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Synthesis of 3-Benzazepines by Metal-Free Oxidative C–H Bond Functionalization–Ring Expansion Tandem Reaction

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Abstract: A metal-free synthesis of biologically important benzazepines is achieved through a single synthetic operation involving an oxidative C–H bond functionalization and ring expansion with diazomethanes as key reagent. This represents a new, strong methodology for the straightforward construction of the seven-ring N-heterocyclic structures under mild conditions using a 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) oxoammonium salt as oxidant. Moderate to good yields are achieved from simple, readily available tetrahydroisoquinolines, and this methodology has been further successfully applied for the synthesis of the 3-benzazepine drug Lorcaserin. A possible mechanistic pathway for the ring expansion step, comprising the extrusion of nitrogen in a concerted asynchronic process, is proposed based on both mechanistic proof and density function theory (DFT) calculations.

Keywords: benzazepines; isoquinolines; metal-free conditions; ring-expansion; tandem reaction

Introduction

3-Benzazepines are a unique class of compounds important in drug discovery. In particular, the tetrahydro-3-benzazepine is a common skeleton in a number of natural and pharmaceutical products.[1] In the last half century, these compounds have been explored as a potent dopaminometic and antidopaminergic agents.[2] They also present other pharmacological activities such as analgesic, antihypertensive or anticancer properties.[3] Thus, for example, (Figure 1) Lorcaserin has serotonergic properties and acts as an anorectic compound, which is currently used as a weight-loss drug.[4] Furthermore, Fenoldopam is employed as antihypertensive agent,[5] whereas Ivabradine is a cardiotonic agent used for the symptomatic management of angina pectoris by inhibition of the funny channel.[6]

The main strategy to synthesize the 3-benzazepine core is based on a Lewis-acid mediated Friedel–

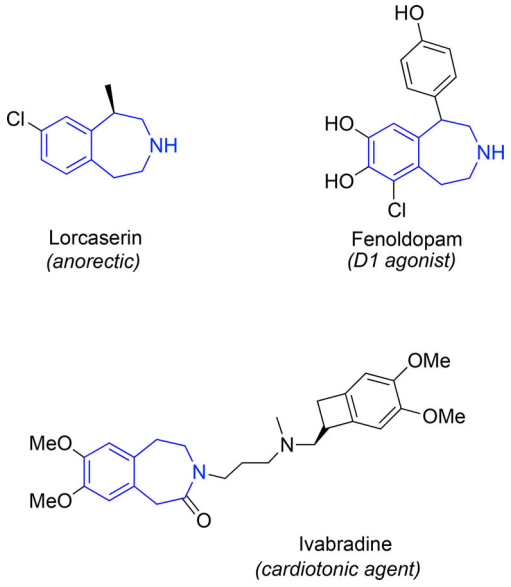
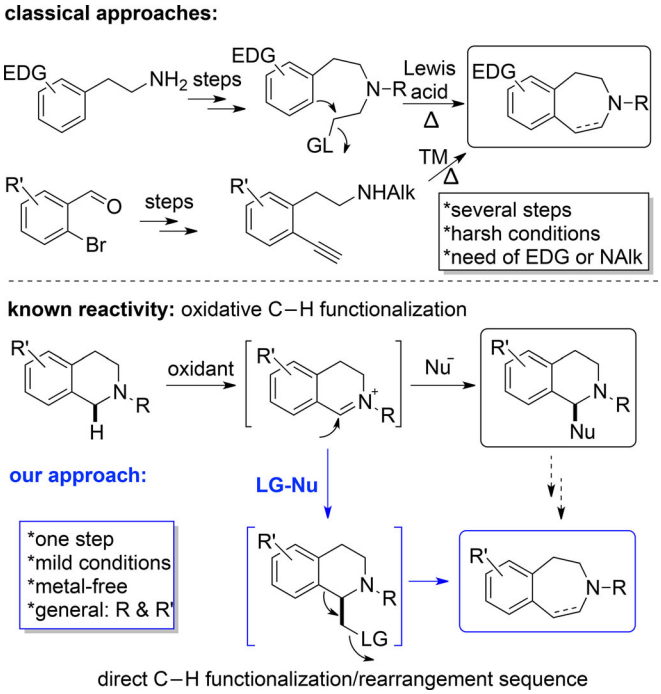


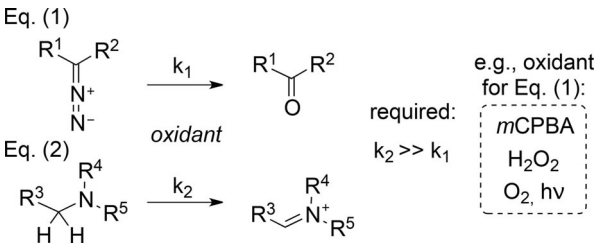
Figure 1. Selected examples of biologically active 3-benzazepines (LG = leaving group, TM = transition metal).



