ORGANIC LETTERS

2011
Vol. 13, No. 15
3806–3809

Highly Enantioslective Synthesis of Multisubstituted Polyfunctional Dihydropyrrole via an Organocatalytic Tandem Michael/Cyclization Sequence

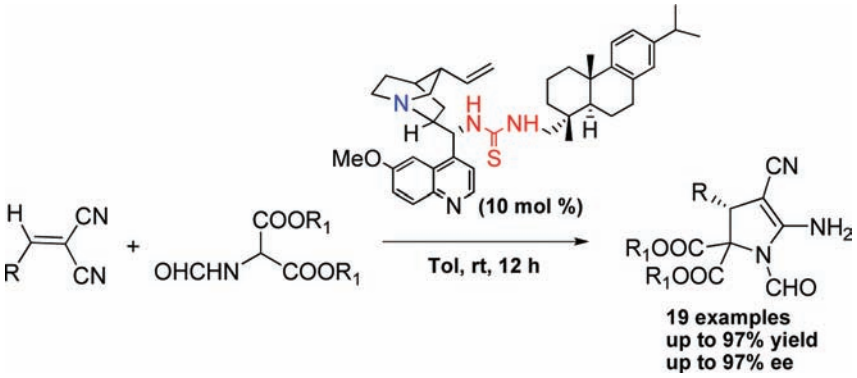
Gen Zhang,[†] Yaohu Zhang,[†] Xianxing Jiang,[†] Wenjin Yan,[†] and Rui Wang*[,†,‡]

Key Laboratory of Preclinical Study for New Drugs of Gansu Province, Institute of Biochemistry and Molecular Biology, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, China, and State Key Laboratory of Chiroscience, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong

wangrui@lzu.edu.cn

Received May 13, 2011

ABSTRACT



A unique approach to asymmetric synthesis of various optically pure multisubstituted 2,3-dihydropyrroles catalyzed by a novel rosin-derived tertiary amine−thiourea via a tandem Michael/cyclization sequence with high yield (up to 97%) and good to excellent enantioselectivities (up to 97% ee) is present. This strategy provides an efficient and convenient method to access enantioenrich nitrogen heterocycles.

Multisubstituted dihydropyrroles bearing a stereogenic center at the 3-position represent an important class of nitrogen heterocycles, which are encountered in a wide range of biologically active natural alkaloids, pharmaceutically active compounds and optoelectronic materials.[1] Optically active 2,3-dihydropyrroles, in particular, can not only be used as a versatile intermediate in the total synthesis of these active compounds but also be readily converted to valuable chiral proline and pyrrolidine derivatives.[2] As such, much effort has been devoted to the synthesis of these privileged heterocyclic motifs.[3] However,

[†] Lanzhou University.
[‡] The Hong Kong Polytechnic University.

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10.1021/ol201299u
Published on Web 07/06/2011

to date, the asymmetric catalytic approaches to construct these heterocycles in enantiomerically pure form are still surprisingly rare and less exploited.[4] Thus, the development of a fascinating and powerful strategy that allowed the rapid construction of enantioenriched and structurally diverse 2,3-dihydropyrroles is particularly appealing.

In recent years, organocatalytic[5] domino reactions where multiple carbon−carbon bond formation is carried out in a "green" process without any troublesome experimental procedures have become one of the most powerful methods for the synthesis of useful and versatile organic molecules. In contrast to the extensive and fruitful studies in this area by using α,β-unsaturated aldehydes, ketones, esters, imides, and nitroolefins as electrophiles,[6] fewer cases have been reported in which α,α-dicyanoolefins serve as the electrophiles, probably because of their high chemical reactivity.[7] Considering α,α-dicyanoolefins could be readily prepared from a simple Knoevenagel condensation of aldehydes with malononitrile,[8] the nitrile as a useful functional group could be easily transformed to other important groups such as carbonyl derivatives or imines.[9] Therefore, an organocatalytic domino reaction using α,α-dicyanoolefins as starting material could provide a direct access to optically active compounds, such as chiral multisubstituted 2,3-dihydropyrroles.

As part of our ongoing interest in developing new methods for the synthesis of useful compounds,[10] we recently succeeded in developing a novel class of bifunctional thiourea catalysis based on rosin[11] and applied it to facilitate various transformations, for instance, the Michael reaction of 1,3-dicarbonyls with nitroalkenes,[10a] aza-Henry reactions with in situ generation of *N*-Boc imines,[10b] Mannich reaction of lactones with *N*-Boc-aldimines,[10c] and aldol reaction of α-isothiocyanato imides to α-ketoesters and isatins.[10d,e] Encouraged by these successful efforts and aimed to demonstrate the efficiency and generality of this rosin-derived thiourea bifunctional catalysis, therefore, we turned our recent attention to employing this novel catalysis for the asymmetric synthesis of optically active 2,3- dihydropyrroles prepared from simple and easily available starting materials under a mild domino reaction.

