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## From A<sup>3</sup>/KA<sup>2</sup> to AYA/KYA multicomponent coupling reactions with terminal ynamides as alkyne surrogates – a direct, green route to $\gamma$ -amino-ynamides†

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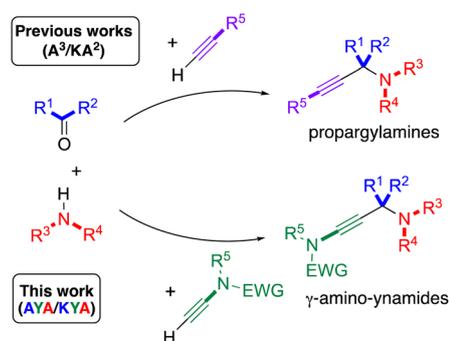
A copper-catalysed three-component coupling reaction between a carbonyl derivative, a terminal ynamide and an amine has been developed for the one-pot green construction of  $\gamma$ -amino-ynamides from simple starting materials and with a broad functional group tolerance. The copper-zeolite-catalysed three-component coupling reaction between an aldehyde or a ketone, a terminal ynamide and an amine is reported. The so-elaborated methods, dubbed AYA (*i.e.* Aldehyde-Ynamide-Amine) and KYA (*i.e.* Ketone-Ynamide-Amine), enable the straightforward one-pot synthesis of  $\gamma$ -amino-ynamides from simple starting materials and with a broad functional group tolerance. Moreover, AYA/KYA processes are performed at room temperature under solvent-free conditions or in ethyl acetate as green solvent in the presence of a copper-based easy-to-recover/-remove catalyst, at low loading (3 mol%), making these synthetic methods fully green.

## Introduction

Multicomponent reactions (MCRs) are among the most important and powerful synthetic tools for implementing Green Chemistry to organic & pharmaceutical chemistry.<sup>1,2</sup> Allowing the convergent one-pot assembly of at least three readily available starting materials, MCRs are indeed in line with most of the standards set by Green Chemistry,<sup>3</sup> such as excellent atom and step economy, no (or very limited) waste generation, resources/assets saving and minimal energy consumption. As a consequence, synthetic organic chemists pay an ever-increasing attention to this field, resulting in the continuous discovery of novel MCRs which allow access to an exceptional level of molecular complexity and diversity.

Although serendipity played a role in the MCR discovery, the emergence of design strategies allowed to explore the chemical space in a more rational way.<sup>4</sup> Among them, the most intuitive one is the so-called Single Reactant Replacement (SRR) strategy,<sup>5</sup> that is the replacement of one reactant with a structurally different reactant which features the same essential reactivity mode for the related MCR. As the structure of the surrogate usually differs by the presence of additional/distinct functional group(s), the synthesis of more complex, and occasionally unprecedented, molecular scaffolds could be accomplished. The popular UGI reaction, allowing access to  $\alpha$ -acylamino-amides,<sup>6</sup> actually is a SRR-guided MCR of the equally popular, 100-year-old PASSERINI reaction,<sup>7</sup> with the use of an imine as surrogate of the native carbonyl component.

Here, we describe an SRR-guided extension of the A<sup>3</sup>/KA<sup>2</sup> coupling reactions, pioneered by C.-J. Li and coworkers,<sup>8</sup> which combine aldehyde/ketone, terminal alkyne and amine into propargylamine in a one-pot transition metal-catalysed coupling (Scheme 1, top).<sup>9,10</sup> Replacing the alkyne component by a terminal ynamide<sup>11,12</sup> could lead to a one-pot synthesis of



**Scheme 1** From propargylamines synthesis via popular A<sup>3</sup>/KA<sup>2</sup> 3-CRs (previous works, top) to  $\gamma$ -amino-ynamides synthesis via unprecedented AYA/KYA 3-CRs (this work, bottom) (EWG = Electron-Withdrawing Group).

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$\gamma$ -amino-ynamides (Scheme 1, bottom). This approach was driven by the following reasoning: (i) despite its interest,<sup>13</sup> accesses to the latter scaffold are so far limited and based on multi-step sequences,<sup>14</sup> a simpler way would thus be beneficial and probably open up new perspectives; (ii) since ynamides are more nucleophilic than alkynes (see *N* parameters),<sup>15,16</sup> they should be more reactive in  $A^3/KA^2$ -type reactions; (iii) although green by essence (see above),<sup>8</sup>  $A^3/KA^2$  reactions could be made greener by avoiding solvent and/or by using recyclable catalyst. For the latter aspect, we already developed the 1<sup>st</sup> heterogeneous  $A^3$  coupling based on  $Cu^I$ -zeolites as catalysts.<sup>17</sup> Other heterogeneous versions have since been proposed.<sup>9</sup>

