[*c*]azepine derivatives.

Results and Discussion

Synthesis of benzazepinium metalates 5

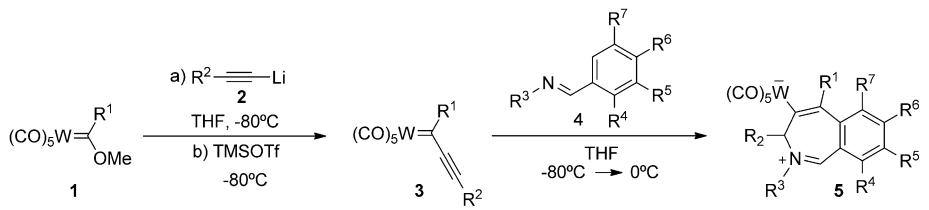
We started from easy-to-handle corresponding Fischer-type methoxycarbenes **1** as precursors of non-heteroatom-stabilized alkynyl carbenes **3**. These compounds were synthesized in situ by the sequential treatment of **1** in THF at −80 °C with various acetylides **2** and trimethylsilyl trifluoromethanesulfonate (TMSOTf).[8] Next, two equivalents of phenylimine **4** were added to this solution, and the reaction mixture was allowed to warm to 0 °C. Removal of the solvent and purification by column chromatography of the residue afforded benzo[*c*]azepiniumpentacarbonyl tungstenates **5a**–**q** in high overall yield from Fischer carbenes **1** (Table 1).[9] The structure of the benzazepinium rings was determined by NMR spectroscopic (mono- and bidimensional) analysis and was unambiguously confirmed by X-ray diffraction studies of a single crystal obtained after recrystallization of **5a** from a mixture of pentane/CH_2Cl_2.[10,11] The high versatility of the reaction in terms of the Fischer carbene precursor **1** as aryl (**5a**–**f** and **5i**–**q**), alkyl (**5g**), and alkynyl (**5h**) carbenes employed can be inferred (Table 1). Additionally, this versatility can also be observed because a wide family of phenylimines **4** can be used, thus allowing the formation of 2-benzazepine derivatives with a high control over the substitution at the four positions of the arene ring (i.e., **5i**–**q**). Thus, the reaction proceeds in the presence of electron-donating (**5j**,**k**) or electron-withdrawing groups (**5l**–**o**). The tolerance to a bromine group (**5o**) should receive a special mention because the field to further cross-coupling reactions is opened. Finally, the use of a cross-conjugated dialkynyl carbene (Table 1, entry h) reveals a totally selective reaction that leads to the formation of the azepine ring **5h**, instead of the synthesis of the corresponding 2-azetinyl carbene with the participation of the triple bond with the aryl group (Scheme 1).

From a structural point of view, this [4+3] heterocycloaddition proceeds with the participation of the imine group as a 1-azadiene unit in a totally regioselective manner. However, this regioselectivity is opposite to that previously observed for formal [4+3]-heterocycloaddition reactions of simple 1-azadienes with chromium[12] heteroatom-stabilized alkynyl carbene complexes[13] or heterocycloaddition reactions with 1-azadienes and other α,β-unsaturated carbene or carbenoid derivatives.[14]

Mechanistic studies

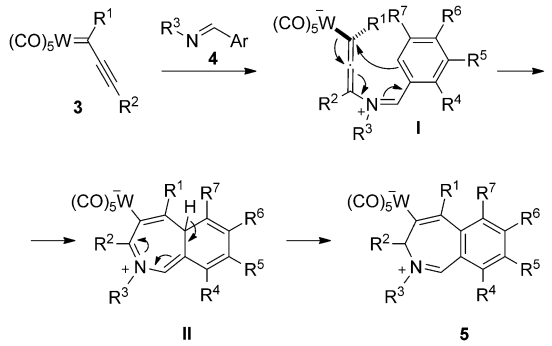
A simplified mechanistic proposal for the formation of azepinium derivatives **5** is outlined in Scheme 2. Thus, after the regioselective attack of imine **4** at C_β on the non-heteroatom-stabilized carbene **3**, the allenyl metalate intermediate **I** could evolve to form intermediate **II** through a cyclization step involving a [1,2]-pentacarbonyltungsten shift.[15] Finally, a [1,5]-

Table 1. Synthesis of azepinium derivatives **5**.



Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield [%][a]
5a	Ph	*c*-C_3H_5	Bu	H	H	H	H	88
5b	Ph	*i*-C_3H_7	Bu	H	H	H	H	95
5c	*p*-Tol	*c*-C_3H_5	Bu	H	H	H	H	82
5d	Ph	*c*-C_3H_5	allyl	H	H	H	H	71
5e	Ph	*i*-C_3H_7	allyl	H	H	H	H	93
5f	Ph	Bu	Bu	H	H	H	H	61
5g	*c*-C_3H_5	*i*-C_3H_7	Bu	H	H	H	H	29
5h	Ph-C≡C	*i*-C_3H_7	Bu	H	H	H	H	82
5i	Ph	*i*-C_3H_7	Bu	H	H	Me	H	92
5j	Ph	*i*-C_3H_7	Bu	H	H	OMe	H	94
5k	Ph	*i*-C_3H_7	Bu	H	H	OTBDMS	H	92
5l	Ph	*i*-C_3H_7	Bu	H	H	NO_2	H	76
5m	Ph	*i*-C_3H_7	Bu	H	H	CO_2Me	H	86
5n	Ph	*i*-C_3H_7	Bu	H	H	CN	H	72
5o	Ph	*i*-C_3H_7	Bu	Br	H	H	H	89
5p	Ph	*i*-C_3H_7	Bu	H	Me	H	H	75[b]
5q	Ph	*i*-C_3H_7	Bu	H	Me	H	Me	84

[a] Overall yield from Fischer carbenes **1** after purification by column chromatography. [b] A 2.8:1 mixture with its isomer (R^5 = H; R^7 = Me). TBDMS = *tert*-butyldimethylsilyl.



Scheme 2. Mechanistic proposal for the formation of benzo[*c*]azepiniumpentacarbonyl tungstenates **5**.

hydrogen shift and re-aromatization would lead to the formation of benzo[*c*]azepinium **5**.

