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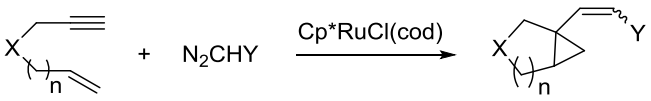
One-Step Ruthenium-Catalysed Transformation of 1,7-Enynes into Strained Bicyclic Amino Esters

Solenne Moulin, Thierry Roisnel and Sylvie Dérien*

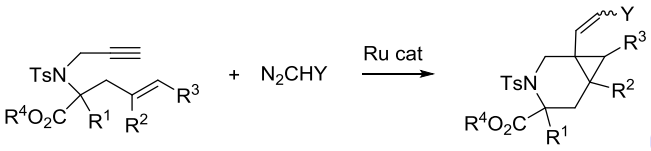
Abstract: The reaction of 1,7-enynes, synthesised from α-amino acids, carried out with diazo compounds in the presence of the Cp*RuCl(cod) catalyst allowed the one-step preparation of various strained bicyclic pipecolic acid derivatives in good yields under mild conditions. The stereoselectivity of the created double bond depends on the nature of the diazoalkane and the diastereoselectivity arises essentially from steric factors.

The selective construction of functionalised carbo-, hetero- and poly-cyclic compounds remains a crucial challenge for the synthesis of natural products and biologically active molecules. Transition-metal-catalysed cyclisations of non-conjugated enynes constitute a powerful and atom-economical methodology for the assembly of architecturally complex molecules under mild conditions in a single step.[1-4] Palladium-[2], ruthenium-[3] or, more recently, platinum- and gold-catalysts[4] have been proven efficient for the cycloisomerisation of enynes providing functionalised cyclic compounds, including bicyclic products.[5] For example, cycloisomerisation of nitrogen-bridged 1,6-enynes offers a direct access to the preparation of azabicyclo[n.1.0] derivatives, which have potential biological activity.[6] The enyne structure and its type of cyclisation can thus open the route to valuable heterocyclic compounds such as cyclic amino acid derivatives. Over the past few decades, the incorporation of non-proteinogenic cyclic α-amino acids into peptides, inducing conformational constraints, offered opportunities in drug discovery processes, exhibiting higher biostability and enhanced biological properties.[7,8] For example, tyrosine has been successfully replaced by a conformationally constrained bicyclic amino acid analogue in protein kinase.[9] Therefore, synthesis of conformationally restricted amino acids has become a subject of major importance for drug design.[10-12] Among them, proline and pipecolic acid derivatives are interesting building blocks, frequently used.[8,11,12] Our studies concerning the catalytic activity of the complex Cp*RuCl(cod) (Cp* = C_5Me_5) to produce ruthenium-carbene species, in situ generated from diazo compounds, led to the discovery of a novel cyclisation of enynes into bicyclic derivatives after a catalytic cascade rearrangement (Scheme 1).[13]



Scheme 1. Ruthenium-catalysed synthesis of bicyclic products.

The mild conditions of this ruthenium-catalysed transformation allowed us to explore the one-step synthesis of bicyclic constrained amino acid derivatives.[14,15] Thus, 1,6-enynes successfully led to strained bicyclic proline derivatives with excellent diastereoselectivities.[15] We then studied the reactivity of a variety of 1,7-enynes containing α-amino ester groups with diversified scaffold decoration. We report here the one-step synthesis of new strained bicyclic pipecolic acid derivatives under mild conditions via an atom-economical ruthenium-catalysed tandem carbene addition / cyclopropanation (Scheme 2).



Scheme 2. Synthesis of bicyclic pipecolic acid derivatives.

