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Regiodivergent synthesis of pyrazino-indolines vs. triazocines *via* α -imino carbenes addition to imidazolidines†‡

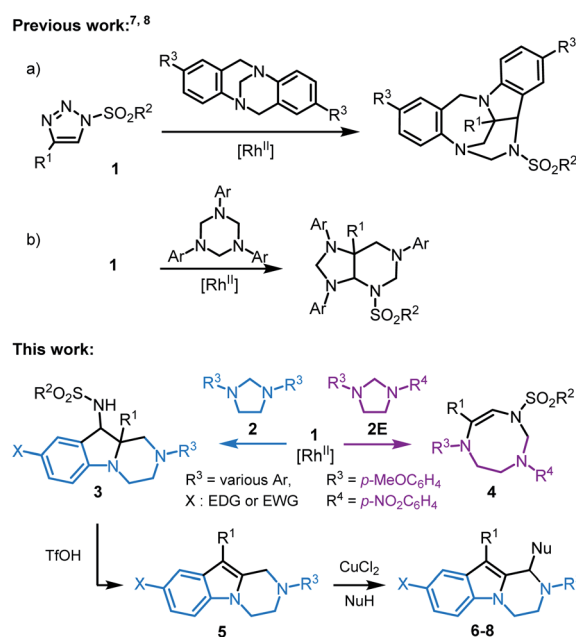
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Hexahydropyrazinoindoles were prepared in a single step from *N*-sulfonyl triazoles and imidazolidines. Under dirhodium catalysis, α -imino carbenes were generated and formed nitrogen ylide intermediates that, after subsequent amination opening, afforded the pyrazinoindoles predominantly *via* formal [1,2]-Stevens and tandem Friedel–Crafts cyclizations. Of mechanistic importance, a regiodivergent reactivity was engineered through the use of a specific unsymmetrically substituted imidazolidine that promoted the exclusive formation of 8-membered ring 1,3,6-triazocines. Based on DFT calculations, an original Curtin–Hammett-like situation was demonstrated for the mechanism. Further derivatizations led to functionalized tetrahydropyrazinoindoles in high yields.

Introduction

N-Sulfonyl-1,2,3-triazoles **1**, readily accessible through Cu(i)-catalyzed azide alkyne cycloadditions (CuAACs),¹ are key building blocks in synthetic, biological and medicinal chemistry.² For the purpose of this study, they also decompose under metal-catalyzed conditions to afford α -imino carbenes.³ These electrophilic unsaturated intermediates have received much attention in recent years, as many synthetically useful and original processes can be afforded, from migrations to ylide-forming reactions and subsequent transformations.^{4,5} Only few studies have been reported on the reactivity of α -imino carbenes with tertiary amines or amins, and on the subsequent ammonium ylide chemistry.⁶ Of special interest to the current study, Tröger bases were shown to react and yield polycyclic indoline-benzodiazepines through a cascade of [1,2]-Stevens, Friedel–Crafts, Grob and amination formation reactions (Scheme 1, top, a).⁷ Also, 1,3,5-triazinanes form octahydro-1*H*-purine derivatives *via* formal [6 + 3] cycloaddition, ring-closure and rearrangements (Scheme 1, top, b).⁸ Herein, in a new development, the intermolecular reactivity of *N*-sulfonyl-1,2,3-

triazoles **1** with imidazolidines **2** is reported (Scheme 1, bottom). Under dirhodium catalysis (3 mol%), hexahydropyrazino[1,2-*a*]indoles **3** are obtained in good yields (up to 90%, diastereomeric ratio (dr) up to 6.8 : 1). Mechanistically, after the initial addition of α -imino carbenes to **2** and subsequent ylide formation, the transformation involves [1,2]-Stevens and Friedel–Crafts reactions. The process is general and yields systematically the polycyclic pyrazino-indolines **3**. However, and



Scheme 1 Reactivity of *N*-sulfonyl triazoles with amins.

