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Studies on Asymmetric Synthesis of Huperzine A

1. Palladium-Catalyzed Asymmetric Bicycloannulation of 5,6,7,8-Tetrahydro-2-methoxy-6-oxo-5-quinolinecarboxylic Esters

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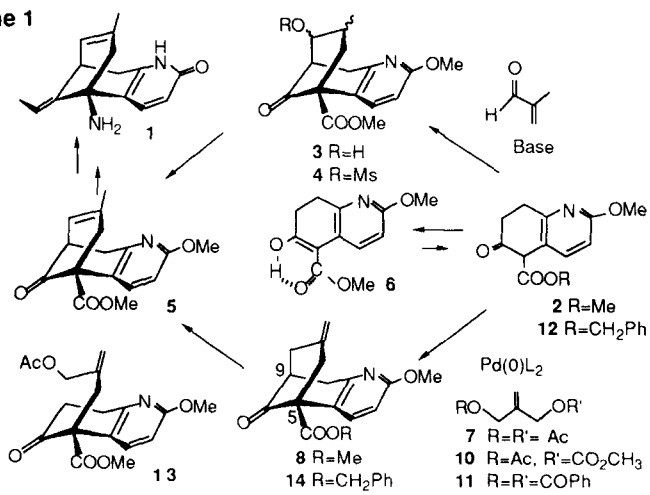
Abstract: A bridged bicyclic compound **8**, the key intermediate for the synthesis of huperzine A (**1**), was prepared by asymmetric palladium-catalyzed bicycloannulation of ß-keto ester **2**. A variety of chiral ligands and reaction conditions were tested. 52% ee values were observed.

Huperzine A (**1**), a new Lycopodium alkaloid isolated from the Chinese traditional medicinal herb *Huperzia serrata*, is a potent and selective inhibitor of acetylcholinesterase.[1] Now huperzine A is one of a number of promising drugs for therapy of Alzheimer's disease(AD) because of its high therapeutic index and longer duration of action.[2] Furthermore, huperzine A is likely to provide a safe prophylactic drug against organophosphate nerve agents.[3]

Michael-aldol reactions of methyl 5,6,7,8-tetrahydro-2-methoxy-6-oxo-5-quinolinecarboxylate (**2**) with methacrolein to form **3** and to construct the unsaturated three-carbon bridge moiety **5**, followed by Wittig olefination, Curtius rearrangement and final deprotections completed the first synthetic route to the racemic target molecule **1** as shown in Scheme 1 by both Ji[4] and Kozikowski[5] groups.

Scheme 1



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Since the natural (-)-**1** exhibits potent inhibitory activity and natural resources are scarce, intensive efforts have been devoted to stereoselective synthesis of **1**, that was initially performed via the Michael reaction.[6,7] The ß-keto ester **2**, usually existing in an enol form **6**, is a versatile intermediate for the asymmetric synthesis of huperzine A (**1**).[8]

Because the elimination of mesylate **4** to form the double bond intermediate **5** was low yielding, Gravel designed palladium-catalyzed bicycloannulation, a preparative method of bicyclo[3.3.1]nonan -9-one bearing an exocyclic methylene group developed by Lu,[9] of 1-methoxycarbonyl-2-tetralone with a bifunctional allylic alkylating agent 1,3-allylic diacetate **7**, via regioselective double bond migration, to afford an endocyclic double bond compound in high yield.[10] Later, Kozikowski group prepared a racemic three-carbon bridge **8** using the bicycloannulation on ß-keto ester **2**[11] (see Scheme 1). Recently, Terashima et al. have reported the enantioselective synthesis of **8** using chiral ferrocenyl phosphine ligands to accomplish the synthesis of natural huperzine A (**1**).[12]

Herein, we would like to describe our preliminary results of asymmetric palladium-catalyzed bicycloannulation of ß-keto ester **2** using various chiral ligands. (R) and (S)- BINAP **9**, excellent ligands for

