Tetrahedron 72 (2016) 512–517

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel chiral thiourea organocatalysts for the catalytic asymmetric oxaziridination

Nan Ji, Jiani Yuan, Shanshan Xue, Junna Zhang, Wei He *

Department of Chemistry, School of Pharmacy, Fourth Military Medical University, Xi'an 710032, PR China

ARTICLE INFO

Article history:
Received 4 October 2015
Received in revised form 30 November 2015
Accepted 2 December 2015
Available online 10 December 2015

Keywords:
Asymmetric catalysis
Oxaziridination
Cinchona alkaloids
Organic catalysis

ABSTRACT

Catalytic enantioselective oxaziridination is one of the challenging reactions in the oxidation of organic molecules. In this article, a series of novel chiral thiourea moleculars were synthesized from natural *cinchona* alkaloids and primary amines. By using these molecules as organocatalysts and *m*-chloroperoxybenzoicacid (*m*-CPBA) as the oxidant, a methodology on highly enantioselective epoxidation of aldimines has been developed. Several optically active oxaziridines have been constructed in good yields (up to 95%) and moderate to excellent enantioselectivities (up to 99% ee). A plausible transition state was also proposed.

1. Introduction

Oxaziridines are pivotal building blocks in many molecules, and are often useful synthetic intermediates for the preparation of some important biologically relevant natural products.[1] In the past two decades, oxaziridine chemistry has been widely expanded into oxygen,[2] nitrogen[3] atom transfer reaction types, transition-metal-promoted rearrangements,[4] and cycloadditions.[5] Because of these potent capabilities, oxaziridines have also been applied in the total synthesis field, including in the synthesis of natural products like rabeprazole,[6] asperlicin,[7] and trigonoliimine.[8] A common way to obtain enantiopure oxaziridines includes the oxidation of chiral imines,[9] chiral camphor derivatives[10] or ketimines[11] with Oxone or *m*-CPBA. However, the approach via asymmetric synthetic oxidation to access optically active oxaziridines is more appealing.

Fortunately, several scientists have recently successfully reported their works on the catalytic enantioselective synthesis of chiral oxaziridines.[12] In 2011, the first catalytic asymmetric oxaziridination was reported by Jørgensen group using *cinchona* alkaloid-derived ether catalyst.[12a] Since then, several other groups have reported enantioselective oxaziridination involving metallic as well as purely organic catalysts. Jin found that the *cinchona* alkaloid sulfurether derivatives could catalyze the reaction to generate high yields and good enantioselectivities for some substrates.[12b] In 2012, Yamamoto reported the first Hf (IV)-catalyzed enantioselective epoxidation of *N*-tosyl imines.[12c] In 2013, Ooi employed the *P*-spiro chiral triaminoiminophosphorane and trichloroacetonitrile in a Payne-type oxidation of *N*-sulfonyl imines.[12d] Besides, in 2014, Yoon reported an elegant kinetic resolution of *N*-sulfonyl oxaziridines catalyzed by Iron.[12e] Although these successful examples have been developed by the research specialist staff noted above, efforts to apply new catalyst systems are worth further investigation.

In the organocatalysts development process, small chiral molecules bearing hydrogen bonding donors, such as chiral thiourea organocatalysts have emerged as an important and popular approach in enantioselective catalysis.[13] By applying the hydrogen bonding, thiourea group is often used to activate the electrophiles and usually plays important roles in the process of designing and building new catalysts.[14] In the past several decades, chiral thiourea organocatalysts have been applied successfully in catalytic asymmetric reactions, such as Strecker, Michael addition, aza-Henry, Baylis–Hillma, Mannich, Acyl-Pictet–Spengler and tandem reaction.[15]

Herein, we report a series of novel *cinchona* alkaloids derived thiourea catalysts and their application in the enantioselective oxaziridination.