Before attempting this novel strategy, we presumed its possibility for the synthesis of chiral 2,3-dihydropyrroles. We envisioned that in the presence of a chiral tertiary amine−thiourea, dibenzyl 2-aminomalonate **2** might be activated through a hydrogen bond: the nitrogen atom of the chiral tertiary amine−thiourea with the carbonyl of **2** to form the enolate intermediate[12] Then the electron-rich α-carbon atom of **2** attacks the electron-deficient cyanoolefins **1** to generate the Micheal adducts **A**, subsequently, through intramolecular cyclization of **A** to afford the cyclized adducts **B**, then through tautomerization of **C** to obtain the desired final product **3** (Scheme 1).

To explore the possibility of the proposed Michael/cyclization sequence, initially, the reaction of 2-benzylidenemalononitrile with diethyl 2-formamidomalonate was used as a model reaction, and a variety of bifunctional organocatalysts (Figure 1) were screened at room

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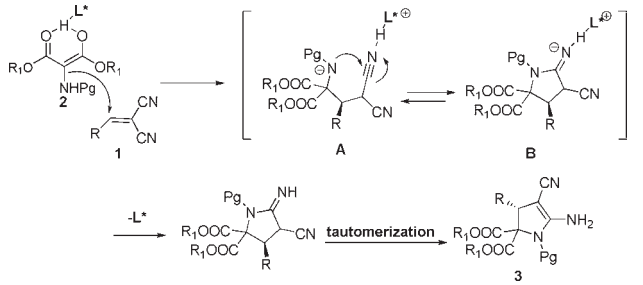
Scheme 1. Strategy for Synthesis of Chiral 2,3-Dihydropyrrole by Chiral Tertiary Amines



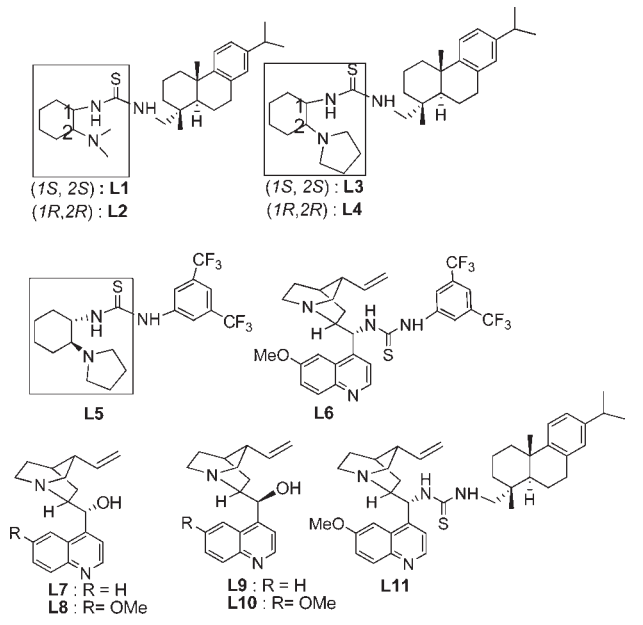


Figure 1. Organocatalysts used in this study.

temperature in toluene for the synthesis of the optically active 2,3-dihydropyrroles; the results are summarized in Table 1. It showed that the bifunctional thiourea catalysis derived from quinine amine[13] based on rosin exhibited good activity and high enantioselectivity (up to 96% ee, entry 11), while other thiourea catalyzes derived from diaminocyclohexane (entries 1−5) and cinchonine or quinine derives (entries 6−10) showed disappointing results. The optimization results of N-terminal protection groups showed that formyl is the best choice (entries 11−17).

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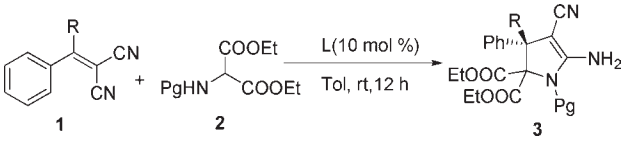
Table 1. Catalyst Screening and Optimization of Reaction Conditions[a]



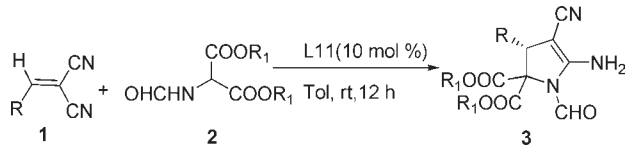
entry	catalyst	R/Pg	yield[b] (%)	ee[c] (%)
1	L1	**H/CHO**	**3a**/76	−30[d]
2	L2	**H/CHO**	**3a**/78	50
3	L3	**H/CHO**	**3a**/83	−77[d]
4	L4	**H/CHO**	**3a**/84	80
5	L5	**H/CHO**	**3a**/79	−71[d]
6	L6	**H/CHO**	**3a**/75	55
7	L7	**H/CHO**	**3a**/71	17
8	L8	**H/CHO**	**3a**/73	15
9	L9	**H/CHO**	**3a**/77	−27[d]
10	L10	**H/CHO**	**3a**/72	−23[d]
11	L11	**H/CHO**	**3a**/92	96
12	L11	**CH_3/CHO**	<10	nd[e]
13	L11	**H/H**	trace	nd[e]
14	L11	**H/Ac**	<10	nd[e]
15	L11	**H/Tos**	**3b**/70	[f]
16	L11	**H/Boc**	**3c**/74	[f]
17	L11	**H/Cbz**	**3d**/62	45

