Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8233-8236, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01754-9

Catalytic Asymmetric Michael Addition of Nitroalkane to Enone and Enal

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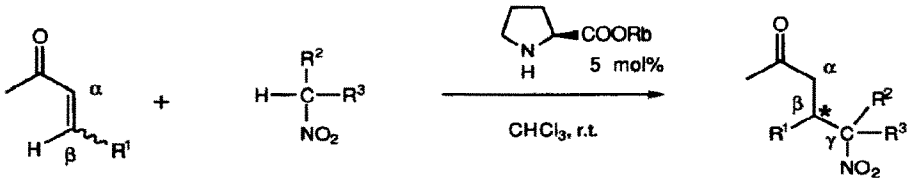
Abstracts. *L*-Proline rubidium salt catalyzes the asymmetric Michael addition of nitroalkanes to enones and an enal. (*R*)-Adducts were obtained from cyclic (*Z*)-enones and (*S*)-adducts from acyclic (*E*)-enones. Bu_3SnH treatment of the products replaced the nitro group with hydrogen atom. The overall transformation allows the asymmetric alkylation of enones at the β-carbon atom.

Catalytic Michael addition of nitroalkanes is a powerful synthetic tool perceiving that the nitro group can be transformed into various functionalities. The conventional asymmetric version of the reaction, however, gave acceptable results only for the reactions of chalcones with nitromethane.[1] Previously, we reported the asymmetric Michael addition of a malonate anion catalyzed by *L*-proline rubidium salt.[2] The methodology is now successfully applied to the asymmetric addition of nitroalkanes to enones and an enal.



Scheme 1.

Treatment of 1.5 mol eq of nitroalkane and enone or enal in the presence of 5 mol% of *L*-proline rubidium salt in chloroform at r.t. gave the optically active γ-nitroketone (Scheme 1 and Table 1).[3] As was observed in the malonate reaction,[2] (*R*)-adducts were obtained from cyclic (*Z*)-enones and (*S*)-adducts from acyclic (*E*)-enones. It suggests the involvement of a similar reaction mechanism in both reactions, the intermediacy of iminium salt. Enantiomeric excesses are higher for bulky nitroalkanes, and 84% ee was attained for the reaction of 2-cycloheptenone and nitrocyclohexane. Approximately equimolar amounts of diastereomers were formed from primary nitroalkanes. Since no isomerization took place by standing the pure diastereomer under the reaction conditions, the ratios were kinetically determined. Both diastereomers possess the same absolute configuration at the β-carbon atom of carbonyl group, which is also consistent with the iminium salt formation mechanism.[2] Nitromethane is less reactive than other primary and secondary nitroalkanes.

Several amino acid rubidium salts with secondary amine moiety were also examined. Four-membered ring amine, rubidium *L*-azetidine-2-carboxylate, exhibited comparable asymmetric induction with *L*-prolinate (Table 1), while both activity and enantiomeric excess were very low with six-membered ring derivative, *L*-piperidine-2-carboxylate. Acyclic amino acid rubidium salts, *N*-methyl-*L*-leucinate, *N*-benzyl-*L*-leucinate, or

