Pergamon

Tetrahedron Letters 42 (2001) 8515–8517

TETRAHEDRON
LETTERS

Calcium-BINOL: a novel and efficient catalyst for asymmetric Michael reactions†

G. Kumaraswamy,* M. N. V. Sastry and Nivedita Jena

Gas-Based Chemicals, Indian Institute of Chemical Technology, Hyderabad 500 007, India

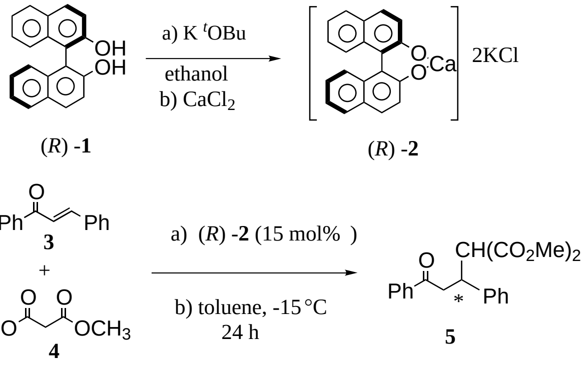
Received 28 June 2001; revised 28 August 2001; accepted 14 September 2001

Abstract—A new calcium-BINOL catalyst has been developed for asymmetric Michael addition reactions of enones and enals. This inexpensive monometallic catalyst functions not only as a Lewis acid but also acts as a Brønsted base. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, Shibasaki et al. have developed most impressive asymmetric Michael reactions catalysed by unique heterobimetallic catalysts. These lanthanoid-alkali metal hybrids of BINOL function presumably as both Brønsted bases and Lewis acids. A synergistic cooperation of the two different metals in the complex promotes formation of the desired products in up to 98% ee.[1]

Based on a recent report,[2] we have initiated a study of calcium complexes for activation of Michael acceptors. Herein, we disclose a new enantioenriched, calcium-BINOL catalyst, which is envisioned to function not only as a Brønsted base but also by controlling the orientation of the enones and enals. This hypothesis was initially tested on *trans*-chalcone **3** and dimethyl malonate **4** using 15 mol% of a catalyst prepared from BINOL and $Ca(OH)_2$ in THF. Although the reaction produced the Michael adduct **5** in good yield, no significant ee was observed (3% ee). After considerable experimentation, we successfully generated a calcium-BINOL catalyst (*R*)-**2** using $CaCl_2$[3] for the activation of Michael acceptors as shown in Scheme 1.

The effect of solvents and temperature were investigated. After screening a variety of solvents (THF 0% ee; THF:toluene (3:7) 10% ee; $C_6H_5CF_3$ 9% ee; DME 0% ee; CH_2Cl_2 24% ee) toluene was found to give the best results at −15°C (ambient temp. 20% ee). A small amount of EtOH was found to accelerate the reaction and increase yields and ee's. The reaction proceeded sluggishly without EtOH, whereas more than 0.1 ml (5 mole equivalent to (*R*)-(+)-BINOL used) of EtOH showed a deleterious effect on optical purity. 10 mol% of the Ca-BINOL catalyst also gave a satisfactory yield with a slightly reduced ee. A Li-BINOL (LiOH+ BINOL) complex also gave the Michael adduct **5** with 28% ee in 85% yield. The supernatant toluene solution of the catalyst (*R*)-**2** gave the adduct **5** in 80% yield with 30% ee and the precipitate as a basic catalyst also gave 40% ee with 90% yield indicating that the active catalyst was the precipitate itself. Thus, we carried out the Michael reactions using all the (*R*)-**2** as the catalyst.[4] Next, we examined the generality of the reaction and our results are shown in Table 1. Cyclic and acyclic enones gave Michael adducts in excellent yields with moderate ee's (entries 1–6). Enals also gave good yields of products albeit with lower ee (entry 8). The nature of the ester group of the malonate affected the ee of the



Scheme 1.

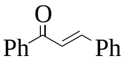
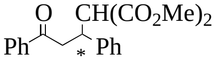
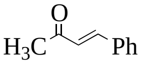
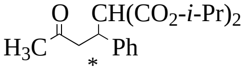
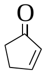
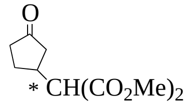
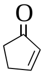
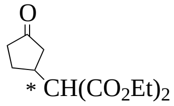
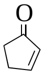
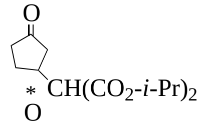
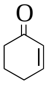
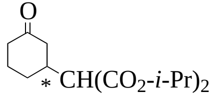
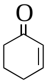
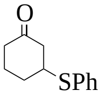
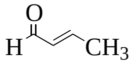
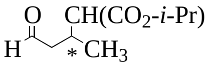
Keywords: calcium-BINOL; Michael reactions; Brønsted base; Lewis acid.

* Corresponding author. Tel.: +91-40-7171382; fax: +91-40-7173757; e-mail: gkswamy_iict@yahoo.co.in

† IICT Communication No. 4837.

