Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1147–1150

TETRAHEDRON: *ASYMMETRY*

Sc(BINOL)$_2$Li: a new heterobimetallic catalyst for the asymmetric Strecker reaction

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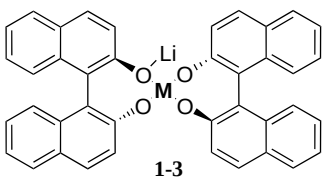
Received 6 March 2001; accepted 21 March 2001

Abstract—The new chiral heterobimetallic complex Sc(BINOL)$_2$Li **1** was prepared and used as a catalyst in the enantioselective addition of a cyanide source (HCN or TMSCN) to several imines. High conversion rates and enantiomeric excesses (e.e.s) as high as 95% were obtained.

1. Introduction

In the last few years, a dramatic breakthrough has been made in the catalytic enantioselective Strecker synthesis.[1] During the course of our own work on this subject,[2] we were interested in the new concept of heterobimetallic catalysts developed by Shibasaki et al.[3] These complexes behave as Lewis acids and also as Brönsted bases. Thus, they enantioselectively catalyse reactions involving deprotonation of a weakly acidic site in the presence of a carbonyl compound, as in Michael or nitroaldolisation reactions. There is some analogy in the addition reaction of HCN to imines. Thus, we decided to investigate the application of such heterobimetallic complexes in the Strecker reaction. Herein, we report that new heterobimetallic catalysts, in particular Sc[(*R*)-BINOL]$_2$Li **1**, can be effectively applied in the Strecker reaction.

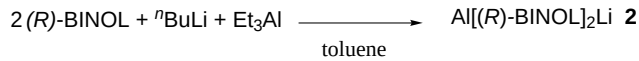


1-3

1: M = Sc^{III}
2: M = Al^{III}
3: M= Ti^{III}

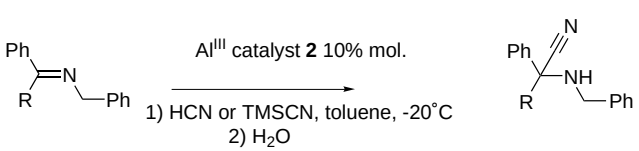
2. Results and discussion

We began our study by testing existing complexes. Initial results were encouraging: a commercial[4] sample of La[(*R*)-BINOL]$_3$Li$_3$ did catalyse the addition,[5] but without any enantioselectivity. In contrast, the complex Al[(*R*)-BINOL]$_2$Li **2**, prepared from LiAlH$_4$ in THF, catalysed the same reaction with modest asymmetric induction. As the hydrocyanation of imines in polar solvents is rapid without a catalyst, we aimed to develop a new procedure for the in situ preparation of **2**. It was found that by reacting hexane solutions of AlEt$_3$ and *n*-BuLi with (*R*)-BINOL in toluene, the complex **2** could be obtained free of THF (Scheme 1).



Scheme 1. Synthesis of Al[(*R*)-BINOL]$_2$Li **2**.

Since excellent methods for the enantioselective hydrocyanations of aldimines have been available since 1996, we focused on the much less documented analogous reactions of ketimines as model substrates (but see Ref. 2). We selected a ketimine as our model substrate since few enantioselective hydrocyanation methods were available in this case when we started (Scheme 2, Table 1). Different sources of cyanide were tested. The e.e.s ranged from 4 to 38%. Substitution of HCN by TMSCN (trimethylsilyl cyanide) led to higher e.e.s when the substrate was a ketimine. Using the more sterically hindered cyanide source, Ph$_3$B(CN)H, resulted in low yields and racemic aminonitriles. Working at a lower temperature (–65°C) slowed down the reaction without improving the enantioselectivity. Use



Scheme 2. Catalytic hydrocyanation with **2**.

