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Proline-Catalyzed Asymmetric Addition Reaction of 9-Tosyl-3,4-dihydro-β-carboline with Ketones

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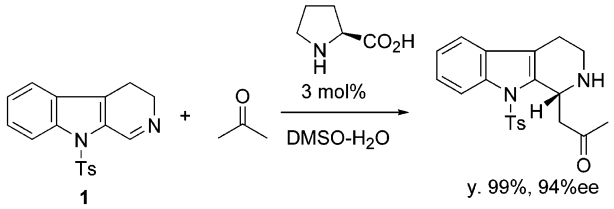
ABSTRACT



9-Tosyl-3,4-dihydro-β-carboline (1) reacted with a ketone in the presence of (*S*)-proline as a catalyst to give the corresponding addition product in good yield and high enantioselectivity. In the process, a small amount of water was found to affect the stereoselectivity of the products. The system was applied to reaction of compound 1 and 3-buten-2-one to give 3,4,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-2-one, which is a versatile precursor for the synthesis of some indole alkaloids.

Asymmetric reactions catalyzed by metal-free chiral organic compounds[1] have become a rapidly expanded research area in organic synthesis because they are more benign to the environment than conventional metal-catalyzed reactions, and intensive studies have revealed that several organic compounds, which include chiral Lewis bases and phase-transfer catalysts, are good enantioselective catalysts. In these reactions, the proline-catalyzed asymmetric reaction[2] is among the most useful processes due to its simple procedure and low cost. Thus, there have been numerous papers reporting proline-catalyzed asymmetric reactions, that is, aldol reactions,[3] Mannich reactions,[4] Michael reactions,[5] α-aminations,[6] Baylis−Hillman reactions,[7] and so on. In the Mannich reactions, imines formed in situ by reaction of aldehydes and amines react with enamines, which are derived from ketones and (*S*)-proline to give β-aminoketones in good stereoselectivities.[4] The amines used as the reactants, however, were limited to aromatic ones, and there are no

(1) (a) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529−532. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748. (c) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495, and references therein.

(2) (a) List, B. *Synlett* **2001**, 1675−1686. (b) List, B. *Tetrahedron* **2002**, *58*, 5573−5590.

(3) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496−497. (c) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (d) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387. (e) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575. (f) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267. (g) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799. (h) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858−860.

(4) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337. (b) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199−201. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833.

(5) (a) Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1088−1089. (b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423−2425. (c) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975−2978. (d) Enders, D.; Seki, A. *Synlett* **2002**, 26−28.

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reports concerning the reaction using cyclic imines as substrates.

In the course of our study of asymmetric addition of β-carboline derivatives,[8] we have now applied the proline-catalyzed reaction, and, as a result, it was found that 9-tosyl-3,4-dihydro-β-carboline (**1**) is a good substrate for the proline-catalyzed asymmetric addition of ketones. Moreover, it was revealed that a certain amount of water played a crucial role in obtaining the high stereoselectivity. Then, the reaction was applied to the synthesis of 12-tosyl-3,4,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-2-one, which is a versatile precursor for the synthesis of some indole alkaloids. This paper describes these results.

1,2,3,4-Tetrahydro-β-carboline derivatives having a substituent at the C-1 position widely exist in nature as a constituent of indole alkaloids, and there have been many reports concerning their syntheses.[9] The Pictet−Spengler reaction[10] and the vinylogous Mannich reaction[11] are among the most representative methods and have been applied to asymmetric syntheses using (*S*)-tryptophan as the starting material. On the other hand, Meyers et al. has developed an (*S*)-valine-derived chiral auxiliary to introduce an alkyl or aryl substituent to the C-1 position of the β-carboline nucleus in a highly diastereoselective manner.[12] In addition, Nakamura et al. reported that a chiral allylzinc reagent reacted with 3,4-dihydro-β-carboline (**2**) to give an allyl adduct in high ee.[13] To the best of our knowledge, however, there is no study on application of the asymmetric catalytic process to the ring system.

