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Tandem Catalytic Carbene Addition/ Bicyclization of Enynes. One-Step Synthesis of Fluorinated Bicyclic Amino Esters by Ruthenium Catalysis

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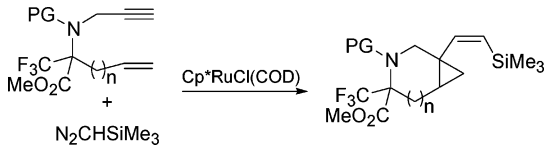
ABSTRACT



The reaction of diazo compounds with enynes, containing a fluorinated amino acid moiety, in the presence of the precatalyst Cp*(Cl)Ru(COD) leads to fluorinated alkenyl bicyclo[3.1.0]hexane and [4.1.0]heptane amino acid derivatives. It is remarkable that the catalyst, in situ generated from ruthenium complex and diazo compound, completely inhibits the ring closing metathesis of enyne to the profit of tandem alkenylation/ cyclopropanation with high stereoselectivity. The study shows that the Cp*(Cl)Ru moiety in ruthenacyclobutane favors reductive elimination versus expected alkene metathesis.

Enynes play an important role in complex molecules synthesis as they are the object of controlled metal-catalyzed skeleton rearrangements leading to higher value cyclic functional products.[1] Nonconjugated enynes are suitable substrates for the catalytic Pauson−Khand reaction,[2] and they are selectively transformed into conjugated alkenylcycloalkenes using alkene metathesis catalysts.[3] Recently, platinum(II) and gold(I) catalysts have promoted the electrophilic rearrangement of enynes into bicyclo[4.1.0]heptene derivatives[4a−c] and of hydroxylated 1,5-enynes into bicyclic ketones.[4d] Consequently, the enyne structure has gained the potential to open the route to heterobicyclic compounds via catalysis, including amino acid derivatives.

The incorporation of cyclic α-amino acids, bringing a conformational restriction into peptides, can be an important tool in drug discovery processes.[5] Tyrosine has been successfully replaced by a conformationally constrained bicyclic

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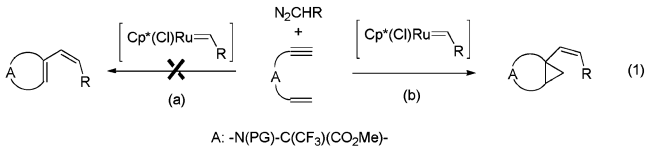
amino acid analogue in protein kinase.[6] The evaluation of strained bicyclic amino acids into peptides, and especially of stabilizing fluorinated analogues, has not been performed yet, likely due to the lack of straightforward method of access.[7]

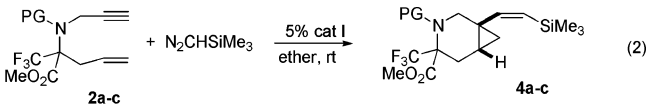
We now report a simple synthesis of fluorinated bicyclo[3.1.0]hexane and [4.1.0]heptane amino esters by ruthenium-catalyzed tandem addition of diazoalkane/bicyclization of fluorinated enynes under very mild conditions. We show that the in situ generated alkylidene−ruthenium catalyst [Cp*(Cl)Ru═CH−R] completely inhibits (a) the ring closing metathesis of enyne to the profit of (b) tandem alkenylation/cyclopropanation with high stereoselectivity (eq 1).



(1)

A: -N(PG)-C(CF_3)(CO_2Me)-

The transformation of mixed propargyl allyl ethers and amides into bicyclo[3.1.0]hexane derivatives was shown via ruthenium-catalyzed reaction with diazoalkanes to take place at 60 °C for 4−5 h.[8] We have found now that when the diazoalkane was produced in ether rather than in hexane, the catalytic transformation of allyl propargyl tosylamide was dramatically accelerated and could be completed at room temperature, under conditions tolerating classical amino acid protecting groups. Then, the new fluorinated enynes **2**−**3** have been prepared from the protected imines $CF_3C(═NPG)CO_2Me$ **1**[9] by nucleophilic addition of allyl or vinylmagnesium bromide followed by reaction with propargyl bromide. The 1,7-enynes **2a**−**c** (1 mmol) were reacted with 1.15 equiv of $N_2CHSiMe_3$ in diethyl ether and 5 mol % of the precatalyst Cp*(Cl)Ru(COD) (**I**) at room temperature for 3−4 h until complete conversion of **2** to the amino esters **4** containing the bicyclo[4.1.0]heptane structure.[10] These compounds were isolated in 68 (**4a**), 64 (**4b**), and 73% (**4c**) yield, respectively (eq 2). Each of them contained both diastereoisomers that have been separated using chromatography on silica gel. Each diastereoisomer shows a *Z*-configuration for the CH═CHSiMe_3 group.

