[2+1] Cycloaddition of Catalytic Ruthenium Vinyl Carbenes: A Stereoselective Controlled Access to (*Z*)- and (*E*)-Vinyl Epoxypyrrolidines

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ABSTRACT: Aza-alkynals undergo a cyclization reaction with diazo compounds in the presence of catalytic amounts of Cp*RuCl(cod) to afford vinyl epoxypyrrolidines, valuable building blocks for the synthesis of biologically active molecules. Ruthenium vinyl carbene intermediates have been invoked to explain the overall [2+1] cycloaddition (epoxy-annulation reaction). The reaction proceeds under mild conditions and in short reaction times (5 - 80 min) with complete (*Z*)- or (*E*)- stereoselectivity on the vinyl substituent depending on the nature of the diazo compound used. Theoretical calculations support a mechanistic rationale to explain this controlled process.

KEYWORDS: carbenes, [2+1] cycloaddition, diazo compounds, pyrrolidines, ruthenium catalyst

Bicyclic oxazaheterocycles are highly valuable structures present in a plethora of biologically active molecules and could also serve as attractive building blocks to access to more complex molecular architectures.[1] In particular, epoxypyrrolidine units, namely 6-oxa-3-azabicyclo[3.1.0]hexanes, are found in many biologically active molecules such as epolactaene,[2] fusarin C[3] or hirsutelone C[4] (Figure 1), and are used as versatile building blocks for the synthesis of a wide variety of natural products like (+)-DMDP,[5] (+)-broussonetine G,[6,5] mytomycin K[7] or berkeleyamide D.[8]

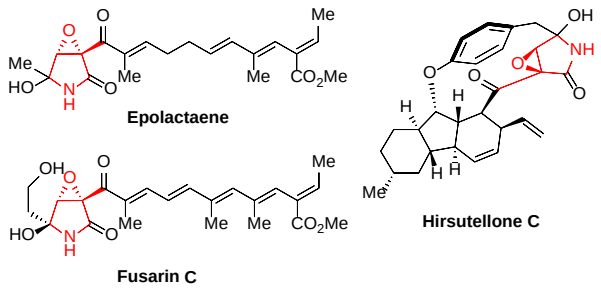
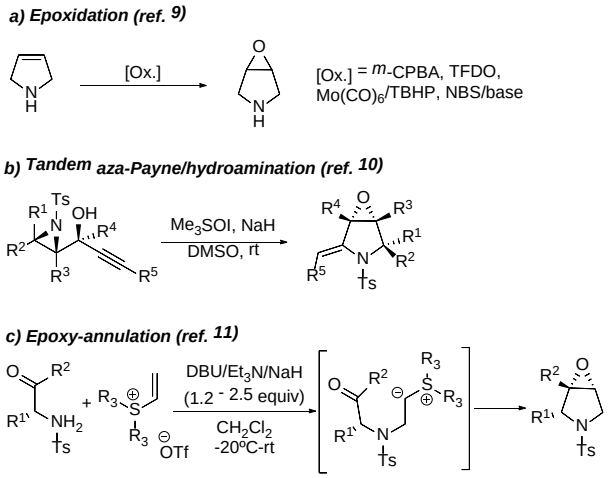


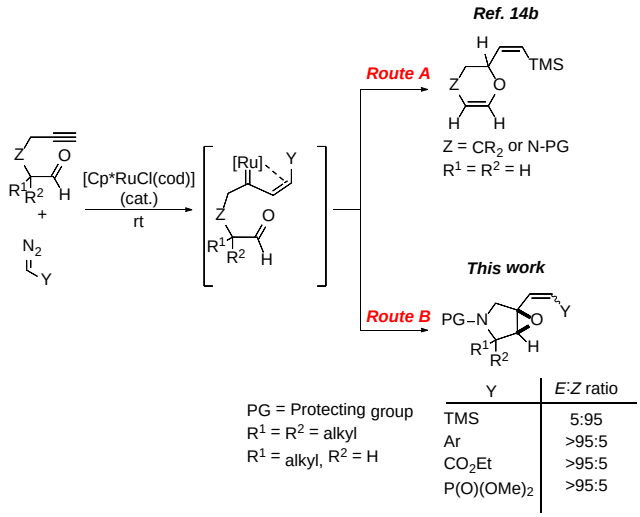
Figure 1. Biologically active epoxypyrrolidines.

