Layered double hydroxides containing chiral organic guests: Synthesis, characterization and application for asymmetric C–C bond-forming reactions

B.M. Choudary *, B. Kavita, N. Sreenivasa Chowdari, B. Sreedhar, and M. Lakshmi Kantam

Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 11 September 2001; accepted 20 November 2001

We designed and developed two heterogeneous enantioselective catalysts, LDH-proline and LDH-BINOL, by incorporating chiral organic molecules *viz*., L-proline and S-BINOL, into layered double hydroxides (LDHs). These catalysts are characterized by IR, UV/vis and TGA analysis. These organo-LDHs have been successfully employed for various asymmetric C–C bond-forming transformations, and the products are obtained with good to excellent yields albeit low enantiomeric excess.

KEY WORDS: C–C bond formation; asymmetric catalysis; immobilization; LDH-proline and LDH-BINOL

1. Introduction

The formation of the carbon–carbon bond is one of the most fundamental reactions in organic synthesis. Asymmetric C–C bond formation is of great importance for the pharmaceutical, agrochemical and fine chemical industries [1]. Interest in asymmetric synthesis continues to increase, and this has heightened the need for the design of highly selective asymmetric catalysts. Most of this research activity concerns homogeneous catalysts, but there is a need for suitable heterogeneous asymmetric catalysts, as these catalysts readily overcome the problems typically encountered with homogeneous systems, *viz*., product recovery and catalyst separation. To date, three approaches have been made in the design of heterogeneous enantioselective catalysts. They are (i) the use of a chiral support for an achiral metal catalyst [2], (ii) modification of an achiral heterogeneous catalyst using a chiral cofactor [3–5] and (iii) the immobilization of homogeneous catalysts [6].

LDHs consist of stacks of positively charged mixed metal hydroxide layers that require the presence of interlayer anions to maintain overall charge neutrality. One such set of LDH is that in which the charge balancing anion is organic. The incorporation of organic guest molecules into inorganic layered hosts in general has been extensively investigated [7,8]. At the same time, proline [9] and BINOL [1] are extensively used as chiral auxiliaries for various asymmetric transformations under homogeneous conditions. Hence, we chose these chiral molecules for preparing organo-LDHs. Here, we report on the preparation, characterization and application of LDH-proline and LDH-BINOL for asymmetric C–C bond-forming reactions for the first time.

The anion-exchange method is the most common method for the preparation of organo-LDHs. The anion-exchange properties of LDHs containing simple inorganic anions are well documented [10–12]. The ease of exchange of monovalent anions is in the order $OH^- > F^- > Cl^- > Br^- > NO_3^-$. Divalent anions such as SO_4^{2-} and CO_3^{2-} have higher selectivity than monovalent anions. LDHs containing nitrate anions are, therefore, the most suitable precursors for anion-exchange synthesis due to the relative ease with which the nitrate anions can be displaced from the interlayer. In general, the anion-exchange reaction is carried out by simply dispersing the precursor LDH in an aqueous solution containing an excess of the organic anion that is to be incorporated.

The coprecipitation method for the direct synthesis of LDHs containing simple inorganic anions has also been developed over a number of years [13–15]. A similar procedure is used for the synthesis of organo-LDHs: the metal M^{2+} and M^{3+} hydroxide layers are nucleated and grown from an aqueous solution containing the anion that is to be incorporated into the LDH. This anion must have a high affinity for the hydroxide layers, otherwise the counter anions of the metal salts may be incorporated, thus contaminating the LDH. For this reason, metal nitrate or chloride salts are commonly utilized because of the low selectivity of LDH towards these anions. In general, the coprecipitation is performed by adding an aqueous solution of the metal nitrate or chloride salts to an aqueous solution of the organic anion. Usually, the coprecipitation is performed at a constant pH by simultaneous addition of aqueous NaOH solution.

* To whom correspondence should be addressed.
E-mail: choudary@iict.ap.nic.in

1011-372X/02/0300-0373/0

2. Experimental section

All the chemicals were of analytical grade (Aldrich) and used without further purification.

2.1. Preparation of LDH-proline

The LDH-proline catalyst was prepared by two methods, *viz*., anion exchange of precursor LDH and direct synthesis by coprecipitation.

2.1.1. Preparation of LDH-proline by anion exchange of LDH-nitrate

Mg-Al-NO_3 LDH was prepared under a nitrogen atmosphere to avoid formation of the carbonate. The Mg-Al-NO_3 LDH was prepared from magnesium nitrate hexahydrate (30.8 g, 0.12 mol) and aluminum nitrate nonahydrate (15.0 g, 0.04 mol) which were dissolved in 100 ml of deionized and decarbonated water. The pH of the solution was adjusted to 10 by the addition of aqueous 2M NaOH solution. The slurry was stirred for 2 h at room temperature under a nitrogen atmosphere, filtered, washed with water under a nitrogen atmosphere and then dried under vacuum at 80 °C for 10 h.

