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A New Access to 4*H*-Quinolizines from 2-Vinylpyridine and Alkynes Promoted by Rhodium–N-Heterocyclic-Carbene Catalysts

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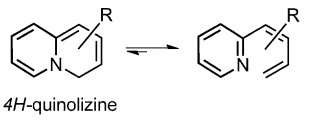
N-Bridgehead heterocycles are prevalent in many natural and synthetic biologically active alkaloids.[1] The development of efficient synthetic methodologies for the preparation of these intricate structures has been the focus of intense research,[2] among which transition-metal catalysts have played a preeminent role.[3] However, derivatives based on the quinolizine skeleton have received little attention, probably due to their instability, and are mainly limited to quinolizidine,[4] quinolizinium salts,[5] or quinolizinone[6] compounds. Indeed, 4*H*-quinolizines are very scarce,[7] particularly the 4-unsubstituted counterparts,[8] and are usually involved in a tautomeric equilibrium with the corresponding butadienylpyridine derivatives (Scheme 1).[9] Interestingly,

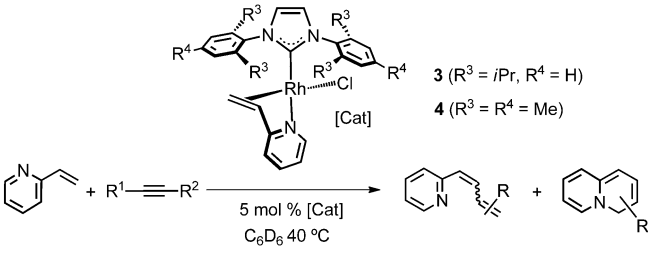


Scheme 1. Tautomerization of 4*H*-quinolizines.

we have now observed that the process can be shifted towards the quinolizine tautomer depending on the presence and position of certain substituents on the dienyl fragment. However, a straightforward and general method for the preparation of butadienylpyridines is still an important challenge for which organometallic catalysts emerge as a crucial node, as they can potentially achieve this task from 2-vinylpyridine and alkynes through sequential C–H activation and C–C coupling reactions.[10] Particularly, we have been interested in the design of rhodium catalysts based on N-heterocyclic carbenes (NHCs)[11] for new C–C and C–X bond-forming reactions.[12] Now, we have discovered that rhodium catalysts bearing NHC ligands give access to the elusive 4*H*-quinolizines with total atom economy under mild conditions.

Our research group has recently reported that isolable mononuclear Rh–NHC species can be obtained by an N-donor-ligand-promoted bridge-cleavage reaction of the corresponding dimer.[12c] Similarly, we have now observed that the treatment of $[\{Rh(\mu\text{-}Cl)(NHC)(\eta^2\text{-}coe)\}_2]$ (NHC = IPr (**1**), IMes (**2**); coe = cyclooctene; IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-carbene; IMes = 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-carbene) with 2-vinylpyridine afforded $[RhCl(NHC)(\kappa\text{-}N,\eta^2\text{-}CH_2{=}CHC_5H_4N)]$ (NHC = IPr (**3**), IMes (**4**)) in good yields (see the Supporting Information for synthetic details and NMR data). The chelating coordination of vinylpyridine is corroborated by an upfield shift for the olefinic protons ($\delta = 3.39$–2.13 ppm) and the occurrence of J_{C-Rh} coupling for the carbon atoms of the alkenyl fragment ($\delta = 16$–12 Hz) in the ^1H and $^{13}C\{^1H\}$ NMR spectra, respectively.

It has been previously described that rhodium-phosphane catalysts efficiently promote the C–C coupling between alkenylpyridines and olefins,[13] although the coupling with alkynes has not been reported to date. Now, we have discovered that the introduction of an NHC ligand in complexes **3** and **4** allow for the straightforward preparation of butadienylpyridines from 2-vinylpyridine and alkynes (Scheme 2). Notably, the use of **3** and **4** enables terminal alkynes to be used in this type of transformation without the observation of competitive dimerization or polymerization processes.



Scheme 2. C–C coupling reactions mediated by Rh–NHC catalysts.