Since we have proven the compatibility of ynamides with zeolitic materials,<sup>18</sup> we embarked on the development of  $Cu^I$ -catalysed MCRs combining aldehyde or ketone, ynamide and amine (respectively AYA or KYA) and we report here *the first* one-step method for preparing  $\gamma$ -amino-ynamides, without solvent or in ethyl acetate<sup>19</sup> as an environmentally benign solvent, catalysed by copper-doped zeolite  $Cu^I$ -USY,<sup>20</sup> as well as a comparison with their parent  $A^3/KA^2$  reactions. It is worth noticing that this approach is quite challenging due to the known high reactivity of the ynamide moiety.<sup>11</sup>

## Results and discussion

### Conditions set up

To assess the feasibility of the AYA/KYA approach towards  $\gamma$ -amino-ynamides, initial investigations were conducted under conditions close to our previously reported  $A^3$  and  $KA^2$  reaction conditions,<sup>17,21</sup> with benzaldehyde **1**, *N*-ethynylsulfonamide **2** and pyrrolidine **3** as model coupling partners and a  $Cu^I$ -zeolite as catalyst (Table 1). Due to its large cage-shaped porous system, the commercial and cheap USY zeolite<sup>†</sup> has often given the best results in catalysing various transformations,<sup>20</sup>

the easy-to-prepare  $Cu^I$ -doped USY was thus used here as catalyst.

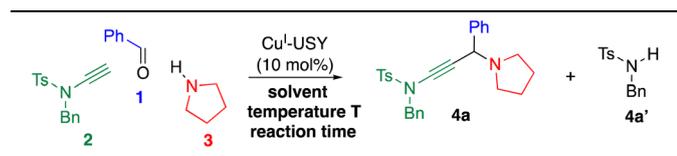
Mixing these three reagents in toluene/acetonitrile (1 : 1) and heating the resulting mixture to 80 °C for three hours led to the formation of the expected  $\gamma$ -amino-ynamide **4a** in a promising isolated yield (entry 1), together with sulfonamide **4a'** as the major product (respectively 35% and 59% yield).<sup>‡</sup> Performing the reaction under neat conditions at 90 °C also led to complete consumption of **2** but with the major formation of **4a'**, although in moderate yield after column chromatography, and with only trace amounts of **4a** (entry 2). Lowering the reaction temperature proved beneficial. Indeed, the coupling efficiency and selectivity could be dramatically improved at 40 °C under neat conditions (entry 3). For comparison, and as solubility and stirring problems could occur depending on the components, reaction in green solvents was also evaluated. Stirring for two hours at room temperature in green 2-methylTHF only led to slow but clean reaction, but after one hour at 40 °C, an encouraging increase in yield and selectivity was achieved (entry 4 *vs.* 1). Interestingly, ethyl acetate as green solvent allowed at 30 °C to produce the expected product **4a** in yield similar to those achieved under neat conditions (entry 5 *vs.* 3). It is worth noticing that in this solvent, the reaction proved to be much faster (30 min *vs.* 2 h).

These results highlight the key influence of the reaction temperature on the coupling selectivity and suggest that the reaction could be efficiently performed with or without solvent.

Following these preliminary results, the solvent-free AYA reaction between **1**, **2** and **3** was used as a bench reaction to perform further optimisation studies *via* the so-called Design of Experiments (DoE) method.<sup>22</sup> We chose to perform a simple experimental design to identify the most crucial variables affecting the yield of  $\gamma$ -amino-ynamides. Six variables, namely temperature, catalyst loading, aldehyde equivalents, stirring rate, stirring bar type and reaction time, were studied in a  $2^{6-3}$  fractional factorial design (FFD) giving a total number of eight experiments, which were run in parallel (see ESI for details<sup>†</sup>). The results of this short DoE study revealed that temperature, followed by reaction time, are the two critical variables providing  $\gamma$ -amino-ynamide **4a** in high yield, while catalyst loading (in a range of 3 to 10 mol%) or the type of stirring bar are not pertinent. Although statistically not significant in this short study, the two last variables, that are the number of aldehyde equivalents and the stirring rate, positively correlated with the yield of **4a**. In light of these DoE results, we turned to the use of equimolar amounts of each coupling partner and set reaction temperature to 30 °C, catalyst loading to the lowest evaluated (*i.e.* 3 mol%) and stirring rate to the highest value investigated (*i.e.* 600 rpm).