LDH-proline was prepared by reacting sodium salt of L-proline with LDH-nitrate as follows. 1.0 g of Mg-Al-NO_3 was suspended in 100 ml of 1 mmol sodium salt of L-proline solution and stirred at 25 °C for 24 h under a nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 ml of water and vacuum dried to obtain LDH-proline (0.225 mmol of proline per gram).

2.1.2. Preparation of LDH-proline by direct synthesis by coprecipitation

LDH-proline was prepared by reacting a mixed metal nitrate solution with a basic solution containing the organic anion. The L-proline (0.126 g, 1.1 mmol) was dissolved in a freshly prepared solution of NaOH (10 mmol in 10 ml of deionized and decarbonated water) and the resulting solution was stirred under nitrogen. A solution containing $Mg(NO_3)_2{\cdot}6H_2O$ (0.58 g, 2.3 mmol) and $Al(NO_3)_3{\cdot}9H_2O$ (0.43 g, 1.1 mmol) in 18 ml of deionized and decarbonated water was deaerated with nitrogen before the slow addition to the organic anion-containing solution. The pH of the reaction mixture remained fairly constant at 11.5–12 during the addition. The resulting precipitate was aged at 65 °C for 24 h and then filtered, washed with water and dried under vacuum to obtain LDH-proline (0.237 mmol of proline per gram).

2.2. Preparation of LDH-BINOL

The LDH-BINOL catalyst was also prepared by two methods, *viz*., anion exchange of precursor LDH and direct synthesis by coprecipitation.

2.2.1. Preparation of LDH-BINOL by anion exchange of LDH-nitrate

LDH-BINOL was prepared by reacting sodium salt of S-BINOL with LDH-nitrate as follows. 1.0 g of Mg-Al-NO_3 LDH was suspended in 100 ml of 1 mmol sodium salt of S-BINOL solution and stirred at 25 °C for 24 h under a nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 ml of water and vacuum dried to obtain LDH-BINOL (0.205 mmol of BINOL per gram).

2.2.2. Preparation of LDH-BINOL by direct synthesis by coprecipitation

LDH-BINOL was prepared by reacting a mixed metal nitrate solution with a basic solution containing the organic anion. The S-BINOL (0.314 g, 1.1 mmol) was dissolved in a freshly prepared solution of NaOH (10 mmol in 10 ml of deionized and decarbonated water) and the resulting solution stirred under nitrogen. A solution containing $Mg(NO_3)_2{\cdot}6H_2O$ (0.58 g, 2.3 mmol) and $Al(NO_3)_3{\cdot}9H_2O$ (0.43 g, 1.1 mmol) in 18 ml of deionized and decarbonated water was deaerated with nitrogen before the slow addition to the organic anion-containing solution. The pH of the reaction mixture remained fairly constant at 11.5–12 during the addition. The resulting precipitate was aged at 65 °C for 24 h and then filtered, washed with water and dried under vacuum (0.214 mmol of BINOL per gram).

3. Results and discussion

3.1 Characterization of organo-LDHs

X-ray powder diffraction patterns of the initial LDH and the organo-LDHs hardly differ in the range $2\theta = 3°-65°$. The observed d_{003} basal spacing of the support that appeared at 7.8 Å remained unchanged even after the anion exchange, which indicates that proline and BINOL are mainly located in the edge positions. The FTIR spectra of LDH-proline show a sharp peak at 1693 cm^{-1} which is assigned to the carbonyl stretching. The LDH-BINOL shows sharp peaks at 1650 and 1572 cm^{-1} which are assigned to the aromatic C−C stretching. The diffuse reflectance UV spectrum of the LDH-proline shows the absorption maxima at 215 nm while the LDH-BINOL shows the absorption maxima at 243 and 277 nm, which indicates the presence of organic guests in LDH. The BET surface area of LDH-proline and LDH-BINOL is found to be 90 and 69 $m^2\,g^{-1}$ respectively.

