Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 2779–2788

A coordinatively unsaturated ruthenium methoxide as a highly effective catalyst for the halogen atom-transfer radical cyclization of *N*-allyl dichloroacetamides and related reactions

Yukihiro Motoyama, Shiori Hanada, Kazuya Shimamoto and Hideo Nagashima*

Graduate School of Engineering Science, Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga, Fukuoka 816-8580, Japan

Received 30 November 2005; revised 29 December 2005; accepted 6 January 2006

Available online 7 February 2006

Abstract—Atom-transfer radical cyclization (ATRC) catalyzed by coordinatively unsaturated ruthenium alkoxides **4**, $[(\eta^5\text{-}C_5Me_5)\text{-}Ru(OR)]_2$, is investigated, and ruthenium methoxide **4a** (R = Me) is found to exhibit excellent catalytic activity for the cyclization of *N*-allyl-α,α-dichloroacetamides at ambient temperature. Addition of some amounts of two-electron donor ligands such as pyridine and triphenylphosphine improves the catalyst efficiency to afford the corresponding γ-lactams in high yields. The high catalytic activity of this catalyst system enables to control the diastereoselectivity of this 5-*exo* cyclization kinetically. The present **4a**/pyridine system is also effective for the 4-*exo* cyclization of *N*-vinylacetamides to afford the corresponding β-lactams in quantitative yields. The **4a**/pyridine system is also active towards the ATRP of methyl methacrylate (MMA) at room temperature to afford the poly(MMA) with narrow molecular weight distributions ($M_w/M_n = 1.2$) at the initial stage.

1. Introduction

Atom-transfer radical reaction (ATRR) has now become one of the most important carbon–carbon bond-forming reactions, being utilized for synthetic organic chemistry and polymer synthesis.[1–3] In particular, our discovery of copper-catalyzed cyclizations of allyl α,α,α-trichloroacetates[4a] and *N*-allyl-α,α,α-trichloroacetamides[4b] offered a research field of transition metal-catalyzed atom-transfer radical cyclization (ATRC), which has afforded powerful synthetic methods for carbo- and heterocycles including macrolide and alkaloid skeletons.[5] From the synthetic point-of-view, it should be noted that requirement of high reaction temperatures is a general disadvantage of ATRR, especially in the reactions involving activation of less reactive carbon–halogen bonds. In our earliest report on the cyclization of α-halogenated *N*-allylacetamides, either $RuCl_2(PPh_3)_3$ or CuCl catalyst was effective at 140 °C.[4b] Later elaboration to improve the reaction conditions revealed that the reaction was facilitated by increasing the halogen atom at the α-position and/or introduction of electron-withdrawing group on the nitrogen atom.[4e,f] This is presumably due to the fact that these substituents lower the LUMO of α-halogenated acetyl moiety and facilitate abstraction of a halogen atom by transition metal catalysts. On the other hand, several reactive catalyst systems, which can promote the reaction at low temperature, were developed; in particular, catalyst systems composed of CuCl and bidentate diamines[4c] and isolable coordinatively unsaturated ruthenium amidinates **1**–**3** were found to be one of the most effective catalysts for ATRR (Fig. 1).[6c,7] Thus, combination of the selection of appropriate substrates, which have suitable electronic structures for ATRR, with powerful catalyst systems realized the cyclization of *N*-allyl-α,α,α-trichloroacetamides below room temperature within a few hours. However, the cyclization of less reactive substrates such as *N*-allyl-α,α-dichloroacetamides is slow even using CuCl/bipyridine and ruthenium amidinates as the catalyst and it is necessary to apply high reaction temperatures (>80 °C) to obtain the product in good yield.[4e,7,8] This indicates the requirement to seek for catalysts more powerful enough to activate a carbon–chlorine bond of *N*-allyl dichloroacetamides with ease to afford the corresponding γ-lactams.

For the development of highly reactive new catalysts, we have been interested in use of coordinatively unsaturated transition metal complexes. ATRC is generally explained by the catalytic cycle shown in Scheme 1. The atom-transfer

Keywords: Coordinatively unsaturated complex; Polymerization; Radical cyclization; Ruthenium.
* Corresponding author. Tel.: +81 92 583 7819; fax: +81 92 583 7819; e-mail: nagasima@cm.kyushu-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.011

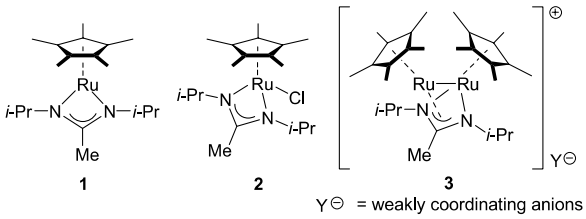
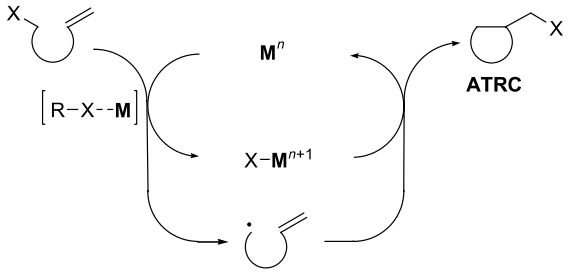


Figure 1. Ruthenium amidinate complexes **1**–**3**.



Scheme 1. Atom-transfer reaction with transition metal complex.

