Homogeneous Catalysis

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

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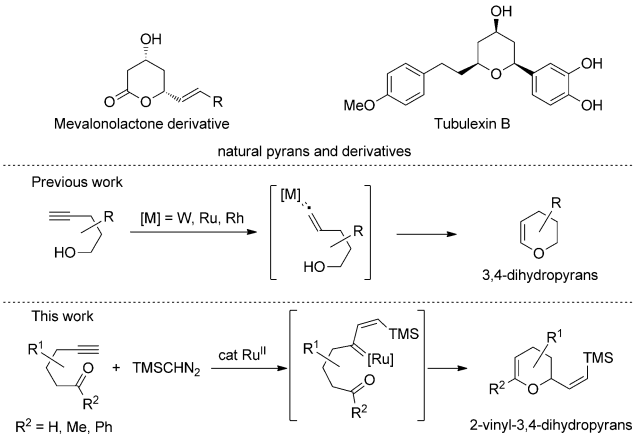
Abstract: *A novel synthesis of 2-vinyldihydropyrans and dihydro-1,4-oxazines (morpholine derivatives) from alkynals and alkynones has been developed. The cyclizations require a mild generation of catalytic ruthenium carbenes from terminal alkynes and (trimethylsilyl)diazomethane followed by trapping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

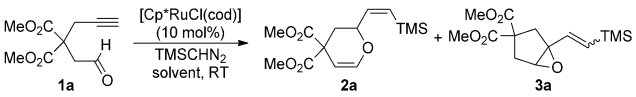
Six-membered oxygenated heterocycles, pyrans, are privileged structures for a large number of natural products and biologically active molecules.[1] Their partially hydrogenated derivatives, for example, 3,4-dihydropyrans,[2] are interesting precursors for tetrahydropyrans[3] and glycals,[4] which are 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] thus affording the corresponding dihydropyran derivatives with high diastereo- and enantioselectivities, and b) *endo* cycloisomerization of alkynols with catalytic metal vinylidenes (W, Rh, and Ru; Scheme 1).[7] Other attractive and useful unsaturated pyran derivatives, 2-vinyltetrahydropyrans, have been accessed through alkyne-, allene-, or allyl-activated *exo* cyclizations using palladium, iridium, gold, and iron catalysts.[8] Although these methods have been very successful, they only allow the expeditious introduction of one valuable alkene functionality at a time to 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 ruthenium carbenes formed in situ by the addition of (trimethylsilyl)diazomethane (Scheme 1).[10] Cyclizations occur under very mild reaction conditions and result in good yields and excellent diastereoselectivities after short reaction times.



Scheme 1. Pyrans from metal-catalyzed heterocyclizations. TMS = trimethylsilyl.

Initial coupling of the alkynal **1a** with $TMSCHN_2$ using our reported reaction conditions[11] gave the cyclized product, 2-vinyl-3,4-dihydropyran **2a**, as a unique *Z* isomer in good yield (Table 1, entry 1).[12] Interestingly, changes in the electronic and steric nature of the ruthenium(II) catalyst by using [CpRuCl(cod)] did not affect the reaction yield, but did influence the double bond geometry of the vinylsilane moiety (*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 **2a**, albeit in a moderate yield (entry 3). The reaction yield remained unaltered upon using a slight excess

Table 1: Optimization of the ruthenium-catalyzed cyclization of the alkynal **1a** with $TMSCHN_2$.



Entry	$TMSCHN_2$ (equiv)	Conditions	Yield [%][a] 2a	3a
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] Yield of isolated product. [b] [CpRuCl(cod)] as catalyst. [c] Mixture of *Z*/*E* isomers (1:4). [d] 5 mol% of catalyst. [e] Complex mixture. cod = 1,5-cyclooctadiene.

