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A new enantioselective Mannich-type reaction catalyzed by bis-binaphthoxy iodo samarium

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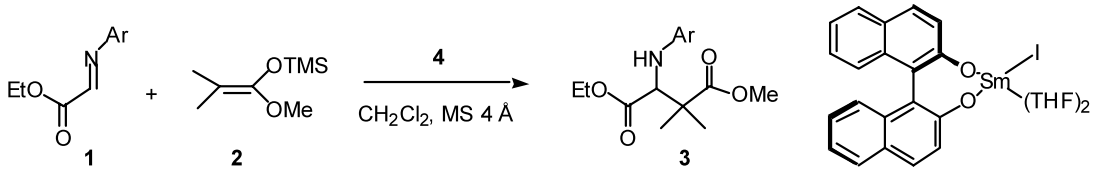
Abstract—A new catalytic enantioselective Mannich type reaction involving a glyoxylic imine and a ketene silyl acetal is described. A chiral samarium catalyst coordinated to a binaphthol ligand is used in the presence of aniline as an additive. Under optimized conditions, at 30°C, enantiomeric excesses up to 90% are obtained.

1. Introduction

Although catalytic asymmetric Mukaiyama aldol reactions have been widely studied,[1,2] similar Mannich reactions involving silicon enolates (ketene silyl acetals, enoxysilanes) have only been recently developed.[3,4] Kobayashi first reported, as Lewis acid type enantioselective catalysts, complexes of zirconium coordinated by substituted binaphthol ligands.[5–8] High asymmetric inductions were obtained only in the presence of additives, and in reactions involving chelating imines with *N*-substituted hydroxyphenyl moieties. Another catalytic system resulting from $FeCl_2$, BINOL and additives has been reported as an asymmetric Lewis acid catalyst for the same reaction.[9] Palladium or copper complexes coordinated by chiral diphosphines such as BINAP or TolBINAP have been described by Sodeoka and Lectka as enantioselective catalysts for the addition of enol silyl ethers to glyoxylic imines,[10,12] *N*,*O*- or *N*,*N*-acetals and hemiacetals.[13,14] Similar methodology was extended by Kobayashi to *N*-acyl imino esters with chiral copper catalysts,[15] and *N*-hydrazino imino esters were employed in enantioselective reactions catalyzed by zinc with chiral diamines as ligands in water/THF mixtures.[16] However the scope of reactivity of these catalytic systems is limited, and to the best of our knowledge, no enantioselective catalyst has been reported for the addition of ketene silyl acetals onto aromatic glyoxylic imines.

In previous studies we have investigated the activity of samarium diiodide as an efficient Lewis acid catalyst for a wide range of reactions,[17] such as Mukaiyama aldol reactions,[18] Diels–Alder reactions[19] and tandem Mukaiyama-aldol reactions.[20] We found that samarium diiodide can be used similarly for reactions involving imines such as Mannich reactions, aza Diels–Alder reactions,[21] and tandem Michael imino-aldol reactions.[22] With the aim to develop asymmetric catalysts based on lanthanides, we prepared lanthanide iodo bis-binaphthoxides which are active catalysts for Diels–Alder reactions albeit with low enantioselectivities.[23] We now report the use of samarium iodo bis-binaphthoxide as an enantioselective catalyst for the addition of ketene silyl acetal on a glyoxylic imine and the optimisation of the catalytic system.



1a Ar = Ph

1b Ar = *p*-anisyl

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Table 1. Influence of reaction conditions and presence of an additive on Mannich reactions

Entry	Imine[a]	T (°C)	t (h)	Amine	Yield(%)	Ee (%)
1	**1a**[b]	20	2		38[e]	10
2	**1a**[c]	20	2		57[e]	14
3	**1a**[c]	0	2		46[e]	38
4	**1a**[d]	0	2		96[f]	31
5	**1b**[c]	20	2		50[f]	0
6	**1b**[b]	20	18	*p*-Anisidine 20%	70[f] (50[e])	20
7	**1b**[c]	20	18	*p*-Anisidine 20%	50[f]	30
8	**1b**[c]	20	2	*p*-Anisidine 10%	50[f]	6
9	**1b**[c]	20	2	*p*-Anisidine 20%	34[f]	25
10	**1b**[c]	20	2	*p*-Anisidine 50%	53[f]	25

[a] All reactions are performed in CH_2Cl_2 using 10% catalyst **4**.
[b] Rapid addition of 1.4 equiv. of **2**.
[c] Slow addition of 1.4 equiv. of **2** with syringe pump within 2 h.
[d] Slow addition of imine **1a** and of 1.4 equiv. of **2** with syringe pump.
[e] Isolated yield in **3**.
[f] Yield in **3** measured by NMR on crude product.

