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Pyridazine *N*-Oxides as Precursors of Metallocarbenes: Rhodium-Catalyzed Transannulation with Pyrroles

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Supporting Information

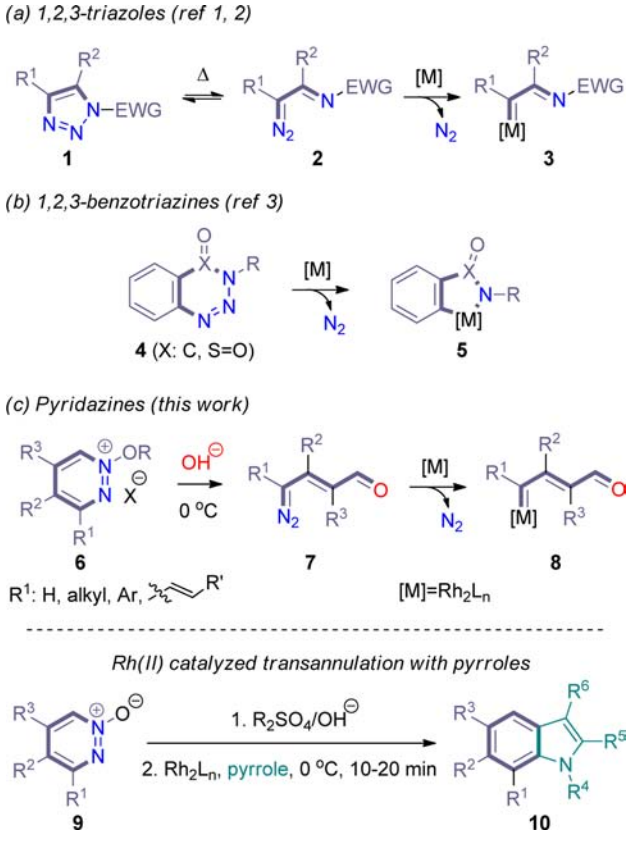
ABSTRACT: Pyridazine *N*-oxides are used for the first time as precursors of metallocarbenes. These nitrogen-rich heterocycles led to the discovery of a novel acceptor and donor−acceptor enalcarbenoids. The synthetic utility of these metallocarbenes was demonstrated in the rhodium-catalyzed denitrogenative transannulation of pyridazine *N*-oxides with pyrroles to the valuable alkyl, 7-aryl, and 7-styryl indoles. The transannulation strategy was applied to the synthesis of a potent anticancer agent.

Recently, nitrogen-rich heterocyclic compounds have emerged as valuable precursors of metallocarbenes and metallacycles in various transition-metal-catalyzed reactions.[1−3] It has been shown that 1,2,3-triazoles and 1,2,3-triazines containing a labile nitrogen triad undergo facile denitrogenative metalation.[1−3] The triazole **1** derived aza-vinylcarbene **3**, discovered by Gevorgyan and Fokin, led to significant developments in the metallocarbene chemistry.[1,2] On the other hand, the Murakami group discovered that 1,2,3-benzotriazine **4** serves as a valuable precursor to aza-metallacycle **5** (Scheme 1b) in various transannulations.[3]

Inspired by these seminal works and in continuation of our ongoing studies on the design of new metallocarbenes,[4] we investigated nitrogen-rich pyridazines as the source of novel carbene precursors. Electron-deficient *N*-alkoxypyridazinium salts are susceptible to nucleophilic ring opening resulting in the vinyldiazo compounds.[5] We envisioned that the (*E*)-enaldiazo compound **7** obtained by the mild hydroxide mediated ring opening of *N*-alkoxypyridazinium salt **6** could serve as a precursor for the novel acceptor and donor−acceptor rhodium enalcarbenoids **8** (Scheme 1c) which are otherwise difficult to access. In comparison to our recently designed diacceptor enalcarbenoids,[4,6] the pyridazine derived acceptor and donor−acceptor enalcarbenoids are expected to offer complementary reactivity, leading to divergent products.[7] Herein, we disclose the first application of pyridazine *N*-oxide **9** as a precursor to metallocarbenes in the rhodium-catalyzed transannulation with pyrroles to the valuable alkyl, 7-aryl, and 7-alkenyl indoles (Scheme 1c).

