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Base-Mediated Generation of Ketenimines from Ynamides: [3+2] Annulation with Azaallyl Anions.

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ABSTRACT: Under basic conditions and heat, ynamides can serve as precursor to ketenimines, whose synthetic potential is often hampered by their difficulty of access. Herein, we report that they can undergo a [3+2] cycloaddition with 2-azaallyl anions, obtained from benzylimines under the same reaction conditions. This reaction between two highly reactive intermediates, both generated *in situ* from bench stable starting materials, gives access to various nitrogen-rich heterocycles. The reaction usually proceeds with excellent diastereoselectivity, in favor of the *cis* adduct. Deuteration experiments and DFT calculation helped rationalize the regio and stereo-selectivity of the process as well as the formation of side-products..

Long before the discovery of penicillin, Staudinger devised a straightforward access to the β -lactam ring by a [2+2] cycloaddition between a ketene and an imine (Scheme 1a).¹ This reaction, named the Staudinger synthesis, set the template for accessing this particular heterocycle and inspired a myriad of synthetic variations.² Our group developed an imino-variant of this transformation by using an ynamide (**1a**)³⁻⁵ to generate *in situ* a highly reactive ketenimine(**2a**)⁶⁻⁸ which can engage in a [2+2] cycloaddition with a diaryl imine (**3a**) to give an azetidimine (Scheme 1b).^{9,10} Exploring this transformation further, we found that when the same reaction conditions were applied to the homologous benzylimine **3b**, the formation of the expected azetidimine was not observed. Instead, 2,5-dihydro-1H-imidazole **6ab** was obtained with a 39% yield (Scheme 1c). We hypothesized that this 5-membered ring arose from a [3+2] cycloaddition between the ketenimine and with semi-stabilized 2-azaallyl lithium **5b**, which was also formed *in situ* under the basic reaction conditions.^{11,12} Overall, reports of 1,3 dipolar cycloaddition with a ketenimine as the dipolarophile remain rather scarce.¹³⁻¹⁵ Moreover, [3+2] cycloadditions with non- or semi-stabilized azallylanions^{16,17} were mostly developed with olefins as the dipolarophiles.¹⁸⁻²⁰ This serendipitous discovery thus gave us the opportunity to explore some unprecedented annulation reactions towards nitrogen-rich heterocycles.

To optimize this transformation we decided to react ynamide **1a** with imine **3c** bearing two *p*-chlorobenzene moieties, which would lead to a symmetrical 2-azaallyl anion (Table 1).

Scheme 1. [2+2] and [3+2] annulations involving ketenes, ketenimines and imines

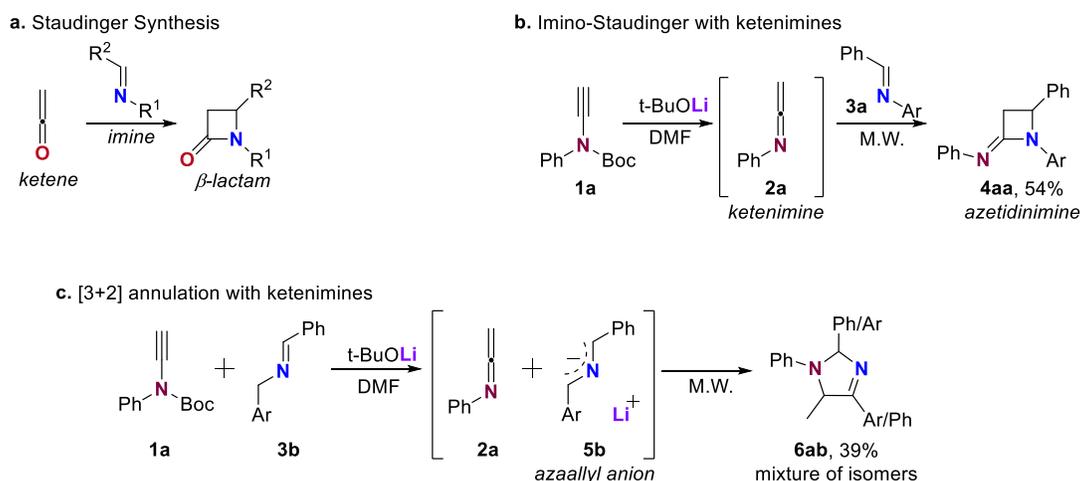
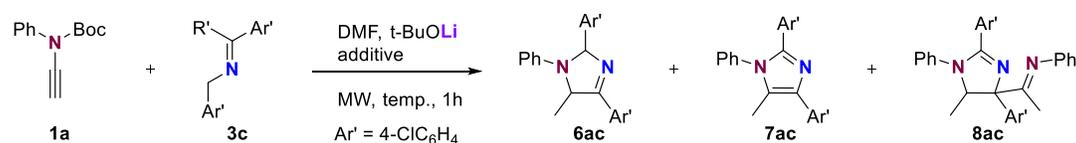


