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Homogeneous catalysis

Vinyl Dihydropyrans and Dihydrooxazines from Cyclizations of Catalytic Ruthenium Carbenes Derived from Alkynals and Alkynones

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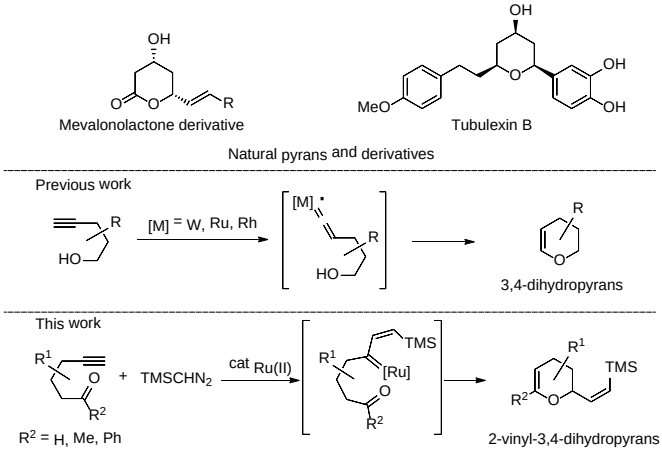
Dedication((optional))

***Abstract**: A novel synthesis of 2-vinyl dihydropyrans and dihydro-1,4-oxazines (morpholine derivatives) from alkynals and alkynones has been developed. The cyclizations require a mild generation of catalytic ruthenium carbenes from terminal alkynes and (trimethylsilyl)diazomethane followed by trapping with carbonyl nucleophiles. Mechanistic aspects of the new cyclizations are discussed.*

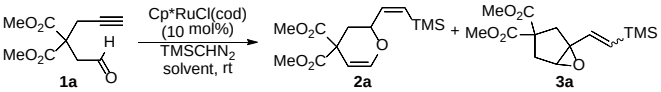
Six-membered oxygenated heterocycles, pyrans, are privileged structures for a large number of natural products and biologically active molecules.[1] Their partially hydrogenated derivatives, e.g. 3,4-dihydropyrans,[2] are interesting precursors for tetrahydropyrans[3] and glycals,[4] which are useful building blocks, particularly in carbohydrate chemistry.[5] Two main synthetic strategies have been exploited for the efficient preparation of 3,4-dihydropyrans and their 4,5-benzoderivatives: (a) hetero Diels–Alder (HDA) reactions of aldehydes and Danishefsky´s diene,[6] which afford the corresponding dihydropyran derivatives with high diastereo- and enantioselectivities; and (b) *endo* cycloisomerization of alkynols with catalytic metal vinylidenes (W, Rh and Ru).[7] Other attractive and useful unsaturated pyran derivatives, 2-vinyltetrahydropyrans, have been accessed through alkyne-, allene- or allyl-activated *exo* cyclizations using Pd, Ir, Au and Fe catalysts.[8] Although these methods have been very successful, they only allow the expeditious introduction of one valuable alkene functionality at a time in the pyran core. Herein we report a new, efficient and direct approach to difunctionalized 2-vinyl-3,4-dihydropyrans[9] (a convenient substitution for the synthesis of natural pyrans) based on the cyclization of alkynals and alkynones through catalytic Ru-carbenes formed in situ by the addition of (trimethylsilyl)diazomethane (Scheme 1).[10] Cyclizations occurred under very mild conditions and usually gave good yields and excellent diastereoselectivities in short reaction times.



Scheme 1. Pyrans from metal-catalyzed heterocyclizations.