To explain the formation of **5** in contrast with the previously reported synthesis of azetinyl carbenes,[7d] a series of theoretical calculations were performed by using the density functional theory with the M06 functional including the solvent (i.e., THF) along the reaction path. Complete reaction-path calculations were carried out starting from carbenes **3** with a different substitution to yield the azetinyl carbene or benzazepinium derivative **5**. We chose R^2 = Bu or Ph as representative examples for both paths in **3** (Scheme 1). Both reaction paths share most of the features (see Figures S1 and S2 in the Supporting Information).

The reactivity of intermediate **I** is the key to understanding the different possibilities found experimentally for the different carbene complexes. The transition structures (TSs) in both cases (R^2 = Bu or Ph) that lead to the formation of the four-membered rings have very similar geometrical features (see Figure S3 in the Supporting Information). In agreement, both TSs appear with quite similar energies (ΔE = 16.8 and 16.5 kcal mol^{-1} above the starting materials, with the Ph derivative slightly more stable).

The main difference among the two reaction paths concerns the transition structures that lead to the seven-membered-ring derivatives **5**. The transition structure has an energy of 15.2 kcal mol^{-1} above the starting materials in the case of R^2 = Bu, whereas the energy for the TS is 22.0 kcal mol^{-1} for R^2 = Ph. Analysis of the geometries for these two TSs (Figure 1) allows understanding of this energy difference. In the case of R^2 = Ph, this phenyl group, the metal moiety (which almost completely migrates), and the incipient seven-membered ring cannot be accommodated in a completely planar conformation (dihedral angle = 28.9°) to account for the energy stabilization through conjugation. The cross-conjugation nature of this intermediate avoids efficient stabilization of the TS, which causes an energetic penalty that leads to an increase in energy for this TS. Accordingly, the path that leads to **5** is clearly hampered by a higher energy barrier for R^2 = Ph.

A direct comparison of the energetics involved in the reaction of intermediates **I** is shown in Figure 2. For the paths taken by the azetinyl carbene, the key transition structures (**TS I-II_aze**) were energetically (ΔE = 16.8 and 16.5 kcal mol^{-1}

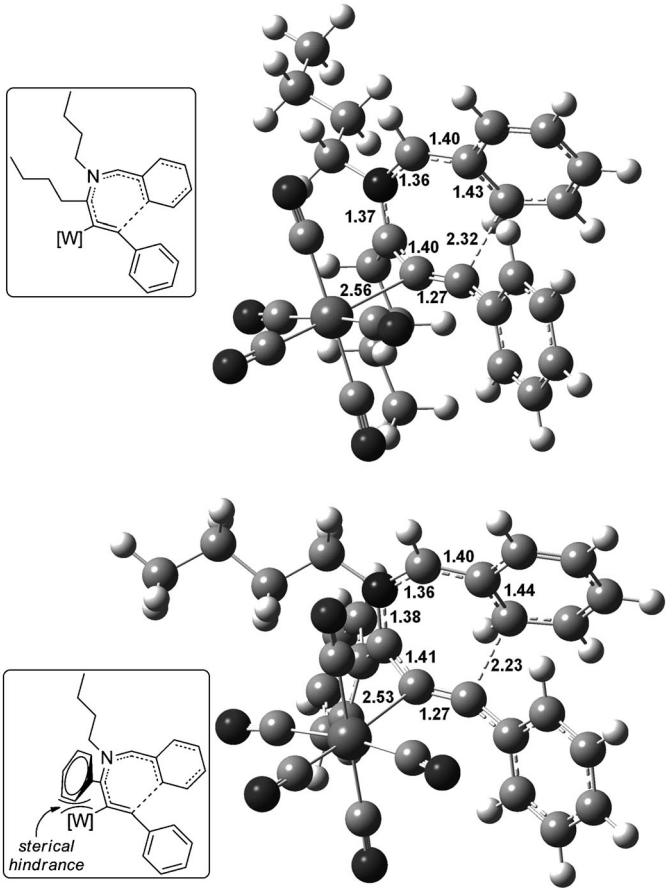


Figure 1. Transition structures that lead to **5** for R^2 = Bu (**TS I-II_Bu**; top) and R^2 = Ph (**TS I-II_Ph**; bottom). Bond distances are expressed in Å.

above the starting materials) and geometrically very similar. However, a clear difference was found in the transition structures that lead to **5**. When R^2 = Bu, the relevant structure (**TS I-II_Bu**) show a geometry without any relevant distortions, which allows an energy barrier of only 15.2 kcal mol^{-1} ($\Delta\Delta E$ = 1.6 kcal mol^{-1} below the energy of **TS I-II_aze_Bu**). The formation of very stable **5** is the reaction driving force. However, when R^2 = Ph, this substituent in **TS I-II_Ph** appears to be twisted and is not coplanar to the metal moiety and the incipient seven-membered ring. Due to this geometry, the energy barrier is 22.0 kcal mol^{-1} ($\Delta\Delta E$ = 5.5 kcal mol^{-1} higher than the competing **TS I-II_aze_Ph**). Thus, changing the R^2 group from Bu to Ph alters the relative energies of the crucial steps through the different electronic features of the groups. The formation of azetinyl carbenes (i.e., **TS I-II_aze_Ph**) is preferred when R^2 = Ph; in contrast, **5** is the main product (i.e., **TS I-II_Bu**) when R^2 = Bu.

