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Asymmetric Strecker reactions of ketimines catalysed by titanium-based complexes

Janice J. Byrne, Murielle Chavarot, Pierre-Yves Chavant and Yannick Vallée *

L.E.D.S.S., associé au CNRS, Université Joseph Fourier, B.P. 53X, 38041 Grenoble, France

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Abstract

The asymmetric addition of TMSCN to a ketimine has been achieved by use of catalytic quantities of chiral titanium(IV) complexes. Fast conversions together with enantiomeric excesses as high as 59% have been achieved.

The classical Strecker synthesis[1] is one of the most convenient methods for the preparation of α-amino acids. Enantioselective approaches to the reaction generally involve the use of preformed imines whereby the nitrogen atom bears a chiral inductor.[2] Recently, enantioselective additions of HCN to imines have been reported, involving either metallic complexes[3] or organic molecules[4] as catalysts. Nevertheless, all the reported data involve additions to aldimines, not ketimines. We focused on the obtention of α-alkylated α-aminonitriles[5] from ketimines and report here our results using titanium based catalysts for this purpose.

As a first approach to this problem we tested several complexes which were known to catalyse asymmetric synthesis of cyanohydrins. We examined the reaction of the *N*-benzyl-phenyl-methyl-imine **1** with cyanotrimethylsilane (TMSCN) in the presence of 0.1 equivalent of the chiral alkoxytitanium(IV) **2** prepared from dichlorodiisopropoxytitanium and (*R*,*R*)-TADDOL.[6] When **1** is treated with TMSCN in the presence of the chiral titanium reagent **2** in dichloromethane at −40°C (Run 1, Scheme 1), the corresponding α-aminonitrile is formed with poor enantioselectivity and a low rate of conversion.

Replacing the chloride ligands by phenoxy based ligands leads to catalysts which show higher rates of conversion (Table 1). In the simplest case where 2,2′-biphenol (BIPOL) replaces the chlorine atoms the reaction rate doubles but the enantioselectivity drops to less than 10%. This may be rationalised by the formation of the complex $Ti(BIPOL)_2$ as a side product, which catalyses the addition reaction without selectivity. We then used chiral 2,2′-binaphtol (BINOL) ligands to replace the halide groups. The presence of either (*R*) or (*S*)-BINOL achieves high conversion rates. The orientation of the enantioselection was found to be still governed by the TADDOL ligand. The complex Ti((*S*)-TADDOL)((*R*)-BINOL)

* Corresponding author. E-mail: yannick.vallee@ujf-grenoble.fr (Y. Vallée)

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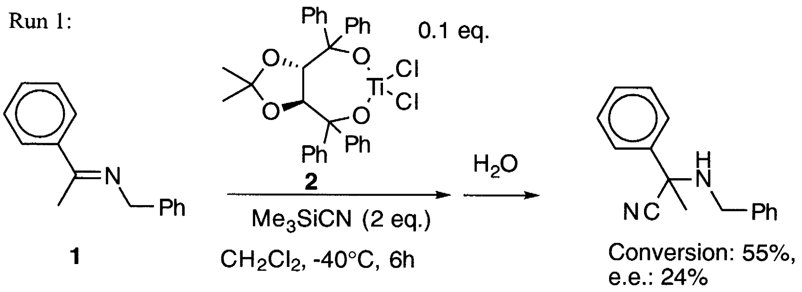
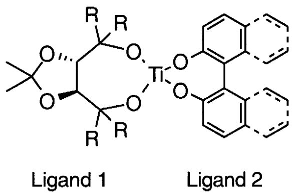


Scheme 1.

catalyses addition of TMSCN to imine **1** with a 31% e.e. Increasing the steric congestion about the metal by replacing TADDOL by its β-napthyl homolog leads to higher enantiomeric excesses. However, further steric congestion about titanium by use of the α-napthyl derivative of TADDOL does not improve the result.

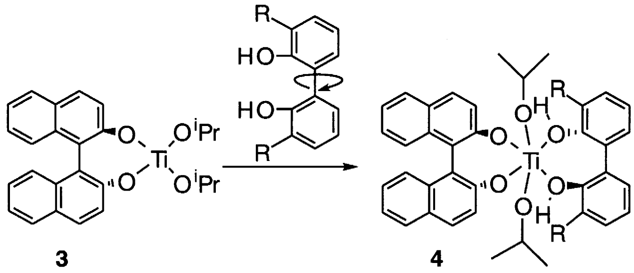
Table 1
Asymmetric hydrocyanation of **1** catalysed by titanium-TADDOL complexes[7]



Run	Ligand 1 : R=	Ligand 2	Time (h)	Conversion (%)	e.e. (%)
2	Phenyl (4*S*, 5*S*)	BIPOL	6	95	8
3	"	*(R)*-BINOL	6	95	31
4	"	*(S)*-BINOL	6	95	13
5	β-napthyl (4*S*, 5*S*)	*(R)*-BINOL	3[8]	80	45
6	α-napthyl (4*S*, 5*S*)	*(R)*-BINOL	3[8]	75	26

These results led us to study the use of BINOLTi(OiPr)$_2$ **3** as a catalyst for TMSCN additions[3a] to imines (Scheme 2). The reaction at −40°C in dichloromethane gives poor conversions and no enantioselection. However, in toluene at −20°C the addition proceeds smoothly with 12% e.e. Activation of the catalyst by a second BINOL ligand[9] leads to a similar effect as that noted in the case of the TADDOL based complex. We then studied the effect[9b] of achiral 2,2′-biphenol (BIPOL) and substituted BIPOL ligands on the e.e. (Table 2, runs 7–14). It is worth noting that all BINOLs activate the titanium complex **3**. In the case of the highly sterically hindered 3,5,3′,5′-tetra^{t}Bu-2,2′-biphenol (Run 14) the enantioselectivity of the TMSCN addition is greatly increased, while conversions are still rapid.