Because  $A^3/KA^2$  reactions can be promoted with various metal cations,<sup>9</sup> we next evaluated the catalytic potential of USY zeolites doped with  $Cu^{II}$ ,  $Zn^{II}$  and  $Mn^{II}$  (Table 2). Under the conditions set above in ethyl acetate,  $Cu^I$ -USY clearly appeared as the best catalytic system, with high conversion and **4a** yield after 3 hours (entry 1). Its oxidized  $Cu^{II}$ -form led to a slow and messy reaction, which resulted in dramatic drop in yield

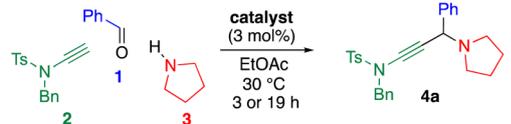
**Table 1** Preliminary optimisation studies for the one-pot formation of  $\gamma$ -amino-ynamide **4a**<sup>a</sup>



Entry	Solvent	<i>T</i> (°C)	Time (h)	<b>4a</b>	<b>4a'</b>
1	PhMe/MeCN (1 : 1)	80	3	35 <sup>b</sup>	59 <sup>b</sup>
2	None <sup>c</sup>	90	1	< 5	43 <sup>b</sup>
3	None <sup>c</sup>	40	2	83 <sup>d</sup>	— <sup>e</sup>
4	2-MeTHF	rt then 40	2 then 1	61 <sup>d</sup>	— <sup>e</sup>
5	AcOEt	30	0.5	82 <sup>d</sup>	— <sup>e</sup>

<sup>a</sup> Reactions run in a sealed tube with benzaldehyde **1** (1.4 equiv.), ynamide **2** (1.0 equiv. with a 1.3 M concentration), pyrrolidine **3** (1.1 equiv.) and  $Cu^I$ -USY (10 mol%), unless otherwise stated. <sup>b</sup> Isolated yield (%) after purification by column chromatography. <sup>c</sup> Reactions performed under neat conditions. <sup>d</sup> Yield (%) estimated by <sup>1</sup>H NMR of the crude using 1,3,5-trimethoxybenzene as internal standard. <sup>e</sup> Not detected in the crude mixture.



**Table 2** Evaluation of catalysts for the one-pot formation of  $\gamma$ -aminoamide **4a**<sup>a</sup>


Entry	Catalyst	Time (h)	Yield <sup>b</sup> (%)	Conversion <sup>b</sup> (%)
1	Cu <sup>I</sup> -USY	3	84	88
2	Cu <sup>II</sup> -USY	19	21 <sup>c</sup>	95
3	Zn <sup>II</sup> -USY	3	31 <sup>d</sup>	46
4	Mn <sup>II</sup> -USY	3	16 <sup>d</sup>	23
5	CuCl	3	32 <sup>c</sup>	100
6	CuBr	3	13 <sup>c</sup>	100
7	CuI	3	32 <sup>c</sup>	100
8	H-USY	19	— <sup>e</sup>	— <sup>e</sup>
9	None	19	— <sup>e</sup>	— <sup>e</sup>

<sup>a</sup> Reactions run in a sealed tube with benzaldehyde **1** (1.0 equiv. with a 0.85 M concentration), ynamide **2** (1.0 equiv.) and pyrrolidine **3** (1.0 equiv.). <sup>b</sup> Yield and conversion estimated by <sup>1</sup>H NMR of the crude using 1,3,5-trimethoxybenzene as internal standard. <sup>c</sup> Formation of several unidentified byproducts. <sup>d</sup> Selective but slow conversion. <sup>e</sup> No traces of **4a** detected and no conversion observed after 19 h.

despite nearly full conversion after 19 hours (entry 2). Similar poor yields were also obtained with Mn<sup>II</sup>-USY and Zn<sup>II</sup>-USY (entries 3 and 4 vs. 2) but in sharp contrast to Cu<sup>II</sup>-USY, the lower yields are not due here to selectivity issues but mainly to significantly lower conversions compared to Cu<sup>I</sup>-USY (entries 3 and 4 vs. 1). With CuCl alone as Cu<sup>I</sup> source, the expected product **4a** was again formed in poor yield despite full conversion (entry 5 vs. 1 and 2). The same issue was obtained with CuBr and CuI, two commercial copper sources commonly used in A<sup>3</sup>/KA<sup>2</sup> coupling reactions (entries 6, 7). Further control experiments confirmed that the coupling reaction was not promoted neither in the presence of the native H-USY (entry 8) nor without catalyst (entry 9). Overall, these data revealed the key, dual role played by the Cu<sup>I</sup> ions and the USY-zeolite for efficiently catalysing this coupling reaction. Accordingly, Cu<sup>I</sup>-USY, at low Cu loading of only 3 mol%, was further employed to investigate the scope and limitations of this three-component reaction.

