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

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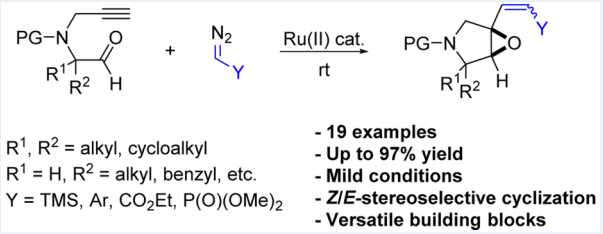
Supporting Information

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 that are 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 hirsutellone C[4] (Figure 1), and are used as versatile building blocks for the synthesis of a wide variety of natural products, such as (+)-DMDP,[5] (+)-broussonetine G,[6,5] mytomycin K,[7] or berkeleyamide D.[8]

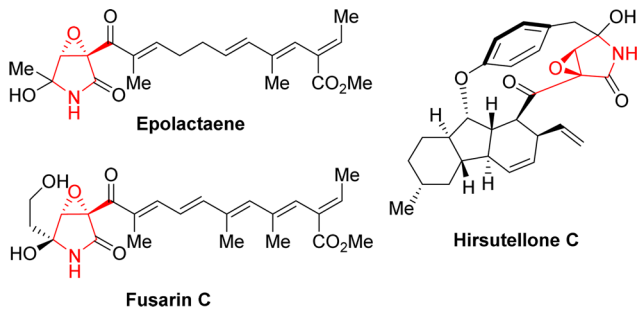
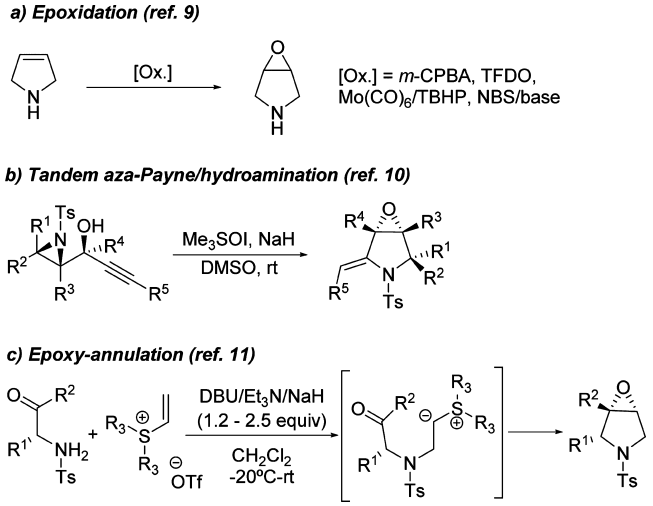


Figure 1. Biologically active epoxypyrrolidines.

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 past few years, catalytic vinyl ruthenium carbenes have proved to be useful intermediates in a variety of relevant synthetic transformations[12−14] and, namely, in carbocyclizations ([2 + 1] cycloadditions between alkenes and allenes to cyclopropane derivatives[13] and neutral redox processes from

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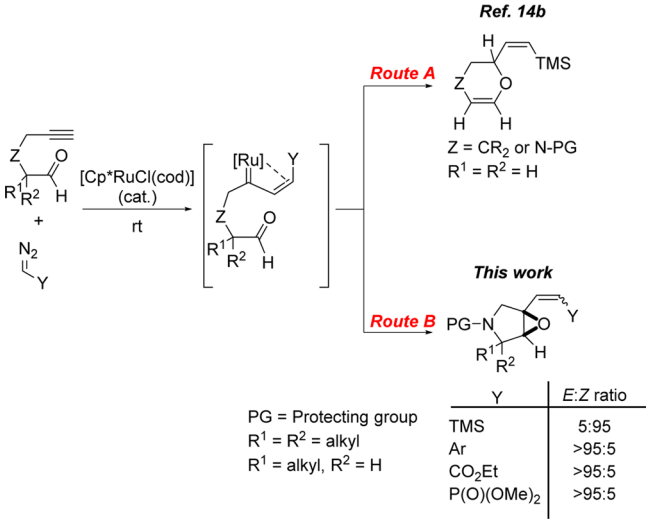
activated C−H substrates[14a]). Recently, we have extended the use of these valuable intermediates to heterocyclization reactions with the stereoselective synthesis of vinyl dihydropyrans and dihydrooxazines from unsubstituted alkynals and aza-alkynals, respectively (see Scheme 2, route A).[14b] We now report a mild

