Multicomponent Reactions

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Stereoselective Synthesis of Tetrahydroindolizines through the Catalytic Formation of Pyridinium Ylides from Diazo Compounds

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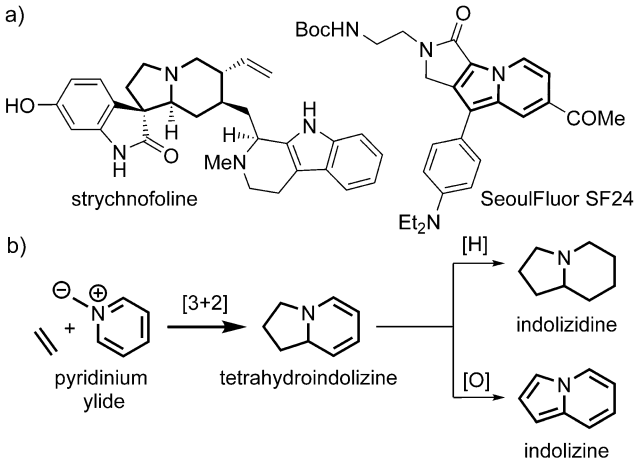
Abstract: *Commercially available iron(III) and copper(I) complexes catalyzed multicomponent cycloaddition reactions between diazo compounds, pyridines, and electrophilic alkenes to give alkaloid-inspired tetrahydroindolizidines in high yield with high diastereoselectivity. Hitherto, the catalytic formation of versatile pyridinium ylides from metal carbenes has been poorly developed; the broad utility demonstrated herein sets the stage for the invention of further multicomponent reactions in future.*

Indolizidines are found in many bioactive alkaloids,[1] whereas their unsaturated indolizine counterparts have valuable photochemical properties.[2,3] Both structures are valued for their therapeutic potential.[4–6] Spirooxindoles have also been identified as privileged scaffolds for drug discovery.[7] Efficient and versatile routes toward these structural motifs are therefore highly desirable.

The convergent synthesis of tetrahydroindolizidines is possible by 1,3-dipolar cycloaddition of pyridinium ylides with electrophilic alkenes. The resulting products may then be converted into indolizines by oxidation,[8–10] or into indolizidines by reduction or other types of functionalization (Scheme 1).[11,12]

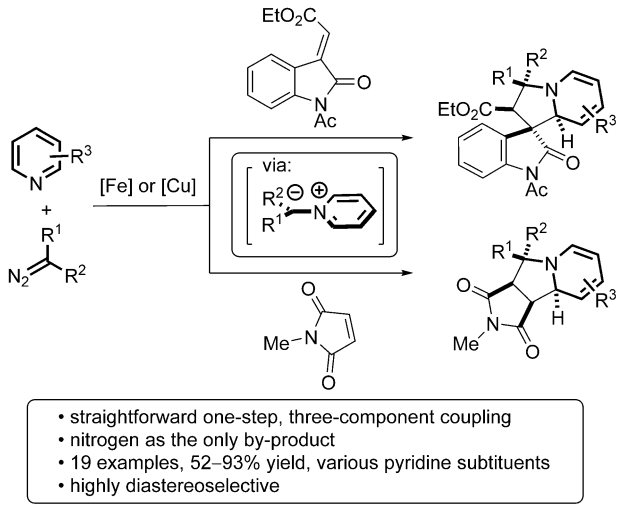
Typically, pyridinium ylides are formed by deprotonation of the corresponding salts, but this method produces stoichiometric conjugate-acid waste and usually requires a separate alkylation step to prepare the pyridinium salts. Such drawbacks significantly restrict the utility of otherwise versatile synthetic intermediates.

In principle, catalytic reactions that directly transform pyridines into their corresponding ylides under aprotic conditions, and in the presence of electrophilic alkenes, open up the prospect of more powerful multicomponent reactions to prepare tetrahydroindolizidines. The addition of Lewis bases to metal carbenes to form ylides has been widely developed for synthesis,[13–20] but there are few reports of catalyzed reactions of pyridines with diazo compounds.[21,22] The generation of pyridinium ylides in this way has received surprisingly little attention; in fact, we could find only a single example of this type of catalyzed three-component reaction to form an indolizine.[23]



Scheme 1. a) Examples of an indolizidine-containing alkaloid and an indolizine dye; b) a cycloaddition route to tetrahydroindolizidines.