Table 1. Optimization of the reaction conditions^a



Entry	equiv. 1a / equiv. 3c	Base (equiv.)	Additive (mol%)	Solvent	Temp.	Yield 6ac (%) ^b	Yield 7ac (%) ^b	Yield 8ac (%) ^b
1	2.0/1.0	<i>t</i> -BuOLi (2.0)	none	DMF (0.5 M)	100°C	23 (±3)	16 (±1)	12 (±1)
2	2.0/1.0	<i>t</i> -BuOLi (2.0)	none	DMF (0.2 M)	100°C	45 (±2)	7 (±2)	12 (±1)
3	2.0/1.0	<i>t</i> -BuOLi (2.0)	none	THF (0.2 M)	100°C	0	0	0
4	2.0/1.0	<i>t</i> -BuOLi (2.0)	none	DMA (0.2 M)	100°C	16 (±3)	15 (±3)	25 (±3)
5	2.0/1.0	none	none	DMF (0.2 M)	100°C	0	0	0
6	2.0/1.0	Cs₂CO₃ (2.0)	none	DMF (0.2 M)	100°C	0	0	0
7	2.0/1.0	DBU (2.0)	none	DMF (0.2 M)	100°C	0	0	0
8 ^c	2.0/1.0	<i>t</i> -BuOLi (2.75)	Zn(OAc) ₂ •2H ₂ O (10)	DMF (0.2 M)	100°C	61 (±3)	8 (±1)	7 (±1)
9 ^c	2.0/1.0	<i>t</i> -BuOLi (2.75)	Cu(OAc) ₂ (10)	DMF (0.2 M)	100°C	55 (±1)	6 (±1)	2 (±2)
10 ^c	2.0/1.0	<i>t</i> -BuOLi (3.3)	Zn(OTf) ₂ (10)	DMF (0.2 M)	100°C	63 (±4)	(8±1)	8 (±2)
11 ^c	2.0/1.0	<i>t</i> -BuOLi (2.75)	Zn(OAc) ₂ •2H ₂ O (10)	DMF (0.2 M)	80°C	60 (±4)	7 (±2)	7 (±2)
12 ^c	1.5/1.0	<i>t</i> -BuOLi (2.75)	Zn(OAc) ₂ •2H ₂ O (10)	DMF (0.2 M)	80°C	50	Traces	Traces
13^c	1.5/1.0	<i>t</i>-BuOLi (4.4)	Zn(OAc)₂•2H₂O (10)	DMF (0.2 M)	80°C	62 (±1)	Traces	Traces

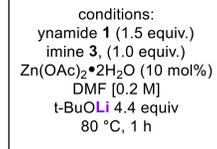
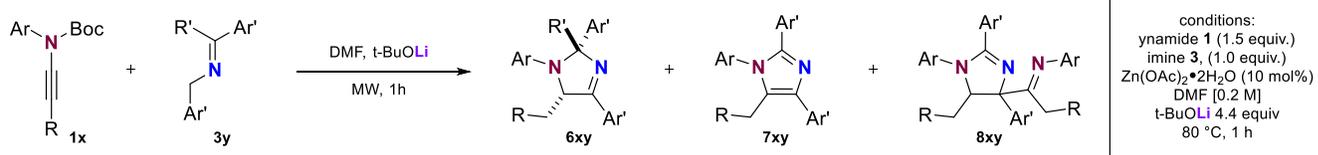
^a All reactions were carried out with 0.15 mmol of **3c**, and in a microwave apparatus; ^b isolated yields, average of two separate reactions; ^c argon was bubbled in the reaction mixture before the addition of the base.

