Ruthenium Complexes of the General Formula $[RuCl_2(PHOX)_2]$ as Precatalysts in Propargylic Substitution Reactions

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Abstract: After activation by chloride abstraction utilizing NaBArF as an activator (BArF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate), a complex of the general formula $[RuCl_2(PHOX)_2]$ was utilized as a catalyst in propargylic substitution reactions, where PHOX is a phosphinooxazoline ligand. Oxygen and nitrogen-centered nucleophiles could be employed in the substitution of a propargylic acetate to obtain the corresponding propargylic substitution products in 87% to 9% isolated yields (45 °C, 16 h reaction time, toluene solvent, 1-2 mol% catalyst loading, 1-2 mol% activator).

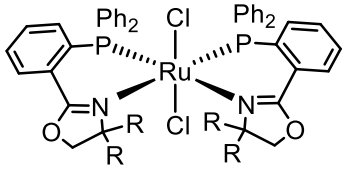
1. Introduction

Propargylic alcohols are valuable starting materials in the synthesis of complex organic molecules such as pharmaceuticals or natural products [1,2,3]. They are easily accessible on small and large scales [4], and enantioselective syntheses of propargylic alcohols are known [5,6]. Propargylic alcohols have a complex reaction landscape and can rearrange [7], thus allowing a plethora of derivatizations to occur with the potential for a quick increase of molecular complexity. The versatility of propargylic alcohols can lead to multiple products from given starting materials [8]. As a consequence, the transformations of propargylic alcohols are in many cases catalyzed by transition metals to reduce the number of side products [9].

Among a number of transition metal complexes,[10,11,12,13] ruthenium complexes [14,15] are widely employed to catalyze propargylic substitution reactions of the OH group by a nucleophile. Ruthenium complexes are known to form allenylidene complexes from propargylic alcohols [16], and these species can potentially function as intermediates for the substitution of the OH group of propargylic alcohols by nucleophiles [1,2,3]. Consequently, ruthenium-catalyzed transformations of propargylic alcohols have been intensively investigated by us [17,18,19,20] and others [1,3,14,15,21], and have resulted in a variety of catalyst systems for the transformation.

However, a drawback of some catalyst systems is that they require higher reaction temperatures than 60 °C [17,19]. These high reaction temperatures are undesired, not only due to the energy demand but the difficulties in achieving enantiomeric excesses and in addition to increasing the number of potential side reactions which lower the overall yields. Despite optimization efforts, catalyst systems investigated in our research group did not result in lower reaction temperatures where temperatures as high as 75 to 90 °C were required for the reactions

of terminal propargylic alcohols to proceed within reasonable time frames [17,19]. We recently published a number of ruthenium complexes of the general formula $[RuCl_2(PHOX)_2]$, where PHOX refers to bidentate phosphino oxazoline ligands [22]. Two examples are shown in Figure 1. These complexes did not show catalytic activity in the activation of propargylic alcohols, but after chloride abstraction with $AgSbF_6$, they were catalytically active in the Mukaiyama aldol reaction. The ruthenium complex with R = Me, which was used for this study, will subsequently be referred to as $[RuCl_2(PHOX)_2]$.



$[RuCl_2(PHOX)_2]$
R = H, Me

Figure 1. Ruthenium PHOX complexes.

It appeared to us that the modification of the mono-nuclear ruthenium complexes did not result in catalyst systems that would perform propargylic substitution reactions at lower temperatures. To achieve this goal and to support the principle that ruthenium complexes should be able to activate propargyl units at lower temperatures, we investigated whether propargylic acetates could be employed in the title reaction. We found that, after activation by chloride abstraction, the complex $[RuCl_2(PHOX)_2]$ is catalytically active for propargylic substitution reactions of a propargylic acetate employing oxygen- and nitrogen-centered nucleophiles.

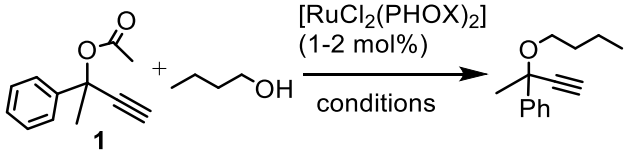
2. Experimental

Experimental details and characterization data are given in the Supplementary information.

