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Cationic ruthenium complex of the formula [RuCl(2,6-diacetylpyridine)$(PPh_3)_2$]BArF and its catalytic activity in the formation of enol esters

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ABSTRACT

A new ruthenium 2,6-diacetylpyridine complex was synthesized and applied in the atom-economic synthesis of enol esters through Markovnikov-directed addition of carboxylic acids to terminal alkynes. The ruthenium complex [RuCl(dap)$(PPh_3)_2$]$^+$BArF$^-$ was synthesized from [$RuCl_2(PPh_3)_2$] and the corresponding ligand 2,6-diacetylpyridine (dap). The complex was characterized structurally. The new ruthenium complex was utilized under ambient conditions as a catalyst in the Markovnikov addition of carboxylic acids to terminal alkynes to afford the corresponding enol esters in 93% to 52% isolated yields (85 °C, 16 h reaction time, 1 mol% catalyst loading).

Introduction

Alkynes are valuable starting materials in organic synthesis, and their transformations can produce a variety of compound classes. Many of these transformations are transition-metal catalyzed, and the palladium-catalyzed Sonogashira coupling between terminal alkynes and aryl- or vinyl halides is a prominent example.[1] The addition of carboxylic acids to terminal alkynes is an atom-economical reaction to afford enol esters, and the reaction requires promotion by a catalyst.[2] The reaction can generate different regioisomers; Markovnikov addition provides the corresponding geminal enol esters **A**, whereas *anti*-Markovnikov addition leads to the corresponding (*E*) and (*Z*) enol esters **B** (Scheme 1). Control of the regioselectivity is, thus, crucial for the reaction to be synthetically useful. Ruthenium catalysts are widely employed for the reaction since the pioneering work of Shvo.[3] There are catalyst systems known that produce primarily the Markovnikov enol esters **A**,[4] and others that give mainly the *anti*-Markovnikov products **B**.[5] Basic additives,[6] the solvent[7] or the architecture and the electronic nature of the ruthenium catalyst[8] may have an influence on the regioselectivity. The addition of carboxylic acids to internal alkynes is less common but it has been reported as well.[9]

The resulting enol esters themselves are valuable starting materials for example in polymerization reactions,[10] in acylation reactions,[11] and in a number of other organic transformations.[12] Several methods to access enol esters are known; among them are Bayer-Villiger-type oxidation of α,β-unsaturated ketones[13] or the cross coupling of alkenyltrifluoroborate salts with carboxylic acids.[14] The addition of carboxylic acids to terminal alkynes is attractive because these starting materials are readily available and the method is atom-economical.

Well-characterized ruthenium complexes play a prominent role in organometallic catalysis; they can be thoroughly characterized using conventional analytical techniques and tend to be configurationally stable.[15] Cationic ruthenium complexes can serve as mild Lewis acids in solution, and are consequently able to exhibit catalytic activity in cases where Lewis acids are the catalytically active species.[16]

As part of our continuing research program centered around ruthenium complexes,[17] we are in continuous search for well-defined ruthenium complexes to be applied as catalysts. The majority of the ruthenium catalysts for the title reaction are based on fairly uncomplicated and/or commercial ruthenium complexes bearing a carbonyl[3,4a,5a] monodentate phosphine,[4a,b,5a,6,9b] hydrido,[7] or carboxylate ligands.[4c] It has been demonstrated that the ligand structure and its electronic properties can have an influence on the selectivity of the reaction.[6] However, systematic investigations of the metal complex structure on the selectivity of the title reactions are scarce. The reaction requires elevated temperatures to proceed and catalyst stability at higher temperatures is not very well investigated.