Using microwave heating at 100°C for 1h in DMF (0.5M) with 2.0 equivalents of *t*-BuOLi gave a mixture of 2,5-dihydro-1H-imidazole **6ac** (23%), imidazole **7ac** (16%) and 4,5-dihydro-1H-imidazole **8ac** (12%) that incorporates two ketenimine fragments (entry 1). When the concentration was increased from 0.2 M to 0.5 M, a mixture was still obtained but the overall yield improved by 13% (entry 2). Other solvents were tested (see Supplementary Information for fully detailed optimization) but were found to be totally ineffective (THF, entry 3) or did not bring any improvement (DMA, entry 4). Presence of the base was found to be essential (entry 5) but alternative inorganic (Cs₂CO₃, entry 6) or organic (DBU, entry 7) bases did not promote the reaction. The formation of the oxidized derivative **7ac** could be almost entirely suppressed by bubbling argon in the reaction mixture (entries 8–13). Various Lewis acid-type additives were screened (entries 8–10), Zn(II) salts giving the best results (entries 8 & 10). The hygroscopic nature of these salts (in particular zinc triflate) led us to increase the number of equivalents of base to compensate for the induced hydrolysis (entries 10). Lowering the temperature to 80 °C did not overly affect the yield (entry 11). Finally, to reduce the formation of **8ac**, the ynamide to imine ratio was diminished (entry 12 & 13) and better and more consistent results were obtained with a larger excess of base (4.4 equivalents, entry 13). These conditions gave the desired adduct **6ac** in 62% yield, mostly avoiding the formation of side-products **7ac** and **8ac** and were selected to explore the scope of this [3+2] annulation.

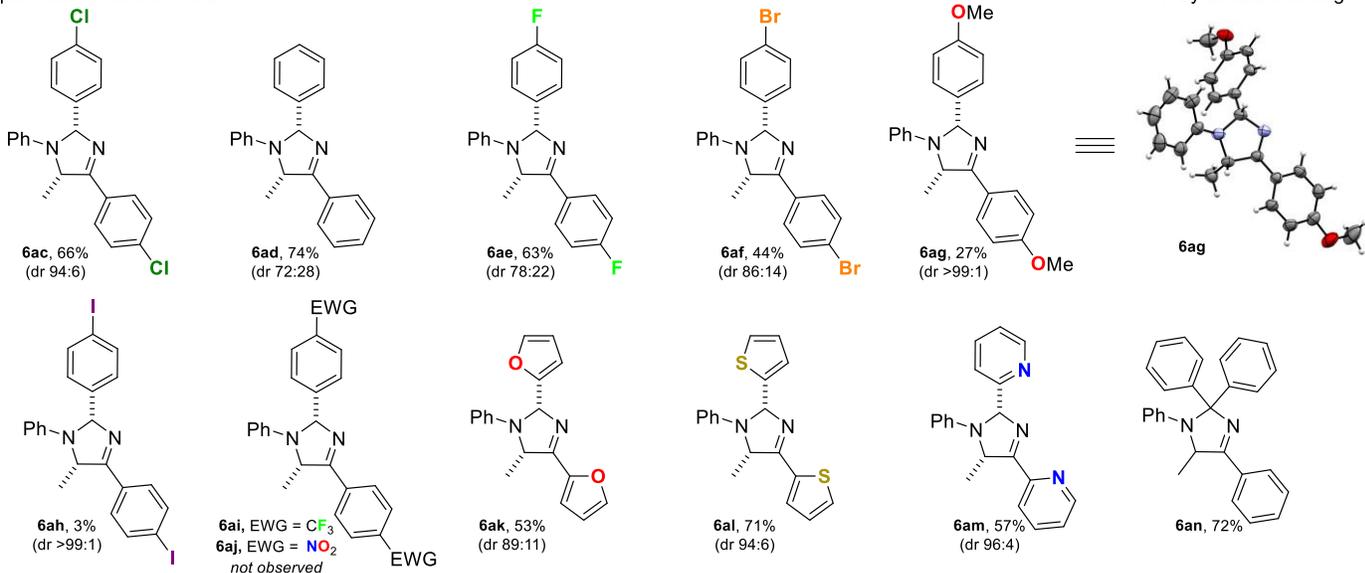
First, benzylic aldimines **3** leading to symmetrical azaallyl anions **5**, having various groups – H (**3d**), halogens (**3e,f,h**), MeO (**3g**) and electron withdrawing groups (**3i,j**) on the para positions, were screened. The 1,5-dihydro-1H-imidazoles **6** were obtained in moderate to good yields with good to excellent diastereoselectivities in favor of the *cis*-isomer (Scheme 2a), as confirmed by single-crystal X-ray diffraction analysis for **6ag** (Scheme 2b). The reaction was not operative for imines bearing strong electron withdrawing groups such as CF₃ or NO₂ (**3i,j**), and the low solubility of diiodo imine **3h** was detrimental to the reaction's success. Nevertheless, imines bearing heterocycles such as 2-furanyl (**3k**), 2-thiophenyl (**3l**) or 2-pyridinyl (**3m**) were well tolerated. Finally, the 1,1-diphenyl-ketimine **3n** was also subjected to the reaction conditions, forming **6al** as a single regioisomer in 72 % yield. This is in sharp contrast to the reactivity of aldimines bearing two different aryl groups, such as **3b** (see Scheme 1), that leads to inseparable mixtures of regioisomers. The scope of the ynamide partner was then delineated (Scheme 2c). As with the imino-Staudinger [2+2] cycloaddition,⁹ only ynamides bearing an aryl group on the nitrogen were suitable for the generation of the ketenimine intermediate and Boc was the best leaving group. N-Aryl ynamides bearing halogens (Cl and Br, **1b,c**), electron-donating (OMe and OEt,