PII: S0040-4039(01)01736-1

Table 1. Asymmetric Michael addition of malonates to enones and enols[a]

Entry	Enones/enals	Malonate	Adducts[c]	$[\alpha]_D^{25}$	Yield(%)[b]	%ee [d,e]
1)		$CH_2(CO_2Me)_2$		+ 14 (c=2, CHCl$_3$)	90	42 (*S*)
2)		$CH_2(CO_2\text{-i-Pr})_2$		+ 8 (c=2, CHCl$_3$)	85	39 (*S*)
3)		$CH_2(CO_2\ Me)_2$		+ 33 (c=5, CHCl$_3$)	75	88(*R*)[f]
4)		$CH_2(CO_2Et)_2$		+ 30 (c=5, CHCl$_3$)	76	87 (*R*)
5)		$CH_2(CO_2\text{-}i\text{-Pr})_2$		- 6 (c=5, CHCl$_3$)	68	24 (*S*)[f]
6)		$CH_2(CO_2\text{-}i\text{-Pr})_2$		+1 (c=5, CHCl$_3$)	55	21.3(*R*)
7)		PhSH		0	80	0
8)		$CH_2(CO_2\text{-}i\text{-Pr})_2$		+5 (c=2, CHCl$_3$)	60	31.25(*S*)

[a] All reactions were carried out on a 2 mmol scale except entries 3, 5 and 6 which were carried out on a 10 mmol scale.

[b] Isolated yields based on enones or enals.

[c] All the adducts gave satisfactory analytical data.

[d] Enantiomeric excess (ee) values were determined by optical rotation and comparison of values from known literature.[6]

[e] Absolute configurations were assigned by comparison of specific rotations with literature value.[6]

[f] Absolute configuration and ee values were determined by chemical correlation to known compounds using decarboxylation and methylation.[7]

product. Higher optical yields were obtained using Me or Et esters with cyclic enones. In the cases of acyclic enones and enals, the diisopropyl ester gave a better ee than the methyl or ethyl esters. Thiophenol as a donor gave a racemic product with 80% yield (entry 7).

In conclusion, we have succeeded in developing a substitute for La(O-i-Pr)$_3$. Although, the Al-Li-BINOL catalyst gave Michael adducts with good ee's, because of its sensitivity to moisture, it is not amenable for large-scale applications.[5] To the best of our knowledge, this new Ca-BINOL catalyst is the first of its kind. Calcium is not only an eco-friendly metal but is also inexpensive and readily available. Tuning the catalyst to achieve higher ee's is under progress in our laboratory.

Acknowledgements

We are grateful to the Director, IICT for his constant encouragement, and for the award of Prolog to Discovery Programme of IICT to G.K. Thanks are also due to UGC (New Delhi) for the award of JRF fellowships to M.N.V.S. and N.J. We also gratefully acknowledge the Gerchem Laboratory Pvt Ltd., Hyderabad for providing *R*-(+)-BINOL.

References

1. (a) For a review, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236; (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473; (c) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506.
2. Ikegami, S.; Yamada, Y. M. A. *Tetrahedron Lett.* **2000**, *41*, 2165.
3. (a) Without $CaCl_2$ the reaction proceeded yielding a racemic product. (b) The reaction of **3** with **4** was also carried out with $CaO+H_2O$; CaH_2+H_2O and $Ca(OAc)_2$ but the product was found to be racemic.

4. A typical procedure for Michael addition of dimethyl malonate **4** to chalcone **3**: To a mixture of (*R*)-(+)-BINOL (100 mg, 0.35 mmol, 15 mol%) and pot.*t*-butoxide (78 mg, 0.69 mmol), abs. ethanol (6 ml) was added at room temperature under an argon atmosphere. After stirring for 1 h, ethanol was evaporated under reduced pressure and to the residue, solid $CaCl_2$ (90%) (46.3 mg, 0.42 mmol) was added. Then, the solid was dried under vacuum (1 mmHg, 15 min) followed by the addition of abs. ethanol (6 ml). The white suspension was stirred for 5 h at ambient temperature and then subsequent evaporation of ethanol under reduced pressure gave a white solid powder. To this solid catalyst, toluene (15 ml) and abs. EtOH (0.1 ml) were added sequentially under argon atmosphere and the mixture was stirred for 12 h at ambient temperature. This reaction mixture was cooled at −15°C for 15 min followed by addition of a toluene solution (0.5 ml) of chalcone (485 mg, 2.3 mmol) at the same temperature. After 15 min, dimethyl malonate (368 mg, 2.7 mmol) was added dropwise via a syringe. The reaction mixture was stirred at −15°C for 24 h. The reaction was quenched with 2N HCl (5 ml) and extracted with EtOAc and dried over anhydrous Na_2SO_4. After concentration, the residue was subjected to column chromatography over aluminium oxide (neutral) (hexane:EtOAc 9:1) gave 565 mg of a white solid (90% yield, $[\alpha]_D^{25}$ +14 (*c* 2, $CHCl_3$)).
5. The production of a chiral binaphthol compound using a non-rare earth metal complex, US Patent 6,090,969 (Nagase and Co. Ltd., Osaka, Japan).
6. (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176; (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194; (c) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520; (d) Manickam, G.; Sundarajan, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2271.
7. Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; Cun-Heng, H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919.