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PII: S0957-4166(01)00144-6

Table 1. Asymmetric hydrocyanation of imines catalysed by Al[(*R*)-BINOL]$_2$Li **2**[a]

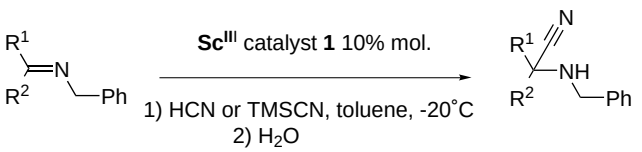
R =	XCN =	*T* (°C)	Time (h)	Conv. (%)[b]	E.e. (%)[c]
Me	HCN	−20	1.5	>95	20
–	–	−65	1.5	80	20
–	TMSCN	−20	6	>95	31
–	Ph_3BCN	−20	3	50	4
H	HCN	−20	1.5	50	38
–	TMSCN	−20	8	50	32

[a] All runs were carried out in toluene in the presence of 10 mol% of **2**.
[b] Determined by ^{1}H NMR of the crude product. Adducts from ketimines decompose on chromatography, to give the ketone.
[c] Determined by chiral HPLC.

of the coordinating solvents diethyl ether or THF led to the formation of racemates.

In an attempt to tune the structures of the catalysts we investigated two new heterobimetallic complexes, based on the transition metal–$BINOL_2$–lithium structure. We chose Ti^{III} and Sc^{III} as metal centres.

The highly sensitive titanium^{III} derivative, Ti[(*R*)-BINOL]$_2$Li **3**, did not lead to an efficient catalytic system. When the ketimine benzyl-(1-phenyl-propylidene)amine was treated with TMSCN in the presence of 10 mol% of the chiral complex **3** in toluene at −20°C over 2 h, a 45% yield of aminonitrile with e.e. of 20% resulted. We suppose that this mediocre result could be linked with the instability of the Ti^{III} oxidation state. We therefore focused our research on the more stable scandium analogue, Sc((*R*)-BINOL)$_2$Li **1**.



Scheme 3. Catalytic asymmetric hydrocyanation of imines with **1**.

Under the previous reaction conditions, using complex **1** gave rise to a more stereoselective reaction. Indeed, an e.e. of 95% was obtained for *N*-benzylidene-benzylamine at −20°C (Scheme 3, Table 2). A slight decrease in e.e. and a marked decrease in the reaction rate was observed as the reaction proceeded, but on standing for a prolonged time the imine/product ratio and the e.e. remained stable. An explanation for such trends is catalyst poisoning or decay.

The enantioselectivity was slightly lower (81%) when HCN was used as the cyanide source and when the substrate was a ketimine, the e.e., although better than reactions with Al(BINOL)$_2$Li, remained poor.

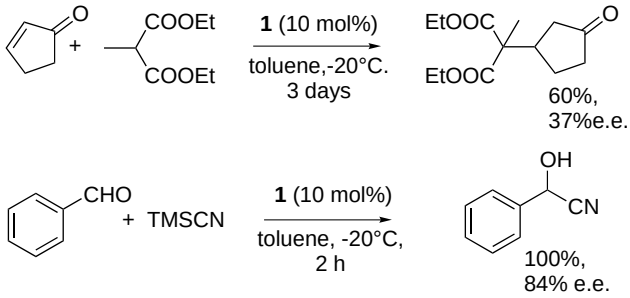
Complex **1** was also found to be a moderate enantioselective catalyst in the Michael reaction between 2-cyclopentenone and diethylmethylmalonate. When the reaction was completed in toluene with 10 mol% of **1** the 1,4-adduct was obtained in 60% yield with an e.e. of 37%.

Notably, **1** induced high enantioselectivity in the addition of TMSCN to benzaldehyde. The reaction was completed with 10 mol% of **1** and gave the corresponding cyanohydrin in quantitative yield and e.e. of 84% (Scheme 4).

