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Rh(I)-catalyzed intramolecular hetero-[4+2] cycloaddition of ω-alkynyl-vinyl oximes

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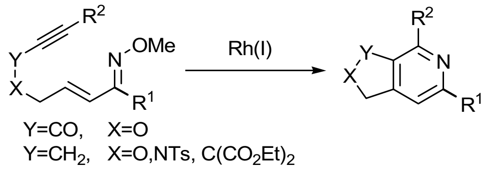
Abstract—Cationic rhodium(I) catalyst derived from $[RhCl(cod)]_2$ and $AgSbF_6$ in hexafluoroisopropanol (HFIP) efficiently catalyzed the formation of bicyclic pyridine derivatives by intramolecular hetero-[4+2] cycloadditions of ω-alkynyl-vinyl oximes.

Hetero-[4+2] cycloaddition of 1-azadienes has provided one of the most straightforward strategies for preparations of pyridine ring systems,[1] which are valuable building blocks for the synthesis of natural products.[2] In particular, the intramolecular version could be considered useful for the highly regio- and stereoselective formation of functionalized bicyclic and polycyclic pyridine compounds. Simple 1-azadienes such as vinyl imine derivatives, however, are difficult to be used as dienes because of the tautomerization into enamines.[1a] Furthermore, there is the possibility of intervention of the [2+2] cycloaddition due to the imine unit.[1a] The successful application of 1-azadienes to the [4+2] cycloaddition was brought about by means of introducing either electron-donating or -withdrawing substituents to the imine nitrogen. Yet, there is certainly room for improvement of the hetero-Diels–Alder reaction of 1-azadienes with simple alkynes or electron-withdrawing dienophiles.[3] Thus, vinyl oximes[4,5] and vinyl hydrazones[6,7] have been applied to the Diels–Alder reaction, while the use of such azadienes was restricted to the reaction with reactive dienophiles (quinones, maleate derivatives etc.).[5,7] In the case of alkyne as a dienophile, even the intramolecular reaction requires a higher reaction temperature and a longer reaction time.[4,6]

For the purpose of the synthesis of heterocycles, the transition metal-catalyzed cycloaddition reaction[8] has attracted our attention since the synchronous formation of bonds can be achieved in a single step under mild conditions.[9] As for the construction of a pyridine nucleus, [2+2+2] cycloadditions[10] of alkynes with nitriles or isocyanates have been largely developed by the use of transition metals.[11–13] In those reactions, however, low regioselectivity hampers the efficiency of the reaction. In the metal-catalyzed [4+2] cycloadditions of 1-azadienes, to the best of our knowledge, efficient catalysts have yet to have been found.[14] Bergman and Ellman's group has reported Rh(I)-catalyzed hydrovinylation of vinyl imine with an inner alkyne giving [4+2]-adduct, albeit with only one example.[15,16] Recently, we developed Rh(I)-catalyzed synthesis of heterocycles[17,18] and found efficient intramolecular cycloadditions of ester-tethered ω-alkynyl-dienes and -vinylcyclopropanes in fluorinated alcohols.[17] We describe herein the Rh(I)-catalyzed intramolecular hetero-[4+2] cycloaddition of ω-alkynyl-vinyl oximes (Scheme 1).

Our initial effort was focused on the evaluation of rhodium catalysts for the hetero-[4+2] cycloaddition of 2-butynoate **1a** (Table 1). It turns out that treatment of **1a** with the cationic rhodium(I) species derived from $[RhCl(cod)]_2$ (5 mol %) and Ag salt (13 mol %) in



Scheme 1.

Keywords: Rhodium; Hetero-[4+2] cycloaddition; Vinyl oxime.