Herein, we describe a new, multicomponent reaction that produces highly functionalized tetrahydroindolizidines in good yields with generally excellent diastereoselectivity (Scheme 2). These reactions involve the catalytic generation of pyridinium ylides via metallocarbenes and in situ cycloaddition with electrophilic alkenes. This highly efficient route generates nitrogen as the only by-product. The reaction



Scheme 2. Formation of pyridinium ylides and their use for the synthesis of indolizidines.

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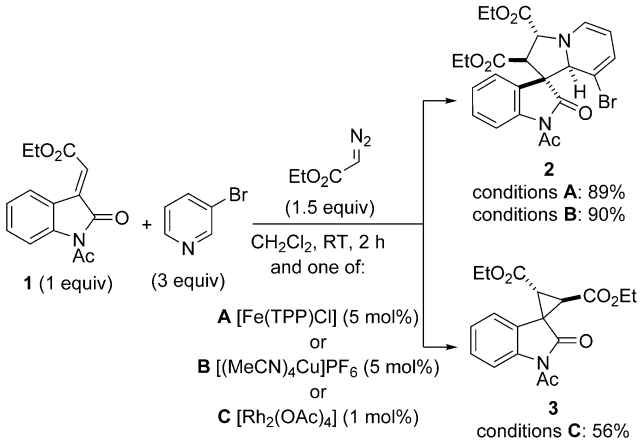
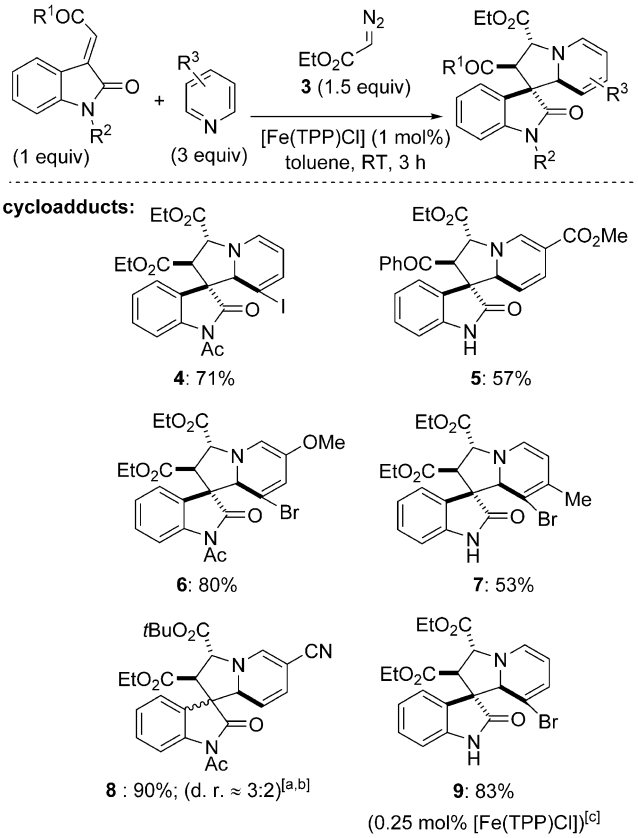


Scheme 3. Rhodium-, copper-, or iron-catalyzed reaction of 3-bromopyridine, ethyl diazoacetate, and ethyl (*E*)-2-(1-acetyl-2-oxoindolin-3-ylidene)acetate (**1**).

outcome depends critically on the choice of catalyst (Scheme 3), the most effective being commercially available complexes derived from the abundant base metals iron(III) or copper(I).

We first examined the reaction between 3-alkenyloxindole **1**, 3-bromopyridine, and ethyl diazoacetate with various catalysts (Scheme 3). Satisfyingly, tetrahydroindolizidine **2** was obtained as the sole product in good yield (89–90%) as a single diastereoisomer when 5 mol% of either [Fe(TPP)Cl] (TPP = tetraphenylporphyrin) or $[(MeCN)_4CuPF_6]$ was used. The NMR data of **2** suggested that the sense of diastereoselectivity was the same as that for related products prepared by conventional base-promoted ylide formation.[24] However, cyclopropane **3** was obtained as the only product when $[Rh_2(OAc)_4]$ (1 mol%) was used as the catalyst. A catalyst loading of 1 mol% of [Fe(TPP)Cl] in toluene led to similar yields of **2** (89%), so these conditions were chosen for further studies.

