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Rhodium-Catalyzed Anti-Markovnikov Intermolecular Hydroalkoxylation of Terminal Acetylenes

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Abstract: We report here the first transition-metal-catalyzed anti-Markovnikov intermolecular hydroalkoxylation of terminal acetylenes to give enol ethers in high yields without using bases. Arylacetylenes as well as alkenyl- and alkylacetylenes were coupled with aliphatic alcohols, and the products were obtained with high *Z* selectivity in most cases. Effective catalysts were 8-quinolinolato rhodium complexes, which are structurally simple but have been relatively unexplored as catalysts.

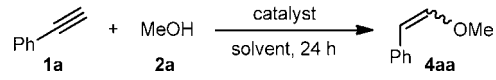
Enol ethers are useful intermediates in organic synthesis.[1] Addition of alcohols to acetylenes should be one of the most straightforward strategies to access enol ethers, but the addition under mild conditions is still rare. Herein we describe a simple rhodium catalyst for the anti-Markovnikov addition of alcohols to terminal acetylenes, giving *Z*-enol ethers selectively.

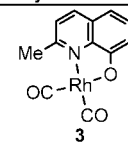
Traditionally, the addition of alcohols to acetylenes needs strong bases under harsh conditions,[2] and arylacetylenes were hydroalkoxylated in an anti-Markovnikov fashion to give β-arylvinyl ethers.[3] Synthesis of enol ethers was also conducted by other methods such as cross-coupling of alkenyl halides with alcohols,[4] elimination of alcohols from acetals,[5] *trans*-alkenylation,[6] Horner−Wittig and Tebbe olefinations,[7] and catalytic substitution of α,β-unsaturated acetals with Grignard reagents.[8] But the simplicity and the high atom economy of the hydroalkoxylation is desirable, and the use of transition metal catalysts has been examined. While various intramolecular cyclizations have been reported,[9] the intermolecular reaction, particularly of terminal acetylenes, for the selective synthesis of enol ethers is difficult to achieve.[10] A $PdMo_3$ cubane-type cluster and AgOTf catalyze the anti-Markovnikov hydroalkoxylation only for acetylenes activated by esters.[11] Addition of allyl alcohol to phenylacetylene was also reported using a ruthenium catalyst but suffers low product selectivity.[12] Therefore, we examined the simple catalytic addition of alcohols to terminal acetylenes to obtain enol ethers with high product selectivity.

When the reaction of phenylacetylene (**1a**) and excess MeOH (**2a**) was performed with 5 mol % of dicarbonyl(2-methyl-8-quinolinolato)rhodium **3** at 65 °C for 24 h, anti-Markovnikov addition of **2a** proceeded to give β-methoxystyrene (**4aa**) in 22% GC yield (Table 1, entry 1). The C−O bond formation took place regioselectively at terminal carbon of **1a**, and no product formed via Markovnikov addition was observed.

Examination of various rhodium, iridium, and ruthenium complexes was carried out but resulted in <5% yield or no observation of **4aa**. The selected results are listed in Table 1 (entries 2−4).[13] The reaction using $[RhCl(CO)_2]_2$ as a catalyst gave acetophenone and phenylacetaldehyde dimethyl acetal in addition to the small amount of **4aa** (entry 2).

Table 1. anti-Markovnikov Addition of **2a** to **1a**[a]



entry	catalyst	temp	solvent	yield of **4aa**[b]
1	5 mol %  **3**	65 °C	–	22%
2	5 mol % $[RhCl(CO)_2]_2$[c]	65 °C	–	<5%
3	5 mol % $IrCl(CO)(PPh_3)_2$	65 °C	–	nd[d]
4	5 mol % $[RuCl_2(CO)_3]_2$[c]	65 °C	–	nd[d]
5	5 mol % **3**	65 °C	toluene	32%
6	5 mol % **3**	65 °C	THF	29%
7	5 mol % **3**	65 °C	DMF	44%
8	5 mol % **3**	65 °C	DMA	59%
9	5 mol % **3**	65 °C	Et_3N	7%
10	5 mol % **3**	65 °C	pyridine	nd[d]
11	5 mol % **3**	70 °C	DMA	62%
12[e]	2 mol % **3**	70 °C	DMA	80%[f] [90/10][g]

[a] Reaction conditions: 1 mmol of **1a**, 1 mL of **2a**, catalyst, solvent, 24 h. [b] GC yield of the mixture of *Z*- and *E*-isomers. [c] Used 2.5 mol % of the dimer. [d] nd = not detected. [e] 48 h. [f] 60% isolated yield. [g] *Z*/*E* ratio of **4aa**.