Initial coupling of alkynal **1a** with $TMSCHN_2$ using our reported conditions[11] gave the cyclized product, 2-vinyl-3,4-dihydropyran **2a**, as the unique *Z* isomer in good yield (65%, Table 1, entry 1).[12] Interestingly, changes in the electronic and steric nature of the Ru(II) catalyst on using [CpRuCl(cod)] did not affect the reaction yield but did influence the double bond geometry of the vinylsilane moiety (**2a**, *Z*/*E* 1:4, entry 2). Decreasing the catalyst loading (5 mol%) while increasing the amount of $TMSCHN_2$ (2.4 equiv) gave the expected dihydropyran **2a**, albeit in a moderate yield (57%, entry 3). The reaction yield remained unaltered on using a slight excess of $TMSCHN_2$ (entry 4).[13] Other polar aprotic solvents like acetone and dichloromethane gave lower yields of **2a** with longer reaction times and, in addition, small quantities of vinyloxirane **3a** as a mixture of *Z*/*E* isomers (entries 5 and 6). Interestingly, while the primary alcohol MeOH gave a complex mixture of products (entry 7), use of the secondary alcohol *i*-PrOH allowed us to isolate dihydropyran **2a** as a unique *Z* isomer in good yield (71%) in a short reaction time (entry 8).

Table 1. Optimization of Ru-catalyzed cyclization of alkynal **1a** with $TMSCHN_2$.



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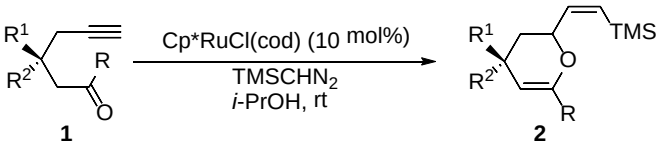
Entry	$TMSCHN_2$ (equiv)	Conditions	Yield **2a/3a** (%)[a]
1	1.1	Et_2O, 1 h	65/-
2[b]	1.1	Et_2O, 1 h	68[c]/-
3[d]	2.4	Et_2O, 18 h	57/-
4	1.8	Et_2O, 1 h	66/-
5	1.8	Acetone, 5 h	57/5
6	1.8	CH_2Cl_2, 5 h	54/10
7	1.8	MeOH, 5 h	-[e]
8	1.8	*i*-PrOH, 1 h	71/6

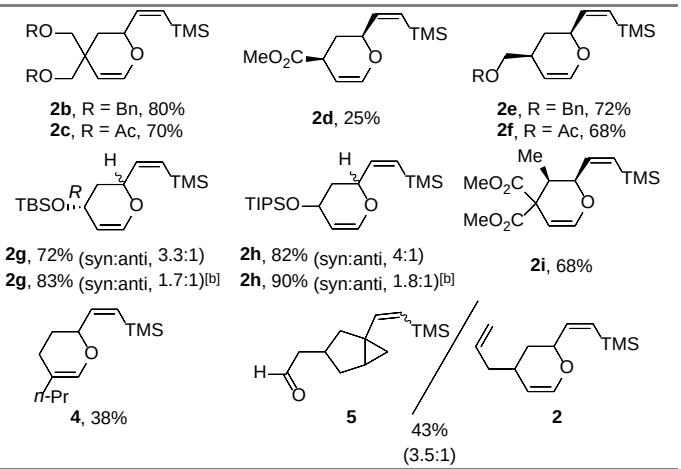
[a] Isolated yields. [b] CpRuCl(cod) as catalyst. [c] Mixture of *Z*/*E* isomers (1:4). [d] 5 mol% of catalyst. [e] Complex mixture.