Catalytic reactions were carried out in an NMR tube in C_6D_6 by using a 1:1 ratio of pyridine/alkyne. Preliminary tests with phenylacetylene under the optimized conditions

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(40 °C at 5 mol % catalyst loading) showed that **4** was slightly more active than **3** (see Table S1 in the Supporting Information). Initially, the formation of (1*Z*,3*E*)-2-(4-phenylbuta-1,3-dien-1-yl)pyridine (Figure 1) was observed, however, unexpectedly it was accompanied with a new set of resonances

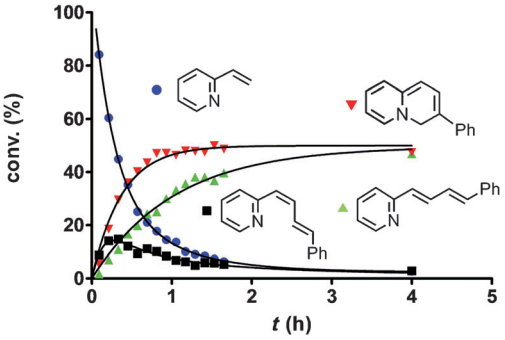


Figure 1. Monitoring of the reaction between 2-vinylpyridine and phenylacetylene catalyzed by **4** in C_6D_6 at 40 °C.

that were unequivocally ascribed to 3-phenyl-4*H*-quinolizine (see below). The formation of this product may arise from a 6π-electrocyclization involving the two conjugated double bonds and one C=N of the pyridine moiety within an undetected (1*Z*,3*gem)*-butadienylpyridine species. A similar transformation has been previously observed for conjugated imines[14] or oximes[15] but dearomatization of a pyridine moiety is considerably more challenging.[16] The similar initial rate for the formation of both organic products points out to a lack of regioisomeric preference in the C–C coupling process, but the (1*Z*,3*E*)-butadienylpyridine product smoothly isomerizes to produce the (1*E*,3*E*) derivative. A conversion of 97 % was reached after 4 h with a $TOF_{1/2}$ value of 35 h^{-1} calculated at 50 % conversion of 2-vinylpyridine. It is noticeable that the formation of 4-phenyl-4*H*-quinolizine was not detected. Both butadienylpyridine isomers were isolated by column chromatography methods but, unfortunately, the quinolizine derivative could not be recovered despite several attempts under different conditions.[14c]

The nature of the new organic product as 3-phenyl-4*H*-quinolizine was confirmed by multinuclear NMR experiments. A striking feature of the ^{1}H NMR spectrum is an unusual set of resonances at higher field (δ = 6.6–4.9 ppm) compared with that corresponding to aromatic protons, which is fully consistent with the presence of non-aromatic bicyclic system. The 4*H*-quinolizine structure was further confirmed by HSQC and HMBC ^{1}H-^{13}C experiments. Remarkably, the methylene fragment at 4-positon of the quinolizine skeleton was observed as a singlet at δ = 4.38 ppm. Moreover, long-range HSQC ^{1}H-^{15}N correlation confirms the presence of a N-bridgehead heterocycle (Figure 2) with a $\delta(^{15}N)$ of 117.5 ppm, which falls within the typical range for a trisubstituted amine. In sharp contrast, the (1*E*,3*E*)-butadienylpyridine compound was observed at δ = 309.8 ppm.

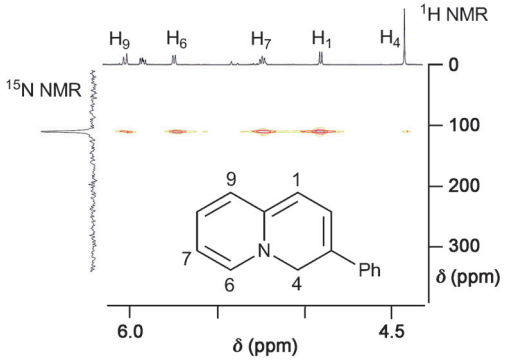
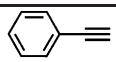
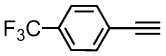
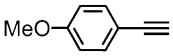
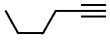
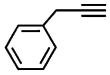
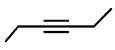
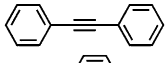
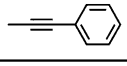


Figure 2. ^{1}H-^{15}N NMR correlation spectrum for a 4*H*-quinolizine.