The incorporation of organic guests was checked by combined TG-DTA measurements (figure 1). The organo-LDHs decompose during heating to 650 °C in several well-defined steps. This behaviour indicates that the catalysts decompose in a relatively well-defined manner and release defined fragments which readily

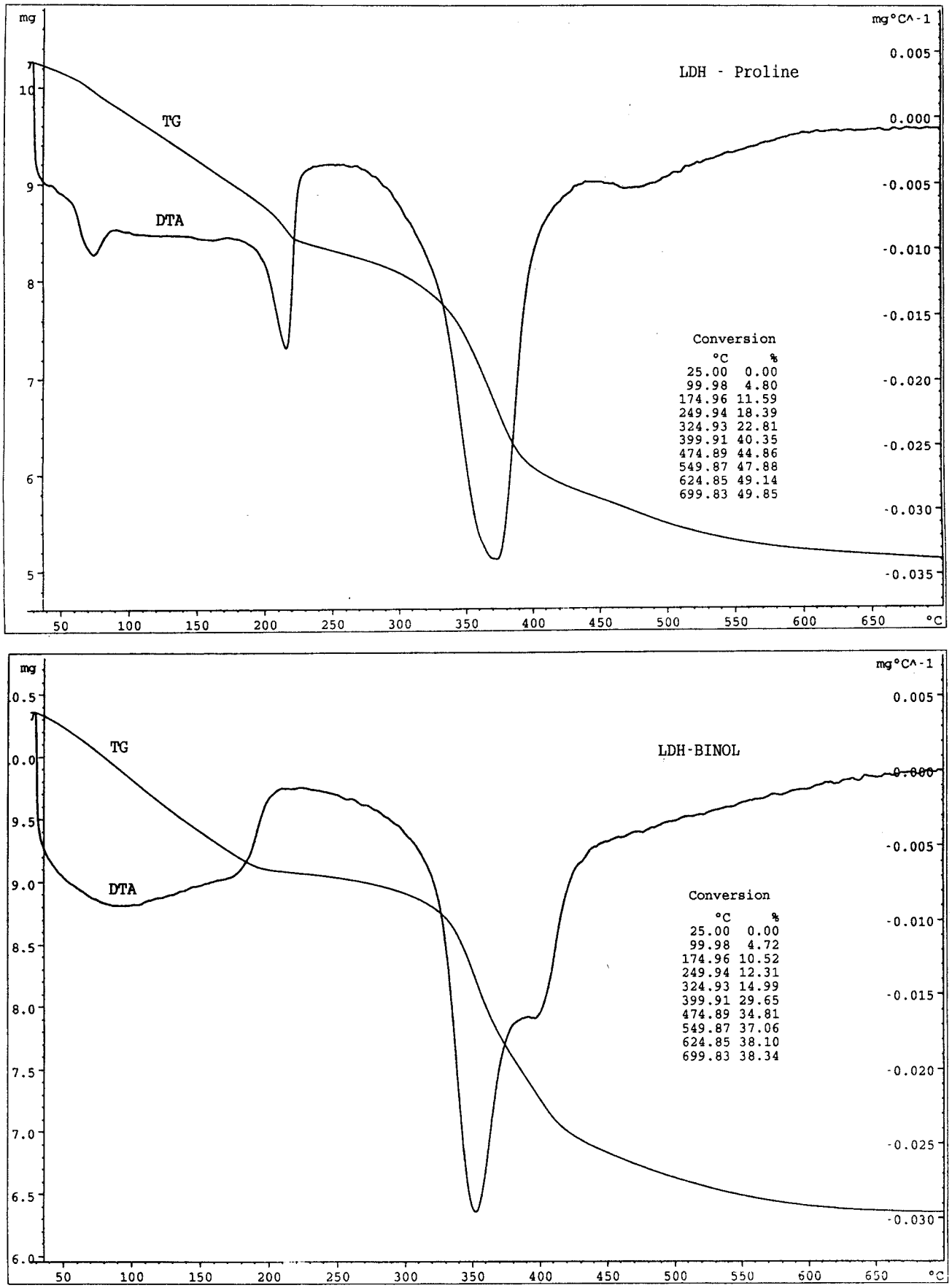
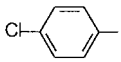


Figure 1. TG-DTA curves of (a) LDH-proline and (b) LDH-BINOL.

Table 1
Aldol reaction catalysed by organo-LDHs

Entry	R	Catalyst	Time (h)	Isolated yield (%)	$[\alpha]_D^{25}$ C = 1,$CHCl_3$	ee (%) [a]
1		LDH-proline	24	92	+4.21	6
		LDH-BINOL	24	90	+6.90	10
2		LDH-proline	24	95	+4.94	8
		LDH-BINOL	24	85	+2.23	3
3		LDH-proline	24	20	—	—
		LDH-BINOL	24	82	—	—

[a] Enantiomeric excess of the products was determined by HPLC analysis using a Chiralpak AD column with hexane/2-propanol as eluant.

burn off. An endothermic weight loss of 14–24% appears at <320 °C, which is attributed to the removal of physiosorbed water at the surface and between the hydroxide layers. The second weight loss of 15–18% between 320–400 °C is assigned to the dehydroxylation of the hydroxide layers. The third weight loss of 5% and 4% appears at >450 °C which may be attributed to the elimination and combustion of organic anions of proline and BINOL respectively.

