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Ruthenium-catalyzed cyclization of 3-en-1-ynyl imines with nucleophiles via tandem 5-*exo-dig* cyclization and nucleophilic addition

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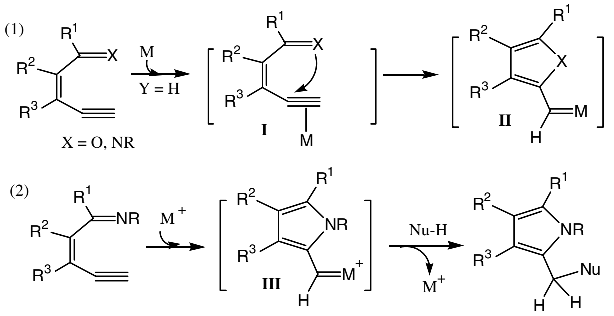
Abstract—Treatment of 3-en-1-ynyl imines with $TpRuPPh_3(CH_3CN)_2PF_6$ catalyst (1 mol%) in DCE (50 °C, 6 h) effected catalytic cyclization with suitable nucleophiles and gave functionalized pyrroles in good yields. The reaction mechanism is proposed to proceed via (2-pyrrolyl)carbenoid intermediates derived from 5-*exo-dig* cyclization. This catalytic reaction works well with various nucleophiles, including water, alcohols and anilines.

The activation of an alkyne functionality with transition-metal species is an efficient method for the in situ generation of metal-carbenoid species, which subsequently leads to interesting products via carbene transfer reactions.[1–4] This approach avoids the use of hazardous diazoalkane as a carbenoid precursor.[5] Metal-carbenoid species have been postulated to be intermediates in the cycloisomerization of α,ω-enynes using electrophilic metal catalysts.[1,2] Recently, Uemura and Iwasawa reported metal-catalyzed 5-*exo-dig* cyclization of 3-en-1-ynyl ketones and imines to generate carbenoid intermediates (**II**) as depicted in Scheme 1 (Eq. 1).[3] This active species reacts with olefin to give cyclopropane derivatives catalytically.[3] (2-Furyl)carbenoids (**II**) of a special type undergo Doyle–Kirmse reaction[6] with insertion into the C–S bond of allylic sulfides by the carbenoid carbon.[3a] One useful application of this catalytic protocol is to decompose carbenoid intermediates (**II**) with nucleophiles[7], but such a process has not yet been achieved. We envision that carbenium species (**III**) derived from a cationic metal catalyst will be prone to nucleophilic addition to give distinct addition products (Eq. 2). In this study, we report a new cyclization of 3-en-1-ynyl imines with suitable nucleophiles using cationic ruthenium species. The proposed ruthenium-carbenoid intermediate (**III**) readily reacts with water, alcohol and amines to liberate useful pyrrolyl derivatives. This catalytic reaction is challenging in synthetic chemistry because terminal alkynes are easily hydrolyzed by electrophilic metal catalysts to give corresponding methyl ketones.[8]



Scheme 1.

Table 1 shows the results of these catalytic reactions over various cationic catalysts and solvents. Treatment of 3-en-1-ynyl imine (**1**) with 5 mol% $TpRuPPh_3(CH_3CN)_2PF_6$ [**A**, Tp = tris(1-pyrazolyl)borate][9,10] and water (1.5 equiv) in hot toluene (100 °C, 12 h) afforded 2-hydroxymethylpyrrole (**2**) in 47% yield in addition to an unknown species **3** (26%). The NMR spectra and mass data suggested species **3** is derived from an unknown cyclodimerization of starting imine **1**, but the structure can not be assigned with certainty. The yield of byproduct **3** can be effectively reduced with

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Keywords: Cyclization; Imines; Nucleophile.

