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$PtCl_2$-Catalyzed Cycloisomerizations of 5-En-1-yn-3-ol Systems

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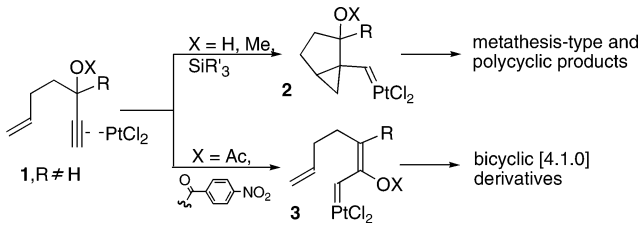
Because of the compatibility and the utilization of very diverse precursors, the $PtCl_2$-catalyzed cycloisomerization of enyne systems has recently witnessed synthetically versatile developments, including notably applications in the total synthesis of natural products.[1] However, these reactions have appeared as highly substrate-dependent, so that further insight into the mechanism of these transformations is desirable.[2] Thus, the reactivity of novel unsaturated systems constitutes an important opportunity in terms of synthetic applications as well as mechanistic findings. We have recently shown that these cycloisomerization processes can be extended to a variety of partners such as enynol derivatives **1**,[3] allenynes,[4] and ene-tosylynamides.[5] Moreover, in the case of substrates **1** ($R \neq H$), the nature of the hydroxy protecting group at the propargylic position is a very practical handle for controlling the outcome of the reaction.[3] When this function is free, or appears as a silyl or a methoxy ether, the presumed cyclopropyl platinacarbene intermediate **2**[1] leads to metathesis-type[6] and polycyclic derivatives, while bicyclic [4.1.0] derivatives are isolated when an *O*-acyl group is present. In the latter case, the electrophilic activation of the alkyne would trigger a 1,2-migration of the *O*-acyl group, which generates the platinacarbene intermediate **3** (Scheme 1).[7,8]

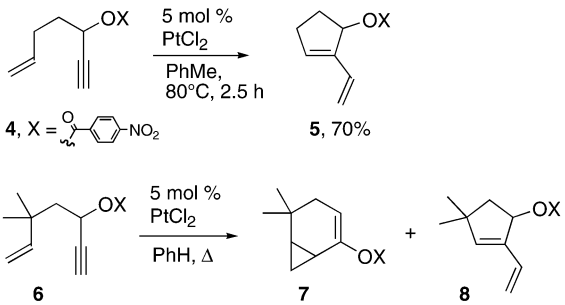
Scheme 1



While delineating the scope of this process, an interesting observation emerged from the fact that secondary analogues of **1** ($R = H$) provided contrasting results (Scheme 2). Precursor **6a** furnished the expected metathesis-type product **8a**.[9] However, for ester precursors, *O*-acyl migration process is significantly retarded compared to this metathesis-type pathway. No bicyclic [4.1.0] derivative was observed in the case of **4**,[10] while the introduction of a *gem*-dimethyl group on the tether as in precursors **6b** and **6c** would slow the formation of intermediate **2** and restore the migration process. It is also worthy of note that both **6b** and **6c** yielded to the same ratio of products **7** and **8**. Although consistent with Uemura's results,[8] but still in need of being fully rationalized,[11] the difficulty of the *O*-acyl migration on these secondary substrates led us to study the analogue enyne precursors shortened by one carbon atom. Indeed, because of a putative highly strained intermediate, the competitive metathesis-type pathway should be now disfavored and only the migration process would remain possible. Herein, we report on the wealth of the reactivity of the previously unexplored secondary 5-en-1-yn-3-ol systems.

We initially focused on the simplest term (precursor **9**) and were pleased to confirm that our assumption was correct since bicyclic [3.1.0] **10** was smoothly obtained in 85% yield (see Scheme 3). Similarly, methallyl precursor **11a** could undergo the transformation (80% of **12a**). The catalyst loading could even be reduced to 2 mol % with no alteration of the yield. Substitution of the alkyne is possible since introduction of an ester still gave a valuable transformation (50% yield of **12b**), albeit under harsher conditions. A styryl moiety proved to be a good partner for the intermediate carbene. Indeed, cyclopropyl derivative **14** was obtained in good

Scheme 2 [a]



6, X	time	**7** : **8** ratio , %	total yield (%)
6a, Me	20 h	0 : 100	42
6b, Ac	37 h	40 : 60	47
6c, NO_2	9 h[a]	35 : 65	63

[a] Reaction was run in refluxing toluene.

yield and as a single diastereomer whose stereochemistry was deduced from NOE studies. Finally, a carbonate substrate could be successfully engaged in these reactions, as demonstrated by the transformation of **15** into **16**. Enol ester **12a** and carbonate **16** were then hydrolyzed to give the same known ketone **17**,[12] thus establishing the regiochemical assignment of these products.

