Tetrahedron Letters 59 (2018) 2418–2421

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Enantioselective α-chlorination of β-keto esters and amides catalyzed by chiral imidodiphosphoric acids

Xukai Guan[a], Dong An[a], Guofeng Liu[a], Heng Zhang[a], Jigang Gao[a], Tianyun Zhou[a], Guangliang Zhang[a,*], Suoqin Zhang[a,b,*]

[a] College of Chemistry, Jilin University, Changchun 130012, PR China
[b] Key Laboratory for Molecular Enzymology and Engineering of Ministry of Education, Jilin University, Changchun 130012, PR China

ARTICLE INFO

Article history:
Received 8 March 2018
Revised 6 May 2018
Accepted 11 May 2018
Available online 12 May 2018

Keywords:
Asymmetric synthesis
Enantioselectivity
α-Chlorinated β-indanone esters and amides
Brønsted acid
Organocatalysis

ABSTRACT

Chiral imidodiphosphoric acids were employed as catalysts for the enantioselective α-chlorination of β-keto esters and amides using NCS as the chlorine source, providing a series of optically active products with good to high enantioselectivities (74–95% ee) and excellent yields (92–99%). This represents the first report of the Brønsted acid catalyzed enantioselective α-chlorination of cyclic β-keto derivatives.

Introduction

Due to the pharmaceutical activity of optically active halogen-containing molecules, as well as their ability to serve as the linchpin for further stereospecific manipulations, the enantioselective construction of carbon-halogen bonds has gained significant attention in modern organic synthesis, drug discovery and material sciences over the past decades.[1] Since Togni and co-workers disclosed the first example of the asymmetric α-chlorination of β-keto esters with an isolated chiral Ti-(TADDOLato) catalyst in 2000,[2] extensive efforts have been devoted to this area.[3] Regarding metal-mediated approaches, the catalytic systems employed include a series of Lewis acidic Cu(II), Pd(II), Ni(II), Cu(I), Co(II) or Zn(II) species accompanied by the corresponding chiral ligands.[4] The results were altered with substrate variations and the field has developed gradually. Other catalytic systems such as VAPOL phosphates were also applied in the asymmetric chlorination of 3-substituted oxindoles.[5]

Organocatalytic strategies for the asymmetric synthesis of α-chloro-β-keto esters have also been developed but remain rarely reported. In 2005 Melchiorre and co-workers reported the first organocatalytic asymmetric α-halogenation of 1,3-dicarbonyl compounds using benzoylquinine as the catalyst.[6] Good to high enantioselectivities (80–96%) were obtained. In 2009 Feng and co-workers described the chiral *N,N′*-dioxide catalyzed enantioselective α-chlorination of β-keto esters using NCS as the chlorine source.[7] A series of six-membered cyclic β-keto esters with aromatic rings were obtained in high enantioselectivities (90–98%) with excellent yields (99%). One year later Díaz-de-Villegas and co-workers applied chiral amino diol derivatives in the enantioselective α-chlorination of β-keto esters.[8] Other organic catalysts such as chiral diterpenoid alkaloid derivatives and diamino methylenemalononitrile were subsequently described in recent years.[9] To the best of our knowledge, there are no chiral-acid organic catalysts reported in this field.[10]

Chiral imidodiphosphoric acids, which have a rigid chiral microenvironment due to the two chiral scaffolds, have been identified for their efficiency and ability to control the stereochemistry in many highly asymmetric transformations.[11] In this work, we applied this type of catalyst in the enantioselective α-chlorination of β-keto esters and amides.

Results and discussion

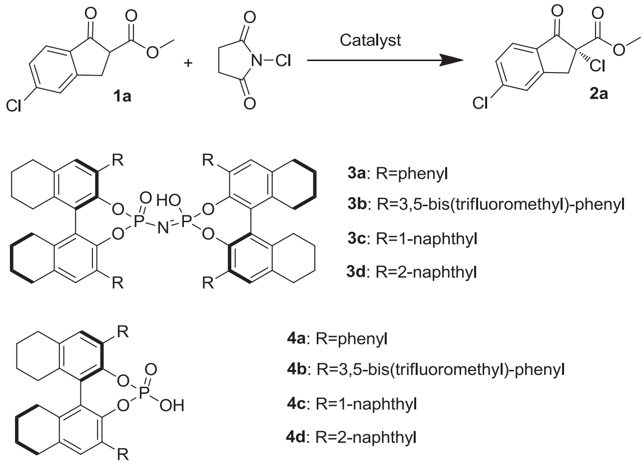
Initially, we examined the background reaction between β-keto ester **1a** and NCS in toluene at 15 °C, as well as the H_8-BINOL type chiral imidodiphosphoric acid catalysts **3a–d** (2 mol%) under the same conditions (Table 1). Among them, catalyst **3b** with 3,5-bis-

