Tetrahedron. Asymmetry Vol 1, No 5, pp 295-298, 1990
Printed in Great Britain

0957-4166/90 $3 00+ 00
Pergamon Press plc

REGIOSELECTIVE ENOLIZATION OF OPTICALLY ACTIVE 3-KETO STEROIDS USING CHIRAL LITHIUM AMIDES

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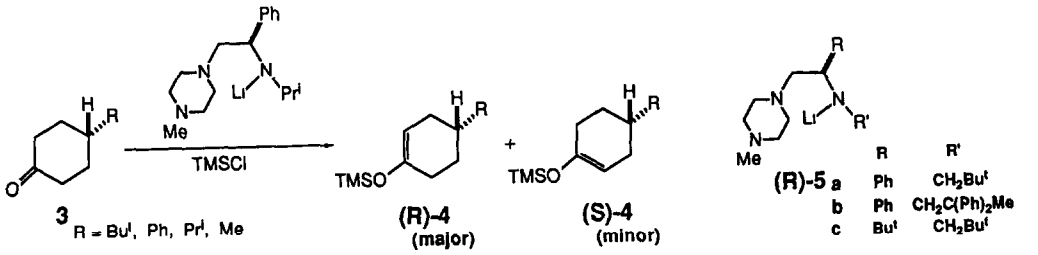
(*Received* 12 *March* 1990)

Abstract Deprotonation of optically active 3-keto steroids (**1**, **2**, **10**, **11**) by chiral lithium amides ((R)- or (S)-**5**) ,in the presence of excess trimethylsilyl chloride gave either regioisomers of their corresponding trimethylsilyl enol ethers in reasonably high selectivities.

Selective conversion of an unsymmetrical ketone to either one of the two possible regioisomeric enolates plays a valuable and basic role in synthesis.[1] Examples are known in which one regioisomeric enolate is obtained selectively under thermodynamically controlled conditions, while the other enolate is obtained selectively by kinetic deprotonation using hindered lithium amides[2] such as LDA. It is shown, however, that the major product is Δ^2-enolate in the reaction of 3-cholestanone (**1**), while it is Δ^3-enolate in the reaction of 3-coprostanone (**2**) under thermodynamically[3] as well as kinetically[4] controlled conditions. Regioselective methods are not known to obtain Δ^3-enolate or Δ^2-enolate directly from **1** or **2**, respectively.

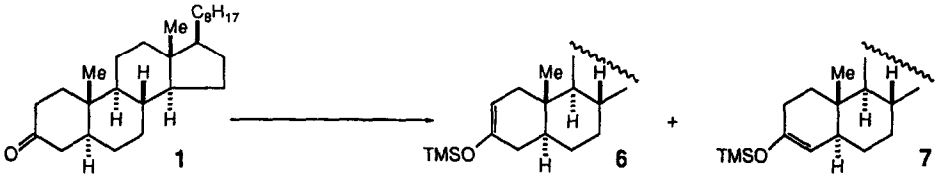
We have previously reported that kinetic deprotonation of prochiral 4-substituted cyclohexanones (**3**) by chiral lithium amides occurs enantioselectively in the presence of excess trimethylsilyl chloride (TMSCl) to give the corresponding trimethylsilyl enol ethers (**4**) in reasonably high enantiomeric excesses.[5,6] Applying this strategy using



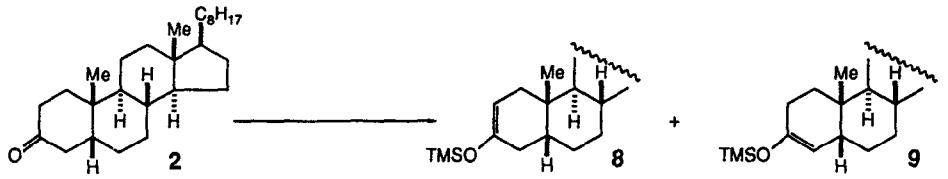
3 R = Bu^t, Ph, Pr^i, Me — **(R)-4** (major) + **(S)-4** (minor)

either enantiomers of chiral lithium amides ((R)- or (S)-**5**), examinations were made on the possibility of increasing or reversing regioselectivity in the synthesis of silyl enol ethers from optically active **1**, **2**, and 19-nor derivatives (**10**, **11**).