Several approaches have been devised to access to epoxypyrrolidines based on a) epoxidation of the preformed dihydropyrrole ring (Scheme 1a),[9] b) sequential formation of the epoxide and pyrrole rings *via* tandem aza-Payne/hydroamination of aziridinols (Scheme 1b),[10] and c) the concurrent formation of both rings *via* intramolecular cyclization of a sulfonium ylide intermediate into an electrophilic carbonyl group. The key intermediate was formed *in situ* from an intermolecular addition of an α-aminocarbonyl derivative to a vinyl sulfonium salt. (Scheme 1c).[11]



Scheme 1. Synthetic approaches to epoxypyrrolidines

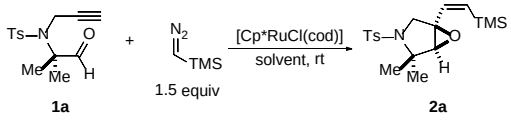
Over the last few years, catalytic vinyl ruthenium carbenes have proved to be useful intermediates in a variety of relevant synthetic transformations[12,13,14] and, namely, in carbocyclizations ([2+1] cycloadditions between alkenes and allenes to cyclopropane derivatives[13a-e] and neutral redox processes from activated C-H substrates[14a]). Recently we have extended the use of these valuable intermediates to heterocyclization reactions with the stereoselective synthesis of vinyl dihydropyrans and dihydrooxazines from unsubstituted alkynals and aza-alkynals, respectively (Scheme 2, route A).[14b] We now report a mild and convenient entry to vinyl epoxypyrrolidines from substituted aza-alkynals (R^1, R^2 = alkyl; R^1 = alkyl, R^2 = H) and diazo compounds based on a novel [2+1] cycloaddition of a π (C=O) bond of an aldehyde to the *in situ* generated catalytic ruthenium vinyl carbene intermediates (Scheme 2, route B). The reaction proceeds with complete (*Z*)- or (*E*)- stereoselectivity depending on the nature of the diazo compound used.



Scheme 2. Synthesis of epoxypyrrolidines via [2+1] cycloaddition of catalytic ruthenium vinyl carbenes

Alkynal **1a** was selected as the test substrate for the optimization process (Table 1). Pleasingly, the reaction of **1a** with 1.5 equiv of $TMSCHN_2$ in the presence of 10 mol% of [Cp*RuCl(cod)] at room temperature afforded the *Z*- vinyl epoxypyrrolidine **2a** in nearly quantitative yield in less than 5 min (entry 1). Polar aprotic solvents did not significantly affect the reaction yield (entries 2 and 3) but the use of polar protic solvents such as methanol or isopropanol resulted in a dramatic decrease in both yield and chemoselectivity (entries 4 and 5). Interestingly, the catalyst loading could be reduced from 10 mol% to just 1 mol% without affecting the reaction yield and time by keeping the catalyst concentration in a 11 mM - 15 mM range (entries 6 – 10). Remarkably, as we had already noticed for the cyclization of α-unsubstituted alkynals and aza-alkynals,[14b] stereoselectivity could be switched by a simple catalyst variation and *E*-vinyl epoxypyrrolidine **2a** could be mainly obtained by using [CpRuCl(cod)] as pre-catalyst without significant detriment of the reaction yield (entry 11).

