Tetrahedron Letters,Vol.30,No.47,pp 6537-6540,1989
Printed in Great Britain
0040-4039/89 $3.00 + .00
Pergamon Press plc

# KINETIC RESOLUTION OF RACEMIC 2-SUBSTITUTED CYCLOHEXANONES BY ENANTIOSELECTIVE DEPROTONATION[1)]

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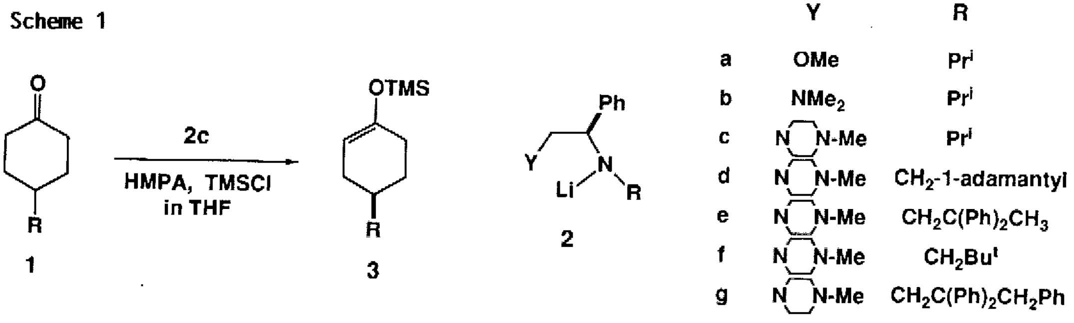
Abstract: Incomplete deprotonation of racemic 2-substituted cyclohexanones (dl-**4**) by chiral lithium amides (**2**) in the presence of trimethylsilyl chloride was found to give the corresponding trimethylsilyl enol ethers (**5**) and the unreacted ketones (**4**) in reasonably high enantiomeric excesses.

The importance of optically active ketones as chiral synthons in organic synthesis calls for their useful and efficient preparations. As racemic ketones are usually available readily, their resolutions by chemical[2)] and biochemical[3)] methods have been extensively explored.[4)]

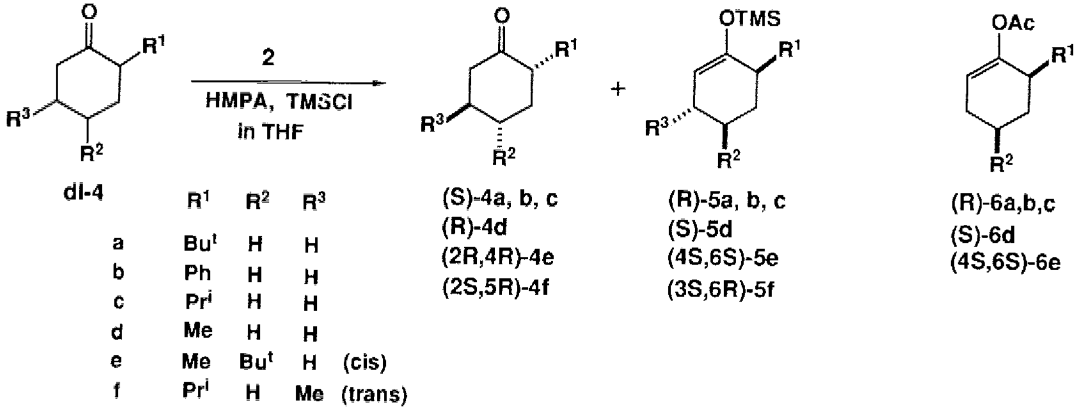
We have previously reported[5)] enantioselective deprotonation of prochiral 4-substituted cyclohexanones (**1**) by chiral lithium amide (for example, **2c**) in the presence of trimethylsilyl chloride (TMSCl) to give the corresponding optically active trimethylsilyl enol ethers (**3**). The stereochemical course of this deprotonation reaction was found to be generalized as shown in Scheme 1.

**Scheme 1**



Based on the fact that deprotonation of 2-substituted cyclohexanones (**4**) by sterically hindered lithium amide bases occurs highly selectively on methylene protons over methine protons under kinetically controlled conditions,[6)] we examined the possibility of kinetic resolution of racemic **4** by the strategy of incomplete deprotonation by chiral lithium amides (**2**) to separate them as their corresponding trimethylsilyl enol ethers (**5**) and the unreacted **4**.

