C–H Activation

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The Ruthenium-Catalyzed Hydrovinylation of Internal Alkynes by Acrylates: An Atom Economic Approach to Highly Substituted 1,3-Dienes**

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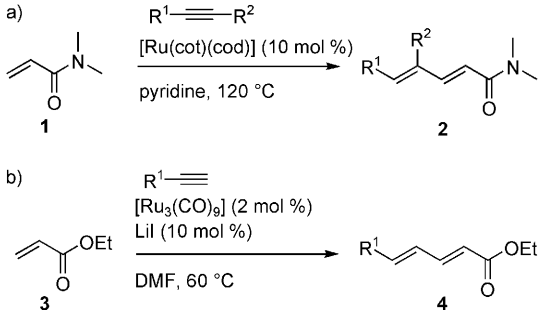
The use of transition-metal-catalyzed reactions often allows for an efficient construction of complex molecular building blocks. The expression "atom economic"[1] has been coined for transformations in which every atom of the starting material is transferred into the final product and such transformations fulfill the requirements of sustainability as defined by the Brundtland report.[2] With regard to this background our group has tried to combine both methodological development and synthetic application over the past few years.[3,4] In the course of a natural-product synthesis we sought a method that allowed fast access to highly substituted sorbic acid derivatives. To allow the desired total synthesis to be performed in a modular and versatile way and to enable ruthenium-catalyzed processes to be combined in a sequential manner the original report by Watanabe[5] and later work by Uemura[6] on the hydrovinylation of alkynes appeared particularly attractive (Scheme 1).

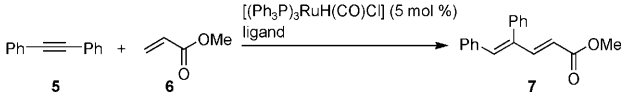


Scheme 1. The ruthenium-catalyzed hydrovinylation of alkynes by a) Watanabe et al.[5] and b) Uemura et al.[6]

It was surprising to find that this co-dimerization between an alkyne and an electron-deficient olefin is rather poorly developed compared to the well-investigated corresponding reaction between an alkyne and a carbonyl-activated aromatic substrate.[7] Within the past few years several approaches using catalytic amounts of ruthenium,[5,6,8] palladium,[9] and most recently rhodium complexes[7i,10] have been described, however, with regard to our attempted application we concentrated on the use of ruthenium complexes. Initially we tried to optimize the existing procedures through a detailed additive and solvent screening. Unfortunately, the Watanabe system[5] proved to be applicable almost only to *N,N*-dialkylacrylamides. Esters, as required for our synthetic application, are only of limited use. This problem might be circumvented using the Uemura system,[6] however, this method is limited mostly to terminal alkynes. Herein we report on the development of a broadly applicable and efficient hydrovinylation of internal and terminal alkynes by highly substituted acrylates.

The catalyst we use $[(Ph_3P)_3RuH(CO)Cl]$ has been applied before by Murai[7a–c,8a] in the carbonyl-directed vinylation of aryl ketones and is obtained as an air and moisture stable yellow solid in one step starting from $RuCl_3$. With regard to our desired reaction the use of the Murai catalyst appeared particularly attractive since the Ru–H species should favor the hydrometallation of an alkyne (Table 1).

Table 1: Influence of solvent and ligand.



Entry	Solvent	Ligand	*T* [°C]	Yield [%][b,c]
1	toluene	–	100	28 (>95:5)
2	heptane	–	100	–
3	dichloroethane	–	100	33 (>95:5)
4	ethyl acetate	–	100	–
5	acetone	–	100	–
6	acetonitrile	–	100	21 (n.d.)
7	DMSO	–	100	75 (>95:5)
8	DMF	–	100	96 (>95:5)
9	DMF	DavePhos	100	72 (86:14)[d]
10	DMF	JohnPhos	100	64 (81:19)[d]
11	DMF	SPhos	100	73 (85:15)[d]
12	DMF	XPhos	100	62 (87:13)[d]
13	DMF	binap	100	59 (>95:5)[e]
14	DMF	dppf	100	33 (80:20)[e]
15	DMF	dppe	100	6 (n.d.)[e]
16	DMF	–	80	92 (>95:5)

[a] 2 Equivalents ester, 5 mol% $[(Ph_3P)_3Ru(CO)HCl]$, solvent (1.5 mL), 24 h. [b] Determined by GC integration of the crude product relative to undecane as internal standard. [c] γ,δ-*E*/*Z*-Selectivities in brackets. [d] 10 mol% ligand. [e] 5 mol% ligand. binap = [1,1′-binaphthalene]-2,2′-diylbis(diphenylphosphine); dppf = 1,1′-bis(diphenylphosphino)ferrocene, dppe = 1,2-bis(diphenylphosphino)ethane.