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‡ Electronic supplementary information (ESI) available: Synthetic protocols, ¹H/¹³C NMR and HR mass spectra. CCDC 2015200–2015204. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc05725h



importantly, with unsymmetrically substituted imidazolidine **2E** ($R^3 = p\text{-MeOC}_6\text{H}_4$ and $R^4 = p\text{-NO}_2\text{C}_6\text{H}_4$), a regiodivergent pathway is obtained favoring the selective formation of 8-membered ring hexahydro-1,3,6-triazocines **4**.

Based on first principles, detailed mechanistic analysis will show that, after regioselective ylide formation and amination ring opening, N-cyclization rather than C-cyclization occurs in this case to form the medium sized heterocycle **4**. The influence of kinetic and thermodynamic preferences, and the occurrence of a Curtin-Hammett type situation in most cases, will be demonstrated and discussed. Furthermore, compounds **3** can be transformed into tetrahydropyrazino[1,2-*a*]indoles **5** and further derivatives **6–8** by oxidative C–C bond forming reactions. Such compounds **3**, **5–8** ought to interest medicinal chemists as pyrazino[1,2-*a*]indoles are commonly found in biologically active compounds with 5-HT_{2C} receptor agonist,⁹ antifungal,¹⁰ antibacterial,¹¹ anticancer,¹² and antiviral activities,¹³ among others (Fig. 1).¹⁴

Results and discussion

Initial experiments were performed by mixing *N*-tosyl-4-phenyl-1,2,3-triazole **1a** (1.5 equiv.), 1,3-di-*p*-tolylimidazolidine **2A** (1 equiv.) and Rh₂(Piv)₄ (1 mol%) in CHCl₃ (0.25 M), and heating the mixture at 80 °C during 63 h. ¹H-NMR spectroscopic analysis of the crude reaction mixture revealed the presence of unreacted starting materials and two new diastereomeric products **3aA'** and **3aA''** (24% and 20% yields respectively). Their structures were determined with certainty, and the relative configuration relationship in particular, only after X-ray diffraction analysis (Scheme 1 and ESI†).

With this result in hand, optimization studies were conducted to improve the synthesis of **3aA** and results are reported in the ESI.† Best conditions involve the use of CH₂Cl₂ as solvent and 3 mol% of Rh₂(Piv)₄ as catalyst.¹⁵ Complete consumption of **2A** is then achieved after 14 h at 80 °C with only a slight excess of **1a** (1.5 equiv., 0.25 M). Diastereomeric products **3aA'** and **3aA''** are then formed in 61% and 17% yields respectively. Treatment of **3aA'** with sodium (Na) and naphthalene in THF led to a complete conversion and afforded free amino **3A** in 83% yield (Scheme 2, top). A 1 mmol scale reaction was also performed affording products **3aA** with comparable yield and diastereoselectivity (77%, dr 3.6 : 1).¹⁶

With the optimized conditions in hand, a series of *N*-sulfonyl-1,2,3-triazoles **1a–1h** was prepared by CuAAC¹⁷ and tested with imidazolidines **2A–2D** (Scheme 2). Mesyl **1b** and nosyl **1c** triazoles afforded products **3bA** and **3cA** in moderate yields and diastereoselectivity (dr up to 6.8 : 1). Triazole

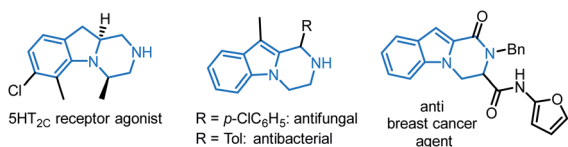
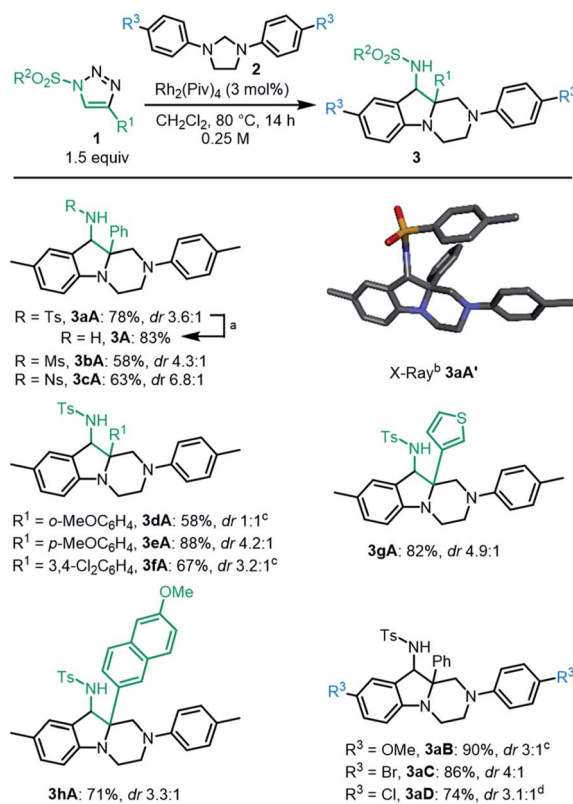