[a] Unless otherwise specified, the reaction was carried out with **1** (0.3 mmol) and **2** (0.2 mmol) in the presence of an organocatalyst **L** (0.02 mmol) in toluene (2.0 mL) at rt for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OD column. [d] The opposite configuration. [e] Not determined. [f] Not determined by chiral HPLC.

With the optimized reaction conditions in hand, we then examined the scope of the reaction for the construction of various optically active 2,3-dihydropyrroles, and the results are summarized in Table 2. In general, the reaction proceeded smoothly to afford the desired products in good yields and excellent enantioselectivities. For the reaction with diethyl 2-formamidomalonate **2a**, a wide range of substituted aromatic α,α-dicyanoolefins **1** were examined (entries 1−12). It was found that α,α-dicyanoolefins **1** with either electron-withdrawing or electron-donating groups on the phenyl ring provided good yields (81−96%) and good to excellent enantioselectivities (83−97% ee values). In addition, good results were also obtained by using 2-furyl as substituent of α,α-dicyanoolefins **1** (entry 13). Then, dibenzyl 2-formamidomalonate **2b** and dimethyl 2-formamidomalonate **2c** were used for the synthesis of desirable optically active 2,3-dihydropyrroles, and good results were also obtained (85−97% yields and 86−94% ee values, entries 15−19). The absolute configuration of products were determined to be *R* by using a single-crystal X-ray diffraction of **3m** (Figure 2).[14]

(14) CCDC808330 (**3m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.

Table 2. Asymmetric Synthesis of 2,3-Dihydropyrrole[a]



entry	R	R_1	yield[b] (%)	ee[c] (%)
1	Ph	**2a/Et**	**3a**/92	96
2	4-ClPh	**2a/Et**	**3e**/91	97
3	4-BrPh	**2a/Et**	**3f**/86	95
4	4-CNPh	**2a/Et**	**3g**/82	83
5	4-MePh	**2a/Et**	**3h**/84	90
6	4-MeOPh	**2a/Et**	**3i**/80	96
7	3-ClPh	**2a/Et**	**3j**/94	92
8	3-BrPh	**2a/Et**	**3k**/95	90
9	2-ClPh	**2a/Et**	**3l**/92	89
10	2-BrPh	**2a/Et**	**3m**/96	94
11	2-MeOPh	**2a/Et**	**3n**/83	85
12	2,5-MeOPh	**2a/Et**	**3o**/81	92
13	2-furyl	**2a/Et**	**3p**/79	78
14	Ph	**2b/Bn**	**3q**/97	94
15	4-FPh	**2b/Bn**	**3r**/93	89
16	4-ClPh	**2b/Bn**	**3s**/94	90
17	4-BrPh	**2b/Bn**	**3t**/90	86
18	Ph	**2c/Me**	**3u**/85	87
19	cyclohexyl	**2a/Et**	**3v**/62	28

[a] Unless otherwise specified, the reaction was carried out with **1** (0.3 mmol) and **2** (0.2 mmol) in the presence of an organocatalyst **L11** (0.02 mmol) and toluene (2.0 mL) at rt for 12 h. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel AD or OD column, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **3m**.

In conclusion, we have successfully developed a unique approach to an asymmetric synthesis of various optically pure 2,3-dihydropyrroles catalyzed by a novel tertiary amine–thiourea based on rosin under a tandem Michael/cyclization sequence with high yield (up to 97%) and excellent enantioslectivities (up to 97% ee). These enantioenriched products will be applied in the synthesis of chiral nitrogen heterocyclic compounds, and this simple operational, excellent enantiocontrol and broad substrate scope transformation will be potentially applied in the synthesis of other chiral nitrogen heterocycles. Further investigation on these new heterocyclic compounds is ongoing in our laboratories.

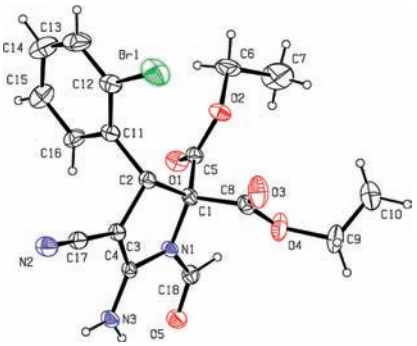


Figure 2. X-ray crystal data of compound **3m**.

Acknowledgment. We are grateful for the grants from the National Natural Science Foundation of China (20932003 and 90813012) and the Key National S & T Project "Major New Drug Development" of the Ministry of Science and Technology (2009ZX09503-017).

Supporting Information Available. Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.