Synthesis of 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes by cyclization of 1,3-bis(silyl enol ethers) with quinazolines†

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A variety of functionalized 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes were prepared by one-pot cyclizations of 1,3-bis(silyl enol ethers) with quinazolines. The mechanism of the cyclization was studied by B3LYP/6-31G(d) density functional theory computations. The products could be functionalized by Suzuki cross-coupling reactions. The reaction of 1,3-bis(silyl enol ethers) with phthalazine afforded open-chain rather than cyclization products.

Introduction

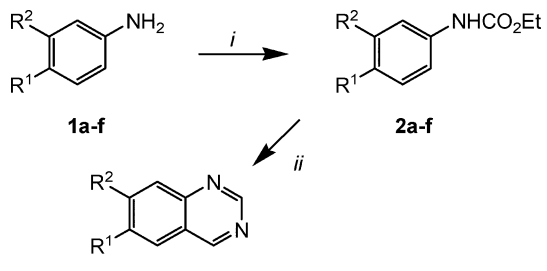
Iminium salts represent important synthetic building blocks.[1] In recent years, cyclocondensation reactions of iminium salts with bis(silyl enol ethers) have been reported, which allow for a convenient synthesis of various bridged and non-bridged N-heterocycles.[2] Recently, we reported[3] the cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[4] with quinazolines. These one-pot reactions allow for the synthesis of densely functionalized 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes, which can be regarded as bridged quinazoline derivatives. Herein, we report the full details of this reaction and a comprehensive study related to the preparative scope. A number of novel quinazolines were prepared for the first time and successfully employed in our cyclization reaction. This includes, for example, derivatives containing an annulated ring or a lipophilic side-chain (hexyl group). It has been shown that the products can be functionalized by Suzuki cross-coupling reactions. In addition, we studied the mechanism of the cyclization by DFT computations. We also studied the reaction of 1,3-bis(silyl enol ethers) with phthalazine. These reactions afforded open-chain rather than cyclization products.

Quinazoline derivatives are of considerable pharmacological importance and occur in a number of natural products (*e.g.* tetrodotoxin, febrifugine, glomerine, or peganine). For example, 1,2,4-triazolo[5,1-*b*]quinazolines show antihypertonic activity.[5] Antirheumatic and antianaphylactic activity has been recognized for 3-heteroaryl-1,2,4-triazolo[5,1-*b*]quinazolines.[6] 1,2,4-Triazolo[1,5-*c*]quinazolines possess antiasthmatic, tranquilizing and neuro-stimulating activity.[7] Aryl- and heteroaryl substituted derivatives have been shown to possess benzodiazepine binding activity.[8] In addition, antiinflammatory, antihypertonic and antiviral activity has been reported.[9] Chlorinated 1,2,4-triazolo-[1,5-*c*]quinazolines and the isomeric 1,2,4-triazolo[4,3-*c*]quinazolines exhibit antiinflammatory and sedative activity.[10]

Results and discussion

Parent quinazoline (**3a**), 7-bromoquinazoline (**3b**) and 6-methyl quinazoline (**3c**) are commercially available. These substrates were used in our preliminary studies. The novel quinanzolines **3d–i** were prepared in two steps according to a procedure reported by Chilin and coworkers (Table 1).[11] Anilines **1a–f** were transformed into the carbamates **2a–f**. Reflux of **2a–f** in the presence of hexamethylenetetramine (HMTA, urotropine) and trifluoroacetic acid (TFA) and subsequent reflux in the presence KOH (EtOH–H_2O 1 : 1) and $K_3Fe(CN)_6$ afforded the novel quinazolines **3d–i**

Table 1 Synthesis of quinazolines **3d–i**



Reagents and conditions: *i*, **1a–f** (1.0 equiv.), NEt_3 (2.0 equiv.), $ClCO_2Et$ (2.0 equiv.), THF, 20 °C, 1 h; *ii*, (a) **2a–f** (1.0 equiv.), HMTA (7.0 equiv.), TFA, reflux, 1 h (b) 10% KOH (EtOH–H_2O = 1 : 1), $K_3Fe(CN)_6$ (7.6 equiv.), reflux, 4 h

1	**3**	R^1	R^2	%(**3**)[a]
a	**d**	Et	H	21
b	**e**	*i*Pr	H	35
c	**f**	*t*Bu	H	30
d	**g**	*n*Hex	H	30
e	**h**	$-(CH_2)_3-$		54
f	**i**	Me	Me	35

[a] Isolated yields (based on **1**).

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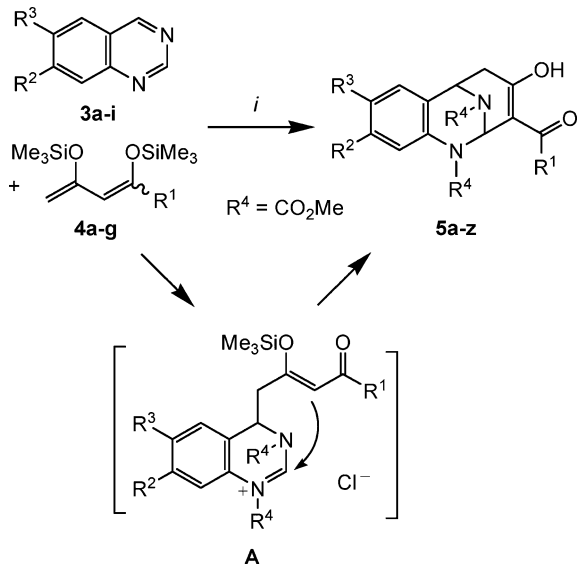
Table 2 Cyclization of 1,3-bis(silyl enol ethers) **4a–g** with **3a–i**



