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Short Communication

Etherification reactions of propargylic alcohols catalyzed by a cationic ruthenium allenylidene complex

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ABSTRACT

The cationic ruthenium allenylidene complex $R_{Ru}R_{ax}$−[Ru(indenyl)L(PPh$_3$)=C=C=CPh$_2$]$^+$PF$_6$ catalyzes the etherification of secondary and tertiary propargylic alcohols in a formal nucleophilic substitution reaction utilizing primary and secondary alcohols as the nucleophiles. At a catalyst loading of only 1.1 mol%, the corresponding propargylic ether products were obtained in 9 to 73% isolated yields (18 h reaction time at 100 °C); no further additives are required. The reaction exhibits an induction period; as shown by a control reaction, the high reaction temperature may chemically change the allenylidene complex to be employed as the catalyst but does not lead to catalyst deactivation.

Propargylic alcohols (**1** in Scheme 1) are valuable starting materials in organic synthesis [1–4]. They are easily accessible, e.g. through addition of acetylides to ketones [5–7]. The functionalization and derivatization of propargylic alcohols can quickly increase structural complexity [8,9]; consequently, propargylic alcohols are often starting materials for the synthesis of natural products or other complex organic molecules [10]. The nucleophilic substitution of the –OH group in propargylic alcohols is one way to modify the propargylic scaffold, as exemplified by the etherification reaction shown in Scheme 1, where an alcohol is the nucleophile and a propargylic ether **2** the product. Different mechanisms for the reaction are discussed in the literature, and one suggested mechanistic pathway proceeds through an allenylidene intermediate **3** (Scheme 1) [1,2]. However, the direct replacement of an –OH group in propargylic alcohols can be challenging. Rearrangement reactions of propargylic alcohols to aldehydes or ketones are often observed as byproducts [1]. These rearrangement reactions to aldehyde and ketones (referred to as Meyer–Schuster [11–13] and Rupe [14,15] rearrangements) can be synthetically useful in their own right, but in the context of propargylic substitution reactions they are yield-diminishing side reactions.

Consequently, catalyst systems for propargylic substitution reactions need to specifically catalyze the substitution while being inefficient for the corresponding rearrangement reactions. Furthermore, –OH groups are poor leaving groups, making their substitution more difficult. As a consequence, the –OH group in propargylic alcohols is often in a first step converted to a better leaving group prior to further functionalization. Nevertheless, substantial progress has been made in recent years towards the *direct* [1,3,4] replacement of –OH groups in propargylic alcohols by carbon- [16,17] oxygen- [18–20], phosphorus- [21] or nitrogen-based nucleophiles [22], and a few enantioselective catalyst systems have been reported as well [23,24]. Ruthenium, iron, gold, copper and rhenium based complexes are the most widely used catalyst systems [1,2].

Still, the number of catalyst systems for substitution reactions is scarce, when compared to its sister reaction, i.e. allylic substitution reactions [25]. Often high temperatures are required for catalytic activity [1], and as a consequence, there is a need for reactive, tunable catalysts, which eventually can be employed in enantioselective versions of the title reaction.

As part of our longstanding research program, we are interested in the catalytic and stoichiometric activation of propargylic alcohols by ruthenium complexes [26–29]. Ruthenium complexes can form allenylidene complexes [Ru=C=C=CR$_2$] from propargylic alcohols [30,31]. They can be attacked by nucleophiles and, thus, potentially serve as intermediates in catalytic propargylic substitution reaction cycles [1,4,30]. We have recently synthesized the cationic ruthenium allenylidene complex $R_{Ru}R_{ax}$−[Ru(indenyl)L(PPh$_3$)=C=C=CPh$_2$]$^+$PF$_6$ (**4**, Fig. 1), where L is a phosphoramidite ligand [27,28].

The complex is chiral at the metal and at the phosphoramidite ligand and was obtained as a single diastereomer. Allenylidene complexes can serve as catalysts for organic transformations, and we speculated as to whether the cationic complex **4** could be catalytically active in the etherification of propargylic alcohols through a propargylic substitution reaction, using alcohols as nucleophiles. The complex is chiral and tunable through the coordinated ligands, and we identified **4** as a good candidate for investigations and for tuning efforts to be performed in future research. Related cationic complexes have previously been employed in propargylic substitution reactions [32,33]. We describe herein the catalytic activity of the complex in the title reaction.