Once the most accessible TS in each case has been surmounted, the reaction can only proceed with the formation of the final products along the corresponding path because these steps are not expected to be reversible due to the high energy barriers for the back-reactions. In the case of R^2 = Bu, the formation of very stable **5** is produced after a hydrogen-atom migration. These data are in accordance with the experimental findings and provide a mechanistic explanation of the ob-

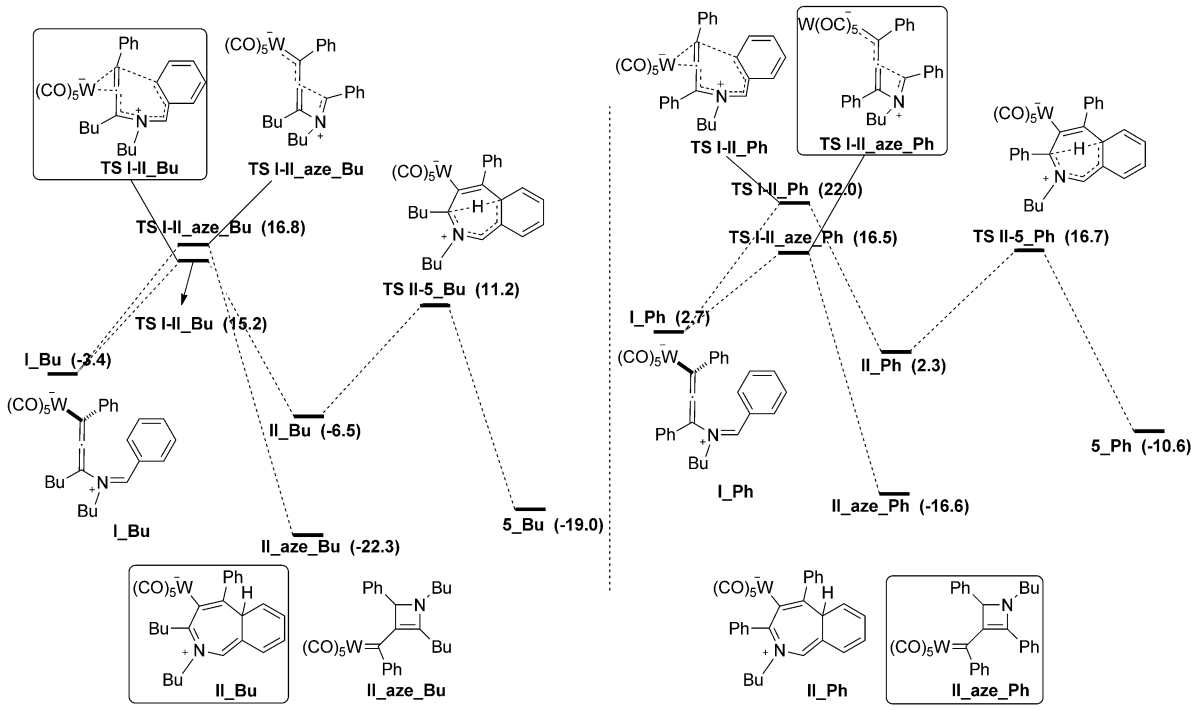
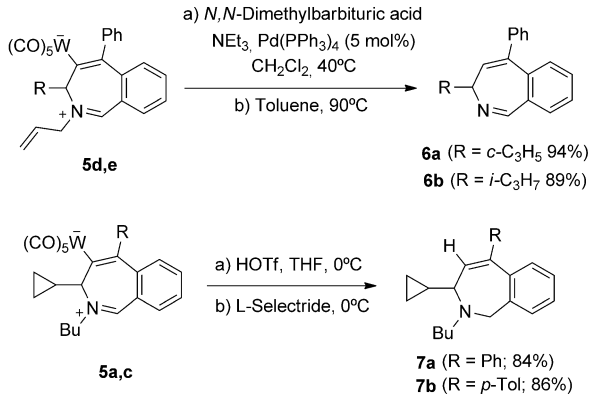


Figure 2. DFT calculations for the key steps along the reaction path for $R^2 = Bu$ (left) and $R^2 = Ph$ (right). The preferred transition states and products are shown in rectangles. The energies given in brackets [kcal mol^{-1}] are relative to the starting materials.

served product formation. The key difference between the two paths (and, thus, the diverse reaction products) is the relative stability of the TSs that arise at the key steps. For the compounds in which $R^2 = Ph$, the energy difference between the two reaction paths ($\Delta\Delta E = 5.5$ kcal mol^{-1}) should lead to high selectivity for the azetinyl carbene. However, the preferred product is the seven-membered ring when $R^2 = Bu$; in this case, it should be noted that the energy difference between both paths ($\Delta\Delta E = 1.6$ kcal mol^{-1}) is below the computational error of the method, although a clear trend, in agreement with the experimental findings, is found. These energy differences should be present as similar substituents are placed as the R^2 group. Therefore, this result can be generalized to other different alkyl and aryl substituents.[16]



Scheme 3. Synthesis of benzazepines **6** and dihydrobenzazepines **7**.

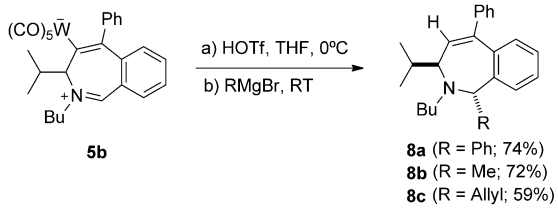
Synthesis of polysubstituted azepines upon transformation of benzazepinium zwitterions 5

Once the synthesis of the azepinium rings could be achieved, we decided to take advantage of the potential reactivity of compounds **5** as the next step to access to a family of metal-free benzo- and dihydrobenzo[*c*]azepine derivatives.

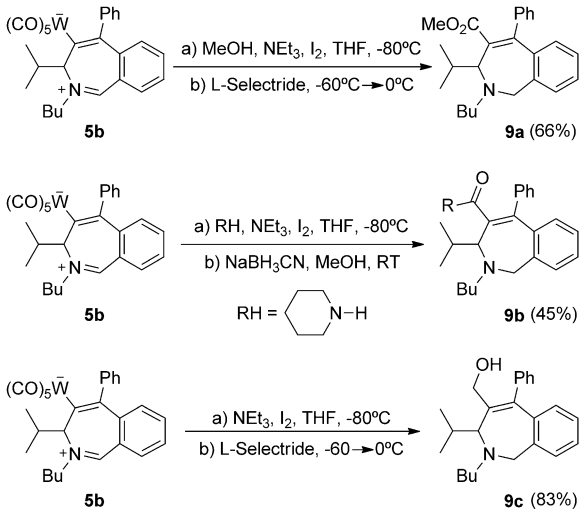
Thus, *N*-allylic azepinium metalates **5d,e** were transformed in high yield into 3*H*-benzo[*c*]azepines **6a,b** through a modification of a palladium-catalyzed Tsuji–Trost deallylation[17] (Scheme 3). On the other hand, the nucleophilicity of C4 and electrophilicity of C1 of azepinium rings **5** allows their transformation into partially reduced compounds. Thus, 2,3-dihydro-1*H*-benzo[*c*]azepines **7a,b** were readily accessed from azepiniums **5a,c** by using a one-pot treatment with trifluoromethanesulfonic acid (HOTf) followed by nucleophilic hydride addition.

