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$Ru_3(CO)_{12}$-catalyzed intramolecular allylic transfer reaction of tethered carbonyl group and allylic acetate moiety

Chan-Mo Yu,* Sungwon Lee, Young-Taek Hong and Seok-Keun Yoon

Department of Chemistry and Laboratory for Metal-Catalyzed Reactions, Sungkyunkwan University, Suwon 440-746, South Korea

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Abstract—A ruthenium catalyzed intramolecular allylic transfer reaction of allylic acetates containing aldehydes or ketones to form *cis*-homoallylic cyclopentanols and cyclohexanols as a major component is described. The use of $Ru_3(CO)_{12}$ (1 mol%) to promote reaction results in a convenient procedure for intramolecular allylation of carbonyl functionalities.

Intramolecular allylic transfer reactions has proved to be useful transformations in the construction of five, six, and even larger rings for the synthesis of carbocyclic and heterocyclic biologically active molecules.[1] Notable methods have been developed in recent years for accessing stereocontrol through the intramolecular allylic transfer reaction, the vast majority of which involve construction of the cyclic systems by carbon–carbon bond formation from carbonyl functionalities via Lewis acid mediated electrophilic cyclization.[1] During the course of our research program aimed at finding new synthetic methods for the stereoselective construction of pyran units via sequential allylic transfer reactions,[2] we disclosed our discovery on the rhodium-catalyzed intramolecular cyclization between allene and carbonyl functionality with silane reagent.[3] It was envisaged that the cyclization with proper modifications of substrate for metalation especially π-allylmetals with catalyst could be realized without using additional reagents in a predictable fashion. π-Allylpalladium complex has been utilized as a versatile electrophile.[4] In addition to palladium, the π-allyl complexes such as Mo,[5] Rh,[6] Ir,[7] and other transition metals[8] have received much attention for allylic substitution reactions as electrophilic intermediates. π-Allylpalladium species could also be transformed to a nucleophilic allylic species. This charge reversal was developed on the basis of the reduction of π-allylpalladium with low valent metals[9] electrochemical methods,[10] addition of heteronucleophiles,[11] and alkyl–alkyl exchange reaction with organozinc reagents.[12] However these conditions require stoichiometric amount of reagent. Recently ruthenium-catalyzed allylic substitution has been reported utilizing ruthenium complex as an electrophiles.[13] Unlike most other π-allylmetal complexes, the wide range of oxidation states energetically accessible to ruthenium allows π-allylruthenium complexes to show nucleophilic character as well as electrophilic behavior.[14,15] Particularly, Kondo and Watanabe reported the intermolecular allylation of aldehydes with allylic acetates catalyzed by a ruthenium complex.[16]

With this issue in mind, our investigations began with **1a** and a variety of transition metal complexes. Initial attempts to an intramolecular allylic transfer reaction of **1a** indicated that the conversion to the corresponding **1a** or **2a** could not be realized with a variety of metal carbonyls including under various reaction conditions mainly due to a lack of reactivity. Fortunately, we found that ruthenium complex could be effective catalyst for this purpose. Initial experiments on the catalytic carbocyclization of **1a** with $Ru_3(CO)_{12}$ (1 mol%) at 20 °C under CO atmosphere for 51 h in $CHCl_3$ afforded encouraging but marginal results. Although product was produced during the reaction, long reaction time and low chemical yield (34% yield) remained to be solved. We subsequently speculated that the nature of catalyst under reaction conditions might be a control factor to regulate catalytic process. After surveying numerous reaction conditions as summarized in Table 1, several key findings emerged: (i) $Ru_3(CO)_{12}$ proved

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* Corresponding author. Tel.: +82-31-290-7067; fax: +82-31-290-7075; e-mail: cmyu@chem.skku.ac.kr

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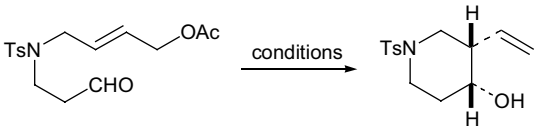
Table 1. Selected preliminary investigations



