Tetrahedron Letters 52 (2011) 3204–3207

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Highly efficient and enantioselective Michael addition of acetylacetone to nitroolefins catalyzed by chiral bifunctional organocatalyst bearing multiple hydrogen-bonding donors

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ARTICLE INFO

Article history:
Received 9 February 2011
Revised 26 March 2011
Accepted 11 April 2011
Available online 16 April 2011

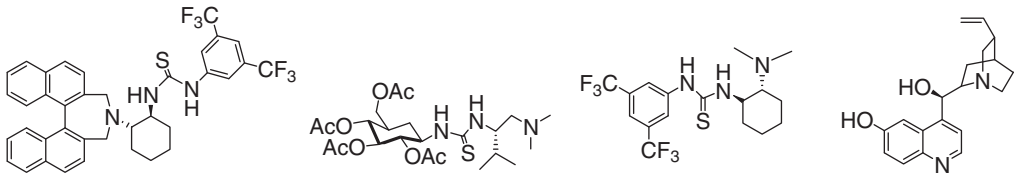
Keywords:
Michael addition
Cinchona alkaloids
Bifunctional organocatalyst
Hydrogen-bonding donor

ABSTRACT

A new efficient catalyst system for the asymmetric addition of acetylacetone to nitroolefins using a chiral bifunctional organocatalyst bearing multiple hydrogen-bonding donors was developed. When using the organocatalyst **2c** derived from natural *cinchona* alkaloid in optimal conditions, up to 98% chemical yield and 98% ee were observed with a variety of aromatic nitroolefins.

Asymmetric Michael addition of ketones/aldehydes to nitroalkenes is one of the most powerful carbon–carbon bond-forming reactions, since the resulting γ-nitrocarbonyl compounds are versatile synthetic building blocks, which can be readily converted into valuable chiral structural scaffolds.[1] In the past decades, remarkable progress has been made in developing efficient asymmetric Michael addition by using chiral metal complexes[2] and transition metal-free organocatalysts.[3] Of the development of organocatalysts, small chiral molecules bearing hydrogen bonding donors have emerged as an important and popular approach in enantioselective catalysis.[4] Chiral bifunctional organocatalysts (Fig. 1) are among the most successful organocatalysts in asymmetric Michael addition reactions,[5] since they would facilely activate the electrophile and the nucleophile simultaneously by the hydrogen bond. In many cases, catalyst loading of 15–30 mol % is usually required to achieve good isolated yields and high enantioselectivities.[6,1f,3h] Therefore, the development of highly efficient and enantioselective chiral catalysts for a broad scope of substrates at low catalyst loading is still in great demand.

As a part of our ongoing program to develop facile and effective chiral catalysts for asymmetric transformations,[7] we were interested in investigating chiral bifunctional amine–thioureas with multiple hydrogen bonding donors[8] based on the 'privilege' skeleton, *cinchona* alkaloids, which use sp^3 nitrogen of the *cinchona* alkaloids as the tertiary amine moiety to activate acetylacetone, while both the thiourea moiety and the hydroxyl group in β-amino



1a 1b 1c 1d

Figure 1. Examples of chiral bifunctional organocatalysts used for Michael addition.

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doi:10.1016/j.tetlet.2011.04.043

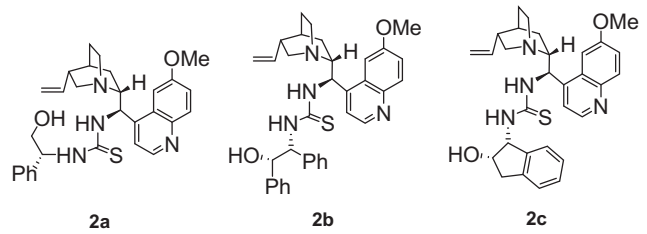
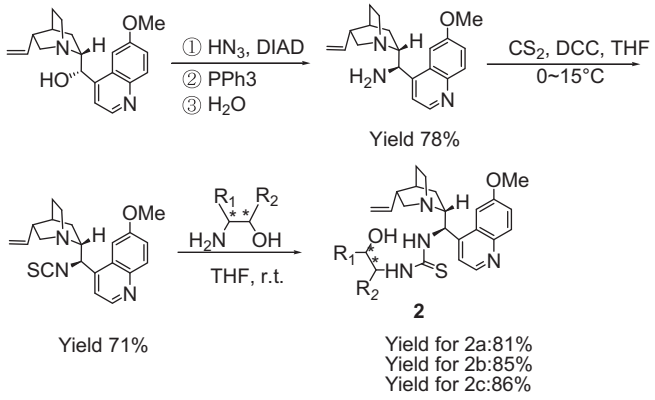


Figure 2. Chiral organocatalysts **2a–c** derived from natural *cinchona* alkaloid.



