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Highly Enantioseletive Biginelli Reaction Using a New Chiral Ytterbium Catalyst: Asymmetric Synthesis of Dihydropyrimidines

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Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry, and diversity-oriented synthesis.[1] The venerable Biginelli reaction, one-pot cyclocondensation of aldehyde, 1,3-ketoester, and urea or thiourea, is inarguably one of the most useful MCRs.[2] Polyfunctionalized dihydropyrimidines (DHPMs) represent a heterocyclic system of remarkable pharmacological efficiency, and many exhibit antiviral, antitumor, antibacterial, and antiinflammatory properties.[3] Notably, monastrol is the only cell-permeable molecule currently known to specifically inhibit mitotic kinesis Eg5 and is considered a lead for the development of new anticancer drugs,[4] while the (*R*)-SQ 32,926 has been identified as potent orally active antihypertensive agent (Figure 1).[3a] Several marine natural products containing the dihydropyrimidine-5-carboxylate core were found to be potent HIVgp-120-CD4 inhibitors.[5] Pharmacological studies concerning the absolute configuration at the C4 stereogenic center were well documented, and in some cases, individual enantiomers perform opposing biological activities.[3] Nevertheless, only a few examples of asymmetric synthesis of this heterocyclic target have been reported.[6] Chemical resolution and enzymatic strategies have thus far been the methods of choice to obtain optically active DHPMs.[7] Access to highly enantiomerically pure DHPMs by catalytic asymmetric synthesis is therefore of considerable current interest and a formidable task.

Lanthanide triflates ($Ln(OTf)_3$) are unique Lewis acids, which are highly effective, water-compatible, and reusable catalysts in organic synthesis.[8] Despite the synthetic utilities of $Ln(OTf)_3$, relatively few successful examples have been achieved in asymmetric syntheses using chiral lanthanide triflates as catalysts.[9] This is intrinsically due to the large radius character and the high coordination number required by the lanthanide ion, while ordinary ligands cannot provide effective environments for asymmetric induction. Herein, we describe the development of a novel chiral ytterbium catalyst and its application in enantioselective synthesis of chiral DHPMs with excellent enantioselectivities by the three-component Biginelli reaction.

In the efforts to develop an efficient catalyst for the Biginelli reaction, hexadentate chiral ligands bearing tertiary amine, phenol, and pyridine functional groups were first designed, as outlined in Scheme 1. The chiral ligands **2a** and **2b** were easily synthesized from corresponding salan compounds and 2-chloromethyl pyridine in THF/DMF under sodium hydride in the respective yields of 85% and 76%.[10] We assumed that the pyridyl groups could coordinate with the central lanthanide ion on different sides, to afford favorable stereochemical control in asymmetric catalytic process.

Initially, we investigated the Biginelli condensation of ethyl acetoacetate, benzaldehyde, and urea catalyzed by $Yb(OTf)_3$ with

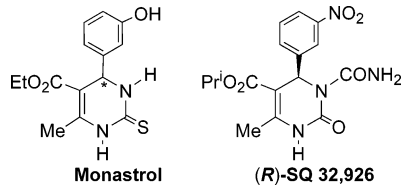
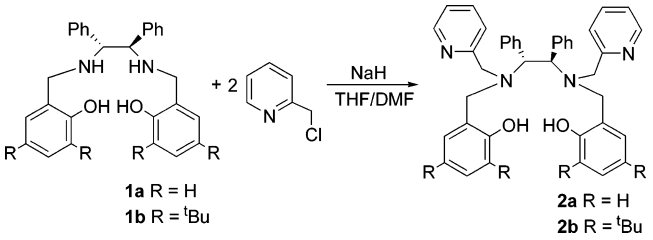


Figure 1. Dihydropyrimidine antagonists.

