An efficient Ru\textsuperscript{III}/BINAP catalytic system for the aldol reactions of ketones with various aldehydes

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Abstract
Synthesis of aldol adducts has been accomplished with moderate to excellent stereoselectivities using a Ru\textsuperscript{III}/(S)-BINAP system at room temperature. Under ultrasound irradiation, the aldol products produced in a reasonably short time.

Keywords: Diastereoselection, aldol, ruthenium catalyst, (S)-BINAP

Introduction

Asymmetric catalysis\textsuperscript{1} is now an important part in drug design and development. The search for new catalysts that display high activity and exquisite selectivity is a major focus of current research in the field of organic synthesis.\textsuperscript{2} One concern of the synthetic organic chemist is to develop new asymmetric catalytic methodologies using transition metal complexes.\textsuperscript{3} In this field, several groups have focused their research on the development of ruthenium catalytic reactions.\textsuperscript{4}

On the other hand, the aldol reaction is one sort of the most important C-C bond formation reactions,\textsuperscript{5} which can generate many valuable biologically optically active β-hydroxy carbonyl compounds. Also, the fact that the biological activity is dependent on their absolute configuration has increased the importance of β-hydroxy ketones in bioorganic and medicinal chemistry. Therefore, a lot of efforts have been devoted to the development of this reaction, and a great success has been achieved in this field.\textsuperscript{6} Shibasaki has reported the first example of a direct asymmetric aldol reaction catalyzed by heterobimetallic complexes.\textsuperscript{7} Since List and Barbas discovered that L-proline may be used as the catalyst for the direct asymmetric aldol reaction,\textsuperscript{8} many groups have developed various proline-based organocatalysts\textsuperscript{9-15} for the direct asymmetric aldol reaction. Among them, N-terminal prolyl dipeptides are effective for the direct catalytic asymmetric aldol reaction.\textsuperscript{16} However, those dipeptides have a low solubility in most of the organic solvents. In addition, the groups of Tomasini and Gong have tried to use N-terminal...
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Those soluble dipeptide esters gave moderate results due to the decrease of the stereoselectivity control ability. So, the development of a catalytic system that is able to catalyze stereoselective reactions in good yield is a true challenge. On the other hand, chiral ligands have been successfully employed in a number of transition metal-catalyzed asymmetric transformations. The most versatile, and consequently most investigated, ligand is the BINAP ligand. It can be coupled to many transition metals, and it catalyzes a wide range of asymmetric reactions.

In this letter, we describe the use of chiral (S)-BINAP ligand in the aldol reaction. To the best of our knowledge, this is the first report on the aldol reaction using ruthenium trichloride hydrate containing the (S)-BINAP ligand as catalyst to establish a stereoselective method for the preparation of β-hydroxy carbonyl derivatives of simple substrates.

**Results and Discussion**

Recently, we have reported an efficient protocol for the cross aldol reaction in the presence of RuCl$_2$(PPh$_3$)$_3$. Ru$^{II}$ catalyzed cross aldol reaction proceeded at 80 °C, furnishing a wide variety of β-hydroxy ketones with moderate diastereoselectivities and in good yields. Based on this precedent, we envision that an aldol reaction can also be performed as an efficient reaction utilizing an aldehyde, a ketone and a RuCl$_3$.nH$_2$O/(S)-BINAP system.

In an initial study, we examined the aldol reaction among cyclohexanone and 4-nitrobenzaldehyde catalyzed by various amounts of RuCl$_3$.nH$_2$O and KOH (0.4 mmol) in dioxane at room temperature. In all cases, the aldol adducts were achieved in good yields but with low stereoselectivities. To improve the selectivity, we searched for an additive. The addition of (S)-BINAP ligand significantly improved the stereoselectivity.