### Reusability and catalyst stability

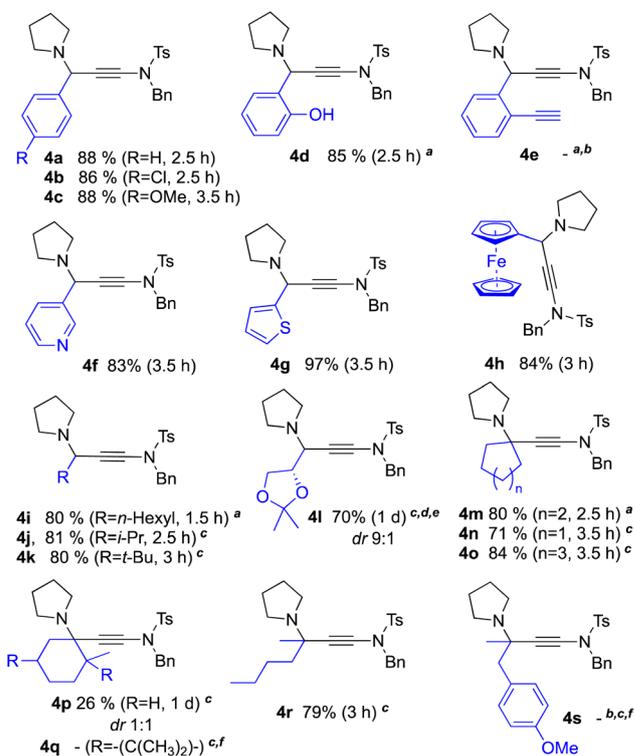
Stability and reusability are key features for heterogeneous catalyst. We have thus evaluated the reusability of the Cu<sup>I</sup>-USY catalyst using the same model reaction involving partners **1**, **2** and **3** in ethyl acetate under the conditions described in Table 1, entry 5. After each reaction run, the reaction mixture was centrifuged and the supernatant was decanted; the recovered zeolite was washed with the same solvent and centrifuged twice. The recovered catalyst was directly engaged in the next run, without cleaning it by heating as usual. The catalyst could be used four times with an excellent selectivity towards **4a** and without much difference in efficiency (68% in average). However, a substantial decrease in product yield was observed on the fifth run (41%) (see ESI for details<sup>†</sup>). Despite this

decrease, it is worth noting that even after the fifth run, the recovered zeolitic materials remain more efficient and selective than typical CuX salts (Table 2, entries 5–7). Such decrease could be due to the slight loss of solids during the recycling/recovery process. Nevertheless, a control experiment (Sheldon test) showed that the reaction could keep running after removal of the solid catalyst by filtration, although at a lower rate. Copper ions could have been extracted by the amine, as one would expect, or tiny amount of copper zeolite could go through and keep being active as catalyst. Such behaviour is common with coordinating substrates and was already observed in the Cu<sup>I</sup>-USY catalysed synthesis of ynamides.<sup>18</sup>

As in other Cu<sup>I</sup>-USY catalysed reactions, XPS analysis revealed that copper ions within the zeolite do not change their oxidation state upon reaction and remain at +I state.

### Scope and limitations

With optimised conditions in hand, we investigated the possibility offered by the AYA/KYA reactions. We first examined the AYA potential with ynesulfonamide **2**, pyrrolidine **3** and various aldehydes as coupling partners (Scheme 2).



**Scheme 2** Carbonyl scope of the Cu<sup>I</sup>-USY-catalysed AYA/KYA coupling reaction. General conditions: reactions run neat at 30 °C in a sealed tube with a carbonyl compound (1.0 equiv.), ynamide **2** (1.0 equiv.), pyrrolidine **3** (1.0 equiv.) and Cu<sup>I</sup>-USY (3 mol%), unless otherwise stated. <sup>a</sup>Reaction run in EtOAc (0.85 M). <sup>b</sup>Complex mixture of unidentified difficult-to-purify products. <sup>c</sup>Reaction run in EtOAc (0.85 M) in the presence of molecular sieves (4 Å, 300 mg mmol<sup>-1</sup>). <sup>d</sup>Reaction set up in EtOAc (0.85 M) at 0 °C and then warmed to room temperature overnight. <sup>e</sup>Lower yield in **4l** obtained at room temperature. <sup>f</sup>No conversion observed for the corresponding ketone.