It can be observed from Table 1 that C1 and C4 are the only two – out of nine – positions of the benzo[*c*]azepine ring that cannot be controlled by the combination of the Fischer carbene **1**, acetylide **2**, and phenylimine **4** substitution patterns. However, after proto-demetalation of azepinium **5b**, a one-pot treatment with aryl-, alkyl- or allylmagnesium bromide rises into the formation of 1-substituted-2,3-dihydro-1*H*-benzo[*c*]-azepines **8a–c** as single diastereoisomers[18] (Scheme 4). The diastereoselectivity of the reaction for the C1 attack emerges from the shielding effect of the alkyl group placed at C3.

Finally, starting from benzazepinium **5b**, functionalization at the C4 position could also be accessed following the methodology developed by Iwasawa and co-workers[19] (Scheme 5);



Scheme 4. Diastereoselective synthesis of dihydrobenzazepines **8**.



Scheme 5. Selective access to 4-substituted dihydrobenzazepines **9**.

thus, methoxycarbonylation of **5b** followed by selective hydride addition rises into the formation of functionalized dihydrobenzazepine **9a**. In a similar approach, the use of piperidine instead of methanol allows the aminocarbonylation of **5b**, thus resulting in the direct introduction of an amide group at that position.[20] After the corresponding reduction step, dihydrobenzazepine **9b** was isolated. Finally, dihydrobenzazepine **9c** could also be obtained in high yield through direct hydroxymethylenation of **5b** when the reaction was performed in the absence of a nucleophile in the first step.

Conclusion

We have established a smooth, simple, and efficient protocol for the intermolecular and regioselective access to polysubstituted stable benzo[*c*]azepinium compounds in a three-component approach. From these compounds, a family of benzo- and dihydrobenzo[*c*]azepines was selectively synthesized with high control over the substitution at all nine positions of the molecule. On the other hand, these results prove the synthetic applicability of Group 6 non-heteroatom-stabilized alkynyl carbene complexes as an alternative to their Fischer-type analogues. The work reported herein represents the first heterocyclization of this type of compound that involves the participation of the carbene carbon atom. In addition, these, until recently, elusive complexes have emerged as modulable compounds because two different heterocyclization reactions, that is, in their reaction with phenylimines, can be accomplished ([4+3] vs. [2+2]), which depend on the substitution of acetylide **2**. In addition, a rationalization of the results can be obtained from the theoretical data, which should help to understand and control the reaction mechanism and plan subsequent modifications of the reaction.

Experimental Section

Synthesis and characterization

General considerations: All the operations were carried out in an argon atmosphere by using conventional Schlenk techniques. All common reagents were obtained from commercial suppliers and were used without further purification, unless otherwise indicated. THF was distilled from sodium/benzophenone and dichloromethane from calcium hydride in a nitrogen atmosphere prior to use. Hexane and ethyl acetate were used from commercial suppliers. TLC analysis was performed on aluminum-backed plates coated with silica gel 60, with an F_{254} indicator or neutral aluminum oxide. Flash column chromatography was carried out on deactivated[21] silica gel 60 (230–400 mesh) or silica gel 60 (230–400 mesh). High-resolution mass spectra were determined on a Finnigan MAT95 spectrometer. NMR spectra were run on Bruker AV-300, DPX-300, AV-400, or AMX-400 spectrometer with $CDCl_3$ or CD_2Cl_2 as solvents. Melting points were performed with a Gallenkamp instrument.

General experimental procedure for the preparation of benzo[*c*]azepiniums 5a–q: Tungsten–alkoxycarbene complexes **1** (0.5 mmol) were added to a freshly prepared solution of lithium acetilyde **2** (0.72 mmol (1.5 mmol for the synthesis of 5 g); acetylene (0.75 mmol), butyllithium (0.72 mmol; 1.6 M in hexane)) in THF (40 mL) in an argon atmosphere at −80 °C. The reaction mixture was stirred for 15 min at that temperature and TMSOTf (0.18 mL, 0.9 mmol) was added to form the non-heteroatom-stabilized metal carbenes **3** (blue solution, except for the synthesis of 5 g (pale red)). At this point, phenylamine **4** (1 mmol) was added to the reaction mixture, which was allowed to warm until a color change was observed (approximately −50–0 °C). Removal of the solvents under reduced pressure followed by column chromatography of the residue on deactivated silica gel yielded the corresponding benzo[c]azepiniumpentacarbonyl tungstenates **5**.

Experimental data for [(2-butyl-3-cyclopropyl-5-phenyl-3*H*-benzo[*c*]azepin-2-ium)-4-yl]pentacarbonyl tungstenate (5a) as a model compound: Red solid, m.p. 109 °C (dec.), yield = 88%, R_f = 0.13 (hexane/ethyl acetate 3:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.34 (s, 1H), 7.65–7.17 (m, 7H), 7.13 (d, J(H,H) = 8.0 Hz, 1H), 6.87 (d, J(H,H) = 6.4 Hz, 1H), 4.54 (m, 1H), 4.31 (m, 1H), 2.47 (m, 1H), 2.38 (d, J(H,H) = 10.1 Hz, 1H), 2.10 (m, 2H), 1.60 (m, 2H), 1.10 (t, J(H,H) = 7.3 Hz, 3H), 1.05 (m, 1H), 0.88 (m, 1H), 0.36 (m, 1H), 0.17 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.7 (C), 203.2 (C), 184.8 (C), 158.2 (CH), 154.6 (C), 149.4 (C), 146.5 (C), 133.0 (CH), 132.6 (CH), 131.7 (CH), 131.3 (CH), 130.8 (CH), 128.5 (CH), 128.3 (CH), 126.5 (CH), 126.1 (C), 125.1 (CH), 82.3 (CH), 55.3 (CH_2), 32.0 (CH_2), 19.8 (CH_2), 17.5 (CH), 13.7 (CH_3), 6.9 (CH_2), 5.7 ppm (CH_2); HRMS (EI) calcd for $C_{23}H_{25}N$ [M−W(CO)$_5$ + H]: 316.2060; found: 316.2049.