Scheme 2



| | $R^1$ | $R^2$ | $R^3$ | |
|---|---|---|---|---|
| a | $Bu^t$ | H | H | |
| b | Ph | H | H | |
| c | $Pr^i$ | H | H | |
| d | Me | H | H | |
| e | Me | $Bu^t$ | H | (cis) |
| f | $Pr^i$ | H | Me | (trans) |

The results are summarized in Table 1. A typical experimental procedure (run 7) is as follows. A solution of lithium amide (**2f**) was prepared under argon atmosphere by adding a solution of n-butyllithium (1.52 mmol) in hexane (1.52 M solution) to a solution of the corresponding amine (1.52 mmol) in tetrahydrofuran (THF) (5.0 ml) under stiring at -78°C. Hexamethylphosphoric triamide (HMPA) (1.52 mmol) was added[5] and then the whole was warmed by stirring without cooling bath for 5 min. This solution was added dropwise during 10 min to a cooled (-105°C) solution of **4a** (1.52 mmol) and TMSCl (7.6 mmol) in THF (10 ml) under argon atmosphere, and the whole was stirred at -105°C for 50 min. After addition of triethylamine (2 ml) and saturated aqueous sodium bicarbonate (4 ml), the reaction mixture was warmed to room temperature. Usual work-up by using pentane as an extracting solvent gave a mixture of **5a** and the unreacted **4a**. A portion of this mixture was subjected to gas chromatographic (GC) analysis (OV-101, quinoline as an internal standard) to show that **4a** and **5a** were obtained in 49% and 51% calculated chemical yield, respectively. A portion of the above mixture was subjected to column chromatography (silanized silica gel, pentane) followed by bulb-to-bulb distillation to isolate (S)-**4a** ($[\alpha]_D^{25}$ -32.6°(methanol)) in 45% yield, and (R)-**5a** ($[\alpha]_D^{25}$ +9.52°(benzene)) in 51% yield.

Absolute configurations of (R)-**4a**,[4a,8] (R)-**4b**,[9] (S)-**4c**,[10] (S)-**4d**,[11] (2R,4R)-**4e**,[12] and (2S,5R)-**4f**[13] are already known. Therefore, absolute configurations of **5a-f** are obvious. Enantiomeric excesses of **5a-f** were estimated by conversion to their corresponding enol acetates (**6a-e**),[14] or to the parent ketone (**4f**).[16]

All chiral lithium amides (**2**) used in the present study showed high levels of regioselectivity in deprotonation. For example, the ratio of regioisomeric silyl enol ethers in the reaction of **4d** using **2g** was found to be over 120:1 by GC analysis. The degree of racemization of **4** during the reaction seems to be quite small as shown in run 9, where (S)-**4b** was obtained in reasonably high enantiomeric excess.

Efficient kinetic resolution of racemic **4** by enantioselective deprotonation is thus achieved. The present method has the following characteristics. (1) High levels of

**Table 1.** Kinetic Resolution of dl-**4**[a)]

| Run | Starting ketone | Base | Equiv. | Temp. (°C) | Recovered ketone[b)] | Yield(%)[d)] | ee(%) | Silyl enol ether[c)] | Yield(%)[d)] | ee(%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | dl-**4a** | **2a** | 0.77 | -78 | (S)-**4a** | 45(49) | 2 | (R)-**5a** | 46(51) | 3 |
| 2 | dl-**4a** | **2b** | 0.77 | -78 | (S)-**4a** | 67(73) | 4 | (R)-**5a** | 22(27) | 15 |
| 3 | dl-**4a** | **2c** | 0.77 | -78 | (S)-**4a** | 53(58) | 27 | (R)-**5a** | 40(42) | 37 |
| 4 | dl-**4a** | **2d** | 1.0 | -78 | (S)-**4a** | 39(45) | 77 | (R)-**5a** | 54(55) | 65 |
| 5 | dl-**4a** | **2e** | 1.0 | -78 | (S)-**4a** | 35(39) | 96 | (R)-**5a** | 60(61) | 63 |
| 6 | dl-**4a** | **2f** | 1.0 | -78 | (S)-**4a** | 54(57) | 61 | (R)-**5a** | 40(43) | 94 |
| 7 | dl-**4a** | **2f** | 1.0 | -105 | (S)-**4a** | 45(49) | 90 | (R)-**5a** | 51(51) | 94 |
| 8 | dl-**4b** | **2f** | 0.8 | -105 | (S)-**4b** | 66 | 30 | (R)-**5b** | 33 | 98 |
| 9 | dl-**4b** | **2f** | 1.3 | -105 | (S)-**4b** | 24 | 94 | (R)-**5b** | 72 | 48 |
| 10 | dl-**4c** | **2f** | 0.8 | -105 | (S)-**4c** | (78) | 18 | (R)-**5c** | (22) | 94 |
| 11 | dl-**4d** | **2g** | 0.7 | -105 | (R)-**4d** | (65) | 38 | (S)-**5d** | (35) | 90 |
| 12 | dl-**4e** | **2g** | 0.8 | -105 | (2R,4R)-**4e** | 48 | 93 | (4S,6S)-**5e** | 52 | 90 |
| 13 | dl-**4f** | **2f** | 0.68 | -105 | (2S,5R)-**4f** | 42(45) | 94 | (3S,6R)-**5f** | 54(55) | 76 |