Next, reactions were performed with a variety of pyridines (Scheme 4). Good yields were generally observed with electron-withdrawing groups at the 3-position of the pyridine. For example, 3-iodopyridine reacted with oxindole **1** analogously to 3-bromopyridine to produce tetrahydroindolizine **4** in similarly good yield (71%). A reaction of ethyl diazoacetate, methyl nicotinate, and 3-phenacylideneoxindole gave cycloadduct **5**, albeit in lower yield (57%). In general, yields were not significantly affected if the 3-alkenyloxindole nitrogen atom was unprotected. Bromopyridines featuring another substituent were also effective reagents. For example, cycloadducts **6** and **7** were prepared in 80 and 53% yield from 3-bromo-5-methoxypyridine and 3-bromo-4-methylpyridine, respectively. The reaction of 3-cyanopyridine with *tert*-butyl diazoacetate and oxindole **1** gave a mixture of two diastereoisomers **8** in 90% combined yield and with a diastereomeric ratio of about 3:2, the minor component corresponding to inversion of the spirocenter.[24] Subsequently, a reaction performed on a 1.3 mmol scale with 0.25 mol% of [Fe(TPP)Cl] gave cycloadduct **9** in good yield (83%); the yield decreased to 25% when a lower catalyst loading (0.1 mol%) was used.

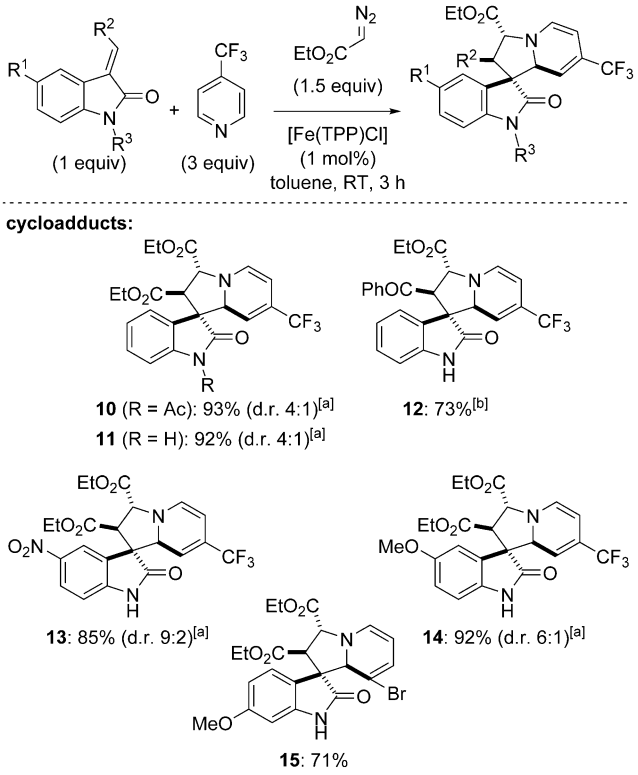


Scheme 4. Synthesis of tetrahydroindolizidines from pyridines. [a] Synthesized from *tert*-butyl diazoacetate. [b] Ratio based on the yield of each diastereoisomer (isolated products). [c] The reaction was carried out on a 1.3 mmol scale with 0.25 mol% of [Fe(TPP)Cl].

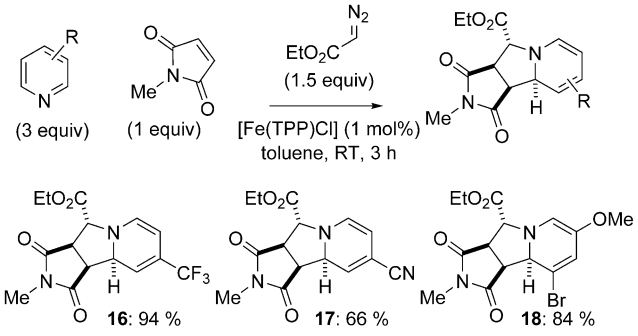
The reaction of 4-trifluoromethylpyridine with various oxindoles was next evaluated (Scheme 5). Cycloadducts **10** and **11** were obtained in excellent yield from **1** or the deacetylated equivalent, respectively (d.r. ≈ 4:1).[25] (*E*)-3-Phenacylideneoxindole was also an effective substrate, and was converted into tetrahydroindolizidine **12** in 73% yield as a single diastereoisomer. Notably, (*Z*)-3-phenacylideneoxindole gave cycloadduct **12** with the same sense of diastereoselectivity in comparable yield. Substrates containing electron-withdrawing ($R^1 = NO_2$) or electron-donating groups (R^1 = OMe) at the 5-position of the oxindole were tolerated, and reacted to give products **13** (85% yield) and **14** (92% yield), respectively. Similarly, cycloadduct **15** was obtained as a single diastereoisomer in 71% yield.

