should be dipole HOMO controlled, and the HOMO polarization is modestly weighted toward carbon rather than nitrogen due to the effect of sydnone carbonyl.[12] Since thial LUMO polarization also has the larger FMO coefficient at carbon,[11] the regiochemistry seen for entry 8 would have to be due to other factors (sterics, lone pair repulsions, dipole LUMO–thial HOMO interactions, etc).

So far, only the previously reported reaction of thiopivaladehyde with ethyl diazoacetate gives detectable products from the more hindered 2 + 3 cycloadduct (ca. 1:1 mixture of regioisomers is formed).[4] A comparison of FMO energies and coefficients for the reactants[11,13] in this case is instructive because both possible FMO interactions (dipole HOMO + thial LUMO; dipole LUMO + thial HOMO) now favor the more hindered regioisomer. The behavior of thioketones with diazo esters is again very similar and opposing steric vs. FMO factors result in regioisomer mixtures.

Overall, there is a close analogy in the behavior of thiopivaldehyde and the previously studied thioketone 2 + 3 cycloadditions. The same trend has also been noted in 2 + 4 cycloadditions and ene insertions which are discussed in other papers from our laboratory.[11,14]

Acknowledgment. This work was supported by the National Science Foundation.

(12) Padwa, A.; Burgess, E. M.; Gingrich, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786.
(13) The FMO coefficients for diazoacetate are given in ref 10c where they are attributed to: Sustmann, R., private communication.
(14) Vedejs, E.; Wilde, R. G., unpublished results. Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.*, submitted for publication.

E. Vedejs,* R. G. Wilde
S.M. McElvain Laboratory of Organic Chemistry
Chemistry Department
University of Wisconsin
Madison, Wisconsin 53706
Received August 27, 1985

The Temperature-Dependent Regioselective Deprotonation of Fluoroacetone Cyclohexylimine

Summary: The temperature-dependent regioselective deprotonation of fluoroacetone cyclohexylimine was developed as a procedure for the regioselective alkylation of fluoroacetone.

Sir: The importance of metalated imines (azaallyl metal reagents) in selective asymmetric synthesis is widely recognized.[1] Regioselective deprotonation, critical when acyclic ketimines are employed, is dependent upon temperature, the nitrogen alkyl substituent, and the steric bulk of the base among other factors.[2] In the course of our studies on the stereoselective synthesis of fluorinated compounds, we sought to develop methods for the selective deprotonation and alkylation of fluorinated imines. As fluorine is not a sterically demanding substituent, fluorination is a severe test of the sensitivity of deprotonation to steric effects. At the same time fluorination will have pronounced electronic effects on the reaction.

Table I. Temperature-Dependent Deprotonations of Fluoroacetone Cyclohexylimine

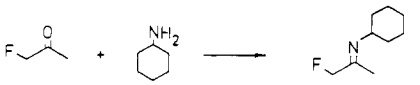
entry	alkyl halide	temp, °C	product composition[a] RCHFO-CH_3	product composition[a] CH_2FCO-CH_2R	yield, %
1	CH_3I	−30	11	89	48[b]
2	CH_3I	−80	96	4	43[b]
3	CH_2=$CHCH_2Br$	−30	9	91	62
4	CH_2=$CHCH_2Br$	−80	97	3	69
5	$CH_3CH_2CH_2CH_2I$	−30	3	97	60
6	$CH_3CH_2CH_2CH_2I$	−80	97	3	81
7	$C_6H_5CH_2Br$	−30	18	82	71
8	$C_6H_5CH_2Br$	−80	93	7	81
9	C_6H_5CH=$CHCH_2Br$	−30	8	92	88
10	C_6H_5CH=$CHCH_2Br$	−80	28	72	79

[a] Product composition determined by gas chromatography and ^{19}F NMR spectroscopy. [b] Yield of crude product.

The utility of stereospecifically fluorinated biologically active compounds, such as γ-fluoroglutamic acid,[3] fluorocitric acid,[4] or 2-deoxy-2-fluoroarabinose,[5] in descerning biochemical pathways is limited only by the difficulty of their preparation. This challenge has been addressed in our[6] and others'[7] earlier investigations of fluorinated enolates. Deprotonated fluorinated imines are particularly attractive enolate equivalents, where the sensitivity of imine deprotonation to subtle steric and electronic effects may be probed.

Halogenated imines[8] have been reported to react with nitrogen bases by intra- or intermolecular displacement of halide.[9] Organometallic reagents also effect displacement reactions as well as imine dimerization.[10] Although fluoro imines have been implicated as intermediates in action of pyridoxal 5′-phosphate with fluoroaspartates in NMR studies,[11] much less is known about the chemistry of fluorinated imines.