1e,f) or electron withdrawing (CF₃, **1g**) groups gave 1,5-dihydro-1H-imidazoles **6** as the major adducts, generally along with minor amounts of double addition compound **8**. Again, the low solubility of the p-iodo compound was responsible for the low yield of **6dc**, while the p-nitro functionality (**1h**) was incompatible with the reaction conditions. The reaction was also successful if the triple bond was substituted by an alkyl (n-Bu, **6ic**), an aryl (Ph, **6jc**) or a silyl (TIPS, **6kc**), albeit with a low 18 % yield in this case.

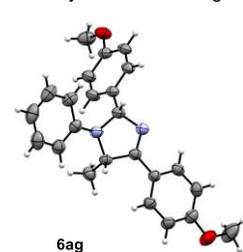
Scheme 2. Scope of the [3+2] annulation



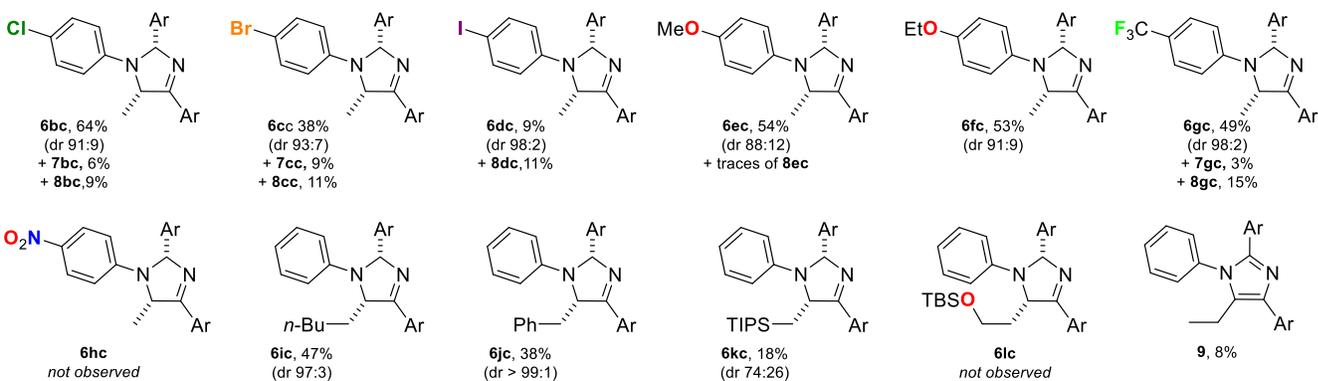
a. scope: variation of the imine



b. X-ray structure of 6ag



c. scope: variation of the ynamide

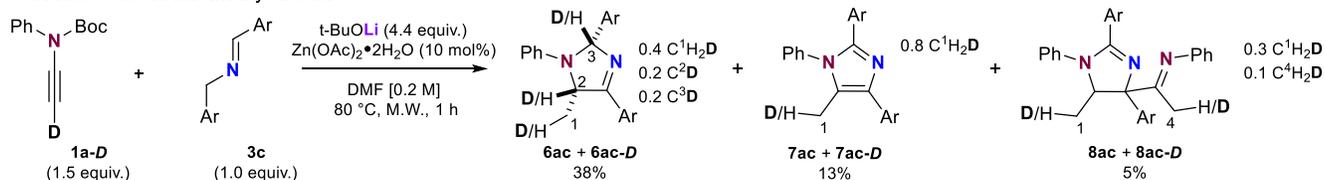


When an ynamide bearing a silyl-protected hydroxymethyl group on the triple bond (**1I**) was submitted to the reaction conditions, instead of the expected **6Ic** imidazole **9** was isolated. The latter would not come from an oxidation process as for imidazole **8**. Instead, it would rather result from a [3+2] annulation with a cumulenimine (see **2I'**, Scheme 4c) to give a vinylated 1,5-dihydro-1H-imidazole, followed by the isomerization of the double bond.

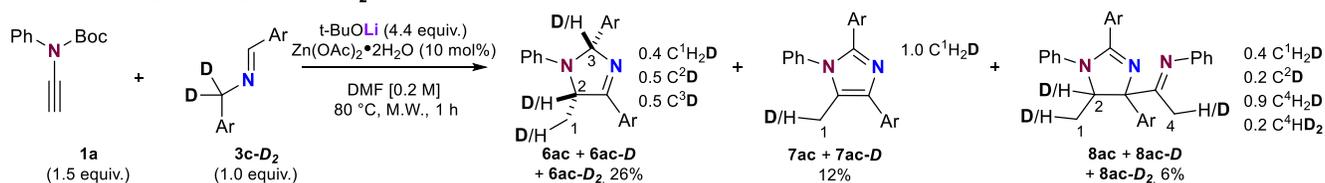
In order to gain more insight on the [3+2] annulation process and the formation of side products **7** and **8**, we performed several control experiments. First, deuterated ynamide **1a-D** was synthesized and reacted with imine **3c** (Scheme 3a). All adducts **6ac**, **7ac** and **8ac** were isolated as mixtures of non- and mono-deuterated compounds, predominantly corresponding to the initial ynamide deuterium position (C1 as well as C4 for **8ac**). For **6ac-D** other deuterium incorporation sites were identified at the C2 and C3 positions of the five-membered ring. A complementary experiment was performed by reacting ynamide **1a** with the bis-deuterated imine **3c-D₂** (Scheme 3b). In this setting, the adducts were obtained as non-, mono- and di-deuterated compounds, again with several deuterium incorporation sites at C1, C2, C3 and/or C4, including a double deuteration at C4 for **8ac-D₂**. This broad distribution pattern seems to indicate that many proton exchange steps take place during the formation of the five-membered adducts. However no deuteration was observed when the reaction was performed in deuterated DMF. To ascertain whether some elemental steps in our manifold are reversible, we resubmitted *cis*-**6ac** to the reaction conditions with 1.5 equivalents of **1a** (Scheme 3c).

