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Enantioselective Mukaiyama-Aldol Reaction of Pyruvates and 1-Phenyl-1-trimethylsilyloxyethene Catalyzed by Lanthanide/Pybox Complexes

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The enantioselective Mukaiyama-aldol reaction between 1-phenyl-1-trimethylsilyloxyethene (**1**) and three pyruvates (**2a**–**c**) is catalyzed by the lanthanide triflate complexes of (4*S*,5*S*)-2,6-bis[5-phenyl-4-(triisopropylsilyloxy)methyl-1,3-oxazolin-2-yl]pyridine (**3**). The best catalysts are the Lu^{III}- and Sc^{III}-based complexes that give high yields of (*S*)-**4a**–**c** and enantiomeric excesses up to 99.5 %. The La^{III}-based complex favors the formation of the opposite enantiomer [77 % *ee* of (*R*)-**4c**]. The rationale of the stereochemical outcome is proposed.

Introduction

In the last two decades, the formation of carbon–carbon bonds through asymmetric catalytic processes has attracted a great deal of interest and one of the most useful tools within this issue is the Mukaiyama-aldol (M.A.) reaction.[1] Because the variables involved in the process are a carbonylic reagent, an enolsilane, a chiral ligand, and a cation acting as the Lewis acid center, it is not astonishing that several hundreds of examples have been reported in the literature. One attractive feature related to this reaction is that the reaction product, in addition to a chiral alcohol, may contain other functional groups: enolsilanes can introduce keto or ester functionalities, whereas activated carbonyl reagents (glyoxylate or pyruvate) can deliver an ester group into the product.

A further important reason justifies the preference of dicarbonylic derivatives as electrophiles. To induce a good level of stereoselection, it is not enough for the chiral complex to have at least one vacant Lewis acid site suitable for coordination and activation of the reagent, but the resulting supramolecular complex [ligand/cation/reagent] must be rigidly oriented to favor a selective attack to the coordinated reagent. α-Keto esters are involved in the formation of the reacting complex through a bidentate coordination to the cationic centre of the catalyst, and the five-membered catalyst–substrate complex can induce a high level of enantioselectivity.

The M.A. reaction can be catalyzed by a great variety of optically active complexes,[1] but an important development to the stereocontrol of the reaction was given by the research of Evans et al.[2] through the use of C_2-symmetric bis(oxazolines) as a ligand having either a single carbon atom or a pyridine ring as the spacer between the two heterocyclic rings (*box*[3] and *pybox*,[4] respectively). The attractive target to obtain enantiomerically enriched tertiary α-hydroxy keto esters led us to investigate the reaction between 1-phenyl-1-trimethylsilyloxyethene (**1**) and pyruvates (**2**) (Scheme 1) by using a pybox class of catalysts obtained from (4*S*,5*S*)-2,6-bis[5-phenyl-4-(triisopropylsilyloxy)methyl-1,3-oxazolin-2-yl]pyridine (**3**) and lanthanide(III) triflates, catalysts that work nicely both in the Diels–Alder and in the Mukaiyama-Michael reactions between 3-acryloyl- or 3-crotonoyl-oxazolidinones and either cyclopentadiene or 2-trimethylsilyloxyfuran.[5] The first set of M.A. reactions were performed by Evans et al.[2e] who used the $Cu(OTf)_2$ complex of (4′*S*)-*t*Bu-box (good yields and excellent *ee*'s), and the reaction was later studied in detail by Bolm et al.[6] with catalysts derived from C_1-symmetric aminosulfoximines and $Cu(OTf)_2$, which, under optimized conditions, gave high yields of product with *ee*'s up to 99 %.

