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

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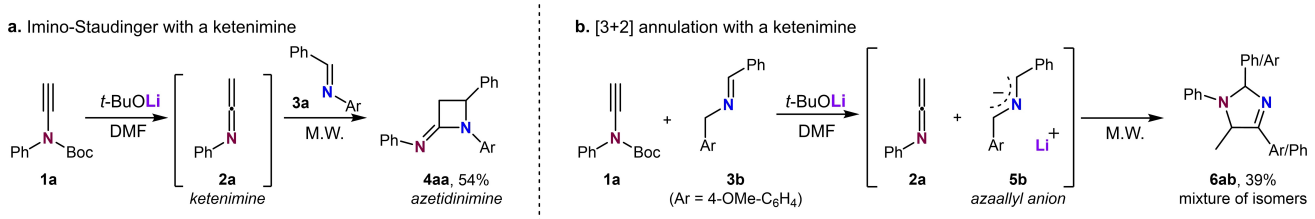
Abstract: Under basic conditions and heat, ynamides can serve as precursors to ketenimines, whose synthetic potential is often hampered by their difficulty of access. Herein, we report that they can undergo a [3+2] cycloaddition with 2-azaallyl anions, obtained from benzylimines under the same reaction 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 calculations helped rationalize the regio- and stereoselectivity of the process as well as the formation of side products.

Keywords: Ynamides; azaallyl anion; ketenimines; cycloaddition

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.[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[3–10] (**1a**) to generate *in situ*[11,12] a highly reactive ketenimine (**2a**)[13–15] which can engage in a [2+2] cycloaddition with a diaryl imine (**3a**) to give an azetidinimine (Scheme 1a).[16,17] Exploring this transformation further, we found that when the same reaction conditions were applied to the homologous benzylimine **3b**, the formation of the expected azetidinimine was not observed.

Instead, 2,5-dihydro-1*H*-imidazole[18] **6ab** was obtained with a 39% yield (Scheme 1b). We hypothesized that this 5-membered ring arose from a [3+2] cycloaddition between the ketenimine and the semi-stabilized 2-azaallyl lithium **5b**, which was also formed *in situ* under the basic reaction conditions.[19,20] Overall, reports of 1,3-dipolar cycloaddition with a ketenimine as the dipolarophile remain rather scarce.[21–25] Moreover, [3+2] cycloadditions with non- or semi-stabilized azaallyl anions[26,27] were mostly developed with

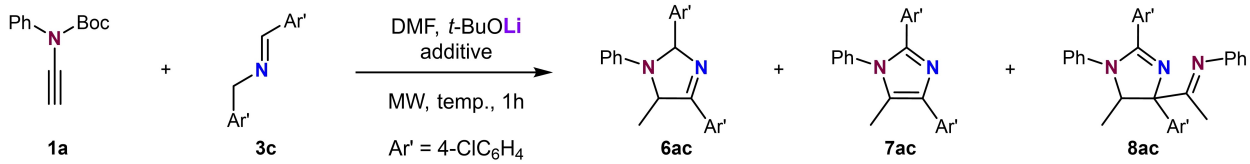


Scheme 1. [2+2] and [3+2] annulations involving ketenimines and imines.

olefins as dipolarophiles.[28–30] 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*-chlorophenyl moieties, which would lead to a symmetrical 2-azaallyl anion (Table 1). Using microwave heating at 100 °C for 1 h in DMF (0.5 M) with 2.0 equivalents of *t*-BuOLi gave a mixture of 2,5-dihydro-1*H*-imidazole **6ac** (23%), imidazole **7ac** (16%) and 4,5-dihydro-1*H*-imidazole **8ac** (12%) that incorporates two ketenimine fragments (entry 1). To minimize the formation of the oxidized derivative **7ac**, a thorough bubbling of argon in the reaction mixture was performed. When the concentration was decreased from 0.5 M to 0.2 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). The presence of the base was found to be essential (entry 5) but alternative inorganic (Cs_2CO_3, entry 6) or organic (DBU, entry 7) bases did not promote the reaction. Various Lewis acid-type additives were screened (entries 8–10), Zn-(II) salts giving the best results (entries 8 and 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 (entry 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 and 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 66% yield, mostly avoiding the formation of side products **7ac** and **8ac**, and were selected to explore the scope of this [3 + 2] annulation.

