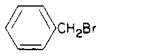
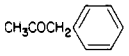
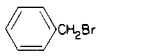
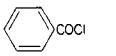
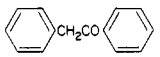
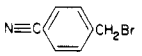
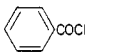
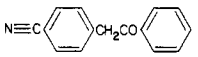
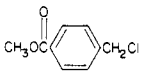
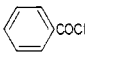
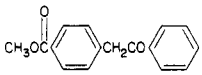
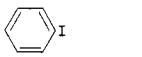
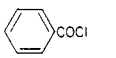
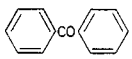
Table III. Preparation of Ketones from Acid Chlorides

RX	RCOCl	ketone	yield, %
$CH_3(CH_2)_4Br$	CH_3COCl	$CH_3CO(CH_2)_4CH_3$	80[a]
	CH_3COCl		40[a]
			90[a]
			33,[a,c] 19[b]
			20[a]
			60[a]

[a] Yields by GLC. [b] Isolated yields. [c] 53% Coupled product by GLC.

emental analysis indicates that the alloy makes up approximately 85% of the mixture.[12] Treatment of the alloy with 1 equiv of I_2 to leach out the majority of the lithium produces a very reactive cadmium metal powder. This metal will react with alkyl and aryl halides, yielding organocadmium reagents.

Table I shows the substrates and reaction conditions for the direct oxidative insertion to a variety of organic halides. The high reactivity of the cadmium metal powders is readily apparent, reacting with benzyl bromides in under 3 h at room temperature and in 18 h in refluxing THF with iodobenzene. This highly reactive metal powder reacts selectively with the benzyl bromide of *o*-bromobenzyl bromide, giving an organocadmium which yields *o*-bromotoluene upon quenching with acid. The organocadmium reagent produced adds to allyl bromide to give the cross-coupled product in high yield. A summary of cross-coupling reactions with allyl bromide is given in Table II.[13] α-Bromo-*p*-tolunitrile reacts with cadmium metal powder at 0 °C, giving an organocadmium reagent which can react with allyl bromide or an acyl chloride to give products with the cyano group intact.

The organocadmium reagents can be used in the standard ketone synthesis from acid chlorides.[14] However, when highly reactive cadmium is used, a variety of new functional groups can be present in the organocadmium reagent. Table III summarizes some of these results.

The preparation of a Reformatsky-type reagent from cadmium metal and *tert*-butyl α-bromoacetate has been reported to proceed in Me_2SO or HMPT.[15] However, the reported yields upon reaction with aldehydes were in the range of 20–60%. The highly reactive cadmium produced by either method A or method C reacts with α-halo esters to give the corresponding Reformatsky-type reagent which adds to aldehydes or ketones in high yields.[16] However, the reaction proceeds much faster and in higher yields when using the cadmium–lithium alloy prepared by method C. In the case of benzaldehyde, the β-hydroxy ester, ethyl 3-hydroxy-3-phenylpropioate, dehydrated over the course of the reaction to give 90% ethyl 3-phenyl-2-propenoate after 24 h in refluxing diethyl ether. However, reaction of the Reformatsky reagent with cyclohexanone gave only the β-hydroxyester, ethyl 1-hydroxycyclohexaneacetate in a yield of 92% at 4 h and 100% at 24 h.[17]

In summary, methods have been presented for the preparation of highly reactive cadmium and a cadmium–lithium alloy. These reactive metals have produced a general route to the direct preparation of organocadmium reagents. This approach now allows the preparation of organocadmium reagents with functional groups not tolerated by previous routes.

Acknowledgment. We gratefully acknowledge support of the work by the Division of Chemical Sciences, Department of Energy (Contract No. De-AC02-80ER0603).

