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Ruthenium-Catalysed Synthesis of Fluorinated Bicyclic Amino Esters through Tandem Carbene Addition/Cyclopropanation of Enynes

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Abstract: The reaction of fluorinated 1,6- and 1,7-enynes, containing the moiety $N(PG)C(CF_3)(CO_2R)$, with diazo compounds in the presence of [RuCl(cod)(Cp*)] (cod = cycloocta-1,5-diene, $Cp^* = C_5Me_5$, PG = protecting group) as the catalyst precursor leads to the formation of fluorinated 3-azabicyclo[3.1.0]hexane-2-carboxylates and 4-azabicyclo-[4.1.0]heptane-3-carboxylates. This catalytic transformation was applied to various protecting groups and has proved to be a selective and a general synthetic tool to form constrained proline or homoproline derivatives in good yields. *Z* stereoselectivity of the created alkenyl group is obtained with $N_2CHSiMe_3$, whereas N_2CHCO_2Et favours selectively the *E* configuration for the same double bond. The diastereoselectivity *exo*/*endo* depends on the size of the created ring. The X-ray structures of two products have been determined, showing the stereochemistry of the compounds. The reaction can be understood by initial [2+2] addition of the Ru=CHY bond, generated from diazoalkane, with the C≡CH bond of the enyne leading to a key bicyclic ruthenacyclobutane, which promotes the cyclopropanation, rather than metathesis. This selective formation of bicyclic [*n*.1.0] compounds results from the ruthenium-catalysed creation of three carbon–carbon bonds in a single step under mild conditions.

Keywords: amino acids · bicyclic products · diazoalkanes · enynes · ruthenium

Introduction

Peptides modified by nonproteinogenic amino acids are useful building blocks for drug discovery. In particular, α,α-disubstituted amino acids have been the subject of growing interest because their incorporation into peptides can lead to specific biological activities,[1] as they are able to stabilize secondary structure elements and to retard proteolytic degradation.[2] Due to the unique properties of the fluorine atom, such as high electronegativity and hydrophobicity, fluorinated compounds have become very important in the field of medicinal chemistry and in pharmaceuticals.[3] Among them, fluorinated amino acids can be considered as interesting building blocks for designing hyperstable protein folds or to obtain highly specific protein–protein interactions.[4] Moreover, ^{19}F NMR spectroscopy is an effective tool for conformational studies of fluorine-containing peptides. As they can considerably improve the profile of bioactive peptides, the synthesis of fluorinated α-amino acids has recently received increasing attention.[5]

The incorporation of cyclic α-amino acids into key positions of peptide chains constitutes the most prominent pathway leading to conformationally constrained peptidomimetics.[6] Although biological activities have been shown by the incorporation of the fluorinated group into bicyclic amino acids,[7] only few fluorinated strained bicyclic amino acid derivatives have been described due to the lack of a straightforward method of access.[5c]

It occurs that a possible approach could involve catalytic carbocyclisation of enynes. Indeed, transition-metal-catalyst-promoted enyne cycloisomerisation is one of the most general and efficient methods for the synthesis of functionalised cyclic and heterocyclic compounds,[8] including bicyclic products.[9–12] Among them, the preparation of bicyclic [*n*.1.0] derivatives is of importance since the cyclopropane ring is a frequent moiety in natural products.[8f] This type of transformation was first reported from allylpropargylethers into 3-oxabicyclo[4.1.0]heptenes in the presence of $PtCl_4$ catalyst.[10a] Later, various bicyclo[4.1.0]heptenes have been obtained by bicyclisation of 1,6-enynes with Pt,[10a–f] Au,[10g–i] Ir[10j] and Rh[10k] catalysts. This cycloisomerisation applied to 1,5-enynes possessing no heteroatom on their tethers led to

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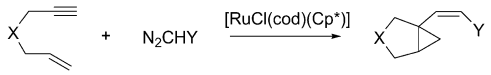
bicyclo[3.1.0]hexenes or hexanes.[11] Few bicyclo-[3.1.0]hexane derivatives have been prepared from 1,6-enynes in the presence of Ru,[12a] Au,[12b] Pt,[12c] Pd[12d–e] or Bi[12f] catalysts. However, none of these examples was applied to amino acid derivative synthesis.

