Rh(II)-Catalysed Condensations of *N*-Sulfonyl-1,2,3-triazoles with Aminals

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Abstract **Key words** aminal, triazole, carbene, ylide, cascade

N-Sulfonyl-1,2,3-triazoles **1**, readily accessible through Cu(I)-catalysed azide alkyne cycloadditions (CuAACs),¹ are key building blocks in synthetic, biological and medicinal chemistry.² In the presence of dirhodium complexes, behaving as decomposition catalysts, they generate α -imino carbenes **2** (Table 1, A).³ These electrophilic unsaturated intermediates afford synthetically useful and original conversions, from migrations to ylide-forming reactions and subsequent transformations.^{4,5} Recently, studies were reported on their reactivity with cyclic diaryl aminals that generate, after ylide formation (**3**) and subsequent ring opening, iminium intermediates of type **4** (Scheme 1). Several synthetic applications have been published using these electrophilic moieties **4** over recent years, in particular a series of cascade reactions (Table 1).⁶ These will be the focus of this Spotlight.

Scheme 1 With aminal and α -imino carbenes **2** as substrates and reagents, respectively, ammonium ylide formation (**3**) leads to the intermediacy of original ring-opened imino iminium intermediates **4** that are the focus of this spotlight.

The first report of this type of reactivity was described using Tröger bases **5** as substrates. Compounds **5** were shown to react with triazoles **1** under Rh₂(Piv)₄ catalysis

Nidal Saleh obtained in 2013 his PhD in chemistry at the University of Rennes-1 with Dr. Jeanne Crassous. After a postdoctoral fellowship with Dr. Arnaud Voituriez at the ISCN-CNRS, he joined the group of Prof. Jérôme Lacour at the University of Geneva in December 2017, where he is holding the position of Maître Assistant. His research interests revolve around chirality; from designing new ligands to enantioselective catalysis, followed by (chir)optical studies.

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(2 mol%) to yield polycyclic indoline-benzodiazepines **6** (Table 1, B). After a [1,2]-Stevens-like rearrangement occurring via the corresponding ring-opened iminium intermediate **4** (Scheme 1), a cascade of Friedel–Crafts, Grob, and aminal formation reactions follows to generate the polycyclic derivatives (Table 1, C, steps i–v).⁷ Products **6** are formed as single isomers (*d.r.* > 49:1, with four stereocenters including two bridgehead N-atoms). Key mechanistic insights were obtained during the study pointing toward the occurrence of metal-bound ylides to explain the regioselectivity of certain reactions. In fact, if a choice is provided on the aminal bridge between an electron-rich and an electron-poor nitrogen atom, then the formation of the ylide proceeds on the formally less reactive N-atom, the electron-deficient one! This counterintuitive observation of a preferred attack by the less-nucleophilic N-atom of the electrophilic carbene

is the consequence of a Curtin–Hammett-type situation that is detailed in the original article.^{7a} In another study, further mechanistic insights were gained to explain the racemization that happens when starting with enantiopure Tröger bases as substrates due to a reversibility of the initial aza-Mannich reaction (Table 1, C, step ii).^{7b} Application of this scaffold towards the formation of chiral donor- π -acceptor red-emitting hemicyanine fluorophores **8** was also achieved in a couple of steps that include an original demethylenation protocol (Table 1, D).⁸ Finally, products **6** are amins in their own standing. Further ring expansions by insertion of a second α -imino carbene were possible, resulting in elaborated polycyclic 9-membered-ring triazonanes **9** (Table 1, E).

1,3,5-Triazinanes, compounds **10** possessing a set of three amins functional groups, were ideal substrates for this type of reactivity and the formation of octahydro-1*H*-purine derivatives **11** with moderate to good yields was described in 2019 (Table 1, F).⁹ Mechanistic studies *via* DFT calculations suggest that the 1,3,5-triazinanes **10** might undergo a formal [6+3] cycloaddition with the Rh(II)-azavinyl carbene intermediates, which are generated from Rh(II)-catalysed denitrogenation of 1,2,3-triazoles. Afterwards, ring closure of the formed nine-membered-ring intermedi-

ate *via* intramolecular nucleophilic addition, followed by subsequent rearrangements afforded the final octahydro-1*H*-purine derivatives.