General experimental procedure for the preparation of 3*H*-benzo[*c*]azepines 6a,b: *N*,*N*-Dimethylbarbituric acid (78 mg, 0.5 mmol), triethylamine (37 μL, 0.5 mmol), and tetrakistriphenylphosphine palladium(0) (7 mg, 5% mol, 0.0125 mmol) were added to a solution of benzazepiniums **5d**,**e** (0.25 mmol) in dichloromethane (10 mL). The reaction mixture was heated to reflux until all

the starting materials had disappeared (a few minutes). After evaporation of the solvent under vacuum and filtration of the residue through a short pad of silica gel, dry toluene (10 mL) was added in a nitrogen atmosphere to the reaction mixture, which was stirred at 90 °C for 4 h (**6a**) or 12 h (**6b**). Final evaporation of the solvent and purification by column chromatography on silica gel yielded the corresponding 2-benzo[*c*]azepines **6**.

Experimental data for 3-cyclopropyl-5-phenyl-3*H*-benzo[c]azepine (6a) as a model compound: Pale-yellow oil, yield = 94%, R_f = 0.16 (hexane/ethyl acetate 10:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.48 (d, J(H,H) = 2.1 Hz, 1H), 7.60 (dd, J(H,H) = 7.0 and 1.9 Hz, 1H), 7.50–7.20 (m, 8H), 6.16 (t, J(H,H) = 4.2 Hz, 1H), 2.0 (m, 1H), 1.59 (m, 1H), 0.69 (m, 2H), 0.37 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.3 (CH), 141.4 (C), 141.4 (C), 139.2 (C), 136.1 (C), 133.2 (CH), 130.1 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 127.6 (CH), 126.8 (CH), 62.3 (CH), 16.6 (CH), 2.9, (CH_2), 2.2 ppm (CH_2); HRMS (EI) for $C_{19}H_{17}N$ [*M*]: 259.1361; found: 259.1355.

General experimental procedure for the preparation of 2,3-dihydro-1*H*-2-benzo[*c*]azepines 7a,b: Trifluoromethanesulfonic acid (27 μL, 0.3 mmol) was added over a solution of benzazepiniums **5a,c** (0.25 mmol) in THF (10 mL) at 0 °C. After the reaction mixture changed from red to yellow, a solution of L-selectride in THF (33 μL, 1.0 M, 0.33 mmol) was added, and the reaction mixture was stirred at 0 °C for 15 min. Removal of the solvents under reduced pressure and purification by column chromatography on silica gel led to the isolation of 2,3-dihydro-1*H*-2-benzo[*c*]azepines **7a,b**.

Experimental data for 2-butyl-3-cyclopropyl-5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepine (7a) as a model compound: Yellowish oil, yield = 84%, R_f = 0.23 (hexane/ethyl acetate 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40–7.21 (m, 8H), 7.10 (m, 1H), 6.42 (d, J(H,H) = 6.3 Hz, 1H), 3.76 (s, 2H), 2.88 (m, 1H), 2.59 (m, 1H), 1.87 (m, 1H), 1.65 (m, 2H), 1.41 (m, 2H), 1.05 (m, 1H), 0.99 (t, J(H,H) = 7.3 Hz, 3H), 0.65 (m, 1H), 0.57 (m, 1H), 0.25 (m, 1H), 0.10 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 143.5 (C), 143.3 (C), 140.5 (C), 137.6 (C), 131.2 (CH), 129.9 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 127.6 (CH), 127.3 (CH), 127.1 (CH), 65.2 (CH), 54.2 (CH_2), 50.8 (CH_2), 30.2 (CH_2), 20.9 (CH_2), 15.0 (CH), 14.8 (CH_3), 6.1 (CH_2), 2.2 pm (CH_2); HRMS (EI) calcd for $C_{23}H_{27}N$ [*M*]: 317.2144; found: 317.2145.

General experimental procedure for the preparation of 2,3-dihydro-1*H*-2-benzo[*c*]azepines 8a–c: Trifluoromethanesulfonic acid (27 μL, 0.3 mmol) was added followed by the corresponding magnesium bromide (1.25 mmol; commercial solution) to a solution of benzazepinium **5b** (160 mg, 0.25 mmol) in THF (10 mL) at 20 °C. After stirring the reaction mixture for 5 min, the solvents were removed in vacuo and the residue purified by chromatography on silica gel to obtain 2,3-dihydro-1*H*-2-benzo[c]azepines **8a–c** as single diastereoisomers.

Experimental data for *trans*-2-butyl-1,5-diphenyl-3-isopropyl-2,3-dihydro-1*H*-benzo[c]azepine (8a) as a model compound: Yellowish oil, yield = 74%, R_f = 0.37 (hexane/ethyl acetate 40:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.53 (d, J(H,H) = 7.1 Hz, 2H), 7.48–7.30 (m, 8H), 7.21–6.99 (m, 3H), 6.71 (d, J(H,H) = 7.4 Hz, 1H), 6.35 (d, J(H,H) = 6.6 Hz, 1H), 4.95 (s, 1H), 2.95 (m, 1H), 2.50 (m, 1H), 2.36 (m, 1H), 1.99 (m, 1H), 1.59 (m, 1H), 1.40–0.85 (m, 3H), 1.07 (d, J(H,H) = 6.5 Hz, 3H), 0.98 (d, J(H,H) = 6.5 Hz, 3H), 0.77 ppm (t, J(H,H) = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 142.9 (C), 142.8 (C), 142.6 (C), 140.9 (C), 140.4 (C), 133.7 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 127.2 (CH), 126.8 (CH), 126.7 (CH), 126.1 (CH), 67.1 (CH), 65.9 (CH), 49.3 (CH_2), 31.2 (CH), 30.9 (CH_2), 21.0 (CH_2), 20.9 (CH_3), 20.6 (CH_3), 14.0 ppm (CH_3); HRMS (EI) calcd for $C_{29}H_{33}N$ [*M*]: 395.2613; found: 395.2616.