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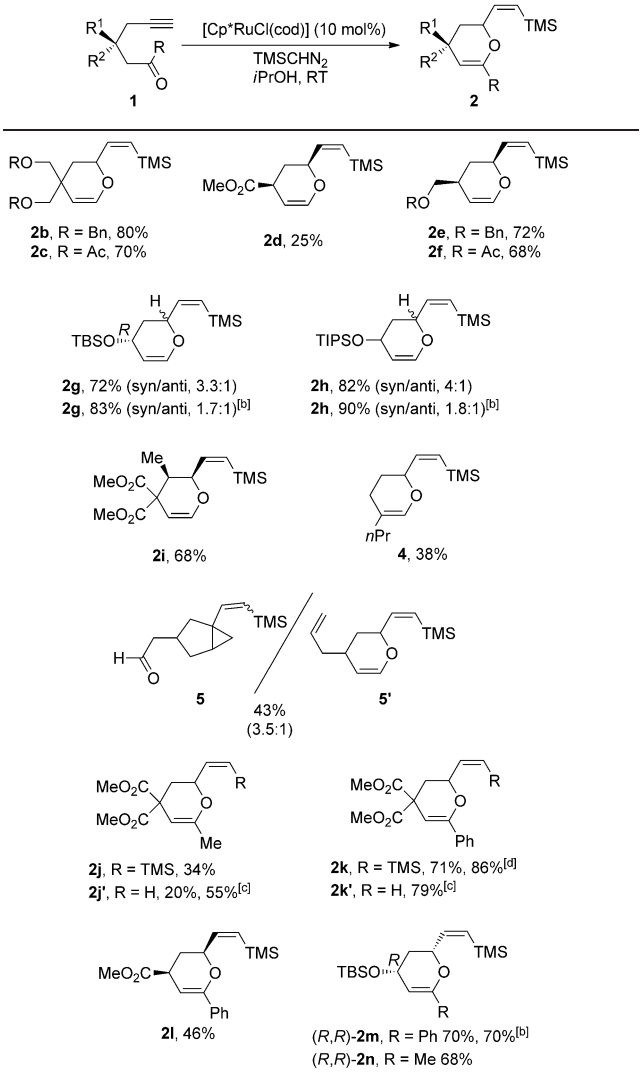
of $TMSCHN_2$ (entry 4).[13] Other polar aprotic solvents like acetone and dichloromethane gave lower yields of **2a** after longer reaction times and, in addition, small quantities of the vinyloxirane **3a**, as a mixture of *Z*/*E* isomers, were observed (entries 5 and 6). Interestingly, while the primary alcohol MeOH gave a complex mixture of products (entry 7), use of the secondary alcohol *i*PrOH allowed the isolation of **2a** as the *Z* isomer in good yield (71%) after a short reaction time (entry 8).

This encouraging result led us to explore the scope and limitations of the cyclization (Table 2). The alkynals **1b,c** (R^1, $R^2 = CH_2OBn$, CH_2OAc), bearing two C_{sp^3}-type substituents at C3, also gave fairly good yields of the corresponding vinyldihydropyrans **2b,c**. The monosubstituted alkynals **1d–g** allowed a study of the diastereoselectivity of the cyclization.

Table 2: Ruthenium-catalyzed cyclizations of the alkynals/alkynones **1** to the 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. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

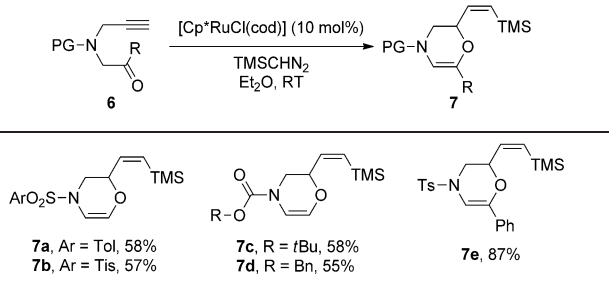
Thus, the methoxycarbonyl alkynal **1d** ($R^1 = CO_2Me$, $R^2 = H$) cyclized to give **2d** as a single *syn* diastereomer, but unfortunately, the yield was low. To our delight, the benzyloxymethyl and acetoxymethyl alkynals **1e,f** ($R^1 = CH_2OBn$ and CH_2OAc, $R^2 = H$) were smoothly converted into **2e,f** in good yields in a completely diastereoselective *syn* fashion. Owing to the critical role of C4 oxygenated substituents in natural dihydropyrans with biological activity,[1] we decided to evaluate the cyclization of the 3-silyloxyalkynal **1g** (*R*) ($R^1 = H$, $R^2 = OTBS$). To our initial surprise, the oxygenated dihydropyran **2g** was obtained in good yield, but the diastereoselectivity was rather low in both *i*PrOH and Et_2O (*syn*/*anti* 3.3:1 and 1.7:1, respectively). We believe that the oxygenated substituent in **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 for the dihydropyran **2h** (*syn*/*anti* 4:1 in *i*PrOH). Interestingly, the C2-monosubstituted 2-propyl-5-hexynal exclusively gave 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 at C3 and C4, 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 **5** derives from the cyclization of the enyne[10] and the minor dihydropyran **5′** derives from the cyclization of the ynal.

