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Rhodium-Catalyzed [2+2+2] Cycloaddition of Oximes and Diynes To Give Pyridines

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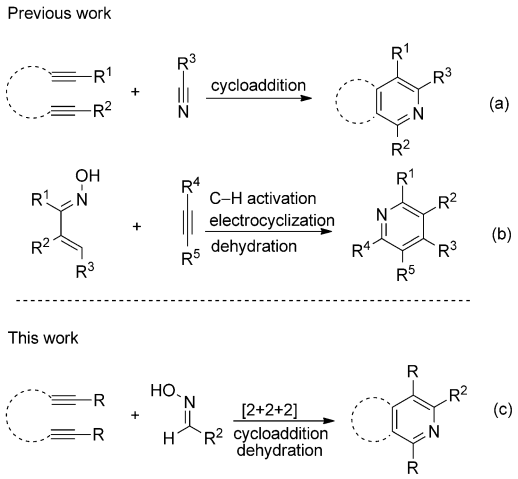
Transition-metal-catalyzed [2+2+2] cycloaddition reactions are valuable for the synthesis of pyridine derivatives with high atom efficiency.[1,2] Despite numerous studies in this field,[3,4] the nitrogen source is restricted to nitriles (Scheme 1a). Therefore the development of a straightforward and efficient strategy for the generation of pyridines is a formidable challenge in this field. An alternative nitrogen source, oximes, can be easily accessed from hydroxylamine and carbonyl compounds (for example, aldehydes and ketones). The reactivity of the C=N bond makes oximes an alternative coupling partner for cycloaddition reactions; however, only the reaction of α,β-unsaturated oximes and alkynes has been reported to generate substituted pyridines (Scheme 1b).[5] In these cases, either intramolecular [4+2] cycloaddition[5a] or C–H bond functionalization[5b–d] was involved, both of which occurred using a rhodium catalyst. Although there are a few reports that show that imines bearing directing groups can undergo [2+2+2] cycloaddition to afford 1,2-dihydropyridines under conditions of high temperature (100 °C),[6] the low reactivity of the C=N bond remains a challenging problem for simple oximes to participate in metal-catalyzed [2+2+2] cycloaddition (Scheme 1c). In addition, avoiding metal-catalyzed rearrangements[7] and the Beckmann rearrangement[8] of oximes to give the corresponding amides are challenges that need to be overcome. Furthermore, water, which would be generated in situ from the dehydration of the initial cycloadduct (for example, *N*-hydroxy-1,2-dihydropyridine) may greatly affect the efficiency of metal catalyzed cycloaddition reaction. Despite these challenges, we surmised that precious metals that could tolerate stoichiometric amounts of water could be used as catalysts for the effective activation of the oxime substrates. Herein, we report the first example of a rhodium-catalyzed cycloaddition of oximes and diynes that gives substituted pyridines (Scheme 1c). Moreover, the formation of pyridines from a one-pot reaction of an aldehyde, a hydroxylamine, and a diyne, as well as a possible reaction pathway are also discussed.



Scheme 1. Synthesis of pyridines through either cycloaddition or C–H bond functionalization.

Based on our previous work on [2+2+2] cycloaddition reactions,[4] we used a combination of $[Rh(cod)_2]BF_4$ and binap as a catalyst system. Initially, the reaction of diyne **1a** with (*E*)-benzaldehyde oxime **2a** was conducted in the presence of a catalytic amount of $[Rh(cod)_2]BF_4$ and binap. The solvent is critical for this reaction. The use of MeOH and CF_3CH_2OH afforded **3aa** in 26% and 31% yield, respectively (Table 1, entries 3 and 4). However, only a trace amount of **3aa** was obtained when the reaction was conducted in either toluene, EtOH, dioxane, or DMF (Table 1, entries 1, 2, 5, and 6). Other bidentate phosphine ligands in combination with $[Rh(cod)_2]BF_4$ were screened for catalytic activity (Table 1). We were pleased to find that the use of dppf as a ligand led to the highest catalytic activity, and pyridine **3aa** was obtained in moderate yield (Table 1, entry 8). Subsequently, we found that increasing the loading of $[Rh(cod)_2]BF_4$ and dppf to 10 mol% and then to 20 mol% led to a decrease in yield (Table 1, entries 13 and 14). Increasing the catalyst-to-ligand ratio from 1:1 to 1:1.2 resulted in a slight improvement in the yield (Table 1, entry 15). Importantly, the efficiency of the reaction could be drastically enhanced by increasing the amount of **2a** from 2 to 4 equivalents (69% yield as determined using HPLC, Table 1, entries 15 and 16). Therefore, the optimized reaction conditions were as follows: $[Rh(cod)_2]BF_4$ (5 mol%), dppf (6 mol%),