Scheme 1. Classical and present synthetic approaches.

Crafts-type cyclization approach (Scheme 1, *top*).[7,8] In all these cases, the 2-arylethylamines are used as starting materials, which have to be derived to an acyclic key intermediate for the final cyclization through several synthetic steps. Recently, *N*-alkyl-3-benzazepines have been afforded by an osmium-catalyzed hydroamination reaction.[9] This methodology also requires multistep substrate synthesis and is limited to *N*-alkyl derivatives. Besides these principal approaches, other synthetic routes include Pummerer cyclizations, electrophilic aromatic substitutions or the condensation of keto acids with amines, among a few others.[8] However, most of these methods required (i) several steps, (ii) harsh conditions, (iii) prolonged reaction times and (iv) do not tolerate a broad substitution pattern on the nitrogen atom and the aromatic ring (e.g., need of electron-rich groups). These issues limit the preparation of diverse substituted 3-benzazepines. Therefore, there is still a need for simple, mild and direct synthetic methods for their synthesis. The common oxidative functionalization of tetrahydroisoquinolines (THIQs) implies the formation of the iminium ion intermediate and the following addition of nucleophiles in the alpha position (Scheme 1, *middle*).[10,11] We have envisioned a new methodology for the construction of the seven-membered ring structures by an oxidative C–H functionalization approach from readily available THIQ.[11] To achieve such a transformation, the nucleophile employed should possess a leaving group in its structure that can promote, after the first addition, a ring expansion process (Scheme 1, *bottom*). Thus, diazomethane derivatives, which will liberate a nitrogen molecule as leaving group, would be ideal as nucleophiles.

However, under the required oxidative conditions, important compatibility issues have to be overcome with this type of reagents in order to avoid their intrinsic reactivity to form the corresponding carbonyl compound [Scheme 2, Eq. (1)].[12] Therefore, the oxidative formation of the iminium species [Eq. (2), k_2] must be faster than the decomposition pathway of the diazo compound [Eq. (1), k_1] to undergo the desired nucleophilic attack.



Scheme 2. Undesired competitive typical oxidation of diazomethanes to carbonyls.

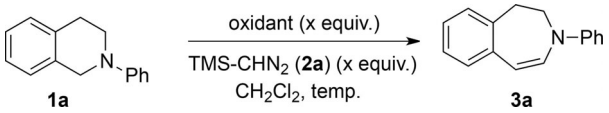
Herein, we present a straightforward preparation of benzazepines by an innovative, mild and functional group tolerant (R and R′) metal-free oxidative C–H bond functionalization–ring expansion process from simple THIQs and diazomethanes.[13–15]

Results and Discussion

We started our screening with *N*-phenyl-THIQ **1a** as model substrate and $TMSCHN_2$ as nucleophile for the optimization study of the reaction conditions (Table 1). A variety of standard oxidants in C–H functionalization were tested in dichloromethane at room temperature (entries 1–8). DDQ (**I**) and *t*-BuOOH (**II**) led to a complex mixture or no conversion, respectively. To our delight, the use of 1.2 equivalents of the TEMPO oxoammonium salt **III** ($T^+BF_4^-$)[16,17] provided for the first time the benzazepine **3a** (entry 3). The initial low conversion of 43% was enhanced to 88% by employing 1.5 equivalents of the oxidant (entry 4). Other TEMPO salts (**IV–VI**) with different counter-anions and substitution in the backbone also promoted this reaction (entries 5–7). With the best oxoammonium salt **III**, the temperature was increased to 60 and 80 °C, finding full conversion in both cases after 4 and 1 hours, respectively (entries 8 and 9). However, when the amount of **2a** was decreased to 1.5 equivalents, lower conversions were found at both 60 and 80 °C (entries 10 and 11).

