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Bifunctional thiophosphinamide catalyzed highly enantioselective Michael addition of acetone to (*E*)-2-azido β-nitrostyrenes and the subsequent reductive cyclization

Hao Zhang, Youming Wang, Zhenghong Zhou*

Institute and State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin, 300071, PR China

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ABSTRACT

We have proven that primary amine/thiophosphinamide incorporating (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine is an efficient catalyst for the asymmetric Michael addition of acetone to (*E*)-2-azido β-nitrostyrenes. Under the optimal reaction conditions, the corresponding Michael addition products were obtained in excellent yields with almost perfect stereocontrol. Upon treatment with $Et_3SiH/InCl_3$, the Michael addition products could be successfully converted to the related 2-methyltetrahydroquinolines in acceptable yields with moderate to excellent diastereoselectivity and without appreciable loss in optical purity. This process provides a highly enantioselective pathway for the synthesis of biologically important 2-methyltetrahydroquinoline derivatives.

1. Introduction

Among various nitrogen-containing heterocycles, the tetrahydroquinoline ring system is a fascinating and privileged structural motif and is found in various biologically active natural products and pharmacologically relevant therapeutic agents [1]. Particularly, their 2-methyl substituted analogues (2-methyltetrahydroquinolines, 2-MeTHQs) exhibit interesting biochemical activities (Fig. 1). For example, Helquinoline (**1**) is a new tetrahydroquinoline antibiotic from *Janibacter limosus* Hel 1 [2], compound **2**, a kind of CRTH2 antagonists, is beneficial for the treatment of allergic diseases [3], 1-benzenesulfonyl-2-MeTHQ (**3**) demonstrated interesting activity against *Trypanozoma cruzi* with low cytotoxicity [4], *N*-formyl-2-MeTHQ (**4**) functions as a potent EPAC inhibitor [5], I-BET726 (**5**) [6] and 1-acetyl-2-MeTHQ (**6**) [7] are selective BET bromodomain inhibitors. Moreover, as a key scaffold of a variety of phosphoramidite ligands, 2-MeTHQ also has wide application in asymmetric catalysis [8]. Due to the significance of these structural units in drug discovery, medicinal chemistry and asymmetric catalysis, the development of new methodologies for the synthesis of 2-MeTHQ derivatives will be of great importance and remains a challenging task. In contrast to the great progress made in the asymmetric synthesis of optically active THQ derivatives through either organo- or metal catalysis [9], the methodology for the asymmetric synthesis of 2-MeTHQs with high enantioselectivity has been rarely explored. Up to date, two strategies were developed for the organocatalytic asymmetric synthesis of enantiomerically enriched 2-MeTHQs, one is the chiral phosphoric acid catalyzed transfer hydrogenation of 2-methylquinolines [10], the other is an in situ generated chiral supramolecular assembly catalyst promoted asymmetric Michael addition of acetone to 2-azido nitroolefins followed by reductive cyclization [11]. However, the later protocol still suffers from some limitations in the Michael addition step, such as low catalytic activity (72 h is needed to ensure the full conversion), moderate yields (50–65%, only one example is over 90%) and unsatisfactory enantioselectivity (89–92% ee). Recently, we have proved that primary amine/thiophosphinamides are efficient catalysts to promote the Michael addition of acetone to simple [12] and *ortho*-hydroxyl nitroolefins [13] in a highly enantioselective manner. We envisioned that this type of catalyst may demonstrate great advantage over the aforementioned chiral supramolecular

* Corresponding author.
E-mail address: z.h.zhou@nankai.edu.cn (Z. Zhou).

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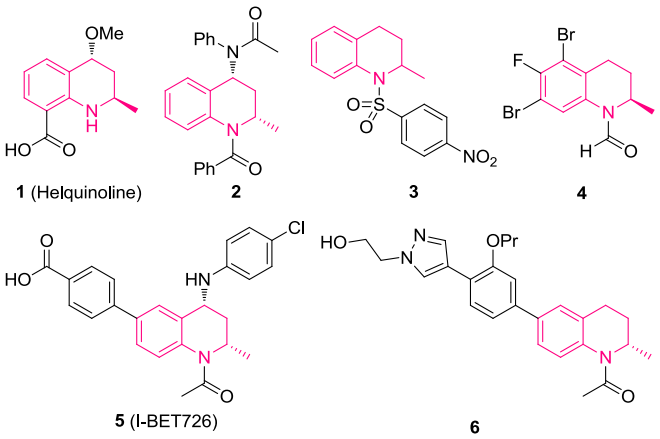


Fig. 1. 2-MeTHQ-based natural products and pharmaceuticals.

assembly catalyst in terms of both catalytic efficacy and enantioselectivity. Herein we report a stereoselective synthesis of 2-MeTHQs via primary amine/thiophosphinamide catalyzed asymmetric Michael addition of acetone to 2-azido nitroolefins and the subsequent reductive cyclization. The corresponding cyclization products were obtained in acceptable yields with good diastereoselectivities and excellent enantioselectivities (93—>99% ee).

2. Results and discussion

We started our investigation by examination of the catalytic activity and stereoselectivity of a series of bifunctional thiophosphoramide or thiophosphinamide-based primary amines **I**–**IV** (Fig. 2) in the model reaction of (*E*)-1-azido-2-(2-nitrovinyl)benzene (**7a**) and acetone in dichloromethane at 20 °C. The results are listed in Table 1.