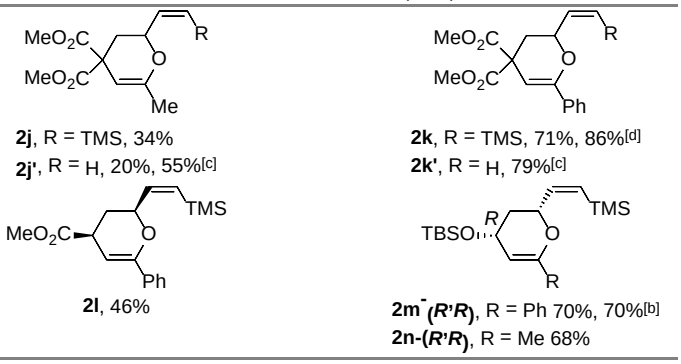
This encouraging result led us to explore the scope and limitations of the cyclization (Table 2). Alkynals **1b,c** (R^1, R^2 = CH_2OBn, CH_2OAc) bearing two C_{sp3} substituents in C-3 also gave fairly good yields of the corresponding vinyldihydropyrans **2b,c**. Monosubstituted C-3 alkynals **1d–g** allowed us to study the diastereoselectivity of the cyclization. Thus, the C_{sp2}-substituted methoxycarbonyl alkynal **1d** (R^1 = CO_2Me, R^2 = H) cyclized to give dihydropyran **2d** as a single *syn* diastereomer but, unfortunately, the yield was low. To our delight, C_{sp3}-substituted benzyloxymethyl or acetoxymethyl alkynals **1e,f** (R^1 = CH_2OBn and CH_2OAc, R^2 = H) were smoothly converted to vinyldihydropyrans **2e,f** in good yields in a completely diastereoselective *syn* fashion. Owing to the critical role of C-4 oxygenated substituents in natural dihydropyrans with biological activity,[1] we decided to evaluate the cyclization of 3-silyloxyalkynal **1g**(*R*) (R^1 = H, R^2 = OTBS). To our initial surprise, oxygenated dihydropyran **2g** was obtained in good yield but the diastereoselectivity was rather low in *i*-PrOH or Et_2O (*syn*:*anti* 3.3:1 and 1.7:1, respectively). We believe that the oxygenated substituent in alkynal **1g** might coordinate to the key ruthenium intermediate and, therefore, modify the diastereoselectivity (see Scheme 3). Even the more bulky 3-silyloxyalkynal **1h** (R^1,R^2 = H, OTIPS) gave only a slightly higher diastereoselectivity of dihydropyran **2h** (*syn*:*anti* 4:1 in *i*-PrOH). Interestingly, the C-2 monosubstituted 2-propyl-5-hexynal gave exclusively the 5-propyl-2-vinyl-3,4-dihydropyran **4** in moderate yield, thus showing the influence of the nature of the reacting conformer in the reaction course.[14] Notably, cyclization of alkynal **1i**, with substituents in C-3 and C-4, again leads to high levels of diastereoselectivity and gave rise exclusively to the *syn* vinyldihydropyran **2i** in fairly good yield.

Chemoselectivity of the reaction was analyzed during cyclization of the difunctionalized enynal, 3-(prop-2-ynyl)hex-5-enal**,** in which the major isolated product, vinylcyclopropane **5**, derives from the cyclization of enyne[10] against the minor dihydropyran **2** (R^1,R^2 = $CH_2CH{=}CH_2$, R = H) from de cyclization of alkynal **(**3.5:1, 43 % overall).

Table 2. Ru-catalyzed cyclizations of alkynals/alkynones **1** (R = H, Me, Ph) to 2-vinyldihydropyrans **2**.





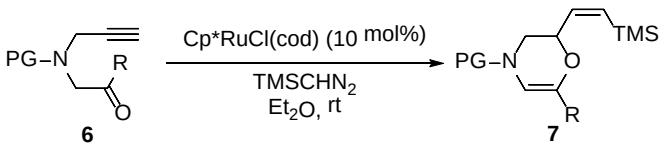


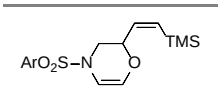
[a] *Typical conditions*: Cp*RuCl(cod) (10 mol%), $TMSCHN_2$ (1.8 equiv), *i*-PrOH, rt, [**1**] = 0.15 M. [b] Et_2O as solvent. [c] MeOH as solvent. [d] CH_2Cl_2 as solvent.

