Simple and fast ruthenium catalyzed direct aldol reaction: scope and limitations

Elahe Keshavarz, Khalil Tabatabaeian, Manouchehr Mamaghani, and Nosrat O. Mahmoodi

Department of Chemistry, Faculty of Sciences, University of Guilan, P.O. Box 41335-1914, Rasht, Iran

Abstract

A microwave-assisted method was developed for the synthesis of aldol adducts using $RuCl_3.nH_2O$-BINAP as an efficient catalyst. Important advantages of this thechnology include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the chemoselectivity and quality of the products.

Keywords: Aldol reaction, Asymmetric synthesis, Microwave technique

Introduction

Cabon-carbon bond formation is the essence of organic synthesis. A aldol reaction, represents one of the classical C-C bond forming processes, and its variants have been used extensively in many important syntheses [1-4]. There has been great demand to develop one-pot procedures for successive reactions for the formation of several C-C bonds. The minimization of steps involved in multistep synthesis not only allows the reduction of waste but also results in the diminution of costs.

The pursuit of all these synthetic targets with increasing complexity has resulted in the development of reactions that emphasize chemo-, regio-, diastereө , and enantioselectivity.

An asymmetric aldol reaction is one of the most common methods for C-C bond formation in organic molecules. It is extensively applied in the synthesis of carbohydrates, amino sugares, steroids, and other valuable chiral organic compounds. It provides an atom-economic approach to β-hydroxyl carbonyls, which make up a large family of chiral intermediates for the synthesis of biologically active substances and natural products [5-9].

The development of a direct catalytic asymmetric aldol reaction, in which the pre-activation of nucleophiles is no longer needed, has been worthy of notice. For example, the catalyst must not only activate the aldehyde in order to high stereoselectivity but also has to abstract an α-hydrogen of the ketone to generate an enolate.

On the other hand, metal-catalyzed reactions have made a great contribution to the recent growth of organic synthesis and a variety of synthetic methods have been reported using transition metal complexes in catalytic amounts [10-12]. Among the transition metal Lewis acids, Ru^{III} salts are known to catalyze a variety of organic transformations, and the investigation of the chemistry of ruthenium continues to be an active area of organometallic chemistry [13-14].

Here, we report a direct aldol reaction of ketones and aromatic aldehydes catalyzed by $RuCl_3.nH_2O$ and chiral ligand.

Results and discussion

The aldol reaction is the most important chemical reactions. Substantial effort has gone into its development using preformed enolates, resulting in a remarkable level of regio- and stereochemical control.

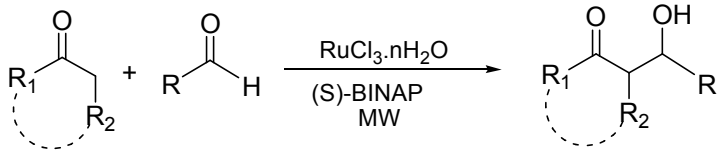
In all of the catalytic asymmetric reactions, preconversion of the ketone moiety to a more reactive species is an unavoidable necessity. Thus, the development of a direct catalytic asymmetric aldol reaction is highly desirable in terms of atom economy.

In continuation of our research in environmentally benign [15-17] and microwave assisted conditions [18], we now report an operationally simple and fast method for the preparation of aldol products by one-pot condition reaction. In this research, the direct aldol reaction of ketones with aromatic aldehydes using catalytic amount of $RuCl_3.nH_2O$ and chiral ligand was irradiated in a 160 W microwave oven and proceeded smoothly to give the corresponding aldol adducts in good yields with moderate to good diastereoselectivity.

The reaction of propiophenone (1.5 mmol) and aldehyde (0.25 mmol) in a minimum amount of solvent was carried out in the presence of BINAP/Ru^{III} (0.010/0.009 mmol).

Typical results of the aldol reactions, under optimized reaction conditions, are shown in table 1. Next, we examined the reaction of cyclopentanone as an enolate source under the same condition described in entries 5 and 6 of Table 1.

Table 1
Ruthenium-catalyzed cross aldol reactions of aldehydes with ketones



Entry[a]	Ketone	R		Yield[b] (%)	Time (min)	Dr (syn:anti)[c]
1	Propiophenone	4-$O_2NC_6H_4$-	**2a**	77	2	47:53
2	Propiophenone	2-$O_2NC_6H_4$-	**2c**	80	7	46:54
3	Propiophenone	4-FC_6H_4-	**2i**	69	5	68:32
4	Propiophenone	C_6H_5-	**2l**	72	5	60:40
5	Cyclopentanone	4-$O_2NC_6H_4$-	**2a**	72	5	67:33
6	Cyclopentanone	2-$O_2NC_6H_4$-	**2c**	65	5	60:40

[a] All products were characterized by ^1H NMR, ^{13}C NMR and IR.
[b] Yields after purification by chromatography.
[c] Identified by comparison with authentic sample [16].

A mechanistic pathway for the catalytic aldol reactionis proposed. Initially, ketone may be captured on the ruthenium complex by the synergic action (i) to form the corresponding ruthenium-enolate (ii) which reacts with aldehyde (iii) to give the ruthenium-aldolate (iv). Finally, when ketone is incorporated, the aldol product is released to regenerate the intermediate ruthenium-enolate (ii). The chiral space derives from the conformational preferences of the BINAP moiety. The planar aryl ring of acetophenone causes less steric distortion of the chiral pocket than the bulk of a tetrahedral carbon such as methyl in the case of cyclopentanone.

The absolute configuration in many cases was assigned by comparison to the literature and assumed to be the same in the other cases.

Conclusions

We have developed a mild and efficient direct aldol reaction using simple substrates in the presence of $RuCl_3.nH_2O$-BINAP Microwave technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of aldol adducts. Retro aldol reactions and self-condensation of aldehydes were prevented as well. Work is currently ongoing to develop an asymmetric variant of the reaction through incorporation of the other chiral system. Additionally, we have begun to explore the use of esters in the context of several aldol reactions.

Experimental

All solvents, organic and inorganic compounds were purchased from Merck and Fluka and used without further purification. All reactions were followed by TLC with detection by UV light. The isolation of pure products was carried out via preparative thin layer chromatography (silica gel 60 GF_{254}, Merck). IR spectra were recorded on Shimadzu FTIR-8400S spectrometer. ^{1}H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and ^{13}C NMR were obtained on a Bruker DRX-125 Avance spectrometer. Samples were analyzed in $CDCl_3$, and the chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as the internal reference.

Typical procedure for ruthenium-catalyzed aldol reaction

A mixture of aldehyde (0.25 mmol), ketone (1.5 mmol), $RuCl_3.nH_2O$ (0.009 mmol), (S)-BINAP (0.010 mmol) and KOH (0.15 mmol) was irradiated in a 160 W microwave oven and monitored by TLC. After the indicated reaction time, the reaction mixture was purified by thin layer chromatography (silica gel, EtOAc-petroleum ether, 4:12) providing the aldol adduct.

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