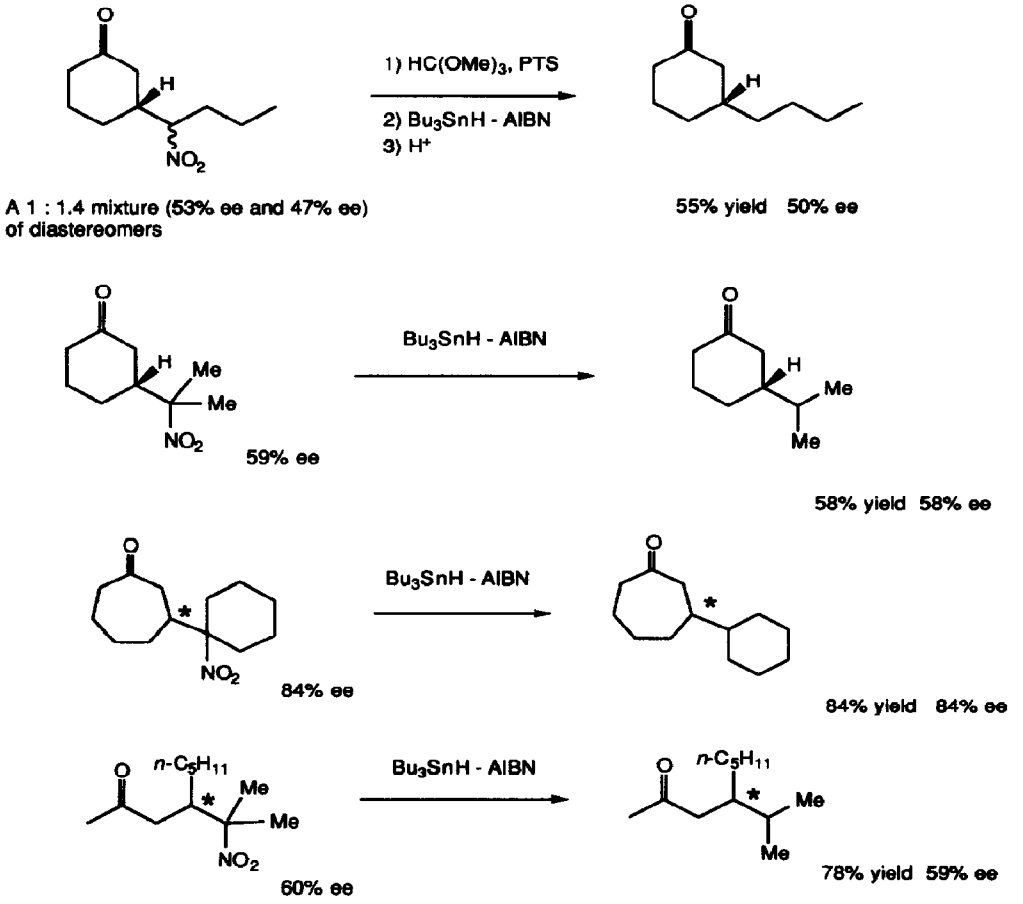
Table 1. Catalytic Asymmetric Michael Addition of Nitroalkane to Enone and Enal.

enone / enal	nitroalkane	time / h	yield / % [a]	ee / % [b]	config. [c]	$[\alpha]_D$ [d]
2-cycloheptenone	CH_3NO_2	43	47 [e]	41		+25.1
	i-$C_3H_7NO_2$	43	79	73		+51.8
	cyclo-$C_5H_9NO_2$	24	74 [f]	67		+34.4
	cyclo-$C_6H_{11}NO_2$	20	84 [f]	84		+41.2
2-cyclohexenone	CH_3NO_2	51	55 [e]	45		+9.4
	n-$C_4H_9NO_2$	19	84 (1 : 1.4)	53, 47	*R*, *R* [g, h]	+18.1, -7.1
	i-$C_3H_7NO_2$	24	81	59	*R* [i]	+15.0
		23	40 [j]	56	*R*	+14.9
(*E*)-3-penten-2-one	CH_3NO_2	17	47 [e]	42		+2.4
	n-$C_4H_9NO_2$	21	64 (1 : 1)	40, 55	*S*, *S* [g, k]	-2.5, [l] 0.0 [m]
	i-$C_3H_7NO_2$	17	74	68	*S* [n]	-8.7
	cyclo-$C_5H_9NO_2$	24	64 [f]	59		-1.4
(*E*)-3-nonen-2-one	*i*-$C_3H_7NO_2$	39	91 [f]	60		+12.0
(*E*)-2-hexenal	*i*-$C_3H_7NO_2$	24	61	29		+9.5