Table 2. Asymmetric hydrocyanation of imines catalysed by Sc[(*R*)-BINOL]$_2$Li **1**[a]

R^1	R^2	XCN	*T* (°C)	Time (h)	Conv. (%)[b]	E.e. (%)[c]
Ph	Me	TMSCN	−20	1	50	95
–	–	–	–	3	80	91
–	–	–	–	9	>95	88
–	–	–	–	96	>95	85
–	–	HCN	−40	1	55	75
–	–	–	−40 to 0	4	95	81
β-Naphthyl	H	TMSCN	−20	3	45	65
–	–	HCN	0	1	60	71
–	–	–	−20	1	80	86
Ph	Me	TMSCN	−20	1	20	55
–	–	–	–	3	42	50
–	–	–	–	6	70	45

[a] All runs were carried out in toluene in the presence of 10 mol% of **1**.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by chiral HPLC.



Scheme 4. Other catalytic applications of **1**.

3. Conclusion

Although the level of enantioselectivity obtained does not currently compete with the beautiful recent achievements in Strecker synthesis, the present work shows a new facet of the versatility of the heterobimetallic catalysts devised by Shibasaki et al. We believe that the readily available new member of the family, Sc[(*R*)-BINOL]$_2$Li **1**,[6] deserves further investigation.

4. Experimental

All reactions were carried out in Schlenk tubes, under inert atmosphere, using freshly distilled solvents. HCN solutions in toluene were prepared from in situ reaction of methanol and TMSCN analogously to Ref. 2.

HPLC analysis were performed on a Shimadzu apparatus (UV diodes array detector) equipped with a chiral column Daicel Chiralpak OD (25 cm).

4.1. Preparation of aluminium–(BINOL)$_2$Li 2

Using standard Schlenk techniques. A solution of $AlEt_3$ (1 M, 26 μL, 0.025 mmol) in toluene was added to (*R*)-BINOL (15 mg, 0.05 mmol, 2 equiv.) in dry toluene (2.5 mL), under an inert atmosphere. After stirring for 1 h at 50°C, the brown solution was cooled and a solution of *n*-BuLi in hexanes (1.6 M, 33 μL, 0.025 mmol, 1 equiv.) was added. The mixture was stirred for a few minutes at room temperature and the solution was cooled to the desired temperature for the addition of the reagents

4.2. Preparation of scandium–(BINOL)$_2$Li 1

A solution of *n*-BuLi in hexane (1.6 M, 130 μL) was added at 0°C to a solution of (*R*)-BINOL (28.5 mg, 0.1 mmol) in Et_2O (5 mL). The mixture was stirred for 0.5 h at room temperature before the addition of $ScCl_3$ (8.5 mg, 0.056 mmol) in THF (4 mL). The reaction mixture was stirred under reflux overnight. Toluene (15 mL) was added and the solvents were removed in vacuo. This was repeated twice in order to ensure the best removal of the polar solvent. The complex was then dissolved in toluene (5 mL) and cooled to the desired temperature for the Strecker reaction. Complex **3** was prepared according to the same procedure but replacing $ScCl_3$ with $TiCl_3$.

4.3. General procedure for the catalytic Strecker reaction

The imine (0.5 mmol) was added to a mixture of the cyanide source (1 mmol, 2 equiv.) and the catalyst (0.05 mmol) in toluene (5 mL) at the required temperature. The resulting mixture was stirred for the indicated time and the reaction was quenched by addition of a saturated solution of Na_2CO_3. The mixture was extracted with Et_2O, the resulting organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo.

Conversions were estimated by NMR analysis of the crude aminonitrile and the e.e. was measured either by NMR (formation of a diastereoisomeric salt by adding (*R*)-camphor-sulfonic acid as a chiral solvating agent[7]) or by chiral HPLC analysis.

4.4. 2-Benzylamino-2-phenylpropionitrile

IR (film): 3320, 3063, 3030, 2984, 2849, 2223, 1958, 1897, 1811, 1603, 1494, 1447, 1372, 1214, 1152, 1075, 1037, 863, 765, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 to 7.32 (m, 10H), 3.87 and 3.56 (dd, $J=13.0$ Hz, 2H), 1.78 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 139.5, 138.8, 128.7, 128.4, 128.3, 128.0, 127.2, 125.3, 121.1, 60.3, 49.3, 31.1. NMR determination of the e.e.: The benzylic CH_2 appears as an AB system at 3.56 ppm. Upon addition of increasing amounts of the chiral solvating agent (*R*)-camphor-sulfonic acid, it splits into two new AB systems between 3.6 and 4.3 ppm. The relative integration of each system gave the enantiomeric ratio of the aminonitrile product. HPLC measurement of the e.e.: cyclohexane/propan-2-ol (99/1), 0.5 mL/min, $t_R=12.0$ min (minor) and 13.5 min (major).