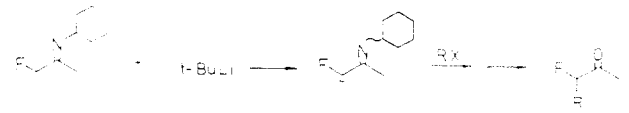
We have found that the cyclohexylimine of fluoroacetone may be simply prepared by treatment of fluoroacetone with cyclohexylamine in the presence of anhydrous potassium carbonate. Distillation under reduced pressure



(1) (a) Bergbreiter, D. E.; Newcomb, M. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: Orlando, 1983; Vol. 2, pp 243–273. (b) Fraser, R. R. In "Comprehensive Carbanion Chemistry"; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; Part B, pp 65–105.
(2) Smith, J. K.; Newcomb, M.; Bergbreiter, D. E.; Williams, D. R.; Meyers, A. I. *Tetrahedron Lett.* **1983**, *24*, 3559–3562.
(3) Dubois, J.; Gaudry, M.; Bory, S.; Azerad, R.; Marque, A. *J. Biol. Chem.* **1983**, *258*, 7897–7899.
(4) Schlosser, M. *Tetrahedron* **1978**, *34*, 3–17.
(5) Penglis, A. A. E. *Adv. Carbohydro. Chem. Biochem.* **1981**, *38*, 195–285.
(6) (a) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720–4721. (b) Welch, J. T.; Seper, K. *Tetrahedron Lett.* **1984**, *25*, 5247–5250. (c) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186–188. (d) Welch, J. T.; Samartino, J. *J. Org. Chem.* **1985**, *50*, 3663. (e) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.*, in press.
(7) (a) Braendige, S.; Dahlman, O.; Moerch, L. *J. Am. Chem. Soc.* **1981**, *103*, 4452–4458. (b) Poulter, C. D.; Mash, E. A.; Argyle, J. C.; Muscio, O. J.; Rilling, H. C. *J. Am. Chem. Soc.* **1979**, *101*, 6761–6763. (c) Molines, H.; Massoudi, M. H.; Cantacuzene, D.; Wakselman, C. *Synthesis* **1983**, 322–324. (d) Elkik, E.; Francesch, D. *Bull. Chim. Soc. Fr.* **1973**, 1277–1280. (e) Elkik, E.; Francesch, D. *Bull. Soc. Chim. Fr.* **1973**, 1281–1285. (f) Elkik, E.; Imbeaux-Oudotte, M. *Bull. Soc. Chim. Fr.* **1975**, 1165–1169. (g) Elkik, E.; Imbeaux-Oudotte, M. *Tetrahedron Lett.* **1979**, 3793–3796.
(8) De Kimpe, N.; Verhe, R.; DeBuyck, L.; Schamp, N. *Org. Prep. Proced. Int.* **1980**, *12*, 49–180.
(9) De Kimpe, N.; Verhe, R.; De Buyck, L.; Sulmon, P.; Schamp, N. *Tetrahedron Lett.* **1983**, *24*, 2885–2888.
(10) De Kimpe, N.; De Cort, B.; Verhe, R.; De Buyck, L.; Schamp, N. *Tetrahedron Lett.* **1984**, *25*, 1095–1098.
(11) Salon, M. C.; Hamman, S.; Beguin, C. G. *Org. Magn. Reson.* **1983**, *21*, 265–270.

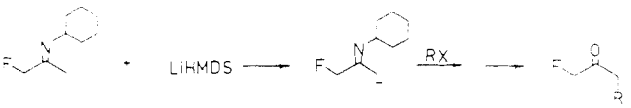
0022-3263/86/1951-0119$01.50/0

yielded material sufficiently pure for our deprotonation studies.[12] By gas chromatography,[13] the fluoroketimine was found to be >95% a single isomer. NOE studies demonstrated that the principal product was the *E* C–N isomer.[14] Deprotonation was effected by slow addition of the fluoroketimine to a solution of lithium hexamethyldisilazide in tetrahydrofuran (THF) solution containing hexamethylphosphoric triamide[15] or *tert*-butyllithium in THF alone. After being stirred for 2 h at the



desired temperature, a solution of the alkyl halide was added over an additional 2 h at low temperature. The less volatile products were conveniently isolated by hydrolysis of the product imine to the ketone with dilute acetic acid (Table I). Deprotonation of the cyclohexylimine of fluoroacetone was regiospecific and temperature dependent. The tendency of the metalated ketimine to alkylate on the carbon bearing fluorine at low temperatures may be rationalized by suggesting that the increased acidity associated with the protons near fluorine acts in concert with steric effects of the *E* C–N configuration of the imine; i.e., steric interactions of the base with the *N*-cyclohexyl group[16] hinders syn approach.

At higher temperatures, alkylation was directed away from the fluoromethyl group. In control experiments alkylation away from the carbon bearing fluorine did not result when ketimine deprotonated at low temperature was allowed to warm to −30 °C for 2 h. Since decomposition



of the deprotonated imine at temperatures greater than −30 °C becomes a serious problem, equilibration at higher temperatures (such as 25 °C, as reported for isomerization of butanone imines[2]) has not been attempted. Deprotonation of the fluoroketimine on the nonfluorinated carbon to form the thermodynamically favored less substituted azaallyllithium reagent would be enhanced by the greater relative stability of compounds where the fluorine is not bound to an sp^2-hybridized carbon.[17] In contrast to studies with 2-butanone imine it is not necessary to invoke isomerization of the imine to accommodate the observed temperature dependent results.[18]

It appears that at low-temperature deprotonation regioselectivity is dominated by steric and acidity effects, where at higher temperatures the thermodynamic stability of the products is controlling the regiochemistry. We are currently investigating the reaction of deprotonated stereogenic imines. Further studies of the scope and limitations of the temperature dependence of the deprotonation reactions of fluoroketimines are also under way.

