side reactions from the cation radical A (such as dimerization and nucleophilic attack on an aromatic ring) even when deprotonation of A is slow due to the weak EWG's or electron-donating substituents on the benzene ring.

Since fluoride ions are much weaker nucleophiles compared to methoxide, it is reasonable that the methoxylation predominated in methanol. In support of this, more strongly nucleophilic ethanol gave higher yields (Table II, runs 4 and 13) compared to the results with methanol; reduction of the amount of methanol to 10:1 equivalents with a sulfide resulted in the formation of the fluorinated sulfide in addition to the methoxylated one (formation ratio, 33:67; Table II, run 3). Contrary to our cases, Shono and Matsumura et al. reported that bromosulfonium ions derived from sulfides and anodically generated positive bromonium ions can be used as so-called mediators for indirect anodic oxidation of alcohols.[19] However, they have never observed the formation of alkoxylated sulfides. In fact, our experiments, chloride and bromide ions other than fluoride ions did not promote the methoxylation at all (Table I, runs 5 and 6).

Thus, it was illustrated for the first time that fluoride ions remarkably promoted anodic substitution of the sulfides. This method has a wide applicability to various sulfides. Utilization of this novel electrochemical method for other synthetic applications is under investigation.

Acknowledgment. We thank Dr. Kokoro Iio of Industrial Products Research Institute for obtaining the high-resolution mass spectra.

Registry No. **1a**, 33740-59-9; **1b**, 134024-36-5; **1c**, 2262-07-9; **1d**, 7605-25-6; **1e**, 53136-40-6; **1f**, 102687-64-9; **1g**, 100-68-5; **2a**, 136764-65-3; **2b**, 134024-37-6; **2c**, 108200-49-3; **2d**, 136764-66-4; **2e**, 136764-67-5; **2f**, 129265-01-6; **2g**, 13865-50-4; **3a**, 136764-68-6; **3e**, 136764-69-7; MeOH, 67-56-1; EtOH, 64-17-5.

Supplementary Material Available: ^{1}H NMR, IR, MS, and high-resolution MS data for all new compounds (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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[19] Shono, T.; Matsumura, Y.; Hayashi, J.; Mizoguchi, M. *Tetrahedron Lett.* 1980, *21*, 1867.

An Improved Synthesis of Chiral Oxazolidine-2-selones: Highly Sensitive ^{77}Se NMR Reagents for the Detection and Quantitation of Chirality

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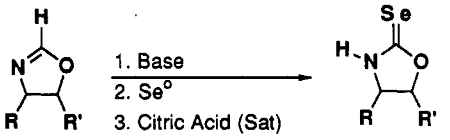
Summary: The synthesis of the title compounds from readily available oxazolines has been accomplished in one step in high yield. These chiral reagents exhibit extraordinary ^{77}Se chemical shift sensitivity and are useful for the detection and quantitation of chirality at remotely disposed chiral centers.

There has been considerable interest in the development of new methods and reagents for the determination of enantiomeric excesses[2] and, to a larger extent, the assignment of absolute configuration.[3] We have recently disclosed the application of the extreme chemical shift sensitivity of the ^{77}Se nucleus for the detection and quantitation of chirality at chiral centers distant from the observing nucleus.[4] To explore the scope and limitation of this novel method, a more efficient general synthetic route to a variety of chiral oxazolidine-2-selones is necessary.[5] In this report, we describe significant improvements in the synthesis of multigram quantities of selones (selenocarbonyl compounds) and demonstrate the remarkable chemical shift sensitivity of these chiral auxiliaries vis a vis the diastereomers which result from the coupling of these reagents to (R,S)-2-phenylpropanoyl chloride.

In recent reports, chiral and achiral selones can be constructed via the reaction of commercially available amino alcohols with carbon diselenide and mercury salts in a one-pot process.[6] While the reported yields were modest to fair (31–53%), the major drawback was the use of carbon diselenide, an expensive and hazardous reagent.[7] We envisioned that "selenonylation" of chiral amino alcohols could be accomplished via the reasily accessible intermediate oxazolines shown in Scheme I.[8]

Scheme I



1 a-g

2 a-g

The chiral oxazolines can be constructed in excellent yield and in enantiomerically pure form by the method of

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[1] Adjunct Professor, Department of Chemistry and Biochemistry, University of South Carolina.