At first, 3,4-dihydro-β-carboline (**2**) was allowed to react with acetone in the presence of (*S*)-proline, and it was found that the substrate decomposed to a complicated mixture. Thus, 9-tosyl-3,4-dihydro-β-carboline (**1**)[14] was selected as the next substrate.

Scheme 1. Reaction of 9-Tosyl-3,4-dihydro-β-carboline (**1**) with Acetone in the Presence of (*S*)-Proline

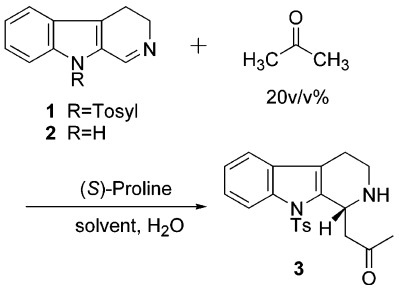


Table 1. Reaction of Compound **1** with Acetone in the Presence of a Catalytic Amount of (*S*)-Proline

entry	solvent	proline (mol %)	H_2O (equiv)	temp	time	yield of **3** (%)	ee (%)[a]
1	CH_2Cl_2	30	b	rt	1.5 h	76	34
2	CH_2Cl_2	30	10	rt	3.5 h	79	80
3	CH_2Cl_2	30	50	rt	1 day	trace[c]	
4	acetone	30	b	rt	2 h	69	24
5	acetone	30	10	rt	2 h	92	80
6	acetone	30	50[d]	rt	2 h	quant	82
7	DMSO	30	b	rt	2 h	quant	5
8	DMSO	30	10	rt	2 h	96	67
9	DMSO	30	50	rt	2 h	quant	80
10	DMSO	30	100	rt	2 h	98	86
11	DMSO	30	150	rt	2 h	quant	87
12	DMSO	30	50	−2 °C[e]	2.5 h	91	93
13	DMSO	30	100	−2 °C[e]	3 h	99	92
14	DMSO	3	2	rt	2 h	91	4
15	DMSO	3	10	rt	2 h	92	60
16	DMSO	3	50	−2 °C[e]	23 h	99	94

[a] All the dominant enantiomers formed have the same chirality except that of entry 7. [b] Although contaminated water was not detected in CH_2Cl_2, a small amount of water was detected by the coulometer in two other solvents (0.70 equiv in acetone, 1.04 equiv in DMSO). The detection limit of water by this system was 0.35 equiv with respect to the substrate. [c] Solvent became a bilayer in this case. [d] In the case of 100 equiv of H_2O, the yield and the ee both decreased. [e] Reaction medium was cooled to −2 °C because it was the lowest temperature at which the solvent did not solidify.

The reaction of **1** with acetone in the presence of 30 mol % (*S*)-proline completed smoothly in dichloromethane, acetone, or DMSO to give the 1-acetonyl-9-tosyl-1,2,3,4-tetrahydro-β-carboline (**3**) in good yields, but the stereoselectivities were quite low (Table 1, entries 1, 4, and 7).[15] Thus, we scrutinized the reaction conditions and found that addition of a small amount of water improved the selectivity. When water was added, however, the reaction rate became slower, probably due to hydrolysis of an intermediary enamine obtained from acetone and (*S*)-proline. Thus, the optimal amount of water, which was analyzed with a coulometer, is about 50−100 equiv with respect to

(6) (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656−5657. (b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790−1793. (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254−6255. (c) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975−978.

(7) Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2001**, *43*, 127−130.

(8) (a) Itoh, T.; Matsuya, Y.; Enomoto, Y.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Tetrahedron* **2001**, *57*, 7277−7289. (b) Itoh, T.; Miyazaki, M.; Ikeda, S.; Nagata, K.; Yokoya, M.; Matsuya, Y.; Enomoto, Y.; Ohsawa, A. *Tetrahedron* **2003**, *59*, 3527−3536 and references therein.

(9) *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley: Chichester, 1994; Part 4, supplement of Vol. 25.