Reactions with different electrophilic alkenes were equally productive. Thus cycloadducts **16**–**18** were obtained in good yields as single diastereoisomers from reactions of *N*-methylmaleimide with 4-trifluoromethylpyridine (94%), 4-cyanopyridine (66%), and 3-bromo-5-methoxypyridine (84%), respectively (Scheme 6).

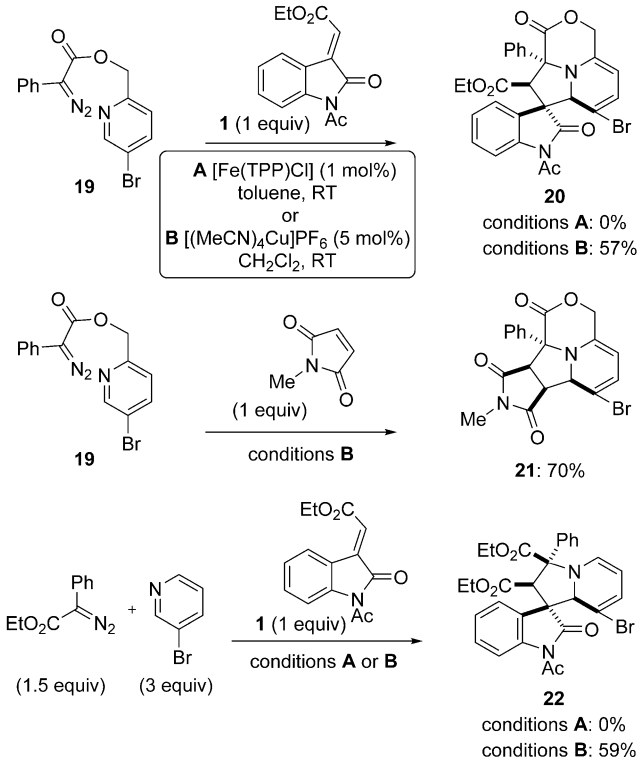
Alternative diazo precursors were investigated with a view to broadening the range of alpha-substituted pyridinium ylides available. Pyridine **19** derived from diazophenylacetic acid did not undergo cyclization with oxindole **1** in the presence of catalytic [Fe(TPP)Cl] in toluene (Scheme 7). However, use of the precatalyst $[(MeCN)_4Cu]PF_6$ (5 mol%)



Scheme 5. Synthesis of tetrahydroindolizidines from various 3-alkenyloxindoles. [a] The diastereomeric ratio was determined by NMR analysis. [b] Synthesized from either (*E*)-3-phenacylideneoxindole or (*Z*)-3-phenacylideneoxindole.

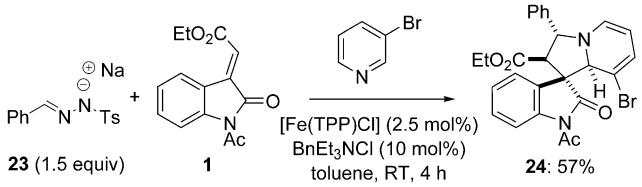


Scheme 6. Synthesis of tetrahydroindolizidines from *N*-methylmaleimide.



Scheme 7. Synthesis of tetrahydroindolizidines from α-branched diazo compounds.

The in situ generation of diazo compounds from tosylhydrazone salts[27] was briefly investigated, and cycloadduct **24** was formed in promising yield (57%) from a reaction of benzylidene hydrazone salt **23** (Scheme 8). This benign reactivity and broad range of possible tosylhydrazones encourages detailed future investigation.

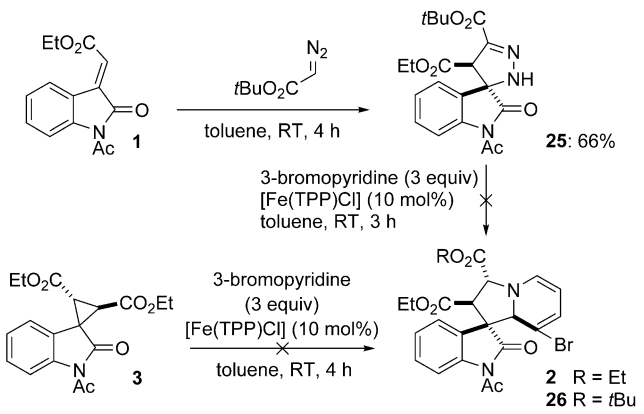


Scheme 8. Synthesis of tetrahydroindolizidine **24** from a diazo compound generated in situ.

in CH_2Cl_2, which previously gave product **2** in high yield (Scheme 3), led to cycloadduct **20** in 57% yield. Cycloadduct **21** was obtained in 70% yield following treatment with *N*-methylmaleimide.