[2] (a) Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron Asymmetry* 1990, *1*(7), 437–440. (b) For an application of ^{77}Se NMR for the determination of enantiomeric purity of alcohols see: Michelsen, P.; Annby, U.; Gronowitz, A. *S. Chem. Scr.* 1984, *24*, 251. (c) For ^{1}H NMR see: Williams, R. M.; Sinclair, P. J.; Ahai, D.; Chen, D. *J. Am. Chem. Soc.* 1988, *110*, 1547. (d) Takeuchi, Y.; Itah, N.; Note, H.; Koizumi, T. *J. Am. Chem. Soc.* 1991, *113*, 6318.

[3] (a) Buist, P. H.; Marecak, D. M. *J. Am. Chem. Soc.* 1991, *113*, 5877. We thank Professor Buist for a preprint of this paper. (b) Harada, N.; Saito, A.; Ono, O.; Gawronski, J.; Gawronska, K.; Sugioka, T.; Uda, J.; Kuriki, T. *J. Am. Chem. Soc.* 1991, *113*, 3842 and references cited therein.

[4] (a) *Chem. Eng. News* June 11, 1990, 25. (b) Silks, L. A.; Odom, J. D.; Dunlap, R. B. *J. Am. Chem. Soc.* 1990, *112*, 4979. (c) Silks, L. A.; Odom, J. D.; Dunlap, R. B. 199th National Meeting of the American Chemical Society, Boston, April 25, 1990; Abstr. No. 283, Organic Division. (d) Silks, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. 201st National Meeting of the American Chemical Society, Atlanta, April 16, 1991; Abstr. No. 176, Organic Division.

[5] Silks, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Chem. Soc., Perkins Trans. 1*, in press.

[6] Skrydstrup, T.; Kjaer, A. *Heterocycles* 1989, *28*, 269.

[7] Carbon diselenide is available from ICN Biomedicals at $184.00/g.

[8] The word "selenonylation" is derived by analogy to carbonylation.

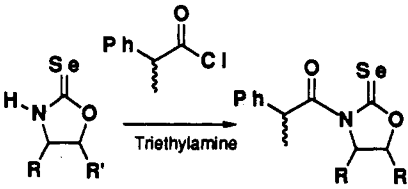
Table I. Yields and ^{77}Se NMR Spectroscopy of Oxazolidine-2-selones

compd (2a–g)	R^a	R′	method^b	yield^c (%) of 2a–g	δ ^{77}Se^{e,f}	J ^{13}C–^{77}Se (Hz); mp (°C)
a	Me (*R*)	Ph	B	91	137	249; 119–120
a′	Me	Ph (*R*)	B	98	137	240
	Me	Ph (*R*)	C	71		
b	CMe_3	H	A	90	119	237; 154–155
c	$CHMe_2$	H	A	92	118	233; 68–71
	$CHMe_2$	H	C	35–85^d		
d	CH_2Ph	H	A	98	139	237; 94–96
	CH_2Ph	H	C	36, 37		
e	CH_2CHMe_2	H	A	90	117	237
f	Ph	Ph (*R*)	B	83	156	229; 155–158
g	Ph (*R*)	H	B	85	140	237; 134–137
	Ph (*R*)	H	A	29		

^{a} Unless otherwise noted the absolute configurations are *S*. ^{b} All reactions were performed using 1–3 g of oxazoline. The reactions were performed using 1.15 equiv of base (generated using 1.2 equiv of methyllithium) and 1.2 equiv of Se^0. Method A: LDA. Method B: LHMDS. Method C: *n*-butyllithium. ^{c} Isolated yields from silica gel column chromatography (using a step gradient of methylene chloride to 2% diethyl ether/methylene chloride). ^{d} This reaction was repeated 10× giving the stated yield range. ^{e} Reference against 60% solution of dimethylselenide in $CDCl_3$.[13] ^{f} The selone ^{77}Se chemical shifts are concentration, solvent, and temperature dependent.

