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Synthetic Methods

Ruthenium-Catalyzed Synthesis of Functionalized Dienes from Propargylic Esters: Formal Cross-Coupling of Two Carbenes**

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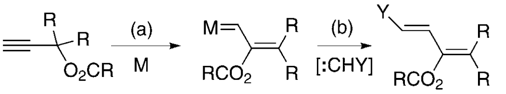
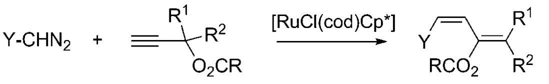
The in situ creation of reactive metal carbene intermediates, especially on interaction of alkyne, enyne, or dienyne substrates with electrophilic catalysts, such as $[RuX_2L_n]$,[1–3] PtX_2,[1,4] or AuX,[5] has recently led to novel skeletal rearrangements and synthetic methods for the building of complex molecules and polycylic motifs.[6] The potential of alkenylcarbene–metal intermediates generated by the Rautenstrauch rearrangement of propargylic esters [Eq. (1a)], catalyzed by Pd^{II} systems,[7] or, more recently, by Ru^{II},[3] Pt^{II},[4d-f,5g] or Au[5g,8–10] catalysts, has been demonstrated by the direct synthesis of functional cyclopropane derivatives,[1–3,8b,c] cyclopentanones,[7,8a] terpenoids,[9] trienes,[3c] and indenes.[3e,4f,10]



(1)

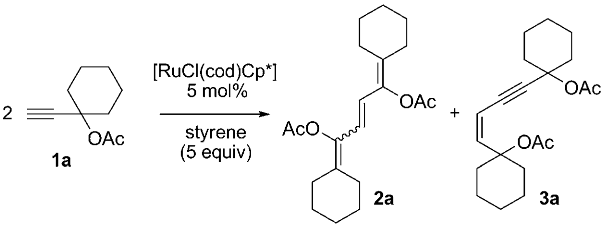
Although Group 6 Fischer-type metal carbene complexes are known to dimerize the carbene ligands into symmetrical alkenes by carbene transfer to a palladium catalyst,[11] the coupling of a vinylcarbene with a different carbene source, to create a double bond and to generate functional conjugated dienes, has not been reported [Eq. (1b)]. However, the enyne metathesis, performed with Grubbs catalyst and leading to alkenylcycloalkenes, can be formally considered as the trapping of the vinylcarbene intermediate by the alkene bond to create the new intracyclic double bond.[12] By contrast, complexes containing the {Ru(X)Cp*} moiety ($Cp^* = C_5Me_5$), which inhibit enyne metathesis,[13] are known to stabilize the formation of *cis* bis(carbene) ruthenium complexes.[14] If a catalyst of the form $[RuX(C_5R_5)]$ could underwent the Rautenstrauch rearrangement of a propargylic derivative into a vinylcarbene, the coupling of the latter with another source of carbene would then be possible [Eq. (1b)].

We report herein that the reaction of propargylic esters with diazoalkanes in the presence of [RuCl(cod)Cp*] (cod = cyclooctadiene) generates functional dienes by the coupling of a vinylcarbene fragment, arising from the rearranged propargylic ester, with the diazoalkane carbene [Eq. (2)]. This catalytic reaction constitutes a formal "cross-coupling" C=C bond formation from two different carbene sources.



(2)

The Rautenstrauch rearrangement promoted by ruthenium catalysts was detected initially with $[\{RuCl_2(CO)_3\}_n]$ by Ohe, Uemura, and co-workers. The resulting unsaturated carbene added to olefins to form vinylcyclopropanes.[3a,b] By contrast, when we attempted the reaction of propargyl acetate **1a** with styrene in the presence of a catalytic amount of [RuCl(cod)Cp*], it did not lead to the cyclopropanation product but to compound **2a**, resulting from the dimerization of the rearranged vinylcarbene, along with a small amount of enyne **3a** [Eq. (3)]. Both the decrease in reaction temperature and the use of toluene rather than dioxane had a positive effect on the formation of **2a**, which was obtained in moderate yields (35%, *E*:*Z* 65:35).[15]



(3)

		2a	3a
Toluene	RT	35 %	5 %
	60 °C	5 %	30 %
Dioxane	RT	22 %	–
	60 °C	–	40 %

As compound **2a** contains two rearranged propargylic groups, and as the {RuXCp*} moiety stabilizes *cis* bis(carbene) ruthenium complexes,[14] it seems possible that **2a** arises from a bis(vinylcarbene) ruthenium moiety, rather than from dimerization of the free vinylcarbene, or by the reaction of the vinylcarbene ruthenium complex with **1**, accompanied by acetate shift.[3d] We have thus investigated the coupling of the in situ rearranged vinylcarbene with a diazoalkane which

