in water (250 mL) was slowly added sulfuric acid (60 mL) at 0 °C, followed by the addition of a solution of sodium nitrite (4.5 g) in water (15 mL). The resulting yellow solution was stirred at 0 °C for 15 min and then slowly added to a solution of sodium iodide (20 g) and iodine (20 g) in water (30 mL) at 0 °C. During the addition methylene chloride (about 50 mL) was added to keep the products in solution. After being stirred at room temperature overnight, the mixture was diluted with methylene chloride (400 mL) and the two phases were partitioned. The organic phase was washed successively with concentrated sodium bisulfite solution and sodium bicarbonate solution and water. After the solution was dried over anhydrous sodium sulfate, the solvent was removed under vacuum. Purification of the residual yellow solids from ethanol afforded bis(4-iodophenyl) disulfide as a yellow amorphous solid: 8.25 g (58.5 %; >99% pure by HPLC); mp 122–123 °C (lit.[13] mp 124.5–125.5 °C).

4-Fluorophenyl 1-Naphthyl Sulfide (2a). Bis(4-fluorophenyl) disulfide (0.134 g, 0.53 mmol) and 1-iodonapthalene (0.572 g, 2.25 mmol) were placed in a Pyrex test tube (1.0 × 15 cm) which was heated to 270 °C in a sand bath. A gentle stream of nitrogen was introduced into the test tube through a Pasteur pipette. Completion was signaled when iodine was no longer produced (1–1.5 h). The reaction mixture was chromatographed on a silica gel column eluted with petroleum ether to give the product as a clear colorless liquid: 200 mg (74.6%); MS (*m/e*) 254 ($M^{\bullet+}$, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.97 (t, 2 H), 7.26 (q, 2 H), 7.42 (t, 1 H), 7.53 (m, 3 H), 7.86 (m, 2 H), 8.38 (m, 1 H).

4-Chlorophenyl 1-Naphthyl Sulfide (2b). Bis(4-chlorophenyl) disulfide (0.290 g, 1.01 mmol) and 1-iodonaphthalene (0.548 g, 2.16 mmol) were reacted as above. The reaction mixture was chromatographed on a silica gel column eluted with petroleum ether to afford the product as white, needle-like crystals: 320 mg (58%); mp 42–44 °C; MS (*m/e*) 270 ($M^{\bullet+}$, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.01 (d, J = 8.6 Hz, 2 H), 7.11 (d, J = 8.6 Hz, 2 H), 7.34–7.48 (m, 3 H), 7.63 (d, J = 6.3 Hz, 1 H), 7.83 (m, 2 H), 8.26 (m, 1 H).

4-(1-Naphthylthio)benzoic Acid (2c). Bis(4-carboxyphenyl) disulfide (608 mg, 2.0 mmol), 1-iodonaphthalene (559 mg, 2.2 mmol), and diphenyl ether (1.0 mL) were placed in a test tube. The reaction mixture was heated at 260–270 °C for 3 h. Vigorous evolution of iodine was noted after heating for 10 min. The crude reaction mixture was chromatographed, eluting with chloroform. The product was isolated as a pale yellow solid: 400 mg (71.4%); mp 165–166 °C; ^{1}H NMR (200 MHz, acetone-d_6/DMSO-d_6) δ 7.6 (d, 2 H), 8.0–8.2 (m, 4 H), 8.3–8.6 (m, 4 H), 8.8 (m, 1 H); MS (*m/e*) 280 ($M^{\bullet+}$, 100).

1,4-Bis(4-fluorobenzenesulfonyl)benzene (5a). Bis(4-fluorophenyl) disulfide (13.33 g, 0.0524 mol), 1,4-diiodobenzene (16.50 g, 0.050 mol), and diphenyl ether (10 mL) were placed in a 250-mL three-necked flask and heated to 220 °C in an aluminum heating block. The flask was equipped with a condenser, a magnetic stirrer, and a pipette through which a gentle stream of nitrogen was bubbled into the reaction mixture. The reaction was allowed to proceed for 4 days (69% yield by HPLC). Immediately thereafter, the contents were dissolved in acetic acid at 100 °C in a 500-mL Erlenmeyer flask. A 30-fold excess of 30% hydrogen peroxide (120 mL) was added in small portions with stirring after which the contents were left to react completely for 1 day at about 50 °C. The resulting pale beige, amorphous solid was filtered and rinsed with cold water. Yield: 15.95 g (81%, 85% pure by HPLC). After purification by recrystallization from acetic acid the pure sulfone was obtained in 61% yield: mp 258–260 °C (lit.[9] mp 260 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2 (t, 4 H, Ar-H ortho to F), 7.9 (q, 4 h, Ar-H meta to F), 8.1 (s, 4 H, Ar-H ortho to sulfone). Anal. Calcd: C, 54.82; H, 3.07; S, 16.26; F, 9.63. Found: C, 54.88; H, 3.22; S, 16.17; F, 9.93.