Scheme 2. Synthesis of Epoxypyrrolidines via [2 + 1] Cycloaddition of Catalytic Ruthenium Vinyl Carbenes

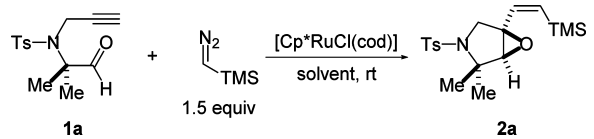


and convenient entry to vinyl epoxypyrrolidines from substituted aza-alkynals (R^1, R^2 = alkyl; R^1 = alkyl, R^2 = H) and diazo compounds based on a novel [2 + 1] cycloaddition of a π (C═O) bond of an aldehyde to the *in situ*-generated catalytic ruthenium vinyl carbene intermediates (see Scheme 2, route B). The reaction proceeds with complete (*Z*)- or (*E*)- stereoselectivity, depending on the nature of the diazo compound used.

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 almost-quantitative yield within <5 min (entry 1 in Table 1). Polar aprotic solvents did not significantly affect the reaction yield (entries 2 and 3 in Table 1) 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 in Table 1). 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 range of 11−15 mM range (entries 6−10 in Table 1). 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 a precatalyst without significant detriment of the reaction yield (entry 11 in Table 1).

After the reaction conditions were optimized, we set out to investigate the substrate scope. The cyclization reaction of tosylamide derivatives of α,α'-disubstituted alkynals **1a** and **1f**−**1i**, derived from readily available α-amino acids, gave the corresponding vinyl epoxypyrrolidines **2a** and **2f**−**2i**, respectively, in fairly good yields (see Table 2). Other sulfonamide protecting groups, such as 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

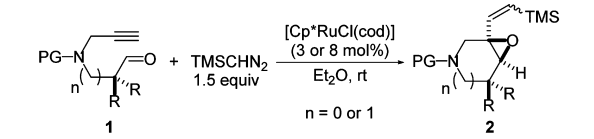
Table 1. Optimization of the Reaction Conditions[a]

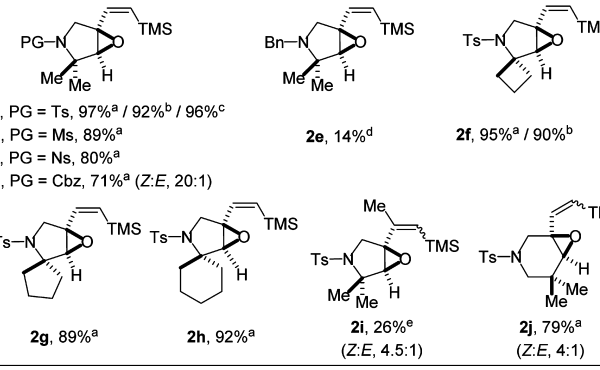


entry	catalyst concentration (mol %)	solvent	*Z*:*E* ratio[b]	yield[c] (%)
1	10	Et_2O	>95:5	95
2	10	acetone	>95:5	90
3	10	PhMe	>95:5	87
4	10	MeOH		CM[d]
5	10	*i*-PrOH	>95:5	68
6	8	Et_2O	>95:5	97
7	3	Et_2O	>95:5	82[e]
8[f]	3	Et_2O	>95:5	92
9[f]	1	Et_2O	>95:5	<50[e]
10[g]	1	Et_2O	>95:5	91
11[h,i]	5.5	Et_2O	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 room temperature (rt). [b]*Z*/*E* ratio, determined by ^1H 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 was used. [g]0.17 mL of solvent was used. [h]Reaction run in a 0.35 mmol scale, using [CpRuCl(cod)] as a catalyst. [i]0.28 mL of solvent were used.

Table 2. Scope of α,α'-Disubstituted Alkynals*





*Conditions: alkynal **1a**−**1j** (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.

the electron-rich benzylamine derivative alkynal **1e** only cyclize upon heating to 60 °C to give **2e** in a low 14% yield. Alkynals **1f**−**1h** smoothly cyclize to spiro-epoxypyrrolidines **2f**−**2h** in excellent yields within <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 formation of the reactive ruthenium vinyl carbene