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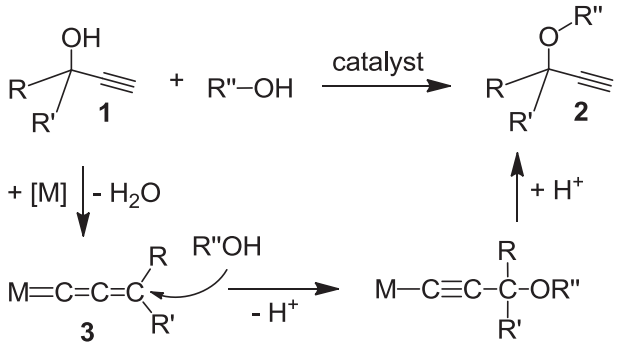


Scheme 1. Propargylic etherification reaction and potential mechanism through an allenlidene intermediate.

Screening efforts (which are not detailed here) were undertaken to identify an appropriate solvent and a temperature for the etherification reaction to be catalyzed by complex **4**. We found that with toluene as a solvent at a temperature of 100 °C complex **4** efficiently catalyzed the reaction of a variety of propargylic alcohol 5 and alcohol 6 to give the corresponding propargylic ethers **7** within 18 hour reaction time (Table 1). At a catalyst loading of only 1.1 mol%, the reacting alcohols were employed in a three to five-fold excess over the propargylic alcohols, and the propargylic ether substitution products were isolated by column chromatography. As assessed by GC, after 18 h at 100 °C, the propargylic starting material had been completely consumed, and a new peak for the product was detected. No side products were observed except for some dehydration products for the cyclic propargylic alcohols in entries 7 to 10 [14]. The isolated yields are lower than the complete conversion observed by GC would suggest, and it might be that some product decomposition occurs during purification by column chromatography.

The identity of the propargylic ether products was readily established by ^{1}H and $^{13}C\{^{1}H\}$ NMR and by IR. The terminal alkyne units gave characteristic chemical shifts, around 2.5 ppm for the terminal proton and around 75 and 85 ppm for the two alkyne carbon atoms. Furthermore, a characteristic υ_{CH} stretch in the IR spectra around 3300 cm^{-1} for the terminal ≡C–H unit was observed. No strong, broad IR stretch around 3300 cm^{-1} originating from alcohols was detected, indicating the absence of starting materials in the isolated products.

Primary alcohols (ethanol, *n*-butanol and benzyl alcohol) and secondary and tertiary propargylic alcohols gave the corresponding propargylic ethers in 28 to 73% isolated yields (Table 1). The secondary alcohol isopropanol gave lower isolated yields (9 to 21%) when reacted with secondary or tertiary propargylic alcohols (entries 5 and 8). We ascribe these lowered isolated yields to the decreased nucleophilicity of the secondary alcohol isopropanol compared to the primary alcohols employed in the study. Control experiments showed that the 18 hour

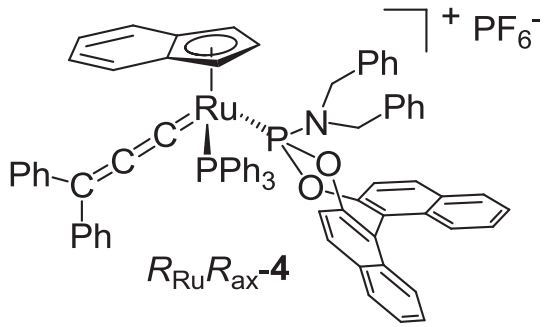
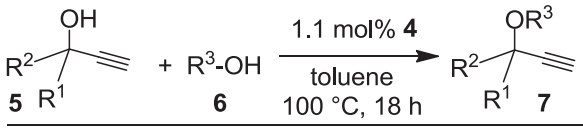
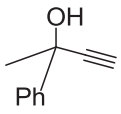
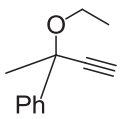
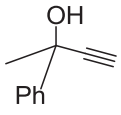
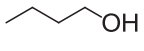
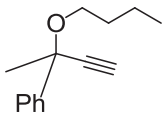
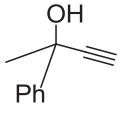
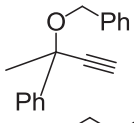
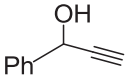
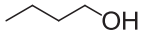
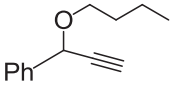
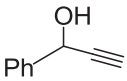
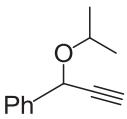
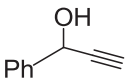
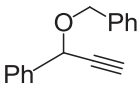
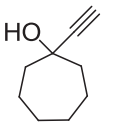
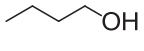
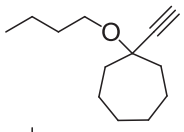
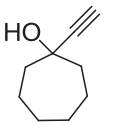
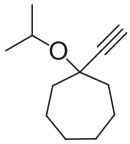
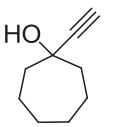
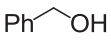
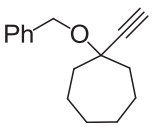
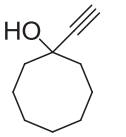
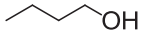
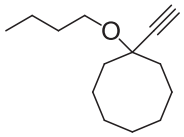


Fig. 1. Cationic ruthenium allenylidene complex $R_{Ru}R_{ax}$–**4** investigated as a catalyst in the current study.