Based on these considerations, we were searching for a new ruthenium complex architecture for the title reaction, that would

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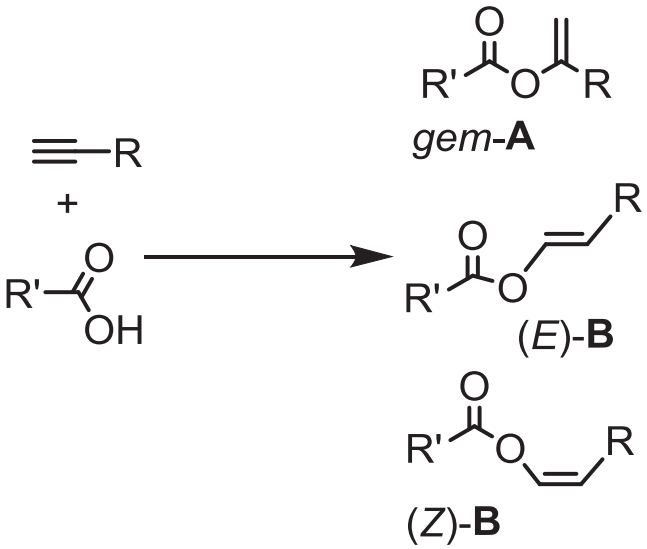


Scheme 1. Enol ester synthesis.

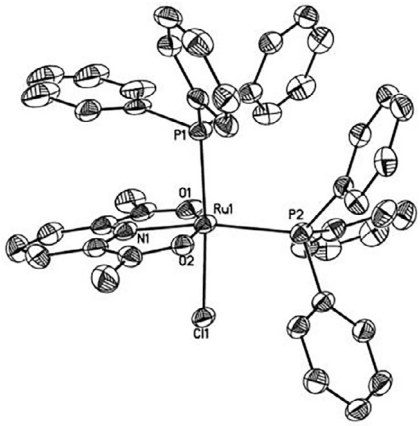


Fig. 1. Molecular structure of [RuCl(dap)(PPh_3)$_2$]BArF depicted with 50% probability ellipsoids; H atoms and the counter ion are omitted for clarity. Key bond lengths (Å) and angles (°): Ru(1)–N(1), 1.990(4); Ru(1)–O(1), 2.141(3); Ru(1)–O(2), 2.082 (3); Ru(1)–P(1), 2.3220(13); Ru(1)–P(2) 2.3855(13); Ru(1)–Cl(1) 2.4210(12); N(1)–Ru(1)–P(1), 92.54(12); N(1)–Ru(1)–P(2), 169.54(12); P(1)–Ru(1)–P(2), 97.54(5); N (1)–Ru(1)–Cl(1), 83.38(11); P(1)–Ru(1)–Cl(1), 173.19(4); P(2)–Ru(1)–Cl(1), 86.84 (4); O(1)–Ru–O(2), 154.01(14).

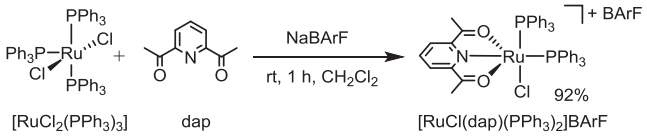
be tunable and that would show high promise of thermal stability. As mentioned, mainly monodentate ligands have been employed previously. We were wondering whether ruthenium complexes bearing tridentate ligands can be employed as catalysts in the formation of enol esters. We envisaged 2,6-diacetylpyridines as a tunable ligand platform, and set out to investigate its ruthenium complex as catalyst for the title reaction. Herein, we present the synthesis and structural characterization of a 2,6-diacetylpyridine ruthenium complex and its application as catalyst for the regioselective addition of carboxylic acids to terminal alkynes. To the best of our knowledge, it is the first ruthenium catalyst bearing a tridentate ligand that promotes this reaction.