Registry No. Br-*o*-$C_6H_4CH_2Br$, 3433-80-5; NC-*p*-$C_6H_4CH_2Br$, 17201-43-3; PhI, 591-50-4; I-*o*-C_6H_4Br, 583-55-1; $CH_3(CH_2)_4Br$, 110-53-2; $PhCH_2Br$, 100-39-0; $CH_3OC(O)$-*p*-$C_6H_4CH_2Cl$, 34040-64-7; CH_3COCl, 75-36-5; PhCOCl, 98-88-4; $BrCH_2CH{=}CH_2$, 106-95-6; $CH_3CO(CH_2)_4CH_3$, 110-43-0; CH_3COCH_2Ph, 103-79-7; $PhCH_2COPh$, 451-40-1; NC-*p*-$C_6H_4CH_2COPh$, 59824-23-6; $CH_3OC(O)$-*p*-$C_6H_4CH_2COPh$, 94161-45-2; PhCOPh, 119-61-9; Br-*o*-$C_6H_4(CH_2)_2CH{=}CH_2$, 71813-50-8; NC-*p*-$C_6H_4(CH_2)_2CH{=}CH_2$, 15451-33-9; $PhCH_2CH{=}CH_2$, 300-57-2; Br-*o*-$C_6H_4CH_2CH{=}CH_2$, 42918-20-7; Cd, 7440-43-9; Cd_3Li, 85133-98-8; TMEDA, 109-76-2; ethyl bromoacetate, 105-36-2; cyclohexane, 110-82-7; ethyl 1-hydroxycyclohexaneacetate, 5326-50-1; benzaldehyde, 100-52-7; ethyl 3-phenyl-2-propenoate, 103-36-6; lithium naphthalide, 25398-08-7; naphthalene, 91-20-3; cadmium chloride, 10108-64-2.

Supplementary Material Available: Full experimental details on the three methods of preparation of highly reactive cadmium and their reactions with alkyl and aryl halides to prepare organocadmium reagents (4 pages). Ordering information is given on any current masthead page.

(10) Zintl, E.; Schneider, A. *Ztschr. Elektrochem.* **1935**, *41*, 294.
(11) Powder Diffraction File, 5-0674, Smith, J. V., Ed.; American Society for Testing and Materials, Philadelphia, 1967.
(12) Elemental analysis by Spang Microanalytical Laboratory as mol %: Cd, 85.4; Li, 28.0; Cl, 1.1; C, 5.9; H, 6.9; O, 7.7.
(13) *o*-Bromobenzyl bromide (2.625 g, 10.50 mmol) is added to the cadmium slurry prepared by method A. (13.496 mmol, washed 3 × 30 mL of glyme to remove the naphthalene) over 10 min at 0 °C. After 7 h at 0 °C, allyl bromide (3.1529 g, 26.061 mmol) is added. Four hours later the reaction mixture was quenched with 5 mL of 1 N HCl and worked up by standard procedures to give 76% 4-(2-bromophenyl)-2-butene.
(14) General reaction procedure: Iodine (7.416 mmol) in glyme was added to the cadmium–lithium alloy (14.79 mmol of $CdCl_2$ reduced). Benzyl bromide (12.6 mmol) was dripped into the black slurry over 30 min. The glyme was stripped off in vacuo and 15 mL of benzene added. Benzoyl chloride (12.1 mmol) was added and stirred 20 h at room temperature. The yield by GLC was 88% benzyl phenyl ketone and 9% bibenzyl. Cadmium powders generated by method A are used without treatment with iodine.
(15) Gaudemar, M. *C.R. Acad. Sci., Ser. C* **1969**, *268*, 1439.
(16) Reformatsky reaction: Metal powders prepared by method C were reacted with ethyl bromoacetate and cyclohexanone in refluxing diethyl ether for 24 h. GLC analysis on hydrolyzed aliquotes showed 100% 1-hydroxycyclohexaneacetate. GLC conditions: 5% SE 30 on Chromosorb GAW 60/80, temperature program of 120 °C for 2 min then increasing at a rate of 32°/min to 240 °C.
(17) All new compounds reported in this manuscript had correct elemental analyses as well as expected spectroscopic properties.

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Asymmetric Carbon to Nitrogen Bond Formation Using Optically Active Allylic Selenides: A New General Method for the Synthesis of N-Protected Optically Active α-Amino Acids

Summary: Optically active allylic selenides undergo oxidative [2,3]-sigmatropic rearrangement to afford optically active, protected allylic amines. The synthetic utility of this process is demonstrated by the synthesis of several N-protected D-α-amino acids in 78–84% enantiomeric excess.