Reagents and conditions: *i*, **3a–i** (1.0 equiv.), **4a–g** (1.4 equiv.), ClR^4 (4.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h

3	4	5	R^1	R^2	R^3	% (**5**)[a]
a	**a**	**a**	OMe	H	H	52
a	**b**	**b**	OEt	H	H	46
a	**c**	**c**	$O(CH_2)_2OMe$	H	H	53
a	**d**	**d**	Me	H	H	63[b]
a	**e**	**e**	*t*Bu	H	H	12
a	**f**	**f**	Ph	H	H	0
b	**c**	**g**	$O(CH_2)_2OMe$	Br	H	23
b	**d**	**h**	Me	Br	H	37
c	**a**	**i**	OMe	H	Me	43
c	**d**	**j**	Me	H	Me	31
d	**a**	**k**	OMe	H	Et	43
d	**b**	**l**	OEt	H	Et	37
d	**d**	**m**	Me	H	Et	26
e	**a**	**n**	OMe	H	*i*Pr	44
e	**b**	**o**	OEt	H	*i*Pr	44
e	**d**	**p**	Me	H	*i*Pr	38
f	**a**	**q**	OMe	H	*t*Bu	50
f	**c**	**r**	$O(CH_2)_2OMe$	H	*t*Bu	38
f	**g**	**s**	O*i*Bu	H	*t*Bu	54
f	**d**	**t**	Me	H	*t*Bu	44
g	**a**	**u**	OMe	H	*n*Hex	37
g	**d**	**v**	Me	H	*n*Hex	53
h	**a**	**w**	OMe	$-(CH_2)_3-$		51
h	**d**	**x**	Me	$-(CH_2)_3-$		53
i	**a**	**y**	OMe	Me	Me	46
i	**d**	**z**	Me	Me	Me	48

[a] Yields of isolated products; all products were isolated as racemates. [b] Product **5d′** was isolated in 38% yield when benzyl chloroformate (R^4 = CO_2Bn) was used.

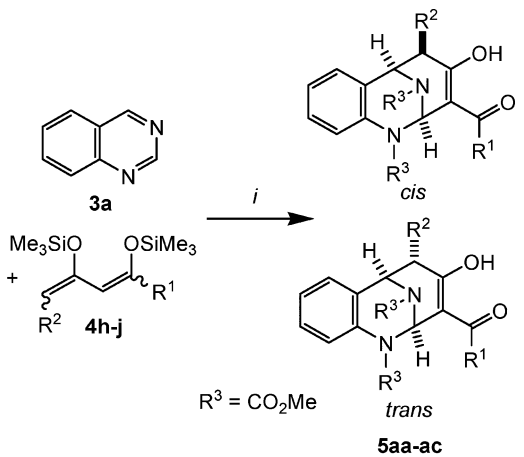
in 21–54% yields. The best yield was obtained for the tricyclic quinazoline **3h**.

1,3-Bis(trimethylsilyloxy)-1,3-butadienes **4a–c** and **4g–j** were prepared from the corresponding β-ketoesters in two steps.[12] Dienes **4d–f** are available from the corresponding 1,3-diketones in one step.[13] The cyclization of parent quinazoline (**3a**) with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4a–c**, in the presence of methyl chloroformate (4.0 equiv.), afforded the 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **5a–c** (Table 2). The use of only 3.0 (rather than 4.0) equivalents of methyl chloroformate resulted in a decrease of the yield. Methyl or benzyl chloroformate was used as the activating agent. The employment of methyl iodide or TFA resulted in the formation of complex mixtures. Optimal yields were obtained when the reaction mixture was directly purified by chromatography (without aqueous work-up) and when the reaction was carried out at room temperature. The formation of the products can be explained by the formation of an iminium salt by reaction of **3a** with methyl chloroformate, and subsequent regioselective attack of the terminal carbon atom of the 1,3-bis(silyl enol ether) onto carbon atom C-4 of the quinazoline. The reaction of the second nitrogen atom with methyl chloroformate again afforded an iminium ion, which is attacked by the central carbon atom of the 1,3-dicarbonyl unit.

The cyclization of **3a** with **4d**, derived from acetyl acetone, gave the acetyl-substituted diazabicyclo[3.3.1]nonene **5d**. The cyclization of **3a** with **4d**, in the presence of benzyl chloroformate, afforded product **5d′**. However, all attempts to induce a reductive cleavage of the protective group failed. The reaction of **3a** with 2,4-bis(trimethylsilyloxy)-5,5-dimethylhexane-1,3-diene (**4e**) afforded a separable mixture of diazabicyclo[3.3.1]nonene **5e** and an open-chain product. Due to the difficult separation, **5e** could be isolated in only low yield. The reaction of **3a** with 1-phenyl-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**4f**) resulted in the formation of a complex mixture. The cyclization of 1,3-bis(silyloxy)-1,3-butadienes with the substituted quinazolines **3b–i** afforded the diazabicyclo[3.3.1]nonenes **5g–z**. The deprotection of **5a** and **5d** failed under various conditions (decomposition).