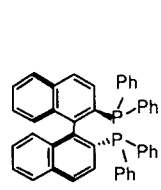
Table 1. Asymmetric Palladium-Catalyzed Bicycloannulation of ß-Keto Ester **2** and Bifunctional Allylic Esters with Chiral Ligand BINAP[a]

entry	solvent	configuration of ligand	reactn temp, °C	reactn time[b]	bifunctional allylic ester	yield[c] %	ee[d] %	remarks
1	dioxane	R	rt	20 h	**7**	82	19.5	
2	DMSO	R	rt	20 h	**7**	75.8	7.3	
3	$CHCl_3$	S	rt	20 h	**7**	~100	38.8	
4	THF	S	rt	20 h	**7**	93.5	10.6	
5	CH_2Cl_2	S	rt	20 h	**7**	99	21.9	
6	$CHCl_3$	S	-20	4 d	**7**	97.3	52	
7	$CHCl_3$	S	-45 to rt	2 d	**10**	52.3	13	e, f
8	$CHCl_3$	S	-55	1 d	**10**	0		e
9	THF	S	-78 to rt	2 d	**10**	65	11	f
10	THF	S	-78 to rt	2 d	**10**	~100	7	f
11	CH_2Cl_2	S	-78 to rt	2 d	**10**	87	21.8	f
12	CH_2Cl_2	S	-78 to rt	2 d	**10**	85	33	f, g
13	THF	S	rt	20 h	**11**	91.8	8.1	
14	$CHCl_3$	S	rt	20 h	**11**	98.2	26.2	
15	CH_2Cl_2	S	rt	20 h	**7**	82.6	24.2	h
16	CH_2Cl_2	S	-78 to rt	2 d	**10**	80	26.8	f, h

a) Catalyst was prepared by 0.020 mmol of $Pd(OAc)_2$ and 0.044 mmol of BINAP in the presence of DBU in 2 ml of solvent, reactions were performed with 0.20 mmol of **2**, 0.25 mmol of bifunctional allylic ester and 0.50 mmol of DBU in 2 ml of the same solvent with the catalyst prepared previously at the given temperature under nitrogen. b) Reaction time was monitored by TLC detection. Besides product **8**, intermediate **13** might be found and, then, the bicycloannulation was completed by raising the temperature. c) Isolated yields by acid-base work-up or by preparative TLC. d) The ee values were determined by ^1H NMR in the presence of chiral shift reagent $Eu(hfc)_3$. e) Acidity of $CHCl_3$ damaged the reaction. f) Reaction evidently did not occur under low temperature for one day and was then allowed to slowly warm to room temperature. g) 0.12 mmol of Bu_4NBr was added. h) ß-Keto benzyl ester **12** was used instead of ß-keto methyl ester **2** to afford the corresponding **14**.

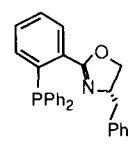
asymmetric reactions,[13] were our first choice for the bicycloannulation. The experimental results are summarized in Table 1.

Some features should be pointed out: (1) The magnitude of asymmetric induction was solvent-dependent, the asymmetric induction was higher with low polar solvents than with polar coordinating solvents (entries 3 and 5 vs. 2 and 4). Purified chloroform seemed to be the best solvent and 52% ee value was obtained at -20 °C (entry 6), but sometimes the acidity in chloroform possibly damaged the reaction (entry 7) and even neither product **8** nor reactant **2** was found (entry 8). (2) Allylic carbonates were very efficient allylating agents for soft nucleophiles.[14] However, 2-methylene-1,3-propanediol mono-acetate mono-carbonate (**10**)[15] was used in the bicycloannulation, the reaction evidently did not occur at -78 °C (entries 9-12 and 16). (3) In order to increase steric interaction, 2-methylene-1,3-propanediol dibenzoate (**11**) was used instead of diacetate **7**, to our disappointment, the enantioselectivities were lower (entries 13 and 14). When ß-keto benzyl ester **12** was used instead of ß-keto methyl ester **2**, the ee values were not improved (entries 15 and 16). While Bu_4NBr, as a counter ion of the nucleophile, was added, the enantioselectivity was somewhat enhanced (Entry 12). (4) Using (R)-BINAP, the major isomer of **8** was of the desired (5S,9S) configuration, that could be transformed into known **5**.[7]



