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

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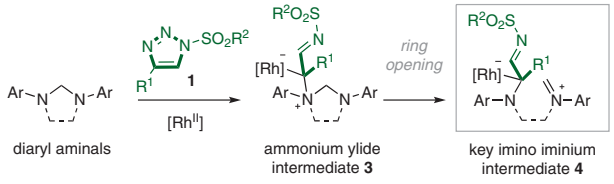
Abstract **Key words** aminal, triazole, carbene, ylide, cascade

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 $Rh_2(Piv)_4$ catalysis (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

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.

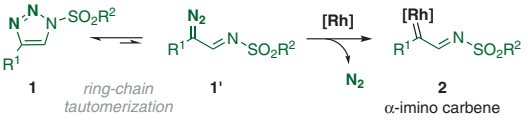
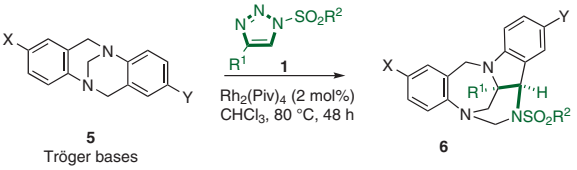
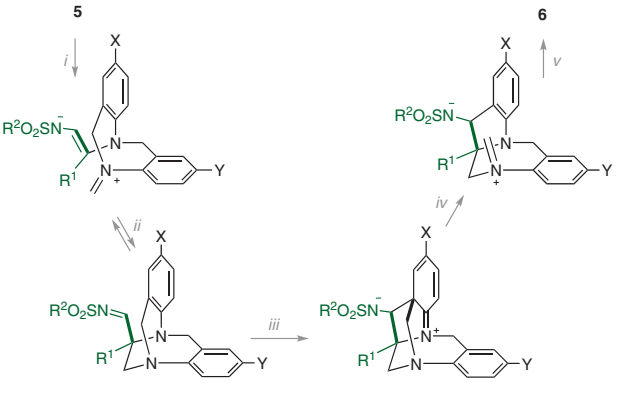
Jérôme Lacour was educated at the École Normale Supérieure (Ulm, Paris). He obtained his PhD in chemistry in 1993 at the University of Texas at Austin with Prof. Philip D. Magnus. After postdoctoral studies with Prof. David A. Evans at Harvard University, he joined the Organic Chemistry Department of the University of Geneva in 1995. He holds a full professor position in the department. Currently, his primary research interests are in asymmetric synthesis, catalysis, and chiroptical spectroscopy using organic, physical organic, organometallic, and coordination chemistry tools

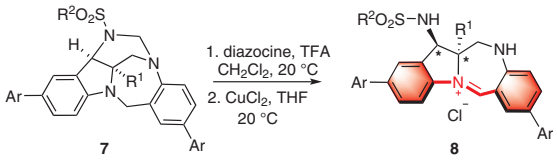
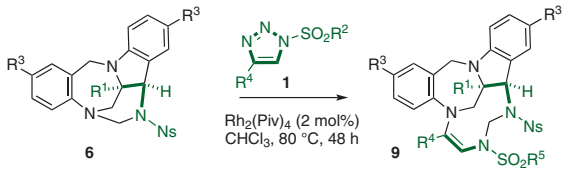
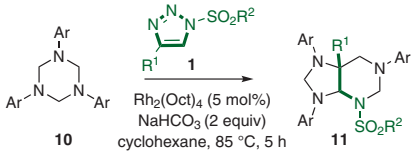
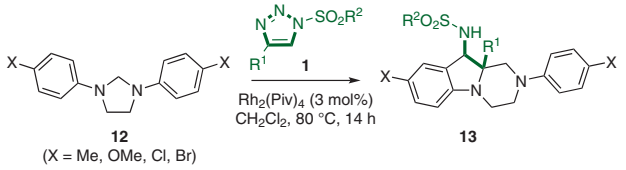
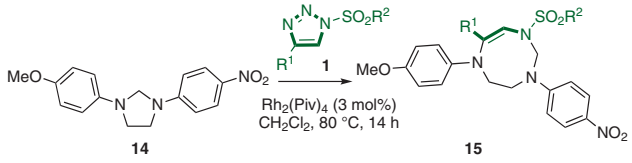
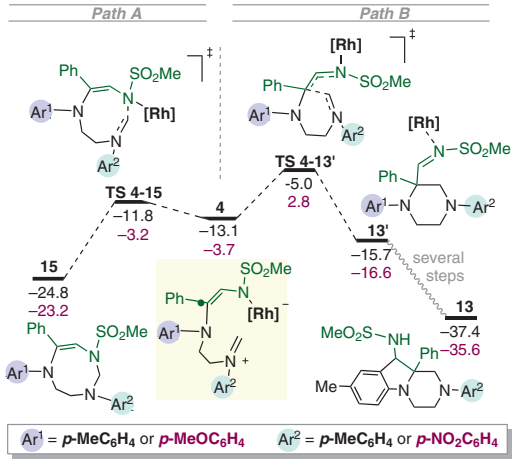
is the consequence of a Curtin–Hammett-type situation that is detailed in the original article.[7a] In another study, further mechanistic insights were gained to explain the racemization that happens when starting with enantiopure Tröger bases as substrates due to a reversibility of the initial aza-Mannich 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 aminals 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 aminal 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 intermediate *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 aminal 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 aminal 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 Aminals and Subsequent Applications

(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.	
(B) **Lacour, 2018** Using Tröger bases **5** as substrates, condensation of α-imino carbenes with the bridgehead aminal group to afford polycyclic indoline-benzodiazepines **6**.	
(C) **Lacour, 2018** Cascade mechanism in the transformation of **5** into **6**: i. aminal opening induced by the ylide formation, ii. reversible aza-Mannich, iii. Friedel–Crafts, iv. Grob-like fragmentation, v. aminal reformation and final cyclization.	

(D) **Lacour, 2020** Application to the synthesis of chiral hemicyanine red-emitting fluorophores **8**. Ar = Ph, *p*-CNPh, *p*-OMePh, naphthyl, thiophenyl, carbazoyl.	
(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**.	
(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*H*-purine derivatives **11**.	
(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 *N*-sulfonyl group and [1,2]-migration of the R^1 moiety.	
(H) **Lacour, 2021** With unsymmetrical substrate **14**, bearing MeO and NO_2 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**).	
(I) **Lacour, 2021** Starting from iminium intermediate **4**, the computed Gibbs energy profile for the 8-membered ring **15** formation by N-cyclization (left) or by C-cyclization to afford the 6-membered ring **13** (right). Donor–donor (Ar^1, Ar^2 EDGs) energies are given in black and donor–acceptor (Ar^1 EDG, Ar^2 EWG) in magenta, all in kcal mol^{-1}.	

Conflict of Interest

The authors declare no conflict of interest.

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