Under the optimized conditions (entry 9), the scope of the reaction was investigated (Table 2). Although we focussed on the synthesis of highly versatile 1,2-

Table 1. Optimization of the reaction conditions.[a]



1a 3a

Ent	Oxidant (x equiv.)	**2a** (equiv.)	*T* [°C]	*t* [h]	Conv. (yield)[b] [%]
1	DDQ (**I**) (1.2)	2.4	r.t.	18	–[c]
2	*t*-BuOOH (**II**) (1.2)	2.4	r.t.	18	–[d,e]
3	$T^+BF_4^-$ (**III**) (1.2)	2.4	r.t.	18	43 (26)
4	$T^+BF_4^-$ (**III**) (1.5)	2.4	r.t.	18	88
5	$T^+ClO_4^-$ (**IV**) (1.5)	2.4	r.t.	18	45
6	T^+OTf^- (**V**) (1.5)	2.4	r.t.	18	88
7	AcNH-$T^+BF_4^-$(**VI**) (1.5)	2.4	r.t.	18	8
8	$T^+BF_4^-$ (**III**) (1.5)	2.4	60	4	>99 (78)
9	$T^+BF_4^-$ (III) (1.5)	2.4	**80**	**1**	>99 (77)
10	$T^+BF_4^-$ (**III**) (1.5)	1.5	60	4	75
11	$T^+BF_4^-$ (**III**) (1.5)	1.5	80	1	88

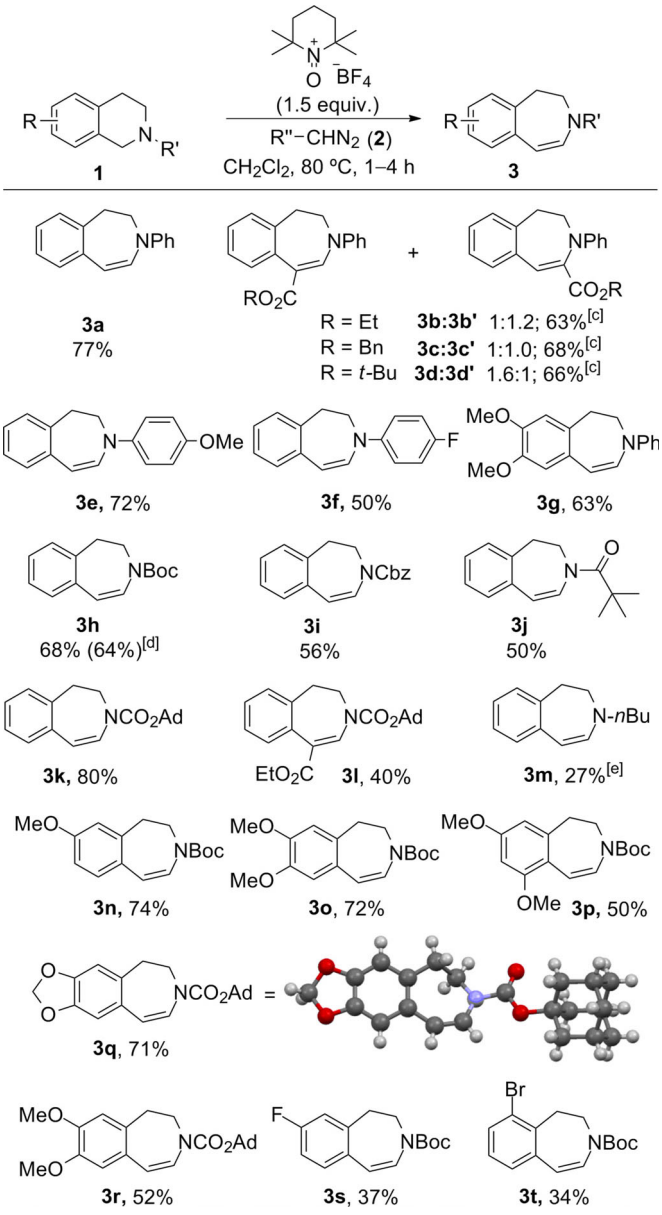
[a] *Conditions:* **1a** (0.2 mmol), oxidant and $TMSCHN_2$ (**2a**) in DCM (0.1 M) at the desired temperature in a sealed tube.
[b] Conversion of **1a** determined by ^1H NMR. Isolated yield in brackets.
[c] Complex mixture.
[d] No reaction observed.
[e] Reaction in MeCN (TEMPO = 2,2,6,6-tetramethyl-piperidine 1-oxyl).