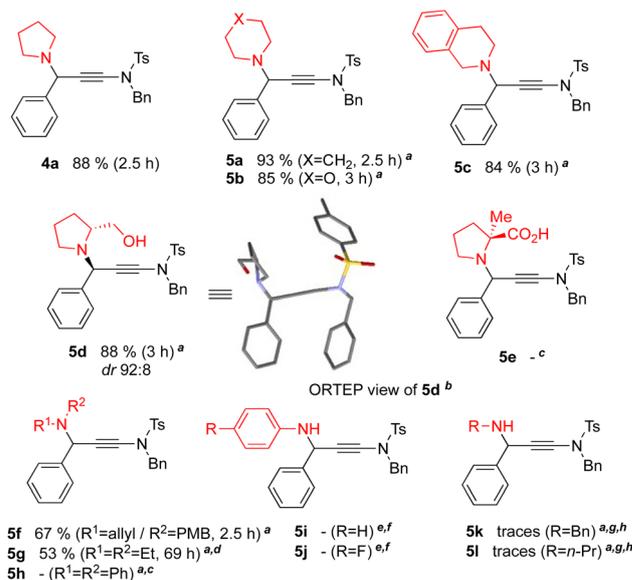


4-Chloro- and 4-methoxybenzaldehydes reacted similarly to benzaldehyde, thus furnishing the expected  $\gamma$ -amino-ynamides **4b,c** without much electronic effects. Salicylaldehyde reacted as well and selectively yielded the AYA product **4d** in high yield. However, 2-ethynylbenzaldehyde led to a complex reaction mixture without traces of the desired product **4e**. Heteroaryl aldehydes, such as 3-pyridinecarboxaldehyde and 2-thiophenecarboxaldehyde, as well as organometallic aldehydes such as ferrocenecarboxaldehyde, also proved to be suitable coupling partners, providing **4f-h** in high to excellent yields within similar reaction times.

Shifting to aliphatic aldehydes had no impact on coupling efficiency.  $\gamma$ -Amino-ynamides **4i-k** could indeed be prepared in similar high yields from either linear *n*-heptanal (cf. **4i**) or branched 2-methylpropanal and 2,2-dimethylpropanal (cf. **4j,k**). Interestingly enough, the use of chiral 2,3-*O*-isopropylidene-glyceraldehyde led to the substrate-controlled asymmetric synthesis of  $\gamma$ -amino-ynamide **4l** in good yield and diastereoselectivity.

The behaviour of ketones was then explored. Cyclohexanone was selected as model partner due to the well-established, beneficial strain energy release during nucleophilic additions involving this cyclic ketone and its iminium form.<sup>23</sup> Satisfyingly, cyclohexanone reacted in the same way as aromatic and aliphatic aldehydes without the need to adjust the optimised reaction conditions. The expected product **4m** was indeed obtained with comparable yield and reaction time. The more challenging cyclopentanone- and cycloheptanone-derived ynamides **4n** and **4o** were obtained with similar efficiency in the presence of molecular sieves (4 Å). Nevertheless, increasing the steric hindrance of the ketones had a deleterious effect on the efficiency of the KYA coupling reaction. Shifting from cyclohexanone to 2-methylcyclohexanone led to a significant drop in yield (cf. 80% for **4m** vs. 26% for **4p**), whereas the more hindered (+)-camphor did not react. Noteworthy is that **4p** was obtained as a 1 : 1 diastereoisomer mixture, while a diastereoselectivity was observed in related KA<sup>2</sup> reactions.<sup>9d</sup> Acyclic aliphatic ketones also reacted similarly, as shown by the coupling of hexan-2-one. The resulting  $\gamma$ -amino-ynamide **4r** was indeed obtained in mostly the same yield as its cyclic counterpart (79% for **4r** vs. 80% for **4m**). In sharp contrast, 4-methoxyphenylacetone as model  $\alpha$ -arylated ketone did not provide the desired KYA product **4s** even at 55 °C, probably due to the high stability of the resulting conjugated enamine which prevents the coupling from taking place.

In a second series of experiments, we varied the amine component, while keeping benzaldehyde **1** and ynesulfonamide **2** (Scheme 3). In ethyl acetate as solvent using additional molecular sieves, cyclic secondary amines, such as pyrrolidine, piperidine, morpholine and tetrahydroisoquinoline, afforded the corresponding AYA products **4a** and **5a-c** in high to excellent yields. Chiral amines were then scrutinised to evaluate the potential of amine-controlled stereoselective AYA reactions. Under standard conditions and without further optimisation, (*R*)-prolinol led to the efficient formation of the expected



**Scheme 3** Amine scope of the Cu<sup>I</sup>-USY-catalysed AYA coupling reaction. General conditions: reactions run neat at 30 °C in a sealed tube with benzaldehyde **1** (1.0 equiv.), ynamide **2** (1.0 equiv.), an amine (1.0 equiv.) and Cu<sup>I</sup>-USY (3 mol%), unless otherwise stated. <sup>a</sup>Reaction run in EtOAc (0.85 M) in the presence of molecular sieves (4 Å, 300 mg mmol<sup>-1</sup>). <sup>b</sup>See ref. 24 for CCDC† deposition number. <sup>c</sup>No conversion of the amine observed. <sup>d</sup>Incomplete conversion. <sup>e</sup>Reaction run in EtOAc (0.85 M). <sup>f</sup>Imine detected. <sup>g</sup>Traces of the expected product detected. <sup>h</sup>Complex mixture of unidentified difficult-to-purify products.