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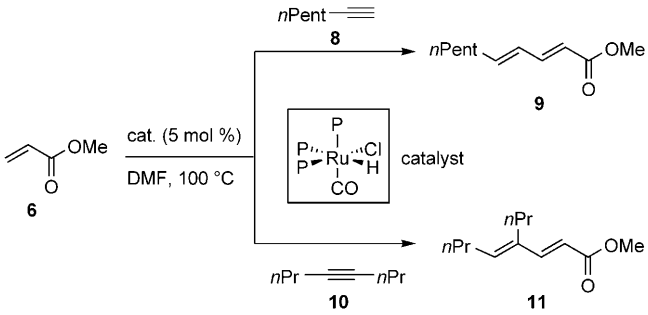
Indeed complex $[(Ph_3P)_3RuH(CO)Cl]$ catalyzes the hydrovinylation of 1,2-diphenyl acetylene with methyl acrylate. Dimethylformamide (DMF) proved to be the solvent of choice. Changing the temperature or the addition of ligands had no beneficial influence on the conversion rate. Furthermore, the catalyst concentration for the reaction of **5** and **6** with **10** can be lowered to 2.5 mol%, however, this is at the expense of reaction time and yield of the product **7**.

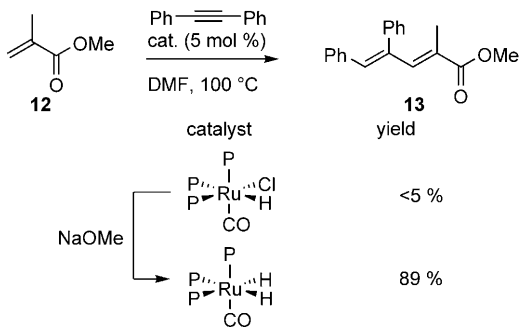
The use of 5 mol% of the ruthenium catalyst allowed the hydrovinylation of both 1-heptyne (**8**) and 4-octyne (**10**) with methyl acrylate (**6**) to the desired 1,3-dienes **9** and **11** in good yields (Scheme 2).



Scheme 2. The ruthenium-catalyzed hydrovinylation of alkynes ($P = PPh_3$).

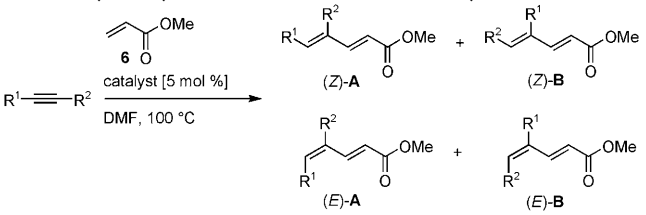
Subsequent studies however revealed this method to be limited with regard to the acrylates used. Substituted acrylates, such as methyl cinnamate, methyl crotylate, or methyl methacyrylate, are either not reactive or react sluggishly both with terminal as well as internal alkynes. Based upon the important preliminary studies by Murai the catalyst was transformed into its corresponding dihydrido species by in situ derivatization using catalytic amounts of NaOMe.[7a] This derivatization proved successful. Hence, methyl methacrylate (**12**) reacted with 1,2-diphenylacetylene to the desired 1,3-diene **13** in good yield and stereoselectivity (Scheme 3).

Under the optimized conditions a variety of alkynes are reactive (Table 2). In each case the desired sorbic acid derivative was obtained in moderate to excellent regioselectivities and high yields. The regioselective course is directed both by steric and electronic parameters. In general the isomer having the sterically more demanding group at the δ-



Scheme 3. Ruthenium-catalyzed hydrovinylation using α-branched olefins ($P = PPh_3$).

Table 2: Hydrovinylation of internal and terminal alkynes.



Entry	R^1	R^2	Prod.[a]	A:B[b]	Z:E[b]	Yield [%][c]
1	C_5H_{11}	H	**9** (A)	>99:1	95:5	69
2	Ph	H	**14** (B)	>99:1	98:2	57
3	C_3H_7	C_3H_7	**11** (A)	–	91:9	76
4	C_4H_9	C_4H_9	**15** (A)	–	91:9	73
5	Ph	Ph	**7** (A)		98:2	96
6	CH_2OBn	CH_2OBn	**16** (B)	–	66:34	52
7	CH_2OBz	CH_2OBz	**17** (B)	–	–	–
8[d]	Ph	CO_2Et	**18** (B)	84:16	32:68	43
9	Ph	CH_2OBn	**19** (B)	>99:1	66:34	71
10	C_3H_7	CH_2OBn	**20** (B)	33:67	95:5	53
11	ClC_4H_8	H	**21** (A)	>99:1	98:2	71
12	NCC_4H_8	H	**22** (A)	>99:1	98:2	73
13	C_5H_{11}	CH_3	**23** (A)	50:50	91:9	65
14	Ph	C_3H_7	**24** (A)	11 :89	98:2	83