Meyers et al.[9] Metalation of the oxazolines can be accomplished using *n*-butyllithium, but consistently better yields are obtained with the use of lithium diisopropylamine (LDA) or lithium bis(trimethylsilyl)amide (LHMDS). After examining a variety of reagents and conditions for deprotonation (Table I), we found that when there was an aromatic substituent on or near the oxazoline ring, the use of LHMDS frequently brought about a remarkable increase in the yield of the product. For example, treatment of **1g** with LHMDS gave rise to a pale yellow solution and an isolated yield of 85% of selenated product. In contrast, treatment with LDA resulted in the formation of a deep emerald solution. Addition of selenium, followed by acidification with citric acid and reaction workup, afforded only 29% isolated yield of the product. In general, the use of *n*-butyllithium gave inconsistent results; the optimized yields for this series of oxazolidine-2-selones ranged from 83–98%.[10] Evidence for the presence of the selenium–carbon double bond is firmly established by comparison of the ^{13}C–^{7}17Se coupling constants (230–240 Hz) with those previously reported.[11,12]

Table II. ^{77}Se Δδ (ppm) of 2-Phenylpropanoyl Acylated Selones



2 a-g

3 a-g

compd	Δδ ($CDCl_3$)^a	Δδ (C_6D_6)
3a	40.9	38.2
3b	43.3	45.6^b
3c	32.0	29.3
3d	25.1	24.1
3e	38.6	41.3
3f	3.5	4.8
3g	35.0	27.0^b

^{a} The ^{77}Se NMR spectra were obtained on a Bruker 300 or AM-200. Measurements were made at, or near, ambient probe temperature in 5-mm NMR tubes. All spectra were acquired in the proton-decoupled mode: generally, 0.15–0.30 M solutions were used and 128–1024 scans were acquired using a pulse angle of 30° and a recycle time of 2.2 s. A resolution of 0.1 ppm was obtained using a 32K data table and a spectral width of 100 ppm. ^{b} [$^2H_8$]-toluene.

Selenium reagents have enjoyed widespread use in synthetic organic chemistry for selective transformations such as selenoxide eliminations,[14] selenium dioxide oxidations,[15] and radical-initiated carbocyclizations that employ selenoesters.[16] However, the selenium atom has only recently been exploited as a novel spectroscopic reporter group in the study of various inorganic, organic, and biochemical systems.[17] The sensitivity of the ^{77}Se nucleus

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(9) For the construction of the valinol-derived oxazoline: Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676. All other oxazolines were constructed by the method of: Meyers, A. I.; Leonard, W. R.; Romine, J. L. *J. Org. Chem.* **1991**, *56*, 1961.