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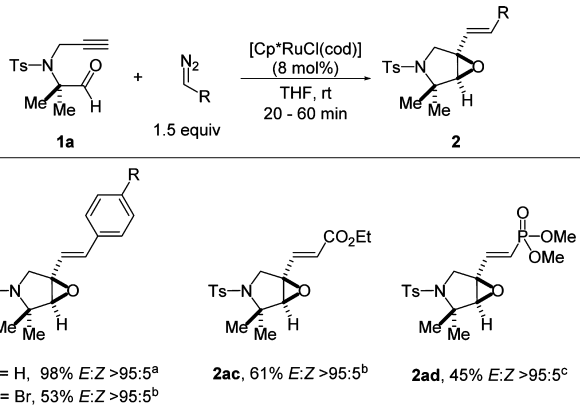
intermediate more difficult. Interestingly, the cyclization reaction could also be applied to the efficient formation of epoxypiperidine **2j**, from the corresponding alkynal **1j**. The epoxy annulation reaction could be easily scaled up, since epoxypyrrolidine **2a** was obtained with an excellent 96% yield in a gram scale, using 1 mol % of [Cp*RuCl(cod)] and 1.3 equiv of $TMSCHN_2$.

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

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]

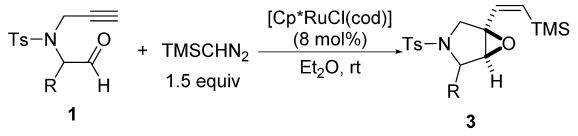
*Conditions: **1a** (0.215 mmol), [Cp*RuCl(cod)] (8 mol %), diazo compound (1.5 equiv), THF (1.5 mL) at rt. [a]Reaction performed in a 0.46 mmol scale. [b]Addition of diazo compound over 30 min. [c]Reaction performed at 40 °C with slow addition of the diazo compound over 1 h.

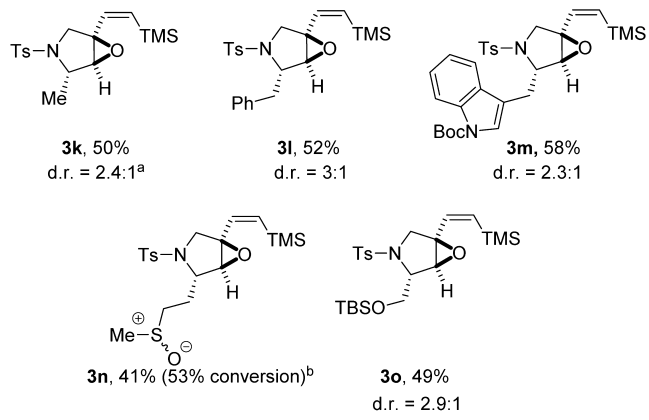
the electronic and steric properties of the diazo compound partner had a remarkable effect in the double-bond geometry of the alkenyl substituent and also in the kinetics of the reaction. First, the employment of partially stabilized diazo compounds such as aryl-substituted or electron-poor diazoalkanes renders the process completely *E*-selective.[16] Second, the homocoupling of the diazo compound became a competitive side reaction with electron-poor compounds, although full conversions were achieved by using THF as a 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.

The use of α-monosubstituted alkynals derived from natural amino acids 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–3o** in moderate yields and diastereoselectivities, albeit at longer reaction times (60–80 min) and 8 mol % of catalyst were necessary to ensure full conversion of the starting materials.

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 by partial racemization at α

Table 4. Scope of α-Monosubstituted Alkynals*

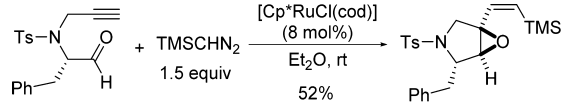




*Conditions: alkynal **1k–1o** (0.215 mmol), [Cp*RuCl(cod)] (8 mol %), $TMSCHN_2$ (1.5 equiv), Et_2O (1.5 mL) at rt. Diastereomeric ratio determined by ^1H NMR analysis of the crude mixture. [a]Traces amounts of a *E* stereoisomer were detected. [b]Diastereomeric ratio could not be determined.

position and (ii) the cyclization occurs with complete stereoretention (Scheme 3), which means that the [2 + 1] cycloaddition occurs under almost 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, because of a lack of hydrogens (or sterically encumbered) at the 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]

To gain insight with regard to the origin of the *Z* or *E* stereoselectivity on the vinyl substituent, according to the diazo compound used, density functional theory (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