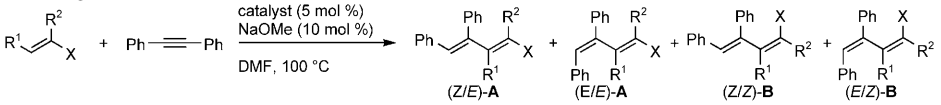
[a] Procedure A: 2 equivalents acrylate, 5 mol% $[(Ph_3P)_3RuH(CO)Cl]$, DMF (1.5 mL), 100°C, 24 h. Procedure B: 2 equivalents acrylate, 5 mol% $[(Ph_3P)_3RuH(CO)Cl]$, 10 mol% NaOMe, DMF (1.5 mL), 100°C, 24 h. [b] Determined by ^1H NMR- and GC-integration of the signals of the crude product. [c] Yield of isolated product. [d] As procedure B, but at 120°C, 48 h.

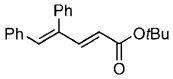
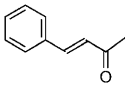
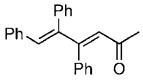
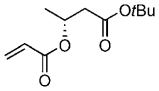
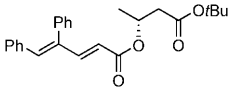
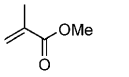
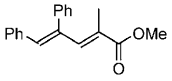
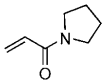
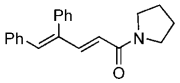
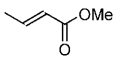
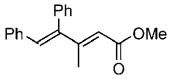
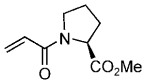
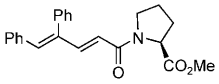
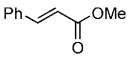
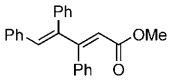
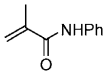
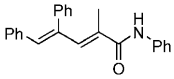
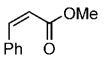
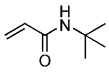
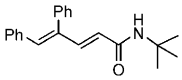
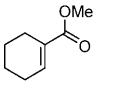
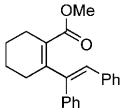
position of the diene moiety is favored. Hence, the vinylation of terminal alkynes proceeds with almost exclusive regioselectivity in favor of the linear products. Moreover, coordinating functional groups are tolerated. However, a significant influence of a substituent in the propargylic position was observed. Thus a benzyloxy group results in the γ,δ-(*E*)-configured product being the main product (Table 2; entries 6, 9, and 10). It is important to note that different from the alkynes used in other methods the present procedure allows for the use of alkynes sensitive to isomerization. An isomerization of the triple bond into a 1,2- or 1,3-diene was not observed.[11]

In addition to the alkynes, the acrylate derivatives were also varied and treated with 1,2-diphenylacetylene under the optimized conditions (Table 3). We were pleased to find this reaction to be broadly applicable. Various substituted sorbates were obtained in good to excellent yields with high *E*/*Z*-selectivity. Hence, substituents in α- or β-position are tolerated as well as esters, amides, ketones, or aldehydes. Even the presence of heterocyclic moieties proved unproblematic. However, thioesters are not compatible with the catalytic conditions. Furthermore the reactivity of the α,β double bond is significantly reduced by electron-donating β substituents (Table 3; entry 7–12). Most interestingly the reaction stops at the stage of the sorbate. The formation of a triene as a result of the hydrovinylation using a sorbate even in the presence of a large excess alkyne was not observed.[12]

Different mechanistic scenarios for the course of the hydrovinylation can be envisioned. To get a first insight into the mechanism for the addition to the alkene, deuterated

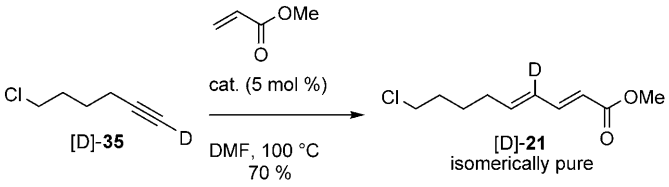
Table 3: Hydrovinylation using different alkenes.