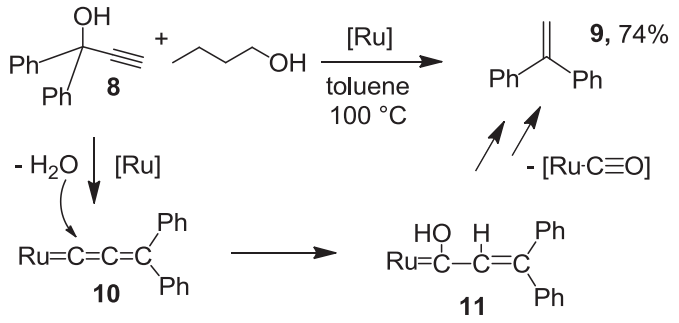
Table 1
Isolated yields.



Entry [a]	Substrate	R^3–OH	Product	Isolated yield
1				29%
2				41%
3				72%
4				73%
5				21%
6				70%
7				65%
8				9%
9				56%
10				28%

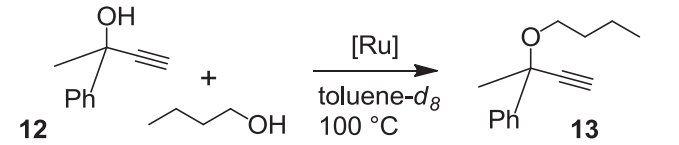
[a] Typical conditions: alkynol (0.7 mmol) and alcohol (3.3 mmol) in toluene (1 mL) catalyzed by **4** (0.008 mmol), at 100 °C for 18 h. The products were isolated by column chromatography.

reaction time reported in Table 1 is a requirement for efficient product formation. Lower reaction times or lower temperatures resulted in an incomplete reaction with propargylic starting material still remaining in the reaction mixture, as assessed by GC measurements. The internal propargylic alcohol 2-methylhex-3-yn-2-ol could not be converted to ether products under the conditions in Table 1. An increase of the catalyst load to 2 mol% did not result in a higher isolated yield, as established for the reaction in entry 2 of Table 1. The catalyst system described herein compares (with respect to reaction conditions and yields) well with other catalysts reported in the literature [1,2,18–20]. However, the catalyst loading for **4** was only 1%, and with one exception



Scheme 2. Reactivity of 1,1-diphenylprop-2-yn-1-ol (**8**).

Table 2
Product formation over time.



Time	Conversion to **13** (NMR)
90 min	0%
200 min	11%
360 min	46%
480 min	66%
1300 min	100%

[18], the other catalyst systems require catalyst loadings of 5 mol% [34] or higher. Furthermore, no additives are required for the catalyst system.

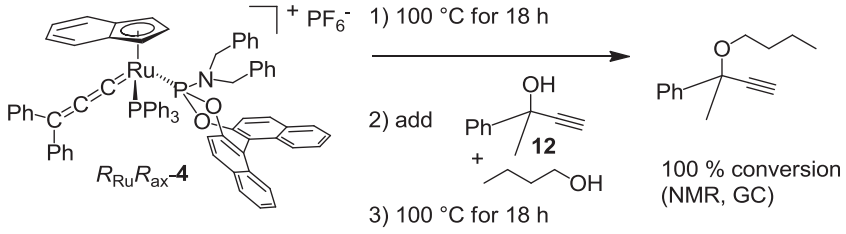
As investigated by GC and NMR, the crude reaction mixtures of the catalytic experiments in Table 1 did not show any signs for rearranged propargylic alcohol starting materials or products derived from them. However, when the propargylic alcohol 1,1-diphenylprop-2-yn-1-ol (**8**) was employed as substrate in combination with *n*-butanol, only very small amounts of the etherification product were observed by NMR. Instead, 1,1-diphenylethylene (**9**, Scheme 2) was obtained in 74% isolated yield after column chromatography. The formation of 1,1-diphenylethylene **9** can be rationalized when assuming that the reaction proceeds through an allenylidene intermediate (**10**, Scheme 2). Allenylidene **10** can be attacked by water that had formed through allenylidene formation, leading to 1,1-diphenylethylene (**9**) and a ruthenium carbonyl complex. Such reactivity has been observed previously by us [26] and others [35]. Benzophenone, which can also be formed as a result of the reaction in Scheme 2 [35], was observed in the reaction mixture as well, as assessed by GC/MS (chromatogram see supporting information). However, workup only resulted in the isolation of 1,1-diphenylethylene. It appears that the diphenyl allenylidene intermediate **10** is prone to the attack of water (or the formation of 1,1-diphenylethylene is especially favorable), whereas the other propargylic alcohols employed in Table 1 react with the alcohol substrates to give the corresponding propargylic ethers.