(10) (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842 and references therein. (b) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998−7010. (c) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827−7828.

(11) (a) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161−6171. (b) Martin, S. F.; Clark, C. C.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236−3242. (c) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79−81. (d) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895−904.

(12) (a) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108−3112. (b) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778−4787. (c) Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091−2096. (d) Meyers, A. I.; Highsmith, T. K.; Buonora, P. T. *J. Org. Chem.* **1991**, *56*, 2960−2964.

(13) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489−8490.

(14) Rey, A. W.; Szarek, W. A. *Can. J. Chem.* **1992**, *70*, 2922−2928.

(15) Among these reactions, contaminated water was not detected in CH_2Cl_2, but a small amount of water was detected by a coulometer in other solvents (0.70 equiv in acetone, 1.04 equiv in DMSO).

Scheme 2. Reaction of Compound **1** with Methyl Ketone in the Presence of (*S*)-Proline

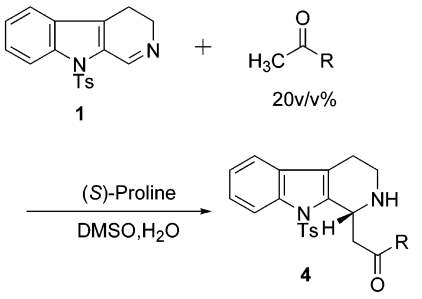


Table 2. Reaction of Compound **1** with a Ketone in the Presence of a Catalytic Amount of (*S*)-Proline

entry	R	proline (mol %)	H_2O (equiv)	temp	time	yield of **4** (%)	ee (%)
1	Et	50		rt	6.5 h	78	28
2	Et	50	10	rt	8 h	81	80
3	Et	50	50	rt	8.5 h	81	87
4	Et	50	50	−2 °C	30 h	85	89
5	Et	5	50	rt	3 days	98	85
6	Et	5	50	−2 °C	5 days	81	91
7	Pr	50		rt	4 h	61	7
8	Pr	50	50	rt	7 h	77	88
9	Pr	50	50	−2 °C	2 days	76	92
10	Pr	5	50	rt	36 h	86	85
11	Pr	5	50	−2 °C	5 days	66	92
12	*i*-BuOC_2H_4	50		rt	26 h	57	20
13	*i*-BuOC_2H_4	50	10	rt	20 h	65	51
14	*i*-BuOC_2H_4	50	30	rt	20 h	72	73
15	*i*-BuOC_2H_4	50	50	rt	20 h	51	75

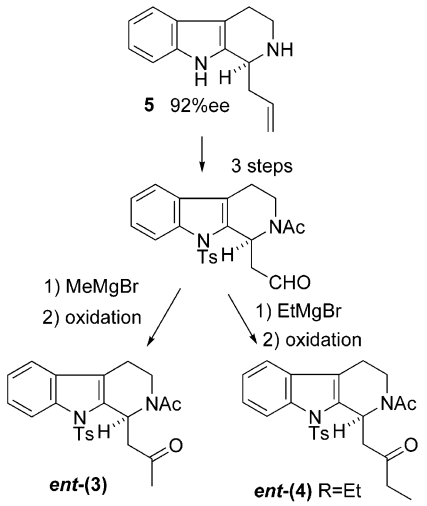
the substrate. A decrease in the amount of the catalyst resulted in no loss of the ee, and even in the presence of 3 mol % (*S*)-proline, good selectivity was observed (entry 16). The effect of water was also shown in these cases (entries 14−16). Therefore, the yield and selectivity were improved by using DMSO solvent and 3 mol % (*S*)-proline in the presence of 50 equiv of water at −2 °C[16] to give compound **3** in 99% yield and 94% ee (Table 1, entry 16).

Next, the same procedure was applied to other ketones, and the results are summarized in Table 2 (Scheme 2). In these cases, the effect of H_2O was observed again, and the products were obtained in a highly enantioselective manner in the presence of water (Table 2, entries 4, 9, and 15) using 50 mol % proline. Although a decrease in the amount of the catalyst lengthened the reaction time, high enantioselectivity was obtained (Table 2, entries 6 and 11).