a) All the products gave satisfactory spectra data (^{1}H-NMR, ^{13}C-NMR, IR, and MS) and elemental analysis (combustion and/or high resolution MS). Ratios of diastereomers are shown in parentheses, which were separable by silica gel chromatography. b) Adducts were converted to ketals of (2*R*,3*R*)-2,3-butanediol, and enantiomeric excesses were determined by ^{13}C-NMR. c) Absolute configurations at the β-carbon atom of carbonyl group. d) In chloroform (c 1.0) at ambient temperature, unless otherwise noted. e) 10 mol eq of nitromethane were used. f) 10 mol% of the catalyst were used. g) Each γ-nitroketone diastereomer was acetalization with (2*R*,3*R*)-2,3-butanediol, and was treated with Bu_3SnH. The configurations of the two reduced products were the same as shown by ^{13}C-NMR, which indicate that the diastereomeric γ-nitroketones possess the same absolute configuration at the β-carbon atom of the carbonyl group. h) The diastereomeric mixture of the γ-nitroketones were reduced with Bu_3SnH giving known (*R*)-3-butylcyclohexanone. $[\alpha]_D^{23}$ +3.9° (c 1.33, $CHCl_3$). *Lit.* $[\alpha]_D^{23}$ +7.23° (c 1.13, toluene), 90% ee. Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.*, **1986**, *108*, 7114. i) The adduct was converted to (*R*)-3-(*i*-propyl)cyclohexanone by Bu_3SnH reduction. $[\alpha]_D^{23}$ +9.0° (c 0.93, $CHCl_3$). *Lit.* $[\alpha]_D^{20}$ +17.3° (c 6.3, $CHCl_3$). Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.*, **1991**, *56*, 6199. j) 10 mol% of rubidium *L*-azetidine-2-carboxylate were used. k) The diastereomeric mixture of the γ-nitroketones were reduced with Bu_3SnH giving known (*R*)-5-methyl-2-octanone. $[\alpha]_D^{26}$ +3.5° (c 1.01, $CHCl_3$). *Lit.* $[\alpha]_D^{25}$ +8.3°. Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.*, **1987**, *109*, 2040. l) c 10.0. m) c 25.6. n) The adduct was acetalized with ethylene glycol, and treated with Bu_3SnH giving 2-(2,3-dimethylbutyl)-2-methyl-1,3-dioxolane. $[\alpha]_D^{25}$ -7.5° (c 2.0, $CHCl_3$). The authentic sample with (*S*)-configuration, $[\alpha]_D^{20}$ -7.7° (c 0.58, $CHCl_3$), was prepared from (*S*)-adduct (76% ee)[2] of 3-penten-2-one and diisopropyl malonate as follows. i) $HO(CH_2)_2OH$, TsOH, benzene, refl., 14 h. ii) $LiAlH_4$, THF, refl., 30 min; 76% (two steps). iii) I_2, PPh_3, imidazole, benzene, r.t., 1 h; 91%. iv) $LiHBEt_3$, THF, r.t., 4 h; 33%.

N-methyl-*L*-alaninate showed essentially no activity. Higher catalytic activities of the four- and the five-membered ring amino acids may be attributable to the less hindered environment of the nitrogen atom. Rubidium *L*-thiazolidine-5-carboxylate and 2-methyl-*L*-thiazolidine-5-carboxylate,[4] however, were not effective.

The nitro group can be replaced with hydrogen by Bu_3SnH treatment under radical conditions[5] without losing the optical purities (Scheme 2). The secondary nitro derivatives are less reactive compared with the tertiary nitro derivatives, and *retro*-Michael addition was observed in an attempted reaction of 5-nitro-4-phenyl-2-hexanone. The carbonyl, therefore, was protected as dimethyl acetal prior to the reduction. The sequence of the nitroalkane addition and the Bu_3SnH reduction allows the asymmetric alkylation of enone at their β-carbon atoms. Since the catalytic asymmetric conjugate additions of organocopper or organozinc derivatives often suffered from unfavorable substrate specificities,[6] the present transformation can be a versatile method for the asymmetric alkylation.



Scheme 2.

A diastereomeric mixture of (3*R*)-3-(1-nitrobutyl)cyclohexanone (1 : 1.4) was reduced with Bu_3SnH as follows: Under an argon atmosphere, the nitroketones (150 mg, 0.76 mmol), $CH(OMe)_3$ (0.4 mL, 3.7 mmol), and a catalytic amount of *p*-toluenesulfonic acid in methanol (2 mL) were stirred at r.t. for 5 min. The reaction was quenched by adding into aqueous $NaHCO_3$, and organic materials were extracted with ethyl acetate. After dried over Na_2SO_4, the solvents were removed *in vacuo*. Benzene (5 mL), AIBN (64 mg, 0.39 mmol), and Bu_3SnH (1 mL, 3.8 mmol) were added to the residue, and the mixture was heated at reflux for 10 h. Then, AIBN (64 mg, 0.39 mmol) and Bu_3SnH (1 mL, 3.8 mmol) were added, and refluxing was continued for 5 h. The reaction mixture was diluted with ether, and washed with 4 M HCl and brine. After drying over Na_2SO_4 and concentrating, (*R*)-3-butylcyclohexanone (64 mg, 55%) was obtained by flash column chromatography on silica gel (3% triethylamine in hexane).

This work was supported by grants from the Ministry of Education, Science and Culture, Japan (No. 06225203).

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(*Received in Japan* 17 *June* 1994; *accepted* 23 *August* 1994)