Sir: Sigmatropic rearrangements are commonly employed for the intramolecular transfer of stereogenicity[2] in organic

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Table I

entry	R	yield (%) 2	3	4	ee (%) of 4
1	H	63	56	65	79
2	C_6H_5	69	64	72	78
3	i-C_3H_7	58	59	67	78
4	n-C_3H_7		45[a]	58[b]	84

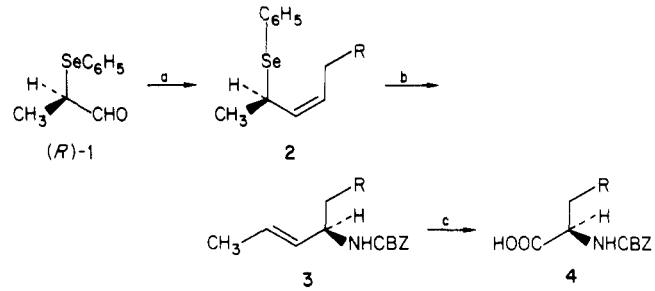
[a] Overall yield for two steps. [b] 5-mmol scale.

synthesis. Reactions of this type frequently proceed with high stereochemical fidelity and thus occupy an important position in the field of asymmetric synthesis. However, the direct asymmetric formation of C to N bonds using sigmatropic rearrangements is rare, due to the limited availability of synthetically practical reactions.[3] We have recently reported a convenient and mild method for the conversion of allylic phenyl selenides to carbamate-protected allylic amines.[4] Available evidence supports a [2,3]-sigmatropic rearrangement[5] as the key C to N bond-forming step in this process. Described herein are results that define the stereochemistry of this reaction with respect to the allylic component and establish the reaction as a useful synthetic technique for the *asymmetric* establishment of C to N bonds. The potential of this approach is demonstrated in the context of a new and general synthesis of N-protected, D-α-amino acids[6] from readily available ethyl (*S*)-lactate.

In order to address simultaneously the issues of stereochemistry and synthetic practicality of the selenide to amine rearrangement, optically active allylic selenides **2** were selected as substrates. The olefin stereochemistry of **2** was chosen to maximize the stereoselectivity of the rearrangement, based on the accepted transition-state model for most [2,3]-sigmatropic rearrangements.[5] Our desire to achieve a *general* amino acid synthesis required a general synthetic approach to selenides **2**. A potential solution, Wittig extension of the selenoaldehyde (*R*)-**1**, was not without risk of racemization, due to the appreciable acidity of the α-H of (*R*)-**1**. In the event, this problem was suppressed by judicious choice of Wittig reaction conditions.

Selenoaldehyde (*R*)-**1** is conveniently available in three synthetic operations from ethyl (*S*)-lactate. Mesylation (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C),[7,8] followed by displacement with sodium phenyl selenide (EtOH, H_2O, 25 °C)[9] afforded ethyl (*R*)-2-(phenylselenenyl)propionate, $[\alpha]_D^{25}$ + 137° (*c* 1.3, EtOH), in 90% overall yield. Reduction of this substance (1.12 Dibal, CH_2Cl_2/hexanes 3:1, −78 °C) followed by careful workup[10] afforded in 80% to 90% yield (*R*)-**1** of ca. 90–98% enantiomeric excess (ee)[11] which was used immediately, without further purification.

Scheme I[a]



[a] (a) 2.0 equiv of $RCH_2CH{=}P(C_6H_5)_3$, $C_6H_5CH_3$, −78 °C; (b) 3 equiv of $C_6H_5CH_2OCONH_2$, 6 equiv of $(C_2H_5)_3N$, 3 equiv of *N*-chlorosuccinimide, CH_3OH, 0 °C; (c) (i) O_3, 5:1 CH_2Cl_2:CH_3OH, −78 °C; (ii) $(CH_3)_2S$, −78 °C to 25 °C; (iii) CrO_3, H_2SO_4, H_2O, CH_3COCH_3.