(10) All new compounds reported herein have been fully characterized by mp, spectral means (^{1}H, ^{13}C, and ^{77}Se NMR, UV, optical rotations, and high-resolution mass spec) and elemental analyses. A typical procedure: In a 500-mL three-neck, round-bottom flask fitted with a septum, ground-glass stopper, and gas (N_2) inlet was placed 15.01 mL (71.32 mmol) of HMDS in 250 mL of THF. The solution was chilled to 0 °C, and 53 mL of methyllithium in Et_2O (74.4 mmol) was added. After gas evolution ceased, the reaction mixture was chilled to −78 °C, and 10.00 g of (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazoline (62 mmol) was added neat. The resulting pale yellow solution was stirred for 30 min, and then 5.6 g of solid Se^0 (70.92 mmol, 100 mesh) was added. The mixture was then allowed to warm to ambient temperature and stirring was continued for 1 h. The reaction was quenched with degassed citric acid (sat) until the pH of the aqueous layer remained acidic (pH ~ 4–5). The reaction was filtered through a pad of Celite, and the organic layer was isolated and dried over Na_2SO_4. Filtration, followed by removal of the volatiles in vacuo, afforded the crude material. The residue was then taken up in CH_2Cl_2 and filtered though a pad of SiO_2. The pad was then washed with 2–5% Et_2O (distilled from benzophenone ketyl)/CH_2Cl_2 until the pad was free of selone (by TLC analysis). The solvents were removed in vacuo. The material was then purified by flash silica gel chromatography (CH_2Cl_2) to give 13.56 g of **2a** (91%): mp 119–120 °C; $[\alpha]_D = +166$ ($c = 1 \times 10^{-3}$, $CHCl_3$); λ_{max} ($CHCl_3$) 278 nm ($\epsilon = 19\,254$); IR ($CDCl_3$) 3400, 3100, 2900, 1630, 1450, 1330, 1260, 1130 cm^{-1}; ^{1}H ($CDCl_3$) δ 0.87 (d, $J = 6.7$ Hz, 3 H), 4.41 (m, 1 H), 5.96 (d, $J = 9.1$ Hz, 1 H), 7.23–7.41 (m, 5 H), ^{13}C δ 16.4, 57.0, 88.2, 126.3, 128.7, 129.0, 133.2, 187.56; ^{77}Se δ = 137; mass spectrum *m/e* calcd $C_{10}H_{11}NO^{76}Se$ 237.0033; found 237.0025. Anal. Calcd for $C_{10}H_{11}NOSe$: C, 50.01; H, 4.62; N, 5.83. Found: C, 49.78; H, 4.76; N, 5.96. We have found that long-term storage (6 months) of selones is best accomplished using $CHCl_3$ solutions at −20 °C in the absence of light. A small quantity of a red precipitate (red selenium) formed during long term storage of chloroform selone solutions in capped brown bottles (1–4 months) on the benchtop at ambient temperature. See ref 5 for a detailed stability study for **2a**.

(11) (a) Cullen, E. R.; Guziec, F. S., Jr.; Murphy, C. J.; Wong, T. C.; Andersen, K. K. *J. Am. Chem. Soc.* **1981**, *103*, 7055. (b) Cullen, E. R.; Guziec, F. S., Jr.; Murphy, C. J.; Wong, T. C.; Andersen, K. K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 473.

(12) We have observed a remarkably large coupling constant of 290 Hz for an isoselenocyanate system; see ref 5.

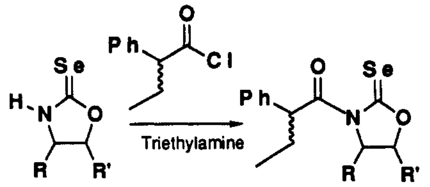
(13) Luthra, N. P.; Dunlap, R. B.; Odom, J. D. *J. Magn. Reson.* **1983**, *52*, 318.

(14) Warpehoski, M. A.; Chabaud, B.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 2897.

(15) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

(16) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4008.

Table III. *R* and *S* Acid Chlorides Coupled to Selones 2a–g: NMR Quantitation



2 a

4 a

compd	acid chloride composition	adduct ratio by ^{1}H NMR	adduct ratio by ^{77}Se NMR	adduct yield
3a	1:1	49.9:50.1	49.6:50.4	96
3b	1:1	49.8:50.2	49.8:50.2	97
3c	1:1	49.6:50.4	49.9:50.1	86
3d	1:1	50.0:50.0	49.9:50.1	98
3e	1:1	49.8:50.2	49.6:50.4	92
3f	1:1	49.9:50.1	49.9:50.1	98
3g	1:1	49.8:50.2	49.8:50.2	99
4a[a]	96.8:3.2[b]	97.0:3.0	97.4:2.6	98
4a[a]	92.2:7.8	92.4:7.6	91.5:8.5	98
4a[a]	55.5:44.5	54.1:45.9	55.9:44.1	99
4a[c]	50.0:50.0	50.4:49.6	50.3:49.7	98
4a[a,d]	60.2:39.8	63.3:36.7	62.2:37.8	98

[a] Ratios (by weight) were calculated using 93.6% ee for the acid chloride. [b] $[\alpha]_D = -86.11$ ($c = 5.8 \times 10^{-3}$, 1,2-dichloroethane).[24] [c] The racemate was used. [d] An excess of acid chloride was used.

