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A catalyst-controlled selective synthesis of pyridines and pyrroles†

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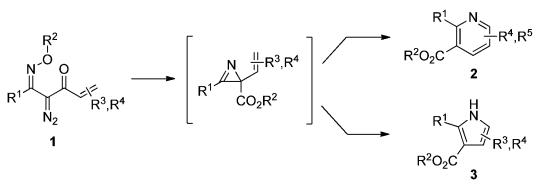
We have developed a dual reaction manifold that enables the selective synthesis of both pyridines and pyrroles from the common substrates α-diazo oxime ethers. The strong propensity of 1,3-dienyl nitrenes for 4π-electrocyclization to give pyrroles could be diverted to 6π-electrocyclization *via* a 1,6-hydride shift or prototropic isomerization, leading to the exclusive formation of pyridines by employing metal nitrene complexes derived from α-diazo oxime ethers under Rh(II) catalysis. Furthermore, an orthogonal catalytic system has been identified that promotes the selective formation of 1*H*-pyrroles from the same substrates by redirecting the reactivity of vinyl 2*H*-azirine intermediates.

Metal nitrenes have drawn considerable interest due to their diverse reactivity.[1–5] Catalytic C–H amination based on metal nitrenes has recently emerged as a powerful tool that allows the introduction of nitrogen functionality into inert C–H bonds and efficient access to a variety of synthetically important amino compounds.[6–13] Meanwhile, through a disparate mechanism, metal nitrenes derived from aryl and vinyl azides have been shown to provide facile access to indoles and other fused N-heterocycles,[14–19] which are core motifs in pharmaceuticals, natural products, and functional materials.[20–22] Recently, Driver *et al.* reported the synthesis of pyrroles and indoles by the metal-catalyzed rearrangement of 1,3-dienyl azides and aryl azides, respectively.[23,24]

Cascade reactions offer great advantages for organic synthesis with respect to the reduction of waste, step efficiency, and alleviating time and efforts in handling intermediates.[25–29] In this regard, we have described a catalytic cascade synthesis of pyrroles from α-diazo oxime ethers under Rh(II) catalysis.[30] Encouraged by these results, we became interested in the reactivity of 1,3-dienyl nitrenes as a platform for N-heterocycle synthesis, which could be readily accessible from α-diazo oxime ethers *via in situ* formation of 2*H*-azirines. These nitrene intermediates could potentially participate in two alternative pathways: (a) 4π-electrocyclization,[24,31] or (b) 6π-electrocyclization *via* a 1,6-hydride shift or prototropic isomerization. However, the strong propensity of 1,3-dienyl nitrenes for 4π-electrocyclization to give pyrroles intrigued us as to whether the modulation of the reactivity of nitrenes with an optimal transition metal catalyst would lead to an alteration of their chemoselectivity towards 6π-electrocyclization to provide pyridines.[32–45] In addition, the challenges included the identification of catalysts with the ability to catalyze sequential formations of metal carbenes and nitrenes from α-diazo oxime ethers in a consecutive catalytic cycle. Furthermore, the development of a catalytic platform that allows exclusive formation of either pyridines or pyrroles[46–53] from common substrates is highly desirable. Herein, we describe the successful development of such a reaction manifold [eqn (1)].



(1) (1)

We began our exploration for the synthesis of pyridines by screening various metal salts, employing α-diazo oxime ether **1a** as a substrate (Table 1).[53–56] The use of Cu(OTf) gave pyridine **2a** in a moderate yield, while Ag and Co catalysts resulted in the formation of a mixture of pyridine **2a** and pyrrole **3a** (entries 1–3). To further optimize the selectivity for pyridine, we examined Rh(II) complexes bearing ligands with different steric and electronic attributes (entries 4–7) and found that Rh(II) complexes with both electron withdrawing and sterically bulky ligands gave moderate yields. Gratifyingly, $Rh(OAc)_2$ provided pyridine **2a** in a 73% yield. The oxidation of dihydropyridine appears to be rapid as there was no observation of dihydropyridine.