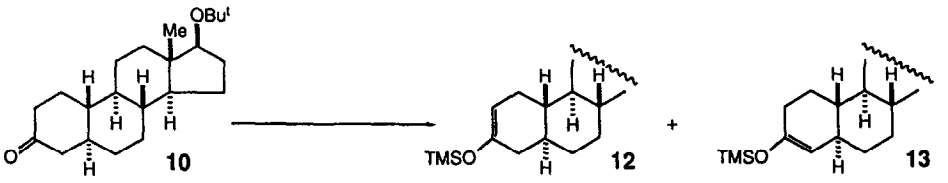
The results are tabulated below. A typical experimental procedure is as follows. A solution of chiral lithium amide ((R)-**5c**) was prepared under argon atmosphere by adding a solution of n-butyllithium (0.50 ml, 0.8 mmol) in hexane (1.60 M solution) to a solution of the corresponding amine (215 mg, 0.8 mmol) in toluene (4 ml) under stirring at -78°C for 10 min. Hexamethylphosphoric triamide (0.14 ml, 0.8 mmol) was added,[5] and the resulting solution was warmed to room temperature and then re-cooled to -78°C. To this solution were added TMSCl (0.26 ml, 2.0 mmol) in toluene (1 ml) quickly, and then a



Condition	Chem y (%)	6	7
Thermodynamic ($HN(TMS)_2$, TMSI)[3]		90	10
Kinetic (LDA)	99	78	22
Kinetic ((R)-5a)	86	39	61
Kinetic ((R)-5b)	98	30	70
Kinetic ((R)-5c)	94	2	98
Kinetic ((S)-5a)	83	98	2
Kinetic ((S)-5b)	98	98	2
Kinetic ((S)-5c)	97	>98	<2

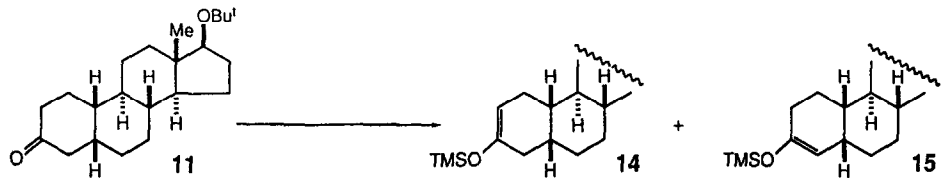


Condition	Chem y. (%)	8	9
Thermodynamic ($HN(TMS)_2$, TMSI)[3]		7	93
Kinetic (LDA)	97	16	84
Kinetic ((R)-5a)	92	84	16
Kinetic ((R)-5b)	99	97	3
Kinetic ((R)-5c)	98	96	4
Kinetic ((S)-5a)	78	<2	>98
Kinetic ((S)-5b)	99	<2	>98
Kinetic ((S)-5c)	90	<2	>98



10 12 13

Condition	Chem y (%)	12	13
Thermodynamic ($HN(TMS)_2$, TMSI)[8]	63	80	20
Kinetic (LDA)	99	64	36
Kinetic ((R)-5a)	97	95	5
Kinetic ((R)-5b)	96	91	9
Kinetic ((S)-5a)	98	24	76
Kinetic ((S)-5b)	92	24	76



11 14 15

Condition	Chem y (%)	14	15
Thermodynamic ($HN(TMS)_2$, TMSI)[8]	88	20	80
Kinetic (LDA)	96	27	73
Kinetic ((R)-5a)	92	89	11
Kinetic ((R)-5b)	99	95	5
Kinetic ((S)-5a)	95	< 2	>98
Kinetic ((S)-5b)	97	< 2	>98

solution of **1** (155 mg, 0.4 mol) in toluene (5 ml) dropwise during 3 min, and the whole was stirred at -78°C for 20 min. After addition of triethylamine (1.5 ml) and saturated aqueous sodium bicarbonate (4 ml), the reaction mixture was allowed to warm to room temperature. Usual work-up using hexane as an extracting solvent gave a crude product, which was subjected to column chromatography (silica gel, hexane-benzene (1:1)) to isolate a mixture of **6** and **7** (172 mg, 94%). The ratio of **6** and **7** was found to be 2 to 98 by proton nmr spectral analysis.[7]

It is shown that regioselectivity of enolization can be increased or reversed depending upon the configuration of **5** used. However, the sense of regioselectivity is opposite in the reaction of **1**, **2**, and **11** to that predicted from the reaction of **3**, while it is the same in the reaction of **10**. This interesting phenomenon is parallel to the fact that, taking A-rings of these steroidal ketones as cyclohexanone derivatives in

chair conformation, **1**, **2**, and **11** have an axial methyl or alkyl group at 4-position (cyclohexanone numbering), while **10** has an axial hydrogen there. Evaluating the stereoelectronic effect in deprotonation reaction[9] in which carbon-hydrogen σ-bond should be parallel to carbon-oxygen π-bond for the hydrogen to be lost, the results obtained here suggest the possibility that deprotonation is occurring in chair conformation in **3** and **10**, while it is occurring in skew-boat conformation in **1**, **2**, and **11**. Examinations using deuterated compounds as substrates are now in progress in our laboratories.

Acknowledgements The authors are grateful to Dr. Norio Takamura for valuable discussions, and to the Japan Foundation for Optically Active Compounds for partial financial support.

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7) The ratio was determined by the areas of olefinic proton signals (in benzene-d_6) centered at 4.92 ppm and 4.70 ppm for **6** and **7**, respectively.
8) This data was obtained by the method reported in ref. 3.
9) P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Pergamon Press, New York, 1983, p. 274.