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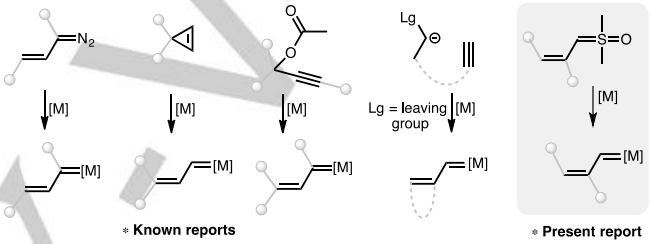
Iron-Catalyzed Carbenoid Transfer Reactions of Vinyl Sulfoxonium Ylides: An Experimental and Computational Study**

Janakiram Vaitla,* Annette Bayer and Kathrin H. Hopmann*

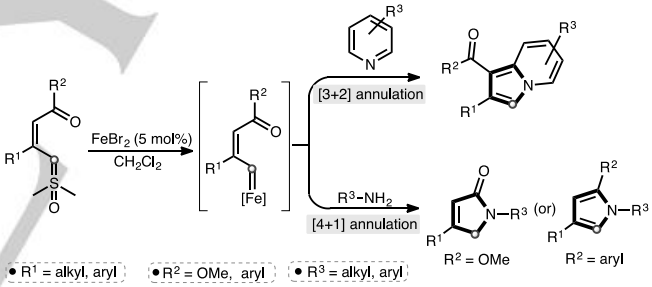
Abstract: *A method for the generation of unprecedented vinyl carbenoids from sulfoxonium ylides has been developed and applied in the synthesis of a diverse array of heterocycles such as indolizines, pyrroles, 3-pyrrolin-2-ones, and furans. The reactions proceed under FeBr2 catalysis at mild reaction conditions with a broad substrate scope. A reaction pathway involving iron carbenoids is proposed based on a series of control experiments and DFT calculations.*

Sulfoxonium ylide-derived metal carbenoids have been explored for X-H (X = N, S, O, C) insertions,[1] and have even been optimized at industrial scale for the production of drug candidates.[2] Despite this recent progress, several challenges need to be addressed to improve the versatility of these ylides in metal catalysis: First, metal-catalyzed sulfoxonium ylide reactions are still restricted to α-keto sulfoxonium ylides only. Second, although these ylides can generate carbenoids with noble metals (Rh, Ir, Au, Ru, Pt, etc.), base metals (for eg: Cu, Fe) have been unsuccessful so far.[1a] Third, sulfoxonium ylide reactions have not been explored beyond X-H insertion reactions. Moreover metal-accelerated competitive homo-coupling of sulfoxonium ylides[1b] restricts the further investigation of these ylides in carbenoid transfer reactions. In fact, the reactivity of sulfoxonium ylides (R-C=SO) are influenced by the substituents adjacent to the ylide carbon.[3] Thus, we hypothesized that structural changes of the sulfoxonium ylides could modulate the generation and reactivity of the corresponding carbenoids[4] and thereby expand their applicability in carbenoid transfer reactions in organic synthesis.[5] Further, from the perspective of sustainable chemistry, it is highly desirable to explore more economic and environmental friendly metal alternatives to catalyze these ylide transformations under mild reaction conditions.[6] With this objective in mind, we embarked on the development of vinyl sulfoxonium ylides, which can serve as unique four-carbon synthons for the generation of vinyl carbenoids.

Over the past two decades, there has been substantial progress in employing vinyl carbenoids for the construction of heterocycles and carbocycles.[7] The presence of an active carbenoid carbon and olefin in their structural framework provides a rich and versatile chemistry. In this area, vinyl diazo compounds have occupied the majority of the current landscape of vinyl carbenoid reactions via cycloadditions [(3+2), (4+2), (3+3)] and annulations with various nucleophiles.[8] However, identifying sustainable and safe alternatives for the generation of vinyl carbenoids has attracted great attention.[9] In this regard, non-diazo starting materials such as cyclopropenes,[10] propargylic esters[11] and alkynes[12] have been explored but they are still rarely used (Scheme 1). Despite significant achievements in this area, to our knowledge, there are no reports on iron-catalyzed vinyl carbenoid transformations.[13]



Scheme 1. Generation of vinyl carbenoids.



