Asymmetric Organocatalytic Synthesis of β-Hydroxyynones with a Quaternary Carbon Center under Aqueous Conditions

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A reação aldólica direta de metil inonas não-modificadas sob condições aquosas catalisada pela amina terciária quiral de tiouréia é descrita. Este procedimento evitou a reação retroaldólica dos produtos β-hidroxinonas, e admite as isatinas (1H-indol-2,3-diona) e os menos ativos ésteres α-ceto acíclicos como aceptores, oferecendo um arranjo estruturalmente diverso de β-hidroxinonas tendo um centro de carbono quaternário, com rendimentos de moderado a bom e enancioseletividade.

The chiral tertiary amine thiourea catalyzed direct aldol reaction of unmodified methyl ynones under aqueous conditions is described. This procedure avoided the retro-aldol reaction of the β-hydroxyynone products, and tolerated both the isatin (1H-indole-2,3-dione) and the less active acyclic α-keto esters as acceptors, affording a structurally diverse array of β-hydroxyynones bearing a quaternary carbon center with moderate to good yields and enantioselectivities.

Keywords: β-hydroxyynones, chiral thiourea, aldol reaction, aqueous condition

Introduction

Enantioriched β-hydroxyynones are highly functionalized building blocks for the synthesis of biologically active compounds and natural products, such as fostriecin1 and maitotoxin.2 Although the aldol reaction is the most efficient way to construct β-hydroxy carbonyl structures, the β-hydroxyynone products are usually synthesized via the addition of alkynyllithium or alkynylmagnesium halide to the corresponding β-hydroxylated Weinreb amides.3-12 This is due to the fact that ynones are good Michael acceptors and the ynone-derived β-hydroxy ketones tend to undergo retro-aldol reactions.13,14 Thus, direct catalytic asymmetric aldol reactions involving ynones are highly desirable. In 2004, Trost et al.13 reported the first enantioselective aldol additions of methyl ynones to α-ketal aldehydes using a chiral dinuclear zinc catalyst. Subsequently, Silva et al.14 found that proline derived sulfonamide could efficiently catalyze the aldol reaction of the methoxymethyl ether (MOM)-protected ynones and aldehyde with good yields and enantioselectivities.14 However, the unmodified simple methyl ynones are not good substrates under proline-sulfonamide catalysis conditions with low yields because of several side products.14 More importantly, no example of the asymmetric catalytic synthesis of β-hydroxyynones resulting in a quaternary carbon center has been reported. Since List et al.15 reported the proline catalyzed cross-aldol reaction between ketones and aldehydes,15 many amine derivatives such as proline-amide type catalysts16-18 have been developed for such transformations,19-22 being most of which based on the enamine-activation mechanism.19-22 However, in comparison with simple ketones, the formation of enamine intermediates with primary or secondary amine catalysts and inactive unmodified ynones remains a great challenge. Based on the fact that DABCO can efficiently catalyze the direct aldol reaction between simple methyl ynone and isatin (1H-indole-2,3-dione) in our pilot experiment, it was envisioned the developing of the chiral tertiary amine catalysts in order to realize this asymmetric transformation. During the preparation of this study, Guo et al.23 and Allu et al.24 reported chiral tertiary amine thiourea and urea catalyzed enantioselective aldol reactions of ketones with excellent results. Herein, we report our preliminary results with chiral tertiary amine thiourea25 catalyzed direct aldol reactions of methyl ynones, affording β-hydroxyynones with a quaternary carbon center under aqueous conditions26 with moderate to good yields and enantioselectivities (Figure 1).
Results and Discussion

The organocatalyzed asymmetric aldol reactions between simple ketones or aldehydes and isatins have been intensely studied, as these chiral 3-alkyl-3-hydroxyindolin-2-one products are important building blocks in both natural products and medicinal compound syntheses. However, the asymmetric aldol reactions between ynones and isatins remain a synthetic challenge since the products tend to undergo retro-aldol reaction in organic solvents. For example, 42% of product 4a converted to starting materials after stirring with 20 mol% DABCO in CH$_2$Cl$_2$ for 24 h, and a similar result was obtained when CHCl$_3$ was used as solvent. Moreover, ynones have the ability to act as both electrophile and nucleophile under certain conditions, such as base catalysis. Initially, our investigation began with the reaction of ynone 1a with N-butyl substituted isatin 2a by using 20 mol% of DABCO as the catalyst. To our delight, the reaction catalyzed by DABCO gave the desired product with 80% yield in 3 days at room temperature in CHCl$_3$. Several solvents were then tested (Table 1, entries 1-6), and water was found to dramatically enhance the reaction rate with 88% yield in 1 h (Table 1, entry 6). Because this β-hydroxyynone product was stable in water, it was supposed that using water as the solvent may not only increase the reaction concentration but also avoid the retro-aldol reaction.