Solvents were then investigated for the hydroalkoxylation.[13] Most of the co-solvents screened, including toluene (entry 5) and THF (entry 6), did not increase the yield significantly. But the use of amides led to the improvement of the yield (entries 7 and 8), and the reaction in a 1:1 ratio of **2a** and DMA afforded the product in 59% yield (entry 8). To examine the effect of the slightly basic nature of amide solvent on the yield, stronger bases, Et_3N and pyridine, were used but only decreased the yield (entries 9 and 10).

Further optimization of the conditions revealed that a slight increase of the temperature to 70 °C (entry 11) and reduction of the catalyst loading to 2 mol % (entry 12) were effective for the reaction, and the product was obtained in 80% yield.[13]

The hydroalkoxylation described here is catalyzed specifically by dicarbonyl(8-quinolinolato)rhodium complexes among the catalysts screened (Scheme 1). Under the optimized conditions (Table 1, entry 12), several rhodium complexes bearing N−O anionic bidentate ligands were employed as catalysts. While a catalyst with unsubstituted 8-quinolinolato ligand provided 67% yield of **4aa**, use of carboxylate ligands was unsuccessful (≤7% yield). Substitution of a CO ligand with PPh_3 or both with COD ligand essentially stopped the desired reaction. It is noteworthy that 8-quinolinolato rhodium complexes have rarely been reported as catalysts, even

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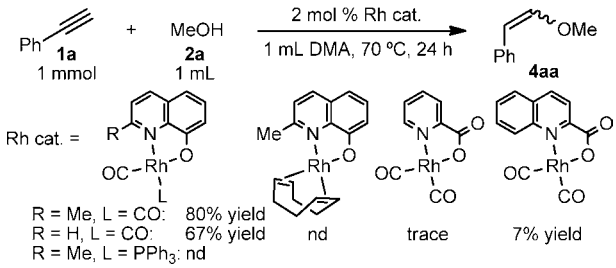
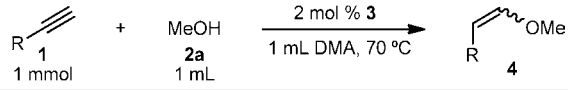
Scheme 1. Effect of Ligands for Hydromethoxylation of **1a**



for well-known reactions,[14] and have never been described as a suitable catalyst for novel reactions.

A variety of aryl- and heteroarylacetylenes were hydroalkoxylated by catalyst **3** to form enol ethers with high *Z* selectivity (Table 2).[15] Arylacetylenes having electron-withdrawing groups at their

Table 2. Hydromethoxylation of Terminal Acetylenes[a]



entry	1	R	4	yield of 4[b]	*Z*/*E*[c]
1	**1b**	*p*-$CF_3C_6H_4$	**4ba**	92% (48%)	94/6
2	**1c**	*p*-NCC_6H_4	**4ca**	85% (54%)	95/5
3	**1d**	*p*-$MeO_2CC_6H_4$	**4da**	82% (64%)	94/6
4	**1e**	*p*-AcC_6H_4	**4ea**	78% (55%)	94/6
5	**1f**	*p*-$O_2NC_6H_4$	**4fa**	73%[c] (57%)	94/6
6[d]	**1g**	*p*-MeC_6H_4	**4ga**	64% (53%)	88/12
7[d]	**1h**	*o*-MeC_6H_4	**4ha**	65% (58%)	70/30
8[e]	**1i**	*p*-$MeOC_6H_4$	**4ia**	64% (55%)	87/13
9	**1j**	2-naphthyl	**4ja**	55% (45%)	91/9
10	**1k**	3-thienyl	**4ka**	64% (52%)	88/12
11	**1l**	2-thienyl	**4la**	32%[c] (25%)	96/4
12	**1m**	*N*-methyl-2-indolyl	**4ma**	66% (39%)	80/20
13	**1n**	2-benzofuryl	**4na**	29%[c] (28%)	90/10
14[f]	**1o**	1-cyclohexenyl	**4oa**	27%[c] (17%)	50/50
15	**1p**	Ph_3C	**4pa**	69% (66%)	100/0

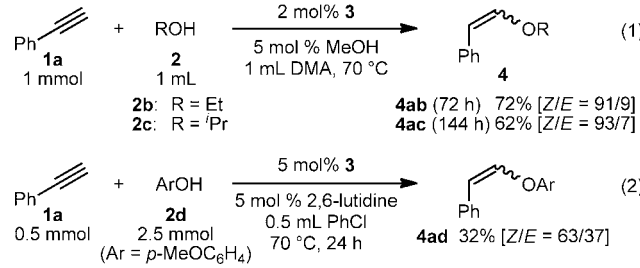
[a] Reaction conditions: 1 mmol of **1**, 1 mL of **2a**, 0.02 mmol of **3**, 1 mL of DMA, 70 °C, 48 h. [b] GC yield of the mixture of *Z*- and *E*-isomers. Isolated yields are in parentheses. [c] Determined by ^{1}H NMR. [d] 6 days. [e] 7 days. [f] 3 days.