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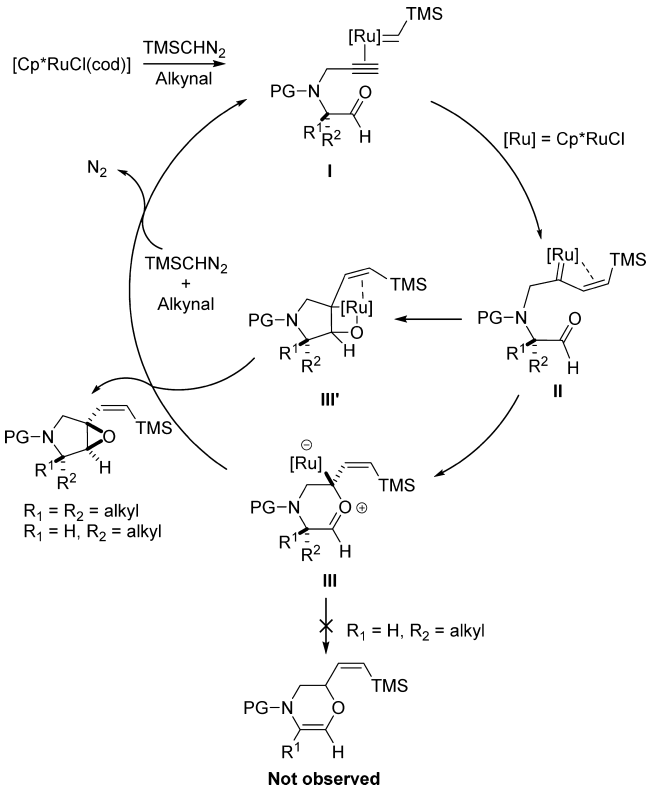
Scheme 4. Mechanistic Hypothesis



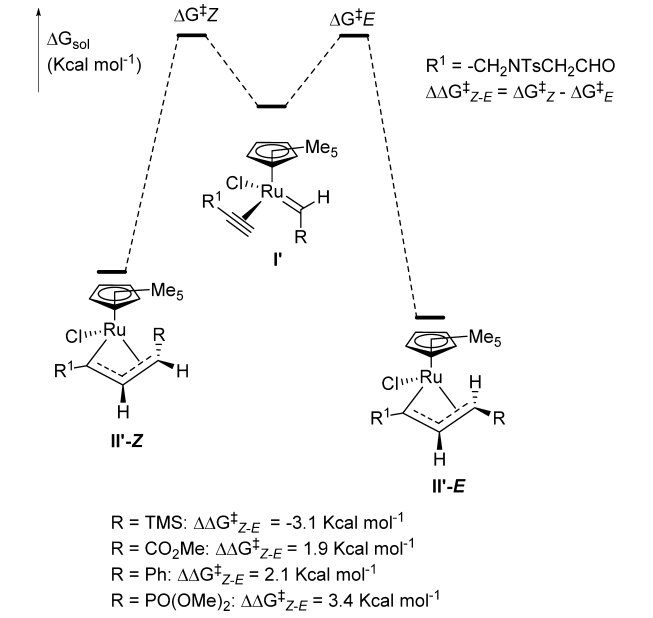


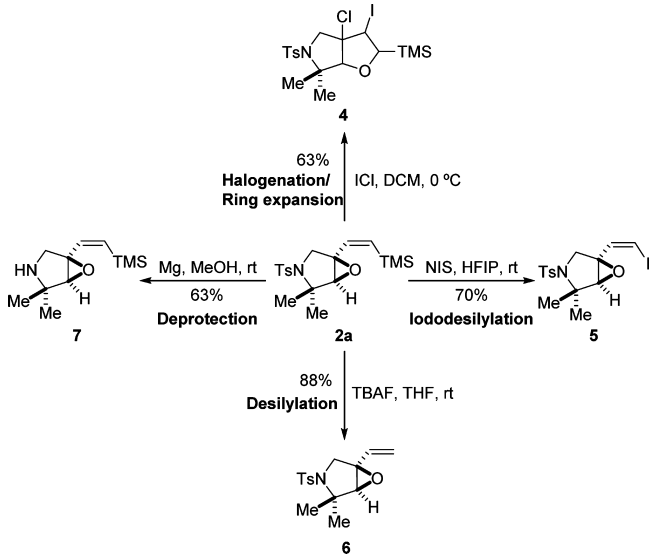
Figure 2. Free-energy profile for the formation of **II′-*Z*** and **II′-*E***.

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, with **II′-*E*** being 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.

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 (see Scheme 5). First, treatment of **2a** with

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



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.

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 chemoselectivity and stereoselectivity of this epoxy-annulation.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02929.

Experimental part including characterization data, deuterium labeling experiments, NMR spectra, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of the late Prof. José Barluenga.

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