Catalyst **4** is a versatile precursor for coupling reactions between 2-vinylpyridine and diverse terminal and internal alkynes (Table 1). Aromatic terminal alkynes reacted faster than aliphatic ones and with higher selectivity to 4*H*-quinolizine (Table 1, entries 1–3 vs. 4–6). Isomerization of the in-

Table 1. Coupling reaction between 2-vinylpyridine and alkynes.[a]

	Substrate	*t* [h]	4*H*-*q*[b]	*Z*-*E*[c]	*E*-*E*[c]	*Z*-*g*[d]	*E*-*g*[d]	vipy[e]	$TOF_{1/2}$ [h^{-1}]
1		4	48	3	46	–	–	3	35
2		1	43	2	48	–	–	7	51
3		6	36	16	31	8	–	8	29
4		5	7	37	–	45	10	1	26
5		9	9	39	–	38	11	3	23
6		20	7	74	2	14	–	2	4
7		14	16	47	–	–	–	37	3
8		14	51	36	12	–	–	1	15
9		12	23	69	6[f]	–	–	2	3
10		3	45[g]	25[h]	23[h]	–	–	6	18

[a] Complex **4** (5 mol %) in C_6D_6 (0.5 mL) at 40 °C, [subs] = 1 M. [b] 4*H*-Quinolizine; ratio of ^{1}H NMR integration. [c] 2-(Buta-1,3-dien-1-yl)pyridine. [d] *gem*. [e] Unreacted 2-vinylpyridine. [f] *E*,*Z* isomer. [g] 4-Methyl. [h] 4-Phenyl.

ternal double bond from *Z* to *E* occurred also faster for aromatic than aliphatic-substituted dienyl derivatives. The presence of an electron-withdrawing substituent on the phenyl ring increased the rate whereas selectivity to the N-bridgehead heterocycle decreased for both, electron-donating or -withdrawing groups (Table 1, entries 1–3).

The presence of bulky substituents in aliphatic alkynes reduced the activity (Table 1, entries 6 and 7). It is noticeable that the key (1*Z*,3*gem*)-butadienylpyridine isomers were detected for aliphatic alkynes, and consequently, the conversion to 3-R-4*H*-quinolizine is lower, which suggests that the tautomerization is disfavored in these cases.[17] Monitoring of the reaction showed that the initially formed *Z*-*gem*-butadienylpyridine isomerizes to *E*-*gem* derivatives and tautomerizes to the 4*H*-quinolizine compounds (Figure 3). Notably, for aliphatic alkynes, the isomerization of 1*Z*,3*E* to 1*E*,3*E* butadienylpyridines was not detected under catalytic conditions,[18] whereas internal alkynes reacted smoothly (Table 1, entries 8–10). The configuration of the conjugated double bonds of the butadienyl products was confirmed by ^{1}H-NOE NMR experiments (see the Supporting Information). In the case of 3-hexyne, the formation of the 1*Z*,3*E* derivative was initially observed with subsequent isomerization to 1*E*,3*E* and 4*H*-quinolizine compounds. However, diphenylacetylene behaved somewhat different. The initial rate for the 4*H*-quinolizine formation was higher but the N-heterocycle underwent a re-opening to afford the (1*Z*,3*E*)-2-(3,4-diphenylbuta-1,3-dien-1-yl)pyridine derivative with both phenyl groups disposed mutually *trans* (Figure 4). Dissymmetric 1-phenyl-1-propyne gave exclusively 4-methyl-3-phenyl-4*H*-quinolizine and 2-(3-methyl-4-phenylbuta-1,3-dien-1-yl)pyridine.