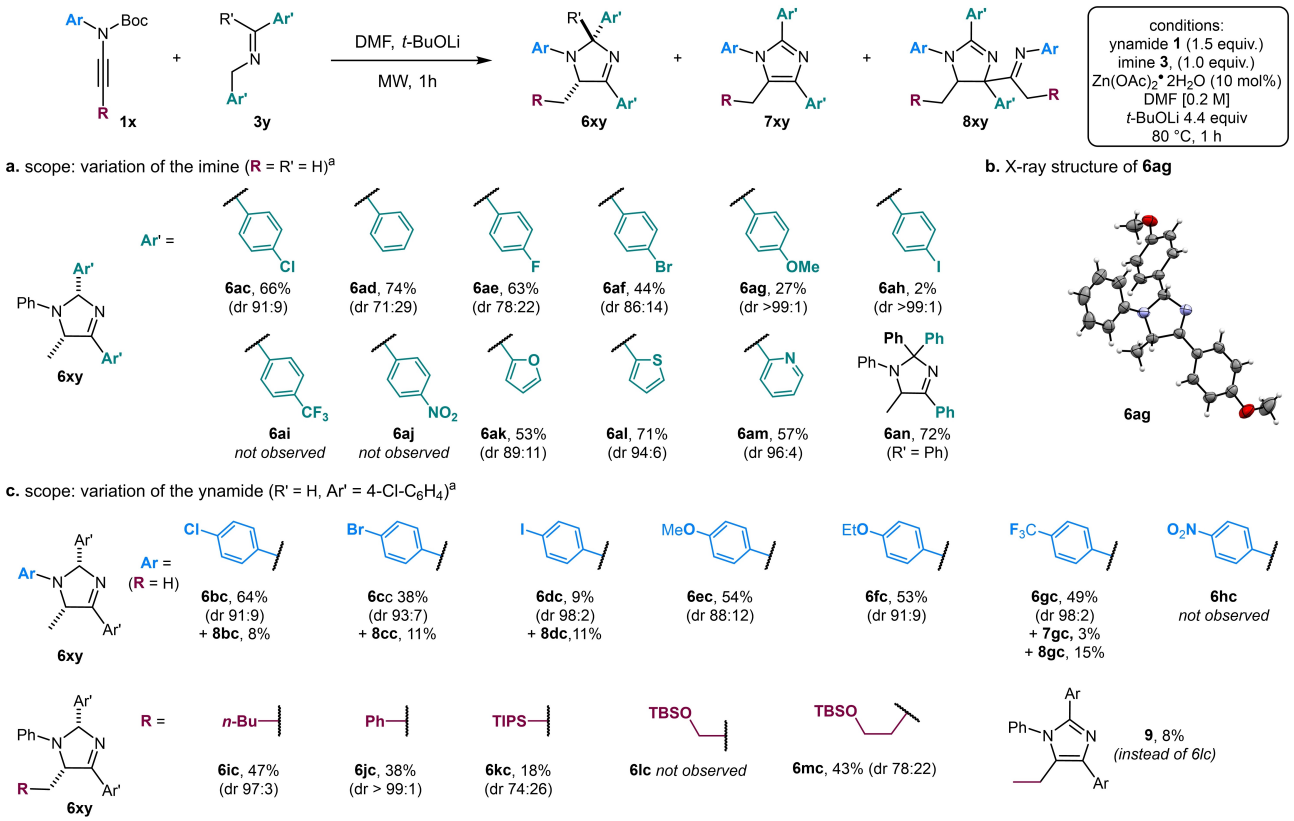
First, benzylic aldimines **3** leading to symmetrical azaallyl anions **5** having various substituents – H (**3d**), halogens (**3e**,**f**,**h**), MeO (**3g**) and electron-withdrawing groups (**3i**,**j**) on the *para* positions – were screened. 1,5-Dihydro-1*H*-imidazoles **6** were obtained in 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 CF_3 or NO_2 (**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 **6an** as a single regioisomer in 72% yield. This is in sharp contrast to the

