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Ruthenium(II)-Catalyzed Regioselective Synthesis of Allyl Ketones from Alkynes and their Silver(I)-Catalyzed Hydroarylation into γ-Functionalized Ketones

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Abstract: The regioselective synthesis of β , γ -unsaturated ketones from terminal alkynes is achieved by cooperative action of tris(acetonitrile)pentamethylcyclopentadieneruthenium hexafluorophosphate [Cp*Ru(NCMe)₃⁺ PF₆⁻] and *para*-toluenesulfonic acid catalysts. These allyl ketones undergo direct regioselective hydroarylation/Friedel–Crafts reaction to introduce an electron-rich aryl group at the γ -position in the presence of ligand-free silver triflate (AgOTf) catalyst. Both catalytic reactions take place with atom economy and provide an alternative to the synthesis of a variety of allyl ketones and γ -arylated ketones.

Keywords: allyl ketones; atom economy; γ -functionalized ketones; ruthenium catalysts; sequential catalysis; silver catalysts

The regioselective hydroarylation of functional alkene C=C bonds constitutes an important synthetic challenge for the functionalization of aromatic compounds, especially when the reaction tolerates functional groups and takes place with atom economy. In this direction an emerging field deals with the metal-catalyzed activation of sp^2 C–H bonds with formal insertion of functional alkenes.^[1,2] However, the most general C=C bond hydroarylation reactions involve a Friedel–Crafts process, corresponding to metal-catalyzed alkylation of aromatic rings, frequently suitable for enantioselective C–C bond formation.^[3,4] A relat-

ed alkylation of aromatics and heterocycles consists in their metal-catalyzed Friedel–Crafts allylation,^[5,6] but these reactions take place with the loss of an allyl leaving group. Among the intermolecular catalytic Friedel–Crafts reactions with C=C bonds, most of them involve activated double bonds conjugated with a functional group,^[4] such as nitroalkenes^[4a-c] or α,β unsaturated carbonyl derivatives.^[4d,e] It is noteworthy that hydroarylation of non-activated alkenes was recently reported to be promoted with a Pt(II)-Ag(I) catalyst,^[4f] an Au(I)/Ag(I) catalyst assisted by microwave irradiation,^[4g] or with an Ag(I) salt for diene addition.^[4h]

Allyl ketones have also the potential to be used as alkylating reagents for aromatic compounds. Several convenient routes already have led to allylic ketones,^[7] such as from allylmetal^[7a,b] and alkenylmetal derivatives,^[7c,d] by the mild oxidation of homoallylic alcohols,^[7e,8] and by the ruthenium-catalyzed hydroacylation of dienes.^[7f-h] However, to the best of our knowledge, the hydroarylation of β , γ -unsaturated ketone C=C bonds has not been performed yet, likely due to the possible lack of regioselectivity in the absence of a conjugated carbonyl group, and their easy isomerization into α , β -unsaturated ketones under electrophilic reaction conditions.

Pursuing our efforts to generate functional dienes, *via* the ruthenium-catalyzed dimerization of terminal alkynes, such as 1,3-dienyl esters^[9] or ethers,^[10] we have explored the possibility to directly generate allylic ketones by hydrolysis of alkynes, *via* 1,3-dienol generation, and to use them for the Friedel–Crafts alkylation of aromatic compounds.

We now wish to report (i) the catalytic synthesis of allylic ketones from terminal alkynes and water with the cooperative actions of both $[RuCp^*(NCMe)_3]PF_6$ and *para*-toluenesulfonic acid (*p*-TSA) catalysts and (ii) the AgOTf-catalyzed regioselective Friedel–Crafts/hydroarylation of β , γ -unsaturated ketones with electron-rich arenes. These sequential catalytic reactions allow the two-step transformation of terminal alkynes into γ -arylated ketones [Eq. (1)].

$$2 \operatorname{R} \xrightarrow{\operatorname{RuCp}^{\star}(\operatorname{MeCN})_{3}^{\star}\operatorname{PF}_{6}^{-}} \operatorname{R} \xrightarrow{O}_{R} \xrightarrow{O}_{R}$$

$$+ \operatorname{H}_{2}O \xrightarrow{\rho-\mathrm{TSA \ cat}} \operatorname{R} \xrightarrow{R}_{R} \xrightarrow{O}_{R} \xrightarrow{O}_{$$