Acknowledgment. We thank the Research Corporation and the the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supplementary Material Available: Analytical and complete spectral data are available (4 pages). Ordering information is given on any current masthead page.

(12) Anal. ($C_9H_{16}FN$) C, H. ^1H NMR ($CDCl_3$) δ 4.63 (d, $J_{H,F}$ = 47 Hz, 2 H, CH_2F), 3.35 (m, 1 H, CH), 1.78 (d, $J_{H,F}$ = 3 Hz, 3 H, CH_3), 1.70–1.10 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 162.1 ($J_{C,F}$ = 20 Hz, C=N), 86.4 ($J_{C,F}$ = 171 Hz, CH_2F), 58.58 (CH), 32.7, 25.1, 24.2, 12.8 (CH_3); ^{19}F NMR ($CDCl_3$) δ −227.1.

(13) Chromatography conditions. OV-101 wall coated on a 25 m× 0.025 mm open tubular fused silica column operated at 70 to 200 °C increasing at 10° per minute.

(14) Irradiation of the resonance at 3.35 ppm resulted in a 4–6% enhancement of the methyl resonance at 1.78 ppm without a concommitant enhancement of the signal at 4.63 ppm.

(15) Typical procedure: for reactions at −30 °C. To a magnetically stirred three-necked round-bottom flask under an inert atomosphere, containing 0.0048 mol of lithium hexamethyldisilazide (prepared by deprotonation of 0.77 g (0.0048 mol) of hexamethyldisilazane in 10 mL of THF with 3 mL (0.0048 mol) of 1.6 M solution of methyl lithium in diethyl ether at −20 °C) dissolved in 10 mL of dry THF and 0.6 g (0.0033 mol) hexamethylphosphoric triamide was slowly added over 1 h 0.5 g (0.0031 mol) of the cyclohexylimine of fluoroacetone dissolved in 10 mL of THF. After the mixture was stirred for an additional hour, 0.0026 mol of the alkyl halide in 10 mL of THF was added over 2 h. After quenching with 20 mL of saturated ammonium chloride, the product imine was extracted with two 20-mL portions of diethyl ether. The extracts were washed with brine, dried over anhydrous potassium carbonate, and concentrated in vacuo. The imine products were dissolved in trichlorofluoromethane and were hydrolyzed with 10 mL of 5% acetic acid over 2 h. The product ketones were isolated by separation of the organic phase, washing with 10 mL of saturated sodium bicarbonate solution, drying over anhydrous magnesium sulfate, and fractional distillation.

(16) Houk, K. N.; Stozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chauqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426–1429.

(17) Dolbier, W. R., Jr.; Medinger, K. S.; Greenberg, A.; Liebman, J. F. *Tetrahedron* **1982**, *38*, 2415–2420.

(18) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1983**, *105*, 4396–4400.

John T. Welch,* Karl W. Seper
Department of Chemistry
State University of New York at Albany
Albany, New York 12222
Received August 2, 1985

Asymmetric Additions to Chiral Naphthalenes. 3. The Synthesis of (+)-*trans*-1,2-Disubstituted-1,2-dihydronaphthalenes

Summary: Organolithium addition to chiral (1-naphthalyl)oxazolines followed by proton quench gives 84–97% diastereofacial selectivity and furnishes the title compounds in high enantiomeric excess after reductive removal of the chiral auxiliary.

Sir: We recently reported the tandem addition of organolithium reagents and various carbon and sulfur electrophiles to (1-naphthyl)oxazoline **1**[1] and its 2-isomer **4**.[2] The nucleophilic addition[3] occurred with a high degree of diastereofacial selectivity followed by alkylation with the electrophile to give very high ratios of trans addition products **2** and **5**. The trans addition was verified in each system by single-crystal X-ray determination. Thus, in either case, the electrophile entered the naphthalene nucleus from the side opposite to that of the organolithium, and the initial facial entry of the organolithium was determined solely by the chirality of the oxazoline moiety (vide infra). It was of considerable interest to assess the stereochemical protonation in this process by introduction of a proton source after the organolithium addition such that 1,2-disubstituted-1,2-dihydronaphthalenes could be obtained. We now report that this is indeed a highly

(1) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865.

(2) Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1984**, *25*, 3667.

(3) For another study involving nucleophilic addition to naphthalenes, as their chromium carbonyl complexes, see: Kundig, E. P.; Simmons, D. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1320.

0022-3263/86/1951-0120$01.50/0