2. Results and discussion

We first investigated the Mannich reaction of glyoxylic imine **1a** with ketene silyl acetal **2** in methylene chloride at room temperature. Rapid addition of **2** afforded the expected product **3a** with a very small enantiomeric excess (Table 1, entry 1). It has been shown that a slow addition of the nucleophile can improve asymmetric induction by lowering the concentration of achiral silyl species generated in situ which may catalyze the formation of the racemic product.[11,24] Indeed, the slow addition of ketene silyl acetal by syringe pump with a decrease in reaction temperature resulted in an increase in enantiomeric excess of up to 38% (entries 2–4). Since the glyoxylic imine **1a** is always contaminated with small quantities of aniline, we tested the reactivity of glyoxylic imine **1b** prepared from *p*-methoxyaniline, which is easily obtained pure, in the same Mannich reaction. Under the conditions which afforded the highest enantiomeric excess for **1a** as well as under various other conditions we always isolated racemic products with **1b** (entry 5). We assumed that the small asymmetric inductions previously observed with **1a** could be explained by the presence of aniline and hence tried to use amines as additives. Effects of additives to optimize asymmetric inductions were exemplified by numerous studies such as Kobayashi,[25,26] and were reviewed by Shibasaki.[27] We first examined the effect of the presence of *p*-anisidine by adding two molecules per samarium atom and were pleased to find that under these conditions, the reaction became enantioselective albeit with a small induction (entry 6). The slow addition of ketene silyl acetal afforded a small increase in enantiomeric excess (entry 7). By the use of one equivalent of *p*-anisidine compared to catalyst the iminoaldol product was nearly racemic (entry 8), while two or five equivalents of *p*-anisidine gave the same enantiomeric excess (25%) after the end of the slow addition (2 h) (entries 9–10). Nevertheless the yield was increased by using a larger amount of amine as additive.

Several amines were investigated as additives for enantioselective Mannich reactions using 15% catalyst in order to try to increase yield and enantioselectivity and the results collected in Table 2. Replacing *p*-anisidine by *o*-anisidine led to an increase in enantioselectivity (Table 2, entries 1 and 2). This can be due to either steric or to chelating effects. However the use of bulky aromatic amines with donor or acceptor substituents (entries 4 and 5) were not successful and similarly secondary or tertiary amines gave low enantioselectivities (entries 6 and 7). The highest yield and enantioselectivity were afforded by aniline (entry 3, 44% ee) which was selected for the following experiments.

We then examined the influence of other parameters on the asymmetric induction of this Mannich reaction, with the first being the effect of temperature. Reactions were carried out with 15% catalyst and two equivalents aniline per samarium (30% compared to imine **1b**) (Table 3). We first found that at room temperature, in CH_2Cl_2, with a slow addition of ketene silyl acetal **2** followed by an 18 h reaction, enantiomeric excess was increased when the silyl derivative **2** was employed only in small excess, 1.1 equiv. instead of 1.4 as in the first experiments (Table 3, entries 1 and 2). The conditions

Table 2. Effect of the nature of amine on Mannich reaction

Entry	Amine	Yield[a,b] (%)	Ee (%)
1	*p*-Anisidine	58	21
2	*o*-Anisidine	49	32
3	Aniline	86[c]	44
4	2,6-Diisopropylamine	77	17
5	3,5-Bistrifluoromethylaniline	58	10
6	*N*-Methylaniline	53	17
7	Triethylamine	25	4

[a] Reaction conditions: 15% catalyst **4** is added to imine **1b**, then 30% amine, followed by slow addition of 1.4 equiv. of **2** with syringe pump within 2 h and by 18 h stirring.
[b] Yield in **3b** measured by NMR on crude product.
[c] Isolated yield 81%.

Table 3. Optimisation of the enantioselectivity of Mannich reaction

Entry	Conditions[a]	Temperature (°C)	Maturation time (h)	Reaction time (h)	Yield (%)[g]	Ee (%)
1	[b]	20	0	18[a]	86	44
2	**A**[c]	20	0	18	80	60
3	**A**[c]	20	0	2	53	45
4	**A**[c]	0	0	4.5	59	31
5	**A**[c]	32	0	18	100	76
6	**A**[c]	37	0	18	100	82
7	**A**[c]	37	0	7	74	57
8	**A**[c]	60[f]	0	18	63	48
9	**A**[c]	80[f]	0	18	40	49
10	[d]	20	4	18	100 (59)	70
11	**B**[e]	20	4	18	95 (52)	82
12	**B**[e]	20	2	18	100	50
13	**B**[e]	20	7	18	100	78
14	**B**[e]	0	4	24	75	74
15	**B**[e]	37	4	18	95 (57)	73
16	**B**[e]	30	4	18	100 (67)	90