Table 1. Optimization of the reaction conditions[a]

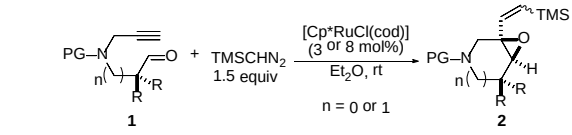


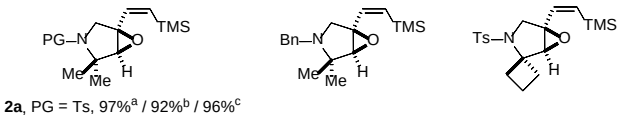
entry	cat./mol%	solvent	*Z*:*E* ratio[b]	yield (%)[c]
1	10	Et_2O	>95:5	95
2	10	Acetone	>95:5	90
3	10	PhMe	>95:5	87
4	10	MeOH	-	CM[d]
5	10	*i*-PrOH	>95:5	68
6	8	Et_2O	>95:5	97
7	3	Et_2O	>95:5	82[e]
8[f]	3	Et_2O	>95:5	92
9[f]	1	Et_2O	>95:5	<50[e]
10[g]	1	Et_2O	>95:5	91
11[hi]	5.5	Et_2O	1:10	77

[a]General procedure: **1a** (0.215 mmol), [Cp*RuCl(cod)], $TMSCHN_2$ (2 M solution in hexane, 1.5 equiv), solvent (1.5 mL) at rt. [b]*Z*/*E* ratio determined by ^{1}H-NMR analysis of the crude mixture. [c]Isolated yields. [d]Complex mixture. [e]No complete consumption of **1a** was observed. [f]0.5 mL of solvent were used. [g]0.17 mL of solvent were used. [h]Reaction run in a 0.35 mmol scale using [CpRuCl(cod)] as catalyst. [i]0.28 mL of solvent were used.

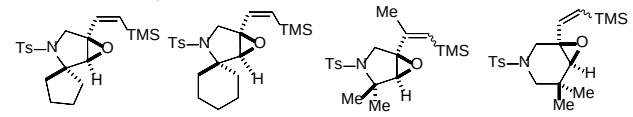
Once having optimized the reaction conditions, we set out to investigate the substrate scope. The cyclization reaction of tosylamide derivatives of α,α'-disubstituted alkynals **1a** and **1f-i**, derived from readily available α-aminoacids, gave the corresponding vinyl epoxypyrrolidines **2a** and **2f-i**, respectively, in fairly good yields (Table 2). Other sulfonamide protecting groups like mesyl, nosyl **1b**, **1c** and carboxybenzyl **1d** were also well tolerated. However, the presence of an electron-withdrawing protecting group proved to be crucial as the electron rich benzylamine derivative alkynal **1e** only cyclize on heating to 60 °C to give **2e** in a low 14% yield. Alkynals **1f-h** smoothly cyclize to spiro-epoxypyrrolidines **2f-h** in excellent yields in less than 5 min. The cyclization of internal alkynal **1i** was also possible, but heating conditions were necessary to afford the corresponding epoxypyrrolidine **2i** in low yield. Most likely, this lower reactivity might be attributed to the steric hindrance caused by the alkyne substituent which makes more difficult the formation of the reactive ruthenium vinyl carbene intermediate. Interestingly, the cyclization reaction could also be applied to the efficient formation of epoxypiperidine **2j**, from the corresponding alkynal **1j**. The epoxy annulation reaction could be easily scaled up since epoxypyrrolidine **2a** was obtained with an excellent 96% yield in a gram scale by using 1 mol % of [Cp*RuCl(cod)] and 1.3 equiv of $TMSCHN_2$.