3. Results and Discussion

As mentioned, the complex $[RuCl_2(PHOX)_2]$ itself did not show catalytic activity in the activation of propargylic acetates, presumably due to the fact that it does not contain open coordination sites. However, we observed catalytic activity in the test reaction between the known [23] propargylic acetate **1** and *n*-BuOH when the complex was activated by chloride abstraction (Table 1).

Table 1. Screening Reactions.



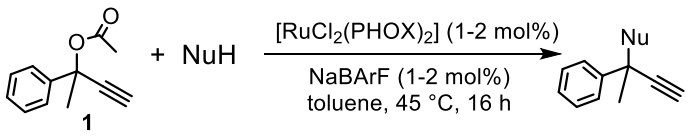
Entry[a]	Conditions	Yield (%) [b]
1	$ClCH_2CH_2Cl$, NaBArF, 45 °C, 16 h	100
2	CH_2Cl_2, NaBArF, 45 °C, 16 h	67
3	THF, NaBArF, 45 °C, 16 h	69
4	*n*-BuOH, NaBArF, 45 °C, 16 h	0
5	toluene, NaBArF, 45 °C, 16 h	100
6	$NaPF_6$, toluene, 45 °C, 16 h	0
7	$NaBF_4$, toluene, 45 °C, 16 h	0
8	NH_4PF_6, toluene, 45 °C, 16 h	0
9	NaBArF, no catalyst, 45 °C, 16 h	0

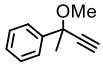
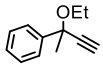
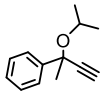
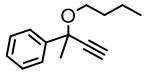
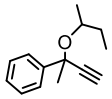
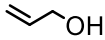
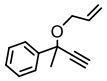
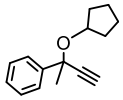
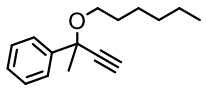
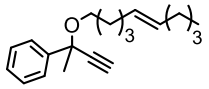
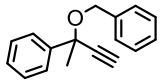
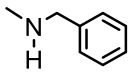
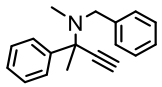
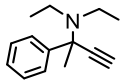
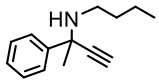
[a] Reaction conditions: propargylic acetate (**1,** 0.250 mmol), alcohol nucleophile (1 mmol), 2 mol% catalyst, 2 mol% activator, solvent (0.5 mL).
[b] Determined by GC

Initial screening of the catalyst system, utilizing the test reaction in Table 1, revealed that the yield strongly depended on the solvent and the activator utilized. As can be seen in Table 1, CH_2Cl_2 and THF were not efficient solvents, whereas in $ClCH_2CH_2Cl$, complete conversion of the acetate starting material to the product was observed by GC. However, in order to avoid chlorinated solvents, we utilized toluene, which worked equally well. Pure *n*-BuOH as the solvent (and the nucleophile) shut down the reaction completely (entry 4); presumably, the strongly coordinating *n*-BuOH permanently occupies open coordination sites on the ruthenium complex when utilized as a solvent. Some sodium and ammonium salts turned out to be inefficient as activators (entries 6-8), which we tentatively ascribed to the lower solubility of the salts in non-polar solvents. We found that NaBArF (BArF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) is the most efficient activator [24]. The activator itself did not catalyze the reaction (entry 9). We also optimized the reaction temperature; the reaction was very slow at room temperature, but at 45 °C, the reaction in Table 1 went to completion after 16 h. Analysis of the reaction mixtures by GC revealed that only small amounts of side products had formed; only starting materials and / or products were observed after reaction.

Under optimized reaction conditions (45 °C, 16 h reaction time, toluene solvent, NaBArF activator), we then employed a number of propargylic alcohol nucleophiles in the etherification of propargylic acetate **1** (Table 2) utilizing a number of alcohols as the nucleophiles. As can be seen from the table, the propargylic ethers were isolated in 87 to 68 % isolated yields (entries 1 to 10). Experimental details and spectroscopic characterization data are listed in the supporting information. Primary and secondary alcohols could be employed as the nucleophiles and unsaturated alcohols worked as well (entries 6 and 9).