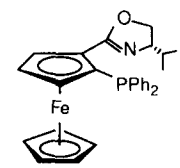
(R)-

9



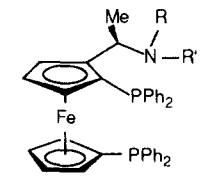
(S)-

15



(S)-(S)-

16



(R)-(S)-

17 R=R'=Me

18 R=H, R'=$(CH_2)_2OH$

19 R=H, R'=$(CH_2)_3OH$

Besides BINAP, we tested other kinds of chiral ligands (**15-19**). The results of the asymmetric bicycloannulation are illustrated in Table 2.

Chiral (phosphinaryl)-oxazolines were recently developed by several groups and have been proved to be

Table 2. Asymmetric Bicycloannulation of ß-Keto Ester **2** with Bifunctional Allylic Ester **7** by Chiral Palladium Catalysts[a]

entry	ligand	solvent	reactn temp, °C	reactn time[b]	yield[c] %	ee[d] %	remarks
17	**15**	THF	0 to rt	2 d	69	4	
18	**16**	THF	0 to rt	2 d	68	2	
19	**17**	THF	0 to rt	1 d	68	25	
20	**18**	THF	-45 to rt	1 d	73	19	
21	**19**	THF	0	1 d	46	34.5	
22	**19**	CH_2Cl_2	-20	2 d	49	52.1	e

a) The reactions were generally performed as follows: to a solution of 0.20 mmol of **2** and 0.50 mmol of DBU in 2 ml of solvent was added, at the given temperature, a previously prepared mixture of 0.030 mmol of ligand, 0.015 mmol of $(\pi\text{-}C_3H_5)PdCl$ dimer and 0.25 mmol of **7** in 2 ml of the same solvent under nitrogen. b, c and d footnotes see Table 1.

e) **10** was used instead of **7** as a bifunctional allylic ester.

highly effective ligands for asymmetric allylation.[16] Moreover, the oxazoline attaching to a ferrocene nucleus has the potential benefits of combining the tetrahedral chirality inherent in the oxazoline with the planar chirality of disubstituted ferrocenes.[17] Surprisingly, these oxazoline ligands such as **15** and **16** were ineffective for the asymmetric bicyclcloannulation (entries 17 and18). Chiral ferrocenyl phosphines, particularly containing a pertinent functional group on the side chain, were efficient ligands for several types of transition-metal complex catalytic stereoselective reactions.[18] Its precursor (S)-(R)-BPPFA **17** was first used in the bicyloannulation and the enantioselectivity was modest (entry 19). The length of linking side chain played a key role in respect of secondary interaction between chiral ligands and substrates.[19] The three-carbon side chain ligand **19** improved the enantioselectivity and 52.1% ee value was observed (entry 22). The best result recently reported was 64% ee value using corresponding four-carbon chain ligand.[12]

Asymmetric palladium-catalyzed allylic substitutions have been developed rapidly,[20] but the intermolecular allylation of ß-keto esters was in low enantioselectivity.[21] However, various chiral ligands have a subtle influence upon allylic alkylations. The enantioselective palladium-catalyzed bicyloannulation for asymmetric synthesis of natural huperzine A represents a unique challenge and opportunity. Further work is under way in our laboratory.

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8. We chose several chiral bases such as (-)cinchonidine, (1R,2S)-N-methyl-ephedrine, (S)-N-isopropyl-phenylalaninol etc. to perform the asymmetric Michael-aldol reactions. After the elimination, *ca* 50% ee on **5** was given by (-)-cinchonidine, similar to reported ee value by quinine,[7] lower ee values (*ca* 10%) were obtained by other bases. Unpublished results.
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