Table 2. Scope of α,α'-disubstituted alkynals





2a, PG = Ts, 97%[a] / 92%[b] / 96%[c]
2b, PG = Ms, 89%[a]
2c, PG = Ns, 80%[a]
2d, PG = Cbz, 71%[a] (*Z*:*E*, 20:1)
2e, 14%[d]
2f, 95%[a] / 90%[b]



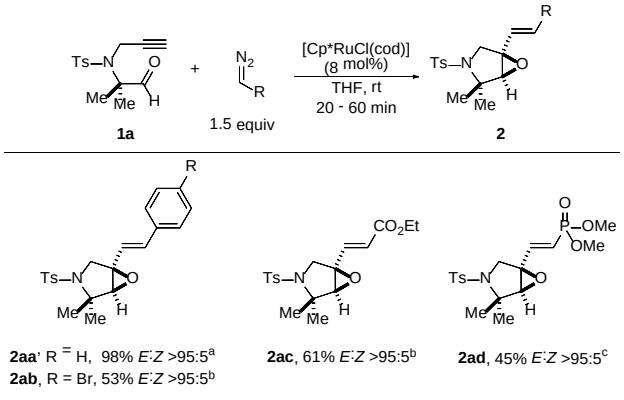
2g, 89%[a]
2h, 92%[a]
2i, 26%[e] (*Z*:*E*, 4.5:1)
2j, 79%[a] (*Z*:*E*, 4:1)

Conditions: alkynal **1a-j** (0.215 mmol), [Cp*RuCl(cod)], $TMSCHN_2$ (1.5 equiv), Et_2O (1.5 mL) at rt. [a][Cp*RuCl(cod)] (8 mol%) and 1.5 mL of Et_2O. [b][Cp*RuCl(cod)] (3 mol%) and 0.5 mL of Et_2O. [c]Scaling up experiment performed with 3.08 mmol, [Cp*RuCl(cod)] (1 mol%), 1.3 equiv of $TMSCHN_2$ and 2.4 mL of Et_2O. [d]60 °C in THF. [e]60 °C in 1,4-dioxane. Ts = p-toluenesulfonyl, Ms = mesyl, Ns = p-nitrobenzenesulfonyl, Cbz = carboxybenzyl, Bn = benzyl.

Epoxy-annulation of alkynal **1a** with other monosubstituted diazo compounds was analyzed next (Table 3).[15] Changes in the

electronic and steric properties of the diazo compound partner had a remarkable effect in the double bond geometry of the alkenyl substituent and also in the kinetics of the reaction. Firstly, the employment of partially stabilized diazo compounds such as aryl-substituted or electron-poor diazoalkanes renders the process completely *E*-selective.[16] Secondly, the homocoupling of the diazo compound became a competitive side reaction with electron-poor compounds, although full conversions were achieved by using THF as solvent in combination with the slow addition of the diazo partner. Thus, while the reaction of **1a** with 1.5 equiv of phenyldiazomethane[17] at room temperature gave rise to vinyl epoxypyrrolidine **2aa** in an excellent 98% yield after 20 min, the mild electron-poor (4-bromophenyl)diazomethane afforded epoxypyrrolidine **2ab** in a moderate 53% yield. The cyclization of **1a** with the more electron-poor ethyl diazoacetate and dimethyl (diazomethyl)phosphonate (Seyferth-Gilbert reagent) provided the corresponding epoxypyrrolidines **2ac** and **2ad** in 61% and 45% yields, respectively.

Table 3. Scope of diazo compounds

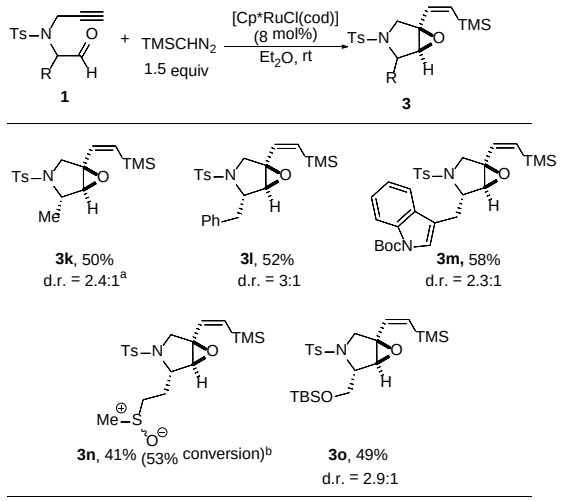


2aa, R = H, 98% *E*:*Z* >95:5[a]
2ab, R = Br, 53% *E*:*Z* >95:5[b]
2ac, 61% *E*:*Z* >95:5[b]
2ad, 45% *E*:*Z* >95:5[c]