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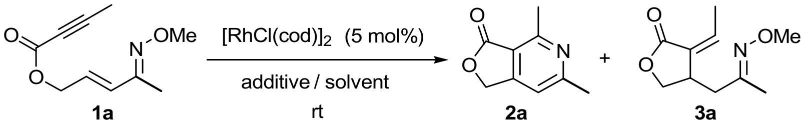
Table 1. Evaluation of Rh-catalysts for the reaction of **1a**



Entry	Rh	Additive (mol %)	Solvent[a]	Temperature (°C)	Time (h)	Yield[b] (%)		
						2a	**3a**	**1a**
1	$[RhCl(cod)]_2$	$AgOTf$ (13)	HFIP	rt	2	18	12	—
2	$[RhCl(cod)]_2$	$AgBF_4$ (13)	HFIP	rt	2	17	13	—
3	$[RhCl(cod)]_2$	$AgSbF_6$ (13)	HFIP	rt	1	52	12	—
4	$[RhCl(cod)]_2$	—	HFIP	rt	2	—	—	93
5	—	$AgSbF_6$ (13)	HFIP	rt	2	—	—	99
6	$[RhCl(cod)]_2$	$AgSbF_6$ (13)	TFE	50	19	31	—	—
7	$[RhCl(cod)]_2$	$AgSbF_6$ (13)	*i*-PrOH	50	6	—[c]	—	—
8	$[RhCl(cod)]_2$	$AgSbF_6$ (13)	THF	50	30	—	—	57
9	$[RhCl(cod)]_2$	$AgSbF_6$ (13)	$(CH_2Cl)_2$	50	24	8	—	—
10	—	—	Xylenes	180	25	14	—	—

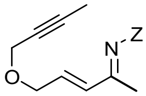
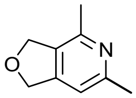
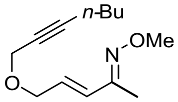
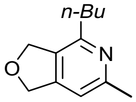
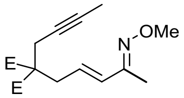
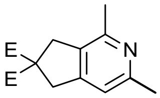
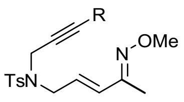
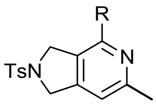
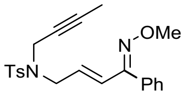
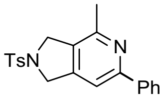
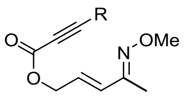
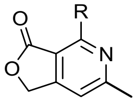
[a] HFIP; 1,1,1,3,3,3-hexafluoro-2-propanol, TFE; 2,2,2-trifluoroethanol.

[b] Isolated yield.

[c] Complex mixture.

hexafluoroisopropanol (HFIP) led to the formation of **2a** at room temperature within 1–2 h (entries 1–3). In particular, the Rh-catalyst derived from $AgSbF_6$ brought about the best result giving rise to **2a** in 52% yield (entry 3).[19] The addition of a phosphine ligand (Ph_3P, Cy_3P, dppb, dppp or dppe) to the present catalytic system, or the sole use of either $[RhCl(cod)]_2$ or $AgSbF_6$ (entries 4 and 5) did not yield **2a**. It should be mentioned that other solvents played inferior roles to HFIP (entries 6–9). The thermal Diels–Alder reaction of **1a** in the absence of the catalyst in xylenes (180 °C in a sealed tube) gave the desirable pyridine **2a** in only 14% yield (entry 10). The metal-catalyzed conditions, which are reported for the hydrovinylation of vinyl imines[15] and

Table 2. Cycloaddition of ω-alkynyl-vinyl oximes[a]

Entry	Substrate		Condition		Product		Yield[b] (%)
			(°C)	(h)			
1		**4a**: Z = OMe	rt	3		**5a**	79
2		**6**: $Z = NMe_2$	80	5		**5b**	0
3		**4b**	rt	6		**5b**	86
4		**7**: $E = CO_2Et$	rt	4		**8**	80
5		**9a**: R = Me	rt	20		**10a**	58
6		**9b**: R = *n*-Bu	rt	20		**10b**	84
7		**9c**: R = Ph	80	20		**10c**	48
8		**9d**: R = H	80	4		**10d**	0
9		**9e**	rt	23		**10e**	61
10		**1a**: R = Me	rt	1		**2a**	51
11		**1b**: R = Ph	rt	29		**2b**	21
12		**1b**	80	15		**2b**	15

[a] 5 mol % $[RhCl(cod)]_2$, 13 mol % $AgSbF_6$/HFIP.