Acknowledgment. This work was supported by the General Electric Co. and the Natural Sciences and Engineering Research Council of Canada.

Registry No. **1d**, 722-27-0; **1e**, 405-31-2; **1f**, 1142-19-4; **1g**, 5335-84-2; **1h**, 6345-64-8; **1i**, 1155-51-7; **2a**, 139564-31-1; **2b**, 127567-57-1; **2c**, 139564-32-2; **5a**, 139564-33-3; *p*-$FC_6H_4SO_2Cl$, 349-88-2; *p*-$N_2^+C_6H_4SSC_6H_4$-*p*-$N_2^+ \cdot 2HSO_4^-$, 139564-34-4; 1-iodonaphthalene, 90-14-2; 4-aminobenzoic acid, 150-13-0; 4-chlorothiophenol, 106-54-7; 4-fluorothiophenol, 371-42-6; 1,4-diiodobenzene, 624-38-4.

Supplementary Material Available: ^{1}H NMR spectra of **2a–c** (3 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 page for ordering information.

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Stereoselective Synthesis of Tetrasubstituted α,β-Unsaturated Esters†

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The stereoselective synthesis of tetrasubstituted α,β-unsaturated esters[1] has met with limited success despite the number of methods available for their general synthesis.[2] While the Arbusov–Wittig[3] and the Peterson reactions[4] are still the best methods available today for their synthesis, they almost always yield a mixture of *E* and *Z* isomers. Furthermore, both methods give low yields when enolizable or bulky ketones are used as one of the substrates.

Although stereoselective synthesis of trisubstituted α,β-unsaturated esters has been reported,[5] these methods have not been extended to tetrasubstituted unsaturated esters. Recently in this laboratory, considerable efforts were directed toward developing a practical stereoselective synthesis of (*E*)-3,4-diphenyl-2-methyl-2-butenoic acid, ethyl ester (**1**), the precursor for the asymmetric synthesis of Darvon alcohol[6] viz. (2*S*,3*R*)-4-(dimethylamino)-1,2-diphenyl-3-methyl-2-butanol. The only reported synthesis[7] of this ester gives an isolated yield of 16%.[8] Our efforts to improve the yield of **1** by resorting to conventional methods available for the synthesis of unsaturated esters met with limited success. As an example, the Peterson reaction of lithio ethyl (trimethylsilyl)propionate[9] with deoxybenzoin give **1** in only 28% yield.

We now report a highly stereoselective synthesis of **1** by the direct S_N2' alkylation of lithium diphenylcuprate[10] with ethyl 2-chloro-2-methyl-3-phenyl-3-butenoate[11] (**2**) in THF (Scheme I).

Ethyl 2-methyl-3-phenyl-2-butenoate[12] obtained as a mixture of *E* and *Z* isomers (65:35) was treated with $Ca(OCl)_2$/AcOH at ice-bath temperature to give the α-chloro-β,γ-unsaturated ester **2** in 92% isolated yield.[11]

Reaction of this halo ester **2** with Ph_2CuLi in THF at ice-bath temperature gave exclusively the desired *E* ester **1** (no trace of *Z* isomer was detected by proton NMR or HPLC) in 89% isolated yield after silica gel flash column chromatography.

Extension of this reaction to other halo esters and dialkyl/diaryl cuprates gave in every instance exclusive S_N2' alkylation, although stereoselectivity dropped slightly in most cases. The results are tabulated in Table I.

It is interesting to note that stereoselectivity drops when the less bulky lithium dimethylcuprate is used as the nucleophile and that the highest stereoselectivity is achieved

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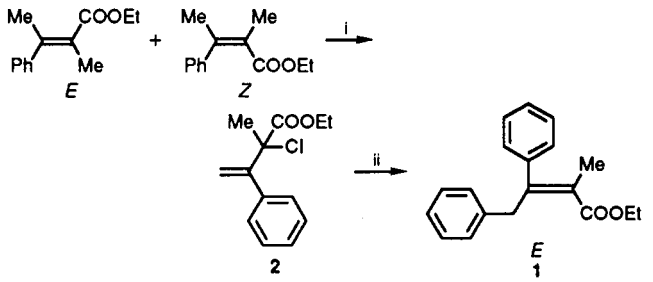
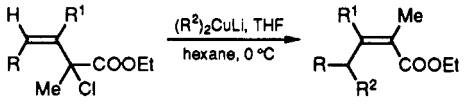
Scheme I[a]



[a] Reagents and conditions: (i) $Ca(OCl)_2$, AcOH, CH_2Cl_2, 92%; (ii) Ph_2CuLi, THF, hexane, 0 °C; 89%.