Scheme 1. Synthesis of the Hexadenate Chiral Ligands



the novel hexadentate ligands. We were pleased to find that the ligands **2a** and **2b** provided high yield and good enantioselectivity with 90% and 83% ee, respectively. Accordingly, the evaluation of $La(OTf)_3$ and $Sm(OTf)_3$ as their **2a** complexes was carried out in the catalyzed condensation, as shown in Table 1 (entries 1,2). A further survey of solvents using 10 mol % of Yb-**2a** revealed that dry THF was the most favorable solvent. The use of 5 mol % of Yb-**2a** catalyst caused a slight decrease in the ee value (entry 7). A control experiment utilizing just the ligand provided no product.

Due to the good results obtained, we applied the optimal protocol to a variety of aldehydes and 1,3-ketoesters, with urea or thiourea. In most cases, the desired DHPM derivatives were obtained in good yields with excellent enantioselectivities as shown in Table 2. Electronic variation on aryl aldehydes caused no appreciable changes in the efficiency and enantioselectivity of the condensations. This reaction also embodies high functional-group tolerance, since nonaromatic conjugated (*E*)-cinnamaldehyde (entry 12), aliphatic phenylacetaldehyde (entry 13), and electron-rich heteroaromatic aldehyde furfural (entry 14) result in good enantioselectivity. High selectivities were obtained at room temperature to ensure a practical and highly efficient process for the synthesis of optically active C4-aryl dihydropyrimidinones.

To our delight, the condensation of *m*-hydroxybenzaldehyde, acetoacetate, and thiourea provided exclusively the (*R*)-enantiomer of monastrol (entry 10). The product obtained from entry 3 could be easily transformed to (*R*)-SQ 32,926 by treatment with trichloroacetyl isocyanate in THF and then by hydrolysis with methanol and silica gel (Scheme 2).[6d] The enantiomeric excess of the obtained (*R*)-SQ 32,926 was over 99% ee, which indicates no racemization occurred during the transformation.

The catalyst could be recovered by pH-controlled extraction and reused several times without evident loss of ee.[12] The resulting complex was identified as mononuclear formulation [YbL(OTf)],[10b]

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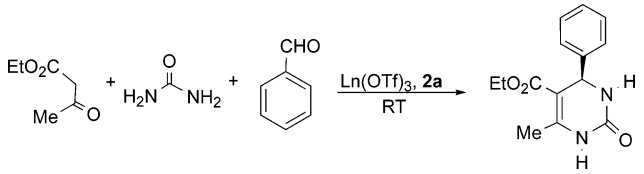
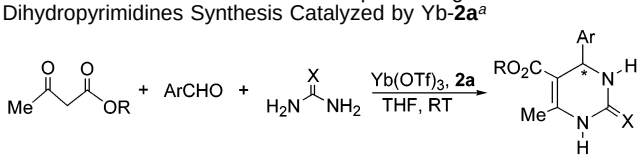
Table 1. Enantioselective One-Pot Biginelli Reaction Catalyzed by Chiral Lanthanide Triflates under Different Conditions[a]

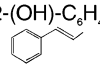


entry	Lewis acid	solvent	yield, %[b]	ee, %[c]	config.[d]
1	$La(OTf)_3$	THF	83	81	R
2	$Sm(OTf)_3$	THF	81	85	R
3	$Yb(OTf)_3$	THF	87	90	R
4	$Yb(OTf)_3$	CH_2Cl_2	80	83	R
5	$Yb(OTf)_3$	CH_3CN	86	82	R
6	$Yb(OTf)_3$	CH_3OH	88	80	R
7	$Yb(OTf)_3$[e]	THF	84	85	R

[a] All reactions were carried out at room temperature with catalyst loading of 10 mol % unless otherwise noted. [b] Isolated yields. [c] The ee's were determined by HPLC with a Daicel Chiralcel OD-H column. [d] The absolute configuration was determined by the comparison of the characteristic CD spectra with DHPMs of known absolute configuration.[11] [e] Catalyst loading of 5 mol %.