1a **2a**

Entry	Conditions	Result
1	$Mo(CO)_6$, DMSO, THF, 90 °C	Decomposition
2	Rh(dppp)ClCO (5 mol%), CO (1 atm)	NR
3	$Ir(COD)Cl_2$ (5 mol%), dppp, CO	NR
4	$[RuCl_2(CO)_3]_2$, Et_3N, CO (1 atm), THF	NR
5	$Ru_3(CO)_{12}$, Et_3N, CO (1 atm), $CHCl_3$, 51 h	34%
6	$Ru_3(CO)_{12}$, Et_3N, CO (15 atm), THF, 16 h[a]	89%
7	$Ru_3(CO)_{12}$, Et_3N, CO (5 atm), THF, 32 h[a]	43%
8	$Ru_3(CO)_{12}$, Et_3N, THF, 12 h in a seal tube[a]	NR

[a] $Ru_3(CO)_{12}$ (1 mol%), Et_3N (3 equiv), at 90 °C.

to be an only effective catalyst for this chemical transformation; (ii) the use of other ruthenium complexes including $RuCl_3 \cdot nH_2O$, $Ru(CO)(H_2)(PPh_3)$, $[RuCl_2(CO)_3]_2$, and $[Cp_2Ru]$ under CO atmosphere turned out to be unsuccessful; (iii) it is critical to run the reaction under the pressure of CO (15 atm) presumably due to the facile regeneration of catalyst; (iv) the use of Et_3N (3 equiv) as a hydride source is essential to promote reaction;[16b] (v) reaction performed at 90 °C in THF resulted in optimal chemical yields in comparison with other solvents such as toluene, CH_3CN, CH_2Cl_2, and $CHCl_3$; (vi) only *cis*-isomer **2a** was formed as determined by the analysis of 500 MHz ^1H NMR spectra of crude products. Under optimal conditions, the allylic-acetate aldehyde **1a** reacted in an autoclave with carbon monoxide (15 atm), Et_3N, and a catalytic amount of $Ru_3(CO)_{12}$ (1 mol%) in THF at 90 °C for 16 h. Work up and column chromatography afforded **2a** in 89% yield.[17]

With the notion that this approach might lead to a general and efficient method for diastereoselective synthesis of **2**, we set out to determine the scope of reaction with various substrates **1** to produce carbocycles and hetero-

Table 2. Carbocyclization of **1** to **2** catalyzed by $Ru_3(CO)_{12}$[a]