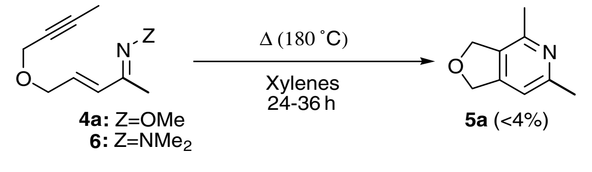
[b] Isolated yield.

hetero-[4+2] cycloaddition of α,β-enones,[14] ended in failure to obtain **2a**. It is interesting to note that the formation of lactone **3a** was inevitably observed in the cationic Rh(I)-catalyzed reactions in HFIP as a solvent (entries 1–3).[20]

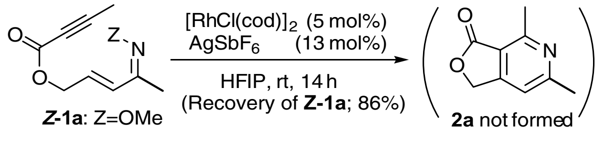
Under the described conditions, Rh(I)-catalyzed hetero-[4+2] cycloadditions of various ω-alkynyl-vinyl oximes in HFIP were carried out (Table 2). Although the thermal Diels–Alder reaction in xylenes (180 °C in a sealed tube) of oxime **4a** or hydrazone **6** yielded only a trace amount of pyridine **5a** (Scheme 2), the cationic rhodium(I) species worked nicely in the reaction of **4a** to give **5a** in 79% yield at room temperature for 3 h (Table 2, entry 1). Rh(I)-catalyzed reaction of hydrazone **6**, however, afforded a complex mixture (entry 2). The present catalyst can be applied to the reactions of ether **4b**, malonate **7** and tosylamide **9** derivatives as well. Thus, in the case of Me and *n*-Bu substituents at the alkyne functional groups, the corresponding pyridines **5b**, **8**, and **10** were obtained in good yields (54–86%, entries 3–6). In contrast, the formation of Ph-substituted compounds **10c** and **2b** was less efficient (entries 7, 11 and 12) and terminal alkyne **9d** resulted in a complex mixture (entry 8). The reaction of **9e**, which has a Ph group at the azadiene unit, proceeded at room temperature for 23 h giving rise to **10e** in 61% yield (entry 9). It should be mentioned that the reaction of (*Z*)-substrate ***Z*-1a** by the present catalytic system ended with the recovery of ***Z*-1a** (Scheme 3).[21]

It should also be mentioned that the formation of 5,6,7,8-tetrahydroisoquinoline skeleton by the reaction of *N*-2-butynyl-*N*-[5-(methoxyimino)-3-hexenyl]-tosylamide was not observed under the aforementioned cationic Rh(I)-catalyzed conditions.

In conclusion, we found the facile hetero-[4+2] cycloadditions of ω-alkynyl-vinyl oximes by cationic rhodium catalyst derived from $[RhCl(cod)]_2$ and $AgSbF_6$ in HFIP. The solvent effect of HFIP is quite notable in the present reaction. At present, we took into consideration that fluorinated alcohols might increase the preferable conformation of substrates to cycloaddition reactions by polar effect[22] and/or accelerate the reactivity of the cationic Rh(I) catalyst, which coordinates to unsaturated bonds. These findings raise new possibilities for the regioselective synthesis of bicyclic pyridine compounds under mild conditions. Further studies on the scope of substrates and the detailed effect of HFIP are underway.



Scheme 2.



Scheme 3.

Acknowledgments

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20. Although the mechanism for the formation of **3a** remains unclear at present, we speculate that the protonation from HFIP to Rh–C and/or Rh–N bonds of rhodacycle generated from Rh, alkyne, and vinyl oxime function may be involved.
21. Throughout the experiment, we employed (*E*)-oxime ethers, which are easily separated from (*Z*)-isomers, for reactions. The geometry of the (*E*)-isomers were confirmed by ^{1}H NMR.
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