Table I. Stereoselective Synthesis of Tetrasubstituted α,β-Unsaturated Esters



R	R^1	R^2	product	yield,[a]	E/Z[b,c]
H	Ph	Ph	1	89	100/0
H	Me	Ph	3	85	92/8
H	Ph	Me	4	91	88/12
H	Me	*n*-Bu	5	88	86/14
H	Me	Me	6	94	85/15
H	Et	Ph	7	80	94/6
H	Ph	*n*-Bu	8	87	90/10

[a] The yield refers to the combined isolated yield of both isomers obtained after flash column chromatography. [b] The *E* isomer always had a lower R_f value in TLC analysis as well as a later retention time in HPLC. [c] The *Z* isomer allylic protons had a lower chemical shift from TMS in the NMR spectra. The isomer ratios were determined by HPLC and were separated by flash column chromatography on silica gel.

when the larger phenyl group is substituted on the β carbon of the chloro ester. Furthermore, using this reaction facile syntheses of highly substituted unsaturated esters such as **7** and **8** are possible. Reactions of several nucleophiles with allylic halides such as **2** have been reported earlier,[11] and in no instance was a direct S_N2'[13] intermolecular alkylation of a carbon nucleophile observed. In the present instance there are two important points that warrant discussion. First, the addition is completely regioselective; i.e., no attack of the organocuprate takes place on the ester carbonyl (1,2 addition).[14] Secondly, the preferential formation of one geometric isomer in which the entering group and the carboethoxy group are syn to each other suggests chelation of carbethoxy group to copper prior to transfer in the transition state.[15]

Use of catalytic amount of CuI and a full equivalent of alkyl/aryl lithium gave a mixture of products resulting from carbonyl additions. This is in sharp contrast to the reactions of Grignard reagents with enone cyanohydrin diethyl phosphates[16] in the presence of catalytic CuI to yield *Z* predominant α,β-unsaturated nitriles and that of enone cyanohydrin acetates with nucleophiles in the presence of palladium–phosphine complex.[17] Furthermore, while a stereospecific synthesis of trisubstituted olefins is possible by the reaction of allylic acetates with dialkylcopper–lithium reagents,[18] this has not been extended to tetrasubstituted ones.

Experimental Section

The ^{13}C NMR spectra were obtained at 75 MHz. ^1H NMR spectra were obtained at 90 or 300 MHz. NMR data were obtained in $CDCl_3$ solution. HPLC analysis was done using a micro Bondapak C18, 3.9- × 300-mm (Waters Associates) column with a flow rate of 1.5 mL/min. Flash column chromatography[19] was performed with silica gel 60 (230–440 mesh) purchased from Merck. All commercial chemicals were used as received. Tetrahydrofuran used was either distilled from $LiAlH_4$ or Gold Label anhydrous grade supplied by Aldrich Chemical Co. Reagent-grade CH_2Cl_2, EtOAc, hexane, and ether were used. All reactions were done under nitrogen unless specified. All products obtained were liquids unless specified otherwise. Diisopropylamine was distilled from calcium hydride prior to use. Anhydrous $MgSO_4$ was used for drying unless specified otherwise. All of the allylic halides used are known compounds and were prepared by literature methods.[11]

(*E*)-Ethyl 3,4-Diphenyl-2-methyl-2-butenoate (1).[7] To a stirred solution of CuI (2 g, 10 mmol) in THF (30 mL) at 0 °C was added a 2 M solution of phenyllithium (10 mL, 20 mmol) in THF dropwise via syringe. The deep black red solution was stirred for 30 min at ice-bath temperature, and a solution of ester **2** (2.4 g, 10 mmol) in THF (5 mL) and hexane (10 mL) was added via syringe in 1 min. The dark green solution was stirred at rt for 2 h and then poured into a mixture of ether (50 mL) and saturated ammonium chloride (20 mL). The two-phase mixture was filtered over Celite and washed with THF (20 mL). The organic layer was separated, washed with 1 N HCl (20 mL), brine (10 mL), and aqueous sodium thiosulphate (2 × 10 mL), and dried. Evaporation gave a yellow oil (3 g). Flash column chromatography on silica gel gave pure *E* ester **1** as a colorless oil (2.5 g, 89%) eluting in 4% ethyl acetate/hexane. ^1H NMR: δ 1.30 (3 H, t), 1.75 (3 H, s), 3.90 (3 H, s), 4.20 (2 H, q), 6.85–7.35 (10 H, m). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 146.78, 141.12, 138.64, 129.15, 128.04, 126.93, 126.84, 125.90, 60.51, 41.82, 17.55, 14.24.