Scheme 2. Synthesis of heterocycles from vinyl sulfoxonium ylides.

Herein, we report a new strategy to generate Z-selective vinyl carbenoids from sulfoxonium ylides using $FeBr_2$ as catalyst. This strategy is successfully applied in the synthesis of heterocycles such as indolizines, pyrroles and 3-pyrrolin-2-ones under mild reaction conditions (Scheme 2). In particular, we were interested to synthesize indolizines, which are known to display important biological activities, including antitumor, anti-inflammatory and antiviral effects.[14] We initiated our investigations for the synthesis of indolzine **3a** using pyridine and vinyl sulfoxonium ylide **1a**,[15] by screening various iron-based catalysts [(TPP)FeCl, Hemin, FeX_3 (X= Cl, Br, OTf), FeX_2 (X = Cl, Br)] and other catalysts (Cu, In, Ni, Zn, Ir).[16] The best results were obtained with pyridine (1.5 equiv), vinyl sulfoxonium ylide **1a** (1.0 equiv) and $FeBr_2$ (5 mol%) in CH_2Cl_2 as solvent at rt for 16 h, providing the desired indolizine **3a** in 82% yield. Although the reaction also was successful under Cu and Ir catalysis with good yields (77% and 78% respectively), the side product 2-methoxy furan **5a** (Scheme 5) was unavoidable under these conditions. With suitable reaction conditions in hand, we investigated the substrate scope of the method (Scheme 3). A range of vinyl sulfoxonium ylides and pyridine analogues were

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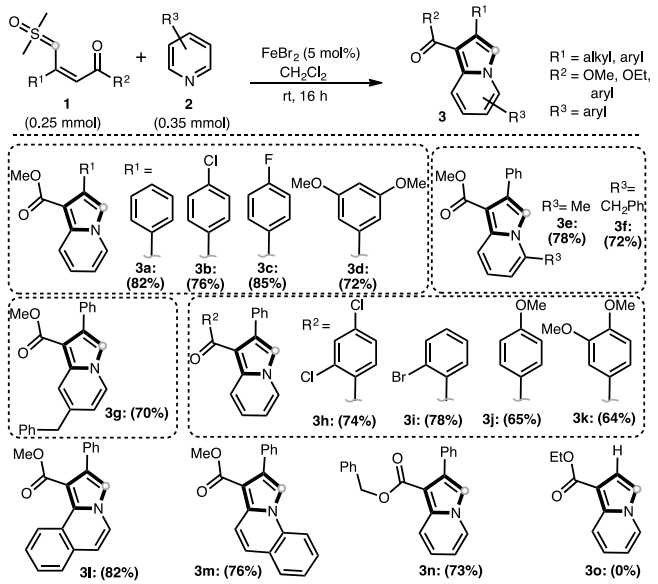
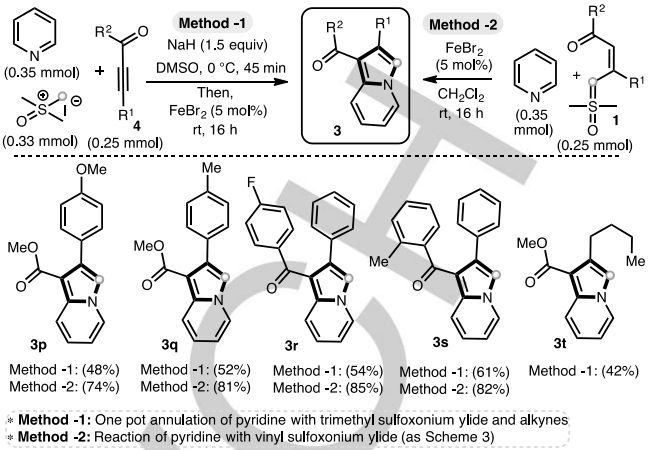
efficiently transformed to their corresponding indolizines **3a−n** in moderate to good yields (64−85%).



Scheme 3. Scope of Iron-catalyzed synthesis of indolizines.