2. Results and discussion

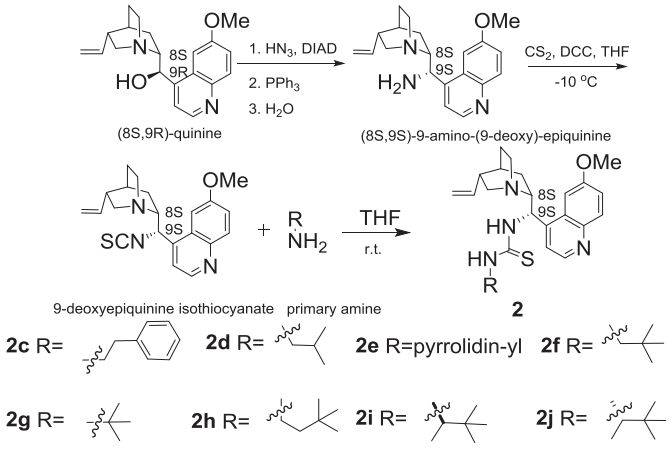
A series of modular bifunctional chiral thioureas were developed by our group recently, and the experimental results show that they could be successfully applied in the aza-Henry reaction and Michael addition.[14a] These studies prompted us to test these

* Corresponding author. Tel.: +86 29 84774470; e-mail address: weihechem@fmmu.edu.cn (W. He).

http://dx.doi.org/10.1016/j.tet.2015.12.010
0040-4020/

modular catalysts in some other catalytic asymmetric reactions. Moreover, in 2011, the work published by the Jørgensen group[12a] investigated a bifunctional hydroquinine-derived thiourea catalyst in the catalytic enantioselective oxaziridination. The results demonstrated that 95% conversion and 40% ee value of the oxaziridine was detected. The data from our repeated experiments also produced moderate results. Both of these encouraged us to test a new series of chiral thiourea organocatalysts in the catalytic enantioselective oxaziridination.

Chiral organocatalysts **2a** and **2b** were synthesized according to our previous publication,[14a] and the synthetic routes of **2c**–**j** were shown in Scheme 1. 9-amino-(9-deoxy)-epiquinine was synthesized according to the known procedure.[16] In this process, the configuration of quinine's 9-position was changed from *R* to *S*. Then the 9-amino-(9-deoxy)-epiquinine was reacted with CS_2 and DCC in THF to obtain the isothiocyanate intermediate, followed by treatment of the isothiocyanate with the corresponding primary amines. Chiral organocatalysts **2c**–**2j** were obtained in good yields (71–82%).



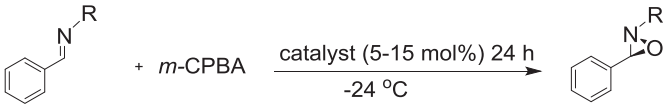
Scheme 1. General synthetic route for organocatalysts **2c**–**j**.

Compounds **2a**–**2b** were initially tested in the oxaziridination of *N*-tosyl benzaldimine with *m*-CPBA (Table 1), and the results were not satisfactory, with only around 10% ee value detected (Table 1, entries 1, 2). After the catalysts were structurally modified to generate a better catalytic effect through the replacement of the chiral alkamine parts with some common primary amines, the new catalysts **2c**–**2e** were developed. The ee value was increased substantially during model reaction (Table 1, entries 3–5) (see Fig. 1).

Based on the observation from the structures of catalysts **2c**, **2d**, and **2e**, we discovered that the ee value was influenced by the steric hindrance of the primary amine and the length of the carbon chain. Therefore, the new catalysts **2f**–**2h** were synthesized for testing. When catalyst **2f** was applied into the reaction, 69% ee value was observed with good yield (Table 1, entry 6). When **2f** loading was decreased to 12 mol %, the ee value was maintained with minimal decrease in yield (Table 1, entry 11). The *N*-*p*-nitrobenzenesulfonyl benzaldimine and *N*-methanesulfonyl benzaldimine were also tested, and the results indicated that the *N*-tosyl benzaldimine was more suitable for this catalytic system (Table 1, entries 14, 15). There was no significant outcome, whether implementing a longer carbon chain amine-derived catalyst like **2h** (Table 1, entry 8), or a shorter carbon chain amine-derived catalyst like **2g** in this reaction (Table 1, entry 7).