Fig. 1 Selected biologically active pyrazino[1,2-*a*]indoles.^{9b,10,11,12b}



Scheme 2 Hexahydropyrazino[1,2-*a*]indoles **3**. ^aFrom **3aA'**: Na, naphthalene, THF, 17 h, –78 °C to 25 °C. ^bStick view of the crystal structure of **3aA'** (major diastereoisomer). ^cInseparable mixture of diastereoisomers. ^d3 equiv. of *N*-sulfonyl-1,2,3-triazole were used.

reagents **1d** to **1f** with electron donating (EDG) or electron withdrawing (EWG) groups at regioisomeric positions on aromatic group R¹ led to the corresponding heterocycles **3dA–3fA** in average to excellent yields (58–88%), but poor to moderate diastereoselectivity. Thiophene derived **1g** and 6-methoxynaphthalene **1h** were also compatible leading to the expected products **3gA** and **3hA** in 82% and 71% yields, respectively.

A series of imidazolidines were prepared following reported procedures¹⁸ and tested with *N*-tosyl-triazole **1a** (Scheme 2). These symmetrical substrates containing EDGs or EWGs at R³ positions led to **3aB–3aD** with very good yields (74–90%) and moderate levels of diastereoselectivity.

To get some insight on the mechanism of this transformation, unsymmetrically substituted **2E** was synthesized, with electron-withdrawing *p*-NO₂ and -donating *p*-OMe substituents on the aromatic rings of the imidazolidine. Compound **2E** was then treated with *N*-tosyl triazole **1a** and Rh₂(Piv)₄ under the optimized conditions. Careful analysis by NMR spectroscopy revealed the presence of a major product as a single regioisomer (57%). This compound was however not the expected hexahydropyrazino[1,2-*a*]indole **3aE** but 8-membered triazocine **4aE**. Interestingly and importantly for further mechanistic discussions, compounds **4aE** contains an amination –NCH₂N– bridge that is formed with the nitrogen atom

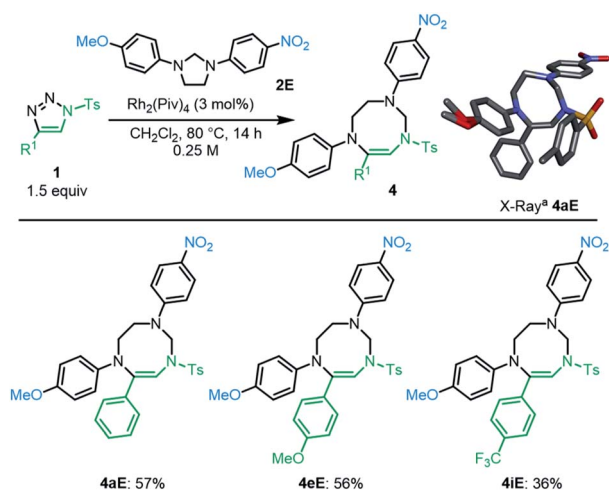


carrying the $p\text{-NO}_2\text{C}_6\text{H}_4$ ring. The structure of **4aE** was confirmed later by X-ray diffraction analysis (Scheme 3, top). Treatment of **2E** with triazoles **1e** and **1i** also led to hexahydro-1,3,6-triazocines **4eE** and **4iE** in 56% and 36% yield, respectively. As mentioned above, these results are important to understand the reactivity pathways involved in this Rh(II)-catalyzed α -imino diazo decomposition and subsequent nitrogen ylide/cyclization processes.

