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Aluminium–SALEN complex: a new catalyst for the enantioselective Michael reaction

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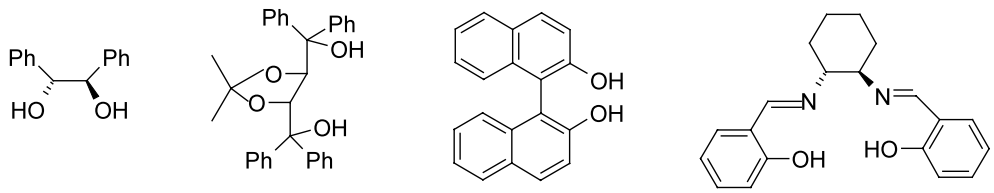
Abstract—A new heterobimetallic complex prepared from a chiral SALEN ligand and Red-Al® was found to catalyse the Michael reaction between various dialkyl malonates and cycloalkenones to give products in high yields with e.e.s of up to 58%.

1. Introduction

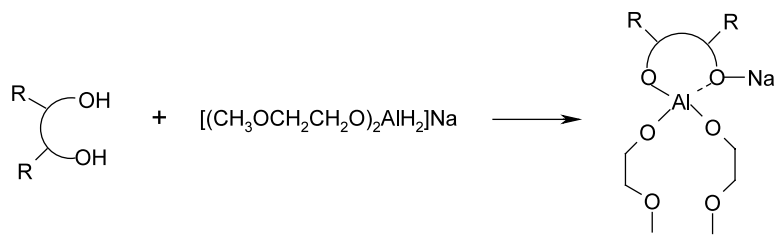
The conjugate addition reaction of carbon nucleophiles to α,β-unsaturated carbon compounds is one the important methods for carbon–carbon bond formation in organic synthesis.[1] Since this reaction can generate stereogenic centre, considerable effort has been devoted to the development of efficient stereoselective methods.[2] In recent years chiral metal complexes have been used as efficient catalysts for the Michael reaction,[3–8] the development of multifunctional lanthanide–BINOL catalysts by Shibasaki et. al. being the most significant development in this area.[9] Herein, we report a new aluminium-based heterobimetallic complex derived from a chiral SALEN ligand.

2. Results and discussion

It has been found by other researchers that alkali metal–aluminium alkoxides act as efficient catalysts for Michael addition.[8,10] It has been also known that the presence of sodium as the counter cation is superior than lithium in this reaction.[11] With these facts in mind, we set out to design a catalyst derived from sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al®), a cheap and commercially available source of these two metals. The obvious modification of this reagent will involve the reaction with a number of known diols having diverse steric and electronic properties. The diols selected for the present study were (*R*,*R*)-stilbene diol **1**,[12] (*R*,*R*)-TADOL **2**,[13] (*R*)-BINOL **3**[14] and (*R*,*R*)-



1 **2** **3** **4**



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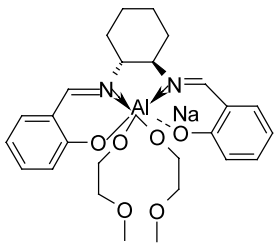
SALEN **4**.[15] These diols reacted smoothly with Red-Al® releasing 2 equiv. of hydrogen.

These complexes were not characterised and the depicted structures are only tentative. We rationalised that the aluminium alkoxide (or phenoxide) moiety would act as a Lewis acid and the sodium alkoxide (or phenoxide) as a Brønsted base. Initially we examined the reaction of cyclopentenone with diethyl malonate. Indeed, all of the complexes examined showed high catalytic activity for the reaction and the reactions were over in less than 15 min at 0°C. The best enantioselectivity (measured by rotation) was provided by the SALEN complex **5**.



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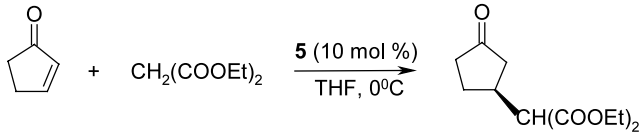
This sodium–aluminium–SALEN complex was isolated as a hygroscopic solid, but could not be characterised by ^{1}H NMR due to line-broadening. Also, we were unable to obtain suitable crystal for XRD analysis. Although we have depicted a hexacoordinate aluminium centre, we believe that the catalytically active species is generated by dissociation of the bond with phenoxide ion leading to a coordinatively unsaturated aluminium centre. The bimetallic nature of the catalyst was proved beyond doubt. Elimination of sodium metal or replacement by lithium resulted in very poor catalytic activity.