The cyclization of alkynones was subsequently explored. Initially, alkynyl methyl ketone **1j** (R^1, R^2 = CO_2Me, R = Me) was subjected to the typical reaction conditions in *i*-PrOH and this gave moderate yields of a mixture of vinyldihydropyrans **2j** (R = TMS) and **2j'** (R = H). It was suspected that the enolizable ketone in *i*-PrOH could cause partial desilylation of $TMSCHN_2$ and this, indeed, gave rise to the mixture of cyclized products. As a result, the reaction was also performed in MeOH and this gave exclusively the expected desilylated **2j'** in similar overall yield.[10] By contrast, non-enolizable alkynyl phenyl ketone **1k** (R^1, R^2 = CO_2Me, R = Ph) cyclized more smoothly and cleanly than **1j** in *i*-PrOH or CH_2Cl_2 to give exclusively the silylated dihydropyran **2k** in fairly good yields. On the other hand, desilylated dihydropyran **2k'** could be obtained in very good yield when the cyclization was performed in MeOH. Pleasingly, C_{sp2}-substituted methoxycarbonyl alkynone **1l** (R^1 = CO_2Me, R^2 = H, R= Ph) cyclized to dihydropyran **2l** as a single *syn* diastereomer in moderate yield as compared to the low yield of alkynal **1d**. To our delight, enantiomerically pure silyloxy phenyl and methylketones **1m**(*R*) and **1n**(*R*) (R^1 = H, R^2 = OTBS) cyclized diastereoselectively to give the corresponding *syn* vinyldihydropyrans **2m**(*R*,*R*) and **2n**(*R*,*R*) in rather good yields. Remarkably, steric factors in the most stable conformer of the key Ru intermediate probably control the diastereoselectivity of the cyclization process (**2m** or **2n** *vs* **2g**).

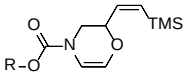
Conformationally locked bicyclic morpholines (dihydro-1,4-oxazines), e.g. oxabispidines and 8-oxa-3-azabicyclo[3.2.1]octanes, have been shown to display a range of biological properties that have attracted interest in the pharmaceutical industry.[15] Typically, derivatives of 2-vinyl-3,4-dihydro-2*H*-1,4-oxazines **7** have been used as pivotal structures to access therapeutic agents. A new synthetic strategy to these relevant structures based on Ru-catalyzed cyclization of *N*-tethered alkynals and alkynones **6** has been developed (Table 3).

Table 3. Ru-catalyzed cyclizations of *N*-tethered alkynals/alkynones **6** to 2-vinyldihydrooxazines **7**.[a]

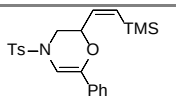




7a, Ar = Tol, 58%
7b, Ar = Tis, 57%



7c, R = *t*-Bu, 58%
7d, R = Bn, 55%



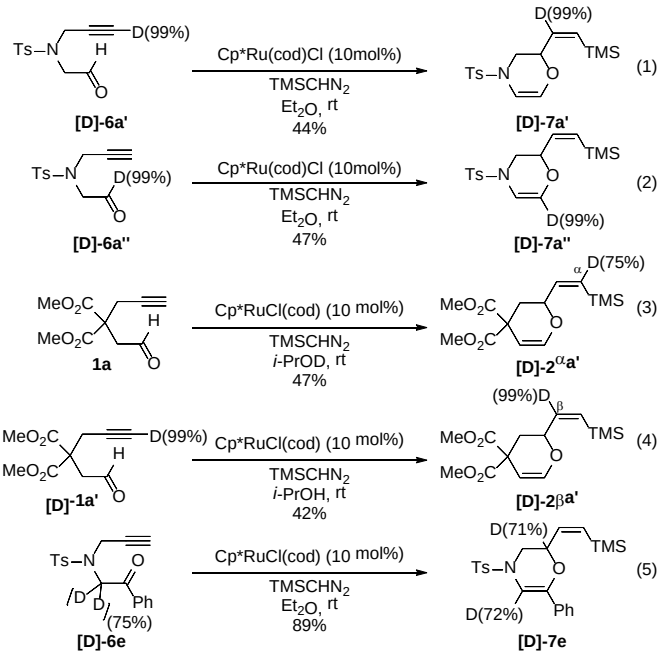
7e, 87%

[a] *Typical conditions:* Cp*RuCl(cod) (10 mol%), $TMSCHN_2$ (1.8 equiv), Et_2O, rt, [**6**] = 0.15 M.