para position, such as CF_3, CN, CO_2Me, Ac, and NO_2 groups, reacted with **2a** smoothly to give *β*-methoxystyrenes **4ba**−**4fa** in high yields with high stereo- and regioselectivities (entries 1−5). The electron-rich arylacetylenes **1g**−**1i** required longer reaction times, and their *Z* selectivity slightly decreased (entries 6−8). The reaction of sterically hindered *o*-tolylacetylene (**1h**) provided the corresponding product **4ha** in a yield similar to that of **4ga** obtained from *p*-tolylacetylene (**1g**). 2-Ethynylnaphthalene was also converted to the enol ether product by **3** (entry 9). 3- and 2-thienylacetylenes (**1k**, **1l**) were coupled with **2a** to give enol ethers **4ka** and **4la**, and the higher yield was obtained for **4ka** (entries 10 and 11). The addition of **2a** to terminal acetylenes having *N*-methyl-2-indolyl (**1m**) and benzofuryl (**1n**) groups also proceeded in the presence of **3** (entries 12 and 13).

The hydroalkoxylation of alkenyl- and alkylacetylenes was also examined. When the reaction was performed with (1-cyclohexenyl)-acetylene **1o**, methoxydiene product **4oa** was obtained with 1:1 *Z*/*E* selectivity (entry 14). The reaction was also found to be applicable to sp^3 carbon-substituted terminal acetylenes.[16] The reaction of tritylacetylene (**1p**) gave the corresponding anti-Markovnikov addition product **4pa** in 69% yield with complete *Z* selectivity (entry 15), and the structure of **4pa** was confirmed by X-ray crystallography.[13]

Internal acetylenes such as 1-phenyl-1-propyne were also investigated as substrates, but the reactions did not give hydroalkoxylation products. In the case of 1-phenyl-2-(trimethylsilyl)acetylene, desilylated enol ether **4aa** was obtained in 59% yield, instead of the simple hydroalkoxylation product.[17]

The hydroalkoxylation was also examined with several alcohols. When EtOH (**2b**) was used instead of **2a**, product **4ab** was obtained in 54% yield, and addition of 5 mol % of **2a** increased the yield to 64%. Extension of the reaction time to 72 h led to full conversion, and a 72% yield of **4ab** was achieved (eq 1). When more sterically demanding ^{i}PrOH (**2c**) was used, much longer reaction time was required to complete the reaction, but the corresponding product **4ac** was obtained in 62% yield with high *Z* selectivity (*Z*/*E* = 93/7).[18]



The addition of phenols was unsuccessful under similar reaction conditions, but in this case, use of a catalytic amount of a weak base, 2,6-lutidine, improved the product yields. When *p*-methoxyphenol (**2d**) was reacted with **1a** in the presence of 5 mol % of 2,6-lutidine in PhCl, aryl ether product **4ad** was obtained in 32% yield (eq 2).

The mechanism of the anti-Markovnikov addition of alcohols to terminal acetylenes is unclear at this point.[19] However, based on the results that the C−O bond is formed only at the terminal carbon and no hydroalkoxylation of internal acetylenes was observed, the reaction may proceed via a vinylidene−rhodium intermediate, followed by addition of alcohol,[20] similar to other additions of *O*-nucleophiles to terminal acetylenes.[21]

We reported here the first transition-metal-catalyzed anti-Markovnikov intermolecular hydroalkoxylation of terminal acetylenes to give the enol ethers in high yields without using bases for aliphatic alcohols. 8-Quinolinolato rhodium complexes were found to be effective catalysts for this transformation, which are structurally simple but relatively unexplored as catalysts. Further optimization of the reaction conditions and elucidation of the reaction mechanism are now underway

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Supporting Information Available: Experimental procedures, spectroscopic data for new compounds, and X-ray crystallographic data for **4pa** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Some isolated yields are much lower than GC (NMR) yields due to their volatility and/or low stability.
(16) The reaction of 1-octyne with **2a** in the presence of **3** gave a small amount (3% NMR yield) of the corresponding anti-Markovnikov addition product.
(17) The reaction of tri(isopropyl)silylacetylene with **2a** afforded only a trace amount (< 10% NMR yield) of the addition product under the standard reaction conditions. Other silyl acetylenes, such as trimethylsilyl-, triethylsilyl-, triphenylsilyl-, and *tert*-butyldimethylsilylacetylene, were not effective as substrates.
(18) Allyl and benzyl alcohol did not give the desired enol ether when used as *O*-nucleophiles. Acetic acid reacted under the standard reaction conditions, and the corresponding anti-Markovnikov addition product, β-styryl acetate, was produced in 28% GC yield (Z/E = 54/46).
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