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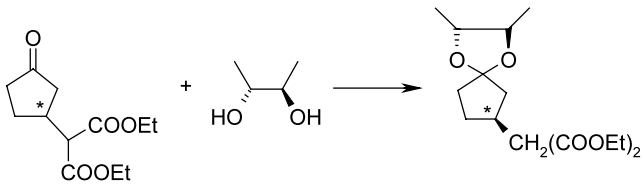
We were perplexed by the specific rotation value of the product. The reported specific rotation value for **6** with an enantiomeric excess of 86% is $[\alpha]_D = +29.9$.[7] However, we observed a much higher value ($[\alpha]_D = +45.7$) than expected even for a product with 100% e.e. We were unable to correct the discrepancy by HPLC since **6** could not be resolved well on a Chiracel®OD or Chiralpak®AS column. We then decided to examine the ^{1}H NMR of diastereomeric ketals **7** from (2*R*,3*R*)-butanediol.



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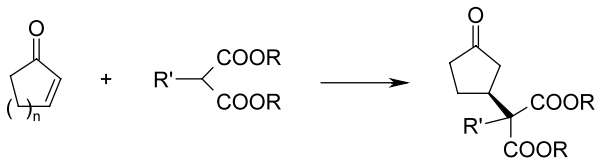
We were pleased to find that the methyne proton of the diastereomeric ketals appears as two well resolved doublets. It was thus possible to determine the e.e. of **6**, which turned out to be a modest 33%. THF was the solvent of choice as compared to diethyl ether, toluene and dichloromethane. Lower temperature (–25°C) did not significantly enhance the enantioselectivity. Having standardised the reaction as well as the analytical procedure, we examined the reaction of a variety of sterically different malonate esters with cycloalkenones. The results are summarised in Table 1. Modest enantioselectivity was observed in all the cases. The (*R*,*R*)-SALEN complex consistently provided products with (*S*)-configuration, as confirmed by the sign of optical rotation for two compounds of known configuration

Table 1. Addition of malonate esters to cycloalkenones in presence of the complex **5**



Entry	Enone	R	R′	Time (min)	Yield (%)[a]	$[\alpha]_D^{25}$ in $CHCl_3$	E.e. (%)
1	$n=1$	Me	H	10	86	−46.2 (*c* 1.60)	58[b]
2	$n=1$	Et	H	15	92	−45.7 (*c* 1.60)	33[c]
3	$n=1$	^{i}Pr	H	15	89	−37.2 (*c* 1.63)	36[c]
4	$n=1$	^{t}Bu	H	45	83	−39.6 (*c* 1.66)	40[c]
5	$n=1$	CH_2Ph	H	240	75	−25.15 (*c* 1.36)	41[c]
6	$n=2$	Me	H	15	85	−1.5 (*c* 2.10)	37[b]
7	$n=2$	Et	H	20	88	−1.2 (*c* 2.56)	34[b]
8	$n=1$	Et	Me	15	88	−37.0 (*c* 1.63)	56[b]

[a] Isolated yield.
[b] By HPLC analysis on a chiral column.
[c] From ^{1}H NMR of the ketal using (2*R*,3*R*)-butanediol.

(entries 6 and 7)[5] and by the fact that in all cases the (*S*)-isomer was second to elute from the Chiralpak®AS column.

3. Conclusion

We have developed a new aluminium complex that promotes the Michael reaction of malonate esters with cyclic enones to give the products in high yield and with modest enantioselectivity. Efforts to optimise the catalyst structure are now underway in our laboratory.

4. Experimental

4.1. General

Red-Al® solution in toluene was purchased from Aldrich as a 65+% wt. solution, diluted to about 1 M, and estimated by gasimetry. 2-Cyclopentenone[16] and various malonate esters[17] were prepared according to the literature procedure. 2-Cyclohexenone was purchased from Aldrich and used after distillation. THF was freshly distilled from sodium benzophenone ketyl. ^{1}H NMR spectra were recorded on Bruker 200 using $CDCl_3$ as solvent and TMS as internal standard. Optical rotations were measured on JASCO-DIP-181 digital polarimeter. HPLC analysis was performed on a Diacel Chiralpak-AS® column.