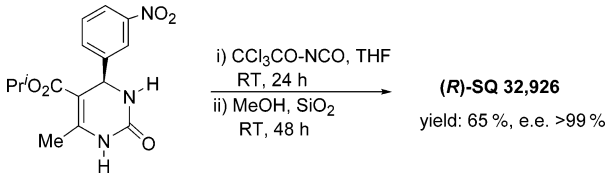
Table 2. Enantioselective Three-component Biginelli Dihydropyrimidines Synthesis Catalyzed by Yb-**2a**[a]



entry	Ar	R	X	yield, %[b]	ee, %[c]	config.
1	C_6H_5	Et	O	87	90	*R*[e]
2	C_6H_5	Et	S	81	99	*R*[e]
3	3-(NO_2)-C_6H_4	^{i}Pr	O	90	>99	*R*[d]
4	3-(NO_2)-C_6H_4	^{i}Pr	S	88	87	*R*[e]
5	3-(F)-C_6H_4	Et	O	80	97	*R*[e]
6	2-(Cl)-C_6H_4	Et	S	73	98	*R*[e]
7	2-(Cl)-C_6H_4	Et	O	78	89	*R*[e]
8	4-(Br)-C_6H_4	Et	O	82	95	*R*[e]
9	3-(OH)-C_6H_4	Et	O	81	91	*R*[e]
10	3-(OH)-C_6H_4	Et	S	80	99	*R*[d]
11	2-(OH)-C_6H_4	Et	O	86	98	*R*[e]
12		Et	O	81	80	*R*[e]
13		Et	O	82	82	*R*[e]
14		Et	O	87	93	*R*[e]

[a] All reactions were performed on 0.5 mmol scale of substrates with 10 mol % of Yb-**2a** at room temperature. [b] Isolated yields. [c] The ee's were determined by HPLC with a Daicel Chiralcel OD-H or AD-H column. [d] Determined by the comparison of the optical rotation values with literature.[7c,d] [e] Assigned by the comparison of the characteristic CD spectra with DHPMs of known absolute configuration.[11]

Scheme 2. Synthesis of (*R*)-SQ 32,926



and the possible structure of Yb-**2a** with molecular mechanics computation is shown in Figure 2a.[13] We propose a transition-state model which explains the absolute configiration of the favored enantiomer in the Biginelli reaction, as shown in Figure 2b. The in situ generated acylimine intermediate could coordinate to the Yb atom. The *si*-face of the coordinated acylimine was schielded by the pyridyl group, allowing nucleophilic attack of the enol ester from the *re*-face.

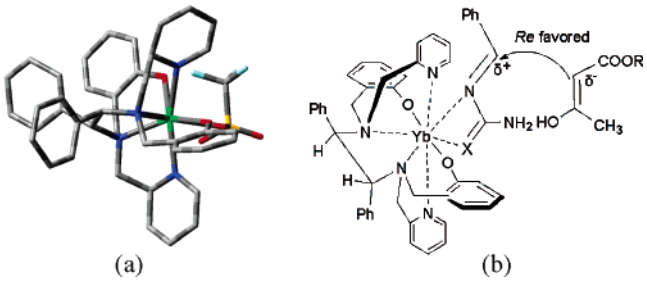


Figure 2. (a) Molecular model of the chiral catalyst Yb-**2a**. (b) Proposed working model for the asymmetric Biginelli reaction catalyzef by Yb-**2a** (other groups omitted for clarity).

In conclusion, a new catalytic approach to highly enantioselective multicomponent Biginelli condensation using a recyclable chiral Yb triflate with a novel hexadentate chiral ligand has been developed. A wide range of optically active dihydropyrimidines with remarkable pharmacological interest was obtained in high yields with good to excellent enantioselectivities (up to 99% ee) using this practical method under mild conditions. Further studies on the utility of this catalyst in other asymmetric syntheses are underway.

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Supporting Information Available: A complete description of experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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