The diverse pyridazinium salts **6** required for our studies were prepared by O-alkylation of the readily accessible pyridazine *N*-oxides **9**.[8] The (*E*)-enaldiazo compound **7** was instantly generated at 0 °C upon exposure of a solution of **6** to aq KOH. Although the parent enaldiazomethane **7a** (R^{1-3} = H) could be isolated, the substituted enaldiazo compounds were highly unstable for isolation.[8] Our initial studies on transannulation of *N*-methoxypyridazinium salt **6a** with pyrrole via enaldiazomethane **7a**, in the presence of 0.5 mol % dirhodium-

Scheme 1. Nitrogen Rich Heterocycles as Precursors of Metallocarbenes or Metallacycles



(II)acetate and Brønsted acid diphenyl phosphate (DPP, **11**), proceeded rapidly under mild conditions and furnished indole

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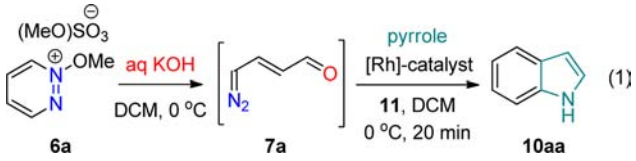
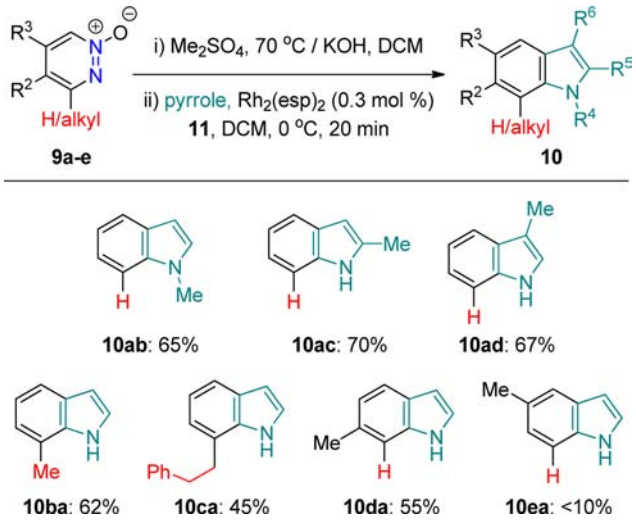
10aa in 62% yield (eq 1).[8−10] Other rhodium(II) catalysts such as $Rh_2(oct)_4$, $Rh_2(S\text{-}DOSP)_4$, $Rh_2(TFA)_4$, and $Rh_2(esp)_2$ were also effective toward the reaction. Among the solvents, chlorinated solvents (DCM, chloroform, and DCE) were found to be compatible while nonpolar (hexane) and oxygenated solvents (ether, THF, ethyl acetate) gave poor yields. An optimal yield of 73% was obtained with 0.3 mol % of the $Rh_2(esp)_2$ in DCM solvent.



With the optimized conditions, the scope of the transannulation was examined toward the synthesis of diverse alkyl substituted indoles (Scheme 2), involving an acceptor type

Scheme 2. Scope of the Transannulation toward Alkylindoles[a,b]