With the optimized reaction conditions in hand, we proceeded to survey the scope of the reaction (Table 2). First, we examined the regioselectivity of the reaction by employing substrate **1b** bearing two different substituents (R^2 and R^3). The subjection of **1b** bearing methyl and isobutyl groups to the

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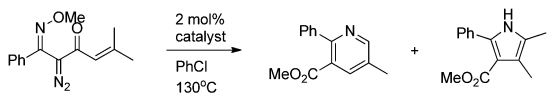
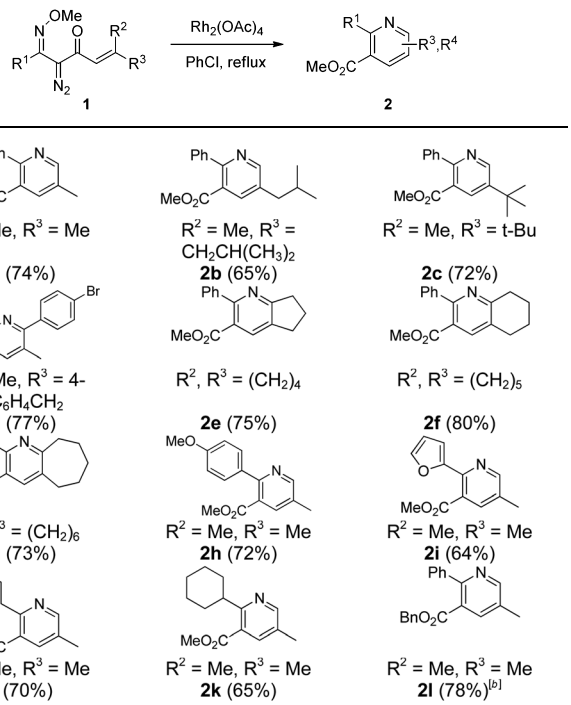
Table 1 Optimization of pyridine synthesis



Entry[a]	Catalyst[d]	Yield[b] [%] 2a	3a
1	Cu(OTf)	53	—
2	Ag(OAc)	25	38
3	$Co(OAc)_2$	28	31
4	$Rh_2(pfb)_4$	45	—
5	$Rh_2(Piv)_4$	57	—
6[c]	$Rh_2(esp)_2$	61	—
7	$Rh_2(OAc)_4$	73	—

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (2 mol%), PhCl (1.0 mL), 130 °C, 24 h. [b] NMR yields. [c] Methyl 2,2-dimethyl-5-phenyl-2*H*-pyrrole-4-carboxylate (16%). [d] pfb = perfluorobutyrate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, Piv = pivalate.

Table 2 Substrate scope of pyridine synthesis[a]

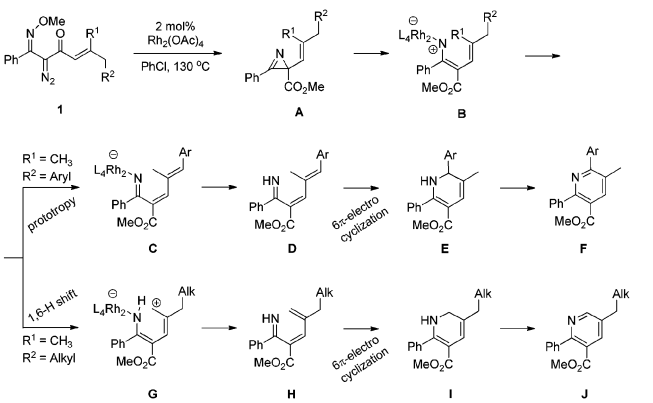


[a] Reaction conditions: **1** (0.2 mmol), catalyst (2 mol%), PhCl (2.0 mL), 130 °C, 24 h. [b] Benzyl oxime ether.

