Halogenation

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Selective Ruthenium-Catalyzed Hydrochlorination of Alkynes: One-Step Synthesis of Vinylchlorides

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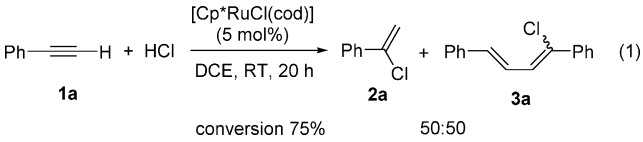
Abstract: *An unprecedented ruthenium-catalyzed direct and selective alkyne hydrochlorination is reported and leads to vinylchlorides in excellent yields with atom economy. The reaction proceeds at room temperature from terminal alkynes and provides a variety of chloroalkenes. Only the regioisomer resulting from the formal Markovnikov addition is selectively formed. Mechanistic studies show the stereoselective syn addition of HCl to alkynes at room temperature and suggest a chloro hydrido Ru^{IV} species as a key intermediate of the reaction.*

The development of straightforward and selective methodology to produce vinylhalides is an important continuing goal. These versatile and reactive substrates constitute valuable intermediates in many organic transformations either in industry or on a bench scale.[1] In the last decade, thanks to the emergence of new ligands, vinylchlorides are becoming increasingly interesting partners in catalyzed cross-coupling processes, notably for C–N and C–C bond formation in palladium-catalyzed amination[2] or Suzuki–Miyaura reactions.[3] This class of compounds also exhibits broad biological activities and many natural or synthetic products contain a vinylchloride moiety.[4–7] Therefore, the straightforward regio- and stereoselective synthesis of vinylchlorides is highly desirable. Vinylchlorides mainly arise from carbonyl compounds,[6,8] by a halogenation reaction with harmful, traditional phosphorous reagents or acid chlorides, or from alkynes.[9] The stoichiometric formation of a boron or metal vinyl intermediate from alkynes, followed by addition of a chloride, is a classical process to provide chloroalkenes.[10] Although the direct addition of HCl to alkynes seems to be one of the most straightforward synthetic methods to produce chloroalkenes, this reaction does not take place in a preparatively useful manner. Historically, first attempts to add a solution of HCl to a triple bond provided mixtures of compounds with low selectivity and/or low yields.[11] Some improvements were obtained in the presence of a Lewis acid catalyst such as $ZnCl_2$ or $FeCl_3$,[12] or by the use of appropriate silica gel or alumina surfaces.[13] Unfortunately, the scope of these reactions is quite narrow. Recently, a preparation of α-chlorovinylethers was also reported and involved the in situ generation of HCl from TMSCl and MeOH.[14] Vapor-phase hydrochlorination of alkynes by gaseous HCl was also realized on immobilized metal chloride catalysts, but good yields were limited to the reaction of acetylene.[15] Finally, a hydrochlorination reaction can proceed with a source of proton along with metal chlorides such as $ZnCl_2$, $MgCl_2$, $FeCl_3$, or LiCl but the requirement of a stoichiometric amount of metallic salt hampers its applicability.[16] To the best of our knowledge, Zhu and co-workers described the unique palladium-catalyzed hydrochlorination of haloalkynes using a LiCl/HOAc system.[16f] Thus, the efficient, ecofriendly, and general formation of vinylchlorides in a stereoselective fashion by a direct hydrochlorination of alkynes still constitutes a challenging objective.

In the course of our studies on the catalytic activity of the complex [Cp*RuCl(cod)] (cod = 1,5-cyclooctadiene, Cp* = C_5Me_5) towards alkynes,[17] we developed a catalytic hydrohalogenative dimerization of alkynes in one step under mild reaction conditions[18] and we observed the formation of alkenylchlorides as side products [Eq. (1); DCE = 1,2-dichloroethane]. Herein we report on a new efficient and productive ruthenium-based catalytic system, which provides selective alkyne hydrochlorination, thus giving access to vinylchlorides in good yields under mild reaction conditions.



