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

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N-Sulfonyl-1,2,3-triazoles 1, readily accessible through Cu(I)-catalysed azide alkyne cycloadditions (CuAACs), are key building blocks in synthetic, biological and medicinal chemistry. In the presence of dirhodium complexes, behaving as decomposition catalysts, they generate α-imino carbenes 2 (Table 1, A). These electrophilic unsaturated intermediates afford synthetically useful and original conversions, from migrations to ylide-forming reactions and subsequent transformations. 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). These will be 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 (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). 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.\textsuperscript{74} 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).\textsuperscript{7b} Application of this scaffold towards the formation of chiral donor–π-acceptor red-emitting hemicyanine fluorophores \textsuperscript{8} was also achieved in a couple of steps that include an original demethylenation protocol (Table 1, D).\textsuperscript{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 \textsuperscript{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-1H-purine derivatives 11 with moderate to good yields was described in 2019 (Table 1, F).\textsuperscript{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-1H-purine derivatives.

Finally, very recently, the intermolecular reactivity of \(N\)-sulfonyl-1,2,3-triazoles 1 with imidazolidines 12 has also been reported.\textsuperscript{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).\textsuperscript{11}

\begin{table}[h]
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\begin{tabular}{|c|c|c|}
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\textbf{Table 1} & \textbf{Rh(II)-Catalyzed Condensations of N-Sulfonyl-1,2,3-triazoles with Aminals and Subsequent Applications} \\
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\textbf{(A)} Harmon, 1970 and 1971 & Evidence of ring-chain tautomerization and \(\alpha\)-imino diazo formation. \\
& Gevorgyan and Fokin, 2008 \\
& Application to the formation of \(\alpha\)-imino carbene intermediates 2 in the presence of dirhodium catalysts. \\
\hline
\textbf{(B)} Lacour, 2018 & Using Tröger bases 5 as substrates, condensation of \(\alpha\)-imino carbenes with the bridgehead aminal group to afford polycyclic indoline-benzodiazepines 6. \\
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\textbf{(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. \\
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Conflict of Interest

The authors declare no conflict of interest.

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References