The preparation of 1,7-enynes **1a-i** was first achieved after tosylation of the amino group and subsequent alkylation with propargyl bromide from alkenyl amino esters which were obtained according to classical procedures (Scheme 3).[16] Enynes **1a-f** were reacted with 3 equivalents of ethyldiazoacetate and 5 mol% of the precatalyst Cp*RuCl(cod) (**I**) in dioxane at 100 °C affording after 3h constrained pipecolic acid derivatives with a bicyclo[4.1.0] heptane core in good yields (Scheme 4). As previously reported,[13] a selective *E* configuration for the created double bond was observed. Two diastereomers were formed and the *trans*/*cis* relationship between the vinyl and methyl ester groups were assigned by NOESY NMR experiments. For **2a-d** the relative *trans* configuration was obtained for the major diastereomer. These data could be confirmed by a crystallographic structure of the minor isomer of **2d** (Figure 1).[17] These reactions proceeded with low diastereoselectivity. An approximately 50/50 ratio was obtained for **2e-f** and it increased until approximately 60/40 for **2a-b**: the steric hindrance of the R^1 group of the amino acid (H → Me → *i*Bu) seems to prevent the diastereoselectivity. For **2e**, two additional diastereomers were produced because of the presence of the methyl group in the R^3 position whereas a methyl substituent for the R^2 group did not modify the diastereoselectivity (**2b**, **2d**). Each diastereomer of bicyclic

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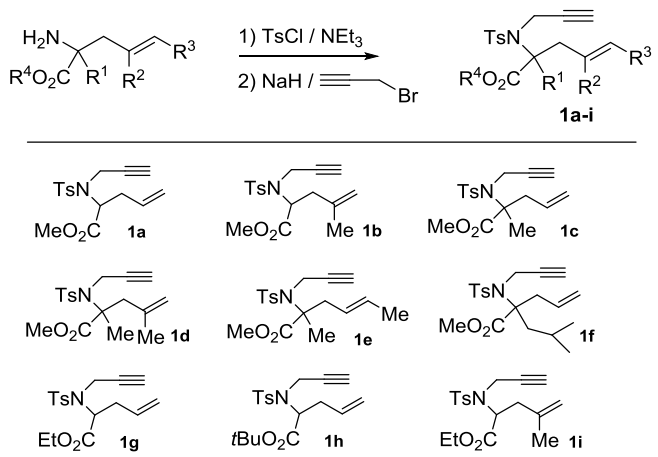
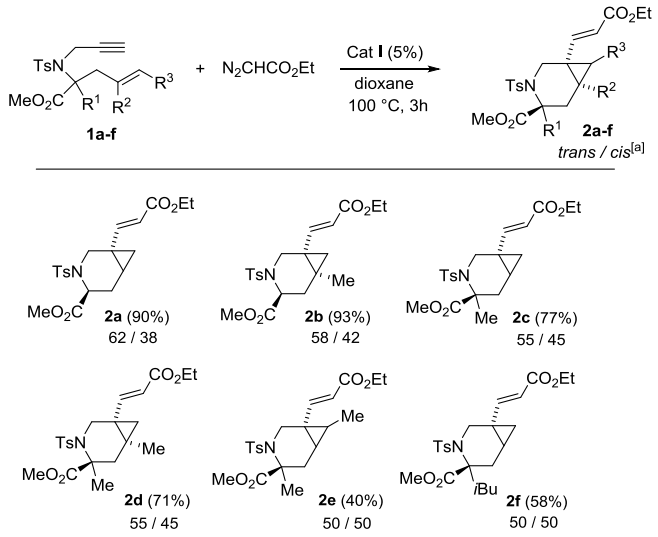
amino esters **2a-b** can be isolated separately using silica gel chromatography.



Scheme 3. Synthesis of 1,7-enynes.



Scheme 4. Reaction of 1,7-enynes **1a-f** with ethyldiazoacetate. [a] The diastereomeric ratio corresponds to the relative *trans*/*cis* configuration of the vinyl and ester groups and was determined by ^{1}H NMR.