(1)

The [Cp*RuCl(cod)] catalyst (**A**) was found to be active in the direct addition of HCl with alkynes to give vinylchlorides. However, a modest yield of **2a** was obtained during our initial attempts [Eq. (1)]. Reaction temperature and concentration had only limited impact, so we investigated the influence of the catalyst (Table 1). The presence of the Cp* ligand seems to be necessary to provide **2a**, whereas half-sandwich (*p*-cymene)ruthenium complexes inhibit the reaction (entries 1 and 2). Gratifyingly, the addition of one equivalent of a phosphine ligand to the [Cp*RuCl(cod)] complex prevented the side formation of a bis(carbene) ruthenium complex intermediate, which leads to dienylchlorides,[18] and afforded **2a** in 98% yield after 10 minutes at room temperature. Only the regioisomer resulting from formal Markovnikov addition was selectively formed. This reaction did not proceed with the sole presence of PPh_3. A lower amount of catalyst (2.5 mol%) still led to a good yield of **2a** (entries 3 and 4). The isolated $[Cp^*RuCl(PPh_3)_2]$ complex was then used as the catalyst precursor to produce similar

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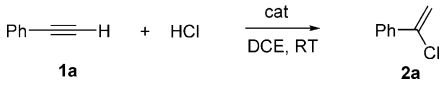
Table 1: Development of the catalytic reaction.[a]



1a **2a**

Entry	Cat (mol%)	[**1a**][b]	HCl/**1a**	*t*	Conv. **1a** [%]	Yield **2a** [%][c]
1	[Cp*RuCl(cod)] (5)	0.25	2.0	20 h	75	25
2	[{(*p*-cymene)$RuCl_2$}$_2$] (5)	0.25	2.0	20 h	0	–
3	[Cp*RuCl(cod)]/PPh_3 (5)	0.25	2.0	10 min	100	98
4	[Cp*RuCl(cod)]/PPh_3 (2.5)	0.25	2.0	10 min	100	97
5	[Cp*RuCl(PPh_3)$_2$] (2.5)	0.25	2.0	10 min	100	97
6	[CpRuCl(PPh_3)$_2$] (2.5)	0.25	2.0	4 h	100	58
7	[Cp*Ru(CH_3CN)$_3$]PF_6/PPh_3 (2.5)	0.25	2.0	10 min	100	95
8	[Cp*RuCl(cod)]/PPh_3 (2.5)	1.0	2.0	10 min	100	97
9	[Cp*RuCl(cod)]/PPh_3 (2.5)	2.0	1.1	10 min	100	99

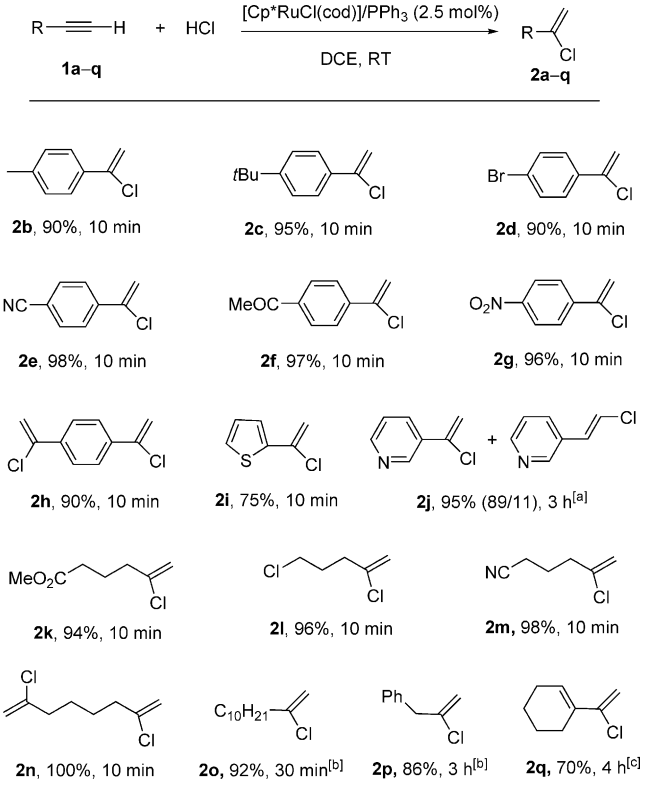
[a] Reaction conditions: **1a** (1.0 mmol), HCl (2 N in Et_2O), DCE, RT. [b] Molar concentration. [c] Determined by ^{1}H NMR analysis of the reaction mixture using naphthalene as an internal standard.