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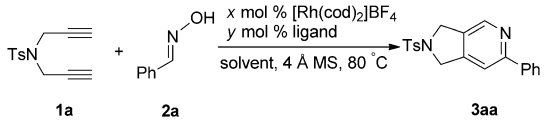
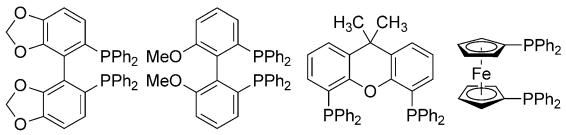
Table 1. Optimization of reaction conditions for pyridine formation.[a]



1a 2a 3aa



segphos MeO-biphep xantphos dppf

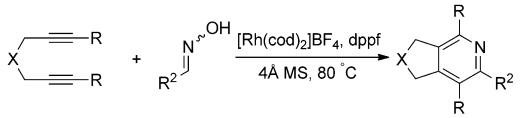
Entry	Solvent	*x*/*y*	Ligand	Yield [%][b]
1	toluene	5/5	binap	trace
2	EtOH	5/5	binap	trace
3[c]	MeOH	5/5	binap	26
4	CF_3CH_2OH	5/5	binap	31
5	dioxane	5/5	binap	trace
6	DMF	5/5	binap	trace
7	CF_3CH_2OH	5/5	segphos	25
8	CF_3CH_2OH	5/5	dppf	44
9	CF_3CH_2OH	5/5	dppe	trace
10	CF_3CH_2OH	5/5	xantphos	trace
11	CF_3CH_2OH	5/5	MeO-biphep	27
12	CF_3CH_2OH	5/5	(*R*)-Tol-binap	24
13	CF_3CH_2OH	10/10	dppf	41
14	CF_3CH_2OH	20/20	dppf	27
15	CF_3CH_2OH	5/6	dppf	53
16[d]	CF_3CH_2OH	5/6	dppf	69

[a] Reaction conditions: diyne **1a** (0.125 mmol), oxime **2a** (2 equiv, 0.25 mmol), $[Rh(cod)_2]BF_4$ (*x* mol%), ligand (*y* mol%), 4 Å molecular sieves (200 mg), solvent (3 mL) at 80°C for 48 h. [b] Determined by HPLC with 1-methylnaphthalene as internal standard. [c] 60°C. [d] **2a** (4 equiv). binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene, dppe = 1,2-bis(diphenylphosphino)ethane, Ts = *p*-toluenesulfonyl.

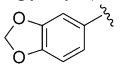
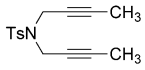
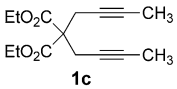
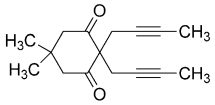
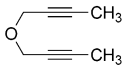
CF_3CH_2OH as solvent, and conducting the reaction at 80°C in the presence of 4 Å molecular sieves (200 mg/0.125 mmol diyne).

With optimized reaction conditions established, we explored the substrate scope using various diynes and oximes (Table 2). In general, a range of electron-rich, electron-neutral, and electron-deficient aryl oximes were tolerated to afford the corresponding products in good yields (Table 2, entries 1–12, 61–88%). Oximes bearing electron-withdrawing groups at the *para* position gave better results than those with electron-donating groups (Table 2, entries 2–6). Notably, the reaction of sterically demanding substrate **2k** (R = 2-MeC_6H_4, Table 2, entry 11) and diyne **1a** led to the corresponding product in a yield that was lower than the reaction of substrate **2h** (R = 3-MeC_6H_4, Table 2, entry 8). Importantly, 2-naphthaldehyde oxime **2l** and heteroaryl oxime **2m** can also be used for this reaction, thus furnishing the pyridine product **3al** and **3am** in 69% and 60% yield, respectively (Table 2, entries 12 and 13). The reaction of diyne **1b** with oxime **2e** gave the cycloadduct **3be** in 74% yield (Table 2, entry 15). When we applied this method to the cycloaddition of C-tethered diynes and an O-tethered diyne, we fortunately found that **3ce**, **3de**, and **4ea** were formed in