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



Entry	equiv. **1a**/ equiv. **3c**	Base (equiv.)	Additive[c]	Solvent (0.2 M)	Temp.	Yield **6ac** (%)[b]	Yield **7ac** (%)[b]	Yield **8ac** (%)[b]
1	2.0/1.0	*t*-BuOLi (2.0)	none	DMF[d]	100 °C	23 (±3)	16 (±1)	12 (±1)
2	2.0/1.0	*t*-BuOLi (2.0)	none	DMF	100 °C	45 (±2)	7 (±2)	12 (±1)
3	2.0/1.0	*t*-BuOLi (2.0)	none	**THF**	100 °C	0	0	0
4	2.0/1.0	*t*-BuOLi (2.0)	none	**DMA**	100 °C	16 (±3)	15 (±3)	25 (±3)
5	2.0/1.0	**none**	none	DMF	100 °C	0	0	0
6	2.0/1.0	**Cs_2CO_3** (2.0)	none	DMF	100 °C	0	0	0
7	2.0/1.0	**DBU** (2.0)	none	DMF	100 °C	0	0	0
8	2.0/1.0	*t*-BuOLi (**2.75**)	$Zn(OAc)_2{\cdot}2H_2O$	DMF	100 °C	61 (±3)	8 (±1)	7 (±1)
9	2.0/1.0	*t*-BuOLi (2.75)	$Cu(OAc)_2$	DMF	100 °C	55 (±1)	6 (±1)	2 (±2)
10	2.0/1.0	*t*-BuOLi (**3.3**)	$Zn(OTf)_2$	DMF	100 °C	63 (±4)	8 (±1)	8 (±2)
11	2.0/1.0	*t*-BuOLi (2.75)	$Zn(OAc)_2{\cdot}2H_2O$	DMF	**80 °C**	60 (±4)	7 (±2)	7 (±2)
12	**1.5/1.0**	*t*-BuOLi (2.75)	$Zn(OAc)_2{\cdot}2H_2O$	DMF	80 °C	50	Traces	Traces
13	**1.5/1.0**	***t*-BuOLi (4.4)**	**$Zn(OAc)_2{\cdot}2H_2O$**	**DMF**	**80 °C**	**66 (±1)**	**Traces**	**Traces**

[a] All reactions were carried out with 0.20 mmol of **3c**, argon was bubbled in the reaction mixture before the addition of the base and the reaction was performed in a microwave apparatus;
[b] isolated yields, average of two reactions;
[c] 10 mol%;
[d] Reaction run at 0.5 M concentration.

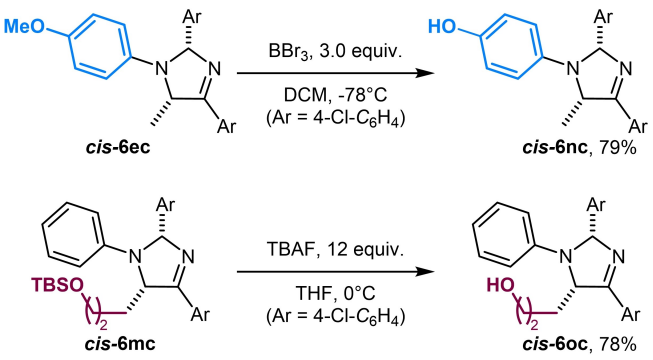


Scheme 2. Scope of the [3 + 2] annulation.

reactivity of aldimines bearing two different aryl groups, such as **3 b** (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,[16] 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, **1 b**,**c**), electron-donating (OMe and OEt, **1 e**,**f**) or electron withdrawing (CF_3, **1 g**) groups gave 1,5-dihydro-1*H*-imidazoles **6** as the major adducts, generally along with minor amounts of double addition compound **8**. The difficulty of purification of the *p*-iodo compound was responsible for the low yield of **6 dc**, while the *p*-nitro functionality (**1 h**) was incompatible with the reaction conditions.

The reaction was also successful if the triple bond was substituted by an alkyl (*n*-Bu, **6 ic**), an aryl (Ph, **6 jc**) or a silyl (TIPS, **6 kc**), albeit with a low 18% yield in this case. When an ynamide bearing a silyl-protected hydroxymethyl group on the triple bond (**1 l**) was submitted to the reaction conditions, imidazole **9** was isolated instead of the expected **6 lc**. The former would not originate from an oxidation process as for imidazole **8**. Instead, it would more likely result from a [3 + 2] annulation with a cumulenimine (see below **2 l'** in Scheme 5c) to give a vinylated 1,5-dihydro-1*H*-imidazole, followed by the isomerization of the double bond. For its part, the homologated substrate led to **6 mc** with 43% yield. It was also possible to further functionalize several adducts (Scheme 3).

For example the *p*-anisyl derivative ***cis*-6 ec** could efficiently be transformed into the corresponding phenol ***cis*-6 nc** by treatment with boron tribromide in 79% yield and desilylation of ***cis*-6 mc** using TBAF led to ***cis*-6 oc** in 78% yield. In both cases, the heterocycle was untouched and no isomerization occurred.