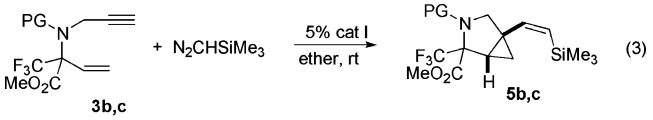


(2)

PG = Boc (**a**), Cbz (**b**), Ts (**c**)

4a (68%,d.r. = 50:50)
4b (64%,d.r. = 55:45)
4c (73%,d.r. = 67:33)

Under similar conditions, the 1,6-enynes **3b** and **3c** react with $N_2CHSiMe_3$ in ether to give the diastereoisomers **5b** (60%) and **5c** (59%) with the bicyclo[3.1.0]hexane structure with the *Z*-configuration of the alkenyl group (eq 3). In that case, the reaction is very fast with respect to that leading to the derivatives **4**, as for instance the reaction of **3b** at room temperature was completed in 10 min to give **5b**. ^{1}H NMR studies showed that the major diastereoisomer contains the *trans*-CO_2Me and *Z*-Me_3SiCH═CH groups. The X-ray structure of the minor diastereoisomer of **5c** confirmed the *cis*-relative positions of these groups.[11]

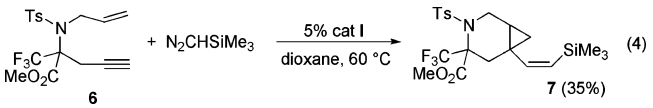


(3)

PG = Cbz (**b**), Ts (**c**)

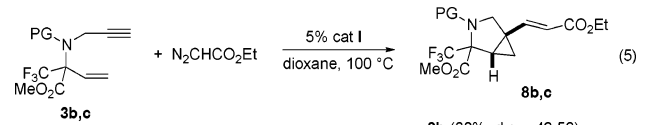
5b (60%, d.r. = 38:62)
5c (59%, d.r. = 36:64)

To study the general access to bicyclo[4.1.0]heptane structures, enyne **6**, with opposite positions of propargyl and allyl groups on the nitrogen and carbon atoms with respect to **2c**, was synthesized and reacted with $N_2CHSiMe_3$ in the presence of 5 mol % of catalyst **I**. The reaction under the initial conditions[8] (dioxane, 60 °C) afforded the bicyclo[4.1.0]heptane amino ester **7** isolated in only 35% yield (eq 4).



(4)

The catalytic transformations of enynes **3** with ethyl diazoacetate required higher temperature and were performed in dioxane at 100 °C for 4 h. **3b** and **3c** led to the bicyclo[3.1.0]hexane amino esters **8b**,**c** (eq 5). These compounds possess the relative *trans* positions of the CO_2Me and the Me_3SiCH═CH groups as for **5b** and **5c**, but they contain an *E*-CH═CHCO_2Et side chain, probably due to thermal factors as the reaction takes place at about 100 °C.



(5)

PG = Cbz (**b**), Ts (**c**)

8b (60%, d.r. = 42:58)
8c (80%, d.r. = 31:69)

The proposed mechanism for this transformation (Scheme 1, R = $SiMe_3$) involves the formation of ruthena-