4.2. Preparation of the ligand

Salicyldehyde (2.10 mL, 20 mmol) dissolved in ethanol (10 mL) was added to a solution of the tartaric acid salt of *trans*-cyclohexyldiamine (2.65 g, 10 mmol) and anhydrous K_2CO_3 (4.15 g, 30 mmol) dissolved in water (30 mL). The mixture was stirred at 60°C for 1 h, diluted with water and extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The viscous residue was dissolved in hexane and cooled to −10°C to obtain (1*R*,2*R*)-bis(salicyldehyde)-*trans*-cyclohexyldiamine **1** as yellow crystals (5.15 g, 80% yield); mp 64–66°C; $[\alpha]_D^{25} = -650$ (*c* 1, MeOH) [lit.[14] −644 (*c* 1, MeOH)].

4.3. Preparation of Al–SALEN complex

To a stirred solution of the ligand (0.064 g, 0.2 mmol) in THF at 0°C, Red-Al (1 M in toluene, 0.2 mmol) was added dropwise and stirred for 15 min. The resulting solution of the complex **5** was used directly.

4.4. General procedure for Michael reaction

The catalyst solution prepared as above was cooled to 0°C. To this, a solution of cycloalkenone (2 mmol) and malonate ester (2 mmol) dissolved in THF (4 mL) was added dropwise. The reaction was monitored by TLC. After completion of the reaction (in the time mentioned in Table 1), the reaction was quenched with 1N HCl and brought to rt. The reaction mixture was then diluted with ether, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was subjected to 'flash chromatography' on silica gel (200–400 mesh) using ethyl acetate–petroleum ether as the eluent to obtain pure product.

4.5. (*S*)-3-[Bis(methoxycarbonyl)methyl]cyclopentanone

Colourless oil; $[\alpha]_D^{25} = -46.2$ (*c* 1.60, $CHCl_3$); ^{1}H NMR: δ 1.45–1.76 (m, 1H), 1.96 (dd, $J = 11.7$ and 19.5 Hz, 1H), 2.06–2.35 (m, 3H), 2.46 (dd, $J = 6.8$ and 18.1, 1H), 2.65–2.95 (m, 1H), 3.34 (d, $J = 9.3$ Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H); ^{13}C NMR: δ 26.7, 35.8, 37.4, 42.1, 51.9, 55.4, 167.9, 168.0, 216.2; MS: m/z 214 (M^+), 132 (base peak). HPLC analysis:[18] Diacel Chiralpak-AS® column (0.46×25 cm), 220 nm detector, ^{i}PrOH in hexane (40%), 2 mL/min flow rate, $t_R = 8.5$ min and $t_S = 9.5$ min.

4.6. (*S*)-3-[Bis(ethoxycarbonyl)methyl]cyclopentanone

Colourless oil; $[\alpha]_D^{25} = -45.7$ (*c* 1.60, $CHCl_3$); ^{1}H NMR: δ 1.18–1.39 (m, 6H), 1.52–1.82 (m, 1H), 2.02 (dd, $J = 11.7$ and 18.6 Hz, 1H), 2.12–2.41 (m, 3H), 2.52 (dd, $J = 7.8$ and 18.6 Hz, 1H), 2.72–3.00 (m, 1H), 3.34 (d, $J = 9.3$ Hz, 1H), 4.10–4.30 (m, 4H); ^{13}C NMR: δ 13.4, 26.8, 35.7, 37.4, 42.1, 55.6, 60.6, 167.6, 216.2; MS: m/z 242 (M^+), 160 (base peak).

Diastereomeric ketal derivative for ^{1}H NMR analysis: A solution of the ketone (0.1 mmol), (2*R*,3*R*)-butanediol (0.1 mmol) and PTSA (10 mg) in toluene (1 mL) was stirred at rt for 24 h. The reaction mixture was diluted with petroleum ether, passed through a short pad of alumina and concentrated under reduced pressure to provide the ketal.

4.7. (*S*)-3-[Bis(*iso*-propoxycarbonyl)methyl]cyclopentanone

Colourless oil; $[\alpha]_D^{25} = -37.17$ (*c* 1.63, $CHCl_3$); ^{1}H NMR: δ 1.09–1.41 (m, 12H), 1.50–1.81 (m, 1H), 2.02 (dd, $J = 11.2$ and 18.1 Hz, 1H), 2.13–2.40 (m, 3H); 2.51 (dd, $J = 7.3$ and 18.1 Hz, 1H), 2.69–3.00 (m, 1H), 3.27 (d, $J = 9.3$ Hz, 1H), 4.90–5.25 (m, 2H); ^{13}C NMR: δ 21.1, 26.9, 35.7, 37.6, 42.3, 56.4, 68.5, 68.6, 167.2, 216.5; MS: m/z 270 (M^+), 104 (base peak).