Scheme 3. Control experiments

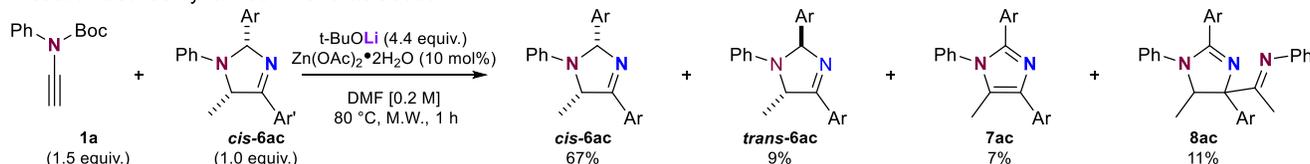
a. reaction with deuterated ynamide **1a-D**



b. reaction with deuterated imine **3c-D₂**



c. reaction between ynamide **1a** and *cis* adduct **cis-6ac**



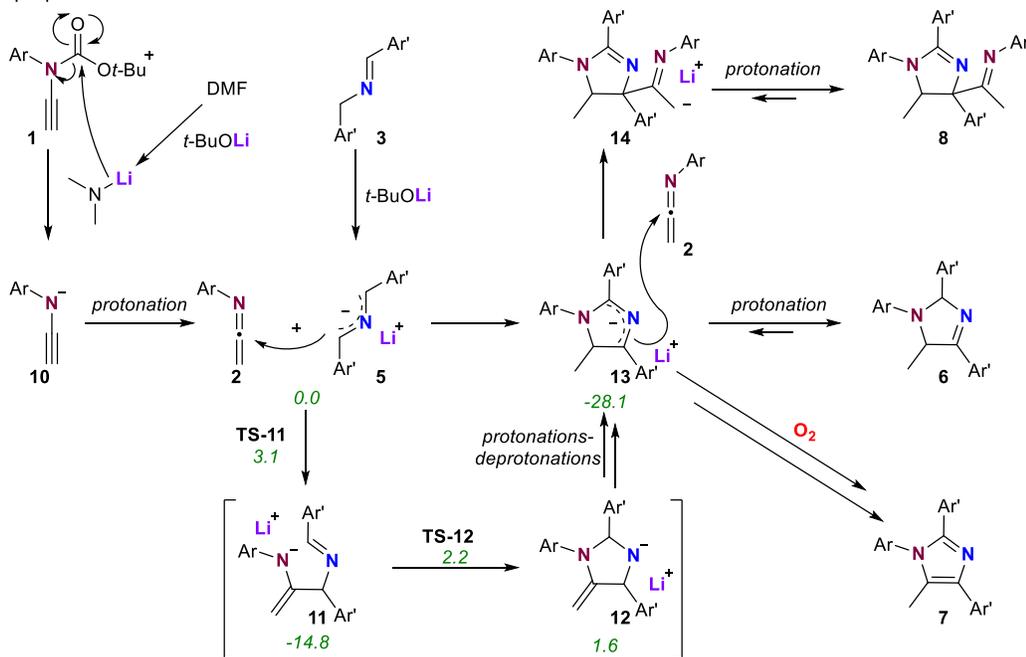
While *cis*-**6ac** was mostly recovered (67% yield), the *trans* isomer (*trans*-**6ac**, 9%), the imidazole resulting from an oxidation (**7ac**, 7%) and the double addition adduct (**8ac**, 11%) were also obtained. Interestingly, **8ac** did not give back **6ac** when it was subjected to the same reaction conditions (minus the ynamide). Finally, heating a DMF solution of **6ac** at 80°C for 1h after bubbling air for 10 min only marginally led to the formation of **7ac** (<5%).

Considering all these results a plausible mechanistic proposal was outlined and validated using DFT calculations (Scheme 4a). Under the strongly basic conditions, and possibly with the assistance of the zinc Lewis acid,⁴⁶ partial decomposition of the DMF to give lithium dimethylamide would be the trigger to initiate the cleavage of the Boc protecting group of ynamide **1** giving the semi-stabilized amide **10** that protonates to give ketenimine **2**. The generation of dimethylamine in the reaction mixture was confirmed by the isolation of amidines **15**, **15-D₆** (when DMF-*D*₇ was used) and **16** (Scheme 4b). The latter appears to be consistent with the formation of cumulenimine **2I'**, rather than the expected ketenimine **2I** (Scheme 4c), from amide **10I**. Thus, its reaction with imine **3c** would give a vinyl-1,5-dihydro-1*H*-imidazole, which isomerization would lead to ethylimidazole **9** (Scheme 2c).