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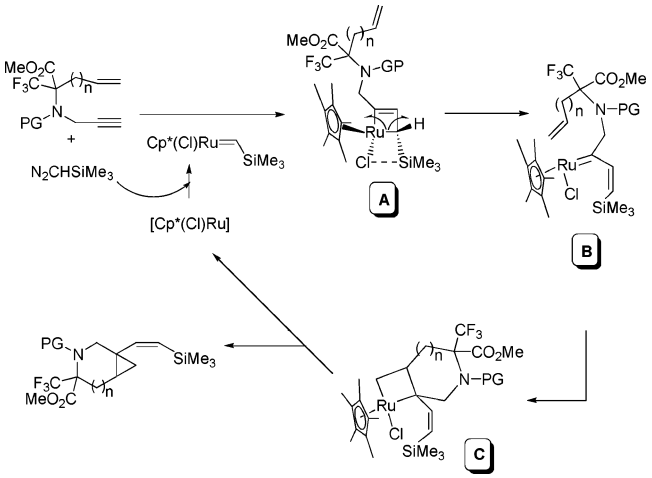
(10) General procedure: in a Schlenk tube under inert atmosphere, to a solution of the enyne (1 mmol) in degassed diethyl ether (2 mL) was added 1.15−1.2 mmol of the 2.0 M trimethylsilyldiazomethane solution in ether. The mixture was stirred at room temperature, and 5 mol % of the precatalyst Cp*RuCl(COD) was then introduced. Pure ethyldiazoacetate was similarly added to a dioxane solution, and the reaction was performed at 100 °C. Reaction completion was monitored using GC or TLC techniques. Diastereoisomers were separated as pure compounds using standard chromatography over silica gel with an ether:pentane eluting mixture. All bicyclic compounds were fully characterized.

(11) See Supporting Information.

Scheme 1. Proposed Mechanism



cyclobutene **A**, as for the initial step of RCM of enynes with alkene metathesis catalysts.[3] Indeed, an initial bicyclization cannot be attained as in the Pt(II)-catalyzed transformation of enynes,[4] as the enyne is unchanged in the presence of Cp*(Cl)Ru(COD) and in the absence of diazoalkane compound. Simple models show that the formation of intermediate **A** requires the *anti* position of Cp* and $SiMe_3$ groups to decrease steric interactions (Scheme 1). The transformation of **A** into the alkenylcarbene **B** is responsible for the initial configuration of the alkenyl group. The opening of the Ru−C bond leading to intermediate **B** requires a "disrotary" process to explain the initial *Z*-configuration of the $-CH{=}CHSiMe_3$ chain. An interaction between the neighboring Me_3Si and Cl groups may be responsible for this stereochemistry. The [2 + 2] addition of the carbene and terminal double bond in **B** is expected to give the metallacyclobutane intermediate **C**, which on reductive elimination leads to the transformation of the bicyclic products **4** and **5**.

It is noteworthy that the same sequential steps **A** → **B** → **C** occur in the transformation of enynes with an alkene metathesis catalyst, such as $RuCl_2(=CHPh)(PCy_3)(IMes)$.[3] Although theoretical calculations have not been performed yet, it appears that the ruthenacyclobutane **C**, when [Ru] is the Cp*(Cl)Ru moiety, favors reductive elimination with respect to the $(IMes)Cl_2Ru$ moiety leading to metathesis.[3] However, in the reaction of an enyne containing an internal triple bond with catalyst $RuCl_2(=CHPh)(PCy_3)(IMes)$, a small amount of bicyclo[3.1.0]hexane was obtained.[12]

This sequential carbene addition and cyclopropanation reactions of the fluorinated enynes **2** and **3** offer a direct route to bicyclic α-amino esters containing the alkenyl bicyclo[3.1.0] and [4.1.0]alkane structure. Previously, only a bicyclic fluorinated lactam was obtained via addition of $N_2C(CF_3)(CO_2Me)$, with $Rh_2(OAc)_4$ catalyst, to benzyl-protected allylamine followed by deprotection via hydrogenation.[13]

The reaction described here constitutes the first observed direct route to bicyclic amino acid derivatives from easily made enynes and to new fluorinated bicyclic compounds. It surprisingly shows that the Cp*(Cl)Ru moiety in the presence of N_2CHR inhibits the RCM of enynes. This simple ruthenium-catalyzed reaction seems to offer potential for the access to a wide variety of amino acid derivatives and functional bicyclic compounds and to become as general as the transformation of enynes into alkenyl cycloalkenes with alkene metathesis catalysts. The adaptation of this reaction to natural amino acid derivatives is under study.

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Supporting Information Available: Spectroscopic data for compounds **4** and **5** and **7** and **8** (PDF), and structural data for minor diastereoisomer **5c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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