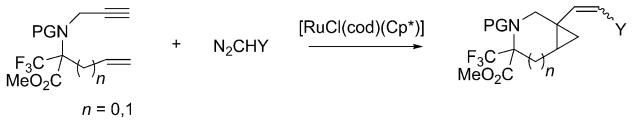
Our studies concerning the catalytic activity of the complex $[RuCl(C_5Me_5)(cod)]$[13] (cod = cycloocta-1,5-diene) showed its ability to produce ruthenium–carbene species, in situ generated from diazo compounds, and their catalytic addition to alkynes.[14] This work led to the discovery of a catalytic cascade rearrangement of enynes into bicyclic derivatives (Scheme 1).[15]



Scheme 1. Synthesis of bicyclic compounds by the catalytic rearrangement of enynes. Cp* = C_5Me_5.

The mild conditions of this ruthenium-catalysed reaction, assuming that it might tolerate classical protecting groups of amino acid functionalities, prompted us to explore the access to novel bicyclic constrained fluorinated amino esters.[16]

We now report the first synthesis of fluorinated 3-azabicyclo[3.1.0]hexane-2-carboxylates and 4-azabicyclo-[4.1.0]heptane-3-carboxylates, according to the same methodology, by ruthenium-catalysed tandem carbene addition/cyclopropanation of fluorinated enynes containing the moiety $N(PG)-C(CF_3)(CO_2R)$, leading to the first fluorinated bicyclic proline and pipecolic acid derivatives (Scheme 2). Indeed, despite the interest of substituted prolines, there are few reports of syntheses of fluorinated proline and pipecolic acid derivatives.[17]

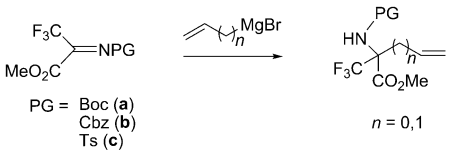


Scheme 2. Synthesis of fluorinated bicyclic proline and pipecolic acid derivatives.

Results and Discussion

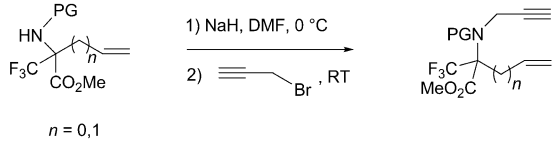
The preparation of the fluorinated enynes **1**–**2** has been first achieved from the protected imines $CF_3C(=NPG)CO_2Me$[18] by nucleophilic addition of vinyl or allyl magnesium bromide to produce fluorinated alkenylamino esters (Scheme 3).[19]

The second step involved the deprotonation of the amino ester derivatives with NaH in DMF at 0 °C and subsequent alkylation with propargylbromide to afford the corresponding 1,6- and 1,7-enynes with various protecting groups (Table 1).



Scheme 3. Synthesis of fluorinated alkenylamino esters.

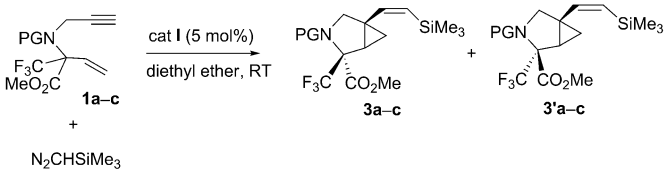
Table 1. Synthesis of fluorinated enynes. Boc = *tert*-butoxycarbonyl; Cbz = carbobenzyloxy.



PG	*n*	Enyne	Yield [%]
Boc	0	**1a**	71
Cbz	0	**1b**	72
Ts	0	**1c**	53
Boc	1	**2a**	51
Cbz	1	**2b**	55
Ts	1	**2c**	60

The 1,6-enynes **1** were reacted with 1.15 equivalents of trimethylsilyldiazomethane in diethyl ether in the presence of 5 mol% of the precatalyst $[RuCl(C_5Me_5)(cod)]$ (**I**) affording a complete conversion of **1** in 4 h at room temperature. Fluorinated bicyclic proline derivatives were obtained (Table 2). These aminoester derivatives **3**/**3′** containing the

Table 2. Reaction of 1,6-enynes with trimethylsilyldiazomethane.