a) For procedure, see text. b) Maximum rotations reported are: $[\alpha]_D^{24.5}$ +36.0°(MeOH) for (R)-**4a**,[4a,8)] $[\alpha]_D^{26}$ +114.7°(benzene) for (R)-**4b**,[9)] $[\alpha]_D^{23}$ -75°(MeOH) for (S)-**4c**,[10)] $[\alpha]_D^{23}$ +14.0°(MeOH) for (S)-**4d**,[11)] $[\alpha]_{365}^{20}$ +60°(cyclohexane) for (2R,4R)-**4e**,[12)] and $[\alpha]_D^{27}$ -32.8° ($CHCl_3$) for (2S,5R)-**4f**.[13)] c) Maximum rotations were calculated to be: $[\alpha]_D^{25}$ +10.1° (benzene) for (R)-**5a**,[14)] $[\alpha]_D^{24}$ +51.4°(benzene) for (R)-**5b**,[14)] $[\alpha]_{365}^{25}$ +79.4° (benzene) for (R)-**5c**,[14)] $[\alpha]_D^{25}$ -26.8°(benzene) for (S)-**5d**,[14)] $[\alpha]_D^{25}$ +18.7°(benzene) for (4S,6S)-**5e**,[14)] and $[\alpha]_{365}^{25}$ -36.9°($CH_3CN$) for (3S,6R)-**5f**.[16)] d) Isolated chemical yield. Calculated chemical yield by using GC is shown in the parentheses.

enantioselectivity ($k_{rel}$[7)] for run 12 was calculated to be 44) and regioselectivity were obtained. (2) Stereochemical course of the reaction can be generalized as shown in Scheme 2, and therefore, is predictable. (3) For cyclohexanones such as **4a-d** having one chiral center, the undesired enantiomer in the products can be recycled via racemization or desilylation followed by racemization to get the desired enantiomer. (4) Chiral bases can be recovered for reuse. (5) The reaction is clean enough to isolate the products in almost quantitative yields.[17)]

## References and Notes

1) This paper is dedicated to Professor Haruaki Yajima on the occasion of his retirement from Kyoto University in March, 1989.

2) a) S. H. Wilen, in "Topics in Stereochemistry," Vol. 6, ed. by N. L. Allinger and E. L. Eliel, Wiley-Interscience, New York, 1971, p. 107. b) P. Newman, "Optical Resolution Procedures for Chemical Compounds," Vol. 3, Optical Resolution Information Center, Manhattan College, New York, 1984, p.484.
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6) See for example: D. A. Evans, in "Asymmetric Synthesis," Vol. 3, ed. by J. D. Morrison, Academic Press, New York, 1984, p. 1.
7) For a review, see: H. B. Kagan and J. C. Fiaud, in "Topics in Stereochemistry," Vol. 18, ed. by E. L. Eliel and S. H. Wilen, Wiley-Interscience, New York, 1988, p. 249.
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13) Cf. C. R. Johnson and J. R. Zeller, *Tetrahedron*, **40**, 1225(1984).
14) Optically active silyl enol ethers (**5a-e**) were converted to the corresponding enol acetates (**6a-e**) (acetic anhydride, 4-dimethylaminopyridine in pyridine, room temperature, overnight[15]). Enantiomeric excesses of **6a-e** were estimated by $^1$HNMR (Eu(hfc)$_3$ or Eu(dppm)$_3$, benzene-$d_6$). (R)-**5a**($[\alpha]_D^{25}$ +8.29°(1.07, benzene)) gave (R)-**6a**($[\alpha]_D^{25}$ -81.4°(0.42, benzene)) of 82% ee. (R)-**5b**($[\alpha]_D^{24}$ -20.5°(1.06, benzene)) gave (R)-**6b**($[\alpha]_D^{24}$ -18.4°(2.05, benzene)) of 40% ee. (R)-**5c**($[\alpha]_{365}^{25}$ +74.4°(1.51, benzene)) gave (R)-**6c** of 94% ee. (S)-**5d**($[\alpha]_D^{25}$ -24.1°(1.37, benzene) gave (S)-**6d**($[\alpha]_D^{21}$ -50.7° (0.58, benzene)) of 90% ee. (4S,6S)-**5e**($[\alpha]_D^{25}$ +16.9°(0.914, benzene)) gave (4S,6S)-**6e**($[\alpha]_{365}^{25}$ -33.4°(1.03, benzene)) of 90% ee. Enantiomeric excesses of **5a-e** were calculated by these data, and should be minimum.
15) Cf. J. K. Rasmussen, *Synthesis*, **1977**, 91.
16) (3S,6R)-**5f**($[\alpha]_{365}^{25}$ -28.0°(1.10, $CH_3CN$)) was converted (10% aqueous HCl in THF, -78°C) to (2R,5S)-**4f**($[\alpha]_D^{27}$ +24.8°(2.13, $CHCl_3$)).
17) This research was assited financially by the Grant-in-Aid for Scientific Research on Priority Areas (01607002) from the Ministry of Education, Science, and Culture, Japan.

(Received in Japan 9 August 1989)