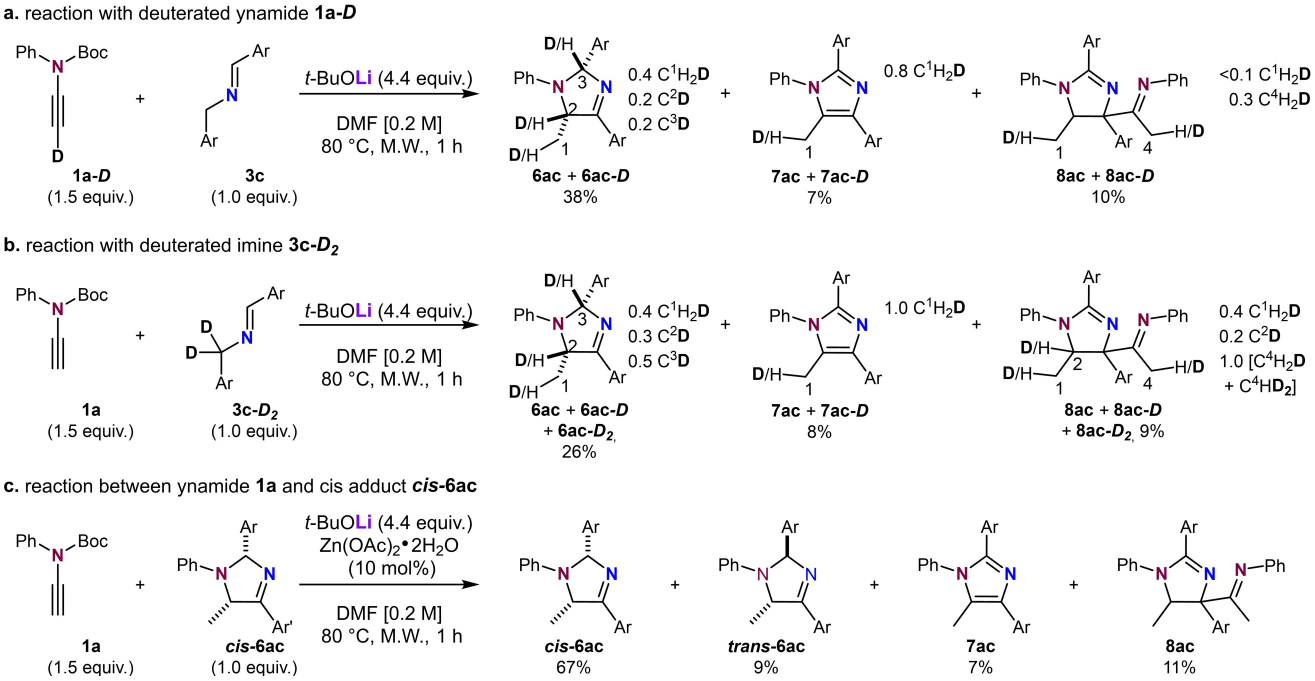


Scheme 3. Functionalization of the [3 + 2] adducts.