The cyclization of **3a** with 1,3-bis(silyl enol ethers) **4h** and **4i**, containing an ethyl group attached to carbon atom C-4, afforded products **5aa** and **5ab** as mixtures of diastereomers (dr = 7 : 3 and 2 : 1, respectively) (Table 3). The cyclization of

Table 3 Cyclization of 1,3-bis(silyl enol ethers) **4h–j** with **3a**



Reagents and conditions: *i*, **3a** (1.0 equiv.), **4h–j** (1.4 equiv.), ClR^3 (4.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h

4	5	R^1	R^2	% (**5**)[a]	dr[b]
h	**aa**	OMe	Et	43	7 : 3
i	**ab**	OEt	Et	50	2 : 1
j	**ac**	Et	Me	75	6 : 1

[a] Yield of isolated products; all products were isolated as racemates. [b] Diastereomeric ratio *trans* : *cis* (by ^1H NMR); the assignment is arbitrary.

3a with **4j**, prepared from heptane-3,5-dione, gave product **5ac** with good diastereoselectivity (dr = 6 : 1). The diastereomeric mixtures of **5aa**, **5ab** and **5ac** could not be separated. Extension of the reaction times did not result in a change in the selectivity or epimerization. Therefore, the diastereomeric mixtures are presumably kinetic products.

The configurations of the 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes **5** were elucidated by NMR spectroscopy (HMBC, COSY, NOESY). For example, in the COSY spectrum of **5b**, correlations were observed between the hydrogen atoms of the NCHCH$_2$ moiety. In addition, NOE effects between the hydrogen atoms of the ring -CH$_2$- group and an aromatic hydrogen atom and the OH-proton were found. The HMBC spectrum showed correlations between the ring-C*H*$_2$ group and the N*C*H, NCH*C*$_{Ar}$, *C*OH and COH*C*CO groups. The relative configurations of **5aa**, **5ab** and **5ac** could not be unambiguously assigned. Due to the hindered rotation of the carbamate moieties, a fine splitting of many of the signals of **5a–ac** was observed in their ^{1}H and ^{13}C NMR spectra. The structures of **5n**, **5q**, **5w**, and **5y** were independently confirmed by X-ray crystal structure analyses (Fig. 1–4)†.[14]

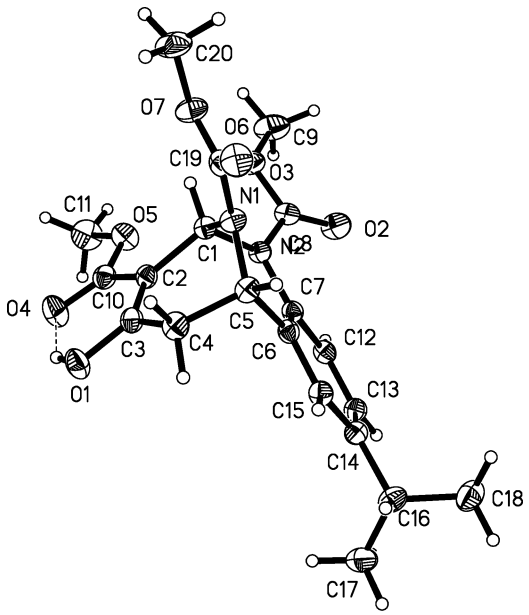


Fig. 1 Molecular structure of **5n** in the crystal form (ORTEP plot, 50% probability level, only one of the two symmetry independent molecules is shown).

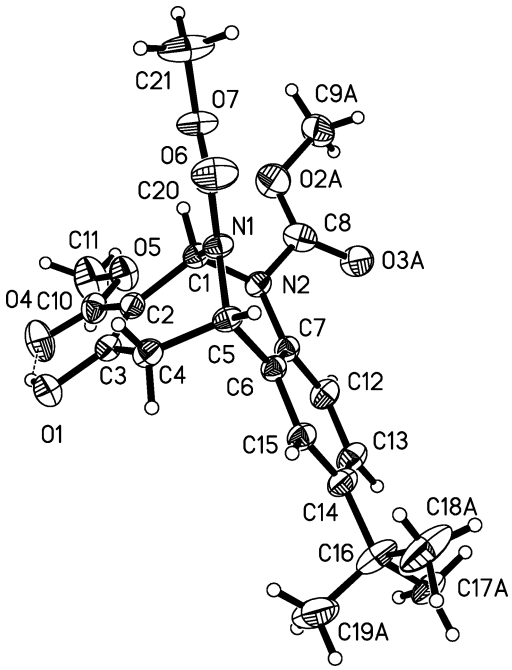


Fig. 2 Molecular structure of **5q** in the crystal form (ORTEP plot, 50% probability level, only one position of the disordered atoms is shown).

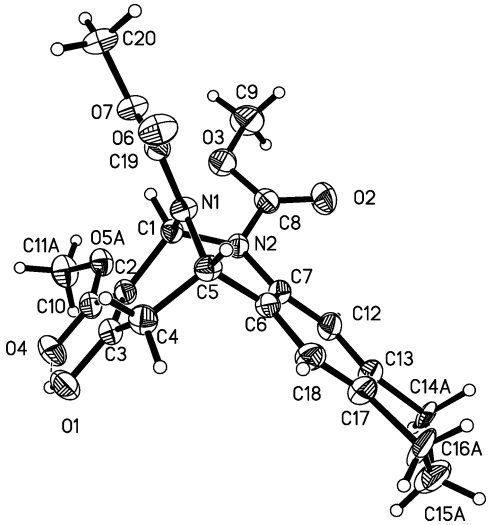


Fig. 3 Molecular structure of **5w** in the crystal form (ORTEP plot, 50% probability level, only one position of the disordered atoms is shown).