Table 2. Isolated yields.



Entry [a]	NuH	Product	Yield (%)[b]
1	CH_3OH		77
2	EtOH		83
3	*i*-PrOH		68
4 [c]	*n*-BuOH		87
5 [c]	*sec*-BuOH		73 [d]
6			80
7	cyclopentanol		74
8 [c]	*n*-hexanol		77
9	(*E*)-dec-5-en-1-ol		77
10	$PhCH_2OH$		74
11 [e,f]			45
12 [c,e]	$HNEt_2$		9
13 [c,e]	H_2NBu		13

[a] Isolated Yields
[b] General conditions: Propargylic acetate (0.25 or 0.5 mmol) and nucleophile (1 or 2 mmol) in toluene (0.5 or 1 mL) catalyzed by $[RuCl_2(PHOX)_2]$ (2 mol%) and NaBArF activator (2 mol%) at 45 °C for 16 h. The products were isolated utilizing preparative column chromatography.
[c] 1 mol% catalyst load.
[d] Isolated as a 1:1 mixture of diastereomers, as determined by NMR.
[e] General conditions: Propargylic acetate (0.53 mmol), nucleophile (2.1 mmol) and Cs_2CO_3 (1.1 mmol) in toluene (1 mL) catalyzed by

$[RuCl_2(PHOX)_2]$ (1,5 mol%) and NaBArF activator (1.5 mol%) at 45 °C for 16 h. The products were isolated utilizing preparative column chromatography.
[f] 3 mol% catalyst load.

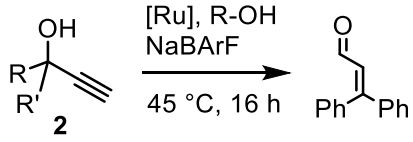
Overall, the reaction worked at lower reaction temperatures compared to other catalyst systems reported by us [17,19] and others [25], where propargylic alcohols were employed as starting materials. As established by GC, the propargylic acetate starting material was completely consumed after 16 h reaction times and only small amounts of side products were observed in the crude reaction mixture. Albeit complete conversions were observed by GC, the isolated yields did not exceed 87%. We tentatively ascribed this loss of yield to possible decomposition on the silica column during workup. Rapid column chromatography helped increase the yields and it turned out that in some cases, addition of small amounts of NEt_3 to the eluent to deactivate the column resulted in higher isolated yields.

The isolated yields compare well with other catalyst systems for the substitution of propargylic alcohols and propargylic acetates [2,3]. The alcohol nucleophile was only employed in a four-fold excess compared to some other catalyst systems, where the alcohol nucleophile is employed as the solvent for the reaction [3,26]. Employment of the propargylic acetate compared to the propargylic alcohol resulted in a lower reaction temperature compared to other catalyst systems for the title reaction [17,19]. The catalyst load of only 1 to 2% is very low.

In principle, the reaction also worked for propargylic amination (Table 2, entries 11 to 13). However, the isolated yields were lower and strongly amine-dependent. Propargylation of *N*-methyl-1-phenylmethanamine gave an isolated yield of 45% (entry 11). The isolated yield decreased to 9% to 13% when *N*,*N*-diethylamine (entry 12) and *N*-butylamine were employed, respectively (entry 13). It appears that the efficiency of amine nucleophiles for the title reaction

does not follow a clear trend; e.g. the sterically bulky *N*-methyl-1-phenylmethanamine gives a higher yield than the less bulky *N*,*N*-diethylamine. This phenomenon is currently under investigation.

Furthermore, the reaction showed strong dependency on the propargylic acetate employed. Secondary propargylic acetates (**2a**) or tertiary aliphatic acetates (**2b**) gave only trace amounts of the propargyl products (Scheme 1). Diphenyl propargylic acetate **2c** gave only small amounts of aldehyde as the rearrangement product; it is known that propargylic alcohols can undergo a Meyer-Schuster rearrangement to aldehydes [7], which appears to be the case here to a minor extent. While somewhat disappointing, these results offer some valuable clues to the mechanism of the reaction. It appears only strongly activated propargylic acetates give substitution products.