Results

The M.A. reaction between **1** and **2a** (Scheme 1) was catalyzed with 10 mol-% of pybox **3** and lanthanide triflates heated at –50 °C in CH_2Cl_2 in the presence of 4 Å molecular sieves, and the results with seven different cations are reported in Table 1. The yields are good with Sc and Lu (Table 1, Entries 1a, 2a) and poor with Yb, Ho, Y, and Eu. In the case of the La-based catalyst, moderate yields are obtained only at ambient temperature (Table 1, Entry 7a). Also, the enantioselectivity strongly depends on the cation: the catalysts derived from $Sc(OTf)_3$ and $Lu(OTf)_3$ give very good enantiomeric excesses of ethyl 2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate (**4a**) (Table 1, Entries 1a, 2a; 92,

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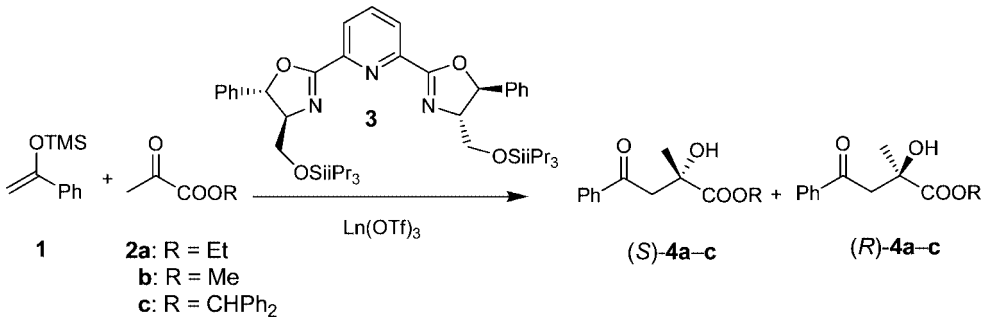

Scheme 1.

Table 1. Mukaiyama-aldol reactions between **1** and **2a–c** at –50 °C in CH_2Cl_2 in the presence of 10 mol-% of complex between **3** and Ln^{III} triflates with 4 Å molecular sieves.

Entry	Triflates	Ionic radius	**2a**			**2b**			**2c**		
		[Å]	Time [d]	Yield[a] of **4a** [%]	**4a** *ee* [%] (conf.)	Time [d]	Yield[a] of **4b** [%]	**4b** *ee* [%] (conf.)	Time [d]	Yield[a] of **4c** [%]	**4c** *ee* [%] (conf.)
1	Sc	0.870	3	92	92(*S*)	3	98	77(*S*)	4	83	98 (*S*)
2	Lu	0.977	5	70	95 (*S*)	4	70	85 (*S*)	4	95	99.5 (*S*)
3	Yb	0.985	5	55	79 (*S*)	4	50	61 (*S*)	5	52	82 (*S*)
4	Ho	1.015	5	45	24 (*S*)	4	41	racemate	1.5	32	44 (*R*)[b]
5	Y	1.019	5	41	48 (*S*)	4	37	racemate	1.5	30	60(*R*)[b]
6	Eu	1.066	5	39	39 (*S*)	4	40	39 (*S*)	1.5	30	68 (*R*)[b]
7	La[b]	1.160	3	45	72 (*R*)	2	44	47 (*R*)	2	35	77 (*R*)

[a] Isolated yields. [b] Reactions run at 20 °C.

95% *ee*, respectively) that are comparable with the best values published by Evans[2e] and Bolm.[6b] Four cations [Yb, Ho, Y, and Eu] give lower *ee*'s (in the range 24–79%), whereas the catalyst derived from La (Table 1, Entry 7a) gives the opposite enantiomer with appreciable *ee* despite the higher reaction temperature.

The reaction with methyl ester **2b**, run under the same conditions, gives the best yield and enantioselectivity of the series again with the catalysts derived from $Sc(OTf)_3$ and $Lu(OTf)_3$ (Table 1, Entries 1b, 2b; 77, 85% *ee*, respectively), the remaining catalysts give the same trend observed with the ethyl ester, but the enantioselectivity is lower.