3,4-Benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-ene **5d** was transformed into its triflate **6**. The Suzuki cross-coupling reaction of **6** with phenyl- and 3,5-dimethylphenylboronic acid afforded products **7a** and **7b**, respectively (Scheme 1).

The reaction of 1,3-bis(silyl enol ethers) **4c** and **4f** with phthalazine (**8**), in the presence of methyl chloroformate (4.0 equiv.), afforded the condensation products **9a** and **9b**, respectively, rather than the cyclization products **10a**,**b** (Scheme 2). All attempts to induce a cyclization, by treatment of **9a**,**b** with methyl chloroformate or with acid (TFA), failed. In all experiments, the starting material was recovered. This might be explained by the steric effect of the carbamate moiety. In addition, the basicity of the imino group of **9a**,**b** is considerably reduced, due to the electron-withdrawing effect of the neighboring carbamate nitrogen. Although a number of reactions of iminium salts of phthalazine with nucleophiles have been reported,[15] double functionalizations are very rare.

Along with our synthetic efforts, we have carried out B3LYP/6-31G(d) density functional theory computations on the cyclization of 1,3-bis(silyl enol ethers) with quinazolines in order to get some mechanistic insight. The reaction of the unsubstituted reactants **3a** and **4a** was studied in detail. At B3LYP/6-31(d), **3a** has a planar structure as the energy minimum (Fig. 5). Since the two nitrogen atoms in **3a** are non-equivalent, its reaction with methyl chloroformate can result in the formation of two different iminium ions, *i.e.* **3a+R1**and **3a+R3**. It is found that **3a+R3** is more stable than **3a+R1** by 5.69 kcal mol^{-1} in Gibbs free energy. Therefore,

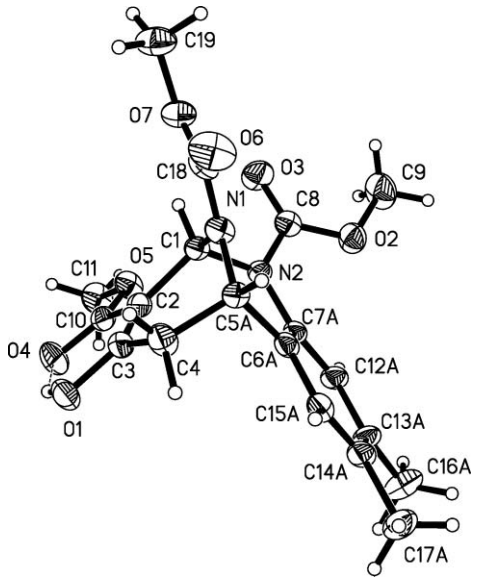
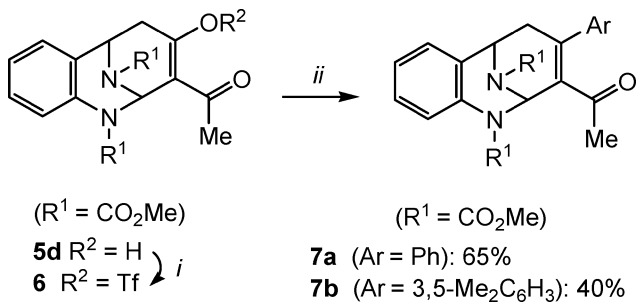
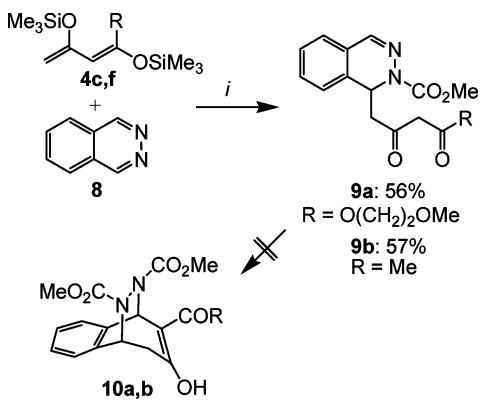


Fig. 4 Molecular structure of **5y** in the crystal form (ORTEP plot, 50% probability level, only one position of the disordered atoms is shown).



Scheme 1 Synthesis of **7a**,**b**: *i*, Tf_2O, pyridine, −78 → 20 °C, 4 h; *ii*, **6** (1.0 equiv.), $ArB(OH)_2$ (1.3 equiv.), K_3PO_4 (1.6 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), 1,4-dioxane, reflux, 20 h.



Scheme 2 Synthesis of **9a**,**b**: *i*, **8** (1.0 equiv.), **4c**,**f** (1.4 equiv.), $ClCO_2Me$ (4.0 equiv.), CH_2Cl_2, 0 °C, 2 h, 20 °C, 12 h.

3a+R3 should be the only product. It should also be noted that **3a+R3** has a rotamer of the carbamate group, which is higher in energy by less than 1.00 kcal mol^{-1}, and the computed rotation free energy barrier is 8.7 kcal mol^{-1}. In addition, we have found two conformers of **4a** which possess *s-trans* (**4a-*trans***) and *s-cis* (**4a-*cis***)