In the sequence, it was examined the asymmetric catalytic ability of chiral thiourea catalysts (Figure 2) at 0 °C instead of water to avoid freezing (Table 1, entries 13). The reactions catalyzed by quinine and cinchonidine proceeded smoothly but with very low enantioselectivities (ee) (Table 1, entries 7-8). Better results were obtained when tertiary amine thioureas were used as catalysts (Table 1, entries 9-13). The screening studies revealed that catalyst 3e was the best choice in terms of enantioselectivity, which gave the desired product with 82% yield and 71% ee after 10 h. The variation of the group bonded to nitrogen of the isatin heterocycle did not increase the enantioselectivity (Table 1, entries 13-17). For example, N-hexyl isatin or N-phenyl isatin led to slightly lower enantioselectivities (Table 1, entries 16-17), while the use of N-methyl isatin afforded the corresponding product 4ab in relatively low ee (Table 1, entry 14), and N-Boc isatin was found inactive when used in this reaction under aqueous condition. Next, several solvents were screened at 0 °C with 5 equivalents of ynone 1a to improve the enantioselectivity (Table 2). The reactions in these screened organic solvents either led to long reaction time and low yield or decreased the enantiocontrol (Table 2, entries 1-5). Further experiments investigated the influence of additives. It was shown that salts affect the enantioselectivity. The best result was obtained when CaCl$_2$ was used as the additive, giving the desired product with 93% yield and 73% ee at 0 °C. Finally, the enantioselectivity was improved to 80% ee by cooling the reaction to −10 °C. Further cooling (−20 °C) was tried, but did not improve the enantioselectivity. The reaction was then performed on a 1 mmol scale of 2a and 5 mmol of 1a in 5 mL of solvent under the optimal conditions (Table 2, entry 13).
However, decreased enantioselectivity was observed (85% yield, 53% ee).

With the optimal reaction conditions in hand, it was then examined the scope of the direct aldol reactions between ynones and active ketones. The reactions were generally conducted in saturated CaCl₂ solution at −10 to 20 °C for 9–72 h. The results are summarized in Table 3. All of the isatins showed high reactivities and...
afforded the β-hydroxyynones containing a quaternary carbon center with excellent yields and moderate to good ees. The position of the substituent on the isatin had an obvious influence on the enantioselectivity. For example, 4-substituted isatins afforded products with low ees (Table 3, entries 2-3, 46-54% ee), while substituents at other positions on the isatin heterocycle led to higher enantioselectivities (Table 3, entries 4-11, 57-78% ee). The electronic nature of the substituents also plays an important role on the enantiocontrol. Isatins with an electron-donating group on the aromatic ring gave similar results to 2a (Table 3, entries 1, 4 and 9), whilst the presence of an electron-withdrawing group resulted in reduced enantioselectivity (such as Table 3, entry 8). Next, other ynones were also tested. Because both of the reactants are solid, the reaction involving 1b was carried out in CH$_3$CN instead of CaCl$_2$ solution, and led to the product 4ba with 53% yield and 78% ee (Table 3, entry 12). When but-3-yn-2-one 1c was used as the donor in this reaction, the racemic product was obtained (Table 3, entry 13). Notably, besides isatins, less active acyclic α-keto esters 2l-2o can also be used as substrates in this reaction under standard conditions, albeit in lower yields.

### Conclusion

In conclusion, we have developed the chiral tertiary amine thiourea catalyzed direct aldol reactions of unactivated methyl ynones, efficiently resulting in β-hydroxyynones containing a quaternary carbon center as the only product with moderate to good yields and enantioselectivities (34-98% yield, 46-80% ee). Importantly, aqueous conditions were found to not only dramatically enhancing the reaction rate, but also increase the enantioselectivity. Notably, besides isatins, less active acyclic α-keto esters can also be used as substrates in this reaction under standard conditions, albeit in lower yields.

### Experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-500 MHz spectrometer. High-resolution mass spectrometry (HRMS, Micromass GCT-MS) spectra were recorded on a P-SIMS-Gly from...
Table 3. Direct aldol reaction of ynone and active ketones

![Reaction Scheme]

<table>
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<tr>
<th>entry</th>
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<th>2</th>
<th>time / h</th>
<th>Yield of 4 / %&lt;sup&gt;e&lt;/sup&gt;</th>
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<td>2a</td>
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<td>2b</td>
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<sup>a</sup>Unless otherwise noted, reactions were carried out with 0.5 mmol of 1, 0.1 mmol of 2 and 10 mol% of catalyst 3e at −10 °C in 0.5 mL saturated CaCl<sub>2</sub> solution; <sup>b</sup>reaction was carried out in CH<sub>3</sub>CN at −5 °C; <sup>c</sup>reaction was carried out at 10 °C; <sup>d</sup>reaction was carried out at 20 °C; <sup>e</sup>isolated yield; <sup>f</sup>ee: enantioselectivity determined by chiral HPLC.

Bruker Daltonics Inc. Infrared (IR) spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. High performance liquid chromatography (HPLC) analysis was performed on a Shimadzu LC-20AT series HPLC. Chiralpak AS, AD, OD and IA were purchased from Daicel Chemical Industries, Ltd. Optical rotation data were acquired on a PolAAR 3005 automatic polarimeter. Solvents for the column chromatography were distilled before use.

General procedure for the asymmetric organocatalytic synthesis of β-hydroxyynones with a quaternary carbon center under aqueous conditions

Active ketone (0.1 mmol) and catalyst 3e (10 mol%) were added to the saturated CaCl<sub>2</sub> solution (0.5 mL) in a tube and the mixture was stirred at the corresponding temperature for 15 min, then the ynone (0.5 mmol) was
added and the resulting mixture was stirred for 9-72 h at the determined temperature (monitored by thin layer chromatography (TLC)). The reaction mixture was extracted with CH₂Cl₂ (3 × 0.5 mL) and the organic phase was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5/1-3/1) to yield pure products.

**Supplementary Information**

Supplementary data are available free of charge at [http://jbcs.sbq.org.br](http://jbcs.sbq.org.br) as a PDF file.

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**References**


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