[a] All reactions were carried out with 15% catalyst **4**, which are added to imine **1b** in CH_2Cl_2 followed by aniline (30% or 60%).
[b] Slow addition of 1.4 equiv. of **2** with syringe pump.
[c] Conditions **A**: addition of aniline (30%), followed by slow addition of 1.1 equiv. of **2** with syringe pump within 2 h.
[d] Catalyst **4** is added to imine **1b**, then 60% aniline and the mixture is left stirring 4 h followed by slow addition of 1.1 equiv. of **2** with syringe pump within 2 h.
[e] Conditions **B**: catalyst **4** is added to imine **1b**, then 60% aniline and the mixture is left stirring; after the maturation time 1.1 equiv. of **2** is rapidly added by syringe.
[f] Reaction in dichloroethane.
[g] Yield measured by NMR on crude product (isolated yields).

of entry 2 are noted as **A** conditions and used in the following experiments. The yield and enantioselectivity were evaluated at the end of the addition of **2** under these conditions and surprisingly we found an enantiomeric excess lower than at the end of reaction (entries 2 and 3). Contrary to our expectations, the enantiomeric excess was improved when the reaction was performed at higher temperatures with 82% enantiomeric excess at 37°C, whereas at lower temperatures, a lower enantioselectivity was observed (entries 2, 4–6). We had previously seen that the variation of the enantiomeric excess is not monotonous with temperature in reactions catalyzed by other lanthanide iodobinaphthoxides.[28] We saw that at 37°C the enantiomeric excess also changed during the reaction and increased with reaction time (entries 6 and 7). Attempts to improve the enantiomeric excess by performing the reaction at higher temperatures using dichloroethane as solvent were unsuccessful (entries 8 and 9).

The increase in enantiomeric excess at the end of the reaction and at higher temperatures in methylene chloride can be explained by the effect of the catalyst aging. Kobayashi has noticed such effects of aging catalysts in systems based on ytterbium triflate, binaphthol and amines which are enantioselective catalysts for Diels–Alder reactions.[29] In these systems aging was detrimental to asymmetric induction. We thus examined the influence of a maturation time of the catalyst in our Mannich reaction. In the following experiments we increased the amount of aniline to four equivalents of aniline per samarium since we previously observed that the yield could be increased by a larger quantity of aniline. The reaction was carried out under the following conditions: after addition of catalyst **4** to the glyoxylic imine **1b** in solution in methylene chloride followed by addition of aniline, the mixture was stirred for 4 h, then **2** was slowly added within 2 h (entry 10). With such a procedure we obtained 100% yield in reaction product **3b** with 70% enantiomeric excess. The following experiment was realized in the same conditions but ketene silyl acetal **2** was rapidly added, and we were pleased to find that this procedure allowed us to obtain the reaction product in high yield at room temperature with 82% enantiomeric excess (entry 11). These reaction conditions are noted as **B**. In some experiments trying to optimize the maturation time did not improve the asymmetric induction (entries 12 and 13). As observed in experiments in conditions **A** without the aging of the catalyst, lowering the reaction temperature led to a decrease in asymmetric induction, the highest value of 90% for enantiomeric excess of the Mannich reaction being obtained at 30°C (entries 14–16).

Conditions **B** have led to higher values of the yields of reaction, as well as higher enantiomeric excesses than conditions **A**. These improvements seem to be due to the maturation time of the catalyst. We checked that in conditions **B**, the enantiomeric excess did not change along the reaction. The unusual effect of temperature on enantiomeric excess is similar to the observations of Sodeoka in enantioselective Mannich reactions catalyzed by palladium enolate complexes.[11] Such a behaviour can be explained by the presence of several catalytic species. In conditions **A** and **B** a reverse order of introduction of substrate and additive (addition of amine prior to glyoxylic imine) produced a decrease in

the enantiomeric excess of Mannich reaction. A new catalytic species can be formed by replacement of the two tetrahydrofuran molecules initially coordinated to samarium by glyoxylic imine or amine. Transformation of samarium iodo binaphthoxide in dimeric species during maturation time, as observed by Kobayashi for zirconium complexes in the presence of additives, could also occur.[29]

3. Conclusion

Our catalytic system allows us to realize, with high asymmetric induction, a new Mannich reaction in mild conditions using commercially available ligand. Further studies are necessary to try to elucidate the structure of the catalyst and rationalize the influence of parameters allowing us to optimize the system, such as the presence of aniline as additive and aging of the catalyst. These first results reflect the potentiality of this new family of enantioselective catalysts that we are currently studying for enantioselective catalysis of other carbon–carbon bond forming reactions.