A variety of conditions for *Z*-selective Wittig reaction were attempted in order to maximize the optical rotation of the resulting allylic selenides. It was found that treatment of (*R*)-**1** with ca. 2 equiv of a salt-free alkylidene triphenylphosphorane[12] (see Scheme I) afforded the (*Z*)-allylic selenides **2** in the tabulated chromatographed yields (see Table I) contaminated with 6–12% of the corresponding *E* isomer.[13] Although the enantiomeric purity of the allylic selenides was not assessed at this stage, the ee's of the D-α-amino acids ultimately produced eliminate the possiblity that appreciable racemization occurred during the Wittig reaction (vide infra). Rearrangement[4a] of **2** afforded (*E*)-**3** in good yield after chromatography. The olefins were ozonized and the crude aldehydes were directly oxidized with Jones reagent to afford protected D-α-amino acids in the tabulated enantiomeric excess.[14,15]

(1) (a) Searle Scholar, 1984–1987. (b) Procter and Gamble Exploratory Grant Recipient, 1983–1986.

(2) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

(3) (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901. (c) Yamamoto, Y.; Shimoda, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247. (d) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037. (e) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1984**, 770.

(4) (a) Shea, R. G.; Fitzner, J. N.; Fankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1984**, *49*, 3647. (b) Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, P. B. *Synth. Commun.* **1984**, *14*, 605. (c) Frankhauser, J. E.; Peevey, R. M.; Hopkins, P. B. *Tetrahedron Lett.* **1984**, *25*, 15.

(5) Review: Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

(6) D-Amino acids are biologically important. See: Davies, J. S. In "Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins"; Weinstein, B., Ed.; Marcel Dekker: 1977; Vol 4, pp 1–28. For other recent optically active α-amino acid syntheses, see: (a) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095. (b) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 66. (c) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. (d) Hoppe, D. *Nachr. Chem. Tech. Lab.* **1982**, *30*, 782, 852.

(7) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

(8) All of the compounds described herein gave satisfactory ^1H NMR spectra (80 MHz or 500 MHz). Compounds **1**, **3**, and **4** were further characterized by IR, low resolution MS, and optical rotation. Comparison samples of racemic DL-, D-, and L-**4** were obtained commercially or prepared by protection of commercial amino acid samples.

(9) Prepared by in situ reduction of diphenyl diselenide with sodium formaldehyde sulfoxylate in basic, aqueous ethanol. The resulting solution was buffered to pH 7 prior to addition of the mesylate. See: Agenas, L.-B. *Acta. Chem. Scand.* **1962**, *16*, 1809.

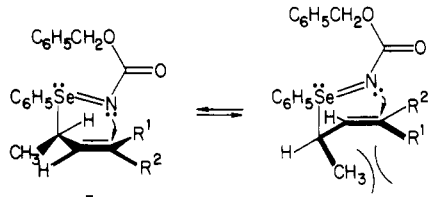
(10) The cold (−78 °C) Dibal reaction mixture was treated with ca. 2.2 molar equiv of dry DMF, stirred 5 min, warmed rapidly to 0 °C, and stirred 5 min. Silica gel (ca. 2 g/mmol ester) was added and the resulting slurry was poured onto a silica gel column and eluted with CH_2Cl_2. Concentration in vacuo afforded crude aldehyde (*R*)-(+)-**1**, $[\alpha]^{25}_D$ +260° to +290° (CH_2Cl_2). Based on ee[11] analysis of these samples, we estimate optically pure (*R*)-(+)-**1** to have $[\alpha]^{25}_D$ +295° (CH_2Cl_2). More conventional workup procedures were less successful (e.g., aqueous workup with ammonium chloride afforded **1**, $[\alpha]^{25}_D$ +15.1°). It was noted during these studies that stock Dibal solutions which were not carefully protected from air gave unsatisfactory ee's.

(11) Determined by 500-MHz ^1H NMR analysis ($CDCl_3$) of the diastereomeric esters produced by reduction of **1** ($NaBH_4$, C_2H_5OH) and esterification with (*R*)-2-methoxy-2-phenylacetyl chloride (pyridine, CH_2Cl_2). A control experiment with racemic acid chloride afforded an authentic 1:1 diastereomeric mixture. See: Haller, R.; Schneider, H. J. *Arch. Pharm. (Weinheim, Ger.)* **1974**, *307*, 31.