---

* Corresponding authors at: College of Chemistry, Jilin University, Changchun 130012, PR China.
E-mail addresses: zhgl_jl@jlu.edu.cn (G. Zhang), suoqin@jlu.edu.cn (S. Zhang).

https://doi.org/10.1016/j.tetlet.2018.05.024
0040-4039/

Table 1
Optimization of the reaction conditions.[a]



Entry	Cat.	Solvent	T [°C]	Time	Yield[b] [%]	ee[c] [%]
1	–	Toluene	15	<10 min	90	0
2	**3a**	Toluene	15	5 min	99	−13
3	**3b**	Toluene	15	5 min	99	23
4	**3c**	Toluene	15	5 min	99	0
5	**3d**	Toluene	15	5 min	99	0
6	**4a**	Toluene	15	5 min	99	0
7	**4b**	Toluene	15	5 min	99	5
8	**4c**	Toluene	15	5 min	99	3
9	**4d**	Toluene	15	5 min	99	2
10	**3b**	CH_2Cl_2	15	5 min	99	31
11	**3b**	CCl_4	15	5 min	99	34
12	**3b**	THF	15	5 min	99	78
13	**3b**	Acetone	15	5 min	99	50
14	**3b**	1,4-dioxane	15	5 min	99	77
15	**3b**	THF	0	30 min	99	82
16	**3b**	THF	−20	4 h	99	85
17	**3b**	THF	−40	10 h	99	75
18	**3b**	THF	−20	4 h	99	86[d]
19[g]	**3b**	THF	−20	4 h	99	88[e]
20	**3b**	THF	−20	5 h	99	84[f]

[a] Reagents and conditions: **1a** (0.1 mmol, 1.0 equiv.), NCS (0.11 mmol, 1.1 equiv.), catalyst (2 mol%), solvent (1.0 mL).
[b] Isolated yield.
[c] Determined by HPLC analysis with a Daicel ChiralPak OD-H column.("−" : *S*, "+" : *R*).
[d] Catalyst loading 5 mol%.
[e] Catalyst loading 10 mol%.
[f] Reagents and conditions: **1a** (1 mmol, 1.0 equiv.), NCS (1.1 mmol, 1.1 equiv.), catalyst (10 mol%), solvent (10 mL).
[g] The configuration of **2a** and **2h** was (*R*) as determined by comparison of the rotation and HPLC reported by Ding and co-workers.4j

tri(fluoromethyl)-phenyl groups at the 3,3′-positions provided product **2a** with the (*R*) configuration (23% ee, 99% yield, entry 3). Interestingly, catalyst **3a** with phenyl groups at the 3,3′-positions provided product **2a** with the (*S*) configuration compared to the other catalysts (13% ee, 99% yield, entry 2). Disapointingly, the other two catalysts (**3c** and **3d**) both provided racemic products. Chiral phosphoric acids **4a–d** bearing the same groups as the diphosphoric acid catalysts werealso tested; the best result was 5% ee afforded by catalyst **4b** which contained the same groups at the 3,3′-positions as catalyst **3b**. Then we turned our attention to solvent screening. A moderate ee (78% ee, entry 12) was obtained when THF was employed. Other polar solvents such as acetone and 1,4-dioxane resulted in ee values of 50% and 77%, respectively. Non-polar solvents such as CCl_4 and CH_2Cl_2 did not provide good results for this reaction, giving ee values of 31% and 34%, respectively. Lowering the reaction temperature to 0 °C and −20 °C to reduce the background reaction (<10 min, entry 1) provided **2a** in 85% ee and 99% yield when the reaction was performed at −20 °C, albeit with a 4 h reaction time (Entry 16). However, further lowering the temperature to −40 °C, did not give a better result (75% ee, entry 17). The result slightly improved when the catalyst loading was increased to 5 mol% at −20 °C (86% ee, entry 18). Finally, the best result was obtained when the catalyst loading was increased to 10 mol% (88% ee, 99% yield, entry 19). The gram-scale reaction between **1a** and NCS was also performed using the optimized condition; the ee value was slightly decreased (84% ee, 99% yield, entry 20).

With the optimized conditions in hand, the substrate scope was explored (Table 2). We found that the size of the ester group had only a minor impact on the enantioselectivity (**2a**–**e**). While the sterically bulky *tert*-butyl ester **1d** gave the best result (99% yield, 95% ee), the *cyclo*hexyl ester **1e** which was expected to be a good