The stoichiometric head-to-head dimerization of alkynes with Cp*Ru complexes leading to a bis-carbene intermediate^[11] was recently used for the catalytic formation of dienyl esters and dienyl ethers with RuCl(Cp*)(COD)^[9] and RuCp*(NCMe)₃⁺ PF₆⁻ catalysts^[10], respectively. However, the direct hydrolysis of the bis-carbene-ruthenium intermediate did not lead to the expected formation of allyl ketones or to their isomerization into α,β -unsaturated ketones, whereas the intramolecular oxidative coupling of non-conjugated diynes with RuCp(NCMe)₃⁺ PF₆⁻ in the presence of water led by contrast to the formation of cyclic α,β -unsaturated ketones under mild conditions.^[12]

We have thus first investigated the direct access to allyl ketones from terminal alkynes in the presence of RuCp*(NCMe)₃⁺ PF₆⁻ catalyst **A**. Whereas the reaction of phenylacetylene with water alone in dioxane and catalyst **A** led to a mixture of compounds, we explored the influence of acids as the bis-carbene intermediate needs to be protonated before nucleophilic addition to give a dienyl product.^[9] The reaction of phenylacetylene **1a** (1 mmol) with 3 equiv. of water and 0.15 mmol of *para*-toluenesulfonic acid monohydrate (*p*-TSA) in dioxane with 4 mol% of RuCp*(NCMe)₃⁺ PF₆⁻ led, after 0.5 h at room temperature, to the quantitative regioselective formation of allyl ketone **2a**, isolated in 96% yield [Eq. (2),

Table 1. Ruthenium-catalyzed synthesis of β , γ -unsaturated ketones directly from alkynes.^[a]

$Cp^*Ru(MeCN)_3^+PF_6^-$ (4 mol%) O							
		2 R-=== 1	+ H ₂ O	%), dioxane, r.	t. 2 (2)		
Entry	Alkyne		Reaction time [h]	Ketone	2	Yield [%] ^[b]	
1	1 a		0.5	2a		96	
2	1b		0.5	2b	° C	88	
3	1c	MeO	3 h	2c	MeO O O O O O O O O O O O O O O O O O O	85 ^[c]	
4	1d	×	1	2d	×	88	
5	1e	F ₃ C	0.5	2e	F ₃ C O CF ₃	78	
6	1f	Br	1	2f	Br O Br	93	

^[a] Reaction conditions: 1 mmol of alkyne, p-TSA[·]H₂O (28.5 mg, 0.15 mmol), H₂O (3 equiv.) and Cp*Ru(MeCN)₃⁺ PF₆⁻ (0.04 mmol) in 1 mL dioxane at room temperature for 0.5 to 3 h.

^[b] Isolated yields.

^[c] Obtained yield in the presence of 15 mol% of ruthenium catalyst **A** after 3 h of reaction.

Table 1, entry 1). The formation of the α , β -unsaturated ketone was not observed. This atom-economical synthetic method to form β,γ -unsaturated ketone 2a under mild contitions was studied for the catalytic transformation of a variety arylacetylenes 1b-1f. All reactions proceeded smoothly and afforded the ketones **2a-2f** in good to excellent isolated yields of 78-96% (Table 1, entries 2–6). However, the reaction is slower with electron-releasing substituent such as for 1c, for which an increase of the catalyst loading was required to reach a decent yield (entry 3). The reaction tolerates a para-bromo substituent (entry 6) thus making possible further modifications of the ketone and derivatives via classical catalytic cross-coupling C-C or C-N bond formation. All ketones 2a-2f possess the E-configuration of their CH=CH bond as shown by ¹H NMR spectroscopy.