results, whereas the [CpRuCl(PPh_3)$_2$] precursor showed a lower reactivity, thus providing **2a** in only 58% yield (entries 5 and 6). The use of the cationic [Cp*Ru(CH_3CN)$_3$]PF_6/PPh_3 system also led to good yield and selectivity in **2a** (entry 7). Interestingly, increasing the concentration of **1a** led to the best results and allowed a decrease in the HCl/**1a** ratio from 2.0 to 1.1 (entries 8 and 9). Further optimization of solvents revealed that the reaction took place in various polar and nonpolar solvents, however the best results were obtained in DCE and in DMC (dimethyl carbonate).

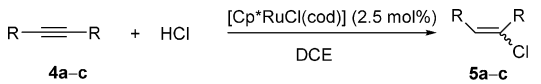
With our optimized reaction conditions, we then examined the scope of the preparation of vinylchlorides from various terminal alkynes (Scheme 1). The reaction proceeded smoothly and appeared to be quite general with various functional groups. Excellent yields of the vinylchlorides **2b–h** (90–99%) were obtained from arylacetylenes containing either electron-withdrawing or electron-donating groups. The reaction of 2 equivalents of HCl with 1,4-diethynylbenzene afforded 1,4-di(chloroethenyl)benzene (**2h**) in 90% yield. Hetero-arylacetylene derivatives also reacted with HCl to give vinylchlorides. Thus, 2-ethynylthiophene led to the volatile compound **2i** in 75% yield and 3-ethynylpyridine produced vinylchlorides **2j** in 95% yield. In this latter case, 10% of a regioisomer, 3-(*E*-2-chlorovinyl)pyridine, was formed. Alkylacetylenes containing either an ester, cyano, chloro, or a second alkynyl functional group gave, quantitatively, the corresponding vinylchlorides **2k–m**, as well as 2,7-dichloroocta-1-7-diene (**2n**) by addition of 2 equivalents of HCl to 1,7-octadiyne. The non-activated alkynes **1o–q** also led to good yields of the compounds **2o–q**, as only one regioisomer, but required slight modifications of the reaction conditions.

Internal alkynes showed lower reactivity but because of the impossible formation of the bis(carbene) species, the addition of PPh_3 was not required. At 30°C, only a 10% conversion of dec-5-yne (**4a**) was observed after 3 hours (Scheme 2). Two stereoisomers for **5a** were produced in a 93:7 ratio. Gratifyingly, at 60°C, complete conversion of **4a** could be obtained after 3 hours, thus leading to a 96% yield in the chlorodecenes **5a**, in a 85:15 ratio for the two stereoisomers. NMR spectroscopic analyses seem consistent with a *syn* addition of HCl to the triple bond for the major isomer, thus leading to the *E* stereoisomer. When the reaction was carried out at 90°C the second stereoisomer, arising from a formal *anti* addition of HCl, became the major one. Similar results were produced from hex-3-yne (**4b**), whereas the more bulky diphenylacetylene (**4c**) was less reactive and afforded only 30% conversion after 3 hours. The conversion and the yield of **5c** increased to 60% after 20 hours with 5 mol% of catalyst, but in a lower *E*/*Z* ratio of 65:35.

During our studies on the dimerization of alkynes, we described an efficient hydrohalogenative system consisting of separate proton and halide sources. The best results were obtained by using a combination of camphorsulfonic acid (CSA)/$BnEt_3NX$.[18] Adjustment of this protocol, through addition of extra PPh_3, resulted in an efficient catalytic system to produce **2a** (for X = Cl) in 97% yield (Scheme 3). Modification of the counteranion of the ammonium salt provided a straightforward methodology to selectively produce the corresponding halides and led to α-bromostyrene (**6a**) and α-iodostyrene (**7a**) in 95 and 88% yield, respectively.