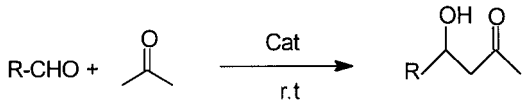
3.2 Application of organo-LDHs for asymmetric C–C bond formation

The activity of organo-LDH catalysts prepared by both methods was tested and found to be almost the same. Organo-LDHs were found to be excellent catalysts for carbon–carbon bond-formation reactions. The LDH support devoid of chiral guest in the control experiments did not show any activity in Aldol and Michael reactions and exhibited reduced activity in nitroaldol and cyanosilylation reactions. Hence, the C–C bond-forming activity and chemoselectivity displayed in the said reactions is correlated to the organo-LDH catalysts.

3.2.1. Aldol condensation

The aldol condensation is of prime importance for fine chemical synthesis and is generally catalyzed by acids or bases [16]. Recently many heterogeneous catalysts such as alumina, zeolites, sepiolite, and LDHs have been used for the aldol condensation. According to earlier reported work on aldolizations, the reactions were performed at relatively high temperatures and the major product was the dehydrated product. We tested the efficacy of LDH-proline/BINOL for aldol condensations (Scheme 1). Aldol products were obtained selectively in excellent yields under mild reaction conditions with low enantioselectivity (table 1).

In a general procedure, benzaldehyde (1 mmol) and LDH-proline/BINOL (0.01 mmol) were stirred in 1:4 acetone/heptane (10 ml) at room temperature. After completion of the reaction as monitored by thin layer chromatography (TLC), the catalyst was filtered, washed with ethyl acetate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the pure product. The recovered catalyst was successfully reused for 5 runs with consistent activity.

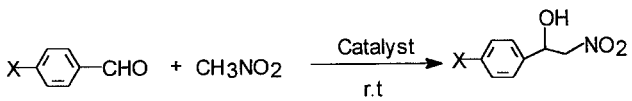


Scheme 1.

3.2.2. Henry reaction

The Henry (nitroaldol) reaction is one of the fundamental C–C bond-forming reactions to afford nitro alcohols, which are known to have potential utility as useful synthetic intermediates for further transformations in synthesis [17]. We employed LDH-proline/BINOL catalysts for the Henry reaction, and 2-nitroalkanols were obtained with 100% selectivity and excellent yields albeit with low enantioselectivity (table 2). Our catalytic systems are mild, simple and very convenient for the selective synthesis of 2-nitro alcohols under heterogeneous conditions.

A mixture of benzaldehyde (1 mmol), nitromethane (10 mmol) and LDH-proline/BINOL (0.01 mmol) catalyst was stirred at room temperature. After completion of the reaction as monitored by TLC, the catalyst was filtered, washed with ethyl acetate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the pure product.



Scheme 2.

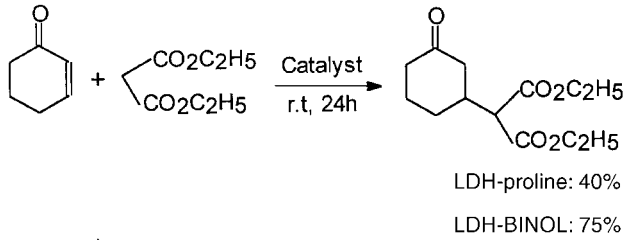
3.2.3. Michael reaction

The catalytic asymmetric Michael reaction is one of the most important synthetic methods for obtaining asymmetric centers [18]. We employed LDH-proline/BINOL catalysts for the Michael reaction and obtained products in moderate to good yields although racemic

Table 2
Henry reaction catalysed by organo-LDHs

Entry	X	Catalyst	Time (h)	Isolated yield (%)	$[\alpha]_D^{25}$ C = 1,$CHCl_3$	ee (%)
1	H	LDH-proline	12	75	+3.78	8
		LDH-BINOL	16	80	+2.83	6
2	NO_2	LDH-proline	1	98	+2.78	5
		LDH-BINOL	24	90	+5.00	9

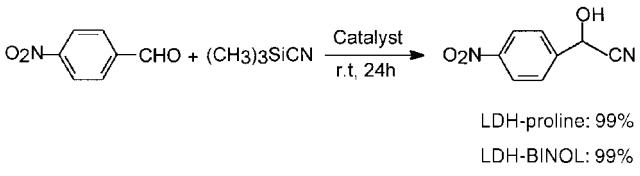
(Scheme 3). In a general procedure, cyclohexenone (1 mmol) and LDH-proline/BINOL (0.02 mmol), were stirred in 5 ml of methanol, then diethyl malonate (1 mmol) was added and stirring was continued for 24 h. The catalyst was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the pure product.