(*E*)-Ethyl 4-Phenyl-2,3-dimethyl-2-butenoate (3). Prepared as above from CuI (2 g, 10 mmol), 2 M phenyllithium (10 mL,

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20 mmol) in THF, and ethyl 2,3-dimethyl-2-chloro-3-butenoate[11] (1.76 g, 10 mmol) to give after flash column chromatography *E* ester **3** as a colorless oil (1.55 g, 72%) eluting in 2% ethyl acetate/hexane. ^{1}H NMR: δ 1.30 (3 H, t), 1.70 (3 H, s), 1.90 (3 H, s), 3.75 (2 H, s), 4.20 (2 H, q), 7.25 (5 H, m). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.89, 142.98, 139.68, 128.93, 128.55, 128.33, 126.84, 60.51, 41.66, 19.38, 15.98, 14.30. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25. Found: C, 77.28; H, 8.41.

(*E*)-Ethyl 3-Phenyl-2-methyl-2-pentenoate (4).[11] To a stirred solution of CuI (2 g, 10 mmol) in THF (30 mL) at −20 °C was added a 1.6 M solution of methyllithium (14.5 mL, 20 mmol) in THF dropwise via syringe. The pale yellow solution was stirred for 15 min at −20 °C, and then a solution of **2** (2.4 g, 10 mmol) in THF (5 mL) and hexane (5 mL) was added via syringe in 1 min. The dark red solution was stirred at rt for 1 h and then poured into a mixture of ether (50 mL) and saturated ammonium chloride (20 mL). Flash column chromatography gave pure *E* ester **4** as a colorless oil (2 g, 80%) eluting in 4% ethyl acetate/hexane. ^{1}H NMR: δ 0.90 (3 H, t), 1.25 (3 H, t), 1.70 (3 H, s), 2.60 (2 H, q), 4.20 (2 H, q), 7.05–7.37 (5 H, m). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 150.58, 141.72, 128.17, 127.84, 126.95, 124.64, 60.51, 29.48, 17.38, 14.32, 12.79.

(*E*)-Ethyl 2,3-Dimethyl-2-octenoate (5).[2b] To a stirred solution of CuI (2 g, 10 mmol) in THF (30 mL) at −20 °C was added a 2.4 M solution of *n*-butyllithium (8 mL, 20 mmol) in hexane dropwise via syringe. The deep black red solution was stirred for 30 min at −20 °C, and a solution of ethyl 2,3-dimethyl-2-chloro-3-butenoate[11] (1.76 g, 10 mmol) in THF (5 mL) and hexane (5 mL) was added via syringe in 1 min. The dark green solution was stirred at rt for 2 h and then poured into a mixture of ether (50 mL) and saturated ammonium chloride (20 mL). Usual workup gave a yellow oil (2 g). Flash column chromatography gave pure *E* ester **5** as a colorless oil (1.35 g, 75%) eluting in 2% ethyl acetate/hexane. ^{1}H NMR: δ 0.90 (3 H, t), 1.25 (9 H, m), 1.75 (3 H, s), 1.85 (3 H, s), 2.25 (m, 2 H), 4.20 (2 H, q). IR (neat): 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 146.70, 122.59, 59.97, 36.41, 32.07, 28.25, 27.14, 22.64, 20.09, 15.87, 14.35.

(*E*)-Ethyl 2,3-Dimethyl-2-pentenoate (6).[11] Prepared as above from ethyl 2,3-dimethyl-2-chloro-3-butenoate (1.76 g, 10 mmol) and 1.4 M methyllithium in ether (15 mL, 20 mmol) and CuI (1.9 g, 10 mmol) to give *E* ester **6** (1.25 g, 80%) as a colorless oil eluting in 2% ethyl acetate/hexane. ^{1}H NMR: δ 0.95 (3 H, t), 1.30 (3 H, t), 1.80 (3 H, s), 1.90 (3 H, s), 2.15 (2 H, q), 4.20 (2 H, q). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 147.96, 122.35, 59.23, 29.45, 27.85, 19.55, 14.23, 12.72. Mass spectrum: *m/e* 156, 141, 127.