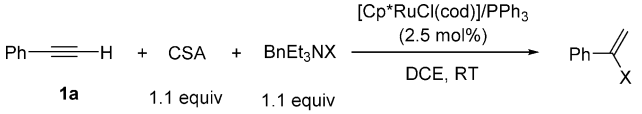


Scheme 1. Ruthenium-catalyzed reaction of terminal alkynes (**1a–q**) with HCl. Reaction conditions: **1** (1.0 mmol), HCl (2 N in Et_2O, 1.1 equiv/triple bond), DCE (0.5 mL), RT, cat **A**/PPh_3 system (**1**/[Ru] in 1:0.025 molar ratio). Yields are for products isolated after purification by silica gel chromatography. [a] 3 equiv of HCl in DCE (4 mL). [b] **1**/[Ru] in 1:0.05 molar ratio. [c] 2 equiv of HCl in DCE (4 mL).



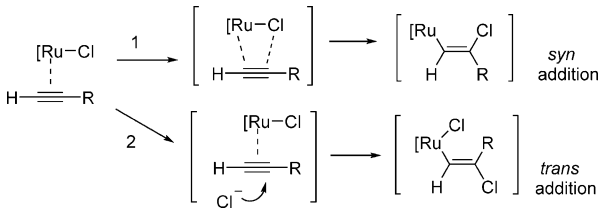
R= Bu (**4a**)	30 °C, 3 h	10% (*E*/*Z* : 93:7)
	60 °C, 3 h	96% (*E*/*Z* : 85:15)
	90 °C, 4 h	80% (*E*/*Z* : 40:60)
R= Et (**4b**)	60 °C, 3 h	85% (*E*/*Z* : 85:15)
R= Ph (**4c**)	65 °C, 3 h	30% (*E*/*Z* : 79:21)

Scheme 2. Ruthenium-catalyzed reaction of internal alkynes with HCl.



X = Cl	1 h	**2a**, 97%
X = Br	2 h	**6a**, 95%
X = I	3 h	**7a**, 88%

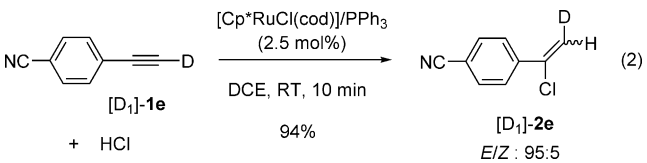
Scheme 3. Ruthenium-catalyzed hydrohalogenation of phenylacetylene with the CSA/$BnEt_3NX$ system.

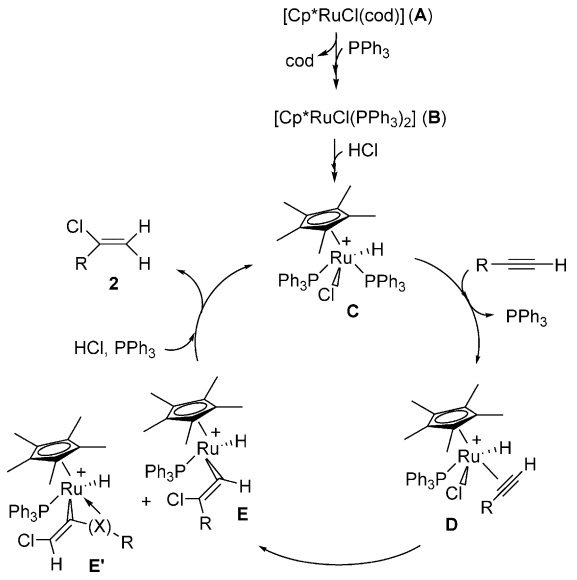


Scheme 4. Key steps of the formation of the vinylchlorides **2**.

Two types of reaction mechanism may explain this ruthenium-catalyzed hydrochlorination of alkynes, thus affording the vinylchlorides **2** by incorporation of the chloride at the more substituted carbon atom of the alkyne (Scheme 4): 1) an intramolecular pathway involving the insertion of the triple bond into the Ru–Cl bond can occur.[19] Because of the steric hindrance of the R substituent, a regioselective chlororuthenation could lead to the *syn* addition product. 2) an external nucleophilic attack of a chloride on the coordinated triple bond results in the *anti* addition of HCl.

To discriminate between these postulated pathways, we performed an experiment using a deuterated alkyne. When the reaction of [D_1]-**1e** was carried out in the presence of HCl under the optimized reaction conditions, [D_1]-**2e** was obtained in 94% yield with an *E*/*Z* ratio of 95:5, as determined by ^{1}H NMR spectroscopy [Eq. (2)]. The observed deuterium labelling showed that the major stereoisomer corresponds to a *syn* addition of HCl to the triple bond. The





Scheme 5. Proposed catalytic cycle.

first mechanistic pathway may be then advocated for terminal alkynes.