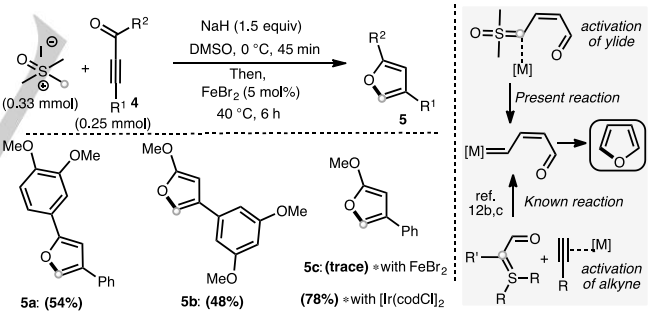
Sulfoxonium ylides having electron-donating or halo substituents (F, Cl, Br) on the *ortho-, meta-* and *para-* positions of the benzene ring of **1** underwent smooth cyclization, resulting in the formation of the corresponding indolizine products. Vinyl sulfoxonium ylides with esters as acceptor groups (R^2 = OMe, Scheme 3) are more reactive and afforded good yields of corresponding indolizines **3a-3d** compared to ketones as acceptor (R^2 = aryl) groups **3h-3k**. With respect to the stability of **1**, ketone acceptors on vinyl sulfoxonium ylides are more stable (bench stable solids) than ester acceptors (stable at 2–8 °C). Preparation of ylides **1** (see SI, Scheme S1) with electron-poor aryl substituents (R^1 = ester, cyano, keto, nitro substituted aryl groups) was unsuccessful and therefore, carbenoid transfer reaction of this class of substrates was not studied further. Indolizines with electron-donating aryl substituents (**3d, 3j, 3k**) were obtained in marginally lower yields. The reaction also afforded pyrroloisoquinolines (**3l**, 82%) and pyrroloquinolines (**3m**, 76%), scaffolds found in bioactive compounds like the lamellarins (a family of anticancer marine alkaloids)[17] and caspase activators[18] respectively.

We further investigated a one-pot approach for the formation of indolizine **3** from *in situ* generated ylide **1** (Scheme 4, method 1). Reaction of pyridine, alkyne **4** and dimethylsulfoxonium methylide (*in situ* generated from trimethylsulfoxonium iodide with NaH) in DMSO, followed by addition of $FeBr_2$ catalyst, provided indolizine **3**. The yields of the one-pot approach (method 1) are low compared to the reaction with isolated ylide **1** (Scheme 4, method 2). However, in situ generated aliphatic substituted ylide **1** (R^1 = *n*-butyl), which is difficult to isolate, can be directly converted to **3t**. It is particularly intriguing to note that the one-pot generation of sulfoxonium-derived vinyl carbenoids (method 1) provides a more facile strategy than the multistep synthesis involving diazo-derived enal carbenoid.[19]



Scheme 4. Scope of one-pot Iron-catalyzed synthesis of indolizines.