Finally, very recently, the intermolecular reactivity of *N*-sulfonyl-1,2,3-triazoles **1** with imidazolidines **12** has also been reported.¹⁰ Under dirhodium catalysis (3 mol%), polycyclic products **13** are obtained in good yields (up to 90%; *d.r.* up to 6.8:1). The process is general and affords systematically the pyrazino-indolines **13** (Table 1, G). However, and importantly, with unsymmetrically substituted imidazolidine **14**, a regiodivergent pathway is obtained favoring the selective formation of 8-membered-ring hexahydro-1,3,6-triazocines **15** (Table 1, H). Based on first principles, detailed mechanistic analysis shows that, after regioselective ylide formation and amins ring opening (Table 1, I, intermediate **4**), *N*-cyclization occurs in this case to form the medium-sized heterocycle **15** (path A, left). Other the other hand, when the amins is symmetrically substituted with electron-rich substituents on the N-atoms for instance, C-cyclization happens due to a reversibility of the kinetically preferred 8-membered-ring formation (Table 1, I, path B); the irreversible Friedel–Crafts reaction driving the whole process toward more stable adduct **13**. For this series, the occurrence of a Curtin–Hammett-type situation is thus again demonstrated (Table 1, I).¹¹

Table 1 Rh(II)-Catalyzed Condensations of *N*-Sulfonyl-1,2,3-triazoles with Amins and Subsequent Applications

<p>(A) Harmon, 1970 and 1971 Evidence of ring-chain tautomerization and α-imino diazo formation. Gevorgyan and Fokin, 2008 Application to the formation of α-imino carbene intermediates 2 in the presence of dirhodium catalysts.</p>	
<p>(B) Lacour, 2018 Using Tröger bases 5 as substrates, condensation of α-imino carbenes with the bridgehead amins group to afford polycyclic indoline-benzodiazepines 6.</p>	
<p>(C) Lacour, 2018 Cascade mechanism in the transformation of 5 into 6: i. amins opening induced by the ylide formation, ii. reversible aza-Mannich, iii. Friedel–Crafts, iv. Grob-like fragmentation, v. amins reformation and final cyclization.</p>	

<p>(D) Lacour, 2020 Application to the synthesis of chiral hemicyanine red-emitting fluorophores 8. Ar = Ph, <i>p</i>-CNPh, <i>p</i>-OMePh, naphthyl, thiophenyl, carbazoyl.</p>	
<p>(E) Lacour, 2018 With adducts 6 carrying nosyl-protecting group, condensation of a second equivalent of α-imino carbene with the aminal functional group is possible and affords 9-membered-ring triazonanes 9.</p>	
<p>(F) Bao, 2019 1,3,5-Triazinane reactivity with triazoles 1 to generate, in a series of 4 cascade reactions from intermediate 4, the octahydro-1<i>H</i>-purine derivatives 11.</p>	
<p>(G) Lacour, 2021 Using symmetrical imidazolidines 12 as substrates (same X on each aryl N-atom substituents), the condensation yields pyrazino-indolines 13 as single products. Further transformations are possible including elimination of the <i>N</i>-sulfonyl group and [1,2]-migration of the R¹ moiety.</p>	
<p>(H) Lacour, 2021 With unsymmetrical substrate 14, bearing MeO and NO₂ groups on the aryl substituents, respectively, a totally regiodivergent pathway is obtained to afford 8-membered-ring hexahydro-1,3,6-triazocines 15, again as single products. The difference with the above reactivity (Table 1, G) stems from the energy barrier for the aminal reopening starting from 15; see below for a full description (Table 1, I).</p>	
<p>(I) Lacour, 2021 Starting from iminium intermediate 4, the computed Gibbs energy profile for the 8-membered ring 15 formation by <i>N</i>-cyclization (left) or by <i>C</i>-cyclization to afford the 6-membered ring 13 (right). Donor–donor (Ar¹, Ar² EDGs) energies are given in black and donor–acceptor (Ar¹ EDG, Ar² EWG) in magenta, all in kcal mol^{−1}.</p>	

Conflict of Interest

The authors declare no conflict of interest.

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