Conditions: **1a** (0.215 mmol), [Cp*RuCl(cod)] (8 mol%), diazo compound (1.5 equiv), THF (1.5 mL) at rt. [a]Reaction performed in a 0.46 mmol scale. [b]Addition of diazo compound over 30 min. [c]Reaction performed at 40 ºC with slow addition of the diazo compound over 1 h.

The use of α-monosubstituted alkynals derived from natural aminoacids allowed us to study both the diastereoselectivity and the more challenging chemoselectivity of the reaction, since dihydrooxazine formation might be a competitive process (Table 4).[14b] To our delight, α-monosubstituted alkynals chemoselectively cyclized to give vinyl epoxypyrrolidines **3k**-**o** in moderate yields and diastereoselectivities, albeit longer reaction times (60 – 80 min) and 8 mol% of catalyst were necessary to ensure full conversion of starting materials.

Table 4. Scope of α-monosubstituted alkynals



3k, 50%
d.r. = 2.4:1[a]

3l, 52%
d.r. = 3:1

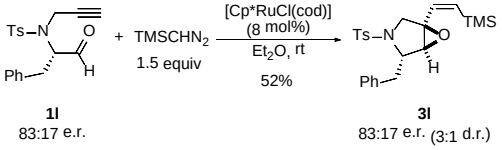
3m, 58%
d.r. = 2.3:1

3n, 41% (53% conversion)[b]

3o, 49%
d.r. = 2.9:1

Conditions: alkynal **1k-o** (0.215 mmol), [Cp*RuCl(cod)] (8 mol%), $TMSCHN_2$ (1.5 equiv), Et_2O (1.5 mL) at rt. Diastereomeric ratio determined by ^{1}H-NMR analysis of the crude mixture. [a]Traces amounts of a *E* stereoisomer were detected. [b]Diastereomeric ratio could not be determined.

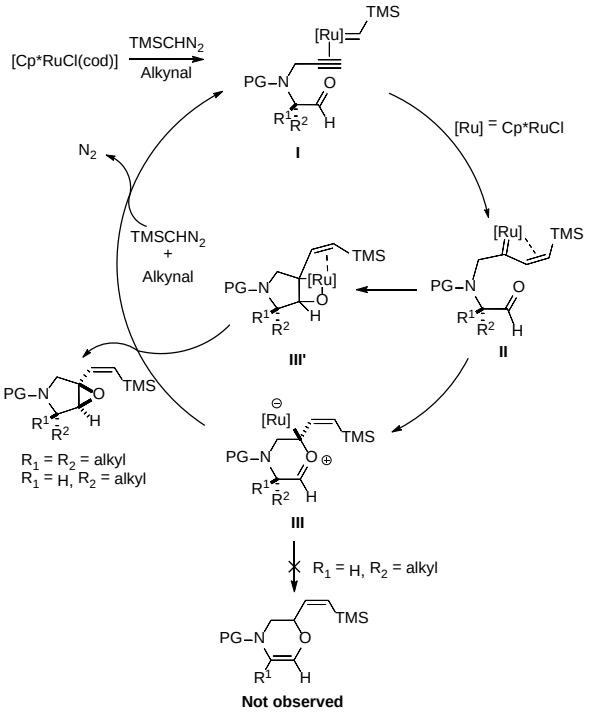
The presence of an easily enolizable aldehyde in α-monosubstituted alkynals led us to examine the possible epimerization during the [2+1] cycloaddition. Chiral HPLC experiments allowed us to conclude that i) the preparation of the starting alkynals is accompanied with partial racemization at α position and ii) the cyclization occurs with complete stereoretention (Scheme 3), which means that the [2+1] cycloaddition takes place under nearly neutral conditions.