On the basis of the mechanism for the catalytic formation of dienyl esters from alkynes, and catalyzed by $Ru(Cl)(COD)Cp^{*}$,^[9] we can suggest that the formation of allylic ketones 2 takes place as shown in Scheme 1. The terminal alkynes react with catalyst A



L = MeCN or solvent

Scheme 1. Proposed mechanism for the catalytic formation of allyl ketones **2** from terminal alkynes.

and lead to the head-to-head dimerization of alkynes and the formation of the bis-carbene intermediate **I** with both Schrock- and Fischer-type behaviour.^[9] Protonation with a strong acid is required for the hydrolysis to take place and thus the intermediate **II** should be formed on protonation of the Schrock-type carbene carbon atom, thus increasing the electrophilic behaviour of the Fischer carbene carbon atom and allowing the addition of water to give the intermediate **III**, that generates the 1,3-dienol intermediate leading allyl ketone **2**.

This bis-carbene intermediate I is expected to be stabilized by the conjugated aryl groups. This is likely the reason why this dimerization reaction cannot be extended to alkylacetylenes such as 1-hexyne.

As the allylic ketones 2 are formed in the presence of a strong acid without their isomerization, we have explored their use for the hydroarylation of electronrich arenes *via* a Friedel–Crafts process.

The ketone 2a and anisole 3a were first reacted with various Brønsted acid and Lewis acid catalysts to favour the hydroarylation reaction (Table 2). Cata-

Table 2. Hydroarylation reaction of 2a with anisole into ketone 4a.^[a]



Entry	Cat.	Solvent	Temp. [°C]	Yield [%] ^[b] of 4a
1	H_2SO_4	1,2-dichloroethane	100	76
2	p-TSA	1,2-dichloroethane	100	22
3	CF ₃ SO ₃ H	1,2-dichloroethane	100	79
4	$Cu(OTf)_2$	1,2-dichloroethane	100	56
5	AgOTf	1,2-dichloroethane	100	91
6	AgOTf	dioxane	100	_
7	AgOTf ^[c]	1,2-dichloroethane	80	34

[a] Reaction performed in a sealed Schlenk tube: 0.5 mmol of 2a, 1.5 mmol of 3a and 0.025 mmol of AgOTf (5 mol%) in 1 mL of solvent in a bath at 100 °C for 1 h.
[b] GC yield with tetradecane as the internal standard.
[c] At 80 °C for 1 h.

lysts such as H₂SO₄, *p*-TSA, CF₃SO₃H, Cu(OTf)₂ can promote the hydroarylation reaction (Table 2, entries 1-4), but the desired product was obtained in relatively low yields. The silver salt AgOTf without an additional ligand led to the best result as 4a was formed in 91% GC yield (Table 2, entry 5). The reaction was found to be highly dependent on the nature of the solvent. Among the various solvents, dichloroethane (DCE) was the most effective one. The reaction gave a mixture of products in coordinating solvents such as dioxane or dimethylformamide (Table 2, entries 6). However, only a 34% yield was found in the presence of AgOTf in DCE at 80°C (Table 2, entry 7). Thus it can be concluded that 5 mol% of AgOTf in dichloroethane is the best system for this transformation performed at 100 °C.

Having optimized the reaction conditions, the scope of this catalytic reaction was investigated in the presence of 5 mol% of AgOTf with various allylic ketones and excess of electron-rich arenes, such as methoxy-,

Entry	2	3		Reaction time [h]	Ketone	4	Yield [%] ^[b]
1	2a	3 a	OMe	0.5	4 a		81
2	2b	3 a	ОМе	0.6	4b		65
3	2c	3 a	ОМе	0.5	4c		85
4	2d	3 a	ОМе	0.5	4d		76
5	2e	3 a	ОМе	1	4e	OMe Br OMe Br Br Br	51
6	2f	3 a	ОМе	2	4f	F ₃ C O CF ₃	< 10
7	2a	3b	MeO	2	4g		62
8	2b	3b	MeO	2	4h	OMe MeO	67
9	2d	3b	MeO	2	4 i	OMe MeO	63
10	2e	3b	MeO	2	4j	Br OMe Br MeO	33

Table 3. Catalytic synthesis of γ -diarylated ketones 4.^[a]

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 Table 3. (Continued)



^[a] Reactions performed in a sealed Schlenk tube: 0.5 mmol of **2** and 1.5 mmol of **3** with 0.025 mmol of AgOTf catalyst in 2 mL of dichloroethane was stirred in a bath at 100 °C for 0.5 to 10 h.