Finally, the optimized conditions were achieved using 3.8 mol% (S)-BINAP and 3.7 mol% ruthenium chloride hydrate catalyst loading whereupon the product was isolated in a good yield of 85%. To investigate the generality of the current process, aldol reactions between a series of aldehydes and cyclohexanone were examined (Table 1). All the reactions took place smoothly and furnished the desired aldol products 3a-k in moderate to good yields (45-85%) with complete diastereoselectivity. As shown in Table 1, we selected methoxy and methyl substituents as the representative electron-donating group and nitro and halogen substituents as the electron-withdrawing groups on the benzene ring. In comparison to electron-donating groups, the yield of electron-withdrawing was significantly higher, with a somewhat shorter reaction time.
Table 1. Aldol reaction of aromatic aldehydes with cyclohexanone in the presence of RuCl$_3$.nH$_2$O/(S)-BINAP$^a$

\[
\begin{align*}
\text{O} & \quad + \quad \text{R} \quad \text{H} \\
\text{RuCl}_3$.nH$_2$O (3.7 mol\%) & \quad (S)$-$BINAP (3.8 mol\%), RT \\
1a & \quad \text{3a-k}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield $^c$ (%)</th>
<th>Time (h)</th>
<th>Ultrasonic Irradiation</th>
<th>Dr (syn:anti)$^d$</th>
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<td>82</td>
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<td>67</td>
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<tr>
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<td>52</td>
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<td>11</td>
<td>4-CH$_3$C$_6$H$_4$-</td>
<td>2k 3k</td>
<td>51</td>
<td>6.5</td>
<td>60</td>
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</table>

$^a$ Reaction conditions: aldehyde (0.5 mmol), cyclohexanone (3 mmol), KOH (0.4 mmol), catalyst, (S)-BINAP, solvent at room temperature. $^b$ All products were characterized by $^1$H NMR, $^{13}$C NMR and IR data. $^c$ Yields after purification by chromatography. $^d$ Determined by $^1$H NMR analysis. $^e$ Solvent free.
Encouraged by these results, we reinvestigated the same synthetic protocol, using ultrasonic irradiation to overcome the problem of somehow prolonged reaction times. Typical results of the ultrasonic-assisted aldolization are shown in Table 1. A mixture of aldehyde (0.5 mmol) and ketone (3 mmol) under the influence of catalytic amounts of RuCl₃·nH₂O (3.7 mol%), (S)-BINAP (3.8 mol%) and 0.4 mmol KOH in dioxane was irradiated with ultrasound in a sealed tube at room temperature (checked by TLC) to give aldol adducts as the main products. These results revealed the promotion of the aldol reaction by ultrasonic irradiation.

To broaden the scope of this transformation, a number of aromatic aldehydes were reacted with ketones 1b-c under the desired conditions to afford the β-hydroxy ketones 4-9 (Table 2). Ruthenium III-catalyzed aldol adducts 4-9 with much lower stereoselectivity, however, the reaction times were somewhat shorter.

**Table 2.** Aldol reaction of aldehydes with ketones in the presence of RuCl₃·nH₂O/(S)-BINAP

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Time (h)</th>
<th>Dr (syn:anti)</th>
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<tbody>
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<td>2c</td>
<td>5</td>
<td>81</td>
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<tr>
<td>3</td>
<td>Propiophenone 1b</td>
<td>4-FC₆H₄</td>
<td>2i</td>
<td>6</td>
<td>70</td>
<td>66:34</td>
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<td>4</td>
<td>Propiophenone 1b</td>
<td>C₆H₅-4-</td>
<td>2l</td>
<td>7</td>
<td>72</td>
<td>62:38</td>
</tr>
<tr>
<td>5</td>
<td>Cyclopentanone 1c</td>
<td>O₂NC₆H₄-2-</td>
<td>2a</td>
<td>8</td>
<td>80</td>
<td>67:33</td>
</tr>
<tr>
<td>6</td>
<td>Cyclopentanone 1c</td>
<td>O₂NC₆H₄-2-</td>
<td>2c</td>
<td>9</td>
<td>79</td>
<td>62:38</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: aldehyde (0.5 mmol), ketone (3 mmol), KOH (0.4 mmol), catalyst, (S)-BINAP, solvent at room temperature. *b* All products were characterized by ¹H NMR, ¹³C NMR and IR data. *c* Yields after purification by chromatography. *d* Determined by ¹H NMR analysis.
Although the precise mechanism of the reaction awaits further studies, a possible mechanistic pathway for the aldol reaction, which rationalizes the formation of products, is presented in Scheme 1.