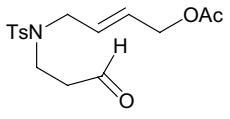
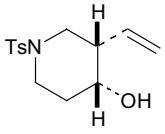
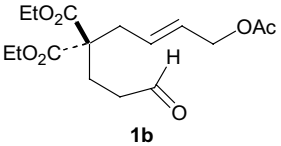
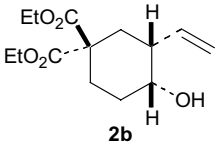
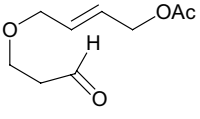
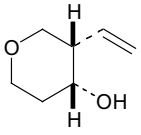
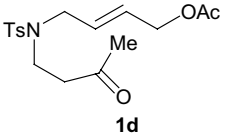
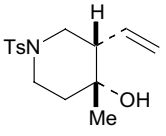
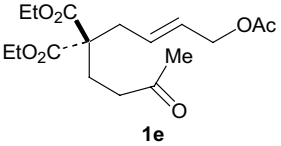
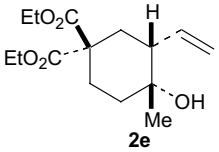
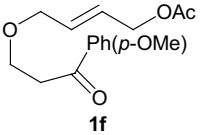
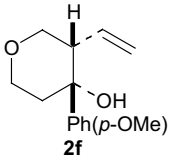
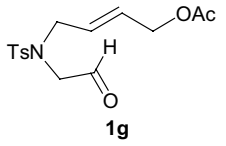
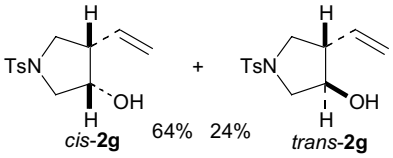
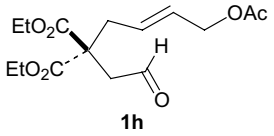
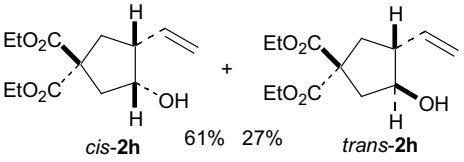
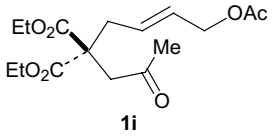
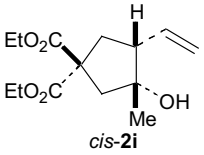
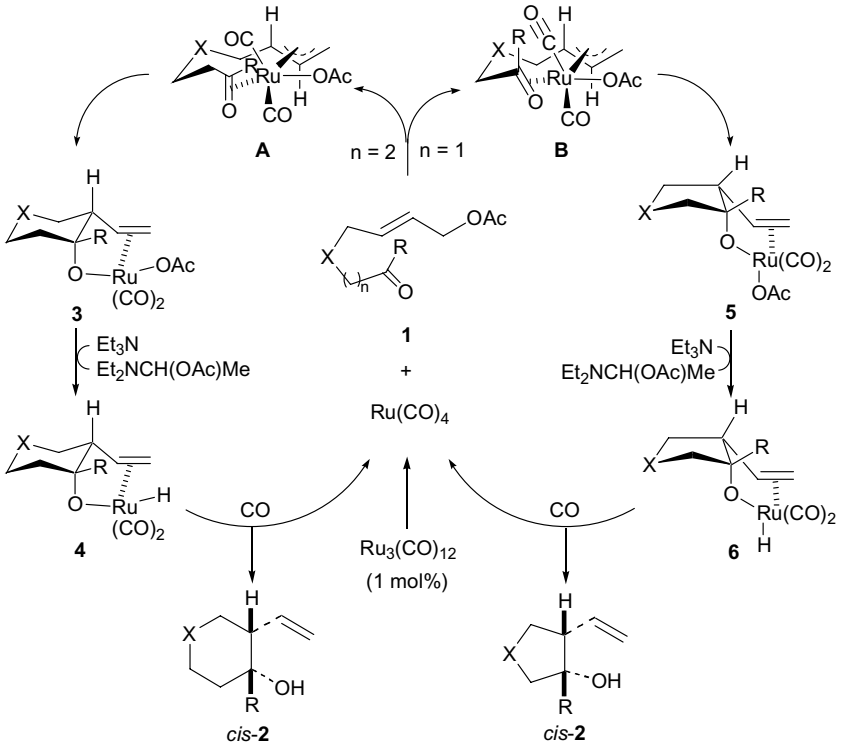
Entry	1	Time (h)	Product	Yield[b] (%)
1	 **1a**	16	 **2a**	89
2	 **1b**	18	 **2b**	87
3	 **1c**	18	 **2c**	78
4	 **1d**	18	 **2d**	91
5	 **1e**	18	 **2e**	71
6	 **1f**	20	 **2f**	68

Table 2 (*continued*)

Entry	1	Time (h)	Product	Yield[b] (%)
7	 **1g**	16	 *cis*-**2g** 64% + 24% *trans*-**2g**	88
8	 **1h**	18	 *cis*-**2h** 61% + 27% *trans*-**2h**	88
9	 **1i**	18	 *cis*-**2i**	90

[a] Reactions were carried out in autoclave with $Ru_3(CO)_{12}$ (1 mol%), Et_3N (3 equiv), CO (15 atm) at 90 °C in THF.
[b] Yields refer to purified yields.