The absolute configuration of the major enantiomer of methyl 2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate (**4b**) obtained with $Sc(OTf)_3$ and $Lu(OTf)_3$ is (2*S*) by comparing its optical rotation with that of the known compound,[2e] whereas the major enantiomer obtained from the reaction catalyzed by $La(OTf)_3$ has the (2*R*) configuration (Table 1, Entry 7b). Transesterification of **4a** with methanol and K_2CO_3 into **4b** proceeds without any racemization and allows the (2*S*) configuration to be assigned to the product obtained from the reaction catalyzed by $Sc(OTf)_3$.

Because the enantioselectivity of the catalyst seems to increase with an increase in the steric hindrance of the ester moiety, diphenylmethyl pyruvate **2c** was tested. Gratifyingly, the enantioselectivity increases significantly with both Sc and Lu catalysts (Table 1, Entries 1c, 2c; 98, 99.5% *ee*, respectively) to give a result that competes with the best ones reported in the literature for the M.A. reaction between **1** and pyruvates. The absolute configuration of diphenylmethyl 2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate obtained with these catalysts was determined to be (2*S*) by transesterification into **4b** with methanol and K_2CO_3. Among the other catalysts, Yb is the only cation active at –50 °C (Table 1, Entry 3c; 82% *ee*), whereas Ho, Y, and Eu (in addition to La) require 20 °C to produce acceptable yields of **4c**. The catalysts that are based on these latter cations (Table 1, Entries 4c–7c) invert the enantioselectivity, and the La-based catalyst gives 77% *ee* of (2*R*)-**4c** (Table 1, Entry 7c).

Discussions and Conclusion

The complexes of pybox **3** with Sc^{III} and Lu^{III}, which are the lanthanides with the smaller ionic radius (Table 1),[7] are the best catalysts for the M.A. reaction between **1** and **2** (Table 1, Entries 1a–c and 2a–c). Hence, the rationale for the enantioselectivity of the reaction cannot exclude the structure of the reacting complex that exists between the cation, the pybox ligands, and the reagent; Sc is the simplest cation to develop such a model. The reacting complex involving Sc^{III} can be derived from the [pybox/Sc^{III}/ethyl glyoxylate] molecular structure reported in the literature[2f] by changing the glyoxylate with pyruvate. Pyruvate **2a** is bound to Sc in a bicoordinated fashion with the ketonic CO in the equatorial position, the ester moiety in the apical position of complex **5**, and a triflate residue *anti* to it (Figure 1). The bulky substituent in the 4′-position of pybox **3** becomes the crucial factor to determine the face selectivity. The favored attack of **1** occurs to the less shielded *Si* face of bound keto ester **2a**, which rationalizes the formation of (*S*)-**4a**. Reacting intermediate **5** also rationalizes the formation of (*S*)-**4b**,**c**.

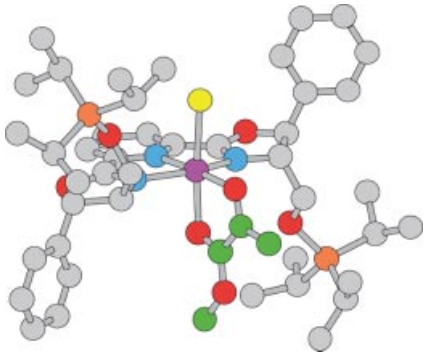

Figure 1. Assumed reacting intermediate **5** for the M.A. reaction between **1** and **2b** catalyzed by the $Sc(OTf)_3$ complex of pybox **3**; the yellow sphere represents the triflate anion.