PG	Yield[a] (**3**+**3′**) [%]	Ratio **3**/**3′**
Boc (**a**)	80	57:43
Cbz (**b**)	60	62:38
Ts (**c**)	59	68:32

[a] Yield of isolated product.

strained bicyclic[3.1.0]hexane structure were isolated in good yields (59–80%) up to 80% for the Boc protecting group. In each case, the selective *Z* configuration of the created double bond was observed. Two diastereoisomers, **3** and **3′**, were formed. NOESY NMR spectroscopic experiments showed the relative *cis* configuration of the vinyl and CF_3 groups for each major isomer, **3a**–**c**. An approximately 60:40 ratio for **3**/**3′** was obtained for the Boc and Cbz protecting groups and it increased until approximately 70:30 for the tosyl group. These reaction conditions have been chosen because they were proved to be the best for the same reaction with simple nitrogenated enynes.[15] For this

reaction, the bulky electron-rich precursor [RuCl(C_5Me_5)(cod)] (**I**) appeared to be a selective catalyst, whereas [$RuCl_2(C_6Me_6)]_2$ or [Ru(C_5Me_5)($CH_3CN)_3$]PF_6 did not catalyse it. The use of the precatalyst [RuCl(C_5H_5)(cod)] led to a lower conversion of enynes even after 24 h and a mixture of isomers was obtained.

Crystals of the minor isomer **3′c** that were suitable for X-ray analysis were obtained and the crystallographic structure displayed a relative *trans* configuration for the vinyl and CF_3 groups and a *Z* configuration for the alkenyl moiety (Figure 1).[20]

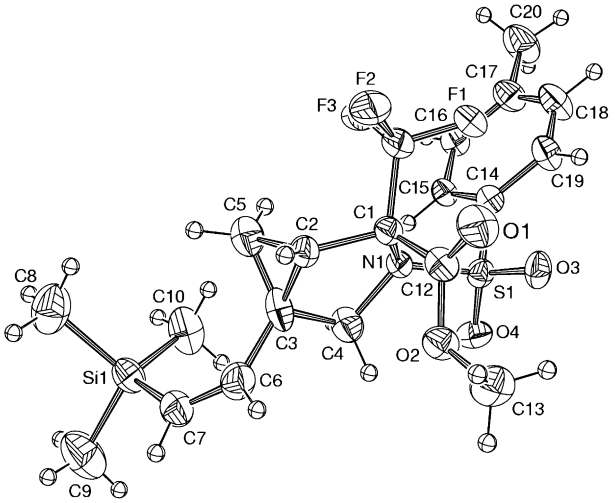
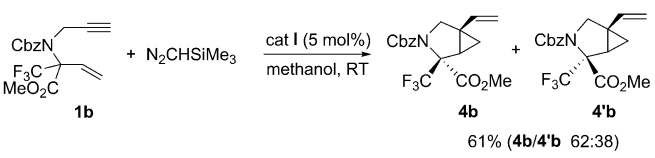


Figure 1. ORTEP drawing of the molecular structure of **3′c**.

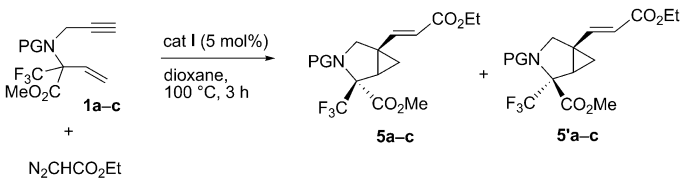
The desilylation of trimethylsilylvinylbicyclo[3.1.0]hexanes appeared not to take place under classical conditions. However the direct formation of bicyclic compounds with a desilylated vinyl group have already been obtained from simple nitrogenated enynes by reaction with $N_2CHSiMe_3$ in methanol, in presence of catalyst **I**. Indeed, the in situ formation of diazomethane from $N_2CHSiMe_3$ could be obtained in methanol.[15b] The reaction of 1,6-enyne **1b** with 1.1 equivalents of trimethylsilyldiazomethane in methanol at room temperature led after 15 min to desilylated fluorinated proline derivatives **4b**/**4′b** in 61% yield (Scheme 4). The ratio of the two diasteroisomers was similar to the ratio **3b**/**3′b**.