Scheme 3.

3.2.3. Cyanosilylation

Cyanohydrins are versatile synthons for the preparation of various useful synthetic intermediates [19]. We also tested LDH-proline/BINOL as heterogeneous catalysts for the addition of trimethylsilyl cyanide to carbonyl compounds (Scheme 4) to give trimethylsiloxy alkanenitriles in quantitative yields under mild reaction conditions. But the enantioselectivity is poor.



Scheme 4.

A 50 ml two-necked round bottomed flask equipped with a magnetic stir bar was charged with LDH-proline/BINOL (0.02 mmol) and 4-nitrobenzaldehyde (2 mmol) in dry toluene (5 ml). Trimethylsilylcyanide (0.36 ml, 3 mmol) was added to the reaction mixture and allowed to stir at room temperature for 24 h. After completion of the reaction as monitored by TLC, the catalyst was filtered and washed with toluene. The combined filtrates were treated with 1 N HCl and upon usual work-up the desired product was obtained in quantitative yield.

In conclusion, we designed and developed two heterogeneous enantioselective catalysts, *viz*., LDH-proline and LDH-BINOL, by incorporating chiral organic molecules, L-proline and S-BINOL, into LDHs. These organo-LDHs have been successfully employed for various asymmetric C–C bond-forming transformations and the products were obtained in good to excellent yields. Although the ees are less at this initiation stage, the work in this new area certainly spurs others to obtain an accomplished catalyst in terms of enantioselectivity too. These new solid catalysts have the advantages of (1) high catalytic activity under very mild liquid phase conditions; (2) easy separation of the catalyst by simple filtration; (3) formation of no side products; (4) use of non-toxic and inexpensive catalysts; (5) reusability; (6) zero emission of pollutants; and (7) eco-friendliness.

Acknowledgment

B.K. and N.S.C. thank the Council of Scientific and Industrial Research, India, for providing research fellowships.

References

[1] M. Shibasaki, H. Sasai and T. Arai, Angew. Chem. Int. Ed. Engl. 36 (1997) 1236.
[2] G.M. Schwarb and L. Rudolph, Naturwissensehaft 20 (1932) 362.
[3] H.U. Blaser, H.P. Jalett, D.M. Monti, A. Baiker and J.T. Wehrli, Stud. Surf. Sci. Catal. 67 (1991) 147.
[4] G. Webb and P.B. Wells, Catal. Today 12 (1992) 319.
[5] A. Baiker, Stud. Surf. Sci. Catal. 101 (1996) 51.
[6] M.A. Kcane and G. Webb, J. Catal. 136 (1992) 1.
[7] G. Lagaly and K. Beneke, Colloid Polym. Sci. 269 (1991) 1198.
[8] B.K.G. Theng, *The Chemistry of Clay-Organic Reactions* (Wiley, New York, 1974).
[9] H. Groger and J. Wilken, Angew. Chem. Int. Ed. Engl. 40 (2001) 529.
[10] S. Miyata, Clays Clay Miner. 31 (1983) 305.
[11] G.W. Brindley and S. Kikkawa, Clays Clay Miner. 28 (1980) 87.
[12] A. Mendibourne and R. Schollhorn, Rev. Chem. Miner. 23 (1986) 819.
[13] W. Feitknecht, Helv. Chim. Acta 25 (1942) 131.
[14] W.T. Reichle, Solid State Ionics 22 (1986) 135.
[15] S. Miyata and A. Okada, Clays Clay Miner. 25 (1977) 14.
[16] T. Bach, Angew. Chem. Int. Ed. Engl. 33 (1994) 417.
[17] G. Rosini, in: *Comprehensive Organic Synthesis*, Vol. 2, ed. C.H. Heathcock (Pergamon, Oxford, 1991) p. 321.
[18] M. Yamaguchi, T. Shiraiashi and M. Hirama, Angew. Chem. Int. Ed. Engl. 32 (1993) 1176.
[19] M. Hayashi, T. Inoue, Y. Miyamoto and N. Oguni, Tetrahedron 50 (1994) 4385.