unsubstituted unsaturated 3-benzazepines, which allow a rich variety of further functionalization of the double bond, other commercially available diazomethanes were also tested to show the generality of the method. Thus, the reaction of **1a** with less nucleophilic diazoacetates such as ethyl (**2b**), benzyl (**2c**) and *tert*-butyl (**2d**) led to a mixture of the corresponding isomeric C-1 and C-2 substituted 3-benzazepines **3/3′** in good yields (**3b/3b′** 1:1.2, 63%; **3c/3c′** 1:1, 68%; **3d/3d′** 1.6:1, 66%). Next, different substituted THIQ derivatives **1** were explored. The reaction with *N*-aryl-THIQs bearing both electron-donating and electron-withdrawing groups proceeded efficiently, providing the 3-benzazepines **3e–g** in 50–72% yield. Furthermore, the reaction tolerated different common *N*-protecting groups like Boc or Cbz (**3h** and **3i**) or acyl groups like pivaloyl (**3j**), and it could be scaled-up to 1.0 mmol with no significant detriment in the final yield (64 *vs.* 68%, **3h**). Further derivatives bearing bulky carbamates like adamantyl derivatives **3k** and **3l** were obtained in moderate to good yields, whereas the alkylic substituted amine **3m** was formed in a lower yield. We next explored the substitution at the aromatic unit of the THIQ. Because a large number of 3-benzazepines contains methoxy or oxygenated groups (see for example, Fenoldopam or Ivabradine, Figure 1), different oxygenated derivatives (**1n–1r**) were next studied. The reaction with the 6-methoxy-substituted THIQ (**3n**, 74%), as well as with 6,8-dimethoxy (**3p**, 50%) and two methoxy groups at the 6 and 7 positions with both an *N*-Boc (**3o**, 72%) and an *N*-adamadyl carbamate (**3r**, 52%) as protecting groups proceeded smoothly. The methylene bridged compound **1q** was also supported without observing partial demethylenation under the oxidative reaction conditions and the structure of **3q** was confirmed by X-ray analysis.[18] Substrates with deactivating electron-withdrawing groups such as fluoro or bromo also provided 3-benzazepines **3s** and **3t**.

The synthetic applicability of the developed methodology was demonstrated by the synthesis of the drug Lorcaserin (Scheme 3). The corresponding THIQ **1u** was prepared in a gram scale in three steps from cheap *p*-chlorobenzaldehyde following a literature procedure.[19] The enantioenriched version can be also accomplished in a longer sequence to achieve (*S*)-**1u** in 90% *ee*.[20] Consequently, our oxidative C–H functionalization/ring expansion methodology was employed, leading to 3-benzazepine **3u**. A further one-pot enamine reduction and *N*-Boc deprotection of **3u** with Et_3SiH in trifluoroacetic acid/dichloromethane, followed by treatment with HCl (1 M in dioxane), provided the targeted derivative Lorcaserin hydrochloride salt in a quantitative yield.

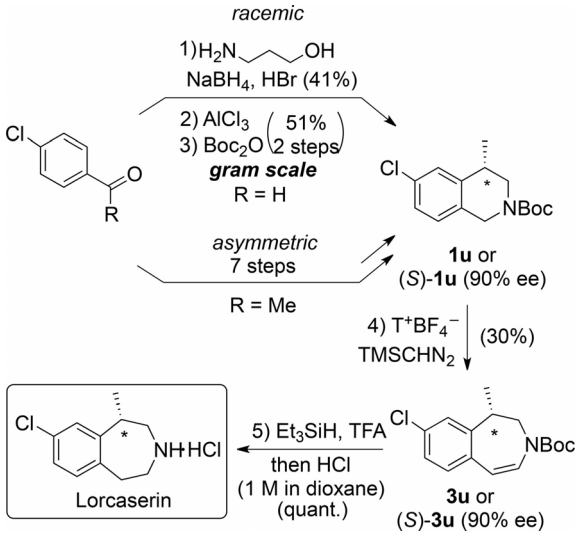
Aiming at bringing some light into the mechanism of the reaction, several experiments were carried out. Initially, a radical mechanistic pathway for the oxidation step to form the key *N*-acyl iminium intermediate was discarded by the reaction with a radical clock as indirect methodology to determine a free-radical reaction (see the Supporting Information for more details).[21] The fact that no ring-opening by-products were observed suggested a direct hydride abstraction *vs.* a radical pathway.[22] This different nature of the TEMPO salt with respect to other more classical radical oxidants might also be the key for the success in