Scheme 3 shows a plausible mechanism for the formation of the 3-R-4*H*-quinolizine compounds. Initially, the activation of a terminal C–H bond of the 2-vinylpyiridine to generate rhodium-alkenyl-hydride species is proposed.[19] The subsequent coordination of the alkyne, migratory insertion and reductive elimination should generate both (1*Z*,3*E*)- or (1*Z*,3*gem*)-butadienyl-pyridine products depending on the regioselectivity. In both cases, the *Z* configuration of the internal double bond is kinetically favored if a concerted insertion mechanism is assumed. Then, formation of 4*H*-quinolizine skeletons can be rationalized through a metal-mediated or thermal electrocyclization. To shed light on this point, a solution of pure *Z*-*gem* isomer, (*Z*)-2-(3-benzylbuta-1,3-dien-1-yl)pyridine, in C_6D_6 was heated at 60 °C. Monitoring of the reaction by NMR spectroscopy evidenced the smooth formation of the 4*H*-quinolizine isomer, thus, pointing to a thermally activated cyclization process. In fact, an equilibrium mixture (butadienylpyridine/heterocycle) of 75:25 was reached after 3 h, which was corroborated by the exchange peaks observed in the ^{1}H-NOE NMR spectrum at 80 °C. It is noticeable that the formation of the *E*-*gem* regioisomer was not observed indicating that metal catalyst accounts for the *Z* to *E* isomerization of the internal double bond. A *cisoidal* configuration of the conjugated double bonds is essential for the electrocyclic reaction to take place, thus isomerization of the internal double bond is a handicap to be overcome. A similar equilibrium mixture was observed after heating the (1*Z*,3*E*)-butadienylpyridine obtained from 3-hexyne, but in

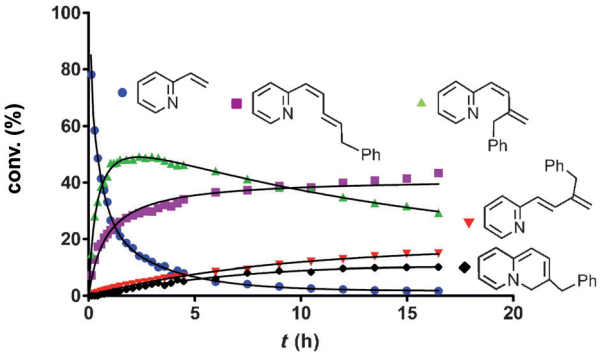


Figure 3. Monitoring of the reaction between 2-vinylpyridine and 3-phenyl-1-propyne catalyzed by **4** in C_6D_6 at 40 °C.

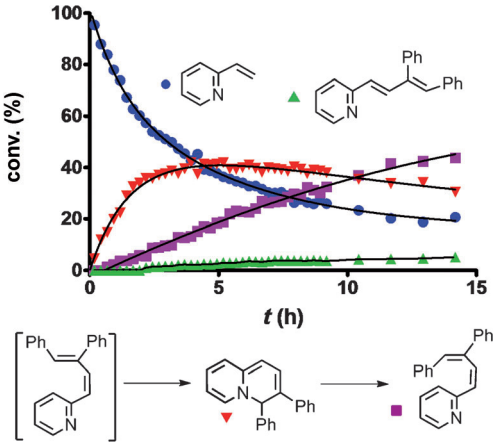
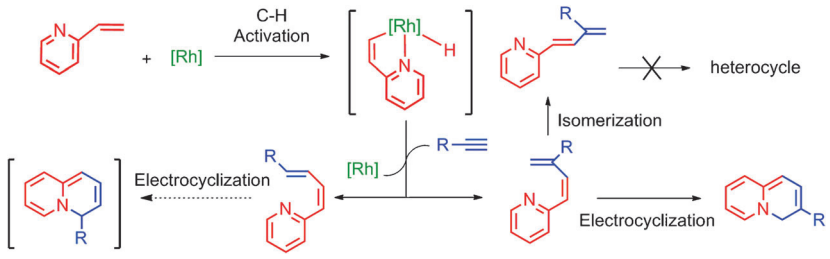


Figure 4. Monitoring of the reaction between 2-vinylpyridine and diphenylacetylene catalyzed by **4** in C_6D_6 at 40 °C.