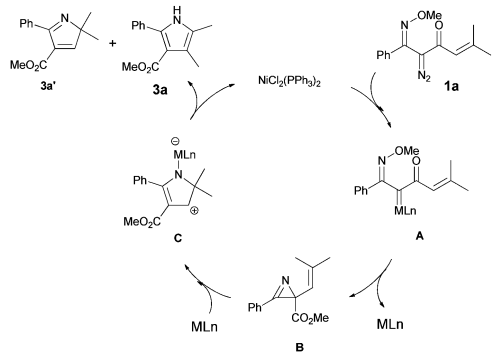
reaction conditions led to the formation of **2b** as a single isomer in which the C–N bond formation occurred at the methyl group, which is *syn* to the nitrene. To our surprise, **1d** bearing a *p*-bromobenzyl group in place of an isobutyl group gave **2d**, resulting from the reaction at the benzylic site. This observation clearly rules out a reaction mechanism based on a direct C–H insertion because of the geometric constraint, which prevents the nitrene from reacting at the benzylic site without prior isomerization. The potential isomerization during the formation of a 2*H*-azirine intermediate was ruled out by an examination of the alkene configuration of the isolated 2*H*-azirine intermediate (see ESI† for NOE experiment). From these experimental results, we propose that the reaction mechanism is dissected into thermodynamic and kinetic pathways depending on the type of substituents for R^2 (Scheme 1). For substrates where R^2 = aryl group, isomerization of the nitrene intermediate **B** to **C** *via* a prototropic isomerization of the benzylic proton provides a more thermodynamically stable 1-azatriene **D**. On the other hand, for those where R^2 = alkyl group, a 1,6-hydride shift from the substituents *syn* to the nitrenes is favored to afford kinetic 1-azatriene **H**.

A variety of fused bicyclic pyridines were readily prepared in good yields by incorporating the desired size of ring into different alkenes (Table 2, **2e–g**). We also examined the tolerability of the R^1 group and found that various types of substituents could be accommodated (**2h–k**). The reaction with substrates bearing electron-rich aryl (**1h**) and heteroaryl (**1i**) groups proceeded smoothly to give the corresponding pyridines in 72% and 64% yields, respectively. Also, those with vinyl and alkyl groups reacted well to give pyridines (**2j** and **2k**, respectively). Different esters can be prepared by employing corresponding oxime ethers. Thus, pyridine with a benzyl ester (**2l**) could be prepared in good yield by using benzyl oxime ether.

Next, we explored the feasibility of the synthesis of pyrroles from the same substrates, α-diazo oxime ethers. A successful catalyst would promote multiple sequential rearrangements initiated by the generation of carbenoid **A**, which undergoes rearrangement to give vinyl azirine **B**. The subsequent isomerization and substituent shift leads to the formation of 1*H*-pyrrole **3a** (Scheme 2). Due to the competitive formation of 2*H*-pyrrole **3a′**, the ability of a catalyst to promote the migration of the *gem*-substituents on intermediate **C** is crucial. While conversion was sluggish with Ni(0) providing the 2*H*-azirine intermediate as the major product (Table 3, entry 1), a substantial improvement was obtained by the use of Ni(II) catalysts along with concomitant formation of **3a′** (entry 2, 62%). While the addition of various ligands did not significantly

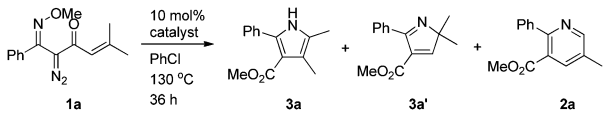


Scheme 1 Proposed reaction mechanism for pyridine formation.



Scheme 2 Proposed reaction mechanism for 1*H*-pyrrole formation.