Syntheses of the ruthenium complex

To the best of our knowledge, ruthenium complexes bearing a tridentate 2,6-diacetylpyridine ligand are unknown. Accordingly, when the known complex [$RuCl_2(PPh_3)_3$], 2,6-diacetylpyridine (dap) and NaBArF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) were stirred at room temperature for one hour in CH_2Cl_2, the deep purple complex [RuCl(dap)(PPh_3)$_2$]$^+$BArF$^-$ could be isolated from the reaction mixture in 92% yield (Scheme 2), which will be referred to subsequently as [RuCl(dap)(PPh_3)$_2$]BArF. The new complex was characterized by multinuclear NMR, IR, MS and microanalysis. The $^{31}P\{^1H\}$ NMR spectrum showed two mutually coupled doublets, demonstrating the presence of two magnetically inequivalent PPh_3 ligands.

In order to unequivocally establish the structure of the complex, its X-ray structure was determined. The molecular structure is depicted in Fig. 1, and key bond lengths and angles are given in the Figure caption. Additional details for the structure determination are given in the Supplementary data.

As can be seen from the bond angles Fig. 1, the complex assumes a distorted octahedral architecture. The X-ray structure reveals that the 2,6-diacetylpyridine ligand is coordinated to the ruthenium center through the nitrogen and the two oxygen atoms in a tridentate fashion. The O(1)–Ru–O(2) "bite" angle of the 2,6-diacetylpyridine ligand is 154°. This angle is smaller than the 180° angle in an ideal octahedral complex, which is believed to be responsible for the fact that the complex is somewhat distorted. The two PPh_3 ligands take a *cis* position to each other, which is in accordance with the $^{31}P\{^1H\}$ NMR spectrum of the complex. The bond lengths are comparable to other, neutral ruthenium chloro PPh_3 complexes,[17a,17b] and it appears that the positive charge has no profound impact on the bond lengths around the ruthenium center.



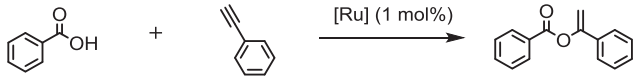
Scheme 2. Synthesis of the ruthenium complex.

Catalytic investigations with the ruthenium complex [RuCl(dap)(PPh_3)$_2$]BArF

The new complex was subsequently investigated as catalyst for the title reaction, and initial screening efforts for a test reaction between phenyl acetylene and benzoic acid are compiled in Table 1. As can be seen, the reaction is dependent on the reaction temperature, the solvent, potential additives, and the reaction time. Toluene was found to be the solvent of choice (Table 1, entry 1). Lower reaction times and temperatures resulted in lower yields or no conversion (entries 2–4), and 18 h at 85 °C gave the highest yield. It has been reported that bases as additive can improve the yield and/or the selectivity of the enol ester formation.[6] However, for our catalyst, it appeared that bases such as DBU, Et_3N, Na_2CO_3 or $NaHCO_3$ completely shut down the reaction (entries 6–9), which we tentatively ascribed to deactivation of the cationic catalyst by the bases. Solvents other than toluene gave significantly lower yields (entries 10–14). As expected, without catalyst no reaction took place (entry 5). For optimum results, the alkyne was employed in a twofold excess over the carboxylic acid substrate. Catalyst loadings as low as 1% were found to be sufficient. In all cases, the Markovnikov product was the major or the only product.

Under the optimized reaction conditions, we employed the catalyst in the synthesis of a number of enol esters and the results are compiled in Table 2. As can be seen, both aromatic and aliphatic carboxylic acids as well as both aromatic and aliphatic alkynes can be employed in the reaction in any combination. The reaction also proceeds when hydroxy acids were employed as substrates (entries 6 and 7). The products were isolated chromatographically

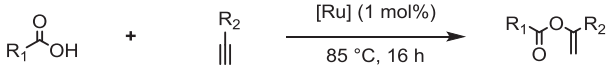
Table 1
Optimization Experiments.