As shown in Table 1, both the chiral diamine skeleton and substituent on phosphorus atom have an important role on the outcome of the reaction. The use of (1*R*,2*R*)-cyclohexane-1,2-diamine derived thiophosphoramide **I** as the catalyst resulted in the formation of the corresponding adduct **8a** in a quite low yield (13%) with 84% ee (entry 1). However, both the yield (53%) and enantioselectivity (95% ee) were markedly improved by employing thiophosphoramide **II** incorporating a (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine skeleton as the catalyst (entry 2 vs. entry 1). A slightly improvement in both yield and ee value were obtained by replacing the phenoxy group with either ethoxy or phenyl group (entries 3,4 vs. entry 2). Thiophosphinamide **IIc** proved to be the most promising catalyst candidate for this transformation affording the product **3a** in 61% yield with ee value of 98% (entry 4). It is worth noting that increase the rigidity of the diamine skeleton is detrimental to the reaction. The use of thiophosphinamide **III** bearing a rigid (*R*,*R*)-9,10-dihydro-9,10-ethanonanthracene-11,12-diamine scaffold resulted in sharply decrease both in yield and enantioselectivity. Additionally, the nucleophilicity of the priamary amine

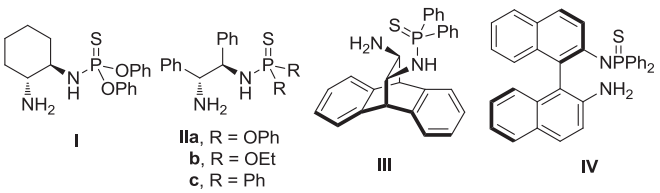
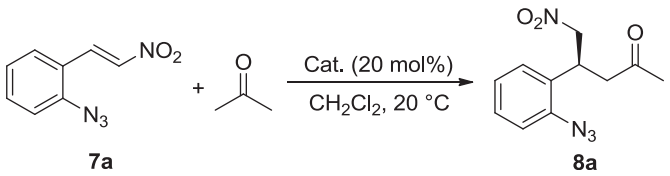


Fig. 2. Catalyst candidates.

Table 1
Catalyst evaluation.[a]



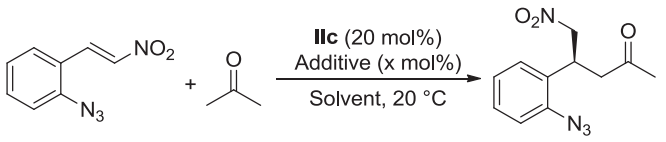
Entry	Catalyst	Time (day)	Yield (%)[b]	Ee (%)[c]
1	**I**	5	13	84
2	**IIa**	7	53	95
3	**IIb**	5.5	58	96
4	**IIc**	4	61	98
5	**III**	4	13	−12
6	**IV**	7	NR	/

[a] All of the reactions were carried out with **7a** (0.3 mmol), acetone (3.0 mmol) and the catalyst (20 mol%) in 1.5 mL of dichloromethane at 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determination by HPLC analysis with a chiral stationary phase.

also have an obvious influence on the catalytic activity. The less nucleophilic thiophosphinamide **IV** derived from (*R*)-1,1′-binaphthyl-2,2′-diamine was completely inactive in the model reaction and failed to afford product **8a**.

With the promising catalyst **IIc** in hand, other factors, such as acidic cocatalyst, solvent, catalyst loading, and reaction temperature, influencing the reaction were thoroughly investigated employing the reaction between (*E*)-1-azido-2-(2-nitrovinyl)benzene (**7a**) and acetone as the model. The results are summarized in Table 2.

Table 2
Optimization of reaction conditions.[a]



Entry	Additive (x mol%)	Solvent	Time (h)	Yield (%)[b]	Ee (%)[c]
1	–	CH_2Cl_2	96	61	98
2	PhOH (20)	CH_2Cl_2	96	40	99
3	$PhCO_2H$ (20)	CH_2Cl_2	10	95	98
4	4-$O_2NC_6H_4CO_2H$ (20)	CH_2Cl_2	72	68	98
5	4-$MeOC_6H_4CO_2H$ (20)	CH_2Cl_2	36	74	98
6	$PhCO_2H$ (5)	CH_2Cl_2	16	95	98
7	$PhCO_2H$ (1)	CH_2Cl_2	40	83	98
8[d]	$PhCO_2H$ (5)	CH_2Cl_2	16	95	98
9[e]	$PhCO_2H$ (5)	CH_2Cl_2	48	86	98
10[d]	$PhCO_2H$ (5)	THF	16	95	98
11[d]	$PhCO_2H$ (5)	Acetone	16	56	99
12[d]	$PhCO_2H$ (5)	CH_3CN	14	60	96
13[d]	$PhCO_2H$ (5)	Ether	16	37	95
14[d]	$PhCO_2H$ (5)	Hexane	20	82	99
15[d]	$PhCO_2H$ (5)	Toluene	16	95	99
16[d,f]	$PhCO_2H$ (5)	Toluene	50	83	98

[a] Unless otherwise specified, all of the reactions were carried out with **7a** (0.3 mmol), acetone (3.0 mmol) and catalyst **IIc** (20 mol%), acidic cocatalyst (x mmol %) in 1.5 mL of solvent at 20 °C.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determination by HPLC analysis with a chiral stationary phase.
[d] The catalyst loading is 10 mol%.
[e] The amount of catalyst is 5 mol%.
[f] The reaction was performed at 0 °C.

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