Table 3 Optimization of pyrrole synthesis



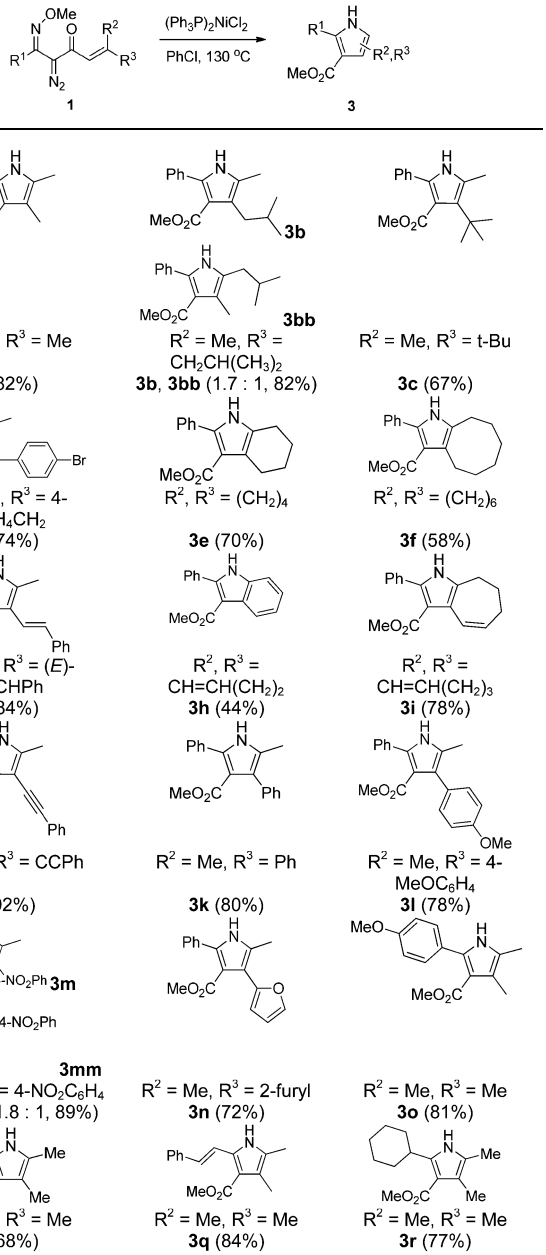
Entry[a]	Catalyst[f]	Yield[b] [%] 3a	3a′	2a
1[c,d]	$Ni(cod)_2/PPh_3$	10	11	—
2	$Ni(acac)_2$	62	13	—
3[e]	$Ni(acac)_2$/dppf	60	23	—
4[d]	$Ni(acac)_2$/dppe	60	6	—
5[e]	$NiCl_2$(dppp)	66	—	21
6[d]	$Ni(acac)_2/PPh_3$	78	—	—
7[d]	$Ni(acac)_2/P(o\text{Tol})_3$	67	6	—
8	$NiCl_2(PPh_3)_2$	82	6	—

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (10 mol%), PhCl (1.0 mL), 130 °C, 36 h. [b] NMR yields. [c] Methyl 2-(2-methylprop-1-en-1-yl)-3-phenyl-2*H*-azirine-2-carboxylate (72%). [d] 20 mol% ligand. [e] 10 mol% ligand. [f] cod = cyclooctadiene, acac = acetylacetonate, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino) propane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, *o*Tol = tri(*o*-tolyl)phosphine.

improve the yield, we were gratified to find that the use of $NiCl_2$ with PPh_3 as ligand gave **3a** in 82% yield (entry 8).

With the optimized conditions in hand, we surveyed the substrate scope of the synthesis of pyrroles (Table 4). Overall, the pyrrole formation proceeded smoothly with good to excellent yields. First, we examined the migratory aptitude of the germinal substituents of the intermediate 2*H*-pyrroles. While substrates bearing similar primary alkyl substituents resulted in the formation of a mixture (**3b** and **3bb**), selective migration was observed with more disparate substituents such as *t*-Bu and benzylic groups (**3c** and **3d**). In contrast to Rh(II) catalysis, it is of note that the formation of pyridine **2d** was completely suppressed under Ni(II) catalysis. Bicyclic pyrroles can be readily prepared by employing cyclic substrates (**3e**, **3f**, **3h**, and **3i**). Consistent with the migratory aptitude, vinyl groups (regardless of being acyclic or endocyclic) smoothly undergo migration over the alkyl groups (**3g–i**). It is noteworthy that an indole **3h** was formed through spontaneous oxidation. Likewise, an alkyne

Table 4 Substrate scope of pyrrole synthesis[a]



[a] Reaction conditions: **1** (0.2 mmol), catalyst (10 mol%), PhCl (2.0 mL), 130 °C, 36 h.

group participates in selective migration (**3j**). The examination of electronic influence on the migratory aptitude revealed that the migration of electron deficient substituents is disfavored (**3k**, **3l** *vs.* **3m**). Also, the reaction with a heterocyclic substrate proceeds selectively to provide the pyrrole with a heterocyclic substituent (**3n**). The reaction also proceeded well with various types of substituents for R^1 such as aryl, heteroaryl, and alkyl groups (**3o–r**).

In summary, a dual reaction manifold that allows for the selective synthesis of both pyridines and pyrroles from the common substrates α-diazo oxime ethers has been developed.

Our mechanistic study indicates the pyridine formation is initiated by a 1,6-hydride shift or prototropic isomerization, depending on the type of substituents. The reaction scope of these transformations demonstrates that a variety of diverse structures of these important N-heterocycles are readily accessible from α-diazo oxime ethers with high efficiency.

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