4.8. (*S*)-3-[Bis(*tert*-butoxycarbonyl)methyl]cyclopentanone

White solid; mp 72°C; $[\alpha]_D^{25} = -39.6$ (*c* 1.66, $CHCl_3$); ^{1}H NMR: δ 1.46 (s, 9H), 1.48 (s, 9H), 1.67–1.87 (m, 1H), 2.01 (dd, $J = 11.3$ and 18.5 Hz), 2.12–2.39 (m, 3H), 2.50 (dd, $J = 7.9$ and 18.5), 2.63–2.92 (m, 1H), 3.13 (d, $J = 9.8$ Hz, 1H); ^{13}C NMR: δ 27.2, 27.7, 36.0, 37.9, 42.6, 58.4, 81.6, 167.2, 217.0; MS: m/z 298 (M^+), 186 (base peak).

4.9. (*S*)-3-[Bis(benzyloxycarbonyl)methyl]cyclopentanone

Colourless oil; $[\alpha]_D^{25} = -25.15$ (*c* 1.60, $CHCl_3$); ^{1}H NMR: δ 1.44–1.75 (m, 1H), 1.98 (dd, $J = 11.2$ and 18.6, 1H),

2.08–2.33 (m, 3H), 2.45 (dd, $J=6.8$ and 18.6, 1H), 2.72–3.10 (m, 1H), 3.44 (d, $J=9.3$ Hz, 1H), 5.14 (s, 2H), 5.16 (s, 2H), 7.11–7.47 (m, 10H); ^{13}C NMR: δ 27.0, 35.9, 37.7, 42.3, 56.0, 66.9, 127.9, 128.2, 134.9, 167.4, 216.5; MS: m/z 366 (M^+), 90 (base peak).

4.10. (*S*)-3-[Bis(methoxycarbonyl)methyl]cyclohexanone

Colourless oil; $[\alpha]_D^{25}=-1.5$ (c 2.10, $CHCl_3$) [lit.[15] +3.33 (c 2.10, $CHCl_3$) for (*R*)-isomer]; ^{1}H NMR: δ 1.32–1.83 (m, 2H), 1.93–2.17 (m, 2H), 2.18–2.66 (m, 5H), 3.37 (d, $J=7.8$ Hz, 1H), 3.76 (s, 6H); ^{13}C NMR: δ 23.9, 28.0, 37.5, 40.2, 44.3, 51.7, 55.7, 167.6, 208.6; MS: m/z 228 (M^+), 97 (base peak).

4.11. (*S*)-3[Bis(ethoxycarbonyl)methyl]cyclohexanone

Colourless oil; $[\alpha]_D^{25}=-1.2$ (c 2.56, $CHCl_3$) [lit.[11] +2.89 (c 2.56, $CHCl_3$) for (*R*)-isomer]; ^{1}H NMR: δ 1.28 (t, 6H), 1.36–1.84 (m, 2H), 1.94–2.16 (m, 2H), 2.26–2.66 (m, 5H), 3.34 (d, $J=7.8$ Hz, 1H), 4.15–4.25 (m, 4H); ^{13}C NMR: δ 13.4, 23.9, 28.0, 37.4, 40.2, 44.3, 56.1, 60.7, 167.1, 167.2, 208.6; MS: m/z 256 (M^+), 160 (base peak).

4.12. (*S*)-3-[1,1-Bis(ethoxycarbonyl)ethyl]cyclopentanone

Colourless oil; $[\alpha]_D^{25}=-37.0$ (c 1.60, $CHCl_3$); ^{1}H NMR: δ 1.27 (t, $J=7.3$, 6H), 1.45 (s, 3H), 1.56–1.93 (m, 1H), 2.00–2.57 (m, 5H), 2.74–3.00 (m, 1H), 4.05–4.34 (m, 4H); ^{13}C NMR: δ 13.7, 17.4, 24.2, 38.0, 40.3, 41.1, 55.2, 61.0, 170.9, 216.9; MS: m/z 256 (M^+), 174 (base peak).

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