Tetrahedron Letters 56 (2015) 4819–4823

Contents lists available at ScienceDirect

Tetrahedron Letters

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

One-pot organocatalytic enantioselective Michael addition and aza-cyclization/dehydration cascade reaction strategy: asymmetric synthesis of highly functionalized 1,4-dihydroquinolines

Hanna Kim, Sung-Gon Kim *

Department of Chemistry, Kyonggi University, 154-42 Gwanggyosan-ro, Yeongtong-gu, Suwon 443-760, Republic of Korea

ARTICLE INFO

Article history:
Received 28 April 2015
Revised 10 June 2015
Accepted 24 June 2015
Available online 2 July 2015

Keywords:
Asymmetric catalysis
Cascade reaction
1,4-Dihydroquinoline
Michael reaction
Organocatalysis

ABSTRACT

A methodology for the synthesis of enantioenriched, highly functionalized 1,4-dihydroquinolines has been developed on the basis of the enantioselective Michael addition of β-keto esters with *N*-protected-2-amino-β-nitrostyrenes using an organocatalyst followed by in situ aza-cyclization/dehydration cascade reaction. Asymmetric catalytic reactions using quinine-derived squaramide as an organocatalyst afforded the desired 1,4-dihydroquinolines in good yields and with excellent enantioselectivities (up to 95.8:4.2 er).

Introduction

In recent years, the organocatalytic cascade reaction is one of the thriving areas in organic chemistry. Due to advantages such as atom economy, operational simplicity, and high reaction efficiency, organocatalytic cascade reaction has been widely applied as a highly efficient and powerful method for the synthesis of molecules with significant structural complexity.[1] In particular, this methodology is applied for the generation of useful, highly functionalized, and enantioenriched building blocks containing multiple stereogenic centers for the synthesis of natural products and biologically active compounds.

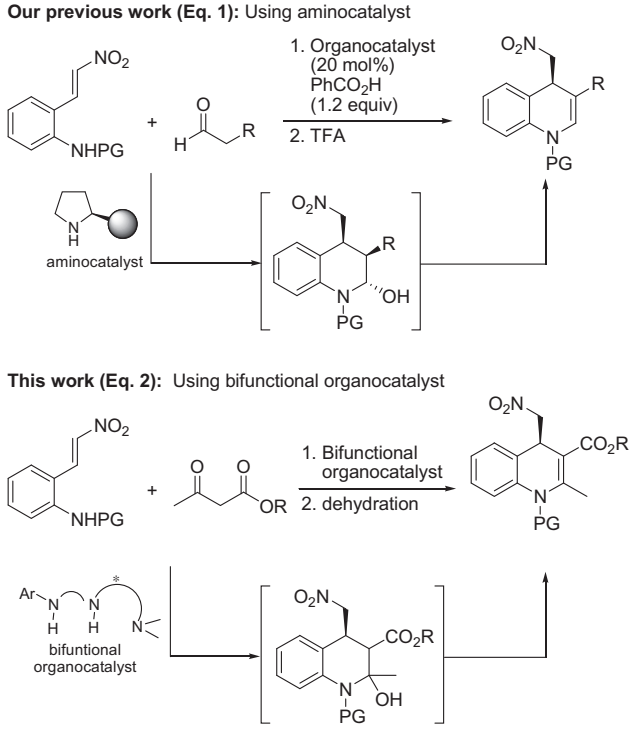
Hydroquinoline is a prevalent heterocyclic structural unit in biologically active natural products and pharmaceutical substances.[2] In particular, chiral hydroquinoline is ubiquitously present as the structural core in several natural products and pharmaceuticals, which exhibit a broad range of biological activities such as anti-HIV, antibacterial, antifungal, antimalarial, antitumor, and cardiovascular effects.[3] In view of the importance of chiral hydroquinoline derivatives, there is an urgent requirement to develop efficient approaches for the synthesis of chiral hydroquinoline scaffolds, and numerous synthetic methods have been developed.[4] However, although 1,2- and 1,4-chiral dihydroquinoline are important pharmaceutical scaffolds and synthetic intermediates for natural product synthesis,[5] asymmetric methods to synthesize these scaffolds have not been extensively explored.[6,7]

Hence, we have focused our attention on developing an efficient enantioselective method for synthesizing chiral 1,4-dihydroquinolines. Herein, we report a new one-pot method to synthesize chiral 1,4-dihydroquinolines by an asymmetric Michael addition of β-keto esters with *N*-protected-2-amino-β-nitrostyrenes using an organocatalyst followed by in situ aza-cyclization/dehydration cascade reaction.

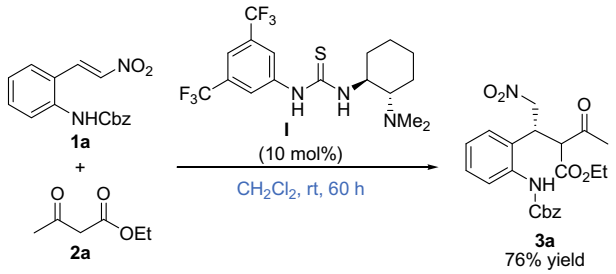
Recently, we have reported an effective approach to the asymmetric synthesis of 3,4-disubstituted 1,4-tetrahydroquinoline derivatives, in which enantioenriched tetrahydroquinolines were obtained by the Michael addition/aza-cyclization cascade reaction of aldehydes with 2-amino-β-nitrostyrenes using diphenylprolinol TMS ether as the organocatalyst with excellent diastereo- and enantioselectivities. Following dehydration, 3,4-disubstituted 1,4-dihydroquinolines were obtained in high yields (Scheme 1, Eq. 1).[8] To investigate the asymmetric synthesis of highly functionalized 1,4-dihydroquinolines via an organocatalytic reaction, we considered the reaction of 2-amino-β-nitrostyrene with a β-keto ester to afford a chiral 2,3,4-trisubstituted dihydroquinoline (Scheme 1, Eq. 2). Unlike the previous method where an aminocatalyst was used for the activation of the aldehyde through the iminium intermediate, a bifunctional organocatalyst is used as the catalyst herein, and the dual activation of 2-amino-β-nitrostyrene