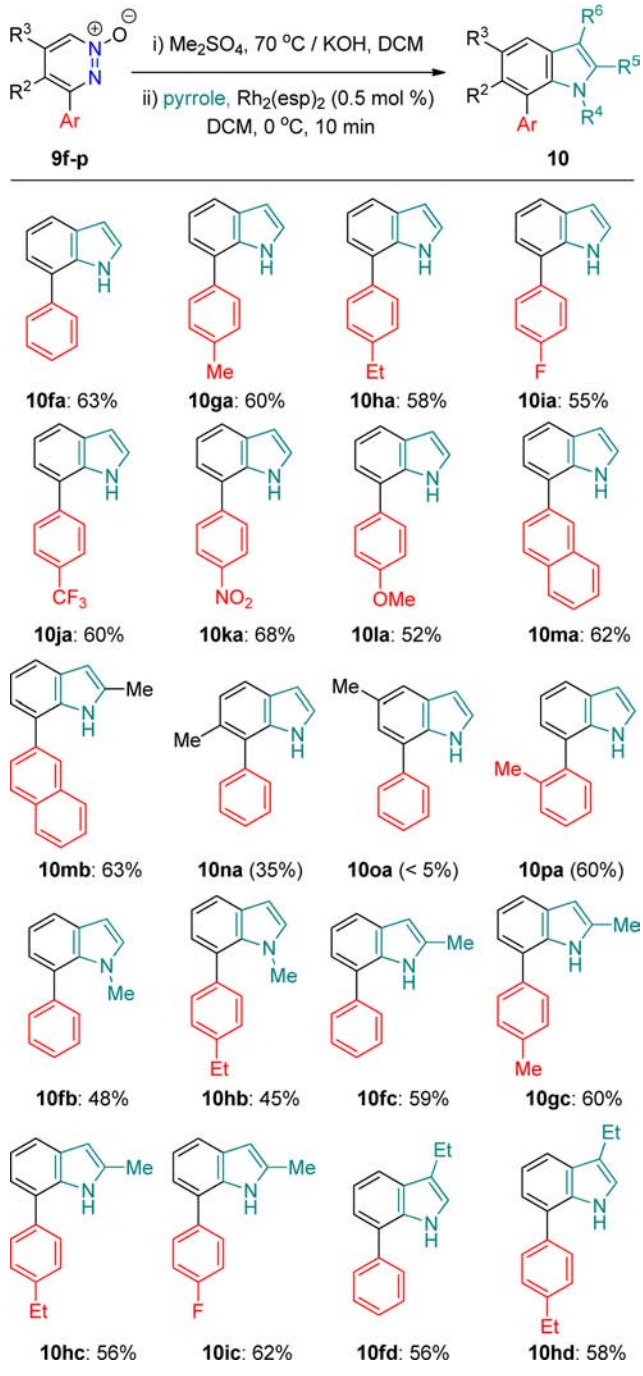


[a]Reaction conditions: **9**/pyrrole/**11**/$Rh_2(esp)_2$ = 1.1 mmol:0.5 mmol:0.5 mmol:1.5 μmol. See the Supporting Information for details. [b]Isolated yields.

enalcarbenoid **8** (R^1 = H, alkyl).[8] The transannulation of parent pyridazine *N*-oxide **9** (R^{1-3} = H) with methyl substituted pyrroles proceeded smoothly leading to 1-, 2-, and 3-methylindoles in good yield (**10ab**−**10ad**). With respect to substituted pyridazines, the reaction of 3- and 4- alkylpyridazine *N*-oxides with pyrrole proceeded regioselectively leading to 7- and 6-alkylindoles (**10ba**−**10da**). The moderate yields of **10ca** and **10da** are due to the highly unstable nature of the corresponding enaldiazo intermediates. It is noteworthy that a potential competitive 1,2-hydride shift in the alkyl substituted rhodium carbenoids was not observed in the transannulation reactions of 3-alkylpyridazine *N*-oxides.[9,11] In the case of 5-methylpyridazine *N*-oxide, the transannulation to **10ea** was inefficient probably due to the prevailing steric crowding during the reaction. Overall, the reaction allowed alkyl substituents at as many as six out of seven available positions on the indole nucleus.

The transannulation reaction was next evaluated with the 3-arylpyridazine *N*-oxides **9** (R^1 = Ar).[8] Interestingly, the reaction proceeded rapidly even without Brønsted acid **11**; however, it required 0.5 mol % of the rhodium catalyst. As shown in the Scheme 3, diverse 7-arylindoles[12,13] were obtained by the

Scheme 3. Scope of the Transannulation toward 7-Arylindoles[a,b]



[a]Reaction conditions: 9/pyrrole/$Rh_2(esp)_2$ = 0.93 mmol:0.37 mmol:1.85 μmol. See the Supporting Information for details. [b]Isolated yields.

regioselective transannulation with pyrroles involving an important class of donor−acceptor rhodium enalcarbenoid **8** (R^1 = Ar). The electronic nature of the aryl group has marginal influence on the transannulation. In general neutral, alkyl substituted and electron-deficient aryl groups gave comparable yields (**10fa**−**10ka** and **10ma**). The electron-rich aryl group