Scheme 3. Plausible mechanism for the formation of 4*H*-quinolizine derivatives mediated by **4**.

this case the equilibrium is further shifted to the quinolizine compound in 60:40 molar ratio.

Theoretical calculations (DFT/m06-2x/kcal mol^{-1}) for the thermodynamics of the tautomerization process were performed. In full agreement with experimental results, it was found that 3-phenyl-4*H*-quinolizine is 1.83 kcal mol^{-1} more stable than *Z*-*gem*-butadienylpyridine whereas the formation of 4-phenyl-4*H*-quinolizine from the (1*E*,3*Z*)-butadienylpyridine isomer is disfavored by 2.04 kcal mol^{-1} (Figure 5). On the other hand, the calculated energies for diphenylacetylene were also in agreement with the experimental results. Although the 4*H*-quinolizine is 3.24 kcal mol^{-1} more stable than the (1*Z*,3*Z*)-butadienylpyridine isomer, not detected in the catalytic reaction, tautomerization to the (1*Z*,3*E*) counterpart is also slightly favored (−0.68 kcal mol^{-1}), thus explaining the smoothly tautomerization observed experimentally (Figure 4).

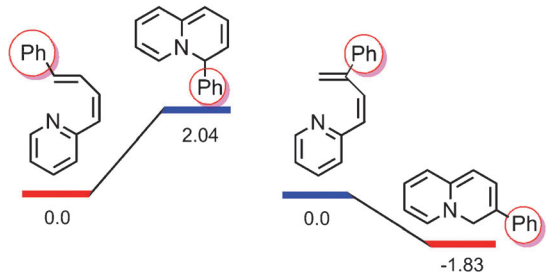


Figure 5. Thermodynamic DFT-calculated free energies (ΔG, kcal mol^{-1}) for the tautomerization of butadienylpyridine↔quinolizine.

In conclusion, we have described the outstanding catalytic performance in C–C coupling reactions of new Rh–NHC catalysts leading to the formation of 4*H*-quinolizine derivatives under mild conditions with total atom economy. We have shown that the thermal 6π-electrocyclization process leading to the formation of N-bridgehead heterocycles is favored for internal- versus terminal-substituted butadienylpyridine derivatives. The design of improved catalysts for selective *Z*-*gem*-butadienylpyridine formation and reduced *Z* to *E* isomerization of the internal double bond is ongoing in our laboratories.

Experimental Section

Synthesis of catalyst 3: A yellow solution of **1** (300 mg, 0.235 mmol) in toluene (10 mL) was treated with 2-vinylpyridine (50 μL, 0.470 mmol) and was stirred at room temperature for 1 h. After filtration through Celite the solvent evaporated to dryness. Addition of hexane caused precipitation of a yellow solid, which was washed with hexane (3×4 mL) and dried in vacuo. Yield: 250 mg (84%). Elemental analysis calcd (%) for $C_{34}H_{43}N_3ClRh$: C 64.61, H 6.86, N 6.65; found: C 64.92, H 6.89, N 6.62.

Synthesis of catalyst 4: The complex was prepared as described for **3** starting from **2** (300 mg, 0.271 mmol) and 2-vinylpyridine (58 μL, 0.542 mmol). Yield: 260 mg (87%). Elemental analysis calcd (%) for $C_{29}H_{35}N_3ClRh$: C 61.38; H 5.70; N 7.67; found: C 61.05, H 5.80, N 7.26.

Standard procedure for the catalytic C–C coupling between 2-vinylpyridine and alkynes: An NMR tube containing a solution of the catalyst (0.025 mmol) in of C_6D_6 (0.5 mL) was treated with 2-vinylpyridine (0.5 mmol) and the alkyne (0.5 mmol) and heated at 40 °C. The reaction course was monitored by NMR and the conversion determined by integration of the corresponding resonances in the ^{1}H NMR spectra of 2-vinylpyridine and the products.

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Keywords: carbenes · C–C coupling · C–H activation · electrocyclization · quinolizine

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