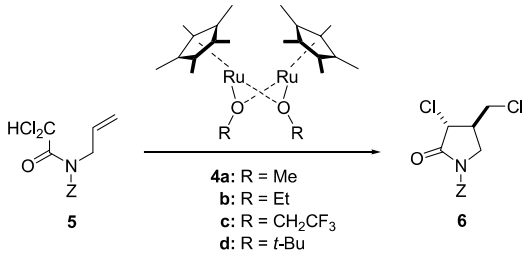
reaction of organic halides (R–X) with transition metals (M) proceeds via the redox mechanism involving a [R–X···M] complex as an intermediary species, and the formal oxidation state of the metal species is increased by one, and M–X is formed by the halogen abstraction.[9] In the [R–X···M] complex, M has to be coordinatively unsaturated, and thus, use of isolated coordinatively unsaturated complexes as the catalyst could facilitate the production of [R–X···M], which subsequently undergoes atom-transfer process to produce the radical species ($R^{\cdot}$) to initiate the reaction. If M has appropriate redox potentials, the catalytic cycle illustrated in Scheme 1 could be successfully operated.

In fact, ruthenium amidinate complexes **1**–**3** showed a coordinatively unsaturated nature, and actually behaved as efficient catalysts for ATRR as described in our previous papers.[6c,7] For further studies in this line, we were interested in isolable ruthenium alkoxides $[(\eta^5\text{-}C_5Me_5)Ru(OR)]_2$ **4**, which exist in solution as coordinatively unsaturated dimers having 32 valence electrons and reversibly forms monomers in contact with appropriate ligands.[10] The formed monomer, which was stabilized by the ligand, is still coordinatively unsaturated (16 valence electrons), being able to accept the coordination of R–X for its activation.[10c,11] In this paper, we wish to report that coordinatively unsaturated ruthenium alkoxides actually behave as the catalyst for the cyclization of *N*-allyl-α,α-dichloroacetamides **5** and related reactions. The scope of these ruthenium alkoxides as catalysts for ATRC is described in relation to the low-temperature activation of organic halides and stereochemical outcomes of the reactions, and their performance is compared with that for atom-transfer radical polymerization (ATRP) (Scheme 2).

2. Results and discussion

2.1. Atom-transfer radical cyclization

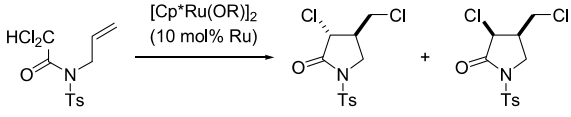
As we expected, $[Cp^*Ru(OMe)]_2$ **4a** was effective for the activation of a C–Cl bond at ambient temperature.



Scheme 2. ATRC of *N*-allyl-α,α-dichloroacetamides **5**.

Treatment of α,α-dichloroacetamide **5a** (0.2 mmol) with **4a** (10 mol% of Ru) in dichloromethane for 4 h under an argon atmosphere afforded the cyclic product **6a** in 50% isolated yield with a trans/cis ratio of 86:14 (Table 1, entry 1). The alkoxy group on the ruthenium apparently affected the catalytic activity; the ethoxy complex **4b** gave **6a** in 34% yield (entry 2), whereas no product was obtained by the use of trifluoroethyl and *t*-butyl derivatives (**4c** and **4d**) as catalysts (entries 3 and 4). It is noteworthy that ruthenium halide complexes such as $[Cp^*Ru^{II}Cl]_4$ and $[Cp^*Ru^{III}Cl_2]_2$ are not effective for this cyclization at ambient temperature (<5% yields). These results showed that the sterically less-hindered alkoxide ligand plays a crucial role in enhancing the reactivity of the ruthenium complexes towards organic halides via the one-electron redox process, which may be related to the π-donation by alkoxide lone pairs. Among the solvents examined, dichloromethane proved to be the most effective for both chemical yield and trans/cis ratio of the product (entries 5–8).

Table 1. Radical cyclization of **5a** with $[Cp^*Ru(OR)]_2$ **4a**–**d**[a]



Entry	Cat.	Solvent	Time (h)	Yield (%)	trans/cis[b]
1	**4a**	CH_2Cl_2	4	50	86:14
2	**4b**	CH_2Cl_2	4	34	85:15
3	**4c**	CH_2Cl_2	4	0	—
4	**4d**	CH_2Cl_2	4	0	—
5	**4a**	CH_2Cl_2	16	64	86:14
6	**4a**	Benzene	16	33	83:17
7	**4a**	MeCN	16	32	82:18
8[c]	**4a**	Et_2O	16	<10	78:22

[a] All reactions were carried out using 0.2 mmol of **5a**, 0.01 mmol of **4** in 1.5 mL of solvent at room temperature.
[b] Determined by ^{1}H NMR analysis.
[c] 0.03 mmol (30 mol% Ru) was used.

Despite the high catalytic activity for the cyclization of dichloroacetamide **5a**, a disadvantage of **4a** is its short lifetime as shown in the reaction profiles (Fig. 2, left; a); the reaction was terminated after some of the starting materials were consumed (~80%, TON≤8). Although the catalytic activity (initial reaction rate) was slightly decreased, addition of pyridine to the reaction mixture depresses inactivation of the catalyst (Fig. 2, left; b). The effects of pyridine and other ligands, which affect the catalytic efficiency in the reaction of **5a** with **4a** in dichloromethane at ambient temperature, are summarized in Table 2.