$\gamma$ -amino-ynamide **5d** with a high level of diastereoselectivity. Crystallization from a CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O mixture by slow evaporation furnished **5d** as fine pale-yellow needles, whose X-ray analysis<sup>24,25</sup> unambiguously confirmed the structure and absolute configuration of this chiral  $\gamma$ -amino-ynamide. This diastereoselective induction is similar to the one reported in related A<sup>3</sup> reactions using (*R*)-prolinol.<sup>26</sup> In sharp contrast, the AYA coupling proved ineffective with  $\alpha$ -methyl-*L*-proline as chiral amine, probably for solubility and/or reactivity issues. Shifting from cyclic to acyclic secondary amines led to more or less efficient coupling reactions. For example, *N*-allyl-4-methoxybenzylamine allowed the formation of the AYA product **5f** together with an unidentified by-product in a yield slightly lower than those achieved so far. However, *N,N*-diethylamine reacted cleanly but much more slowly than its cyclic pyrrolidine surrogate (cf. 53% for **5g** after 69 hours vs. 88% for **4a** after 2.5 hours), and the less nucleophilic *N,N*-diphenylamine did not even react.

Primary amines were found even trickier to work with. Aniline, as well as 4-fluoroaniline<sup>¶</sup>, proved to be reactive but both reactions stalled at the imine intermediates. Aliphatic primary amines, including benzylamine and *n*-propylamine, also proved to react but unfortunately led to complex mixtures in which trace amounts of the expected products **5k,l** could be detected together with ynamide-derived oligomers probably resulting from the initial formal hydroamination of the amine onto ynamide **2** (Scheme 4). Performing the imines and trap-

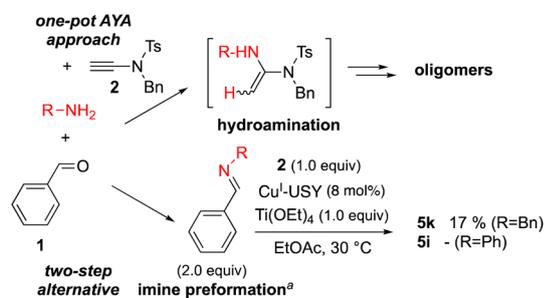


ping them by the ynamide partner was envisaged as a two-step approach to circumvent the suggested hydroamination pathway. The feasibility of this alternative approach was demonstrated with the formation of the  $\gamma$ -amino-ynamide **5k** from preformed *N*-benzylaldimine and ynamide **2** in the presence of titanium tetraethoxide as additional Lewis acid (Scheme 4). Applying similar conditions to *N*-phenylbenzaldimine unfortunately failed to form the  $\gamma$ -amino-ynamide **5i**.

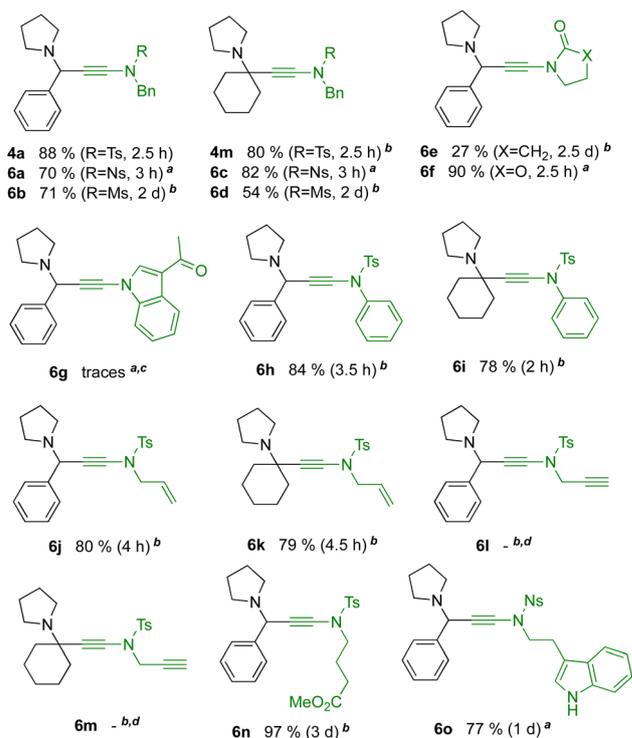
In a last series of experiments, the scope of the three-component AYA/KYA coupling reactions was investigated by varying the ynamide partner (Scheme 5). The influence of the electron-withdrawing group substituting the nitrogen atom was first explored. Regarding sulfonyl groups, the tosyl, nosyl and mesyl groups were tested and found amenable to AYA/KYA reactions to access the corresponding  $\gamma$ -amino-ynamides **4a,m** and **6a–d** in moderate to high yields. Nevertheless, the sulfonyl group nature proved to exhibit a significant impact on the reaction efficiencies and kinetics. While tosylated products **4a** and **4m** were obtained in only 2.5 hours, their nosyl derivatives **6a** and **6c** necessitated the addition of molecular sieves to be formed with similar rates and yields. For mesyl derivatives **6b** and **6d**, several days were required to reach full conversions.  $\gamma$ -Amino-ynamides bearing a lactam (cf. **6e**) or an oxazolidinone (cf. **6f**) moiety were also obtained, in low and high yields respectively. Unfortunately, the vinylogue indole-based product **6g** could only be detected as trace amounts in a complex mixture of unidentified products. Diverse substitutions on the amino group of *N*-tosyl-ynamides were also scrutinised. In addition to the benzyl group (cf. **4a** and **4m**), phenyl and allyl groups were perfectly tolerated (cf. **6h–k**). However, and not so surprisingly, the propargyl group was found to be incompatible with our catalytic conditions with no traces of products **6l,m** detected. Other functional groups, such as ester and indole, were also compatible in the AYA reaction; the corresponding  $\gamma$ -amino-ynamides **6n** and **6o** were indeed obtained in good to excellent yields.