Table 2. Synthesis of pyridines from diynes (**1a**–**1e**) and oxime (**2a**–**2n**).[a]

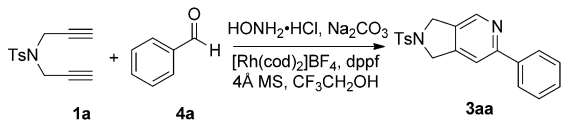


1a–1e 2a–2n

Entry	Diyne	R^2	Yield [%][c]
1	**1a**	C_6H_5 (**2a**)	69 (**3aa**)
2	**1a**	4-$MeOC_6H_4$ (**2b**)	67 (**3ab**)
3	**1a**	4-MeC_6H_4 (**2c**)	69 (**3ac**)
4[b]	**1a**	4-ClC_6H_4 (**2d**)	75 (**3ad**)
5[b]	**1a**	4-FC_6H_4 (**2e**)	88 (**3ae**)
6	**1a**	4-$CF_3C_6H_4$ (**2f**)	76 (**3af**)
7	**1a**	3-BrC_6H_4 (**2g**)	78 (**3ag**)
8[b]	**1a**	3-MeC_6H_4 (**2h**)	81 (**3ah**)
9[b]	**1a**	3-$CF_3C_6H_4$ (**2i**)	61 (**3ai**)
10	**1a**	3-FC_6H_4 (**2j**)	78 (**3aj**)
11[b]	**1a**	2-MeC_6H_4 (**2k**)	67 (**3ak**)
12	**1a**	2-napthyl (**2l**)	69 (**3al**)
13	**1a**	4-pyridyl (**2m**)	60 (**3am**)
14	**1a**  **2a**		41 (**3an**)
15	 **1b**	4-FC_6H_4 (**2e**)	74 (**3be**)
16	 **1c**	4-FC_6H_4 (**2e**)	40 (**3ce**)
17	 **1d**	4-FC_6H_4 (**2e**)	26 (**3de**)
18	 **1e**	C_6H_5 (**2a**)	46 (**4ea**)

[a] **1a**–**1e** (0.25 mmol), **2a**–**2n**(1 mmol), $[Rh(cod)_2]BF_4$ (5 mol%), dppf (6 mol%), and CF_3CH_2OH (6 mL) in the presence of 4 Å molecular sieves (0.4 g); then stirred for 48 h. [b] **1a** was added slowly by syringe. [c] Yield of isolated product.

moderate yield (Table 2, entries 16–18). Notably, the use of a one-pot procedure (Scheme 2) was successful for the synthesis of pyridine **3aa** from aldehyde **4a**, hydroxylamine, and diyne **1a**, albeit with a yield that was lower than that of the two-step protocol (60% versus 69% yield; Table 2,

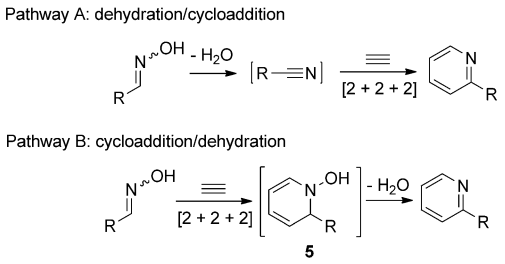


1a 4a 3aa

4 equiv

60 % yield
(as determined using
HPLC)

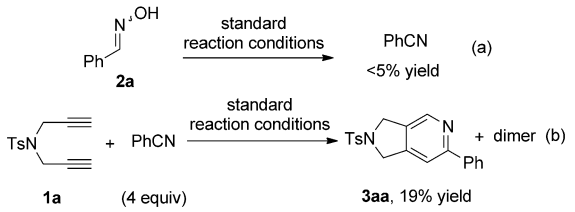
Scheme 2. One-pot formation of pyridines from aldehyde **4a**, hydroxylamine, and diyne **1a**.



Scheme 3. Possible pathways to form pyridines.

entry 1); this lower yield might be due to the influence of residual aldehyde[9] and the relatively low amount of oxime.