Some studies[9a] on biphenolate species of titanium(IV) have suggested that when **3** is activated by a second BINOL, the latter coordinates to the metal without removal of the isopropoxy ligands. We became curious to know the effect of replacement of one of the phenolic ligands by its bis-*O*-methyl derivative on conversions and e.e. (Table 2). The best results were obtained when the bis-methyl ether of BIPOL was combined with the BINOL-titanium catalyst **3**. The combination of (*R*)-BINOL with this (*S*)-bismethyl ether also gave the same enantiomeric excess as those obtained with the (*R*)-BINOL-(*R*)-bismethyl ether pair. Thus, the orientation of enantioselection is always governed by the BINOL group and the chirality of the ether ligand does not play a role in the asymmetric induction.



Scheme 2.

Table 2

Asymmetric hydrocyanation of **1** catalysed by titanium-(*R*)-BINOL complexes (0.1 equiv./imine), in the presence of additives[6]

Run	Activator	Amount (eq.// imine)	Time (h)	conversion (%)	e.e. (%)
7	None	0.1	1	50	12
8	*(R)*-BINOL	0.1	1	80	33
9	BIPOL	0.1	1	87	30
10	3,3',5,5',-tetrachloro-BIPOL	0.1	1.6	86	30
11	3,3',5,5',-tetrabromo-BIPOL	0.1	1.5	95	28
12	3,3'-diphenyl-BIPOL	0.1	1.5	95	28
13	3,3',5,5,-tetranitro-BIPOL	0.1	1.5	80	16
14	3,3',5,5,-tetra^{t}butyl-BIPOL	0.1	1	90	48
15	2,2'-methoxy-biphenyl	0.1	1.5	80	47
16	*(R)*-2,2'-methoxy-binaphtyl	0.1	1	40	33
17	*(S)*-2,2'-methoxy-binaphtyl	0.1	1	60	41
18	3,3'-dibromo-2,2'-methoxy-biphenyl	0.1	1	66	30
19	Et_2O	0.2	1	85	37
20	"	1.0	1	50	32
21	$(MeOCH_2)_2$	0.1	1	73	30
22	$(^iPr)_2NH$	0.4	1	60	33
23	Pyridine	0.2	2	20	26
24	$(^iPr)_2EtN$	0.2	2	66	25
25	TMEDA	0.2	1	80	56
26	Et_3N	0.2	1.5	25	59
27	"	0.2	4	66	50

We also checked the effect of simple non-chiral ethers or amines additives.[10] Excesses as high as 59% were achieved when Et_3N was present in catalytic quantities. The use of tertiary amines led to higher e.e.s than secondary amines and pyridine, although increasing the bulkiness of the amine (run 24) appeared to be unsatisfactory.

In conclusion, we have achieved enantioselective additions of TMSCN to a ketimine. Many species containing a mixture of chiral and/or achiral ligands bound to the central metal atom have been tested. In the case of titanium–TADDOL complexes, adding BIPOL lowers the e.e. while raising the rate of conversion. In the case of addition of a BINOL ligand to the titanium–TADDOL complex the match pair corresponds to the system where all possible catalytic species present in equilibrium direct additions towards the same enantiomer. The steric demand of the β-napthylTADDOL derivative may inhibit equilibration with $(TADDOL)_2Ti$ species and therefore limit the number of possible sub-catalysts present in solution; thus, one catalyst which is of moderate enantioselectivity is present. Table 2 supports a similar theory. The (BINOL)(BIPOL)Ti species shows higher stereoselectivity when a bulky substituent is present on the BIPOL unit. The best results were achieved in the presence of TMEDA. Although the exact nature of the amine-activated complexes is unknown, we propose the formation of a TMEDA-chelated, monomeric metal species.

Acknowledgements

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7. Typical experimental procedure: Imine **1** (105 mg, 0.5 mMol) was added to a mixture of TMSCN (0.13 mL, 1.0 mMol) and the particular catalyst (0.05 mMol) in dichloromethane (5 mL) at −40°C (runs 1–6) or in toluene (5 mL) at −20°C (runs 7–26). The resulting mixture was stirred for the given time and the reaction quenched by addition of a saturated solution of Na_2CO_3, extracted with ether, dried and concentrated. Conversions were measured from ^{1}H NMR and enantiomeric excesses measured by HPLC analysis (Daicel Chiralpak AD, 25 cm; eluant cyclohexane:^{i}PrOH, 99:1; 1 mL/min; retention times 12 min and 13.5 min). In all runs described, the latter enantiomer is in excess.
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