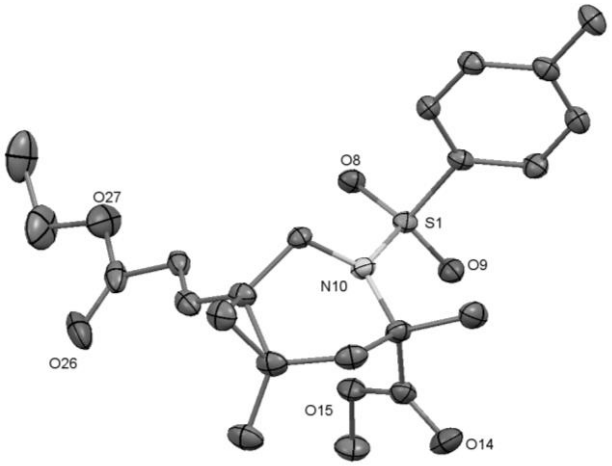
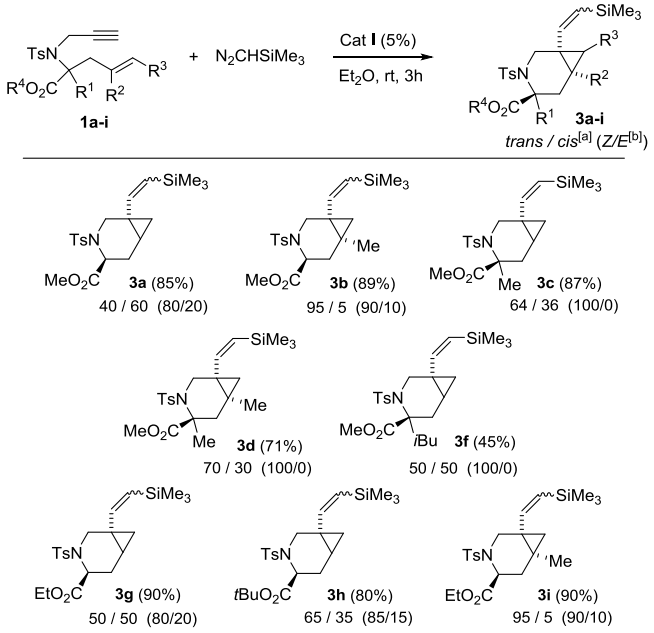


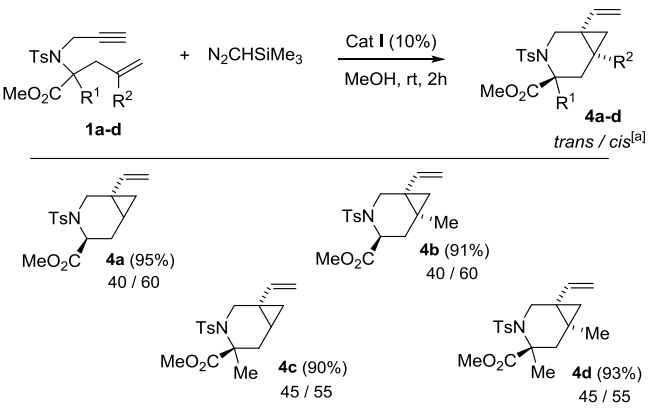
Figure 1. ORTEP drawing of the molecular structure of the minor isomer of **2d**.

1,7-Enynes **1a-i** were then reacted with 1.2 equivalents of trimethylsilyldiazomethane in diethyl ether in the presence of 5 mol% of Cp*RuCl(cod) providing after 3h at room temperature a complete conversion of **1** to lead to bicyclic amino ester derivatives **3** in good yields (Scheme 5). For compounds derived from glycine (R^1 = H, **3a-b**, **3g-i**), the newly created double bond was formed in a *Z*/*E* mixture. The introduction of a $R^1 \neq$ H substituent (alanine or leucine derivatives) led to a total *Z* configuration for the double bond. A 50/50 diastereomeric ratio was again obtained from leucine-derived enyne **1f** and no reaction occurred from enyne **1e**. From enynes **1a-d** with a methyl ester substituent (R^4 = Me), the diastereoselectivity was improved for bicyclic compounds derived from glycine or alanine (**3a-d**) by comparison with the results achieved with ethyldiazoacetate. From enyne **1c** with a non-substituted double bond, a 64/36 ratio was gained in favour of the diastereomer with a relative *trans* configuration. The presence of the methyl substituent in R^2 position seemed particularly important as enyne **1d** led to a 70/30 ratio for the diastereomers **3d**. The best result was obtained from enyne **1b**. Indeed, the diastereomer with the relative *trans* configuration was produced with a diastereoselectivity up to 90%. Surprisingly, in the case of **3a**, the major diastereomer formed was the one with a relative *cis* configuration. As for products **2**, only the diastereomers of compounds **3a-b** could be isolated separately. We also studied the effect of the steric hindrance of the ester group of enynes, derived from glycine, on the diastereoselectivity. From new enynes **1g-i**, expected bicyclic compounds were produced in very good yields. From **1a** (R^2 = H, R^4 = Me), the introduction of a bulkier substituent on the ester group (**1g**, R^4 = Et; **1h**, R^4 = *t*Bu) led to a reversal of the relative configuration of ester and vinyl groups: with the bulkier *t*Bu group, the relative *trans* configuration was now obtained for the major isomer of **3h**. The presence of a methyl substituent in the R^2 position (**3b**, **3i**) allowed again to afford the best diastereoselectivity.