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

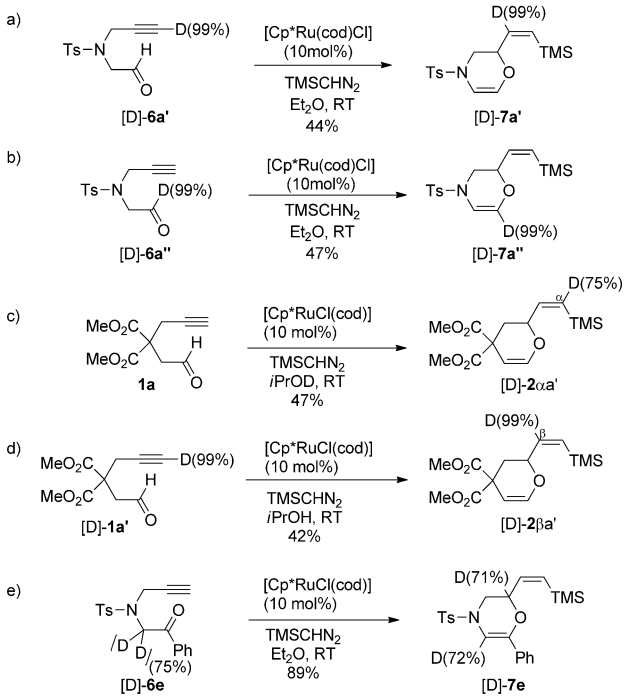
Conformationally locked bicyclic morpholines (dihydro-1,4-oxazines), for example, oxabispidines and 8-oxa-3-azabicyclo[3.2.1]octanes, have been shown to display

a range of biological properties which 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 access these relevant structures. based on ruthenium-catalyzed cyclization of N-tethered alkynals and alkynones (**6**), has been developed (Table 3). Either the

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



[a] Typical conditions: [Cp*RuCl(cod)] (10 mol%), $TMSCHN_2$ (1.8 equiv), Et_2O, RT, [**6**] = 0.15 M. Cp* = C_5Me_5, PG = protecting group, Tis = 2,4,6-triisopropylphenyl, Ts = 4-toluenesulfonyl.

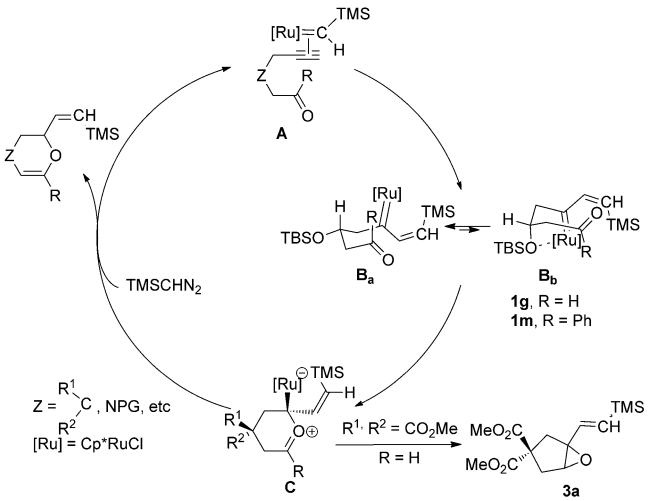


Scheme 2. Deuterium-labeling experiments.