(12) Salt-free ylide, 2 equiv (ca. 0.2 M solution in toluene/hexane from the supernatant afforded by addition of a slight deficiency of 2.1 M *n*-BuLi in hexanes to a suspension of the requisite phosphonium salt in toluene at 25 °C, stirring for 1 h, cooling to −78 °C, and centrifugation), at −78 °C was treated with 1 equiv of a ca. 0.5 M solution of **1** in toluene, stirred 1 h at −78 °C, warmed rapidly to 0 °C, and isolated by standard techniques. A wide variety of more conventional Wittig olefination procedures afforded good chemical yields of products of significantly lower specific optical rotation.

(13) *Z*/*E* ratio determined from 500-MHz ^1H NMR or capillary VPC. An authentic sample of the *E* isomer of **2** (R = H) was prepared by alkylation of **2**(*E*)-butenyl phenyl selenide (1. LDA, THF, −78 °C; 2. CH_3I). See: Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570.

We have previously suggested[4a] that the NCS/carbamate promoted rearrangement of allylic selenides to N-protected allylic amines (i.e., **2** → **3**) proceeds via [2,3]-sigmatropic rearrangement of an intermediate selenimide. This conclusion was based upon both the olefin stereochemistry and allylic transposition observed in the isolated products. The results described herein further support the involvement of a [2,3]-sigmatropic rearrangement, since, qualitatively, the conversion of (*R*)-(*Z*)-**2** to (*R*)-(*E*)-**3** demonstrates that the rearrangement reaction is suprafacial with respect to the allylic component. This is consistent with rearrangement occurring via transition state **5** (R_1 = alkyl; R_2 = H), rather than it rotamer **6** (R_1 = alkyl; R_2 = H), in order to minimize allylic $A^{1,3}$ strain during C–N bond formation.[5] The additional observation that the *E* isomer of racemic **2** (R = H) rearranges in ca. 50% yield to racemic **3** (R = H) of greater than 97% E configuration[16] allows the quantitative assessment of the enantiomeric excess data. This observation implies that the *E* isomer of (*R*)-**2**, a contaminant in (*R*)-(*Z*)-**2**, is responsible for the production of the undesired (*S*)-(*E*)-**3**, and ultimately the protected L-α-amino acids.[17] After correction for the presence of ca. 3% of the enantiomer of (*R*)-**1** in the starting aldehyde and the implied formation of the enantiomer of **3** from (*E*)-**2**, the overall enantiomeric excess values of 78–84% found for the protected amino acid products are consistent with the rearrangement step proceeding with high stereogenic[2] fidelity and as represented by transition state **5**.[18]



5 **6**

In addition to providing a nonresolutive, general synthesis of N-protected, D-α-amino acids from an inexpensive optically active precursor, these results clearly establish the selenide to amine rearrangement reaction as a stereocontrolled process which has appreciable potential in the synthesis of stereochemically complex amines.[19]

Registry No. (*R*)-**1**, 94292-14-5; **2** (R = H), 94202-76-3; **2** (R = C_6H_5), 94234-87-4; **2** (R = $CH(CH_3)_2$), 94202-77-4; **2** (R = $(CH_2)_2CH_3$), 94202-78-5; **3** (R = H), 94202-79-6; **3** (R = C_6H_5), 94202-80-9; **3** (R = $CH(CH_3)_2$), 94202-81-0; **3** (R = $(CH_2)_2CH_3$), 94202-82-1; **4** (R = H), 26607-51-2; **4** (R = C_6H_5), 2448-45-5; **4** (R = $CH(CH_3)_2$), 28862-79-5; **4** (R = $(CH_2)_2CH_3$), 15027-14-2; H_3C-$CH{=}P(C_6H_5)_3$, 1754-88-7; $C_6H_5CH_2CH{=}P(C_6H_5)_3$, 53213-08-4; $(CH_3)_2CHCH_2CH{=}P(C_6H_5)_3$, 39110-24-2; $CH_3(CH_2)_2CH_2CH{=}P(C_6H_5)_3$, 29541-98-8; $C_6H_5CH_2OC(O)NH_2$, 621-84-1; ethyl (*S*)-lactate, 687-47-8; sodium phenyl selenide, 23974-72-3; ethyl (*R*)-2-(phenylselenenyl)propionate, 94202-83-2; CH_3SO_2Cl, 124-63-0.