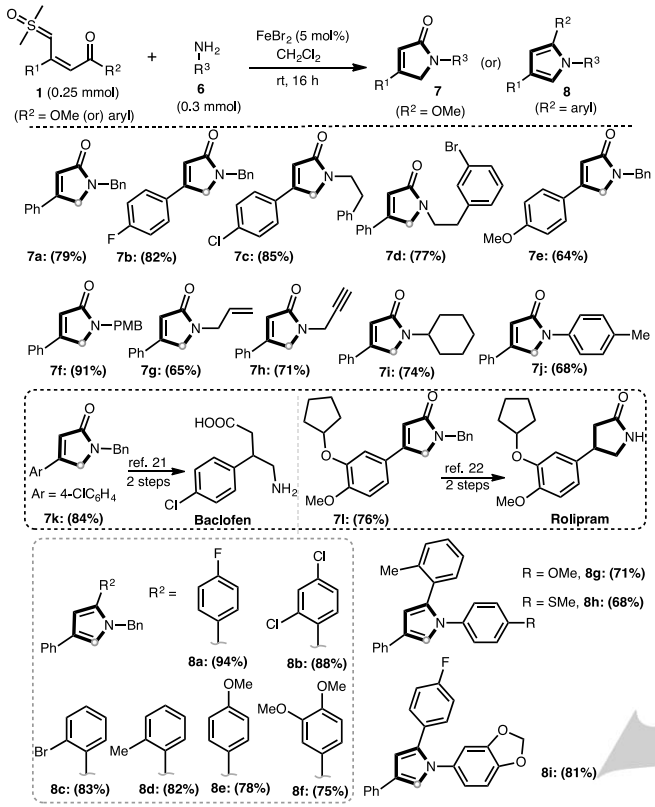
We extended our study to evaluate the reactivity of sulfoxonium ylide-derived carbenoids in absence of pyridine. One pot reaction of *in situ* generated dimethylsulfoxonium methylide with alkynes (with EDG groups on aryl substituents) in DMSO, followed by addition of $FeBr_2$ catalyst, gave furans **5a** (54%) and **5b** (48%) (Scheme 5). Although, the reaction is substrate selective and failed to afford furan **5c** under $FeBr_2$ catalysis,[20] it was successful in the presence of 2 mol% of $[Ir(cod)Cl]_2$ and yielded **5c** in 78% yield after 2 h, at rt. In 2012, the groups of Skrydstrup[12b] and Maulide[12c] generated furans via coupling of cationic Au(I) complex-activated alkynes with nucleophilic stable sulfoxonium ylides. In our method, the relevant metal carbene intermediates are probably formed via activation of vinyl sulfoxonium ylide **1** with $FeBr_2$.



Scheme 5. One pot reaction for furan synthesis.

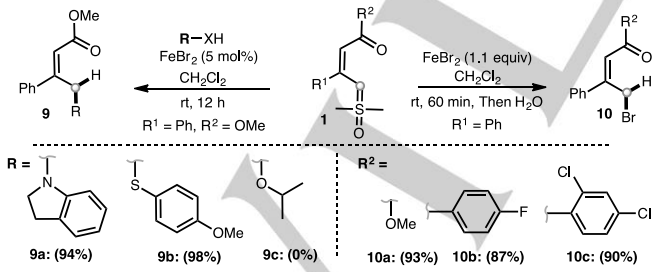
Next, to further broaden the scope of vinyl sulfoxonium ylides **1**, we envisioned N-H insertion of ylide **1** with primary amines (Scheme 6). Although, metal-catalyzed N-H insertions of α-keto sulfoxonium ylides are known,[1a-e] sustainable metal catalysts have so far not been applicable for this transformation. Treatment of ylides **1** with ester groups (R^2 = OMe) with amines **6** in the presence of $FeBr_2$ (5 mol%) afforded 3-pyrrolin-2-ones (**7a - 7l**) in reasonable yields (64-91%). Notably, allyl and propargyl amines were effectively converted to the corresponding products 3-pyrrolin-2-ones (**7g, 7h**) without cyclopropanation of the unsaturated bonds by intermediate metal carbenoids. The products **7k** and **7l** are reported intermediates in the syntheses of the pharmaceuticals Baclofen[21] and Rolipram[22], respectively. Analogously, treatment of ylides **1** with ketone substituents (R^2 =

Aryl) under the same conditions gave pyrroles (**8a – 8i**, Scheme 6).



Scheme 6. Scope of iron-catalyzed synthesis of 3-pyrrolin-2-ones and pyrroles.

The present approach transforms simple primary amines and ylide **1** to pyrroles with a cheap, sustainable catalyst under mild reaction conditions, whereas previous reports required enamides, α-keto sulfoxonium ylides and a precious metal catalyst at high temperatures.[1d] The X-H insertion of ylide **1** is also successful with secondary amines and thiols with excellent yields (Scheme 7). Treatment of vinyl sulfoxonium ylide **1** with 1.1 equiv of $FeBr_2$ afforded allyl brominated compounds **10a – 10c** in 87-93% yields.



Scheme 7. X-H insertion insertion and bromination of ylide **1**.