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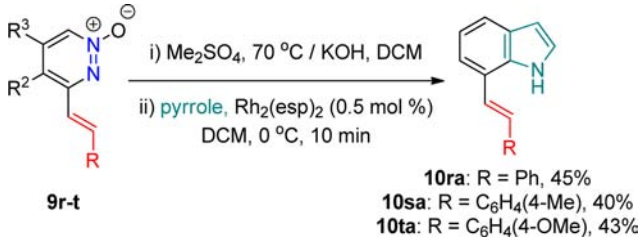
gave a slightly lower yield (**10la**) due to the highly unstable nature of the diazoenal intermediate. Polar groups such as F, CF_3, NO_2, and OMe (**10ia**–**10la**) are well tolerated. The reaction was sensitive to C-4 and C-5 substituents on the pyridazine. Although a C-4 methyl substituent was partially tolerated leading to 6,7-disubstituted indole **10na**, a C-5 methyl substituent severely hampered the transannulation (**10oa**) likely due to steric crowding. The ortho-methyl group on the aryl substituent was well tolerated (**10pa**). With respect to pyrroles, C-2 and C-3 alkyl pyrroles gave higher yields (**10fc**–**10ic**, **10mb**, **10fd**, **10hd**) compared to *N*-alkyl pyrrole (**10fb** and **10hb**).[14] *N*-Benzyl and electron-deficient pyrroles (*N*-Boc, *N*-Ts, 3-acetyl) remained unreactive in the transannulation reaction.

Interestingly, 3-vinylpyridazine *N*-oxides **9r**–**t** allowed us to investigate the reactivity of an unusual donor–acceptor type vinyl substituted rhodium enalcarbenoid **8** (R^1 = vinyl) sharing the features of both a vinylcarbenoid and an enalcarbenoid. Remarkably, transannulation of **9r**–**t** with pyrrole proceeded regio- and chemoselectively leading to 7-vinylindoles **10ra**–**10ta** (Scheme 4), through the preferential reactivity of the

Scheme 4. Scope of the Transannulation toward 7-Vinylindoles[a,b]

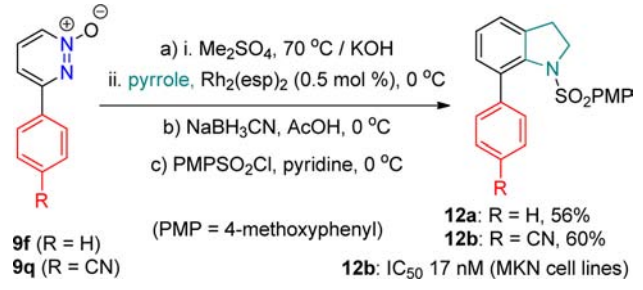


[a]Reaction conditions: **9**/pyrrole/$Rh_2(esp)_2$ = 0.93 mmol:0.37 mmol:1.85 μmol. See the Supporting Information for details. [b]Isolated yields.

enalcarbenoid moiety.[8,15] The moderate yields could be attributed to the rapid decomposition of the highly unstable vinyldiazoenal intermediate. The transannulation developed here constitutes a direct approach toward the 7-vinylindole core of biologically active raputindole B, luteorides A–C, and DG-041.[16]

The transannulation was successfully employed in the synthesis of 7-arylindoline based anticancer agents **12a,b** (Scheme 5).[8,17] Transannulation of **9f** and **9q** (R = H, CN) with pyrrole followed by reduction and *N*-sulfonylation gave indolines **12a** and **12b** respectively. It is noteworthy that 4-(1-((4-methoxyphenyl)sulfonyl)indolin-7-yl)benzonitrile **12b** (R = CN) is known to have potent antiproliferative activity against