Table 2. Substrate scope.[a,b]



[a] *Conditions*:**1** (0.2 mmol), $T^+BF_4^-$ (1.5 equiv.) and $RCHN_2$ (1.5–2.4 equiv.) in DCM (0.1 M) at 80 °C for 1–4 h (see the Supporting Information for each case).
[b] Isolated yield.
[c] Isomeric ratio determined by ^1H NMR.
[d] 1.0 mmol scale.
[e] Concomitant formation of the corresponding *N*-methylated salts.

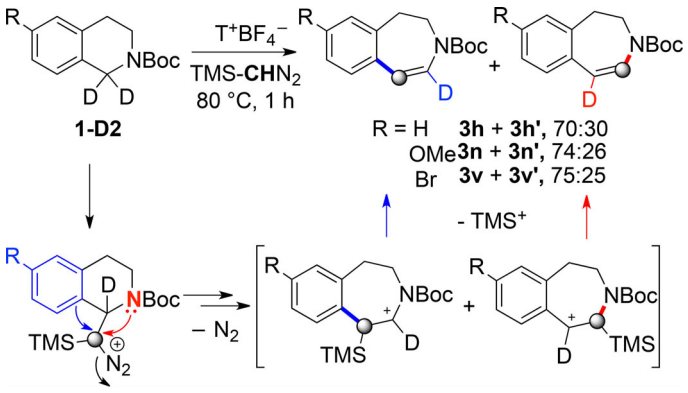
this reaction with sensitive diazomethane nucleophiles. Additionally, considering the observed substrate-dependent **3:3′** selectivity with substituted diazomethanes (Table 2, for example, **3b:3b′** *vs.* **3l** as single isomer), further experiments with representative deuterium containing *N*-Boc precursors were carried out, indicating two possible competitive parallel mechanisms for the second step with $TMSCHN_2$. In



Scheme 3. Synthetic application: synthesis of the drug Lorcaserin.

particular, the reactivity of labelled **1h**, **1n** and **1v** with dissimilar substituents at *para* position to the reactive center was studied (Scheme 4). Differences on reactivity were found, showing a higher reactivity for the more electron-rich derivative **1n-D2** bearing the *p*-MeO substituent, whereas the *p*-Br substituted THIQ **1v-D2** was the least reactive. However, only slightly changes in the final isomeric ratio of the two possible labelled deuterated compounds were found. Thus, in all cases a mixture nearly to 70:30 of the regioisomers, presenting the deuterium atom in the proximal (3) and distal (3′) positions with respect to the nitrogen moiety, was obtained.

To get a deeper understanding of such pathways, DFT calculations using the M06 functional and 6-31G(d,p) basis set were performed (see the Supporting Information for details).[23] In particular, the reaction of **1h**, **1n** and **1v** with $TMSCHN_2$ was studied. For each substrate, we considered the (*R*,*R*) and (*S*,*R*) diasteroisomers, which have been specifically oriented



Scheme 4. Mechanistic studies with D-labelled THIQs **1**.

to allow the aromatic C-atom or the N-atom to act as the nucleophilic center, respectively (Figure 2). For simplicity, the scenario found for the starting material **1h** is primarily presented (for **1n** and **1v** see the Supporting Information). First, the (*S*,*R*) diastereoisomer is significantly more stable ($\approx$2 kcal mol^{-1}) than the (*R*,*R*). It is also observed that the activation energies of the nucleophilic attack are just slightly lower for the initial C–C bond formation [from the most stable (*S*,*R*) isomer, Ea = 6.8 kcal mol^{-1} for C–C pathway and 8.6 kcal mol^{-1} for C–N pathway, see Figure 2].