cycles as summarized in Table 2. Indeed, the method is successful with **1** to afford five- and six-membered products **2** in terms of chemical yields as can be seen in Table 2. It is worthy to note that the reaction of **1a**–**f** (entries 1–6) produced always the six-membered *cis*-products **2a**–**f** with none or only trace amounts of *trans* products (less than 5%) according to the analysis of 500 MHz ^{1}H NMR spectra of crude products. However, treatment of aldehyde-allylic acetate sulfonamide **1g** under the same conditions provided *cis*-**2g** (64%) as a major product together with *trans*-**2g** (24%) as a minor product (entry 7). Similarly, malonate branched allylic acetate-aldehyde **1h** provided the *cis*-**2h** (61%) and *trans*-**2h** (27%). On the other hand, the reaction of ketone analog **1i** resulted in the formation of *cis*-**2i** as a sole product. The relative stereochemical relations of six-membered products **2a**–**c** were unambiguously established by NMR experiments. The stereochemical assignments were based on the magnitudes of the vicinal coupling constants of products for each case. Small



Scheme 1. Plausible stereochemical courses.

coupling constants (2–4 Hz) of protons at ring juncture clearly indicated the *cis* stereochemical relationships. Stereochemistry of **2d**, **2e**, **2g**, and **2h** was determined by NOESY technique with molecular modeling together the distances with NOE cross-peaks between the juncture protons and vinyl protons. Finally, compounds **2a**, **2c**, **2d**, **2e**, **2g**, **2h**, and **2i** were also confirmed by comparison of ^{1}H NMR spectra with authentic samples prepared from corresponding vinylsilanes under acidic conditions.[3]

Although the exact mechanistic aspects of this transformation including geometrical features for the active ruthenium species have not been rigorously elucidated, the following pathway could be probable stereochemical routes on the basis of product formation as illustrated in Scheme 1. Reaction of ruthenium carbonyl with allylic acetate in **1** could undergo the formation of π-allylruthenium complexes **A** and **B**. A carbonyl compound can interact with a metal species either one of the oxygen lone pairs (σ-complex) or through the π-system of the carbonyl group (π-complex). Based on the product distribution, π-complexation could be a proper orientation in **A** and **B**. Since carbonyl addition would lead to the particular product **3** and **5** via stereochemical models **A** and **B**, the major reaction pathway could be dependent on the stability in the transition state under a kinetic control. Thus, we believe that the origin of the *cis* stereochemical outcomes for five- and six-membered ring of this reaction might be a subtle geometrical preference for orientation in the transition states offered by substituents, reagents, and ligands. The stereochemical course of this catalytic process is likely to be due to a geometrical preference of **A** with six-membered rings and **B** with five-membered rings for a minimum strain with existing components as depicted in Scheme 1. After hydride exchange between Et_3N and RuOAc,[16b] reductive elimination of **4** and **6** led to the products **2** along with the regeneration of ruthenium catalyst.

In summary, the ruthenium-catalyzed intramolecular allylic transfer reaction of allylic acetates containing carbonyl functionalities to form *cis*-homoallylic cycloalkanols has been accomplished in a general and efficient way, which promises to be widely useful. Investigations into the versatility of this process including relative stereocontrol are currently underway.

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17. The following procedure is representative. A stainless autoclave was charged with **1a** (120 mg, 0.35 mmol), $Ru_3(CO)_{12}$ (2.3 mg, 3.5×10^{-3} mmol), triethylamine (0.15 mL, 108 mg, 1.07 mmol), and THF (3 mL) and the system was flushed with 15 atm of CO three times. It was then pressurized to 15 atm. The resulting reaction mixture was stirred at 90 °C for 16 h. After the mixture was cooled to rt, dilute hydrochloric acid (1 N) was added, and then the reaction mixture was extracted with ether (3×20 mL). The extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure, and the crude product was purified by SiO_2 column chromatography (3:1 hexane/ethyl acetate) to afford the cyclized product **2a** (88 mg, 0.31 mmol, 89%) as a white solid.