The same catalytic rearrangement could be carried out by using another diazoalkane as the substituent source for the formed alkenyl moiety. 1,6-Enynes **1a–c** were reacted with 1.2 equivalents of ethyldiazoacetate and 5 mol% of [RuCl(C_5Me_5)(cod)] in dioxane at 100°C affording the corresponding bicyclo[3.1.0]hexane derivatives **5**/**5′** in good yields (65–77%; Table 3). Temperatures of 60 and 80°C were found to be inefficient for this transformation.



Scheme 4. Reaction of 1,6-enyne **1b** with trimethylsilyldiazomethane in methanol.

Table 3. Reaction of 1,6-enynes with ethyldiazoacetate.

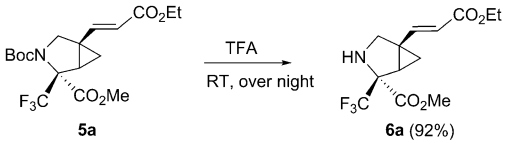


PG	Yield[a] (**5**+**5′**) [%]	Ratio **5**/**5′**
Boc (**a**)	70	57:43
Cbz (**b**)	65	56:44
Ts (**c**)	77	69:31

[a] Yield of isolated product.

A complete selectivity towards the *E* configuration of the double bond for each compound was observed. Two diastereoisomers, **5** and **5′** were isolated by silica gel chromatography and the *cis*/*trans* relationship between the vinyl and CF_3 groups for each major isomer were assigned by NOESY NMR spectroscopic experiments, which indicated that the major diastereoisomer was the same as for the proline derivatives **3**/**3′**. For the Boc and Cbz protecting groups, the ratio **5**/**5′** was only approximately 55:45 but a higher ratio of 69:31 was obtained with the tosyl group.

To demonstrate the possible further synthetic application of bicyclic amino acid derivatives, for example, in peptide synthesis, the deprotection of amino function in the corresponding Boc derivatives was performed. Proline derivative **5a** was treated with TFA at room temperature to lead to the desired free amino ester **6a** in 92% yield (Scheme 5).

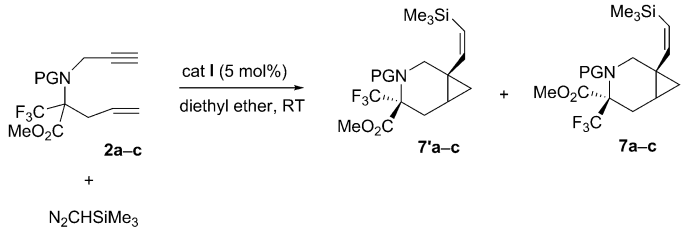


Scheme 5. Deprotection of Boc-derivative **5a**. TFA = trifluoroacetic acid.

Fluorinated bicyclic pipecolic acid derivatives were thus expected to be produced by extension of the catalytic transformation to 1,7-enynes **2a–c**. By reaction with trimethylsilyldiazomethane in diethyl ether at room temperature, the corresponding 4-azabicyclo-[4.1.0]heptane-3-carboxylates **7**/**7′** were produced in 64–73% yields (Table 4). As for the reaction of the 1,6-enynes with $N_2CHSiMe_3$, a *Z* configuration for the double bond was obtained for each compound **7**/**7′**.

Two diastereoisomers **7** and **7′** were isolated but contrary to the reaction of the 1,6-enynes, NOESY NMR spectroscopic experiments showed that the diastereoisomer **7′** with the relative *trans* configuration of the vinyl and CF_3 groups

Table 4. Reaction of 1,7-enynes with trimethylsilyldiazomethane.