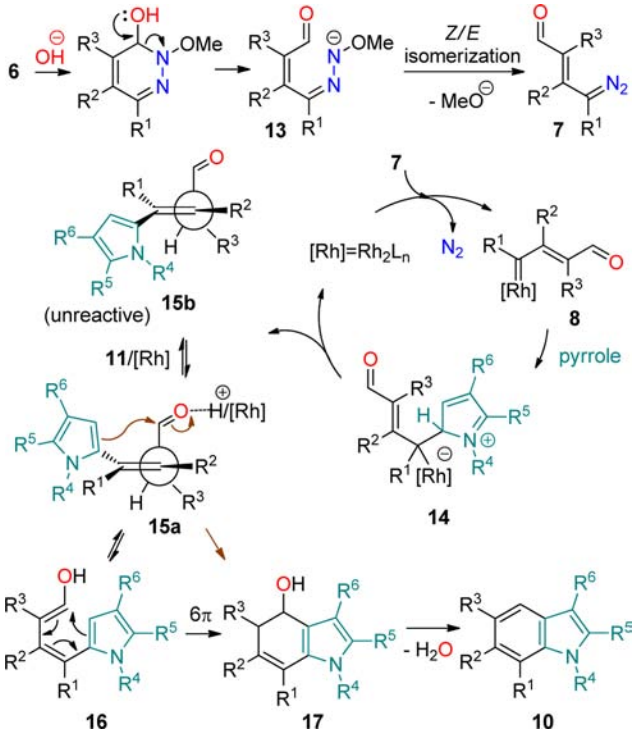
Scheme 5. Synthetic Applications of Transannulation



a variety of human cancer cell lines, including MDR resistant KB-vin10 lines with IC_{50} values ranging from 17 to 32 nM.

As shown in Scheme 6, a plausible mechanism for the transannulation was proposed. Initially, base-mediated ring

Scheme 6. Proposed Mechanism of Transannulation



opening of pyridazinium salt **6** followed by *Z*/*E* enal isomerization and loss of methoxide in **13** leads to the (*E*)-enaldiazo compound **7**.[5] Rhodium-catalyzed denitrogenation of **7** to the transient (*E*)-enalcarbenoid **8** followed by rapid regioselective C-2 functionalization of pyrrole gives the zwitterion **14**. Subsequent proto-demetalation of **14** leads to the isomeric (*E*)- and (*Z*)-4-pyrrolyl-3-butenal intermediates **15a,b**.[8] Intramolecular Friedel–Crafts reaction of the reactive isomer **15a** either by the assistance of a rhodium catalyst or by DPP **11** gives dihydroindole **17**. Finally, dehydration of **17** delivers the indole **10**. In the case of 3(*H*)- and 3-alkylpyridazines (R^1= H, alkyl), the sterically less hindered unreactive isomer **15b** predominates. Hence, the DPP assisted isomerization to the strained reactive isomer **15a** facilitates the transannulation. However, in the case of 3-aryl and 3-styrylpyridazines (R^1 = Ar, styryl), both **15a** and **15b** will be in rapid equilibrium as they experience similar 1,3-allylic strain due to the sterically crowded pyrrole and aryl/styryl substituents on the allylic C-1 carbon. Therefore, relief of strain due to the intramolecular cyclization of the strained reactive isomer **15a** accelerates the transannulation reactions of the 3-aryl and 3-styrylpyridazines, without the need for **11**. An alternative mechanism involving 6π-electrocyclization of trienol **16** also leads to **10**.[4a]

In summary, we have demonstrated that pyridazine *N*-oxides are versatile precursors for the metallocarbenes. The synthetic importance of the novel acceptor and donor–acceptor rhodium enalcarbenoids has been successfully demonstrated in the rhodium-catalyzed transannulation of pyridazine *N*-oxides with pyrrole to diverse alkyl, 7-aryl, and 7-vinyl substituted indoles.

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Transannulation was used in the synthesis of a potent anticancer agent. Complementary to our recently reported diacceptor enalcarbenoids, the pyridazine derived acceptor and donor−acceptor enalcarbenoids are expected to impart unique reactivity in various metal-catalyzed carbene transfer reactions. We hope that the new pyridazine derived diverse enalcarbenoids, and the transannulation reaction will find wide applications in synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03064.

Optimization studies, experimental procedures, characterizations, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

X-ray data for **10fc** (CIF)

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Notes

The authors declare no competing financial interest.

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