The attack on the opposite enantioface of **2** when bound to La^{III} can be explained by intermediate **6** that was already proposed for both the Diels–Alder and the Mukaiyama–Michael reactions between 3-alkenoyl-2-oxazolidinones catalyzed by [**3**-$La(OTf)_3$].[5] This reacting complex is derived from the X-ray crystal structure of [La^{III} (*trans*-4′,5′-diPh-pybox) $(H_2O)_4$·$(OTf)_2$],[8] where pybox **3**, with its increased steric hindrance of the substituent in the 4′-position, determines a deformation of the catalyst geometry without any change in the cation coordination sphere. The presence of two apical triflate groups shifts **2** in the equatorial region of the complex (Figure 2), again the bulky substituent in the 4′-position of pybox **3** becomes the crucial factor to determine the face selectivity, but now the favored attack of silyloxyethene **1** occurs to the less-shielded *Re* face of bound keto ester **2** to favor the formation of (*R*)-**4.**

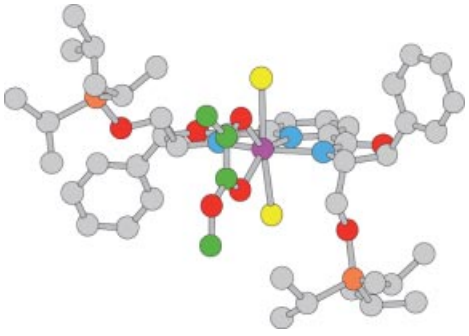

Figure 2. Assumed reacting intermediate **6** for the M.A. reaction between **1** and **2b** catalyzed by the $La(OTf)_3$ complex of pybox **3**; the yellow spheres represent the triflate anions.

The lower *ee*'s obtained with other lanthanides (Table 1, Entries 4–6) could be due to different reasons: (1) The competition between **5** and a reacting intermediate with the same face selectivity of that involved in the La-catalyzed reaction (**6**), (2) a less selective reacting intermediate with different coordination number (this is not unusual if the crystal structures of the lanthanide complexes of pybox that have a coordination number in the range 6–9 are taken into account),[4,9] (3) an effect of the temperature in the inversion of the enantioselectivity of the reaction with **2c** shown by Ho, Y, and Eu.

In conclusion, whereas the complexes derived from Yb, Ho, Y, Eu, and La have little or no synthetic relevance, those obtained from pybox **3** and Sc^{III}- or Lu^{III}-triflate can be considered among the best catalysts for a reaction that several groups have taken as the benchmark for the efficiency of an enantioselective M.A. catalyst.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and full characterization data for all compounds synthesized, as well as ^1H- and ^{13}C NMR spectra for **4a**,**c** and some significant HPLC chromatograms.

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[1] a) C. Palomo, M. Oiarbide, J. M. Garcia, *Chem. Eur. J.* **2002**, *8*, 36–44; b) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137–1141.
[2] a) D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815; b) D. A. Evans, M. C. Kozlowski, J. S. Tedrow, *Tetrahedron Lett.* **1997**, *42*, 7481–7484; c) D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894; d) D. A. Evans, D. W. C. MacMillan, K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860; e) D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay, *J. Am. Chem. Soc.* **1999**, *121*, 686–699; f) D. A. Evans, C. E. Masse, J. Wu, *Org. Lett.* **2002**, *4*, 3375–3378.
[3] G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.
[4] G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119–3154.
[5] G. Desimoni, G. Faita, M. Guala, A. Laurenti, M. Mella, *Chem. Eur. J.* **2005**, *11*, 3816–3824.
[6] a) M. Langner, C. Bolm, *Angew. Chem. Int. Ed.* **2004**, *43*, 5984–5987; b) M. Langner, P. Rémy, C. Bolm, *Chem. Eur. J.* **2005**, *11*, 6254–6265.
[7] R. Anwander, W. A. Herrmann, *Topics in Curr. Chem.* **1996**, *179*, 1–32.
[8] G. Desimoni, G. Faita, S. Filippone, M. Mella, M. G. Zampori, M. Zema, *Tetrahedron* **2001**, *57*, 10203–10213.
[9] H. C. Aspinal, *Chem. Rev.* **2002**, *102*, 1807–1850.

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