Similar results were obtained for intermolecular ylide generation from ethyl diazophenylacetate; $[(MeCN)_4Cu]PF_6$ gave cycloadduct **22** in 59% yield, but no cycloadduct was produced with [Fe(TPP)Cl]. All cycloadducts **20**–**22** were obtained as single diastereoisomers. Single-crystal X-ray diffraction of **22** revealed both ester groups to be on the same face, unlike in the preceding examples.[26]

Next, control experiments were conducted to rule out a noncatalyzed reaction pathway (Scheme 9). The reaction of *tert*-butyl diazoacetate with oxindole **1** in toluene at ambient temperature only gave the spiropyrazole cycloadduct **25** (66%).[26] Similar pyrazoles have been reported to contract to cyclopropanes upon heating,[28–30] but this possibility was ruled out when starting materials were returned upon the treatment of spiropyrazole **25** with 3-bromopyridine and [Fe(TPP)Cl] (10 mol%) in toluene at room temperature. Cyclopropanes could also undergo non-catalyzed ring expansion with pyridine,[31,32] but only starting materials were obtained from

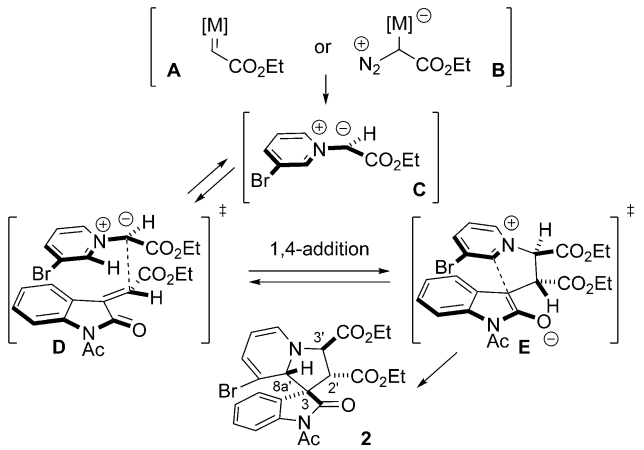


Scheme 9. Control experiments.

a reaction of cyclopropane **3** under the latter reaction conditions.

These control experiments reinforce the idea that nucleophilic pyridines add to a metal carbene **A** or diazonium ylide **B** to give a pyridinium ylide **C** (Scheme 10). The formation of cycloadduct **12** regardless of the configuration of the starting oxindole suggests a stepwise mechanism involving 1,4-addition of the pyridinium ylide to the alkenyloxindole via transition state **D**, followed by cyclization of a zwitterionic intermediate via transition state **E**. The observed *anti* relative configuration of the ester groups at C3′ and C2′ in the products can be explained by minimized dipole–dipole repulsions between the respective carbonyl groups in transition state **D**.[33] The relative configuration of the spirocyclic center (C3) and ring junction (C8a′) in the cycloadducts can be explained by an attractive interaction between the electron-deficient pyridinium ring and electron-rich oxindole during ring-closing step **E**.

In conclusion, we have developed iron- and copper-catalyzed stereoselective reactions of pyridines, diazo compounds, and electrophilic alkenes that enable the efficient synthesis of alkaloid-like tetrahydroindolizidines, which are a privileged scaffold for drug discovery.[7] An important observation is that the production of pyridinium ylides from metal carbenes is general and compatible with multicomponent reactions, since this aprotic route to pyridinium ylides has received little attention to date. We envisage that these findings will stimulate the development of a much wider repertoire of reactions by variation of electrophile and catalysts.



Scheme 10. Proposed mechanism to rationalize the observed stereoselective formation of tetrahydroindolizidines through reactions involving the catalytic production of pyridinium ylides from diazo compounds.

Acknowledgements

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Keywords: carbenes · cycloaddition · diazo compounds · homogenous catalysis · pyridinium ylides

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