Scheme 3. Stereoretention in [2+1] cycloaddition

Based on our previous results and labeling experiments[18] we propose the following mechanism for the Ru-catalyzed epoxy-annulation (Scheme 4). The starting complex, [Cp*RuCl(cod)], easily loses its cod ligand in the presence of $TMSCHN_2$, with the concomitant release of N_2, and binds to the alkynal to give the ruthenium carbene species **I**, which would directly evolve to the coordinatively saturated ruthenium vinyl carbene species **II**.[19,16] This electrophilic species could induce a nucleophilic attack by the carbonyl group to afford the zwitterionic intermediate **III** which finally collapses to the observed epoxypyrrolidine.[20] In this case, intermediate **III** cannot evolve by deprotonation/protonation steps due to lack of hydrogens (or sterically encumbered) at α position, which blocks the formation of the dihydrooxazine.[14b] Alternatively, vinyl carbene **II** could evolve *via* a formal [2+2] cycloaddition to the oxaruthenacycle **III'** followed by reductive elimination.[21]

Scheme 3. Mechanistic hypothesis



Scheme 4. Mechanistic hypothesis

To gain insight with regard to the origin of the *Z* or *E* stereoselectivity on the vinyl substituent according to the diazo compound used, DFT calculations[22] were performed (Figure 2). The initial ruthenium carbene **I′** was found to be in conformational equilibrium with two possible isomers arising from the rotation along the Ru=C bond. Both isomers irreversibly evolved to the η^3-vinyl carbene, one of them afforded the *Z* isomer (**II′-*Z***) and the other gave rise to the *E* isomer (**II′-*E***). As we had already established, the formation of such species is subjected to the Curtin-Hammett principle;[16] thus, the difference between Gibbs free energies of activation ($\Delta\Delta G^{\ddagger}_{Z-E}$) and their comparison with electronically and sterically different ruthenium carbenes (R = TMS, CO_2Me, Ph, $PO(OMe)_2$) would offer an explanation for the stereochemical outcome of the epoxy-annulation. These investigations revealed that the **II′-*Z*** isomer is favored ($\Delta\Delta G^{\ddagger}_{Z-E}$ = -3.1 kcal mol^{-1}) if R = TMS, being **II′-*E*** the preferred configuration if R ≠ TMS. This stereochemical divergence might be attributed to severe steric interactions between the Cp* ligand and the bulky TMS group.

Figure 2. Free energy profile for the formation of **II'-*Z*** and **II'-*E***.

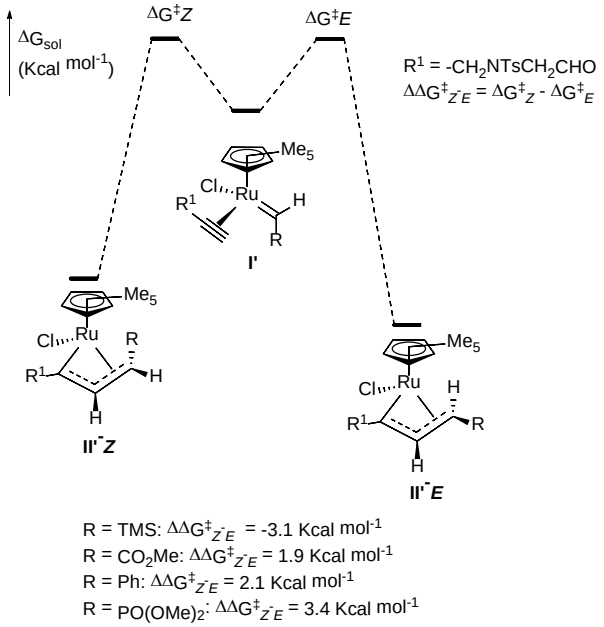
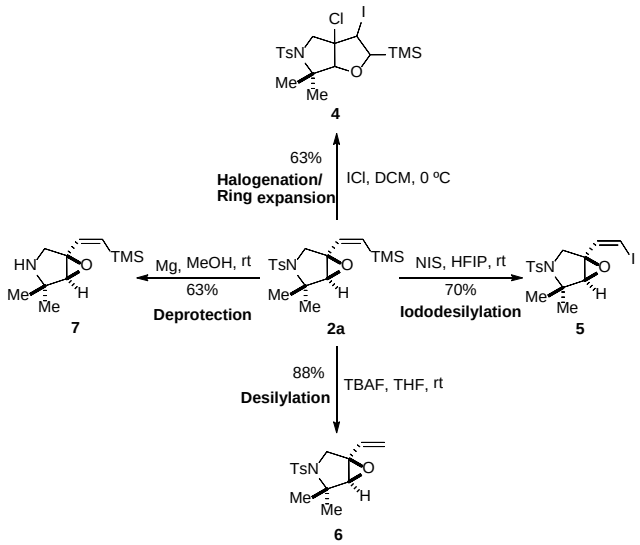