Theoretical study

To rationalize the above substrate-dependent synthetic divergence toward either pyrazino-indole or triazocine products, DFT calculations were performed using the α -imino carbene complex **A** as starting point. Geometrically, in relation with the imidazolidine skeleton, the Rh-carbene faces either the aminal bridge or the $-\text{CH}_2\text{CH}_2-$ backbone of the 5-membered ring. Both approximation modes were studied and only the most favored path is detailed here (Fig. 2 and S8[†]). From complex **A**, the computed transition state **TS A-B** involves the C-N bond formation between the carbene complex and the imidazolidine substrate ($\Delta G^\ddagger = 7.7 \text{ kcal mol}^{-1}$), achieving the nitrogen ylide intermediate **B**. The system rapidly evolves to **B'** by switching the Rh catalyst from the C to the N atom of the former α -imino carbene, in an exergonic step of $2.7 \text{ kcal mol}^{-1}$. In this disposition, the aminal opening occurs through **TS B'-C** with a low activation barrier ($\Delta G^\ddagger = 2.2 \text{ kcal mol}^{-1}$) leading to the iminium intermediate **C** with a relative energy of $13.1 \text{ kcal mol}^{-1}$ below the initial reactants (full details in Fig. S1[†]). The computed results for the donor OMe – acceptor NO_2 system (**2E**) show the same two-step process although in this case the aminal opening requires higher activation energy ($\Delta G^\ddagger = 7.2 \text{ kcal mol}^{-1}$) and the final iminium intermediate **C** (OMe-NO_2) is stabilized by only $3.7 \text{ kcal mol}^{-1}$ (see further details in Fig. S4[†]).

At this stage, intermediate **C** can evolve either towards N- or C-cyclizations. Pathway A (Fig. 3, left) depicts the progression of intermediate **C** through an N-cyclization process, **TS C-4**, in



Scheme 3 Access to substituted hexahydro-1,3,6-triazocines **4**. ^aStick view of the crystal structure of **4aE**. Hydrogen atoms are omitted for clarity and the MeO group presents a local disorder.

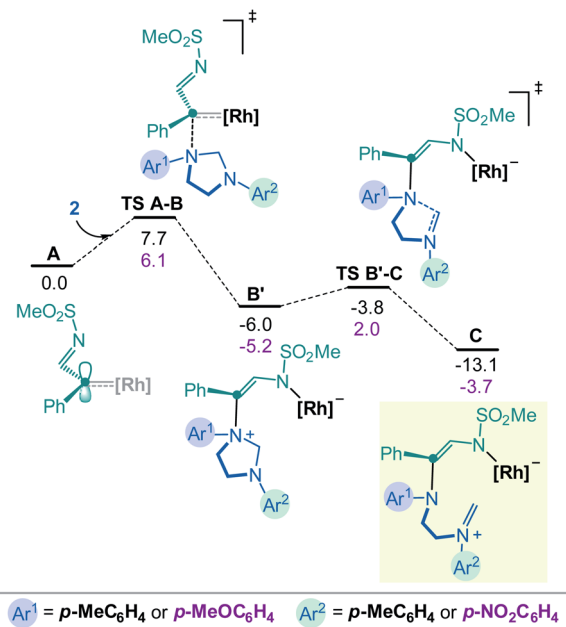


Fig. 2 Computed Gibbs energy profile for the formation of the iminium intermediate **C**. Donor-donor energies (Ar^1, Ar^2 EDGs) in black and donor-acceptor (Ar^1 EDG, Ar^2 EWG) in magenta, all in kcal mol^{-1} .

a quasi-barrier less step ($\Delta G^\ddagger = 1.3 \text{ kcal mol}^{-1}$) affording the formation of the 8-membered-[Rh] complex. The Rh catalyst is then released and hexahydro-1,3,6-triazocine product **4** is formed in an exergonic reversible manner ($\Delta G = 11.7 \text{ kcal mol}^{-1}$ below **C**). The C-cyclization reaction is shown in Pathway B (Fig. 3, right). First, *via* **TS C-D'**, the 6-membered-[Rh] complex **D'** is formed with an activation barrier of