PG	Yield[a] (**7**+**7′**) [%]	Ratio **7′**/**7**
Boc (**a**)	68	53:47
Cbz (**b**)	64	55:45
Ts (**c**)	73	67:33

[a] Yield of isolated product.

was now the major isomer in each case. These data could be further confirmed by a crystallographic structure of the major isomer **7′c** (Figure 2).[20]

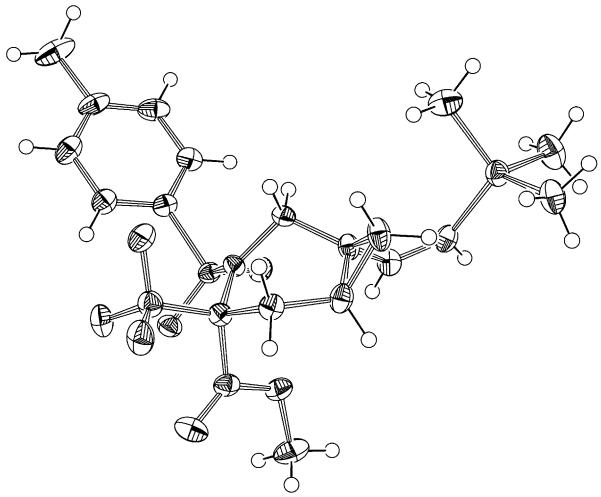
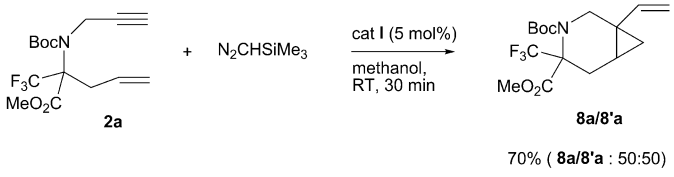


Figure 2. ORTEP drawing of the molecular structure of **7′c**.

When the reaction of N-Boc-protected 1,7-enyne **2a** with $N_2CHSiMe_3$ was performed in methanol, desilylated bicyclic pipecolic acid derivatives **8a**/**8′a** were obtained in 70% yield with a ratio of 50:50 for the two diastereoisomers (Scheme 6).

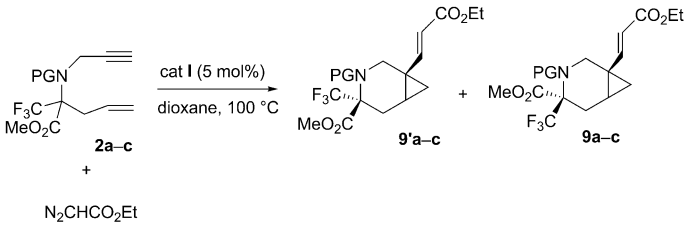
With ethyldiazoacetate, 1,7-enynes **2a–c** afforded in dioxane at 100°C after 4–5 h the corresponding bicyclic amino-



Scheme 6. Reaction of 1,7-enyne **2a** with trimethylsilyldiazomethane in methanol.

ester derivatives **9**/**9′** in reasonable yields (48–57%) (Table 5). An *E* stereochemistry was obtained for the double bond as for the reaction of the 1,6-enynes under sim-

Table 5. Reaction of 1,7-enynes with ethyldiazoacetate.

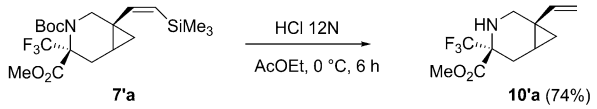


PG	Yield[a] (**9**+**9′**) [%]	Ratio **9′**/**9**
Boc (**a**)	48	60:40
Cbz (**b**)	49	58:42
Ts (**c**)	57	68:32

[a] Yield of isolated product.

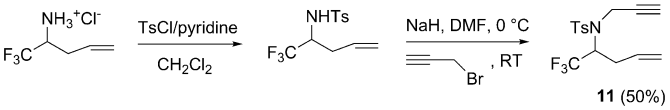
ilar conditions. Diastereoisomer **9′** with the relative *trans* configuration of the vinyl and CF_3 groups, established by NOESY NMR spectroscopic experiments for each compound, was the major isomer formed as for the reaction of the 1,7-enynes with $N_2CHSiMe_3$ giving pipecolic acid derivatives **7**/**7′**.

The N-deprotection of pipecolic acid derivatives has been carried out from a silylated compound. The reaction of Boc-derivative **7′a** with HCl 12N in AcOEt at 0°C led to simultaneous desilylation and N-deprotection affording free amino ester **10′a** (Scheme 7).



Scheme 7. Deprotection of Boc-derivative **7′a**.