Either *N*-SO_2Ar protected alkynals **6a,b** or *N*-Boc and *N*-Cbz protected alkynals **6c,d** were smoothly converted into 2-vinyldihydrooxazines **7a–d** in moderate-to-good yields under the typical reaction conditions (Et_2O as solvent). To our delight, *N*-SO_2Ar protected alkynone **6e** was successfully transformed into the corresponding 2-vinyl-6-phenyldihydroxazine **7e** in excellent yield.[16]

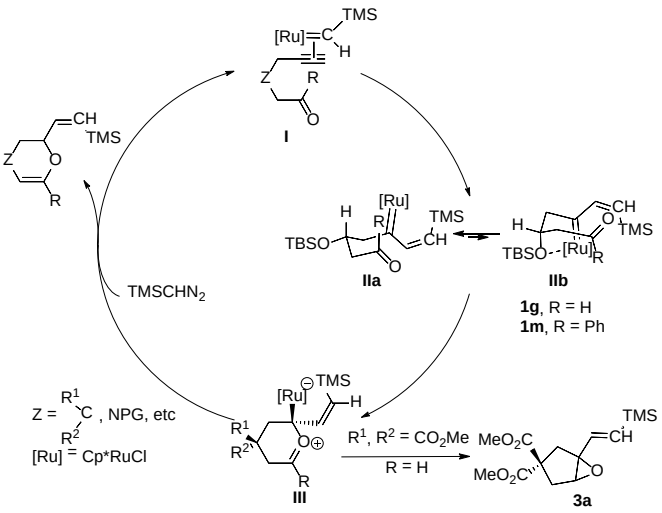
In an effort to gain further insights into the cyclization process, a series of deuterium labeling experiments were conducted. Alkynal **[D]-6a'**, with a deuterium atom in the terminal alkyne, was transformed into the corresponding 2-vinyldihydroxazine **[D]-7a'** with deuterium located in the expected β-vinylic position (Scheme 2, eq 1). Similarly, alkynal **[D]-6a"** with deuterium in the aldehyde group gave the corresponding 2-vinyldihydroxazine **[D]-7a"** in which the deuterium was in the expected α-enolether position (Scheme 2, eq 2). Two experiments were performed to evaluate the influence of a protic solvent during the reaction course. When the reaction of alkynal **1a** was carried out in *i*-PrOD, the deuterium was incorporated selectively (75% deuterium incorporation) into the α-vinylic position of **[D]-2$_\alpha$a'** (Scheme 2, eq 3), whereas reaction of alkynal **[D]-1a'** gave dihydropyran **[D]-2$_\beta$a'** in which the deuterium remains in the expected β-position without any deuterium scrambling with the protic solvent (Scheme 2, eq 4). These last two results show the crucial role of the solvent during the cyclization process. Finally, cyclization of dideuterated alkynone **[D]-6e** in Et_2O gave the dideuterated 2-vinyldihydrooxazine **[D]-7e** in the expected allylic and enolether positions (Scheme 2, eq 5).

With all of these results in hand, the labeling studies would strongly support the initial mechanistic hypothesis shown in Scheme 3. The starting complex Cp*RuCl(cod) easily loses its cod ligand in the presence of $TMSCHN_2$ and alkynals/alkynones, thus leading to ruthenium carbene species **I**. Oxidative coupling to ruthenacyclobutene followed by ring opening would lead to the Ru vinyl carbene **II** (for diastereoselectivity purposes, carbenes leading to **2g** and **2m** are shown).[10]



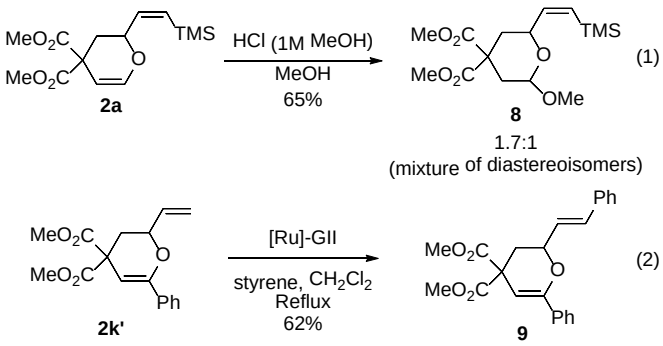
Scheme 2. Deuterium labeling experiments.