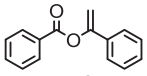
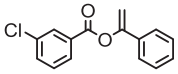
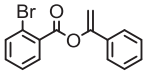
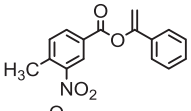
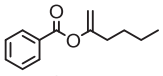
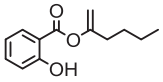
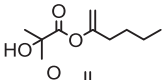
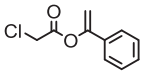
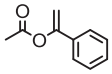
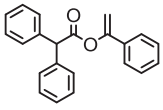


Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Additive	Yield (%)
1	toluene	85	1	none	85
2	toluene	80	5	none	61
3	toluene	65	5	none	65
4	toluene	45	5	none	0
5	toluene	85	none	none	0
6	toluene	85	1	DBU	0
7	toluene	85	1	Et_3N	0
8	toluene	85	1	Na_2CO_3	0
9	ethyl acetate	85	1	$NaHCO_3$	0
10	ethyl acetate	85	1	none	57
11	EtOH	70	5	none	11
12	$ClCH_2CH_2Cl$	70	5	none	9
13	THF	70	5	none	4
14	CH_3NO_2	70	5	none	11

General conditions: Carboxylic acid (0.57 mmol), alkyne (1.14 mmol), and Ru (1–5 mol%) at the specified temperature for 12–18 h. All products were isolated by silica gel chromatography and isolated yields are given.

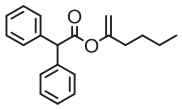
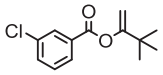
Table 2
Isolated Yields.



Entry	R_1/R_2	Product	Yield (%)
1	Ph/Ph		85[a] 57[b]
2	3-chloro-phenyl/Ph		83[a]
3	2-bromo-phenyl/Ph		91[a]
4	4-methyl-3-nitro-phenyl/Ph		70[a] 79[b]
5	Ph/*n*-Bu		70[a]
6	2-hydroxyphenyl/*n*-Bu		89[a]
7	2-hydroxy-2-propyl/*n*-Bu		74[b]
8	CH_2Cl/Ph		93[b]
9	CH_3/Ph		52[a] 24[b]
10	Ph_2CH/Ph		81[a]

(*continued on next page*)

Table 2 (*continued*)

Entry	R_1/R_2	Product	Yield (%)
11	Ph_2CH/n-Bu		74[a]
12	3-chlorophenyl/$C(CH_3)_3$		72[a]

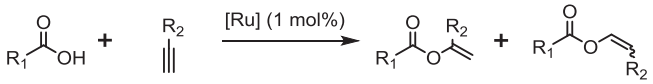
General conditions: Carboxylic acid (0.57 mmol), alkyne (1.14 mmol), and Ru (1 mol%) for 16 h at 85 °C. All products were isolated by silica gel chromatography and isolated yields are given.
[a] Toluene.
[b] Ethyl acetate.

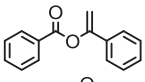
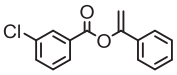
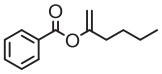
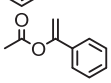
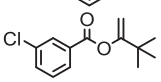
in 93 to 52% yields. With one exception (entry 4), toluene appears to be the solvent of choice, as ethyl acetate gave lower isolated yields in entries 1 and 9, as expected from the screening experiments in Table 1. While ethyl acetate was not as good of a solvent as toluene, it was an acceptable solvent for some cases, where the carboxylic acids were better soluble in ethyl acetate as compared to toluene. Yields and selectivities compare well with other ruthenium catalysts for the reaction, and the reaction conditions are comparable. Advantages of the [RuCl(dap)$(PPh_3)_2$]BArF catalyst are the low catalyst loading of only 1% and, more significantly, no additives are required.

All reactions in Table 2 afforded the geminal enol esters as the major products resulting from Markovnikov addition to the alkyne. The products in entries 3, 4, 6, 7, 10 and 11 were isolated as a single isomer, and at most trace quantities of the other isomers were detected by NMR. The other products were isolated with detectable amounts of the other isomers, which were, like the major isomer, identified based on the coupling constants of the alkene protons, as performed previously by others.[4e,13] As can be seen in Table 3, the products in entries 1, 2, and 5 contain only 4 to 5% of the other two isomers. However, the products in entries 9 and 12 of Table 3 contained 17 to 24% of the other isomers. The Markovnikov product was still the major one, however. Both the (*E*) and (*Z*) isomers of the *anti*-Markovnikov products were detected in the reaction mixtures, with a slight excess of the (*Z*) over the (*E*) isomer.