To further explore the scope of the reaction and to gain some hints about the catalytically active species and the mechanism, additional experiments were performed. First, the reaction between the propargylic alcohol **12** and the *n*-butanol was followed by ^{1}H NMR measurements in toluene-d_8 over time under the same reaction conditions reported in Table 1. Some conversion rates over time are reported in Table 2 (as determined by integration of the ≡C–H signals of the starting material **12** and the product **13**). The reaction seemed to exhibit an induction period, as can be seen from the low conversions in the first 3 h of the reaction. Further research is necessary to investigate the cause for the induction period. It appears reasonable to assume that the catalytically active species forms in the early stage of the reaction, causing a delay in product formation. This assumption is corroborated by the fact, that the ^{31}P{^{1}H} NMR signals of the catalyst **4** disappeared over time in the experiment in Table 2. The catalyst **4** exhibits two doublets for the two coordinated phosphorus atoms in the ^{31}P{^{1}H} NMR spectrum, which completely disappeared by the end of the 18 hour reaction time. The ^{31}P{^{1}H} NMR spectrum of the sample after heating at 100 °C for 18 h exhibited signals for free PPh_3 and oxidized PPh_3 as well as a peak resulting from the oxidation of the phosphoramidite ligand (spectrum see supporting information). The spectrum, however, does not establish a catalytically active ruthenium species nor allows for the conclusion that the catalytically active species is ligand-free. The ^{31}P{^{1}H} NMR signals for the active species could (due to the low concentration of the catalyst in solution) also be hidden in the baseline.

We investigated further whether a chemical transformation of complex **4** generates the catalytically active species for the reactions in Table 1. We first heated the catalyst in toluene-d_8 to 100 °C in the absence of any substrates for 18 h (Scheme 3), after which the characteristic doublets in the ^{31}P{^{1}H} NMR spectrum for complex **4** had disappeared. Then, the propargylic alcohol **12** and *n*-butanol were added to the solution, and the mixture was heated for another 18 h. It was observed that the complex **4**, when first heated for 18 h, also completely converted the propargylic alcohol **12** to the corresponding propargylic ether. Besides the product, no propargylic alcohol starting material **12** was detected by GC and NMR. Thus, it appears that complex **4** might decompose during heating over time, but the decomposition product is still catalytically active. The decomposition product might even be the only catalytically active species in solution, as judged from the induction period established in Table 2.

However, the results in Scheme 2 and Table 2 do not allow for establishing a mechanism for the reaction. For the reactions in Table 1, virtually no optical rotation for the products was observed. Consequently, other mechanisms (e.g. through carbocation intermediates) might apply as well, and further investigations are necessary to obtain information about the catalytically active species and to establish a mechanism for the title reaction.

In conclusion, we demonstrated the catalytic activity of a cationic, chiral-at-metal ruthenium allenylidene complex $R_{Ru}R_{ax}$–[Ru(indenyl)L(PPh_3)=C=C=CPh_2]$^{+}PF_6$ for the etherification of secondary and tertiary propargylic alcohols to obtain the corresponding propargylic ethers in 9 to 73% isolated yields (1.1 mol% catalyst loading, 18 h at 100 °C in toluene). Preliminary investigations related to the mechanism and the identity of the catalytically active species revealed that the reaction proceeds through an induction period and that



Scheme 3. NMR experiment to determine catalytic activity after heating the catalyst.

the high reaction temperatures do not destroy the catalytic activity of the ruthenium complex to be employed for the reaction. The complex $R_{Ru}R_{ax}$−[Ru(indenyl)L(PPh_3)═C═C═CPh_2]$^+PF_6$ constitutes a tunable platform for further investigations, and research to improve catalytic activity and the identification of the catalytically active species in solution is currently underway.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data to this article (experimental details, ^1H and $^{13}C\{^1H\}$ NMR spectra of the catalysis products in Table 1 and Scheme 2, a representative GC chromatogram and the $^{31}P\{^1H\}$ NMR spectrum associated with 2) can be found online at http://dx.doi.org/10.1016/j.catcom.2014.01.002.

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