(6.93×10^{-3} with respect to ^{1}H and 2.98 compared to ^{13}C), its natural abundance (7.5%) and spin ($I = {}^1/_2$) make it an excellent candidate for a nuclear magnetic resonance (NMR) reporter nucleus. Selenium has the special feature of possessing a large chemical shift range (~3400 ppm), and the selenium nucleus is extremely sensitive to its electronic environment.[18] For example, comparison of ^{77}Se and ^{31}P chemical shifts reveals that the sensitivity of the selenium shielding to changes in electronic structure is several times greater than that of phosphorus.[19] In an effort to gain insight into the electronic and structural features which affect the chemical shift sensitivity of these systems, reagents **2a–g** were coupled with (*R*,*S*)-2-phenylpropanoyl chloride. The results presented in Table II suggest that the greatest chemical shift sensitivity is observed with **3b**, which exhibited a remarkably large 45.6 ppm ([^{2}H$_8$]toluene) chemical shift difference for the diastereomers. Interestingly, the smallest $\Delta\delta$ occurred for **3f**, which possessed a $\Delta\delta$ of 3.5 ppm. This $\Delta\delta$ could be increased 37% (4.8 ppm) by using [^{2}H$_6$]benzene as the NMR solvent. Similar solvent dependency on $\Delta\delta$ has previously been observed.[20]

In order for chiral oxazolidine-2-selones to be useful reagents for determining enantiomeric purities of chiral carboxylic acids, the acylation of the selone must proceed without disturbing the integrity of the chiral center in the acid. 2-Phenylbutanoyl and 2-phenylpropanoyl chlorides are ideal candidates for the investigation of retention of chiral integrity for the following reasons: (1) The chiral center is adjacent to the carbonyl coupling center, thereby maximizing its influence on the coupling reaction. (2) The groups attached to the asymmetric carbon are bulky. (3) The side-chain chiral center is easily epimerized. Furthermore, triethylamine, a base known in solution-phase peptide synthesis to promote racemization, was employed. The data obtained from the coupling of mixtures of (*R*)- and (*S*)-2-phenylbutanoyl chloride of known enantiomeric composition and racemic 2-phenylpropanoyl chloride to **2a–g** are shown in Table III.[21] The diastereomeric ratios were determined from the integration of the ^{1}H and ^{77}Se NMR resonances.[22] However, erroneous results can be obtained (entry 12, Table III) when using an excess of acid chloride, thus suggesting that one enantiomer is reacting at a faster rate. Taken collectively, these data suggest that the coupling reaction proceeds easily without detectable racemization or epimerization and that the integrated ^{77}Se NMR resonances accurately represent the enantiomeric purities of the acids.

An examination of the scope and limitation of the use of selones[23] for the quantitation and absolute configurational assignment of remotely disposed chiral centers as well as their potential use in stereoselective syntheses is in progress in our laboratories.

Acknowledgment. We gratefully acknowledge partial financial support from the National Stable Isotopes Re-