Scheme 1. Proposed mechanism for aldol reaction in the presence of RuCl₃.nH₂O/(S)-BINAP.

Conclusions

In continuation of our work on the catalytic reactivity of ruthenium, we have developed an easy approach to β-hydroxy ketones via the cross aldol reactions of different aldehydes and ketones in the presence of a RuCl₃.nH₂O/(S)-BINAP system at room temperature. With this new catalytic promoting system, various aldehydes were coupled to generate syn-products. The reaction is versatile and also offers several advantages, such as shorter reaction times, cleaner reaction profiles and simple experimental and work-up procedures. Further studies concerning the enantioselectivity and scope of Ru³⁺ catalysis are ongoing.

Experimental Section

General. All reactions were followed by TLC with detection by UV light. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ¹H 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. Elemental analyses were made by a Carlo-Erba EA1110 CHNO-S analyzer and agreed with the calculated values. Ultrasonication was performed in a TECNO-GAZ Tecna 3 ultrasonic cleaner with a frequency of 5060 kHz and a normal power of 250 W. The isolation of pure products was carried out via preparative thin layer chromatography (silica gel 60 GF$_254$, Merck). Excess of solvent was evaporated under reduced pressure at a bath temperature of 50 °C and 60 °C. All solvents, organic and inorganic compounds were purchased from Merck and Fluka and used without further purification.

**Typical method**

A catalytic amount of RuCl$_3$·nH$_2$O (4 mg, 0.018 mmol) was added to a vial containing aldehyde (0.5 mmol), ketone (3 mmol), KOH (22.4 mg, 0.4 mmol), (S)-BINAP (12 mg, 0.019 mmol) and dioxane (0.8 ml). The reaction mixture was stirred at room temperature and monitored by TLC. After the indicated reaction time the reaction mixture was purified by thin layer chromatography (EtOAc/petroleum ether 1:4 v/v), providing the aldol adduct.

The aldol products 3a-k (Table 1) and 6-9 (Table 2) are known compounds and spectroscopic data of them were consistent with those reported in the literature.$^{22-25}$

**3-Hydroxy-2-methyl-3-(2-nitrophenyl)-1-phenylpropan-1-one (4).** Yellowish oil, IR (neat): ν (cm$^{-1}$): 3390, 3372, 2930, 1667, 1515, 1468. Data for anti isomer, $^1$H NMR δ 1.25 (d, $J = 5.3$ Hz, 3H), 2.02 (s, OH), 4.25 (m, 1H), 5.14 (d, $J = 7.0$ Hz, 1H), 7.49 (m, 2H), 7.51 (m, 2H), 7.60 (m, 1H), 7.85 (m, 2H), 8.24 (m, 2H); Data for syn isomer, $^1$H NMR δ 1.24 (d, $J = 5.2$ Hz, 3H), 3.69 (s, OH), 3.86 (m, 1H), 5.38 (d, $J = 2.5$ Hz, 1H), 7.58 (m, 2H), 7.66 (m, 2H), 7.71 (m, 1H), 7.81 (m, 2H), 8.31 (m, 2H); $^{13}$C NMR δ 12.4, 16.5, 46.9, 47.9, 67.4, 73.7, 123.9, 124.1, 127.3, 127.8, 128.3, 128.4, 128.8, 128.9, 129.2, 129.4, 134.3, 134.4, 136.4, 136.6, 137.5, 149.6, 150.1, 204.8, 205.6.

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References