### Comparison and mechanistic aspects

These results allow to start comparing the present reactions to their parent  $A^3/KA^2$  versions. From a practical point of view,



**Scheme 4** Attempts towards  $\gamma$ -amino-ynamides derived from primary amines – the one-pot AYA approach vs. a two-step alternative with imine preformation as initial step. <sup>a</sup>Imine preformed under conventional conditions.



**Scheme 5** Ynamide scope of the  $Cu^I$ -USY-catalysed AYA/KYA coupling reactions. General conditions: reactions run neat at 30 °C in a sealed tube with benzaldehyde or cyclohexanone (1.0 equiv.), an ynamide (1.0 equiv.), pyrrolidine **3** (1.0 equiv.) and  $Cu^I$ -USY (3 mol%), unless otherwise stated. <sup>a</sup>Reaction run in EtOAc (0.85 M) in the presence of molecular sieves (4 Å, 300 mg mmol<sup>-1</sup>). <sup>b</sup>Reaction run in EtOAc (0.85 M). <sup>c</sup>Traces of the expected AYA product. <sup>d</sup>Complex mixture of unidentified difficult-to-purify products.

the former can only be performed using  $Cu^I$ -USY as catalyst (see Table 2), while the more classical  $A^3/KA^2$  reactions can be performed under homogeneous as well as heterogeneous conditions. When strictly comparing the present AYA/KYA reactions to their parent  $A^3/KA^2$  versions,<sup>17,21</sup> both catalysed by  $Cu^I$ -USY (Table 3), some discrepancies can be highlighted, although both are closely related in term of efficiency and scope. The major one has to do with primary amines and anilines. Although effective in  $KA^2$  reaction, primary amines failed as coupling partners for the AYA/KYA processes. In a

**Table 3** Major discrepancies between AYA/KYA reactions and their parent  $A^3/KA^2$  versions using the identical  $Cu^I$ -USY catalyst

	AYA/KYA <sup>a</sup>	$A^3/KA^2$ <sup>b</sup>
Challenging substrates	Primary amines Anilines	Acyclic ketones
Reaction time	<5 h <sup>c</sup>	>15 h
Optimal temperature	30 °C	80 °C
Competing pathway	Hydroamination with primary amines	Hydroamination with secondary amines <sup>d</sup>

<sup>a</sup>This work. <sup>b</sup>Previous works. For details, see ref. 17 and 21. <sup>c</sup>Observed in most cases. <sup>d</sup>In the case of  $KA^2$  reactions.



similar way, anilines were found ineffective in the AYA/KYA coupling, while enabling the A<sup>3</sup>/KA<sup>2</sup> coupling depending on their substitution pattern. On the contrary, hexan-2-one as model aliphatic acyclic ketone proved as effective as its cyclic surrogates under KYA conditions (*cf.* **4r** vs. **4m** in Scheme 2), while appearing less effective and thus more challenging under KA<sup>2</sup> conditions.<sup>9d,21\*\*</sup>

The comparison of reaction times and optimal temperatures clearly shows that shifting from a terminal alkyne to a terminal ynamide induces a huge rate acceleration of such MCRs. Obviously, both Cu<sup>I</sup>-USY-catalysed A<sup>3</sup>/KA<sup>2</sup> and AYA/KYA reaction mechanisms are similar, with the *in situ* formation of copper acetylide which adds to *in situ* formed imine or iminium as the key steps (Scheme 6). Due to the polarisation of their triple bond, ynamides are nevertheless more nucleophilic than their alkyne derivatives (see *N* parameters),<sup>15,16</sup> and so may be the corresponding copper acetylides. However, the formation of the latter requires a C–H activation step – most probably a deprotonation – which should be disfavoured due to increasing electron density throughout this bond.

Because much faster reactions were achieved with ynamides than with alkynes (2–5 vs. 15–18 h), as well as milder conditions (30 vs. 80 °C), it seems that the zeolitic Cu<sup>I</sup>-USY catalyst overcomes these opposite trends, suggesting confinement effect. It is worth noticing that related enhanced reactivity has been assigned to differences in the respective rates of acetylide formation in CuAAC reactions.<sup>27</sup> It is thus probable here that the enhanced  $\pi$ -nucleophilicity of the ynamide favours the formation of the  $\pi$ -ynamide complex **I**<sub>1</sub> and thus accelerates the formation of the copper acetylide intermediate **I**<sub>2</sub>, possibly in a rate-determining step. In this scenario, the observed reaction kinetics should be in line with the donation ability of the *N* lone pair to the  $\pi$  system of the alkyne moiety: the most donating the *N* lone pair, the faster the formation of the  $\pi$ -ynamide complex **I**<sub>1</sub>. This trend is well confirmed by the observed differences in rate when comparing reactions from ynesulfonamides and yncarbamates with those from ynelactams or yneindoles (respectively 2–4 h and more than 2 d; see Scheme 5).