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(17) (a) McFarlane, H. C. E.; McFarlane, W. *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983; Vol. 2, p 275. (b) Iwamura, J.; Nakanishi, W. *Yuki Gosei Kayaku Kyokaishi* 1981, *39*, 795. (c) Stadtman, T. C. *FASEB J.* 1983, *1*, 375. Odom, J. D. *Struct. Bonding (Berlin)* 1983, *54*, 1. (d) Luthra, N. P.; Dunlap, R. B.; Odom, J. D. *Anal. Biochem.* 1981, *117*, 94. (e) Luthra, N. P.; Dunlap, R. B.; Odom, J. D. *J. Magn. Reson.* 1982, *46*, 152. (f) Luthra, N. P.; Costello, R. B.; Dunlap, R. B.; Odom, J. D. *J. Biol. Chem.* 1982, *257*, 1142. (g) Mullen, G. P.; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* 1985, *107*, 7187. (h) Mullen, G. P.; Dunlap, R. B.; Odom, J. D. *Biochemistry* 1986, *25*, 5625. (i) Boccanfuso, A. M.; Griffin, D. W.; Dunlap, R. B.; Odom, J. D. *Bioorg. Chemistry* 1989, *17*, 231. (j) Gettins, P.; Dowd, D. *Magn. Reson. Chem.* 1988, *26*, 1. (k) Gettins, P.; Wardlaw, S. A. *J. Biol. Chem.* 1991, *266*, 3422. (l) Gettins, P.; Crews, B. C. *J. Biol. Chem.* 1991, *266*, 4804–4809. (m) Reich, H. J.; Jasperse, C. P. *J. Am. Chem. Soc.* 1987, *109*, 5549. (n) Krief, A.; Dumont, W.; Clarembeau, M.; Berard, G.; Badaoui, E. *Tetrahedron* 1989, *45*, 2005. (o) Laitinen, R. S.; Pakkanen, T. A. *Inorg. Chem.* 1987, *26*, 2598. (p) Duddeck, H.; Wagner, P.; Gegner, S. *Tetrahedron Lett.* 1985, *26*, 1205. (q) Poleschner, H.; Radeglia, R.; Meyer, H. *Org. Magn. Reson.* 1984, *22*, 480.

(18) (a) Rabenstein, D. L.; Tan, K.-S. *J. Magn. Reson.* 1988, *26*, 1079. (b) Dunlap, R. B.; Odom, J. *Phosphorus Sulfur Relat. Elem.* 1988, *38*, 217. (c) Gombler, W. *Naturforsch* 1981, *36b*, 1561. (d) Gombler, W. *Phosphorus Sulfur Relat. Elem.* 1988, *38*, 231. (e) Luthra, N. P.; Boccanfuso, A. M.; Dunlap, R. B.; Odom, J. D. *J. Magn. Reson.* 1988, *354*, 51. (f) Silks, L. A.; Dunlap, R. B.; Odom, J. D. 199th National Meeting, of the American Chemical Society, Boston, April 25, 1990; Abstr. No. 283, Organic Division.

(19) McFarlane, H. C. E.; McFarlane, W. In *NMR and the Periodic Table*; Harris, R. K., Mann, B. E., Eds.; Academic Press: New York, 1978; p 402–12.

(20) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* 1984, *106*, 5019.

(21) For a typical coupling reaction procedure: A mixture of acid chloride and selone (1.2 equiv) was stirred at 0 °C in dried (over CaH_2), distilled CH_2Cl_2. To this was added dropwise 1.2 equiv of triethylamine (neat). Within 1–5 min the reaction solution became bright yellow (the progress of the reaction was also monitored by TLC). Upon completion, usually within a period of 1 h, the mixture was filtered through a pad of SiO_2, and the pad was rinsed with CH_2Cl_2 until free of the acylated selone. The mixture was then concentrated to give the bright yellow crude material. Silica gel chromatography was performed using CH_2Cl_2/hexane (usually 1:1; v/v) mixtures as the eluent.

(22) For a very nice example of the utility of ^{77}Se NMR integrated resonances see: Maryanoff, B. E.; Rebarchak, M. C. *J. Org. Chem.* 1991, *56*, 5203. We thank Dr. Maryanoff for a preprint of this paper. For acid systems which possess α-chiral centers, we have found that for accurate integration of the diastereomers which resulted from the reaction of the acid chloride with the selone, a recycle time of $9 \times T_1$ should be used. For systems in which the chiral center is further removed from the observed nucleus this condition is apparently not necessary. Studies designed to clarify this observation will be reported in due course.

(23) U.S. and international (P.C.T.) patent applications have been filed to cover the use of chiral selones for the detection of enantiomeric excesses and absolute configurational assignment at chiral centers.