(14) Enantiomeric excess determined by HPLC analysis of the dansyl derivatives (1. 20% $Pd(OH)_2/C$, cyclohexene, EtOH; 2. dansyl chloride, H_2O, THF, Et_3N). See: Lam, S.; Chow, F.; Karmen, A. *J. Chromatogr.* **1980**, *199*, 295). We find UV detection at 335 nm to be a satisfactory alternative to fluorescence detection.

(15) Substitution of *tert*-butyl carbamate for benzyl carbamate permits the preparation of *t*-BOC-protected D-α-amino acids. Thus we have prepared *t*-BOC-D-norleucine in yield and ee comparable to CBZ-D-norleucine.

(16) A comparison sample of (*Z*)-**3** was prepared from ethylidenetriphenylphosphorane and *N*-Cbz-alanal.[13] The conversion of racemic (*E*)-**2** to nearly exclusively racemic (*E*)-**3** was anticipated on the basis of a previously reported allylic *N*-tosylselenimide rearrangement.[4c]

(17) Rigorous demonstration that (*R*)-(*E*)-**2** rearranges to (*S*)-(*E*)-**3** is currently precluded by the unavailability of the requisite optically active allylic selenides but will be pursued in due course.

(18) We are currently unable to comment on the role played by chirality at selenium during this rearrangement. Illustrations **5** and **6** are not meant to accurately describe stereochemistry with respect to the selenimide functionality.

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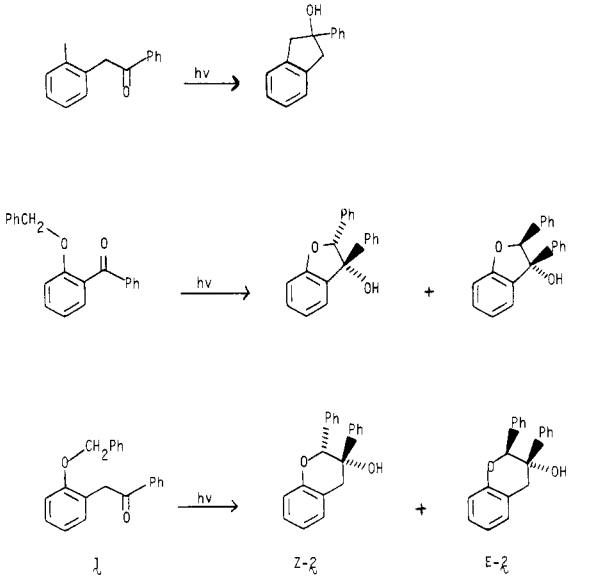
Photocyclization of α-[*o*-(Benzyloxy)phenyl]acetophenone: Triplet-State ε-Hydrogen Abstraction

Summary: The first example of efficient photocyclization due to ε-hydrogen abstraction by a triplet ketone is reported.

Sir: We recently reported the highly efficient photocyclization of α-(*o*-tolyl)acetophenones to 2-phenyl-2-indanols.[1] This reaction proceeds via triplet-state δ-hydrogen abstraction. *o*-Alkoxyphenyl ketones are also well known to photocyclize via triplet-state δ-hydrogen abstraction.[2,3] We decided to see whether a heretofore unknown ε-hydrogen abstraction might be possible in the title compound **1**, which combines the structural features which promote the two efficient δ-hydrogen abstractions.

Preparation of **1** from commercial *o*-hydroxybenzaldehyde was straightforward: benzylation of the phenol, reduction of the aldehyde, conversion of alcohol to chloride, displacement of Cl by lithium 2-phenyl-1,3-dithiolane, and mercuric-catalyzed hydrolysis. A cyclohexane solution of **1** (1.2 g in 200 mL) was purged with nitrogen and irradi-



1 **Z-2** **E-2**

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