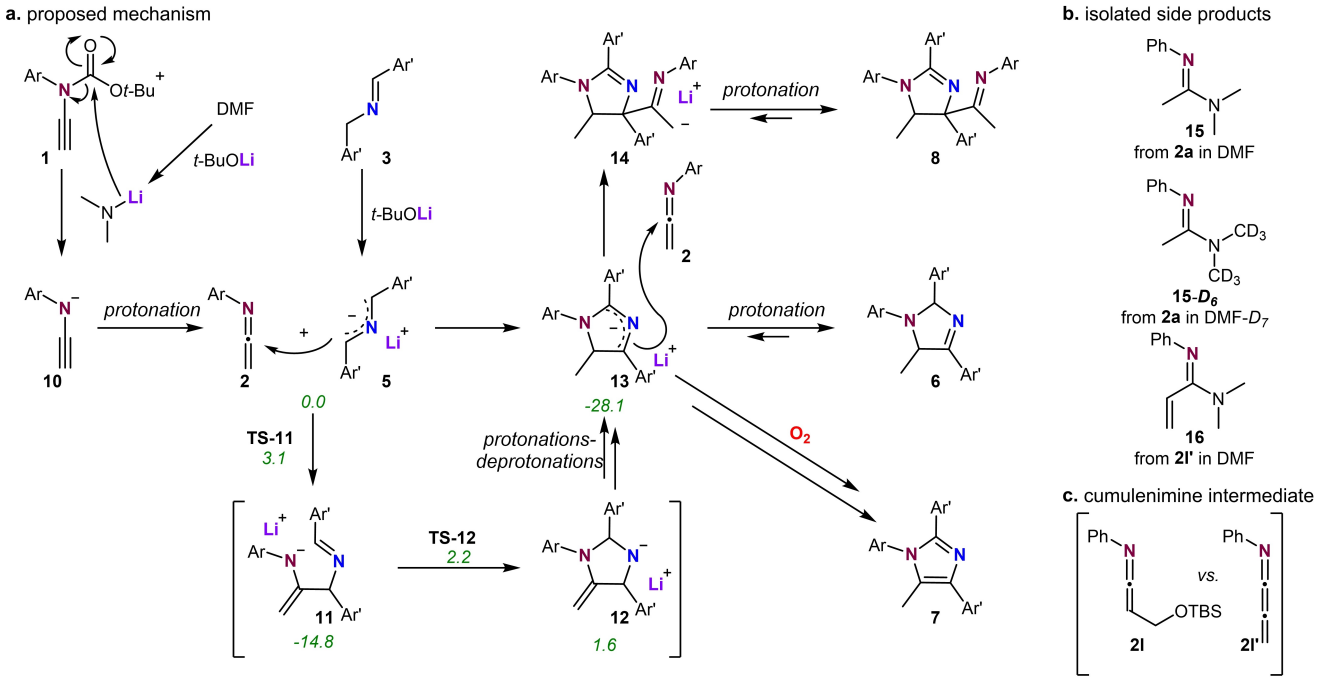
In order to gain more insight on the [3+2] annulation process and the formation of side products **7** and **8**, we performed several control experiments. First, deuterated ynamide **1a-D** was synthesized and reacted with imine **3c**. As could be expected, when the hydrated zinc salt additive was included, no deuteration was observed. In the absence of the additive, however, all adducts **6ac**, **7ac** and **8ac** were isolated as mixtures of non- and mono-deuterated compounds (Scheme 4a), 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–D$_2$** (Scheme 4b). 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–D$_2$**. 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 4c). 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 1 h 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 5a). Under the strongly basic conditions, and possibly with the assistance of the zinc Lewis acid,[31] 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 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-*D*$_6$** (when DMF-D_7 was used) and **16** (Scheme 5b). These would result from the addition of a lithium amide on ketenimine **2a** and, in the latter case, on cumulenimine **2l'**. This cumulenimine would come from amide **101**, instead of giving birth to the expected ketenimine **21** (Scheme 5c). Thus, its reaction with imine **3c** would give a vinyl-1,5-dihydro-1*H*-imidazole, and eventually ethylimidazole **9** after isomerization (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 imidazolidine **12**. Overall, this process is nearly energy neutral ($\Delta G = 1.6$ kcal.mol^{-1}), the first step being exergonic by 14.8 kcal.mol^{-1}, with a rather low



Scheme 4. Control experiments.



Scheme 5. Proposed mechanism.

activation barrier (3.1 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 4a and 4b). 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 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 kcal.mol^{-1}. A final reversible (as evidenced by the experiment in Scheme 4c) 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 the aminal position, of **13** to give anion **14** thus leading to the observed regioisomer **8**, was indeed favored thermodynamically by 5.6 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 kcal.mol^{-1} *vs.* 8.4 kcal.mol^{-1} for the *trans* isomer (Figure S3). Moreover, in the presence of oxygen in the reaction medium, **13** could be oxidized to **7**, presumably through an intermediate peroxide anion that would readily aromatize.

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. Preliminary evaluation of these compounds as β-lactamase inhibitors has been initiated with promising results[32] and a more thorough study of the therapeutic potential of theses heterocycles is currently underway in our laboratory.

Experimental Section

General Procedure for the [3+2]-Cycloaddition

To an oven-dried microwave vessel under argon was added $Zn(OAc)_2{\bullet}2H_2O$ (10 mol%), the ynamide (1.5 equiv.), the imine (1.0 equiv., 0.20 mmol) and anhydrous DMF (0.2 M). The reaction mixture was stirred with argon bubbling for 5–10 min before *t*-BuOLi (2.2 M in THF, 4.4 equiv.) was added.[1] The vessel was sealed, vortexed and placed in a Microwave apparatus for 1 h at 80 °C. The reaction mixture was then concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction

[1] During the addition of the base a deep dark color develops, if this color fades an excess base should be added until the color stays.

mixture was performed to measure the diastereomeric ratio before subjecting the crude product to purification by flash chromatography.

For full experimental data, see Supporting Information, containing:

Experimental procedures, characterization data, computed energies and Cartesian coordinates of all the DFT-optimized structures, and NMR spectra for all products (PDF)

CCDC-2032327 (6ag) and CCDC-2032328 (7ac) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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UPDATES

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