Pergamon

Tetrahedron Letters, Vol. 36, No. 8, pp. 1363-1364, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(94)02478-2

Enantioselective Michael-Mukaiyama Additions of Silylketene acetals to 2-Carboxycyclopentenones Promoted by Chiral Ti Complexes.

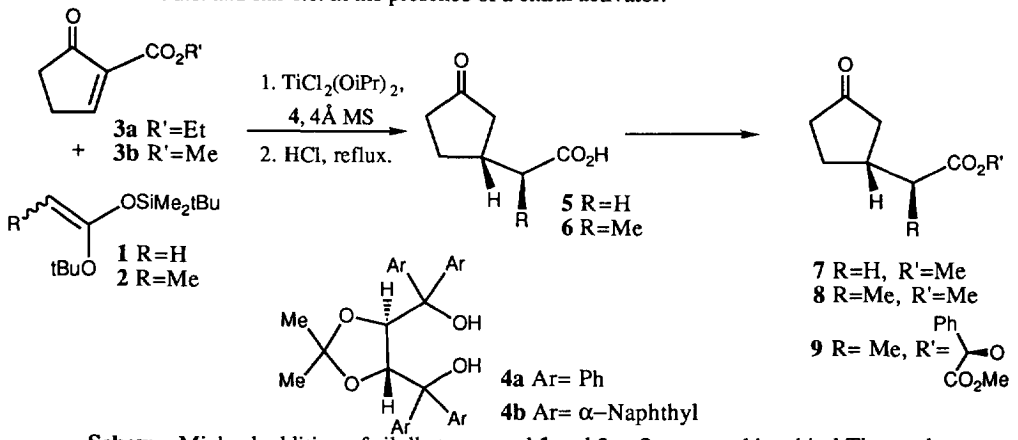
Anna Bernardi, Katia Karamfilova, Giovanna Boschin and Carlo Scolastico**

Dipartimento di Chimica Organica e Industriale, Centro CNR per lo Studio delle Sostanze Organiche e Naturali, via Venezian 21, 20133 Milano, Italy.

Abstract: *The conjugate addition of t-butylpropionate silylketeneacetal 2 to 2-carboxycyclopentenones **3a-b** promoted by TADDOL-derived Ti chlorides gives the ketoacid **6** with excellent d.e. and e.e. up to 47%.*

The conjugate addition of enolates and their analogues to activated double bonds (Michael addition) is among the most useful carbon-carbon bond forming reactions. Asymmetric versions of this reaction employing chiral auxiliaries on either donor or acceptor molecules have been described.[1] Some catalytic asymmetric Michael reactions of malonate-type donors have been achieved in the presence of chiral crown ether-KOtBu complexes,[2] the Rb salt of proline,[3] or a chiral La complex.[4] 2-Cyanopropionates give enantioselective conjugate additions in the presence of a Rh catalyst with a chiral (ferrocenyl)diphosphine ligand.[5] Recently Mukaiyama has reported that the conjugate addition of thiolacetate silylketeneacetals can be catalyzed by a chiral oxotitanium complex with e.e. up to 90%.[6]

In this paper we report our results on the enantioselective Michael addition of silylketeneacetals **1** and **2** to 2-carboxycyclopentenones **3a-b** in the presence of TADDOL-derived titanium chlorides (Scheme).[7] To the best of our knowledge, this is the first time that an acid catalyzed conjugate addition of simple propionates is found to proceed in excellent d.e. and fair e.e. in the presence of a chiral activator.



Scheme. Michael addition of silylketeneacetal **1** and **2** to **3** promoted by chiral Ti complexes.

The chiral Lewis acids were prepared *in situ* by stirring a solution of $TiCl_2(OiPr)_2$ with 1 mol equiv of the appropriate diol **4** over night at RT in the presence of 4Å MS.[8] Addition of **1** to **3a** in toluene in the presence of **4a**·$TiCl_2$ gave a mixture of ketoester and silylated material. After water quenching, the chiral diol was recovered by filtration from hexane, and the crude was treated in refluxing HCl[9] to give ketoacid **5** with 12% e.e., as determined by ^{1}H-NMR of ketoester **7** in the presence of $Eu(hfc)_3$ (Table, Entry 1). The configuration of the

major enantiomer was found to be (R) by comparison of the optical rotation of **5** and **7** with literature data.[9]