Although, iron-catalyzed diazo-derived carbenoid transfer reactions are known,[23] the unexpected formation of an allyl bromide **10** led us to postulate the involvement of an iron carbene in the mechanism (Scheme 2), which may form a bromide intermediate via metal halo exchange.[24] We carried out several control experiments,[16] however, these did not provide conclusive evidence about the underlying mechanism. To our knowledge, there are no mechanistic investigations on iron carbenoids generated from non-Iron(III)corrole/phorphyrin catalyst to compare our hypothesis too. We therefore turned to performing computational studies, in order to establish plausible intermediates of the reaction of sulfoxonium ylide **1a** with pyridine, catalyzed by $FeBr_2$ in CH_2Cl_2 (Scheme 3). Calculations were performed at the PBE-D3/6-311G(d,p),IEFPCM(DCM) level of theory (for optimized coordinates, see SI).[25],[26],[27] Gibbs free energies were calculated at 298 K. In our computations, the $FeBr_2$ complex prefers a quintet (S = 2) spin state, both in absence of other ligands and with **1a** bound (Table S1 and S2, SI). During the reaction, we anticipate that pyridine may also coordinate to iron, generating the reactant complex Fe-Sub-Pyr (Fig. 1).

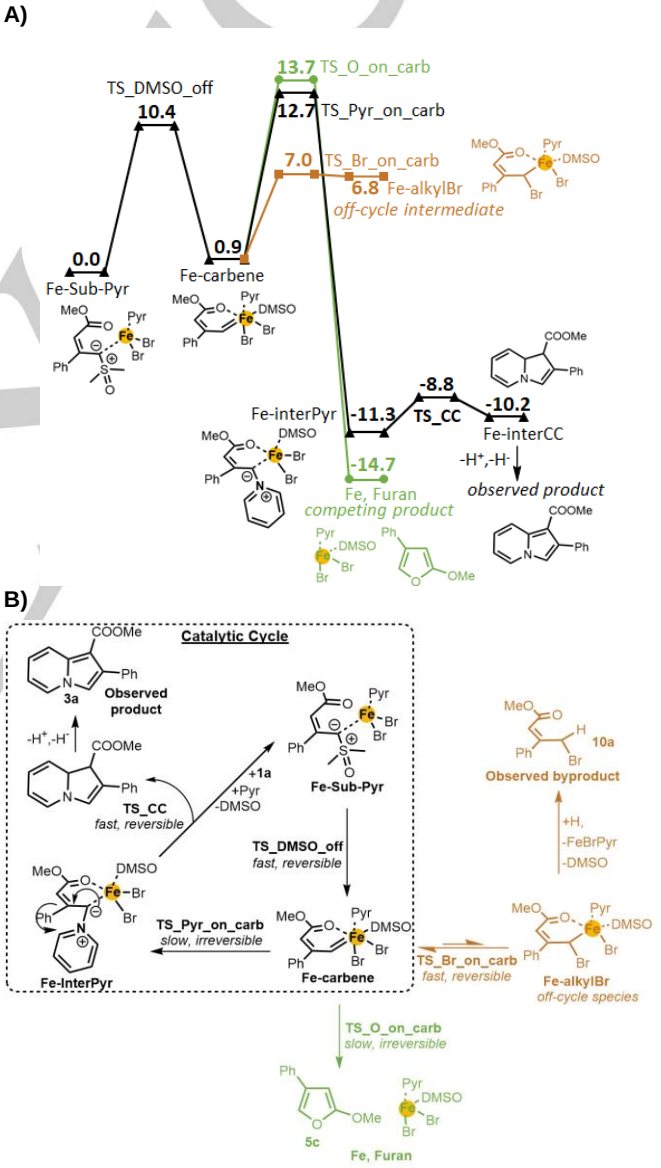


Figure 1. A) Computed free energies for the $FeBr_2$-catalyzed reaction of **1a** with pyridine (PBE-D3/6-311G(d,p),IEFPCM, kcal/mol, 298 K), ***B)*** Computed mechanism for the $FeBr_2$-catalyzed reaction of **1a** with pyridine (Sub = **1a**).