* Corresponding author. Tel.: +82 31 249 9631; fax: +82 31 253 1165.
E-mail address: sgkim123@kyonggi.ac.kr (S.-G. Kim).

http://dx.doi.org/10.1016/j.tetlet.2015.06.071
0040-4039/



Scheme 1. Asymmetric synthesis of 1,4-dihydroquinolines via Michael/aza-cyclization cascade/dehydration strategy.



Scheme 2. Organocatalytic Michael addition using thiourea catalyst **I**.

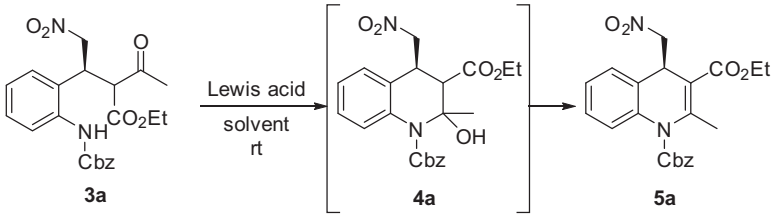
and a β-keto ester triggers the reaction. Although organocatalytic Michael addition reactions of 1,3-dicarbonyl compounds to nitroalkenes have been extensively explored,[9] to the best of our knowledge, their application for the synthesis of 1,4-dihydroquinolines has not been previously reported.

Results and discussion

We initiated the investigation of the reaction between *o*-*N*-Cbz-amino-β-nitrostyrene (**1a**) and ethyl 3-oxobutanoate (**2a**) using 10 mol % of the Takemoto bifunctional thiourea catalyst **I**[10] (Scheme 2). When the reaction was conducted in CH_2Cl_2 at room temperature, the Michael adduct **3a** was obtained in 76% yield. The desired tetrahydroquinolin-2-ol **4a** did not appear in this reaction condition. And the formation of any other tetrahydroquinolinone or dihydroquinoline was not observed, as might have been expected. Hence, we planned to directly synthesize 1,4-dihydroquinoline **5a** having one stereocenter, and envisioned that Lewis acid would not only activate the ketone functional group in **3a** to facilitate the ring formation, but also catalyze the dehydration of tetrahydroquinolin-2-ol **4a** to yield 1,4-dihydroquinoline **5a**. The reaction conditions for the aza-cyclization/dehydration of **3a** were screened for the synthesis of **5a**. According to our previous results,[8] **3a** was treated with TFA, and the desired dihydroquinoline **5a** was observed in 44% yield (Table 1, entry 1). Moreover, after the screening of several reaction conditions, we found that the optimal conditions for the aza-cyclization/dehydration cascade reaction of **3a** were as follows: boron trifluoride diethyl etherate (1.2 equiv) at room temperature (Table 1, entry 8).

We also screened the bifunctional alkaloid organocatalysts (Fig. 1) for their ability to promote the enantioselective Michael addition and aza-cyclization/dehydration cascade reaction of **1a** with **2a** for asymmetric the synthesis of **5a**. For this purpose, the reaction performed in CH_2Cl_2 using **1a** (1 equiv) and **2a** (1.5 equiv) with 10 mol % of the catalyst. Dehydration was conducted without purification of the produced Michael adduct **3a** after the complete consumption of **1a**, and the presence of the **3a** was confirmed by TLC. The results revealed that the catalysts exhibit considerably different activity and stereoselectivity for the reaction. The Takemoto bifunctional thiourea catalyst **I** afforded the product in moderate yield (41%) and with er value of 11:89 after 60 h for the first step (Table 2, entry 1). Meanwhile, cinchona-derived

Table 1
Screeening of aza-cyclization/dehydration conditions for the synthesis of dihydroquinoline **5a**[a]



Entry	Lewis acid	Additive	Temp	Solvent	Time (h)	Yield[b] (%)
1	TFA (2 equiv)	—	Rt	CH_2Cl_2	24	44
2	TFA (2 equiv)	$MgSO_4$ (10 equiv)	rt	CH_2Cl_2	24	55
3	TFA (2 equiv)	$MgSO_4$ (10 equiv)	rt	CH_2Cl_2	24	64
4	TCA (3 equiv)	$MgSO_4$ (10 equiv)	rt	CH_2Cl_2	24	46
5	PTSA (20 mol %)	$MgSO_4$ (10 equiv)	100 °C	Toluene	2	78
6	PTSA (20 mol %)	—	100 °C	Toluene	2	73
7	PTSA (20 mol %)	—	50 °C	Toluene	24	25
8	$BF_3{\cdot}OEt_2$ (1.2 equiv)	—	rt	CH_2Cl_2	2	72

[a] All of the reactions were carried out in solvent (0.1 M) with **3a** (0.10 mmol) in the presence of Lewis acid.
[b] Isolated yield after chromatographic purification.