Figure 2. Free energy profile for the formation of **II'-*Z*** and **II'-*E***.

Taking into account the unique reactivity of vinyl epoxides[23] and vinylsilane functionalities,[24] we explored some manipulations of the final products to prove their synthetic utility as useful building blocks (Scheme 5). First, treatment of **2a** with ICl[25] promotes the diastereoselective ring expansion/halogenation of the vinyl epoxide moiety to give the polyfunctionalized furopyrrole **4** as a single diastereoisomer in 63% yield.[26] The stereoretentive iododesilylation was successfully accomplished in good yield using the conditions reported by Zakarian,[27] enabling further transformations through cross-coupling reactions. Desilylation of **2a** could also be accomplished under mild conditions to render the terminal olefin **6** in very good yield. Finally, deprotection of the tosyl group was satisfactorily performed under reducing conditions, providing epoxypyrrolidine **7** in 63% yield.

Scheme 4. Reactivity of *Z*-1-(2-trimethylsilyl)vinyl) epoxypyrrolidine 2a



Scheme 5. Reactivity of *Z*-1-(2-trimethylsilyl)vinyl) epoxypyrrolidine 2a

In summary, we have developed a [2+1] cycloaddition of catalytic ruthenium vinyl carbenes and the π C=O bond of aldehydes (from readily available aza-alkynals) to vinyl epoxypyrrolidines. The bicyclization proceeds under mild conditions and in short reaction times and provides straightforward access to epoxy-fused azaheterocycles in moderate to excellent yields. Key features of our method are the *in situ* formation of ruthenium vinyl carbenes from available diazo compounds and alkynes, the employment of low ruthenium catalyst loadings, the formation of a bicyclic heterocycle from an acyclic system in a single step and, mainly, the total stereocontrol of the *Z*- and *E*- configuration of the vinyl substituent according to the diazo compound used. The easy transformation of the products into valuable derivatives in a stereocontrolled manner is also remarkable. Mechanistic studies are currently underway in our laboratory in order to gain further insights into the chemo- and stereoselectivity of this epoxy-annulation.

ASSOCIATED CONTENT

Supporting Information. Experimental part including characterization data, deuterium labeling experiments, NMR spectra and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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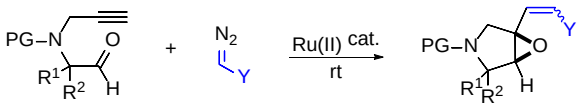

R^1, R^2 = alkyl, cycloalkyl
R^1 = H, R^2 = alkyl, benzyl, etc.
Y = TMS, Ar, CO_2Et, $P(O)(OMe)_2$

- **19 examples**
- **Up to 97% yield**
- **Mild conditions**
- ***Z*/*E*-stereoselective cyclization**
- **Versatile building blocks**