The iron-coordinated **1a** easily looses DMSO (TS_DMSO_off, barrier 8.4 kcal/mol, Fig. 1A) to form an Fe-carbene (0.9 kcal/mol

above Fe-Sub-Pyr, Fig. 1A). Direct attack of Br onto **1a** was not successful in our calculations. This result, including the low barrier for DMSO dissociation, indicates that Fe-carbene formation is the initial step of the reaction. The carbene can then undergo intermolecular attack by the nucleophiles Br or pyridine. Attack by Br has a low barrier (TS_Br_on_carb, 6.1 kcal/mol relative to the Fe-carbene) and leads to an unstable Fe-alkylBr intermediate (5.8 kcal/mol above Fe-carbene, Fig. 1A). We conclude that the brominated alkyl species **10a** observed in experiments (Scheme 7) is formed from the off-cycle Fe-alkylBr intermediate, which is in rapid equilibrium with the on-cycle iron-carbene. Attack of pyridine on the carbene has a higher barrier than Br attack, 11.8 kcal/mol relative to the Fe-carbene (TS_Pyr_on_carb, Fig. 1A). However, the resulting intermediate is low in energy (-12.2 kcal/mol below the carbene), making this step irreversible. Subsequently, very fast C-C bond formation occurs (barrier of only 2.5 kcal/mol, Fig. 1A). The cyclized intermediate may undergo loss of a hydride and a proton to form the final aromatized product[8b] observed in our experiments (Scheme 3). The overall mechanism, as deduced from our computations and in agreement with our experimental observations, is shown in Fig. 1B.

It can be noted that iridium-carbenes in similar reactions readily form a furan-type product (Scheme 5), which originates from intramolecular oxygen attack on the carbene. With iron-carbenes, we observed furans (**5a, 5b**) from substrates with electron-rich aryl groups, however, **1a** only provided trace amounts of the corresponding furan **5c** in experiments (Scheme 5). In our calculations, the barrier for O-C bond formation is 1 kcal/mol above the barrier for pyridine attack (Fig. 1A). We believe that the two processes (intramolecular oxygen vs. intermolecular pyridine attack on the carbene) are in competition and that small changes in the substrate may result in kinetic preference for one pathway over the other. For substrate **1a,** pyridine attack on the carbene is kinetically preferred, as supported by both experiment and computation.

In summary, we have reported a novel strategy for the catalytic generation of iron vinyl carbenoids from sulfoxonium ylides. The carbene intermediates can be efficiently trapped with pyridines and amines for the synthesis of heterocycles such as indolizines, pyrroles, and 3-pyrrolin-2-ones. In situ generation of S-ylide/Iron-carbenoid/N-ylide followed by annulation sequence to give a one-pot indolizine further demonstrates the efficiency of this method in vinyl carbenoid-mediated transformations. Notably, the present method generates Z-selective vinyl carbenoids from an inexpensive, low toxic, environmentally benign and air stable $FeBr_2$ catalyst. The mechanistic studies further disclosed the nature and reactivity of iron carbenoids generated with $FeBr_2$. We predict that our findings will open further avenues for the development of new catalytic transformations using vinyl sulfoxonium ylides.

Acknowledgements

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Keywords: Carbenoids • Sulfur ylides • Heterocycles • Iron catalysis • Indolizines

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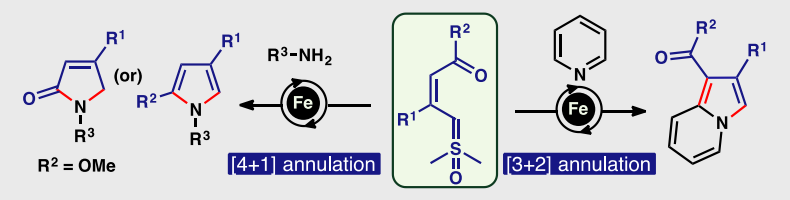

Metal-carbenoids: *A new method for vinyl carbenoid transfer using sulfoxonium ylides is reported. In situ generation of S-ylide/Iron-carbenoid/N-ylide followed by annulation to give a one-pot indolizine synthesis further demonstrates the efficiency of this method in vinyl carbenoid-mediated transformations.*

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