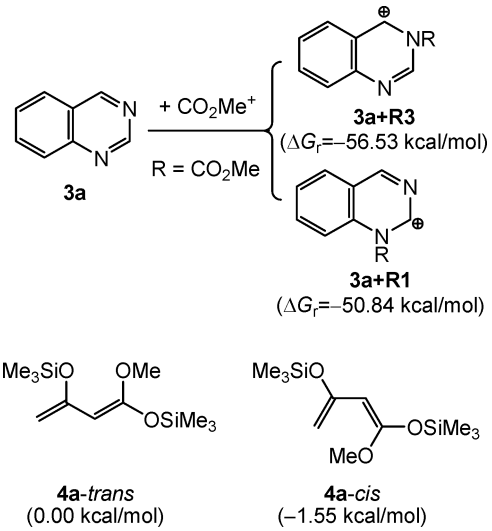


Fig. 5 Reaction free energies (ΔG_r) and relative free energies (B3LYP/6-31G(d) at 298K).

butadiene moieties. The latter is more stable by 1.55 kcal mol^{-1} and the expected equilibrium ratio of **4a-*cis*** to **4a-*trans*** should be 93% to 7%. The computed rotation free energy barriers between **4a-*cis*** and **4a-*trans*** are in the range of 4.32–4.71 kcal mol^{-1}. On the basis of this equilibrium, we have considered for comparison the cyclization of **4a-*cis*** and **4a-*trans*** with **3a+R3**.

The reaction of **3a+R3** with **4a-*cis*** or **4a-*trans*** results in the formation of a racemic mixture. We have calculated the intermediates derived from the *R*-enantiomer. The reaction maps are shown in Fig. 6 along with the reaction free energies (ΔG_r) and relative free energies. Upon orientation of the butadiene moiety of **4a-*cis*** and **4a-*trans*** with the six-membered ring in **3a+R3** there are two competitive allylic intermediates for each: **allyl-*cis-endo*/allyl-*cis-exo***, and **allyl-*trans-endo*/allyl-*trans-exo***. It is found that **allyl-*trans-endo*** is the most stable intermediate, while **allyl-*cis-endo*** and **allyl-*cis-exo*** are higher in free energy by 3.07 and 4.31 kcal mol^{-1}, respectively. The large energy differences reveal that the addition of **4a-*cis*** to **3a+R3** is not competitive, as compared to that of **4a-*trans***. Thus, we have paid our attention to the addition of **4a-*trans*** to **3a+R3** (right side of Fig. 6). However, the data for the addition of **4a-*cis*** to **3a+R3** are shown for comparison (left side of Fig. 6). **Allyl-*trans-endo*** and **allyl-*trans-exo*** are close in free energy (1.29 kcal mol^{-1}), and the expected ratio should be 89% to 11%. For the neutral intermediates, formed by removing Me_3Si^+, **A-*trans-endo*** is more stable than **A-*trans-exo*** by 3.32 kcal mol^{-1}, and the expected ratio should be larger than 99% to 1%. Further nucleophilic addition of $^+CO_2Me$ results in **B-*trans-endo*** and **B-*trans-exo***, and the former is more stable than the latter by 1.08 kcal mol^{-1}. On the basis of all these energetic differences, one would expect that **B-*trans-endo*** should be the principal intermediate.

The next step is the intramolecular electrophilic substitution to form the products. Due to the proper orientation of the C=C double bond, the expected product of **B-*trans-endo*** is **5a-*exo*-ketone**, formed when the cation attacks the C=C double bond along with the extrusion of Me_3Si^+. Due to the orientation of the Me_3SiO group, the expected product of **B-*trans-exo*** is **5a-pyran-*cis***, formed when the cation attacks the oxygen atom along with the extrusion of Me_3Si^+. It has been found that **5a-*exo*-ketone** is more