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, the alkynone **6e** was successfully transformed into the corresponding 2-vinyl-6-phenyldihydroxazine **7e** in excellent yield.[16]

In an effort to gain further insight into the cyclization process, a series of deuterium-labeling experiments were conducted. The alkynal [D]-**6a′**, with a deuterium atom on the terminal alkyne position, was transformed into the corresponding 2-vinyldihydroxazine [D]-**7a′** with deuterium located in the expected β-vinylic position (Scheme 2a). Similarly, the alkynal [D]-**6a″** with deuterium as part of the aldehyde group gave the corresponding 2-vinyldihydroxazine [D]-**7a″** in which the deuterium was in the expected α-enolether position (Scheme 2b). Two experiments were performed to evaluate the influence of a protic solvent during the reaction course. When the reaction of **1a** was carried out in *i*PrOD, the deuterium was incorporated selectively (75% deuterium incorporation) into the α-vinylic position of [D]-$\mathbf{2_\alpha a'}$ (Scheme 2c), whereas reaction of [D]-**1a′** gave the dihydropyran [D]-$\mathbf{2_\beta a'}$ in which the deuterium remains in the expected β-position without any deuterium scrambling with the protic solvent (Scheme 2d). These last two results highlight the crucial role of the solvent during the cyclization process. Finally, cyclization of the di-deuterated alkynone [D_2]-**6e** in Et_2O gave the di-deuterated 2-vinyldihydrooxazine [D_2]-**7e** at the expected allylic and enolether positions (Scheme 2e).

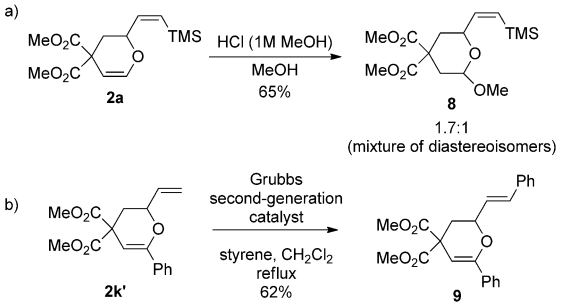
With all of these results in hand, the labeling studies strongly support the initial mechanistic hypothesis shown in Scheme 3. The starting complex [Cp*RuCl(cod)] easily loses its cod ligand in the presence of $TMSCHN_2$ and alkynals/alkynones, thus leading to the ruthenium carbene species **A**. Oxidative coupling to the ruthenacyclobutene, followed by ring opening would lead to the ruthenium vinyl carbene **B** (for diastereoselectivity purposes, carbenes leading to **2g** and **2m** are shown).[10] The electrophilic ruthenium carbene could induce a nucleophilic attack by the carbonyl group to afford the zwitterionic intermediate **C**. Finally, deprotonation and re-protonation of C–Ru bond will generate the observed 2-vinyldihydropyrans with recovery of the catalytic ruthenium carbene in the presence of $TMSCHN_2$. Direct attack of the C–Ru bond onto **C** will produce the minor vinyloxirane **3a**.



Scheme 3. Mechanistic hypothesis.

Diastereoselectivity seems to be controlled by the chairlike conformer of the vinyl ruthenium carbene intermediate $\mathbf{B}_a$ with all substituents in equatorial positions. The lower diastereoselectivity found for **1g** (R = H) could derive from the equilibrium between the two chairlike structures $\mathbf{B}_a$ and $\mathbf{B}_b$ 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 $\mathbf{B}_a$. In contrast, deuteration of $TMSCHN_2$ in *i*PrOD followed by deprotonation could generate variable amounts of $TMSCDN_2$ and this would explain the formation of [D]-**2αa′** from alkynal **1a** (Scheme 2c).[17]

To demonstrate the synthetic utility of the products, we further investigated different reactions to selectively functionalize both double bonds (Scheme 4). Firstly, acetalization



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

of the vinyl ether of **2a** occurred smoothly under acidic conditions to give the tetrahydropyranyl ether **8** in 65% yield as a mixture of diastereomers (Scheme 4a).[18] Secondly, in situ formation of the desilylated 2-vinyldihydropyran **2k′** with subsequent cross-metathesis with styrene afforded the *trans*-β-(dihydropyranyl)styrene **9** in a good overall yield (Scheme 4b).[19]

In conclusion, we have developed a novel synthesis of 2-vinyl dihydropyrans and dihydrooxazines from readily available alkynals and alkynones through ruthenium(II)-catalyzed cyclizations. Vinyl ruthenium 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 ruthenium(II) catalysts as $[Cp^*RuCl(PPh_3)_2]$, $[\{RuCl_2(p\text{-cymene})\}_2]$, and Grubbs carbene (second-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 1,4-dioxane at 100 °C.

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

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