Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 21 (2010) 167–170
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Synthesis of chiral dihydrofuran compounds by thiourea derivatives-catalyzed ''interrupted'' Feist-Bénary reaction

Hui Chen [a], Ru Jiang [a], Qiao Feng Wang [a], Xiao Li Sun [a], Jing Luo [b], Sheng Yong Zhang [a,*]

[a] *Department of Chemistry, Fourth Military Medical University, Xi'an 710032, China*
[b] *Department of Shannxi Institute for Food and Drug Control, Xi'an 710061, China*

Received 25 June 2009

Abstract

In this study, six thiourea derivatives of cinchona alkaloids with 9-nat or 9-epi-configuration were synthesized. After characterized the structures, we adopted them to the asymmetric ''interrupted'' Feist-Bénary (IFB) reaction of α-haloketones with β-dicarbonyl compounds, to give optically active dihydrofurans. Various thiourea derivatives as organocatalysts were examined. The corresponding chiral hydroxyl dihydrofurans have been obtained in excellent yields and moderate *ee*s. To the acyclic substrate, we obtained exciting and promising result.

Keywords: ''Interrupted'' Feist-Bénary (IFB) reaction; Chiral; Thiourea; Dihydrofuran

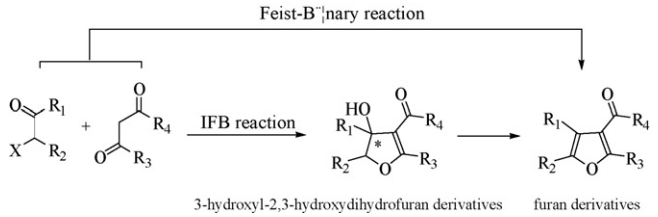
The preparation of 2,3-dihydrofuran-containing molecules has been promising in organic synthesis as a result of their broad application to organic and medicinal chemistry [1]. The ''interrupted'' Feist-Bénary (IFB) reaction of α-haloketones with β-dicarbonyl compounds serves as a powerful synthetic method in this area of dihydrofuran chemistry [2,3]. To date reports of this reaction are sparse [4], while an asymmetric version of this reaction would furnish enantiomerically enriched adducts. A great deal of effort has been directed toward the research of this reaction (Scheme 1).

Recently, we have disclosed an organo-catalytic enantioselective approach for the IFB reaction in high yields (91–98%) with up to 96% *ee* [5–7]. The ester derivatives of cinchona alkaloids were found to present good asymmetrically catalytic activities. However, they had poor chiral induce to acyclic substrates (2–21% *ee*). Enantiomerically products from acyclic β-dicarbonyl compounds are more valuable chemicals in their own right. They serve as starting materials in the preparation of a wealth of enantiomerically pure pharmaceuticals, and many other types of chiral compounds [2,3].

In our continuing effort, we wish to describe our investigation which has led to the development of an efficient method for carrying out enantioselective IFB reactions by using cinchona alkaloid thiourea derivatives. In addition, a family of chiral thiourea catalysts had been previously identified to catalyze enantioselective reactions [8,9]. Intrigued

* Corresponding author.
E-mail address: syzhang@fmmu.edu.cn (S.Y. Zhang).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.10.012



Scheme 1. IFB reaction.

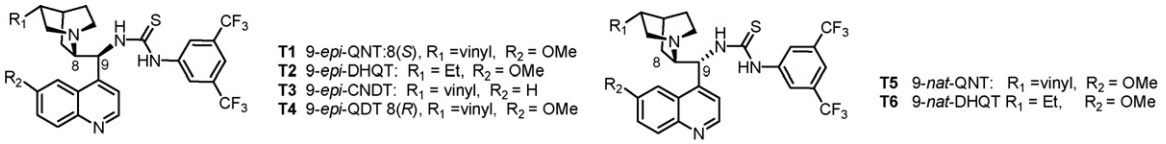


Fig. 1. Structures of **T1**–**T6**.

by the possibility that these compounds might constitute an emerging class of privileged enantioselective catalysts, we investigated their activity in the asymmetric IFB reaction. The structures of the organocatalysts are listed below (Fig. 1).

1. Results and discussion

To test their catalytic ability to promote asymmetric IFB reaction, a reaction between ethyl bromopyruvate **1**(R = H) and 1,3-cyclohexadione **2** in the presence of 10 mol% catalyst in THF at −78 °C was carried out. The results reveal that the organocatalyzed processes proceeded smoothly (10 min) in high yields (>90%). Among the organocatalysts probed, natural configuration derivatives of **T5**–**T6** displayed lower enantioselectivity than that of epi-configuration **T1**–**T4** (Table 1, entries 5, 6 vs. entries 1–4). The change of 9-configuration did not enhance the asymmetric induce, but decreased it (Scheme 2).

The catalytic activities of the β-substituted substrates were tested. Two stereogenic centers formed in these reactions, leading to two pairs of enantiomers. With β-phenyl ethyl bromopyruvate (R = Ph) as the substrate, the two pairs of enantiomers (*R*,*S*)−/(*S*,*R*)− and (*R*,*R*)−/(*S*,*S*)− were obtained, and the (*R*,*S*)−/(*S*,*R*)−configuration was the main product (Table 1, entries 7–12). In case of natural configuration derivatives **T5**–**T6**, a drop in the *ee* was noticed (entries 11, 12), which is similar to the previous IFB reaction result in entries 1–6 (R = H).

Table 1
IFB reaction results of **1** and **2** using different catalysts[a].

Entry	Cat*	R	syn:anti[b]	Yield (%)[c]	%*ee* (*syn*)[c]	Entry	Cat*	R	syn:anti[b]	Yield (%)[c]	%*ee* (*syn*)[c]
1	**T1**	H	–	91	58 (*S*)	10	**T4**	Ph	64:36	93	55
2	**T2**	H	–	92	65 (*S*)	11	**T5**	Ph	84:16	89	5
3	**T3**	H	–	94	55 (*S*)	12	**T6**	Ph	78:22	90	26
4	**T4**	H	–	94	45 (*R*)	13	**T1**	Pr	93:7	92	48
5	**T5**	H	–	92	36 (*S*)	14	**T2**	Pr	96:4	92	53
6	**T6**	H	–	94	7 (*S*)	15	**T3**	Pr	94:6	91	47
7	**T1**	Ph	81:19	89	56	16	**T4**	Pr	95:5	90	70
8	**T2**	Ph	79:21	92	59	17	**T5**	Pr	95:5	91	10
9	**T3**	Ph	85:15	93	55	18	**T6**	Pr	97:3	90	4

Cat*: thiourea catalyst.
[a] The reactions were carried out using 10 mol% catalysts at −78 °C in THF.
[b] Isolated yield.
[c] Determined by HPLC analysis.