Experimental procedure for the preparation of 4-methoxycarbonyl-2,3-dihydro-1*H*-2-benzo[*c*]azepine 9a: Methanol (242 μL, 6 mmol), triethylamine (209 μL, 1.5 mmol), and iodine (171 mg, 0.675 mmol) were sequentially added to a solution of benzazepinium **5b** (96 mg; 0.15 mmol) in THF (15 mL) at −80 °C. The reaction mixture was allowed to warm to −30 °C, and the solvents were removed under reduced pressure. Next, the residue was redissolved in THF (15 mL) and the solution was cooled to −60 °C. L-Selectride in THF (0.975 mL, 1 M, 0.975 mmol) was added at this temperature to the reaction mixture, which was allowed to warm to 0 °C. Finally, the solvents were removed under reduced pressure and the residue purified by column chromatography on silica gel (hexane/ethyl acetate 20:1) to obtain benzazepine **9a** (37 mg, 66%).

2-Butyl-3-isopropyl-4-methoxycarbonyl-5-phenyl-2,3-dihydro-1*H*-benzo[*c*]azepine (9a): Colorless oil, yield = 66%, R_f = 0.50 (hexane/ethyl acetate 20:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.45–7.15 (m, 9H), 6.80 (d, J(H,H) = 7.7 Hz, 1H), 3.70 (d, J(H,H) = 10.4 Hz, 1H), 3.54 (d, J(H,H) = 10.4 Hz, 1H), 3.44 (s, 3H), 3.15 (d, J(H,H) = 10.1 Hz, 1H), 2.67 (m, 2H), 1.62 (m, 2H), 1.35 (m, 1H), 0.95 (t, J(H,H) = 7.1 Hz, 3H), 0.86 (d, J(H,H) = 6.0 Hz, 3H), 0.74 (d, J(H,H) = 5.7 Hz, 3H), 0.70 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.2 (C), 147.6 (C), 141.7 (C), 141.4 (C), 138.9 (C), 132.0 (C), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 69.8 (CH), 58.7 (CH_2), 55.8 (CH_2), 51.6 (CH_3), 31.5 (CH), 30.1 (CH_2), 21.0 (CH_2), 20.5 (CH_2), 19.9 (CH_2), 14.1 ppm (CH_2); HRMS (EI) calcd for $C_2H_2NO_2$ [*M*−H]: 376.2277; found: 376.2278.

Experimental procedure for the preparation of 4-(piperidine-1-carbonyl)-2,3-dihydro-1*H*-2-benzo[*c*]azepine (9b): Piperidine (887 μL, 9 mmol), triethylamine (418 μL, 3 mmol), and iodine (171 mg, 0.675 mmol) were sequentially added to a solution of benzazepinium **5b** in THF (15 mL, 96 mg, 0.15 mmol; −80 °C). The reaction mixture was allowed to warm to −30 °C, and the solvents were removed under reduced pressure. The residue was redissolved in methanol (15 mL) at room temperature, and sodium cyanoborohydride (75 mg, 1.2 mmol) was added to the reaction mixture, which was stirred for 1 h. Removal of the solvents under reduced pressure and purification by column chromatography on silica gel (hexane/ethyl acetate 10:1) led to the isolation of benzazepine **9b** (29 mg, 45%).

2-Butyl-3-isopropyl-5-phenyl-4-(1-piperidinecarbonyl)-2,3-dihydro-1*H*-benzo[*c*]azepine (9b): Colorless oil, yield = 45%, R_f = 0.19 (hexane/ethyl acetate 10:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.45–7.15 (m, 8H), 6.82 (d, J(H,H) = 7.6 Hz, 1H), 3.79 (d, J(H,H) = 10.5 Hz, 1H), 3.54 (d, J(H,H) = 10.5 Hz, 1H), 3.50–3.30 (m, 3H), 3.02–2.90 (m, 3H), 2.75–2.55 (m, 2H), 1.80–1.05 (m, 8H), 0.95 (t, J(H,H) = 7.3 Hz, 3H), 0.84 (t, J(H,H) = 7.6 Hz, 3H), 0.82 (d, J(H,H) = 7.6 Hz, 3H), 0.76–0.58 (m, 1H), 0.57–0.40 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.3 (C), 141.8 (C), 140.8 (C), 140.6 (C), 138.6 (C), 133.4 (C), 130.3 (CH), 129.1 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.4 (CH), 71.4 (CH), 59.0 (CH_2), 56.6 (CH_2), 47.4 (CH_2), 42.2 (CH_2), 31.8 (CH), 30.4 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.2 (CH_2), 21.4 (CH_3), 20.5 (CH_2), 19.9 (CH_3), 14.1 ppm (CH_3); HRMS (EI) calcd for $C_{26}H_{31}N_2O$ [*M*−C_3H_7 + H]: 387.2436; found: 387.2439.

Experimental procedure for the preparation of 4-hydroxycarbonyl-2,3-dihydro-1*H*-2-benzo[*c*]azepine 9c: Iodine (57 mg, 0.225 mmol) was added to a solution of benzazepinium **5b** in THF (15 mL, 96 mg, 0.15 mmol; −80 °C), and the reaction mixture was allowed to warm. When the mixture reached −60 °C, L-selectride in THF (0.525 mL, 1 M, 0.525 mmol) was added and allowed to warm to 0 °C. Finally, the solvents were removed under vacuum and the

residue was purified by column chromatography on silica gel (hexane/ethyl acetate 3:1) to yield benzazepine **9c** (44 mg, 83%).