With the propionate acetal **2** the same procedure afforded the *syn* ketoacid **6** in moderate yield and excellent diastereomeric ratios (Table, Entry 2).[10] The e.e. of **6** was determined either by ^{1}H-NMR of **8** in the presence of Eu(hfc)$_3$ or by reaction of **6** with (R)-methylmandelate and integration of the benzyl proton signals of **9**.[11] The absolute configuration of the major enantiomer was assumed to be (3R) by analogy with what found for **5**. Toluene was found to be the solvent of choice for this reaction: both yield and selectivity dropped when the reaction was performed in CH_2Cl_2 (Entry 3). CH_3CN, CH_3CH_2CN and CH_3NO_2 were also tested: in all cases yields and selectivity were disappointing compared to toluene. Using diol **4a** a dramatic increase of enantioselectivity was observed when the substrate was changed from 2-carbethoxycyclopentanone **3a** (Entry 2, 16% e.e.) to the corresponding methyl ester **3b** (Entry 4). Starting from the latter, the acid **6** was isolated in 43% e.e. Use of the α-naphthyl substituted diol **4b** (Entry 5) improved the e.e. to 47%.[12]

Table. Michael addition of silylketeneacetal **2** to **1** promoted by chiral Ti complexes.[a]

Entry	R	R'	Diol	Solvent	*syn : anti* [b]	e.e. (%)[c]	Yield (%)[d]
1	H	Et	**4 a**	Toluene	=	10[e]	25
2	Me	Et	**4 a**	Toluene	96:4	16[e]	55
3	Me	Et	**4 a**	CH_2Cl_2	92:8	11[e]	21
4	Me	Me	**4 a**	Toluene	97:3	43[f]	38
5	Me	Me	**4 b**	Toluene	98:2	47[f]	50

a. All reactions were run for 5 h at -78°C in 0.1M solution, using 1.0 mol equiv of Ti complex, 2 mol equiv of silylketene acetal, and 100 mg/mmol of 4Å MS. **b.** By GC of **8. c.** Configuration of major enantiomer (3R); see *ref. 9.* **d.** Of the isolated acids **5** or **6. e.** Eu(hfc)$_3$ of Me esters **7** or **8** in C_6D_6 **f.** ^{1}H-NMR of **9** in C_6D_6.

Further studies to clarify the reaction mechanism and to improve selectivities are in progress.

Acknowledgments. This work was supported by funding from MURST. K.K. gratefully acknowledges the Hoechst Foundation for a graduate fellowship.

REFERENCES AND NOTES.

1. Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* **1989**, *19*, 227-407; *ibid.* **1991**, *20*, 87-170.
2. a) Cram, D.J.; Sogah, G.D.Y. *J.Chem.Soc.Chem.Commun.* **1981**, 625-628; *J.Am.Chem.Soc.* **1985**, *107*, 8301-8302. b) Alonso-López, M.; Martin-Lomas, M.; Penadés, S. *Tetrahedron Lett.* **1986**, 3551-3554; Alonso-López, M.; Jimenez-Barbero, J.; Martin-Lomas, M.; Penadés, S. *Tetrahedron* **1988**, *44*, 1535-1543. c) Takasu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943-6946; Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229-7230; *Heterocycles* **1992**, *33*, 493-495.
3. Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew.Chem.Int.Ed.Engl.* **1993**, *32*, 1176-1178.
4. Sasai, H.; Arai, T.; Shibasaki, M. *J.Am.Chem.Soc.* **1994**, *116*, 1571-1572.
5. Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439-4454.
6. Kobayashi, S.; Yamada, M.; Mukaiyama, T. *Chem.Lett.* **1994**, 97-100.
7. Beck, A.B.; Bastani, B.; Plattner, D.A.; Petter, W.; Seebach, D.; Braunschweiger, H.; Gysi, P.; La Vecchia, L. *Chimia* **1991**, *45*, 238-244 and references therein.
8. Control experiments revealed that the same results can be achieved using $TiCl_2$·**4** obtained by azeotropic distillation of iPrOH from an equimolar solution of **4** and $TiCl_2(OiPr)_2$ in toluene.
9. Kuritani, H.; Takaoka, Y.; Shingu, K. *J.Org.Chem.* **1979**, *44*, 452-454.
10. The *syn/anti* ratios were determined by ^{13}C-NMR of **6** or GC analysis of the corresponding Me ester **8**: Ficini, J.; Giungant, A. *Nouv.J.Chim.* **1980**, *4*, 421-422.
11. Parker, D. *J.Chem.Soc. Perkin Trans II* **1983**, 83-88.
12. Complexes prepared from $TiCl_2(OiPr)_2$ and (R)-binaphthol or β-naphthyl substituted TADDOL (**4**, Ar=β-naphthyl) were found to be less effective than those derived from **4a-b**. Use of chiral disulphonamide ligands was also attempted with unsatisfactory results.

(*Received in UK* 30 *November* 1994; *accepted* 21 *December* 1994)