A possible catalytic cycle for the formation of the vinylchlorides **2** is presented in Scheme 5. In the presence of PPh_3, the complex [Cp*RuCl(cod)] (**A**) can lose its cod ligand to produce the complex [Cp*RuCl(PPh_3)$_2$] (**B**). Indeed, when one equivalent of PPh_3 was added to a solution of **A** in CD_2Cl_2 under Ar, ^{1}H and ^{31}P NMR signals corresponding to **B** appeared. In acidic medium, by adding one equivalent of HCl, **B** probably ionizes, thus leading to the cationic complex [Cp*RuHCl(PPh_3)$_2$]$^+$ (**C**).[20] Indeed, when we followed the reaction of **1a** with one equivalent of the system CSA/$BnEt_3NBr$ in the presence of 10% of [Cp*RuCl(cod)]/PPh_3, we observed the almost exclusive formation of bromide derivative at the beginning of the reaction, thus showing the dissociation of the complex **B** and the oxidative addition of HX reagent. In addition, the ruthenium(IV) chloro hydrido complexes [Cp*RuHCl(PEt_3)$_2$]BAr_4 and [Cp*RuHCl($PMeiPr_2$)$_2$]BAr_4 were isolated and characterized by Valerga and co-workers after oxidative addition of HCl to the cationic 16e$^-$ complexes [Cp*Ru(PEt_3)$_2$]BAr_4 and [Cp*Ru($PMeiPr_2$)$_2$]BAr_4.[20] The compounds [Cp*RuHCl(PMe_3)$_2$]X (X = PF_6[21] or CF_3SO_3[22]) were also obtained from the complex [Cp*RuCl(PMe_3)$_2$] by addition of NH_4PF_6 or CF_3SO_3H. For all these chloro hydrido complexes, the ^{1}H NMR spectra display one triplet resonance in the hydride region, and it results from the coupling with the two equivalent phosphorus atoms. To evaluate the possible formation of a cationic [Cp*RuHCl(PPh_3)$_2$]$^+$ intermediate, we performed the addition of one equivalent of HCl (2N in Et_2O) to a solution of [Cp*RuCl(cod)]/PPh_3 in CD_2Cl_2 at room temperature. The ^{1}H and ^{31}P NMR spectra, obtained after 2 hours, revealed the presence of both free cod ligand and **B**, as well as new resonances. The ^{1}H NMR spectrum exhibited the methyl resonance of a Cp* ligand as a broad singlet at $\delta = 1.26$ ppm and one triplet resonance in the hydride region, at $\delta = -7.73$ ppm ($^2J_{PH} = 33$ Hz), whereas the

$^{31}P\{^{1}H\}$ NMR spectrum displayed a new singlet arising at $\delta =$ 32.3 ppm. These observations are consistent with the formation of a cationic Ru^{IV} hydrido intermediate. Thus, we postulate the formation of the complex **C** as catalytic species which can coordinate one molecule of alkyne, after displacement of one PPh_3 ligand, thus leading to species **E** by insertion of the triple bond into the Ru–Cl bond.[19] The regioselective chlororuthenation favors the addition of the chloride at the more substituted carbon atom. However, if the alkyne possesses a substituent which can coordinate to the ruthenium center [e.g. the 3-ethynylpyridine (**1i**)], the product resulting from the opposite regioselectivity can be obtained (**E′**). These species **E** are subject to reductive elimination to give the vinylchlorides **2**, *syn* addition products, and to regenerate the catalyst **C**. In the case of internal alkynes, and in the absence of PPh_3 ligand, another mechanistic pathway cannot be ruled out.

In summary, we have successfully developed an unprecedented, efficient, and selective alkyne hydrochlorination by a ruthenium-catalyzed process. This straightforward access to aliphatic and aromatic vinylchlorides proceeds in excellent yields and constitutes a good example of an atom-economic transformation. A sole regioisomer is selectively formed and mechanistic studies show a stereoselective *syn* addition of HCl to alkynes at room temperature.

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