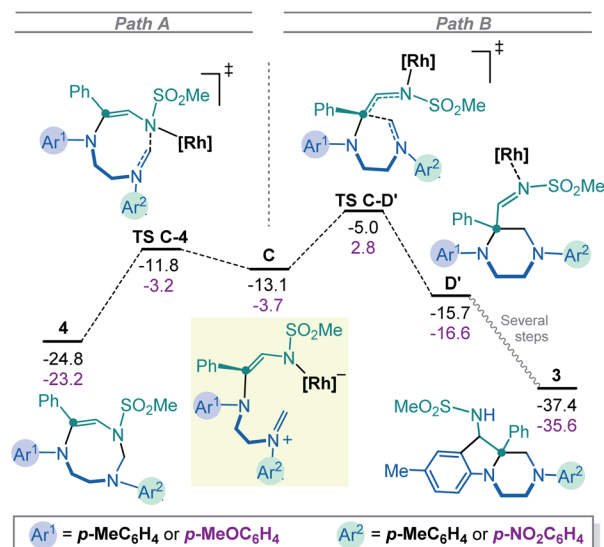


Fig. 3 Computed Gibbs energy profile for the 8-membered (left, N-cyclization) or 6-membered (right, C-cyclization) ring formation from the iminium intermediate **C**. Donor-donor (Ar^1, Ar^2 EDGs) energies in black and donor-acceptor (Ar^1 EDG, Ar^2 EWG) in magenta, all in kcal mol^{-1} .



8.1 kcal mol⁻¹. This transition state involves the bond formation between the C atom of the iminium ion and the C atom of the former carbene. It is worth to mention that the process described from **B** to **D'** corresponds to a formal [1,2]-Stevens rearrangement.¹⁹ Finally, to proceed towards the formation of hexahydropyrazino[1,2-*a*]indole **3**, intermediate **D** evolves through a Friedel-Crafts cyclization with the assistance of the Rh₂(Piv)₄ catalyst (see details in Fig. S3†). These final steps require an overall activation energy close to 20 kcal mol⁻¹ and lead to the formation of the most stable product **3** with a relative energy of 37.4 kcal mol⁻¹ below the initial reactants. The analysis of the full reaction path follows a clear Curtin-Hammett behavior. Compound **4**, the kinetically-preferred product formed *via* **TS C-4**, can reopen in the reaction conditions again and, *via* **TS C-D'** ($\Delta G^\ddagger = 19.8$ kcal mol⁻¹), the formation of the thermodynamic product **3** is then favored. This last step is irreversible as 32.4 kcal mol⁻¹ are required to overcome **TS C-D'** from **3**.

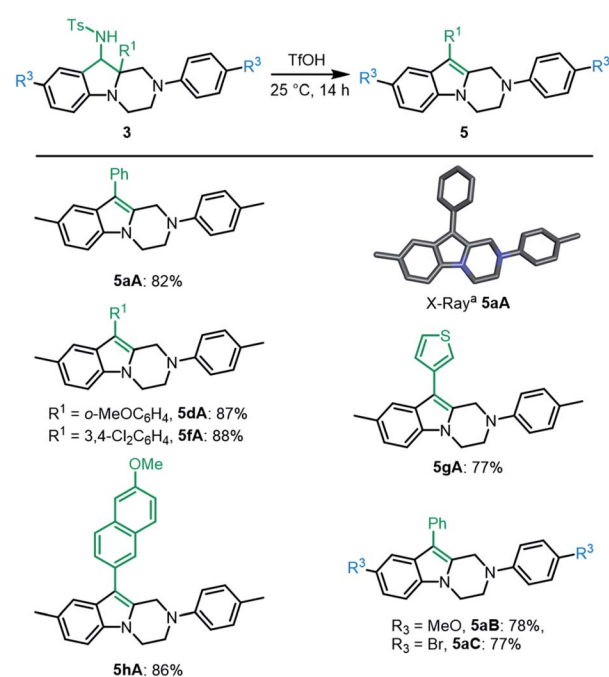
Fig. 3 also depicts the energies for the donor-acceptor system (Ar¹ EDG, Ar² EWG, numerical values in magenta). Interestingly, in this case, **TS C-D'**_(OMe-NO₂)²⁰ has an energy of 2.8 kcal mol⁻¹ above the initial reactants which is sufficient to suppress the Curtin-Hammett behavior. In fact, once product **4** is formed, the reversibility of the opening reaction is no longer feasible. The formation of product **3** would require *ca.* 26 kcal mol⁻¹, which is not permitted in the reaction conditions. The selectivity of the carbene towards the different N atoms was also calculated when unsymmetrically substituted imidazolidine **2E** is used as substrate. The results show that the attack on the N-atom bearing the *p*-MeOC₆H₄ group is favored, in agreement with the experimental observations (see details in Fig. S12†).