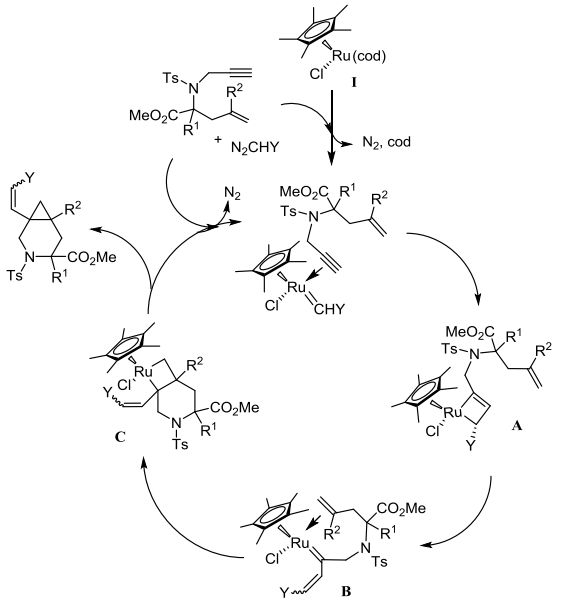
Scheme 5. Reaction of 1,7-enynes **1a-i** with trimethylsilyldiazomethane. [a] The diastereomeric ratio corresponds to the relative *trans*/*cis* configuration of the vinyl and ester groups and was determined by ^{1}H NMR.[b] The *Z*/*E* ratio corresponds to the configuration of the double bond.

The formation of bicyclic compounds with a desilylated vinyl group can be obtained by reaction of enynes with $N_2CHSiMe_3$ in methanol in the presence of catalyst **I**.[13] So, the reaction of 1,7-enynes **1a-d** with 1.1 equivalents of $N_2CHSiMe_3$ in methanol at room temperature led after 2h to desilylated derivatives **4a-d** in very good yields (Scheme 6). Two diastereomers were produced with a 40/60 ratio for glycine derivatives and a 45/55 ratio for alanine derivatives. No improvement was brought by the methyl substituent in R^2 position. Surprisingly, for all compounds **4a-d** a relative *cis* configuration was obtained for the major diastereomer. Gratifyingly, each diastereomer of these bicyclic compounds with a desilylated vinyl group was isolated separately using silica gel chromatography.

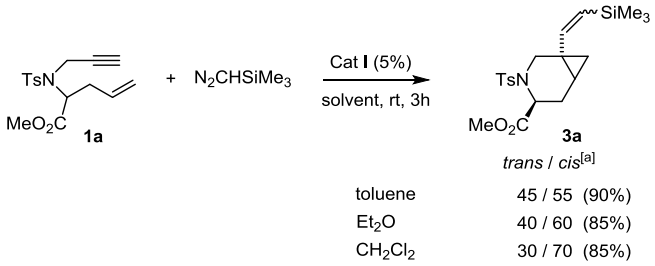


Scheme 6. Reaction of 1,7-enynes **1a-d** with trimethylsilyldiazomethane in methanol. [a] The diastereomeric ratio corresponds to the relative *trans*/*cis* configuration of the vinyl and ester groups and was determined by ^{1}H NMR.