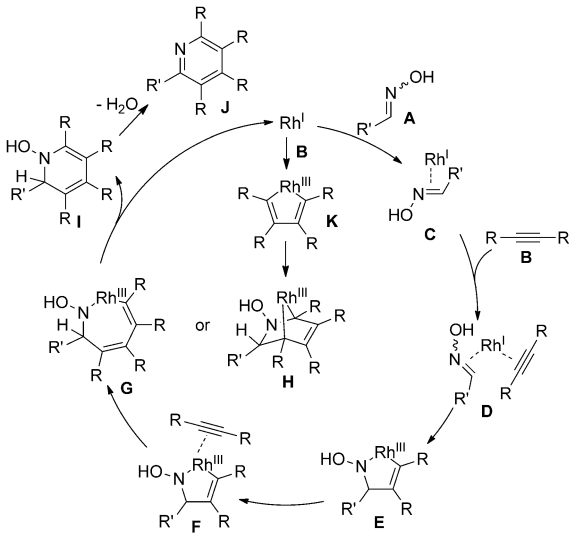
Two possible pathways for the formation of pyridines are shown in Scheme 3: 1) pathway A: dehydration of the oxime to generate the corresponding nitrile followed by the cycloaddition of the nitrile and the alkynes to afford the pyridine; 2) pathway B: cycloaddition of the oxime and the alkynes to form intermediate **5**, which then undergoes dehydration (Scheme 3). To determine which one of these hypotheses was more likely, two experiments were first carried out (Scheme 4). The reaction of oxime **2a** under standard



Scheme 4. Control experiments for determining the feasibility of pathway A.

reaction conditions (Table 2) only gave a trace amount of benzonitrile (<5%, Scheme 4a). In addition, when benzonitrile was subjected to the reaction with diyne **1a** instead of oxime **2a** (Scheme 4b), the corresponding pyridine product **3aa** was detected in less than 20% yield (compare with 69% yield, Table 2, entry 1) together with a side product derived from dimerization of the diyne. Therefore, pathway A in Scheme 3 is not feasible for the formation of pyridines.

Although attempts to isolate the key intermediate, *N*-hydroxy-1,2-dihydropyridine, did not succeed, on the basis of the cycloaddition of an imine reported by both Ogoshi et al.[6b] and Yoshikai and co-workers,[6c] we suspected that this reaction would begin with the oxidative coupling between the alkyne and the oxime, thus affording five-membered azametallacycle **E** (Scheme 5). Subsequent alkyne insertion could afford seven-membered aza-metallacycle **G**, which could then undergo reductive elimination and dehydration to provide the final pyridine product, **J**. Alternatively, the reaction could start with intramolecular oxidative cyclization of two alkyne moieties to obtain metallacyclopentadiene intermediate **K**. The coordination of oxime **A** could then be



Scheme 5. Proposed mechanism for the [2+2+2] cycloaddition of alkynes and oximes.

followed by its incorporation into the metallacycle either by a [4+2] cycloaddition or an insertion process. Finally the product, **J**, could be obtained by regeneration of the catalyst and dehydration.

In conclusion, we have developed a new method for the preparation of pyridine derivatives; the method involves a rhodium-catalyzed [2+2+2] cycloaddition of diynes and oximes, can be conducted under mild conditions, and gives the pyridine products in moderate to high yields. This transformation complements traditional metal-catalyzed cycloaddition reactions used for the synthesis of pyridines. Moreover, the ability to form these pyridines by using a one-pot reaction of an aldehyde, a hydroxylamine, and a diyne makes this method a more practical alternative because simple aldehydes can be used as starting materials. Investigations of other cycloaddition reactions involving oximes are currently underway.

Experimental Section

Representative procedure: $[Rh(cod)_2]BF_4$ (5.1 mg, 0.0125 mmol) and dppf (8.3 mg, 0.015 mmol) were dissolved in CF_3CH_2OH (6 mL) in the presence of 4 Å molecular sieves, and the mixture was stirred at room temperature for 5 min. Oxime was added and the resulting mixture was stirred at 80 °C for 30 min. To this solution was added diyne (0.25 mmol). Then the mixture was stirred at 80 °C for 48 h. The 4 Å molecular sieves were filtered off and the filtrate was evaporated. The oily residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (4:1 to 1:2) as eluent to afford products.

Acknowledgements

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Keywords: cycloaddition · heterocycles · oximes · pyridines · rhodium

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