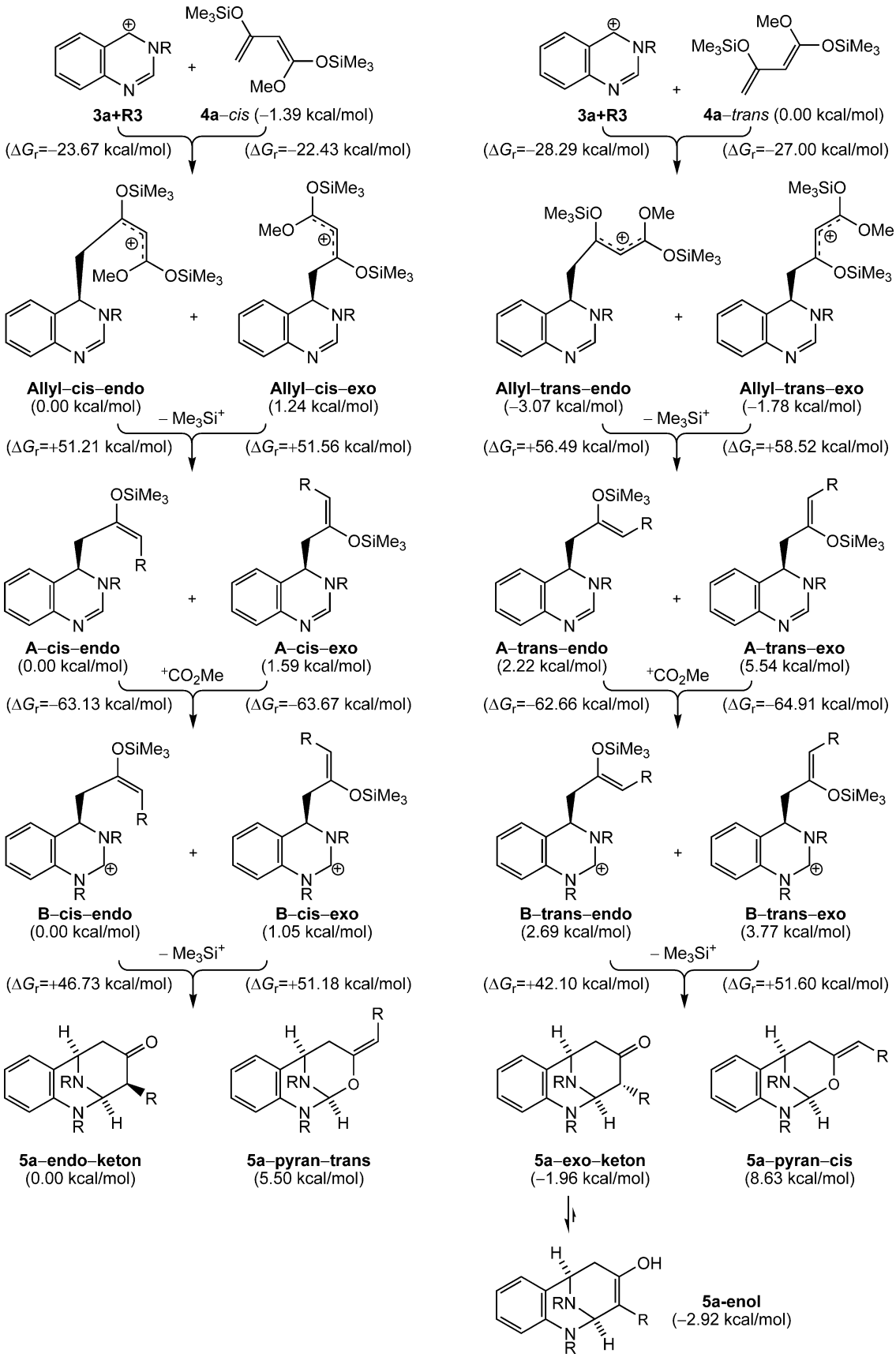


Fig. 6 Reaction free energies (ΔG_r) and relative free energies (B3LYP/6-31G(d) at 298K), R = CO_2Me.

stable than **5a-pyran-*cis*** by 10.59 kcal mol^{-1}. Therefore, **5a-*exo*-ketone** is the only product. We have also calculated the transition state for the ring closure of **B-*trans-endo***; the activation barrier is 27.62 kcal mol^{-1}. In addition, we have calculated the enol form of the final product (**5a-enol**), which is more stable than **5a-*exo*-ketone** by 0.96 kcal mol^{-1}. The expected ratio should be 86% to 14%. This result agrees reasonably with the experimental findings.

It can be concluded that the addition reaction takes place through the **allyl-*trans-endo*** intermediate, formed by the reaction of **3a+R3** with **4a-*trans***. The total reaction free energy from **3a** + **4a-*trans*** + 2 $ClCO_2Me$ to give **5a-enol** + 2 Me_3SiCl is highly exergonic, by 50.50 kcal mol^{-1} at the B3LYP/6-31G(d) level, and this should be the driving force for the complete reaction.

Conclusions

In conclusion, we have reported the synthesis of a variety of functionalized 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes by the one-pot cyclization of 1,3-bis(silyl enol ethers) with quinazolines. In addition, B3LYP/6-31G(d) density functional theory computations have been performed to get some insight into the reaction mechanism. It is worth noting that the reaction of 1,3-bis(silyl enol ethers) with phthalazine afforded open-chain rather than cyclization products, which can be explained by steric and electronic reasons.

Experimental section

Computational details. All structures were optimized at the B3LYP/6-31G(d)[16] level of density functional theory. All optimized structures were characterized by frequency calculations as energy minima without imaginary frequencies (NImag = 0) or transition states with only one imaginary frequency (NImag = 1) at the same level of theory.[17] The thermal corrections to the Gibbs free energies at 298 K at B3LYP/6-31G* from the frequency calculations were added to the total electronic energies for analyzing the selectivity, which was estimated on the basis of the relationship of $\Delta\Delta G = -RT\ln K$, in which $\Delta\Delta G$ is the difference in the Gibbs free energy, and K presents the considered equilibrium constant of the two competing reactions. All calculations were carried out by using the Gaussian 03 program package.[18]

General. Chemical shifts of the ^{1}H and ^{13}C NMR are reported in parts per million using the solvent as the internal standard (chloroform, 7.26 and 77.0 ppm, respectively). Infrared spectra were recorded on a FTIR spectrometer. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). Melting points are uncorrected. Analytical thin layer chromatography was performed on 0.20 mm 60 Å silica gel plates. Column chromatography was performed using 60 Å silica gel (60–200 mesh). All cyclization reactions were carried out in Schlenk tubes under an argon atmosphere. The bis(silyl enol ethers) were prepared as described in the literature. Crystallographic data were collected on a Bruker X8Apex with $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The structures were solved by direct methods using SHELXS-97 and refined against F^2 on all data by fullmatrix least-squares with SHELXL-97. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were refined in the model at geometrically calculated positions and refined using a riding model.

General procedure for the synthesis of the substituted quinazolines 3. To a solution of aniline **1** (10.0 mmol) in THF (100 mL) were added triethylamine (20.0 mmol) and ethyl chloroformate (20.0 mmol). The solution was stirred for 1 h at 20 °C, filtered and concentrated *in vacuo*. To the residue was added ethyl acetate (100 mL) and the solution was washed with water (2 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. To the residue was added TFA (70 mL). Hexamethylenetetramine (HMTA) (9.800 g, 70.0 mmol) was added and the solution was heated under reflux for 1 h. To the solution was added hydrochloric acid (4 M, 400 mL) and the solution was filtered and concentrated *in vacuo*. To the residue was added a 1 : 1 mixture of water and ethanol (600 mL). To the solution was added KOH (66.60 g) and $K_3Fe(CN)_6$ (25.00 g) and the solution was heated under reflux for 4 h. Water (600 mL) was added and the solution was extracted with toluene (5 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, heptane → heptane–EtOAc = 2 : 1).