Interestingly, while the N-attack results in the formation of an aziridine intermediate, the cyclopropane analogue (C-attack) has not been found as a minimum in the potential energy surface. Exhaustive exploration of the reaction coordinates indicate that, although a saddle region corresponding to geometries close to the cyclopropane putative intermediate is

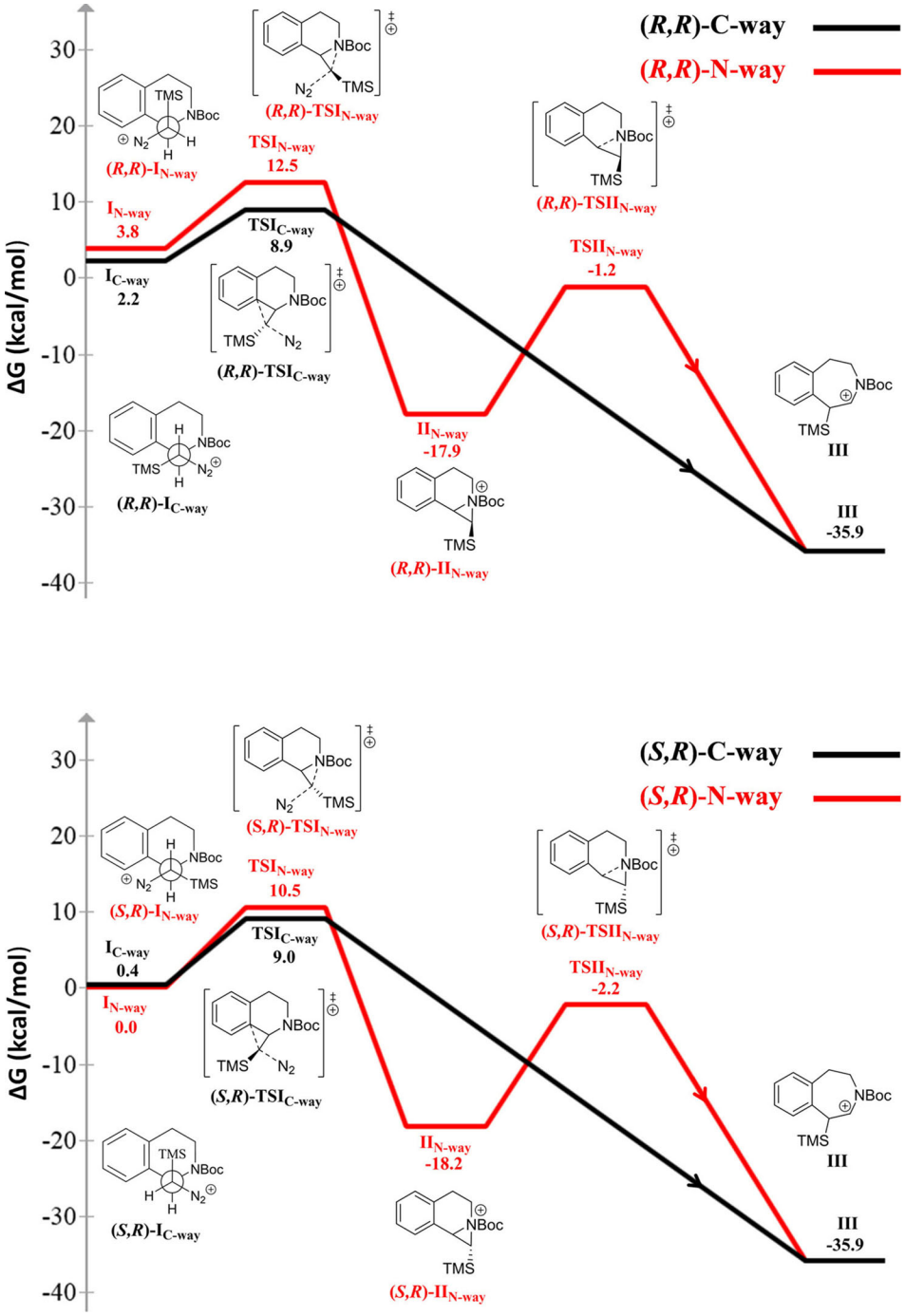


Figure 2. DFT-calculated reaction pathways for THIQ **1h**.