The stereochemistry of compounds **3** and **4** (R = Et) thus obtained was determined by an alternative synthesis from a chiral (*S*)-1-allyl-1,2,3,4-tetrahydro-*β*-carboline (**5**), whose absolute configuration was confirmed by our group[8a] (Scheme 3).

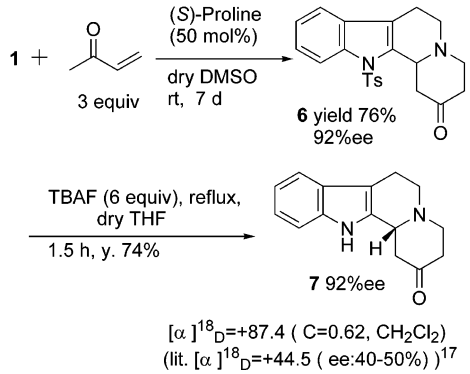
The obtained compounds shown in Scheme 3 had the same NMR spectra and opposite specific rotations to those of **3** and **4**; thus, the absolute configuration of **3** and **4** was assigned as (*R*).

Scheme 3. Alternative Synthesis of **3** and **4** (R = Et) from Chiral **5**



Then, 3-buten-2-one was used as a ketone to construct the D-ring of indole alkaloids, and the results are shown in Scheme 4. The reaction using compound **1** was carried out

Scheme 4. Reaction of Compound **1** with 3-Buten-2-one in the Presence of (*S*)-Proline



in DMSO, and 12-tosyl-3,4,6,7,12,12b-hexahydro-1*H*-indolo-[2,3-*a*]quinolizin-2-one (**6**) was formed in 76% yield with 92% ee even in the absence of H_2O. The addition of H_2O in this system resulted in only retardation of the reaction progress without variation of the stereoselectivity. The absolute configuration of **6** was determined by derivatization of **6** to detosylated compound **7**,[17] which has been reported as a versatile precursor for the syntheses of some indole alkaloids such as yohimbine[18] and deserpidine.[19]

(16) Reaction medium was cooled to −2 °C because it was the lowest temperature at which the solvent remains liquid.

(17) Waldmann, H.; Braun, M.; Weymann, M.; Gewehr, M. *Tetrahedron* **1993**, *49*, 397−416.

(18) Kametani, T.; Hirai, Y.; Kajiwara, M.; Takahashi, T.; Fukumoto, K. *Chem. Pharm. Bull.* **1975**, *23*, 2634−2642.

In this paper, we have disclosed the first catalytic asymmetric addition reaction of 3,4-dihydro-β-carboline using (*S*)-proline as the chiral catalyst. Although the stereoselectivity shown in this work[20] is in accord with the mechanism proposed by List et al.,[4b] the effect of H_2O on the stereoselectivity in our reaction system remained unclear. As shown in Table 1 (entries 7−9 vs 14−16), the ratio of water to (*S*)-proline seldom affected the enantioselectivity. Thus, this suggests that the effect of water derives from the interaction of H_2O with the substrate rather than with proline. In the case of 3-buten-2-one, the addition of H_2O only resulted in decrease of the reaction rate, and the high selectivity was observed in the absence of water. Thus, there might be alternative reaction pathways in the addition to cyclic imine systems. Study of the detailed reaction mechanism, a search for other substrates, and application of the reaction products to the synthesis of indole alkaloids are now in progress.

Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Szántay, C.; Blaskó, G.; Honty, K.; Szabó, L.; Töke, L. *Heterocycles* **1977**, *7*, 155−160.

(20) Substrate of the present reaction has the (*Z*)-imine structure; thus, the transition state was supposed to be similar to that of the aldol reaction (ref 3, *Re* face attack) rather than the one for the (*E*)-imine Mannich reaction (ref 4, *Si* face attack).