The electrophilic Ru carbene could induce a nucleophilic attack by the carbonyl group to afford the zwitterionic intermediate **III**. Finally, deprotonation and re-protonation of C-Ru bond will generate the observed 2-vinyldihydropyrans with recovery of the catalytic Ru carbene in the presence of $TMSCHN_2$. Direct attack of C-Ru bond onto the oxacarbenium ion **III** will produce the minor vinyloxirane **3a**. Diastereoselectivity seems to be controlled by the chair-like conformer of the vinyl Ru carbene intermediate **II**$_a$ with all substituents in equatorial positions. The lower diastereoselectivity found in alkynal **1g** (R = H) could derive from the equilibrium between the two chair-like structures **II**$_a$ and **II**$_b$ in which the oxygenated substituent could coordinate to the ruthenium. If this coordination is hampered by the carbonyl substituent, as in phenyl ketone **2m** (R = Ph), complete diastereoselectivity is recovered by the prevalence of conformer **II**$_a$. On the other hand, deuteration of $TMSCHN_2$ in *i*-PrOD followed by deprotonation could generate variable amounts of $TMSCDN_2$ and this would explain the formation of deuterated **D-2a'** from alkynal **1a** (eq 1).[17]



Scheme 3. Mechanistic hypothesis.

To demonstrate the synthetic utility of the products, we further investigated different reactions to functionalize selectively both double bonds (Scheme 4). Firstly, acetalization of the vinyl ether of **2a** occurred smoothly under acidic conditions to give tetrahydropyranyl ether **8** in 65% yield as a mixture of diastereomers (eq 1).[18] Secondly, in situ formation of desilylated 2-vinyldihydropyran **2k'** followed by cross-metathesis with styrene afforded the *trans*-β-(dihydropyranyl)styrene **9** in a good overall yield (eq 2).[19]



Scheme 4. Reactivity of 2-vinyldihydropyrans **2**.

In conclusion, we have developed a novel synthesis of 2-vinyl dihydropyrans and dihydrooxazines from readily available alkynals and alkynones via Ru(II)-catalyzed cyclizations. Vinyl Ru carbenes derived from alkynes and $TMSCHN_2$ are proposed as the key intermediates of the cyclization processes. Dihydropyrans and dihydrooxazines were obtained in moderate-to-high yields under mild reaction conditions with good functional group tolerance and these could be further transformed into a variety of important derivatives. Further mechanistic studies and enantioselective applications are underway in our laboratory.

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[12] Other Ru(II) catalysts as $Cp^*RuCl(PPh_3)_2$, $[RuCl_2(p\text{-cymene})]_2$, and Grubbs carbene (2nd generation) were unreactive in Et_2O at rt.

[13] A very low yield of the corresponding dihydropyran **2** was obtained when diazoester $EtOOCCHN_2$ (3 equiv) was employed in dioxane at 100 °C.

[14] The corresponding vinyl epoxide **3** has not been detected by GCMS.

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[16] For TBAF desilylations of dihydropyrans and dihydrooxazines, see SI.

[17] Coordinating solvents (Et_2O, *i*-PrOH) could help to stabilize unsaturated ruthenium species formed during the catalytic cycle.

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Homogeneous catalysis

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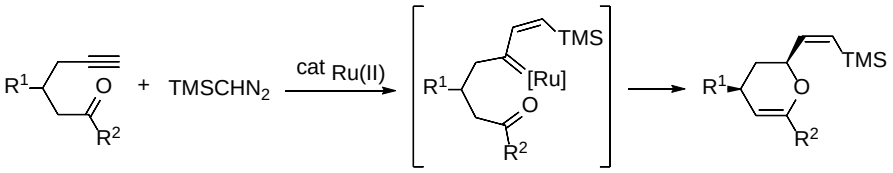
Vinyl Dihydropyrans and Dihydrooxazines from Cyclizations of Catalytic Ruthenium Carbenes Derived from Alkynals and Alkynones



A novel synthesis of 2-vinyl dihydropyrans and dihydro-1,4-oxazines (morpholine derivatives) from alkynals and alkynones has been developed. The cyclizations require a mild generation of catalytic ruthenium carbenes from terminal alkynes and (trimethylsilyl)diazomethane followed by trapping with carbonyl nucleophiles. Mechanistic aspects of the new cyclizations are discussed.