Catalysts **2i**–**2j** were synthesized to further test whether the optical activity primary amine part could influence the

Table 1
Screening of the thiourea catalysts in the asymmetric oxaziridination



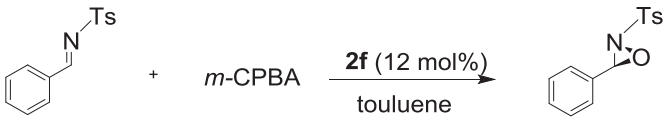
Entry[a]	R	Cat	Cat loading (mol %)	Yield[b] (%)	Ee[c] (%)
1	Ts-	**2a**	15	75	11
2	Ts-	**2b**	15	80	5
3	Ts-	**2c**	15	83	42
4	Ts-	**2d**	15	80	57
5	Ts-	**2e**	15	88	38
6	Ts-	**2f**	15	85	69
7	Ts-	**2g**	15	82	60
8	Ts-	**2h**	15	87	58
9	Ts-	**2i**	15	83	63
10	Ts-	**2j**	15	81	61
11	Ts-	**2f**	12	83	69
12	Ts-	**2f**	5	79	55
13	Ts-	**2k**	12	80	−62
14	Ns-	**2f**	12	76	51
15	Ms-	**2f**	12	55	35

[a] All reaction were performed with **1a** (0.20 mmol), *m*-CPBA (0.24 mmol) and catalyst **2** (5–15 mol %) in toluene (2 mL) at −24 °C. Ts-=*p*-toluenesulfonyl. Ns-=*p*-nitrobenzenesulfonyl. Ms-=methanesulfonyl.
[b] Isolated yield; reaction for 24 h.
[c] Enantiomeric excess of **3a**, determined by chiral HPLC analysis using Chiralcel OD-H column. Absolute configuration was established by comparing with the literature data.[12a]

configuration of the product. The experimental results demonstrated that the primary amine exert little effect on the absolute configuration of the product (the configuration was not changed). Also the ee value and yield were not influenced significantly by either catalyst derived from primary amine bearing *R*, or *S* configuration (Table 1, entries 9, 10). Catalyst **2k**, which was derived from quinidine gave the opposite enantiomer as the major product, but with a lower ee value (Table 1, entry 13). These results indicate that the absolute configuration of the oxaziridines was determined by *cinchona* skeleton. In the end, catalyst **2f** was chosen to catalyze this reaction, on which further condition optimization was based.

Temperatures were also tested for the reaction, and the results are shown in Table 2. When the temperature was decreased from −24 °C to −40 °C, the ee value increased (Table 2, entries 1, 2). When the reaction temperature reached −55 °C, the de-escalation of the yield was obvious; at the same time the ee value did not increase (Table 2, entry 3). When the temperature reached −78 °C,

Table 2
Effects of concentration and temperature on the **2f** catalyzed asymmetric oxaziridination of *N*-tosyl benzaldimine



Entry[a]	Temp (°C)	Conc (M)	Yield[b] (%)	Ee[c] (%)
1	−24	0.10	83	69
2	−40	0.10	81	75
3	−55	0.10	73	71
4	−78	0.10	55	7
5	−40	0.05	85	85
6	−40	0.15	80	70

[a] Reactions were carried out on varied content of **1a** in toluene with catalyst **2f** (12 mol %) and *m*-CPBA (1.2 equiv) in different reaction temperatures.
[b] Isolated yield; reaction for 24 h.
[c] Enantiomeric excess of **3a**, determined by HPLC on a Chiralcel OD-H column.