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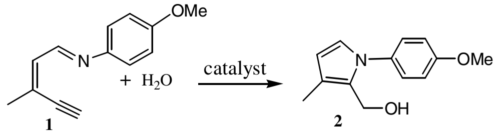
Table 1. Catalytic cyclization of 3-en-l-ynyl imine **1** with water



Entries	Catalysts[a]	Solvents[b]	Conditions	Yields[c] (%)
1	**A** (5.0 mol%)	Toluene	100 °C (12 h)	47 (26)[d]
2	**A** (5.0 mol%)	Benzene	80 °C (48 h)	7
3	**A** (5.0 mol%)	DME	80 °C (48 h)	N.R.
4	**A** (5.0 mol%)	CH_3CN	80 °C (48 h)	N.R.
5	**A** (5.0 mol%)	DCE	50 °C (4 h)	58 (23)[d]
6	**A** (1.0 mol%)	DCE	50 °C (4 h)	80
7	**B** (5.0 mol%)	DCE	50 °C (4 h)	41
8	**C** (5.0 mol%)	DCE	50 °C (4 h)	40
9	**D** (5.0 mol%)	DCE	50 °C (4 h)	46
10	**E** (5.0 mol%)	DCE	50 °C (4 h)	32

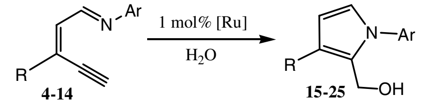
[a] Catalysts: $TpRuPPh_3(CH_3CN)_2PF_6$ (**A**), $CpRuPPh_3(CH_3CN)_2PF_6$ (**B**), $CpRuP^n Bu_3(CH_3CN)_2PF_6$ (**C**), $CpRuP^t Bu_3(CH_3CN)_2PF_6$ (**D**), $CpRuPCy_3(CH_3CN)_2PF_6$ (**E**).

[b] [**1**] = 1.5 M, 1.2 equiv H_2O.

[c] Yields were reported after separation from a silica column.

[d] The values in parentheses represents the yields of unknown **3**.

Table 2. Catalytic cyclizations of 3-en-l-ynyl imines with water



Imines[a]	Pyrroles[b]
(1) Ar = C_6H_5 R = Me (**4**)	**15** (78%)
(2) Ar = p-MeC_6H_4 R = Me (**5**)	**16** (83%)
(3) Ar = C_6H_5 R = ^{n}Pr (**6**)	**17** (80%)
(4) Ar = p-MeC_6H_4 R = ^{n}Pr (**7**)	**18** (83%)
(5) Ar = p-$MeOC_6H_4$ R = ^{n}Pr (**8**)	**19** (84%)
(6) Ar = C_6H_5 R = ^{n}Bu (**9**)	**20** (85%)
(7) Ar = p-MeC_6H_4 R = ^{n}Bu (**10**)	**21** (86%)
(8) Ar = p-$MeOC_6H_4$ R = ^{n}Bu (**11**)	**22** (84%)
(9) Ar = C_6H_5 R = $^nC_6H_{13}$ (**12**)	**23** (82%)
(10) Ar = p-MeC_6H_4 R = $^nC_6H_{13}$ (**13**)	**24** (84%)
(11) Ar = p-MeC_6H_4 R = $^nC_6H_{13}$ (**14**)	**25** (87%)

[a] Water (1.2 equiv), [imine] = 1.5 M 1 mol% catalyst **A**, DCE, 50 °C, 6 h.

[b] Yields were reported after elution through a silica column.

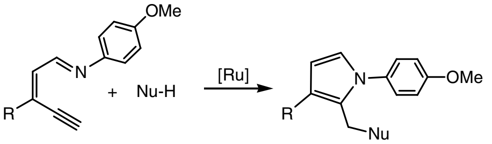
low loading of catalyst (vide ante). Benzene, dimethoxyethane (DME) and acetonitrile were far less active in this catalytic cyclization (entries 2–4), whereas 1,2-dichloroethane (DCE) gave the desired alcohol **2** in an improved yield (58%) even at 50 °C (entry 5). Notably, a low loading of catalyst **A** (1.0 mol%) was more effective, and gave alcohol **2** with in a yield up to 80%. Entries 7–10 show catalytic reactions over various cationic ruthenium complexes including $CpRuPPh_3(CH_3CN)_2PF_6$ (**B**), $CpRuP^n Bu_3(CH_3CN)_2PF_6$ (**C**), $CpRuP^t Bu_3(CH_3CN)_2PF_6$ (**D**) and $CpRuPCy_3(CH_3CN)_2PF_6$ (**E**), and no catalytic activities were observed with these catalysts.