Entry	Alkene	Product		Yield [%][d,e]	Entry	Alkene	Product		Yield [%][d,e]
1[a]			**25**	84 (98:2:0:0)	7[b]			**31**	42 (82:0:18:0)
2[a]			**26**	81 (98:2:0:0)	8[b]			**13**	89 (98:2:0:0)
3[b]			**27**	83 (71:2:25:2)	9[b]			**32**	41 (32:2:64:2)
4[b]			**28**	73 (63:2:33:2)	10[b]			**33**	76 (47:2:47:2)
5[b]			**29**	53 (94:2:2:2)	11[b]				39 (81:1:16:2)
6[b]			**30**	88 (69:2:27:2)	12[c]			**34**	56 (0:0:98:2)

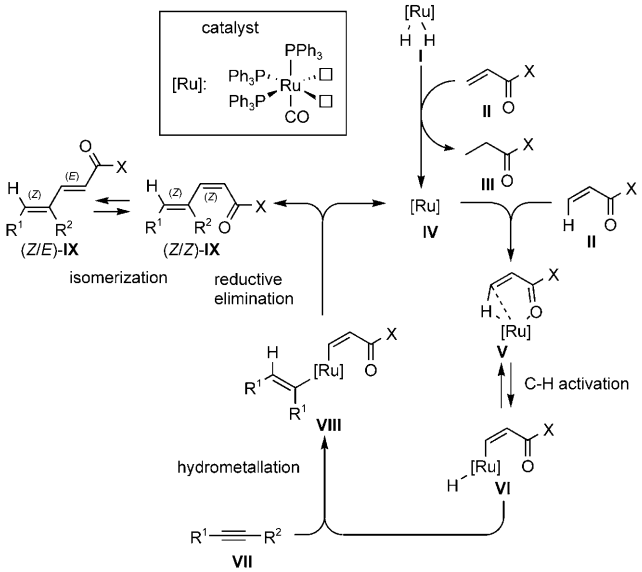
[a] Procedure A: 5 mol% $[(Ph_3P)_3Ru(CO)HCl]$, DMF (1.5 mL), 100°C, 24 h. [b] Procedure B: 5 mol% $[(Ph_3P)_3Ru(CO)HCl]$, 10 mol% NaOMe, DMF (1.5 mL), 100°C, 24 h. [c] As procedure B but at 120°C, 48 h. [d] Determined by ^{1}H NMR- and GC-integration of the crude product ratio: (*Z*/*E*)-**A**/(*E*/*E*)-**A**/(*Z*/*Z*)-**B**/(*E*/*Z*)-**B** in parenthesis. [e] Yield of isolated product.

alkyne [D]-**35** was employed in the reaction. The corresponding γ-deuterated sorbate [D]-**21** was obtained in isomerically pure form in 70% yield (Scheme 4). Hence, a mechanism via an in situ formed allenylidene ruthenium species can be excluded.[6]



Scheme 4.

Another important result is the comparative reaction of *E*- and *Z*-configured methyl cinnamate (Table 3; entries 10 and 11). Under the given conditions the *E*-configured alkene displays a significantly higher reactivity. The *Z*-configured isomer, in which the β-substituent and the carbonyl group are oriented in a *cis* fashion, undergoes isomerization of the C=C bond into the thermodynamically more favorable *trans* isomer prior to the hydrovinylation event. The experimentally derived hypothesis, that alkyne activations occurs through hydrometallation by a Ru-H species and alkene activation requires an H atom *cis* to a carbonyl group for a β-C-H activation, are summarized in the mechanistic model shown in Scheme 5.[7a–f] The isomerization of the α,β-double bond in the primarily formed (*Z*,*Z*)-**IX** is most likely thermally driven



Scheme 5. Mechanistic model of the hydrovinylation.

and not ruthenium catalyzed. Test experiments revealed that this process is not accelerated by the ruthenium catalyst.

In conclusion, we report a broadly applicable hydrovinylation of terminal and internal alkynes with electron-deficient olefins. The reactions are catalyzed by an air and moisture stable ruthenium hydride complex that is prepared in one step starting from $RuCl_3$ and activated by addition of NaOMe prior to use. Highly substituted 1,3-dienes are accessible in good to excellent yields. These investigations

build the base for the development of further applications in sequential catalysis and natural-product synthesis.

Experimental Section

General procedure (method B) for the hydrovinylation of alkynes: A 2 mL Wheaton vial was capped by a Mininert valve and flushed with nitrogen by two pump–flush cycles. [$RuHClCO(PPH_3)_3$] (23.8 mg, 0.025 mmol), NaOMe (2.7 mg, 0.05 mmol), and dry DMF (1 mL) were placed into the vial and heated to 100 °C for 15 min. After cooling to room temperature a solution of the alkyne (0.5 mmol) and acrylate (1 mmol) in dry DMF (0.5 mL) were added by syringe through the septum. The closed vessel was heated to 100 °C for 24 h. After cooling to room temperature the crude mixture was directly subjected to a column chromatography (petroleum ether/ethyl acetate). The 1,3-dienes were obtained as colorless to yellowish oils. Alternatively the reactions might be stopped by the addition of water followed by extraction of the aqueous layer using ethyl acetate. The combined organic layers were re-extracted twice with water and once with 0.1N aqueous citric acid solution. After drying over Na_2SO_4 and filtration the organic layer was concentrated in vacuum.

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