General procedure for the reaction of the 1,3-bis(silyl enol ethers) with quinazolines. To a solution of quinazoline **3** (4.0 mmol) in CH_2Cl_2 (40 mL) were added at 0 °C the 1,3-bis(silyl enol ether) (5.6 mmol) and the chloroformate (16.0 mmol). The solution was stirred for 2 h at 0 °C and for 12 h at 20 °C. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, heptane → heptane–EtOAc = 2 : 1).

11-Hydroxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,10,13-tricarboxylic acid trimethyl ester (5a). Starting with quinazoline **3a** (0.521 g, 4.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-buta-1,3-diene **4a** (1.460 g, 5.6 mmol) and methyl chloroformate (1.512 g, 16.0 mmol) in CH_2Cl_2 (40 mL), **5a** was obtained as a colorless solid (0.750 g, 52%); mp 133–135 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.41 (dd, ^2J = 17.5 Hz, ^3J = 1.5 Hz, 1H, CH_2), 2.99 (br dd, 1H, CH_2), 3.76, 3.80 (2 s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 5.40 (br, 1H, NC*H*CH_2), 7.03–7.13 (m, 2H, Ar), 7.20–7.26 (m, 1H, Ar), 7.38 (br, 1H, NCHN), 7.75 (br, 1H, Ar), 12.26 (s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 38.0 (CH_2), 48.7 (br, N*C*HCH$_2$), 52.0, 53.2, 53.3 (OCH_3), 58.9 (NCH), 98.0 (*C*CO_2CH_3), 124.2, 124.4, 126.8, 127.6 (CH_{Ar}), 126.3, 134.4 (br) (C_{Ar}), 153.4, 154.0 (NCOO), 170.6 (COO), 173.2 (br, COH). IR (Nujol, cm^{-1}): ν = 3080 (w), 1707 (s), 1652 (m), 1613 (m), 1494 (m), 1335 (m), 1287 (s), 1263 (m), 1230 (s), 1196 (m), 1142 (m), 1111 (m), 1064 (m), 1039 (m), 1008 (m), 778 (m). MS (EI, 70 eV): m/z (%) = 362 (M$^+$, 10), 303 (100), 271 (36), 212 (23), 180 (21), 239 (13). Anal. calcd for $C_{17}H_{18}N_2O_7$ (362.33): C, 56.35; H, 5.01; N, 7.73. Found: C, 56.35; H, 5.13; N, 7.46.

Preparation of 10-acetyl-11-trifluoromethanesulfonyloxy-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,13-dicarboxylic acid dimethyl ester (6). To a CH_2Cl_2 solution (21 mL) of **5f** (0.723 g, 2.1 mmol) and pyridine (0.331 g, 4.2 mmol) was added trifluoromethanesulfonic acid anhydride (0.708 g, 2.5 mmol) dropwise at −78 °C. The solution was allowed to warm up to

20 °C within 4 h and was then concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, heptane → heptane–ethyl acetate = 2 : 1) to give **6** as a yellowish oil (0.570 g, 57%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.36 (s, 3H, $COCH_3$), 2.53 (dd, ^2J = 17.7 Hz, ^3J = 1.53 Hz, 1H, CH_2), 3.21 (br dd, ^2J = 17.7 Hz, ^3J = 5.2 Hz, 1H, CH_2), 3.78 (s, 3H, $COOCH_3$), 3.87 (s, 3H, $COOCH_3$), 5.46 (br, 1H, NC*H*CH_2), 7.08–7.19 (m, 2H, Ar), 7.28 (m, 1H, Ar), 7.52 (br, 1H, NCHN), 7.70 (br m, 1H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.7 (CO*C*H_3), 37.5 (CH_2), 49.4 (br, N*C*HCH_2), 53.6, 53.9 ($COOCH_3$), 60.4 (NCHN), 118.1 (q, ^1J = 320.4 Hz, CF_3), 124.2, 125.0, 126.4, 128.5 (CH_{Ar}), 125.6, 128.8, 134.0 (C_{Ar}, *C*CO), 150.8 (br, COS), 153.3, 153.8 (NCOO), 194.8 (C*C*OCH_3). ^{19}F NMR (235 MHz, $CDCl_3$): δ = −117.6 (CF_3). MS (EI, 70 eV): *m*/*z* (%) = 478 (M^+, 34), 345 (22), 269 (100), 251 (17), 211 (8), 117 (5), 63 (23). HRMS (EI): calcd for $C_{18}H_{17}F_3N_2O_8S$ (M^+) 478.06522, found 478.064923.

General procedure for the synthesis of 7a,b. To a solution of triflate **6** (1.00 mmol) in 1,4-dioxane (2.5 ml) at 20 °C were added boronic acid (1.30 mmol), potassium phosphate (1.60 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.03 mmol). The solution was refluxed for 20 h. After cooling to 20 °C a saturated aqueous solution of ammonium chloride (3 ml) was added. The solution was diluted with CH_2Cl_2 (15 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (20 ml). The collected organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, heptane → heptane–ethyl acetate = 2 : 1).