(24) The acid chloride was generated using neat oxalyl chloride (2 equiv) at room temperature for 24 h. The reaction was monitored using ^{1}H NMR spectroscopy. The rotation corresponds to a 3.2% racemization of the acid chloride. Racemization evidently occurred during storage of the acid or in the generation of the acid chloride. For the synthesis of (*R*)-2-phenylbutanoyl chloride using thionyl chloride see: Feibush, B.; Figueroa, A.; Rosita, C.; Onan, K. D.; Feibush, P.; Karger, K. L. *J. Am. Chem. Soc.* 1986, *108*, 3310. These authors observed 2.1% racemization in the acid chloride generation.

source, NIH Division of Research Resources (RR 02231). Support of high-field NMR spectrometer purchases at the University of South Carolina by the NSF (CHE84-11172) and the NIH (1-S10-RR02425) is acknowledged. Work done at Los Alamos National Laboratory was performed under the auspices of the U. S. Department of Energy. We would especially like to thank Dr. "Bud" Whaley for his input on the preparation of this manuscript and Debbie Ehler for obtaining elemental analyses and for her editing skills.

Registry No. **1a**, 136846-24-7; **1b**, 132377-00-5; **1c**, 132376-99-9; **1d**, 75866-71-6; **1e**, 136794-50-8; **1e**, 136846-25-8; **1g**, 132377-01-6; **2a**, 127399-16-0; **2b**, 136794-51-9; **2c**, 136794-52-0; **2d**, 136794-53-1; **2e**, 136794-54-2; **2f**, 136794-55-3; **2g**, 136794-56-4; **3a** (isomer 1), 136794-57-5; **3a** (isomer 2), 136794-64-4; **3b** (isomer 1), 136794-58-6; **3b** (isomer 2), 136794-65-5; **3c** (isomer 1), 136794-59-7; **3c** (isomer 2), 136794-66-6; **3d** (isomer 1), 136794-60-0; **3d** (isomer 2), 136794-67-7; **3e** (isomer 1), 136794-61-1; **3e** (isomer 2), 136794-68-8; **3f** (isomer 1), 136794-62-2; **3f** (isomer 2), 136794-69-9; **3g** (isomer 1), 136794-63-3; **3g** (isomer 2), 136822-50-9; LHMDS, 4039-32-1; Se, 7782-49-2; (*R*,*S*)-2-phenylpropanoyl chloride, 59981-93-0.

Relative Bond Dissociation Energies for Some NADH Model Compounds from Hydride Transfer/Electron Transfer Equilibria in Acetonitrile[1]

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Summary: Electrochemical oxidation potentials of a number of *N*-alkylpyridinyl radicals (measured using photomodulation voltammetry) were combined in a thermochemical cycle with hydride transfer equilibrium data to provide an estimate of the relative C–H bond dissociation enthalpies of the NADH model compounds.

Recently, Bordwell and his co-workers[2] have shown that reliable relative bond dissociation energies (BDE) can be obtained by combining relative pK_a and redox data in a thermochemical cycle (eqs 1–3). This acidity oxidation

$$R^- + R'H \rightarrow RH + R'^- \qquad \Delta G^\circ = 2.303RT\Delta pK_a \qquad (1)$$

$$R^\bullet + R'^- \rightarrow R^- + R'^\bullet \qquad \Delta G^\circ = 23.06\Delta E^\circ \qquad (2)$$

$$R^\bullet + R'H \rightarrow RH + R'^\bullet \qquad \Delta G^\circ \approx \Delta BDE \qquad (3)$$

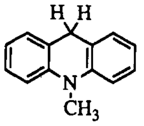
potential approach (ΔAOP) has provided bond energy estimates for a number of R–H bonds that are not amenable to direct measurement. The efficacy of this approach is based essentially on two assumptions. It is assumed that the differences in the irreversible potentials are the same as the differences in the standard potentials, E° (the vast majority of oxidation potentials of the anions are irreversible electron processes). This assumption will be justified provided that the electrode mechanisms for the reactions being compared are the same and the rates of the homogenous follow-up reactions do not vary by more than a factor of ten.[3] It also is assumed that the entropy contributions cancel since the pK_a and E° values are free energies while the BDE's are enthalpies. This assumption has been shown to be justified for most simple hydrocarbons.[4]