(*E*)-Ethyl 3-Benzyl-2-methyl-2-pentenoate (7). Prepared from ethyl 2-chloro-2-methyl-3-ethyl-3-butenoate[11] (1.9 g, 10 mmol), 2.0 M phenyllithium (10 mL, 20 mmol) in THF, and CuI (1.9 g, 10 mol) at −20 °C to give *E* ester **7** (1.75 g, 75%) eluted in 2% ethyl acetate/hexane. ^{1}H NMR: δ 1.05 (3 H, t, *J* = 7.1 Hz), 1.25 (3 H, t, *J* = 7 Hz), 1.95 (3 H, s), 2.04 (2 H, q, *J* = 7.1 Hz), 3.75 (2 H, s), 4.205 (2 H, q, *J* = 7.1 Hz), 7.20 (5 H, m). IR (neat): 1710, 1625, 1660 cm^{-1}. ^{13}C NMR: δ 169.94, 148.58, 139.71, 128.98, 128.54, 126.05, 60.51, 39.12, 25.65, 15.45, 14.24, 12.82. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.58; H, 8.62. Found: C, 77.37; H, 8.55.

Ethyl 2-Methyl-3-phenyl-2-octenoate (8). ^{1}H NMR: δ 0.90 (3 H, t), 1.25 (9 H, t), 1.70 (3 H, s), 2.25 (2 H, t), 4.20 (2 H, q), 7.05–7.37 (5 H, m). IR (neat): 3060, 3020, 2980, 1710, 1625, 1660, 1490, 1250 cm^{-1}. ^{13}C NMR: δ 169.94, 150.58, 141.72, 128.17, 127.84, 126.95, 124.64, 60.51, 36.23, 28.25, 27.14, 22.61, 20.09, 15.85, 14.32. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.46; H, 9.23. Found: C, 78.31; H, 9.38.

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Registry No. 1, 100191-02-4; (*E*)-3, 139244-08-9; (*Z*)-3, 139244-09-0; (*E*)-4, 139244-10-3; (*Z*)-4, 139244-11-4; (*E*)-5, 67275-07-4; (*Z*)-5, 67275-08-5; (*E*)-6, 14622-00-5; (*Z*)-6, 13979-29-8; (*E*)-7, 139244-12-5; (*Z*)-7, 139244-13-6; (*E*)-8, 139244-14-7; (*Z*)-8, 139244-15-8; (*E*)-ethyl 2-methyl-3-phenyl-2-butenoate, 52094-27-6; (*Z*)-ethyl 2-methyl-3-phenyl-2-butenoate, 52094-28-7; ethyl 2-chloro-2-methyl-3-phenyl-3-butenoate, 127229-67-8; ethyl 2-chloro-2,3-dimethyl-3-butenoate, 127229-64-5; ethyl 2-chloro-3-ethyl-2-methyl-3-butenoate, 128191-95-7; $(Ph)_2CuLi$, 23402-69-9; $(Me)_2CuLi$, 15681-48-8; $(n\text{-}Bu)_2CuLi$, 24406-16-4.

The Use of Triphosgene in Preparation of *N*-Carboxy-α-amino Acid Anhydrides

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N-carboxy-α-amino acid anhydrides (NCAs), or Leuchs' anhydrides,[1] constitute a special category of mixed anhydrides which achieve both amino group protection and carboxylate activation of α-amino acids simultaneously. The apparent advantage of the concurrent amine protection and carboxylate activation in NCAs is, however, counterbalanced by their high reactivity. These reagents are sensitive to moisture and are prone to polymerization,[2] therefore, difficulties are encountered in controlling amide bond formation. The use of NCAs in biphasic carbonate buffer, as described by Japanese workers, largely overcomes this limitation.[3] In addition, the recent application of urethane-protected NCAs allows for their facile use in stepwise synthesis of peptides on solid support.[4]

N-carboxyanhydrides are often formed by the reaction of unprotected amino acids with an excess of phosgene gas.[5] The use of standardized phosgene solutions in preparation of NCAs has been reported by Fuller et al.[6] Furthermore, trichloromethyl chloroformate (diphosgene)[7] and bis(trichloromethyl)carbonate (triphosgene)[8] have both been used as phosgene precursors in reactions with unprotected amino acids at high temperatures to afford NCAs. Alternative preparations for NCAs included the reaction of urethane-protected α-amino acids with PBr_3, PCl_5, or $SOCl_2$.[9] Reaction of oxalyl chloride with the silyl esters of *N*-(*tert*-butoxycarbonyl)-α-amino acids (i.e., *N*-BOC-amino acids) to give NCAs is a milder version of the above reactions with urethane-protected amino acids.[10] Comprehensive reviews on the preparation and reactions

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