The cyclization of 3-en-1-ynyl imine **1** with water is synthetically interesting because many metal complexes catalyze the hydration of terminal alkyne to give methyl ketone derivatives.[8] Surprisingly, such a reaction does not occur in the present catalytic system. We prepared various 3-en-1-ynyl imines **4**–**14** to examine the generality of this cyclization with water; 1.0 mol% catalyst **A** promoted the reaction in hot DCE (50 °C, 6 h) without the formation of other byproducts. The yields of pyrrolyl alcohols **15**–**25** are given after isolation from a silica column. Entries 1–2 show the application of this process to 3-en-1-ynyl imines **4**–**5** bearing a tolyl and p-methoxyphenyl groups respectively, to give the desired alcohols **15**–**16** in 78–83% yields. This method is compatible with changes in both the R and Ar substituents (R = ^{n}Pr, ^{n}Bu, $^nC_6H_{13}$; Ar = C_6H_5, p-MeC_6H_4, entries 3–14) of the starting imines **6**–**14**, and gives the corresponding alcohols **17**–**25** in yields exceeding 80%.

We next examined this catalytic cyclization with other nucleophiles to enhance its synthetic utility; and the results are depicted in Table 2. Cyclization of imine **1** with various alcohols ROH (R = Me, ^{i}Bu, $CH_2 = CHCH_2$, ^{i}Pr, ^{t}Bu, entries 1–5) proceeded smoothly and gave functionalized pyrrolyl **26**–**30** products in reasonable yields (63–86%). This process was successfully extended to aniline and methylaniline to give products **31**–**32** in 68%–74% yields (entries 6 and 7). 3-En-1-ynyl imine **12** showed similar catalytic activity towards methanol and methylaniline, and gave the products **33**–**34** in 81–89% yield. Cyclization of imine **1** with phenol, diethyl- or diisopropyl amines gave a complicated mixture of products. This observation suggests that nucleophiles with acidic or basic nature are not compatible with this cyclization. Terminal alkynes tended to react with ruthenium (**II**) species to give alkynyl metal species in the presence of basic amines[11] (Table 3).

We have attempted similar catalytic cyclizations on 3-en-1-ynyl ketones and aldehydes with water, isobutanol and aniline, but we failed to obtain the expected furan products. This cyclization is not applicable to those 3-en-1-ynyl imines bearing an internal alkyne although it is compatible with π-alkyne reaction intermediates.

Table 3. Cyclization of 3-en-l-ynyl imines with alcohols and amines



Imines	Nu–H	Pyrroles[a]
(1) R = Me (**1**)	MeOH	**26** (86%)
(2) R = Me (**1**)	^{i}BuOH	**27** (82%)
(3) R = Me (**1**)	$CH_2{=}CHCH_2OH$	**28** (86%)
(4) R = Me (**1**)	^{i}PrOH	**29** (78%)
(5) R = Me (**1**)	^{t}BuOH	**30** (63%)
(6) R = Me (**1**)	$PhNH_2$	**31** (68%)
(7) R = Me (**1**)	PhMeNH	**32** (74%)
(8) R = $^nC_6H_{13}$ (**12**)	MeOH	**33** (89%)
(9) R = $^nC_6H_{13}$ (**12**)	PhMeNH	**34** (81%)

[Ru] = 1 mol% catalyst **A**, [imine] = 1.50 M, NuH (1.2 equiv), DCE, 50 °C, 6 h.

[a] Yields were reported after purification from a silica column.

In summary, we have reported a new cyclization of 3-en-1-ynyl imines with suitable nucleophiles, including water, alcohols and aniline, to afford functionalized pyrroles in good yields. In the case of water, we did not observe the hydration of 3-en-1-ynyl imines like other catalytic systems. A low loading (1 mol%) of $TpRuPPh_3(CH_3CN)_2PF_6$ catalyst (**A**) promotes the catalytic cyclization without the formation of byproducts. This process is thought to involve (2-pyrrolyl)carbenoids derived from 5-*exo*-*dig* cyclization of the starting imines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.069. Synthetic procedures and spectral data for all reaction products is available.

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