Overall, thanks to the DFT calculations that are summarized in Scheme 4, an elaborate Curtin-Hammett behavior is evidenced with derivatives **3** and **4** as the thermodynamically- and kinetically-preferred products, respectively. With symmetrical imidazolidines as substrates (Ar¹ = Ar² EDGs or weakly EWGs), the corresponding 8-membered ring derivatives of type **4** are

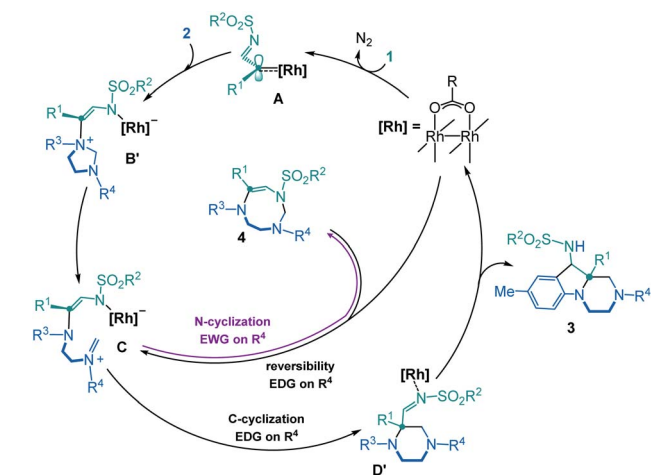
unstable in the reaction conditions and evolve towards hexahydropyrazino[1,2-*a*]indoles **3**, after a reversible ring opening. Such a behavior does not occur anymore when donor-acceptor **2E** is used as reactant (Ar¹ strong EDG, Ar² strong EWG). This substrate-dependent reactivity is controlled by **TS C-D'**, the transition state at the origin of the synthetic divergence.

Extension

Finally, with hexahydropyrazino[1,2-*a*]indoles **3** in hand, care was taken to extend the chemistry to further heterocycles and addition derivatives. First, treatment of **3aA** (dr 3.6 : 1) with concentrated triflic acid (25 °C, 14 h) led to further derivatization. In fact, ¹H-NMR analysis of the crude reaction mixture revealed a full conversion and the formation of single product **5aA**, which was easily isolated in good yield (82%). Its exact structure was determined by X-ray diffraction analysis (Scheme 5, bottom). Such 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole of type **5** is probably formed through protonation and elimination of TsNH₂ followed by a 1,2-shift of the aryl group (R¹) and a final proton loss (see Scheme S2†). Isolated single diastereoisomers **3aA'** and **3aA''** were treated independently with TfOH under the reaction conditions. Product **5aA** was formed in both instances and isolated with the same yield. A series of derivatives **3A** was treated under these reaction conditions. Both electron donating and electron withdrawing substituents on the migrating phenyl group (R¹) afforded the corresponding products **5dA** and **5fA** in very good yields (87% and 88%, respectively). Other substituents R¹ such as thiophene **3gA** and 6-methoxynaphthalene **3hA** were also compatible leading to the expected products **5gA** and **5hA** in 77% and 86% yields, respectively. *p*-MeO and *p*-Br



Scheme 5 One-step access to tetrahydropyrazino[1,2-*a*]indoles **5**. [†]Stick view of the crystal structure of **5aA**. Hydrogen atoms are omitted for clarity.