The utility of the Bordwell method can be attributed to the large number of pK_a values for weak carbon acids that are available in the literature.[5] However, this approach is not restricted to proton-transfer equilibria. In this work, we have used hydride-transfer equilibrium data that are available for a number of NADH model compounds (**1H**–**3H**, eq 4)[6,7] along with the reduction potentials of the corresponding pyridinium salts (1^+–3^+) in acetonitrile (eq 5) in order to determine the relative C–H BDE's for these species. To our knowledge, this is the first time that this approach has been used. Furthermore, we have addressed the issue of the use of irreversible electrode potentials in the thermochemical cycles. Thus, we have determined the reduction potentials of the pyridinium salts (by cyclic volammetry) and, under the same conditions (i.e., solvent, electrolyte, electrode material) determined the oxidation potential of the corresponding pyridinyl radical (by photomodulation voltammetry[8]). Under these conditions, E° must be bracketed by the two measurements.[9] Both of the electrochemical techniques have been described in detail elsewhere.[8,10]

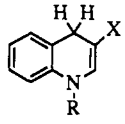
$$R^+ + R'H \rightarrow RH + R'^+ \qquad \Delta G^\circ = 2.303RT\Delta pK_{H^-} \qquad (4)$$

$$R^\bullet + R'^+ \rightarrow R^+ + R'^\bullet \qquad \Delta G^\circ = 23.06\Delta E^\circ \qquad (5)$$

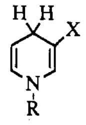
$$R^\bullet + R'H \rightarrow RH + R'^\bullet \qquad \Delta G^\circ \approx \Delta BDE$$



1H



2Ha, R = CH_3; X = CN
2Hb, R = $PhCH_2$; X = CN



3Ha, R = $PhCH_2$; X = CN
3Hb, R = $PhCH_2$; X = C(O)CH_3
3Hc, R = $PhCH_2$; X = C(O)NH_2

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(2) (a) Bordwell, F. G.; Cheng, J. P.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* 1988, *110*, 1229. (b) Bordwell, F. G.; Harrelson, J. A. *Can. J. Chem.* 1990, *68*, 1714. (c) Bordwell, F. G.; Cheng, J. P. *J. Am. Chem. Soc.* 1991, *113*, 1736. (d) Bordwell, F. G.; Zhang, X.; Cheng, J. P. *J. Org. Chem.* 1991, *56*, 3216.

(3) Bard, A. J.; Faulkner, L. R. In: *Electrochemical Methods. Fundamentals and Applications*; John Wiley and Sons: New York, 1980.

(4) Griller, D.; Wayner, D. D. M. *Rev. Chem. Int.* 1986, *7*, 31.

(5) Bordwell, F. G. *Acc. Chem. Res.* 1988, *21*, 456 and references cited therein.

(6) (a) Kreevoy, M. M.; Kotchevar, A. T. *J. Am. Chem. Soc.* 1990, *112*, 3579. (b) Kreevoy, M. M.; Ostovic, D.; Lee, I. H.; Binder, D. A.; King, G. W. *J. Am. Chem. Soc.* 1988, *110*, 524. (c) Ostovic, D.; Lee, I. H.; Roberts, R. M. G.; Kreevoy, M. M. *J. Org. Chem.* 1985, *50*, 4206. (d) Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *Faraday Discuss. Chem. Soc.* 1982, *74*, 257.

(7) Anne, A.; Moiroux, J. *J. Org. Chem.* 1990, *55*, 4608.

(8) Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* 1988, *110*, 132.

(9) *Organic Electrochemistry: An Introduction and a Guide*; Lund, H., Baizer, M. M., Eds.; Marcel Dekker: New York, 1991.