^[b] Isolated yields.

dimethoxybenzene and toluene. The results are summarized in Table 3. The reaction proceeded smoothly and was completed within 0.5 to 2 h at 100 °C in a closed Schlenk tube to afford a variety of polysubstituted γ -arylated ketones in moderate to excellent yields (Table 3, entries 1–5 and 7–13), except for **4f** arising from the allyl ketone **2f** with a strong electron-withdrawing group on the ketone aryl groups (entry 6). However the bromo-substituted allyl ketone **2e** was able to form the corresponding Friedel–Crafts products **4e** and **4j** in moderate yields (entries 5 and 10). The reaction does not occur with *N*,*N*-dimethylaniline or phenylpyridine even after prolonged reaction times.

This reaction leads to high regioselectivity of hydroarylation as the ¹H NMR spectra showed the CHCH₂CH₂CO fragment. The structure of the representative example **4d** was confirmed by its HMBC spectra: they showed the correlation of the carbonyl carbon with α -methylene and β -methylene protons, with no correlation with the γ -proton (see Supporting Information for **4d**).

This selective formation of ketones **4** indicates that AgOTf does not isomerize the ketones into α,β -unsaturated ketones. The formation of γ -functionalized ketones **4** can be rationalized by an interaction of the allyl ketone C=C bond with a silver cation leading to a more electrophilic γ -benzylic carbon cation, as in the alkylation and allylation of aromatic compounds with silver salts.^[6] The oxophilicity of the silver cation^[13] may also allow its coordination with the neighbouring ketone oxygen atom, as it was proposed



Scheme 2. Possible interaction of AgOTf with allyl ketones favouring Friedel–Crafts reaction.

for mechanistic studies of Ag^+ -promoted C–C bond formation^[13] (Scheme 2).

In conclusion, a new catalytic and regioselective method to make β , γ -unsaturated allylic ketones, without isomerization, from terminal arylalkynes is presented by the cooperative action of ruthenium and p-TSA catalysts. The potential of the resulting allyl ketones has been shown in the direct regioselective hydroarylation/Friedel-Crafts reaction to introduce an electron-rich aryl group at the γ -position in the presence of ligand-free AgOTf catalyst. Both catalytic reactions take place with high atom economy and provide an alternative to the synthesis of γ -arylated ketones. Thus it appears that a Ag(I) catalyst promotes the intermolecular hydroarylation of allylic ketones in the presence of an aromatic partner, whereas Cu(II) salts favour the intramolecular formation of furans from allyl ketones arising from dienyl ethers.^[9]

Experimental Section

Typical Procedure for Synthesis of the Allylic Ketone 2a

The catalyst RuCp*(MeCN)₃⁺ PF₆⁻ (20 mg, 0.04 mmol, 4 mol%) and *para*-toluenesulfonic acid monohydrate (*p*-TSA) (0.15 mmol, 28.5 mg) were dissolved in 1 mL of 1,4-dioxane: then phenylacetylene **1a** (1 mmol, 102 mg), H₂O (3 mmol) were added, and the mixture was stirred under argon protection at room temperature for 0.5 hour. Then petroleum ether (5 mL) was added, the resulting mixture was directly filtered through a pad of silica and concentrated to afford the crude product, which was purified by recrystallization in pentane, to give the white solid **2a**; yield: 107 mg (96%).

General Procedure for Synthesis of Saturated Ketone 4a from 2a

A Schlenk tube equipped with a rubber septum and a magnetic stirring bar was charged with 2a (0.5 mmol, 111 mg) and AgOTf (0.025 mmol, 6.4 mg, 5 mol%) under an argon atmosphere. Anisole (1.5 mmol, 162 mg) and 1,2-dichloro-ethane (1 mL) were added by syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath at 100 °C. After stirring for 0.5 h, it was cooled down to room temperature. The resulting mixture was directly filtered through a pad of silica and concentrated to afford the crude product, which was purified by flash column chromatography on silica, eluting with petroleum ether: ethyl acetate (25: 1) to give 4-(4-methoxyphenyl)-1,4-diphenylbutan-1-one 4a as a light yellow oil; yield: 134 mg (81%).

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