2-Butyl-4-hydroxymethyl-3-isopropyl-5-phenyl-2,3-dihydro-1*H*-benzo[c]azepine (9c): Pale-yellow oil, yield = 83%, R_f = 0.45 (hexane/ethyl acetate 3:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.45–7.10 (m, 8H), 6.72 (dd, J(H,H) = 7.5 and 1.5 Hz, 1H), 4.24 (d, J(H,H) = 12.1 Hz, 1H), 4.11 (d, J(H,H) = 12.1 Hz, 1H), 3.70 (d, J(H,H) = 10.3 Hz, 1H), 3.38 (d, J(H,H) = 10.3 Hz, 1H), 2.93 (d, J(H,H) = 9.6 Hz, 1H), 2.75 (m, 2H), 1.62 (m, 3H), 1.42 (m, 3H), 0.98 (t, J(H,H) = 7.3 Hz, 3H), 0.87 (d, J(H,H) = 5.9 Hz, 3H), 0.69 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 143.1 (C), 141.6 (C), 141.8 (C), 138.8 (C), 138.2 (C), 130.6 (CH), 129.4 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 71.1 (CH), 66.8 (CH_2), 59.3 (CH_2), 56.8 (CH_2), 32.4 (CH), 31.4 (CH_2), 21.5 (CH_3), 23.9 (CH_2), 20.8 (CH_3), 14.6 ppm (CH_3); HRMS (EI) calcd for $C_{21}H_{24}NO$ [$M-C_3H_7+H$]: 306.1858; found: 306.1848.

Computational details

All the calculations were carried out in the framework of density functional theory (DFT) by using the M06 functional[22] as implemented in the Gaussian 09 program package.[23] For the C, O, N, and H atoms, the standard split-valence 6–31G* basis set[24] was employed. For the tungsten atom, the Hay–Wadt effective core potential[25] was used with the minimal basis-set split to [441/2111/21]. Solvation was taken in account by using the SMD model[26] with THF as the solvent (ε = 7.4257). All the geometry optimizations were carried out in solution with no restrictions. All the points were characterized by vibrational-frequency calculations to check the stationary points and characterized them as minima (without imaginary frequencies) or transition states (with one imaginary frequency). Further, the connectivity of the transition states was confirmed by relaxing the transition-state geometry toward the reactant and product. Gibbs-energy corrections at 298.15 K and 105 Pa pressure were computed, including zero-point energy corrections. All the reported energies herein correspond to Gibbs energies in solution, obtained from potential energies (including solvation) and Gibbs-energy corrections.

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Keywords: alkynes · carbenes · heterocycles · imines · regioselectivity

[1] J. D. Eckelbarger, J. T. Wilmot, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 10370 – 10371.

[2] M. Seto, N. Miyamoto, K. Aikawa, Y. Aramaki, N. Kanzaki, Y. Iizawa, M. Baba, M. Shiraishi, *Bioorg. Med. Chem.* **2005**, *13*, 363 – 386.

[3] K. Jamerson, M. A. Weber, G. L. Bakris, B. Dahlof, B. Pitt, V. Shi, A. Hester, J. Gupte, M. Gatlin, E. J. Velázquez, *N. Engl. J. Med.* **2008**, *359*, 2417 – 2428.

[4] J. Marco-Contelles, M. d. C. Carreiras, C. Rodríguez, M. Villarroya, A. G. García, *Chem. Rev.* **2006**, *106*, 116 – 133.

[5] For intermolecular benzazepine synthesis, see: a) J. S. Yadav, B. V. Subba Reddy, M. Kumar Gupta, A. Prabhakarb, B. Jagadeeshb, *Chem. Commun.* **2004**, 2124 – 2125; b) S. Fantauzzi, E. Gallo, A. Caselli, C. Piangiolino, F. Ragaini, N. Re, S. Cenini, *Chem. Eur. J.* **2009**, *15*, 1241 – 1251; c) H. He, W.-B. Liu, L.-X. Dai, S.-L. You, *Angew. Chem.* **2010**, *122*, 1538 – 1541; *Angew. Chem. Int. Ed.* **2010**, *49*, 1496 – 1499; d) P. M. Truong, M. D. Mandler, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* **2013**, *15*, 3278 – 3281; e) N. Iqbal, A. Fiksdahl, *J. Org. Chem.* **2013**, *78*, 7885 – 7895.

[6] For recent reviews, see: a) K. H. Dötz, *Metal Carbenes in Organic Synthesis, Vol. 13 (Topic in Organometallic Chemistry)*, Springer, New York, **2004**; b) J. Barluenga, J. Santamaría, M. Tomás, *Chem. Rev.* **2004**, *104*, 2259 – 2283; c) J. Santamaría, *Curr. Org. Chem.* **2009**, *13*, 31 – 46; d) K. H. Dötz, J. Stendel, *Chem. Rev.* **2009**, *109*, 3227 – 3274; e) M. A. Fernández-Rodríguez, P. García-García, E. Aguilar, *Chem. Commun.* **2010**, *46*, 7670 – 7687; f) I. Fernández, F. P. Cossío, M. A. Sierra, *Acc. Chem. Res.* **2011**, *44*, 479 – 490; for an annual survey of related compounds, see: g) J. W. Herndon, *Coord. Chem. Rev.* **2013**, *257*, 2899 – 3033.

[7] a) J. Barluenga, P. García-García, D. de Sáa, M. A. Fernández-Rodríguez, R. Bernardo de La Rúa, A. Ballesteros, E. Aguilar, M. Tomás, *Angew. Chem.* **2007**, *119*, 2664 – 2666; *Angew. Chem. Int. Ed.* **2007**, *46*, 2610 – 2612; b) J. Barluenga, D. de Sáa, A. Gómez, A. Ballesteros, J. Santamaría, A. de Prado, M. Tomás, A. L. Suárez-Sobrino, *Angew. Chem.* **2008**, *120*, 6321 – 6324; *Angew. Chem. Int. Ed.* **2008**, *47*, 6225 – 6228; c) J. Barluenga, A. Gómez, J. Santamaría, M. Tomás, *J. Am. Chem. Soc.* **2009**, *131*, 14628 – 14629; d) J. Barluenga, A. Gómez, J. Santamaría, M. Tomás, *Angew. Chem.* **2010**, *122*, 1328 – 1330; *Angew. Chem. Int. Ed.* **2010**, *49*, 1306 – 1308; e) J. Barluenga, E. Tudela, R. Vicente, A. Ballesteros, M. Tomás, *Chem. Eur. J.* **2011**, *17*, 2349 – 2352.