These results are in agreement with the mechanism suggested for the cyclisation of simple enynes under similar conditions (Scheme 7).[13,14] According to classical reaction steps, the Cp*RuCl moiety interacts with diazo compounds to produce ruthenium-carbene species which is able to coordinate the triple bond of the enyne and leads to ruthenium-vinyl carbene **B** after a [2 + 2] cycloaddition.[18,19] A metallacyclobutane intermediate **C** can be then obtained by interaction between the Ru=C bond and the C=C bond. A subsequent favoured reductive elimination gives the bicyclic amino ester derivative. As expected,[13,14] the stereochemistry of the created double bond arises from the opening of the metallacycle **A**. With Y = CO_2Et, an *E* configuration is obtained probably because of electronic repulsion between CO_2Et and Cl groups. For Y = $SiMe_3$ a strong interaction between Cl and $SiMe_3$ groups leads to a *Z* configuration.[18] This interaction can be disturbed by the potential coordination of the homoallylic arm, if the steric hindrance of this arm is not important enough. In this case, the *E* configuration is also partially obtained. Two diastereomers can result from the formation of the intermediate **C** and the diastereoselectivity seems to strongly depend on steric effects. In general, the diastereomer with the relative *trans* configuration of the ester and vinyl groups is favoured. The *cis* diastereomer becomes the major one only when the steric hindrance decreases: with $R^1 = R^2 = R^3 = H$, R^4 = Me (compound **3a**, Scheme 5) or with Y = H (compounds **4**, Scheme 6). Furthermore, when the substituent in R^4 position turns more hindered (Me → Et → *t*Bu), the *trans*/*cis* ratio increases (**3a** → **3g** → **3h**, Scheme 5). The nature of the reaction solvent can also have an effect on this ratio. Indeed, when the reaction of **1a** with trimethylsilylacetylene takes place in polar solvents, the diastereomer with the relative *cis* configuration of ester and vinyl groups is favoured (Scheme 8). This could also explain the diastereoselectivity observed for the reaction performed in methanol (compounds **4**, Scheme 6).



Scheme 7. Proposed catalytic cycle.



Scheme 8. Reaction of 1,7-enyne **1a** with trimethylsilyldiazomethane in different solvents. [a] The *trans*/*cis* diastereomeric ratio was determined by ^{1}H NMR and corresponds to the relative configuration of the vinyl and ester groups.

We have successfully opened a straightforward access to the preparation of novel highly strained bicyclic pipecolic acid derivatives via a one-step, atom-economical Cp*RuCl(cod)-catalysed transformation of enynes. A variety of 1,7-enynes, based on different α-amino acids, with diversified scaffold decoration, could lead to constrained analogues of natural amino acid derivatives in good yields under mild conditions. Good stereoselectivities for the created double bond were observed, depending on the nature of the diazo compounds. The last step of the catalytic cycle of this reaction involves a constrained ruthenacyclobutane species which leads to two diastereomers. The study of the diastereoselectivity implies that steric factors can favour one diastereomer. So, a diastereoselectivity up to 90% could be obtained. Further studies aimed at the application of this catalytic process to the synthesis of enantiomerically enriched strained α-amino acids.

Experimental Section

Typical procedure for catalytic reaction: In a Schlenk tube under inert atmosphere, to a solution of the enyne (1 mmol) in degassed diethy ether, dioxane or methanol were added 1.1 mmol of a 2.0 M trimethylsilyldiazomethane solution in diethyl ether or 3.0 mmol of ethyldiazoacetate. 5 mol% of the precatalyst Cp*RuCl(cod) were then introduced. The mixture was stirred at room temperature or at 100 °C for 2-3 h. The solvent was removed under vacuum and the diastereomers were purified using standard chromatography over silica gel with a diethylether/pentane eluting mixture.

All procedures and characterisation data are presented in the Supporting Information.

Acknowledgements

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Keywords: amino acids • bicyclisation • diazoalkanes • enynes • ruthenium

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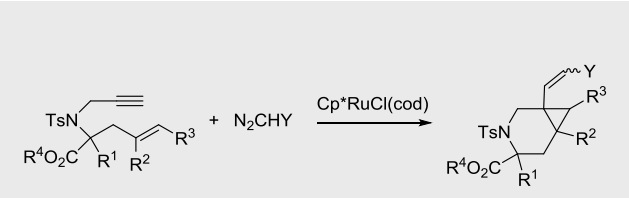

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