Scheme 4 Global mechanistic rationale.



substituents at R³ position led to **5aB** and **5aC** in 78% and 77% yields.

Then, compounds **5** were further functionalized *via* oxidative C–C bond forming reactions using conditions similar to that reported for tetrahydroisoquinolines.²¹ In fact, treatment of **5aA** with one equivalent of CuCl₂ in THF/MeNO₂ (1 : 1) led to the corresponding iminium intermediate,^{22,23} which upon addition of Hünig's base (^tPr₂EtN, 1.1 equiv.) led to the clean formation of **6** (92% yield) by an *in situ* aza-Henry reaction (Scheme 6). Further oxidative derivatizations of **5aA** were possible with silyl ketene acetals and cyanide anion as nucleophiles to afford the corresponding ester **7** and nitrile **8** in 73% and 93% yields, respectively.

Conclusions

In summary, novel hexahydropyrazinoindoles **3** were prepared in a single step from *N*-sulfonyl triazoles **1** and imidazolidines **2**. Under dirhodium catalysis, α -imino carbenes were generated and formed nitrogen ylide intermediates that, after subsequent amination opening, afforded derivatives **3** predominantly *via* a formal C-reactivity/[1,2]-Stevens pathway and tandem Friedel–Crafts cyclization. Of mechanistic importance, a regiodivergent reactivity could be engineered through the use of unsymmetrically substituted imidazolidine substrate **2E** that promoted the exclusive formation of 8-membered ring derivative **4**. Importantly, DFT computed results demonstrated a mechanistic Curtin–Hammett-like situation. First, compounds of type **4** are formed as kinetic products and reopened reversibly with the aid of the Rh₂(Piv)₄ catalyst. Given time and energy, the system evolves towards the formation of the thermodynamically preferred product **3**, after an irreversible Friedel–Crafts alkylation that seals the multi-step pathway. With imidazolidine **2E** as reagent, the formation of **4** becomes irreversible and the 8-

membered heterocycle is formed preferentially as a unique regioisomer. Finally, with derivatives **3** in hand, tetrahydropyrazinoindoles **5** were prepared efficiently upon treatment with triflic acid; compounds **5** being themselves suitable for late-stage functionalization *via* oxidative C–C bond forming reactions giving products **6** to **8**.

Conflicts of interest

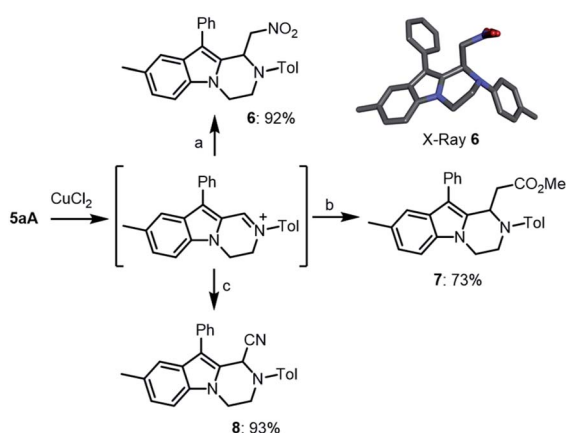
There are no conflicts to declare.

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Scheme 6 Late stage functionalization of **5aA** *via* oxidative C–C bond formation: (a) (i) CuCl₂ (1 equiv.), THF/MeNO₂ (1 : 1), 25 °C, 3 h; (ii) ^tPr₂EtN (1.1 equiv.), 25 °C, 2 h. (b) (i) CuCl₂ (1 equiv.), THF, 25 °C, 16 h; (ii) 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (2 + 1 equiv.), 25 °C, 6 h. (c) CuCl₂ (1 equiv.), THF, 25 °C, 16 h; (ii) NaCN (1.5 + 1.5 equiv.), MeOH, 25 °C, 6 h. Insert: stick view of the crystal structure of **6**. Hydrogen atoms are omitted for clarity and the CH₂NO₂ chain presents a local disorder.



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