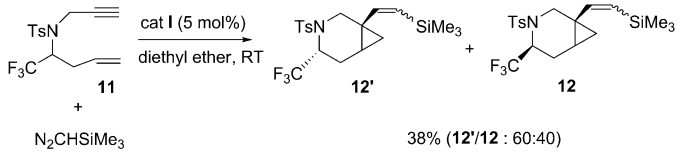
To study the effect of the CF_3 substituent on the obtained diastereoselectivity, the synthesis of monosubstituted 1,7-enyne **11**, with only a CF_3 group, was performed. This 1,7-enyne **11** was obtained from α-(trifluoromethyl)homoallylamine,[21] which was first protected by a tosyl group and then alkylated with propargylbromide (Scheme 8).



Scheme 8. Synthesis of 1,7-enyne **11**.

The reaction of trifluoromethylated 1,7-enyne **11** with $N_2CHSiMe_3$ in the presence of 5 mol% of catalyst **I** at room temperature in diethyl ether led to the corresponding bicy-

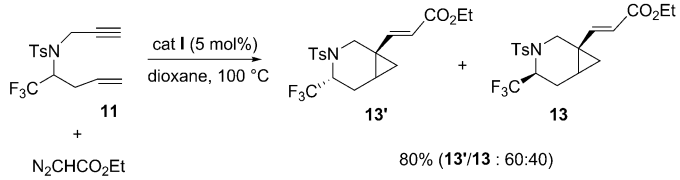
clic compounds **12**/**12′** as a mixture of isomers in a low yield (38%; Scheme 9). However, it was possible to determine that the double bond was formed in a *Z*/*E* mixture with a ratio of 80:20. Two diastereoisomers, **12′** and **12** were observed by ^{1}H NMR spectroscopy in a ratio of 60:40.



Scheme 9. Reaction of 1,7-enyne **11** with trimethylsilyldiazomethane.

Based on the comparison of the ^{1}H NMR spectroscopic chemical shifts of the other fluorinated pipecolic acid derivatives, we arrived at the conclusion that the major diastereoisomer had the CF_3 and vinyl groups in a *trans* relationship as in the derivatives **7′**. This hypothesis was confirmed by the following experiment.

When the reaction of 1,7-enyne **11** was carried out with N_2CHCO_2Et at 100°C, a good yield of compounds **13**/**13′** (80%) was obtained with the complete *E* stereochemistry for the double bond (Scheme 10). The two diastereoisomers



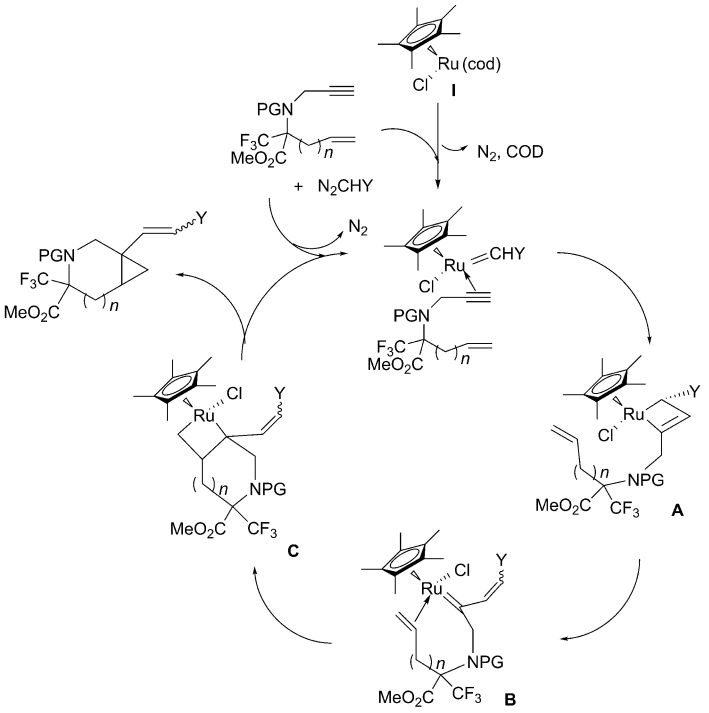
Scheme 10. Reaction of 1,7-enyne **11** with ethyldiazoacetate.

were formed with a ratio **13′**/**13** of 60:40. NOESY NMR spectroscopic experiments confirmed the relative *trans* configuration for the CF_3 and vinyl groups for the major isomer **13′** as for derivatives **9′**. The comparison with derivatives **9**/**9′c** possessing two substituents (CF_3 and CO_2Me groups) showed that a loss of diastereoselectivity was observed.