4.5. 2-Benzylamino-2-phenylacetonitrile

Purified by flash chromatography over silica (eluent: pentane/dichloromethane, 5/95); yield = 61%; IR (film): 3331, 2963, 2931, 2857, 2229, 1951, 1886, 1805, 1649, 1600, 1455, 1380, 1265, 1094, 1029, 800, 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 to 7.24 (m, 10H), 4.74 (s, 1H), 4.0 (dd, 2H), 1.85 (broad s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 138.1, 134.7, 128.9, 128.6, 128.4, 127.6, 127.2, 118.7, 53.4, 51.2. HPLC measurement of the e.e.: cyclohexane/propan-2-ol (99/1), 0.5 mL/min, $t_R=17.1$ min (minor, (*S*)-enantiomer) and 18.0 min (major, (*R*)-enantiomer). $[\alpha]_D^{20}=+41.1$ (*c* 0.88, $CHCl_3$), measured on a sample of 58% e.e.

Absolute configuration: 53 mg of this isolated sample was dissolved in formic acid (1 mL), and dry HCl gas was bubbled through the solution for 1 h. After standing overnight at 20°C, the solvent was evaporated. The obtained α-aminocarboxamide was hydrogenolysed in methanol (3 mL), with Pd/C (10%, 100 mg) and ammonium formate (150 mg) under reflux for 2 h, the mixture was filtered through Celite and evaporated. The sample, in ethanol (1.00 mL), had $[\alpha]_D^{20}=+2.13$ (lit.[8] for the (*R*)-enantiomer: $[\alpha]_D^{22}=+103$ (*c* 1.2, EtOH)).

4.6. 2-Benzylamino-2-naphthylacetonitrile

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.15 to 7.37 (m, 12H), 5.04 (d, $J=9.5$ Hz, 1H), 4.16 (broad dd, 2H), 2.07 (broad s, 1H). NMR determination of the e.e.: The benzylic CH_2 appears as an AB system at 4.16 ppm. Upon addition of the chiral solvating agent (*R*)-camphor-sulfonic acid, it is split into two new AB systems between 5.6 and 5.4 ppm.

4.7. Michael reaction

To catalyst **1** (0.1 mmol), prepared as above, were added cyclopentene-2-one (42 mg) and dimethylmethylmalonate (87 mg). After stirring for 3 days at 20°C, the reaction mixture was treated with aqueous HCl (1 M, 5 mL) and extracted with diethyl ether. After washing the combined ethereal extract with $NaHCO_3$ (1 M), drying and concentrating, NMR analysis of the crude indicated 60% conversion. The e.e. of the adduct[9] was 37% by HPLC analysis: 97% cyclohexane/^{i}PrOH, 0.5 mL/min, $t_R=13.1$ min (major) and 13.7.0 min (minor).

4.8. Cyanohydrin preparation

To catalyst **1** (0.1 mmol), prepared as above in toluene (3 mL) at 20°C, were added benzaldehyde (60 mg) and trimethylsilylcyanide (0.13 mL). After 2 h at 20°C, the mixture was hydrolysed with aqueous HCl (1 M). The mixture was extracted with ether, dried over sodium sulfate and concentrated; NMR analysis of the evaporation residue indicated complete conversion. For HPLC analysis, the crude material was acylated[10] (^{i}PrCOCl, pyridine, cat. DMAP, in dichloromethane overnight). HPLC analysis indicated 84% e.e.: 99.5% cyclohexane/^{i}PrOH, 0.5 mL/min, $t_R=19.6$ min (major) and 21.7 min (minor).

Acknowledgements

We thank the Aventis Crop Science Co. for financial support and Dr. V. Henryon for fruitful discussions.

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