4. Experimental

All manipulations were carried out under an argon atmosphere using standard Schlenk or glovebox techniques. CH_2Cl_2 and $C_2H_2Cl_4$ were distilled from CaH_2 and degassed immediately prior to use. Glyoxylic imines were prepared according to published method.[10] Bruker AM 250 and AM 400 spectrometers, operating at 250 and 400 MHz for ^1H, 62.9 and 100.8 MHz for ^{13}C were used for the NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane for spectra in $CDCl_3$. Infrared spectra were recorded as Nujol mulls using NaCl plates on a Perkin–Elmer 1000 FT-IR spectrometer and are reported in cm^{-1}. HRMS were measured with a Perkin–Elmer Finnigan-Mat 955 spectrometer. Optical rotations were determined using a Perkin–Elmer 241 Polarimeter at room temperature, using a cell of 1 dm of length and $\lambda = 589$ nm. Data are reported as follows: $[\alpha]_D^{20}$ (concentration in g/100 mL, solvent). Enantiomeric excesses were measured by chiral stationary-phase HPLC on a Chiracel® OD-H column.

4.1. Preparation of catalyst

[(*R*)-1,1′-(Bi-2,2′-naphthoxide)]-iodosamarium-bis-tetrahydrofuran **4** was prepared as previously described.[23] To a solution of (*R*)-1,1′-binaphthol (0.286 g, 1.0 mmol) in 5 mL THF under magnetic stirring was added potassium hydride (0.088 g, 2.2 mmol). After 0.5 h the suspension was added within 5 min to a suspension of $SmI_3(THF)_3$ (0.747 g, 1.0 mmol) in 5 mL THF. The reaction mixture turned light-yellow with a white precipitate of KI. After 18 h the KI was filtrated and the supernatant solution evaporated under vacuum yielding a yellow powder of **4** which was used without purification (0.57 g, 81% yield). ^1H NMR ($CHCl_3$, 250 MHz) δ: 8.7–6.0 (m, 12H), 3.8 (l, 8H), 1.72 (l, 8H).

4.2. General procedures for the Mannich-type reactions

Method A: In a glovebox, to a solution of glyoxylic imine **1b** (52 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) were added 4 Å molecular sieves (25 mg) and catalyst **4** (25 mg, 0.037 mmol). Aniline (7 μL, 0.075 mmol) was then added by syringe outside of the glovebox at room temperature. The mixture was then warmed or cooled at the desired temperature and a solution of ketene silyl acetal **2** (57 μl, 0.275 mmol) in CH_2Cl_2 (5 mL) was slowly added by syringe pump during two hours at the selected temperature. The whole reaction mixture was stirred for 18 h then hydrolyzed (10 mL H_2O) and extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated. The residue was purified by preparative silica gel thin-layer chromatography (heptane/AcOEt = 70/30, $R_f = 0.6$) to afford **3b** (63 mg, 81%).

Method B: In a glovebox, to a solution of glyoxylic imine **1b** (52 mg, 0.25 mmol) in CH_2Cl_2 (4 mL) were added 4 Å molecular sieves (25 mg) and catalyst **4** (25 mg, 0.037 mmol). Aniline (14 μl, 0.15 mmol) was then added by syringe outside of the glovebox at room temperature. After being stirred at room temperature for 4 h, the mixture was then warmed or cooled at the desired temperature and the ketene silyl acetal **2** (57 μl, 0.275 mmol) added by syringe. The whole reaction mixture was stirred for 18 h then treated as described above.

4-Ethyl 1-methyl 3-(4-methoxy-phenylamino)-2,2-dimethylsuccinate: **3b**: Yellow oil. $[\alpha]_D^{20} = -20.1$ (*c* 0.84, $CHCl_3$). ^1H NMR ($CDCl_3$): δ: 6.70 (q, 4H, $J = 9.3$ Hz), 4.22 (l, 1H), 4.11 (m, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.19 (t, 3H, $J = 7.32$ Hz). ^{13}C NMR ($CDCl_3$): δ: 176.10, 172.08, 153.03, 141.31, 116.06, 114.65, 64.72, 61.15, 55.58, 52.09, 46.02, 22.17, 21.70, 14.09. IR: ν_{max} 1733. HRMS calcd for M^++Na ($C_{16}H_{23}NNaO_5$) 332.1472; found 332.1473. HPLC (Chiracel® OD-H, hexane/*i*-propanol: 98/2, 1 mL/min, 254 nm, $t = 7.78$ min and $t = 8.84$ min).

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