found, an energy minimum cannot be located with such a structure. Therefore, when the initial step consists in the formation of the C–C bond, the system evolves barrier-less towards the benzazepine product. In contrast, when the initial step consists in the C–N bond formation, an aziridine intermediate is produced, which further evolves through a ring expansion process to generate the final benzazepine product. Such a process from the aziridine intermediate has a significant activation energy of 16–17 kcal mol^{-1}. The high thermodynamic stability of the aziridine **II** intermediate (18 kcal mol^{-1} more stable than **I**), makes very improbable the backward reaction to **I**, which should overpass the activation energy of ≈27 kcal mol^{-1}. Thus, regardless of the pathway followed, once the first transition state is overpassed, the reaction proceeds irreversibly towards the benzazepine product. Therefore, the formation of an aziridine intermediate does not affect the overall tendency of the system to evolve through one or the other pathway. In fact the comparable values for the initial activation energies suggest that both pathways are plausible and that the disappearance of the substrate **1h** through one or the other pathway should follow similar kinetics. Interestingly, while the consumption of **1h** by means of the C–C pathway proceeds to the direct formation of the product, in the case of the C–N pathway the accumulation of the aziridine intermediate could result in a slower rate for the benzazepine production.[24] One of the most surprising results of the mechanistic investigations shown above is the fact that the occurrence of one or the other pathway is independent of the electronic nature of the phenyl ring. *A priori*, if the reaction pathways were triggered by the initial nucleophilic attack of either the aromatic carbon or the nitrogen center, the substitution on the aromatic ring should direct the reactivity towards one or the other mechanism. In particular, electron-donating groups should enhance the C–C pathway and electron-withdrawing groups should tip the scales towards the C–N mechanism. However, such a tendency was not observed experimentally. Regarding the analysis of the values of natural charges and the geometries in relevant atoms present in reagents and transition states,[25] we found that the extrusion of the nitrogen molecule is the driving force for the formation of the species **III** from the intermediate **I**. Once the N_2 fragment is taking place, the formation of the carbocation and the C- or N-driven nucleophilic attack takes place in a barrier-less concerted asynchronic process. In consequence, the modulation of the nucleophilicity of the aromatic carbon has a minor effect on the reaction pathway that results in the formation of the 3-benzazepine structures.

Conclusions

In conclusion, we have developed a metal-free methodology for the direct synthesis of important 3-benzazepines from readily available tetrahydroisoquinolines (THIQs). Our approach involves the oxidative formation of an iminium ion intermediate, followed by the addition of a diazomethane derivative $RCHN_2$ as nucleophile and subsequent rearrangement and ring expansion. Moreover, we have shown two concurrent possible operative mechanistic pathways based on experimental proof and DFT calculations. Finally, the synthetic utility of this methodology was proven by the preparation of the 3-benzazepine drug Lorcaserin.

Experimental Section

General Methods

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 (reference signals: ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm, $CDCl_3$) on a Bruker ARX-300 and a Bruker Advance 300, 400 or 600 MHz instrument. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (J) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F_{254} and a solution of $KMnO_4$ or phosphomolybdic acid served as staining agent. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). Exact masses (HR-MS) were recorded on an Agilent Q-TOF 6540 UHD spectrometer (samples in CH_3OH as solvent) using electrospray (ESI) or electron (EI) ionization techniques. Chiral high pressure liquid chromatography (HPLC) analyses were performed on an Agilent 1200 series instrument. CH_2Cl_2 and Et_3N were distilled over CaH_2. THF and Et_2O were distilled and dried over Na.

General Procedure for the Ring Expansion Process

In a flame-dried pressure Schlenk tube, the TEMPO oxoammonium salt $T^+BF_4^-$ (72.9 mg, 0.30 mmol, 1.5 equiv.) and the corresponding tetrahydroisoquinoline **1** (0.20 mmol, 1.0 equiv.) were suspended in dry DCM (0.1 M) under an argon atmosphere. Afterwards the nucleophile $RCHN_2$ (**2**) (0.48 mmol, 2.4 equiv.) was added dropwise. Depending on the substrate, the reaction mixture was stirred at 80 °C for 1 h, 4 h or overnight. After evaporating the solvent, the crude product was purified by flash column chromatography (see the Supporting Information).

Acknowledgements

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[25] The values of natural charges in relevant atoms in both the reagents and the TS were evaluated. The C or the N atoms involved in the nucleophilic attack did not present significant differences, whereas the C–N_2^+ fragment showed the main electronic rearrangement. Furthermore, an increase in the electron density of atoms in the diazo group and a decrease of the adjacent C-atom was observed (see the Supporting Information).

Synthesis of 3-Benzazepines by Metal-Free Oxidative C–H Bond Functionalization–Ring Expansion Tandem Reaction

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