Pergamon

Tetrahedron Letters 39 (1998) 7557–7558

TETRAHEDRON LETTERS

Catalytic Asymmetric Michael Addition of Nitromethane to Enones Controlled by (*R*)-LPB

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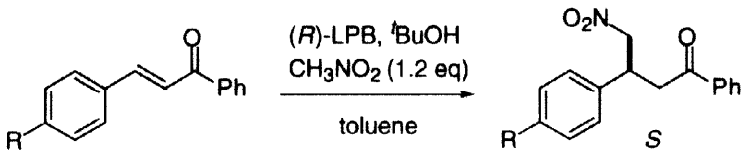
Received 9 July 1998; revised 24 July 1998; accepted 31 July 1998

Abstract

The multifunctional catalyst LPB controls the Michael addition of nitromethane to chalcones with ≥95% ee.

Keywords: LPB; Michael reaction; nitromethane; ^{t}BuOH

The catalytic asymmetric Michael addition of nitroalkanes provides a powerful synthetic tool. Recent reports in this area [1,2,3] prompt us to disclose our preliminary results that the multifunctional catalyst (*R*)-LPB (LaK_3tris((*R*)-binaphthoxide)) [4,5] controls the Michael addition of nitromethane to chalcones with excellent enantioselectivity.



1: R = H, **2**: R = Cl

3: R = H, **4**: R = Cl

Catalyzed by (*R*)-LPB (20 mol %), nitromethane reacted with chalcone **1**, at -20 °C in toluene, to afford the Michael adduct **3** in 33% yield and 89% ee (Table, entry 1). We have found that a beneficial effect on both the chemical yield and the ee occurred when ^{t}BuOH (120 mol %) was added, giving **3** in 59% yield and 97% ee (entry 2) [6]. At 0 °C, the yield increased to 85% with the ee remaining high (93%) (entry 3). When the amount of catalyst was reduced to 10 mol %, **3** was obtained in 61% yield and 88% ee (entry 4). The absolute configuration of the major enantiomer of **3** was determined to be *S* from the optical rotation [7]. Next, we chose 4-chlorochalcone **2** as another substrate, because the Michael adduct **4** would represent a key synthetic precursor for the central muscle relaxant baclofen [8]. By using 20 mol % of (*R*)-LPB, **4** was obtained in 71% yield and 95% ee in the presence of ^{t}BuOH at -20 °C (entry 6) [9]. In the absence of ^{t}BuOH, however, **4** was obtained in only 28% yield and 89% ee (entry 5). Thus, the positive effect of ^{t}BuOH seems to be general. Furthermore, reducing the amount of catalyst to 10 mol % still afforded **4** in 59% yield and 93% ee (entry 7).

Although the role of ^{t}BuOH is not clear at this point, *tert*-butoxide may form and become involved in the catalytically active species, thus accelerating the deprotonation of nitromethane [10,11]. This should enhance the reactivity of the newly formed catalyst relative to LPB, therefore resulting in higher chemical yield and ee. Mechanistic investigations as well as

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01644-X

efforts to further improve the catalytic activity are now underway [12].

Table
Catalytic Asymmetric Michael Addition of Nitromethane to **1** and **2** controlled by (*R*)-LPB

entry	1/2	LPB/mol %	^{t}BuOH/mol %	temp/°C	time/h	product	yield/%	ee/%
1	**1**	20	0	-20	107	**3**	33	89
2	**1**	20	120	-20	109	**3**	59	97
3	**1**	20	120	0	112	**3**	85	93
4	**1**	10	100	8	158	**3**	61	88
5	**2**	20	0	-20	45	**4**	28	89
6	**2**	20	200	-20	140	**4**	71	95
7	**2**	10	100	0	62	**4**	59	93

General Procedure (entry 2): To a solution of (*R*)-BINOL (86 mg, 0.30 mmol) in toluene (2.0 mL) and THF (0.5 mL), was added a 0.20 M solution of La(O^{i}Pr)$_3$ (0.50 mL, 0.10 mmol, purchased from Kojundo Chemical Laboratory Co., Ltd.) in toluene at ambient temperature. The solution was stirred for 30 min and then a solution of KHMDS in toluene (0.60 mL, 0.30 mmol) was added. After stirring for further 30 min, the solvent was evaporated under reduced pressure at rt and the resulting white solid was dried in vacuo for 6 hrs. Toluene (2.1 mL) and ^{t}BuOH (57.4 μL, 0.60 mmol) were added and the resulting white suspension was cooled to -20 °C. To this suspension were added a 0.30 M toluene solution of chalcone (1.67 mL, 0.50 mmol) and a 0.50 M toluene solution of nitromethane (1.2 mL, 0.60 mmol). The reaction mixture became a pale yellow solution and was stirred for 109 hrs. Quenching with 1 N HCl and usual workup, followed by purification by column chromatography (silica gel, acetone/hexane = 1/4) gave the target material in 59% yield. The enantiomeric excess was determined to be 97% by chiral HPLC analysis (Daicel CHIRALPAK AS, ^{i}PrOH/Hex = 1/9, flow rate: 1.2 mL/min, 14 min (major *S* isomer) and 19 min (minor *R* isomer)).

Acknowledgements: We thank CREST for the financial support.

References and Notes

[1] Yamaguchi M, Shiraishi T, Igarashi Y, Hirama M. Tetrahedron Lett. 1994; 35: 8233-8236 and references cited therein.

[2] Bakó P, Kiss T, Tõke L. Tetrahedron Lett. 1997; 41: 7259-7262.

[3] Bakó P, Vizvárdi K, Bajor Z, Tõke L. Chem. Commun. 1998; 1193-1194.

[4] Shibasaki M, Sasai H, Arai T. Angew. Chem. Int. Ed. Engl. 1997; 36: 1237-1256.

[5] Shibasaki M, Iida T, Yamada YMA. J. Synth. Org. Chem. Japan 1998; 56: 344-356.

[6] The amount of ^{t}BuOH did not have a dramatic effect: in the presence of 20, 60, 120, 240, and 480 mol % of ^{t}BuOH, the chemical yields and ees are 50% and 98% ee, 46% and 99% ee, 59% and 97% ee, 55% and 99% ee, and 62% and 98% ee, respectively. Addition of 20 mol % of H_2O resulted in 7% yield in 75% ee.

[7] Botteghi C, Paganelli S, Schinonato A, Boga C, Fava A. J. Mol. Cat. 1991; 66: 7-21.

[8] Keberle M, Faigle JW., Wilhelm M. Swiss pat. 1968; 449,046 (C1.C07c); Chem. Abstr. 1968; 69: 106273f.

[9] The absolute configuration of **4** was assumed to be the same as that of **3**. **4** (95% ee): $[\alpha]^{27}_D$ -28.0 (c 1.1, CH_2Cl_2).

[10] Arai T, Sasai H, Yamaguchi K, Shibasaki M. J. Am. Chem. Soc. 1998; 120: 441-442.

[11] An enhancement of reactivity has been realized by the self-assembled catalyst in the nitroaldol reaction: Arai T, Yamada YMA, Yamamoto N, Sasai H, Shibasaki M. Chem. Eur. J. 1996; 2: 1368-1372. However, in the case of this Michael reaction, the self-assembled catalyst of (*R*)-LPB and potassium nitronate resulted in low yield (< 5%), which suggests that the proton source in the catalyst is important.

[12] Similar reaction conditions to isobutylideneacetophenone, cyclohexylmethylideneacetophenone, and phenylpropylidene-acetophenone gave moderate ees (45-54%) in moderate yields (up to 40%).