Hydroamination of the  $\pi$ -complex **I**<sub>1</sub> proved to take place in both cases as a competing pathway, with contrasting results

depending on the class of the amine partner (Scheme 6). While  $\pi$ -alkynyl complexes require secondary amines to undergo the hydroamination event (as previously discussed in ref. 21),  $\pi$ -ynamide complexes proved here enough reactive to undergo this unwished event with less nucleophilic primary amines.

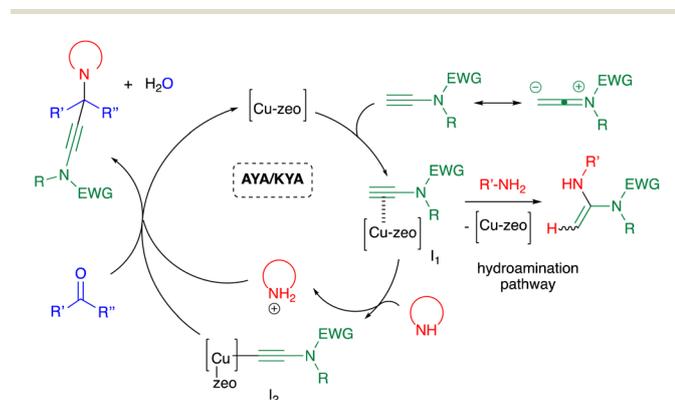
When compared to homogeneous conditions, the present zeolite-based conditions clearly offer an efficient and fruitful alternative. Indeed, decomposition-polymerisation occurred with simple copper(I) halides as catalysts (see Table 2), while cleaner and efficient reactions were achieved with Cu<sup>I</sup>-USY as catalyst. The latter seems to act as nanoreactor, confining the various partners within zeolite pores and avoiding/limiting such degradation.

## Conclusions

In summary, we presented herein the first one-pot synthesis of  $\gamma$ -amino-ynamides. The developed approach relies on the copper-zeolite-catalysed reaction between a carbonyl compound, a terminal ynamide and an amine as readily available coupling partners. These AYA/KYA three-component coupling reactions were shown to proceed under simple, mild conditions (*i.e.* room temperature or 30 °C, neat or ethyl acetate as benign solvent, easy-to-remove/-recover catalyst), with low copper loading (3 mol%) and generally short reaction times. It is worth highlighting here that the present Cu<sup>I</sup>-USY-catalysed reactions are the only one able to readily produce  $\gamma$ -amino-ynamides, since homogeneous conditions with classical copper halides as catalysts induce decomposition.

Moreover, the present conditions offer a wide scope and tolerate a variety of functional groups (*i.e.* halide, alkene, hydroxy, ether, acetal, ester, sulfonyl, lactam, oxazolidinone, *etc.*). Water being moreover the sole by-product formed, AYA/KYA processes emerge as powerful atom-, energy- and step-economical methods for preparing  $\gamma$ -amino-ynamides, in full agreement with Green Chemistry standards.

Further works are under way in our group to explore the synthetic potential of  $\gamma$ -amino-ynamides.



Scheme 6 Mechanistic rationale for the AYA/KYA reactions.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

‡ For information, the cost of the commercial  $\text{NH}_4\text{-USY}$  used as zeolitic precursor of  $\text{Cu}^1\text{-USY}$  is 0.6€ per gram, thus cheap.  $\text{Cu}^1\text{-USY}$  is readily produced by heating under  $\text{N}_2$  flux a mixture of  $\text{H-USY}$  and  $\text{CuCl}$  (see ESI for details†).

§ As sulfonamide **4a'** was not detected in the  $^1\text{H}$  NMR spectrum of the crude mixture, this unanticipated compound is thought to result from a by-product which is unstable in the presence of silica and thus prone to decompose during column chromatography.

¶ When 4-fluoroaniline was used, the hydrated form of terminal ynamide **2a** was detected among other unidentified reaction products.

|| In the absence of molecular sieves, the model reactions provided **6a** and **6c** in lower yields (i.e. 48% for **6a** and 62% for **6c**), together with nonnegligible amounts of the hydrated ynamide as side-product.

\*\* Under our  $\text{KA}^2$  coupling conditions, hexan-2-one proved much less effective than its cyclic surrogate (cf. 54% vs. 92%). For more details, see ref. 21.

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