Proposed mechanism

Catalytic cycle: A possible mechanism for this formation of fluorinated 3-azabicyclo[3.1.0]hexane-2-carboxylates and 4-azabicyclo-[4.1.0]heptane-3-carboxylates is shown in Scheme 11. This catalytic cycle is similar to that proposed for the cyclisation of simple enynes under similar conditions.[15b]

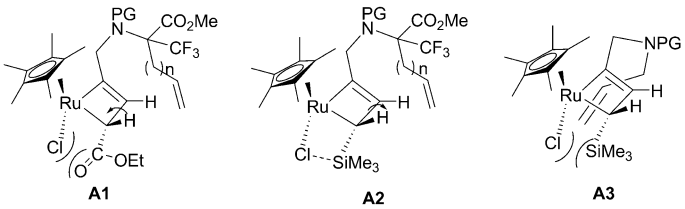
It is known that the complex [RuCl(C_5Me_5)(cod)] easily loses its cod ligand in the presence of unsaturated substrates, thus offering two vacant coordination sites for the activation of two unsaturated bonds. Diazo compounds are expected to interact with the precatalyst [RuCl(C_5Me_5)(cod)] to give ruthenium–carbene species, which first react with the terminal triple bond of the enyne.[14] A classical [2+2] cycloaddition of Ru=C and C≡C bonds gives the metallacyclobutene **A**, leading to the ruthenium vinylcarbene **B**. The intramolecular interaction of the Ru=C bond with the terminal C=C bond of **B** is expected to give the metallacyclobutane intermediate **C**, which is subject to reductive elimination to give a fluorinated bicyclic aminoester.



Scheme 11. Proposed catalytic cycle.

The catalytic enyne metathesis has been shown to easily proceed with Grubbs catalyst[22] and the proposed mechanism involves the interaction of the Ru=C bond with the triple bond by means of a mechanism similar to that in Scheme 11, with [$RuCl_2$(=CHPh)(IMes)(PCy_3)], except for the last step. In this latter case, the intermediate **C** exclusively leads to a metathesis process. Thus, the present reaction differs from enyne metathesis only by the ability of the {Cp*RuCl} moiety to favour reductive elimination. DFT calculations have been performed with simple enynes[15b] and have confirmed that the {(C_5R_5)RuCl} fragment favours the formation of a cyclopropanation product and inhibits the enyne metathesis.

Stereochemistry: Simple molecular models show that the formation of intermediate **A** requires the *anti* position of Cp* and Y groups to decrease strong steric interactions present in the *syn* isomer. Thus, the stereochemistry of the double bond results from the opening of the metallacyclobutene **A** (Scheme 12). With Y = CO_2Et, electronic repulsion between Cl and CO_2Et groups favours the opening leading to lower steric hindrance giving an *E* configuration (**A1**). For Y = $SiMe_3$, a strong interaction between $SiMe_3$ and Cl groups is



Scheme 12. Stereochemical aspects of intermediates **A**.

expected and can be responsible for the opposite opening in spite of steric interactions leading to *Z* configuration (**A2**).

However, when $Y=SiMe_3$, it was shown with simple enynes[15] that the stereoselectivity depends also on the allyl arm substitution. A substituted double bond on the allyl arm induced a total *Z* stereoselectivity, whereas with a terminal double bond a *Z*/*E* mixture (*Z* favoured) was obtained. A possible coordination of this double bond, when it is not substituted, on the ruthenium centre in intermediate **A**, can disturb the Cl—$SiMe_3$ interaction and partially leads to *E* stereochemistry (**A3**). A hindered double bond is not able to coordinate the ruthenium and thus only the expected *Z* stereochemistry is obtained. In the case of aminoester derivatives, the same results are obtained with the substitution of the alkenyl chain by introduction of two substituents (CF_3 and CO_2Me groups) close to the N atom. All the compounds with CF_3 and CO_2Me groups produce exclusively *Z* stereochemistry (**A2**), whereas the products **12**/**12′** with CF_3 group only are obtained with a *Z*/*E* stereochemistry.