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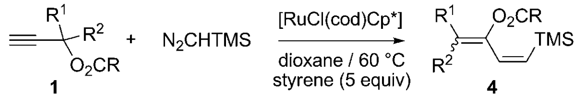
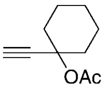
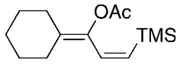
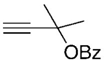
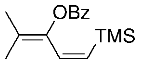
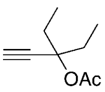
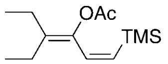
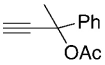
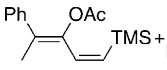
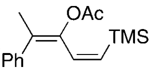
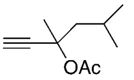
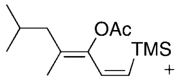
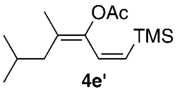
Table 1: Catalytic formation of dienes from propargylic esters and TMS diazomethane.[a]



Substrate **1**	Reaction time	Diene **4**	Yield [%][b]	Stereoselectivity (*E*:*Z*)
 **1a**	5 min	 **4a**	99	–
 **1b**	5 min	 **4b**	99	–
 **1c**	4 h	 **4c**	68[c]	–
 **1d**	2 h	 **4d** +  **4d'**	89	65:35
 **1e**	2 h	 **4e** +  **4e'**	99	65:35

[a] Reaction conditions: propargylic carboxylate (1.2 mmol, 1 equiv), styrene (5 equiv), trimethylsilyldiazomethane 2 M in diethyl ether (1.1 equiv), [RuCl(cod)Cp*] (5 mol%), 60°C in 1 mL of dioxane. [b] Yield of compound isolated by chromatography on silica gel. [c] Conversion of 70%.

easily generates a ruthenium carbene on reaction with [RuCl(cod)Cp*].[13,17]

The reaction of propargylic acetate **1a** (1.2 mmol) with N_2CHTMS (1.1 equiv 2 M in Et_2O, TMS = trimethylsilyl), styrene (5 equivalents) and [RuCl(cod)Cp*] (5 mol%) in dioxane for 5 min at 60°C led to the formation of the conjugated diene **4a**, which was isolated in 99% yield (Table 1).

The propargylic esters **1b–e**, with two substituents at the propargylic position, reacted under the same reaction conditions and gave the products **4b–e** in times of 5 min–2 h, in good yields (89–99%) that were not influenced by the substituent bulkiness (Table 1).

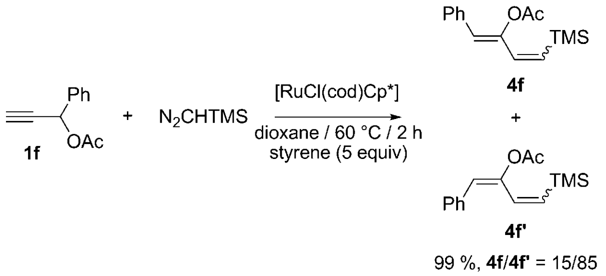
As for the vinylcarbene dimerization [Eq. (3)], the presence of styrene was beneficial: without 5 equivalents of styrene, dienes **4d** and **4d'** were obtained in only 50% yield. Coordination of styrene to the ruthenium intermediate may temporarily protect the coordinatively unsaturated ruthenium carbene species.

With disubstituted propargylic carboxylates **1a–e**, the formation of the TMS-substituted double bond in dienes **4** was highly stereoselective (100% *Z*) Table 1. When the two substituents on **1** were different (**1d–e**), a mixture of two isomers in 65:35 ratio was obtained, arising from the *Z* and *E* configurations of the tetrasubstituted double bond, as shown by NOESY experiments.

The monosubstituted propargylic carboxylate **1f** led to a mixture of four isomers of type **4** with a 99% total yield [Eq. (4)]. The two major isomers, **4f'** with *E* configuration of the acetate-substituted double bond (**4f'$_1$** (*EZ*)/**4f'$_2$** (*EE*): 80/20), and the two minor ones, **4f** (**4f$_1$** (*ZZ*)/**4f$_2$** (*ZE*): 80/20), were obtained in the ratio 85:15. The major products have a silylalkenyl bond with *E* configuration, in contrast to disubstituted derivatives **4a–4e**.

The desilylation of compounds **4** was not easy to perform. Thus, the reaction was carried out with in situ-generated diazomethane, by using trimethylsilyldiazomethane in methanol as solvent with **1a** in the presence of styrene (5 equivalents). After only 15 min of reaction at 60°C, the corresponding desilylated diene **5** was isolated with a good yield (91%) [Eq. (5)].

Other diazoalkanes proved less reactive than N_2CHTMS for the formation of dienes. The reaction of **1a** with phenyldiazomethane in the presence of styrene (5 equivalents) at 60°C after 16 h led to the corresponding conjugated diene **6** in moderate yield (51%). However, the phenyl-substituted double bond in **6** has the *E* configuration [Eq. (6)].