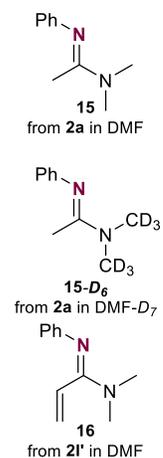
Deprotonation of the imine **3** would give the semi-stabilized diaryl azaallyl anion **5** that can add onto the ketenimine to give enamide **11**, followed by cyclization to yield imidazolinide **12**. Overall this process is nearly energoneutral ($\Delta G = 1.6 \text{ kcal.mol}^{-1}$), the first step being exergonic by $14.8 \text{ kcal.mol}^{-1}$, with a rather low activation barrier ($3.1 \text{ kcal.mol}^{-1}$) (Figure S1). From this intermediate, successive protonations and deprotonations as well as tautomerization of the enamide and/or imine moieties can take place explaining the complex deuteration patterns that we observed (Scheme 3a & 3b). These experiments also indicate that the imine is the major purveyor of protons and that the ynamide only contributes to a lesser extent; the protons being channeled either by direct deprotonation or through the *tert*-butanol generated from an initial deprotonation with the lithium *tert*-butoxide. By modelling the various anions resulting from these events (Figure S2) we were able to identify azaallyl anion **13** as being the most favored at $-28.1 \text{ kcal.mol}^{-1}$. A final reversible (as evidenced by the experiment in Scheme 3c) protonation would give **6**. Alternatively, its reaction with another equivalent of ketenimine would lead to **8**. Calculations indicated that addition at the benzylamine position, rather than at the aminal position, of **13** to give anion **14**, leading to the observed regioisomer **8**, was indeed favored thermodynamically by $5.6 \text{ kcal.mol}^{-1}$ (Figure S3). Although the stereochemistry of **8** could not be unambiguously ascertained, the *cis* stereoisomer would be obtained as the activation barrier would only be $3.2 \text{ kcal.mol}^{-1}$ vs. $8.4 \text{ kcal.mol}^{-1}$ for the *trans* isomer (Figure S3). Moreover, in the presence of dioxygen in the reaction medium, **13** it could be oxidized to **7**, presumably through an intermediate peroxide anion that would readily aromatize.

Scheme 4. Proposed mechanism

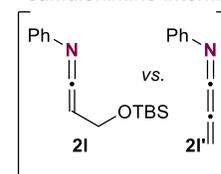
a. proposed mechanism



b. isolated side products



c. cumulenimine intermediate



To conclude we have been able to develop a novel [3+2] annulation between ketenimines and azaallyl anions (both generated in situ from ynamides and benzylarylimines, respectively) to access five-membered heterocycles. The reaction mechanism was elucidated by using a combination of control experiments and DFT calculations, which seem to exclude a concerted process. Taken together our results open new synthetic opportunities towards nitrogen-containing heterocycles and evaluation of these as therapeutically relevant compounds is currently underway in our laboratory.

ASSOCIATED CONTENT

The Supporting Information contains:

Experimental procedures, characterization data, and NMR spectra for all products (PDF)

Computed energies and Cartesian coordinates of all the DFT-optimized structures (TXT)

X-ray crystallographic data for **6ag** (CCDC 2032327) (CIF)

X-ray crystallographic data for **7ac** (CCDC 2032327) (CIF)

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Author Contributions

This study was conceived by K. Cariou & R. H. Dodd. Synthesis and characterization of the compounds were performed by A. C. A. D'Hollander, E. Romero, K. Vijayakumar and C. Le Houérou. X-ray crystallography was performed by P. Retailleau. Computational studies were performed by B. I. Iorga. K. Cariou drafted the manuscript which was amended and commented on by all authors.

Notes

The authors declare no competing financial interest

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GRAPHICAL ABSTRACT