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

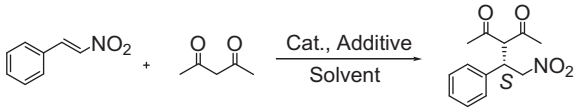
alcohol serve as the hydrogen bonding donors to activate the nitro group. We anticipate that the organocatalysts with multiple hydrogen bonding donors would show high regioselectivity and enantioselectivity in Michael addition. In this Letter, we wish to communicate our investigation on the asymmetric addition of nitroolefins to acetylacetone using bifunctional organocatalyst **2a–c** (Fig. 2) derived from natural *cinchona* alkaloid.

Chiral organocatalysts **2a–c** were synthesized from natural *cinchona* alkaloid quinine as shown in Scheme 1. 9-Amino-(9-deoxy)-epiquinine was synthesized according to the known procedure.[9] Then it was reacted with carbon disulfide and DCC in THF to obtain the isothiocyanate intermediate. The synthesis of thiourea organocatalysts **2** can be conducted by treatment of isothiocyanate with the corresponding chiral β-amino alcohol.[10,11]

When these organocatalysts **2a–c** were examined in the asymmetric Michael addition reactions between acetylacetone and a-nitrostyrene (**3a**) in CH_2Cl_2 at −30 °C for 24 h, high yields, and moderate enantioselectivities were achieved and **2c** gave the best enantioselectivities (Table 1, entries 1–3).

After selecting **2c** as the most efficient catalyst, we proceeded to investigate the influence of different experimental parameters including additive, temperature, solvent, and catalyst loading in the asymmetric Michael addition reaction. The results were also summarized in Tables 1. It has been reported that the presence of additive has a significant influence on the asymmetric reaction.[12] When using KI, KF, and NaCl as additives, both yields and ee value were inferior (Table 1, entries 4–6 vs 3). When TFA was used, the reaction became sluggish and no enantioselectivity was observed (Table 1, entry 7). As the literature reported,[13] the

Table 1
Optimization of reaction conditions for asymmetric Michael addition reactions between 1,3-carbonyl compounds (**4**) and a-nitrostyrene (**3a**)[a]



3a 4a 5a

Entry	Catalyst	Catalyst loading (mol %)	Michael donors	Additive	Solvent	Time (h)	Temperature (°C)	Yield[c] (%)	ee[d] (%)	Product config.[e]
1	2a	10	**4a**	—	CH_2Cl_2	24	−30	71	25	S
2	2b	10	**4a**	—	CH_2Cl_2	24	−30	80	15	S
3	2c	10	**4a**	—	CH_2Cl_2	24	−30	91	56	S
4	2c	10	**4a**	KI	CH_2Cl_2	24	−30	30	35	S
5	2c	10	**4a**	KF	CH_2Cl_2	24	−30	44	46	S
6	2c	10	**4a**	NaCl	CH_2Cl_2	24	−30	56	26	S
7	2c	10	**4a**	TFA	CH_2Cl_2	24	−30	10	rac	S
8	2c	10	**4a**	MS4Å[b]	CH_2Cl_2	24	−30	94	60	S
9	2c	10	**4a**	MS4Å[b]	CH_2Cl_2	15	−20	95	57	S
10	2c	10	**4a**	MS4Å[b]	CH_2Cl_2	10	0	96	51	S
11	2c	10	**4a**	MS4Å[b]	CH_2Cl_2	24	−40	90	66	S
12	2c	10	**4a**	MS4Å[b]	$CHCl_3$	24	−40	97	21	S
13	2c	10	**4a**	MS4Å[b]	Et_2O	24	−40	93	41	S
14	2c	10	**4a**	MS4Å[b]	EtOH	24	−40	75	71	S
15	2c	10	**4a**	MS4Å[b]	THF	24	−40	90	79	S
16	**2c**	**10**	**4a**	**MS4Å[b]**	**MeCN**	**24**	**−40**	**93**	**98**	**S**
17	2c	10	**4a**	MS4Å[b]	toluene	24	−40	78	31	S
18	2c	10	**4a**	MS4Å[b]	DMF	24	−40	26	9	S
19	2c	20	**4a**	MS4Å[b]	MeCN	24	−40	96	91	S
20	2c	5	**4a**	MS4Å[b]	MeCN	24	−40	91	90	S
21	2c	2	**4a**	MS4Å[b]	MeCN	24	−40	90	90	S
22	2c	1	**4a**	MS4Å[b]	MeCN	24	−40	83	85	S
23	2c	10	**4b**[f]	MS4Å[b]	MeCN	24	−40	20	10	S
24	2c	10	**4c**[g]	MS4Å[b]	MeCN	24	−40	95	75	S

[a] The Unless otherwise specified, reaction was carried out with 2 equiv of 1,3-carbonyl compounds **4** and 1 equiv of a-nitrostyrene **3a** in the presence of catalyst and additive on a scale of 0.1 mmol of **3a** in 1 mL solvent.
[b] 20 mg MS4Å.
[c] Isolated yields.
[d] Enantiomeric excess (ee) was determined by chiral HPLC analysis (Chiralpak AD–H).
[e] Absolute configuration was determined by comparison with available literature HPLC data.[14,15]
[f] **4b** is diethyl malonate.
[g] **4c** is ethyl acetoacetate.