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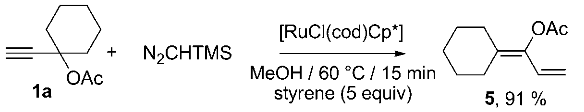
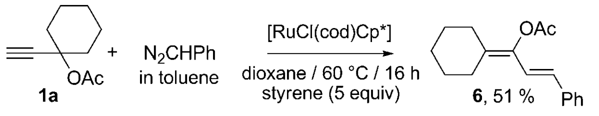
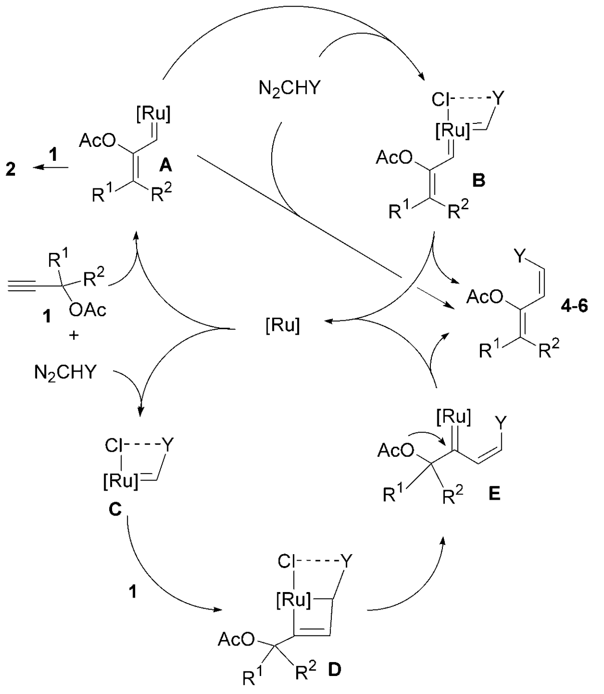


(5)



(6)

At this stage, the reaction mechanism has not been elucidated as the initial adduct of [RuCl(cod)Cp*] with **1a** or N_2CHTMS could not be detected. Two possible approaches can be considered (Scheme 1). The first potential mechanism



Scheme 1. Possible catalytic cycles for the synthesis of dienes from propargylic esters and diazoalkanes. Y = TMS, Ph, or H.

involves the initial formation of the ruthenium vinylcarbene intermediate **A**, after the Rautenstrauch rearrangement of the propargylic carboxylate[7] in the presence of the [RuCl(cod)Cp*] catalyst. Addition of the diazoalkane then leads to the formation of a ruthenium bis(carbene)–metal intermediate **B**, leading to the formation of the C=C bond and diene **4**, or to the direct reaction of intermediate **A** with diazoalkane to give **4**.[18] The reaction of intermediate **A** with **1** could lead to formation of **2**.

Another possible mechanism involves the initial interaction of the catalyst with the diazoalkane, leading to carbene **C**, which undergoes [2+2] cycloaddition with the triple bond of **1**, leading to intermediate **D**, as in enyne metathesis,[12,13] followed by formation of the vinylcarbene–ruthenium intermediate **E**.[19] The 1,2-shift of the acetate to the carbene carbon of **E** would form **4**.[3d,5g] The preferred *Z* configuration of the silylalkenyl bond may arise from the interaction of the silyl group with the chloride (upper cycle),[13] or by ring-opening of intermediate **D**, similar to that of 3-silylcyclobutenes (lower cycle).[20]

In summary, the [Ru(Cl)Cp*]-catalyzed formation of conjugated dienes proceeded with good yields and selectivities by cross-coupling of two carbene fragments arising from two different sources, a vinylcarbene fragment resulting from a propargylic ester rearrangement and a diazoalkane carbene. This method provides a novel approach to the synthesis of dienes, precursors of α,β-unsaturated silylated ketones, and has potential, owing to the large number of in situ generated metal–vinylcarbenes, to create a variety of functionalized dienes. This C=C bond forming reaction is currently under study.

Experimental Section

Typical procedure for ruthenium-catalyzed cross-coupling of carbenes: [RuCl(cod)Cp*] (5 mol %) was added as a solid to a solution of propargyl acetate **1a**–**1e** (1.2 mmol), styrene (5 equiv) and trimethylsilyldiazomethane (1.1 equiv, 2 M solution in diethyl ether) in dioxane (1 mL) at 60 °C under an inert atmosphere. The reaction mixture was stirred for 5 min–2 h. The solvent was removed under vacuum, and the products were isolated by column chromatography on silica gel, eluted with mixed solvent (pentane/diethyl ether).

Full experimental details and characterization data are given in the Supporting Information.

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[15] Higher temperature (60 °C) favored the classical dimerization of terminal alkyne **1a** before its rearrangement by acetate transfer, into enyne **3a**. This process is known to proceed by insertion of the vinylidene intermediate into a Ru–alkynyl bond.[16]

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