The selectivity of the ruthenium catalyst to generate the Markovnikov product and the selectivities in Table 3 can, in part, be explained based on steric considerations. It has been suggested that coordination of the alkyne in an η^2-fashion (species **A** in Fig. 2) gives nucleophilic attack at the Cβ carbon of the alkyne to afford the Markovnikov product, while the isomeric vinylidene species **B** (Fig. 2) gives the *anti*-Markovnikov products through nucleophilic attack at the Cα carbon. The electronic and steric factors that lead to either Markovnikov or *anti*-Markovnikov addition are not very well understood.[8] However, as can be seen in Table 3, for the present catalyst system, the *anti*-Markovnikov product forms with either a small carboxylic acid (acetic acid) or with a sterically demanding alkyne (3,3-dimethylbut-1-yne). A sterically demanding alkyne might exhibit some tendency to form the vinylidene species **B** and a small carboxylic acid might favor the attack of the α carbon atom in **B**, giving rise to the formation of some of the *anti*-Markovnikov product. In general, the complex [RuCl(dap)$(PPh_3)_2$]BArF can be tuned sterically through the acyl units and

Table 3
Regioselectivity of Selected Products as Determined by ^{1}H NMR.



Entry	Major product	Isolated yield (%)	*gem*: (*Z*): (*E*) % selectivity[a]
1		88	96:2:2
2		87	94:4:2
5		74	95:3:2
9		70	74:14:12
12		79	75:15:10

General conditions: Carboxylic acid (0.57 mmol), alkyne (1.14 mmol), and [Ru] (1 mol%) for 16 h at 85 °C in toluene. All products were isolated by silica gel chromatography.
[a] The ratio of constitutional isomers was determined by the ratio of discrete peaks in the ^{1}H NMR.

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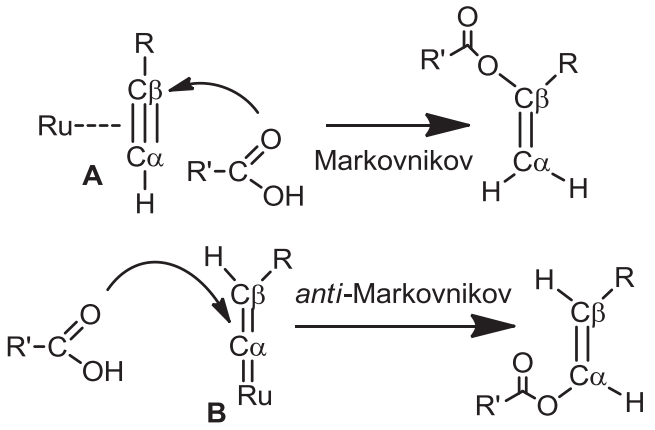

Fig. 2. Potential intermediates.

electronically through the pyridyl ring system. Thus, the complex can be modified to better understand the steric and electronic factors that determine the selectivity of the title reaction.

Conclusion

In conclusion, we have synthesized a ruthenium complex of the formula [RuCl(dap)(PPh_3)$_2$]BArF as a tunable catalyst for the atom-economic Markovnikov addition of carboxylic acid to terminal alkynes to afford enol esters in 93 to 52% isolated yields. The catalyst does not require any additives and in the majority of the cases, at best trace amounts of other isomers were detected in the isolated products. The complex [RuCl(dap)(PPh_3)$_2$]BArF constitutes a tunable platform as catalyst for the title reaction and allows for future investigation of steric an electronic factors on the selectivity of the title reaction.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.029.

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