[8] J. Barluenga, R. B. de La Rúa, D. de Sáa, A. Ballesteros, M. Tomás, *Angew. Chem.* **2005**, *117*, 5061 – 5063; *Angew. Chem. Int. Ed.* **2005**, *44*, 4981 – 4983.

[9] The low overall yield for **5g** (29%) can be partially explained because approximately 30% of the corresponding Fischer carbene complex **1** was recovered.

[10] CCDC-959023 (**5a**) 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.

[11] A similar structure to **5a** (R^1 = Ph; R^2 = *c*-C_3H_5) was obtained by starting from the analogous chromium compound.

[12] For tungsten equivalents, a [4+2] heterocycloaddition was observed: J. Barluenga, M. Tomás, J. A. López-Pelegrín, E. Rubio, *Tetrahedron Lett.* **1997**, *38*, 3981 – 3984.

[13] a) J. Barluenga, M. Tomás, E. Rubio, J. A. López-Pelegrín, S. García-Granda, P. Pertierra, *J. Am. Chem. Soc.* **1996**, *118*, 695 – 696; b) J. Barluenga, M. Tomás, E. Rubio, J. A. López-Pelegrín, S. García-Granda, M. Pérez Priede, *J. Am. Chem. Soc.* **1999**, *121*, 3065 – 3071; for a photochemical example of this type of cyclization with imines and tungsten complexes, see: c) M. Blanco-Lomas, A. Caballero, P. J. Campos, H. F. González, S. López-Sola, L. Rivado-Casas, M. A. Rodríguez, D. Sampedro, *Organometallics* **2011**, *30*, 3677 – 3682.

[14] With alkenyl Fischer carbenes: a) J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, F. López-Ortiz, *J. Chem. Soc. Chem. Commun.* **1994**, 321 – 322; b) J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, R. J. Carbajo, F. López-Ortiz, S. García-Granda, P. Pertierra, *Chem. Eur. J.* **1996**, *2*, 88 – 97; for interesting catalytic [4+3]-heterocycloaddition reactions with 1-azadienes, see: with rhodium: c) M. P. Doyle, W. Hu, D. J. Timmons, *Org. Lett.* **2001**, *3*, 3741 – 3744; with gold: d) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244 – 9245; e) H. Liu, X. Li, Z. Chen, W. Hu, *J. Org. Chem.* **2012**, *77*, 5184 – 5190.

[15] Ring closure to seven-membered rings involving a [1,2]-{$W(CO)_5$} shift is well documented: a) J. Barluenga, S. Martínez, A. L. Suárez-Sobrino, M. Tomás, *J. Am. Chem. Soc.* **2002**, *124*, 5948 – 5949; b) J. Barluenga, P. García-García, M. A. Fernández-Rodríguez, E. Aguilar, I. Merino, *Angew. Chem.* **2005**, *117*, 6025 – 6028; *Angew. Chem. Int. Ed.* **2005**, *44*, 5875 – 5878; c) for an NMR spectroscopic study, see ref. [14b].

[16] Formation of the benzazepinium ring was not observed with an electron-donating group attached to the arene ring (R^2 = *para*-methoxyphenyl).
[17] F. Garro-Helion, A. Merzouk, F. Guibé, *J. Org. Chem.* **1993**, *58*, 6109 – 6113.
[18] The relative configuration of the new stereogenic center was determined by using COSY and NOESY experiments.
[19] a) N. Iwasawa, T. Ochiai, K. Maeyama, *Organometallics* **1997**, *16*, 5137 – 5139; b) K. Fuchibe, N. Iwasawa, *Tetrahedron* **2000**, *56*, 4907 – 4915.
[20] Although it follows a similar approach to methoxycarbonylation developed by Iwasawa and co-workers, no reports of this method have been found to the best of our knowledge.
[21] The silica gel was deactivated as follows: silica gel (125 g) was stirred in a solution of $KHSO_4$ (4% in water) at room temperature for 3 h, filtered, and dried for 48 h at 120 °C.
[22] Y. Zhao, N. E. Schultz, D. G. Truhlar, *J. Chem. Theory Comput.* **2006**, *2*, 364.
[23] Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford, CT, **2009**.
[24] P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213.
[25] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.
[26] S. A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.

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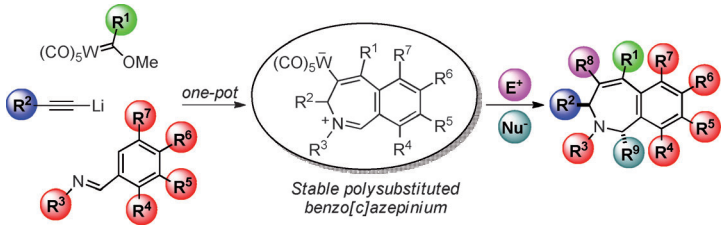

Choose your substitution pattern: Non-heteroatom-stabilized tungsten–carbene complexes synthesized in situ have been used in a modular approach to provide access to 2-benzazepinium isolable intermediates as a starting point to fully substituted 2-benzazepine derivatives (see figure). These intermediates were obtained under very mild conditions from simple compounds, such as acetylides, Fischer-type alkoxycarbenes, and phenylimines. An acetylide substitution pattern controls the reaction.

Heterocycles

J. González, A. Gómez, I. Funes-Ardoiz, J. Santamaría, D. Sampedro*

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Intermolecular and Regioselective Access to Polysubstituted Benzo- and Dihydrobenzo[*c*]azepine Derivatives: Modulating the Reactivity of Group 6 Non-Heteroatom-Stabilized Alkynyl Carbene Complexes