For these trifluoromethylated bicyclic proline and pipecolic acid derivatives, the diastereoselectivity *exo*/*endo* depends strongly on the size of the created ring. The fluorinated proline derivatives favour the diastereoisomer with the relative *cis* configuration of the vinyl and CF_3 groups, whereas the six-membered ring derivatives favour the diastereoisomer with the *trans* configuration. This diastereoselectivity *endo*/*exo* is probably due to electronic (strong electronegativity of CF_3 group) and steric effects. The electronic repulsion between Cl and CF_3 groups is expected to strongly induce the favoured position of the CF_3 group. For proline derivatives, the X-ray analysis shows a restricted space above the five-membered ring on the side of cyclopropane ring. This can explain the *anti* position of the cyclopropane ring and the CF_3 group for the major diastereoisomer for these compounds.

Conclusion

We have successfully developed a straightforward synthetic route for the synthesis of novel highly constrained α-trifluoromethyl α-amino acid derivatives. This catalytic reaction leads to the first trifluoromethylated bicyclic proline and pipecolic acid derivatives, under mild conditions, in one step from easily accessible enynes. This [$RuCl(C_5Me_5)$(cod)]-catalysed transformation can be applied to various protecting groups and has proved to be a selective and general synthetic tool as it can be used as well to form proline derivatives than to produce homoproline derivatives, in good yields. High stereoselectivities for the created alkenyl chain can be obtained, depending on the nature of the diazoalkane: *Z* isomer with $N_2CHSiMe_3$ and *E* isomer with N_2CHCO_2Et. These results allow us to consider a ruthenium vinyl–carbene species as a key intermediate of the reaction, responsible for the stereoselectivity. Importantly, the last catalytic step involving the formation of ruthenacyclobutane species selectively forms a cyclopropane ring by reductive elimination instead of an alkenylcycloalkene by an alkene metathesis process. This single-step access route to amino acid derivatives represents an alternative synthesis for the formation of constrained analogues of natural amino acids.

Experimental Section

General: All catalytic reactions were carried out under inert atmosphere in Schlenk tubes. The complex [$RuCl(C_5Me_5)$(cod)] was prepared according to the reported method.[23] ^1H and ^{13}C NMR spectra were recorded on Bruker 300, 400 and 500 MHz and DPX 200 spectrometers in deuterated chloroform solutions at 298 K. Mass spectra were obtained on VARIAN MATT 311 high-resolution spectrometer in Centre Regional de Mesures de l′Ouest (CRMPO) of the University of Rennes1. Characterization data are presented in the Supporting Information.

Typical procedure for enynes synthesis: In a Schlenk tube under an inert atmosphere, a solution of alkenylamino acid derivative[19] (3 mmol) in dry DMF (2 mL) was added to a suspension of NaH (3.3 mmol) in dry DMF (2 mL) at 0 °C. After stirring for 1 h at room temperature propargyl bromide (6 mmol) was added and reaction mixture was stirred overnight. Cold water was added and solution was extracted with ether. The organic layer was washed with brine and dried with $MgSO_4$. The organic solvent was then removed under reduced pressure and the crude product was purified by silica gel chromatography.

Typical procedure for catalytic carbene addition/cyclopropanation of enynes: (Trimethylsilyl)diazomethane solution in diethyl ether (2.0 M, 1.15 mmol) or ethyldiazoacetate (1.2 mmol) was added in a Schlenk tube under inert atmosphere to a solution of the enyne (1 mmol) in degassed diethyl ether, dioxane or methanol (2 mL). Precatalyst [$RuCl(C_5Me_5)$(cod)] (5 mol %) was then introduced. The mixture was stirred at room temperature or at 100 °C for 4–5 h. Reaction completion was monitored by using GC or TLC techniques. The solvent was removed under vacuum and diastereoisomers were separated as pure compounds by using standard chromatography over silica gel with a diethyl ether/pentane eluting mixture.

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