10-Acetyl-11-phenyl-8,13-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene-8,13-dicarboxylic acid dimethyl ester (7a). Starting with **6** (0.546 g, 1.14 mmol), phenyl boronic acid (0.181 g, 1.48 mmol), potassium phosphate (0.387 g, 1.82 mmol and tetrakis(triphenylphosphine)palladium(0) (0.040 g, 0.03 mmol) in 1,4-dioxane (3 ml), **7a** was obtained as a yellow solid (0.303 g, 65%); mp 130–131 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.51 (s, 3H, $COCH_3$), 2.66 (dd, ^2J = 18.3 Hz, ^3J = 1.5 Hz, 1H, CH_2), 2.97 (dd, ^2J = 18.3 Hz, ^3J = 1.2 Hz, 1H, CH_2, rotamers), 2.99 (dd, ^2J = 18.3 Hz, ^3J = 1.2 Hz, 1H, CH_2, rotamers), 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.48 (br, 1H, NC*H*CH_2), 6.96–7.00 (m, 2H, Ar), 7.14–7.32 (m, 6H, Ar), 7.49 (br, 1H, Ar), 7.76 (br, 1H, NCHN). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.8 (CO*C*H_3), 40.4 (CH_2), 49.1 (N*C*HCH_2), 53.1, 53.5 (NCOO*C*H_3), 60.4 (NCHN), 123.7, 124.3, 124.3, 126.1, 127.3, 127.6, 127.8, 128.7, 129.1 (CH_{Ar}, rotamers), 134.9, 134.9, 135.1, 138.9 (C_{Ar}, NCH*C*CO), 143.5 (br, CH_2*C*C), 153.7, 154.0 (NCOO), 201.9 (C*C*O). IR (KBr, cm^{-1}): ν = 3027 (w), 2955 (w), 2927 (w), 2853 (w), 1717 (s), 1491 (m), 1448 (s), 1413 (m), 1374 (m), 1332 (m), 1273 (s), 1222 (m), 1134 (m), 1059 (m), 1024 (m). MS (EI, 70 eV): *m*/*z* (%) = 406 (M^+, 58), 347 (100), 315 (62), 256 (22), 212 (7), 180 (8), 128 (5). HRMS (EI): calcd for $C_{23}H_{22}N_2O_5$ (M^+) 406.15232, found 406.152301.

1-[3-(2-Methoxyethoxycarbonyl)-2-oxo-propyl]-1*H*-phthalazine-2-carboxylic acid methyl ester (9a). Starting with phthalazine (0.521 g, 4.0 mmol), **4c** (1.705 g, 5.6 mmol) and methyl chloroformate (1.512 g, 16.0 mmol) in CH_2Cl_2 (40 ml), **9a** was isolated as a yellow, viscous oil (0.775 g, 56%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.31 (br m, 1H, NCHCH_2, enol), 2.59 (br m, 1H, NCHCH_2, enol), 2.82 (dd, ^2J = 16.3 Hz, ^3J = 4.4 Hz, 1H, NCHCH_2, keto), 3.03 (dd, ^2J = 16.3 Hz, ^3J = 8.7 Hz, 1H, NCHCH_2, keto), 3.32 (d, ^2J = 15.7 Hz, 1H, $COCH_2CO$), 3.33 (s, 3H, CH_2OCH_3), 3.45 (d, ^2J = 15.7 Hz, 1H, $COCH_2CO$), 3.55 (m, 2H, CH_2OCH_3), 3.89 (s, 3H, $COOCH_3$), 4.21 (m, 2H, $COOCH_2$), 4.83 (s, 1H, CO*C*H*C*OH, enol), 6.00 (dd, ^2J = 8.4 Hz, ^3J = 4.4 Hz, 1H, NC*H*CH_2), 7.14–7.46 (m, 4H, Ar), 7.70 (s, 1H, NCONCH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 39.7 (NCH*C*H_2), 47.3 (CO*C*H_2CO, rotamers), 49.2 (CH_2OCH_3), 49.5 (CO*C*H_2CO, rotamers), 54.0 (N*C*HCH_2), 58.9, 59.0 ($COOCH_3$), 63.1 (*C*H_2OCH_3, enol), 64.3 (*C*H_2OCH_3, keto), 70.1, 70.3 ($COOCH_2$, rotamers), 92.0 (CO*C*HCOH, enol), 123.3, 123.4 (C_{Ar}, rotamers), 125.9, 126.0, 126.2, 126.9, 128.1, 128.7, 129.0, 131.8, 132.0, 132.3 (CH_{Ar}, keto, enol, rotamers), 132.7 (C_{Ar}), 143.2 (NCON*C*H), 154.3 (NCOO), 166.6 (*C*OOCH_2), 172.0, 173.0 (COH, enol, rotamers), 199.0 (CH_2*C*OCH_2). IR (neat, cm^{-1}): ν = 2955 (m), 2932 (m), 2894 (m), 2821 (w), 1742 (s), 1711 (s), 1655 (m), 1566 (m), 1445 (s), 1379 (s), 1321 (s), 1197 (s), 1157 (s), 1128 (s), 1099 (m), 1040 (m), 983 (w), 924 (m), 847 (w), 766 (m), 551 (m), 531 (m). MS (EI, 70 eV): *m*/*z* (%) = 348 (M^+, 3), 289 (9), 203 (20), 189 (100), 145 (84), 130 (26), 117 (13), 76 (8). Anal. calcd. for $C_{17}H_{20}N_2O_6$ (348.35): C, 58.61; H, 5.79; N, 8.04. Found: C, 58.42; H, 5.93; N, 7.84.

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