We next turned our attention to the possibility of promoting a 1,2-hydride shift[13] on these subtrates as suggested in Scheme 4, which would imply the existence of a nonparticipating OX group at the propargylic position.[14] This could be easily demonstrated by using OTBS precursors **18** and *even more gratifyingly with free hydroxy substrates **20** and styryl **22**!*

It should be noted that ketone **21** is regioisomeric with respect to **17**, thus demonstrating that access to both products is straightforward by simple tuning of the OX group. In the case of styryl precursors, stereochemical information of the precursor double bond was retained, furnishing high yields of bicyclic derivatives **23** and **24** as single distinct diastereomers whose relative stereochemistries were established by NOE.

Finally, this chemistry can be useful for the synthesis of important molecules in the aroma and fragrance industry. This is illustrated

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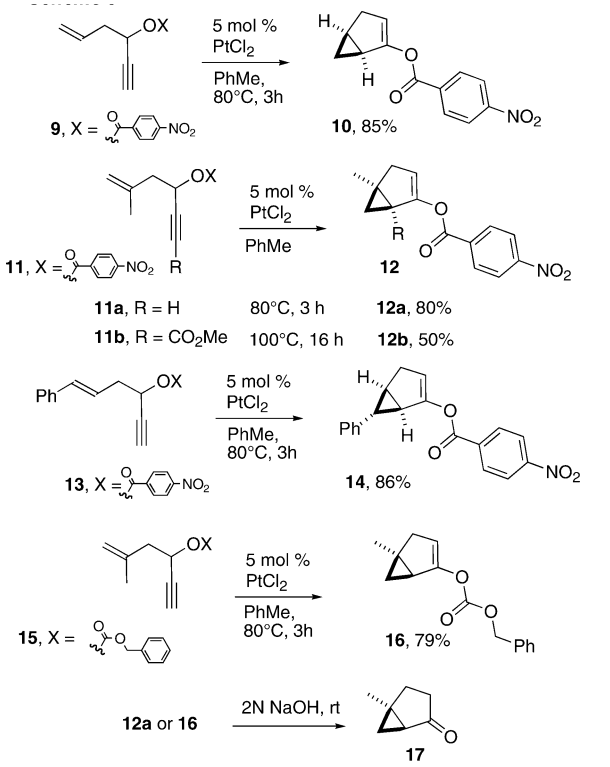
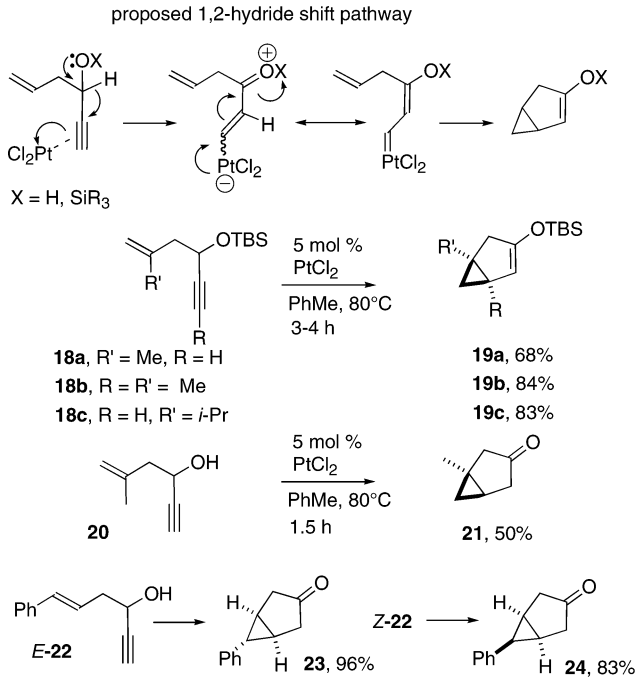
Scheme 3



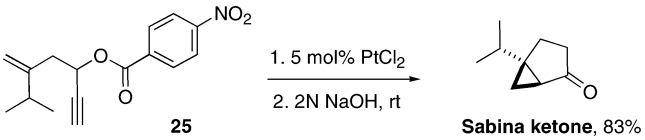
Scheme 4



herein by the expeditive synthesis of the sabina ketone from precursor **25** (see Scheme 5). Sabina ketone is a natural product that is a key intermediate for the synthesis of important monoterpenes such as sabinene and sabinene hydrates.[15]

In conclusion, we have shown that 5-en-1-yn-3-ol substrates bearing a free hydroxyl group or an acyl group are highly versatile partners for $PtCl_2$-catalyzed cycloisomerizations. Electrophilic

Scheme 5



activation of the alkyne moiety triggers at wish a hydride or an *O*-acyl migration yielding at the end to regioisomeric keto derivatives. The efficient preparation of an important monoterpene precursor has been worked out. Further applications of this process in complex natural product synthesis as well as asymmetric catalysis are being pursued.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) This moderate yield of **6a** is presumably attributable to the volatility of this material.

(10) Other dienic isomers (15%) contaminated product **5**.

(11) One hypothesis is that due to orbital stereocontrol, the 1,2-migration is not a concerted process, so that a certain degree of positive charge (carbocation) stabilization is required at the propargylic position. This would take place in the case of tertiary substrates.

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