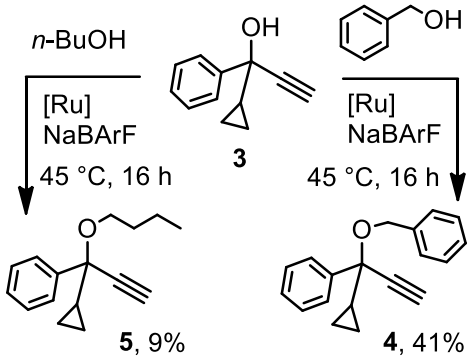


R = H, R' = Ph, **a**, no reaction
R = R' = Me, **b**, no reaction
R = R' = Ph, **c**, no reaction,
some rearrangement

Scheme 1. Substrate scope

In order to probe the mechanism further, we intended to employ cyclopropyl substituted acetates in the title reaction. Cyclopropyl substituents next to a reaction center can serve as radical clocks [27]. Radical clocks rearrange if a radical is formed; in the case of cyclopropyl substituents, a rearrangement to an alkene would take place [28]. We failed to convert the known cyclopropyl-substituted propargyl alcohol **3** (Scheme 2) into the corresponding acetate; only an inseparable mixture of compounds resulted. However, somewhat surprisingly, when the propargyl alcohol **3** was employed in propargylation reactions with benzyl alcohol and *n*-BuOH,

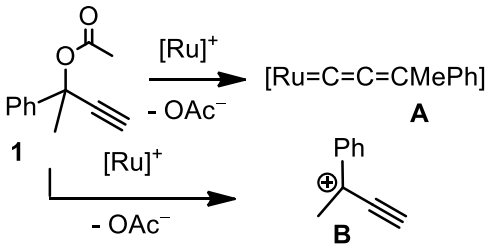
the corresponding propargyl ethers **4** and **5** were obtained in 41% and 9% isolated yields. Again, the isolated yields are not very high in these cases. However, besides starting materials, no other products formed. Most significantly, the cyclopropyl ring system remains intact. As such, it appears unlikely that radicals are involved in the reaction, although they have been suggested as potential intermediates in the conversion of propargylic alcohols [29]. The cyclopropyl ring obviously activates the propargyl alcohol **3** towards substitution, and an ionic intermediate seems to be in play.



Scheme 2. Cyclopropyl alcohol substitutions

Based on the data available, it is not possible to firmly establish a mechanism for the reaction. However, some speculations about a potential intermediate can be made. Based on the results in Scheme 2, a radical mechanism can be excluded. On the other hand, it is known that cyclopropyl substituents stabilize carbocation intermediates [30], which might be responsible for the enhanced reactivity of the cyclopropyl-substituted propargylic alcohol **3** in the substitution reaction. As mentioned, compound **3** is the only propargylic alcohol that was substituted under the conditions in Table 2. The title reaction has also been suggested for some catalyst systems to proceed through an allenylidene intermediate **A** (Scheme 3) [31]. However, under the reaction conditions in Table 2, we were not able to either detect or to independently generate an

allenylidene species **A**. On the other hand, as established in Table 2 and Scheme 2, only highly substituted, tertiary propargyl acetates can be employed in the title reaction. It is, thus, reasonable to assume that the ruthenium catalyst assists in formation of a propargylic cation **B** [32], which could subsequently be attacked by a nucleophile.



Scheme 3. Potential intermediates.

4. Conclusion

In conclusion, we investigated a catalyst system based on the ruthenium complex $[RuCl_2(PHOX)_2]$, which showed catalytic activity in the etherification and amination of a tertiary propargylic acetate. We demonstrated that NaBArF can activate a ruthenium chloro precursor complex to develop catalytic activity for the title reaction. Through employment of a propargylic acetate, the reaction temperature could be lowered compared to other catalyst systems utilized in the etherification of propargylic alcohols. A cyclopropyl substituted propargyl alcohol could also be employed in the title reaction; the cyclopropyl ring system stays intact during the reaction, excluding a radical mechanism and suggesting that a carbocation intermediate in the title reaction is more likely.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article (experimental details, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of the catalysis products in Table 2 and Scheme 2) can be found online at xxx.

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