

Stereoselective Radical-Radical Disproportionation

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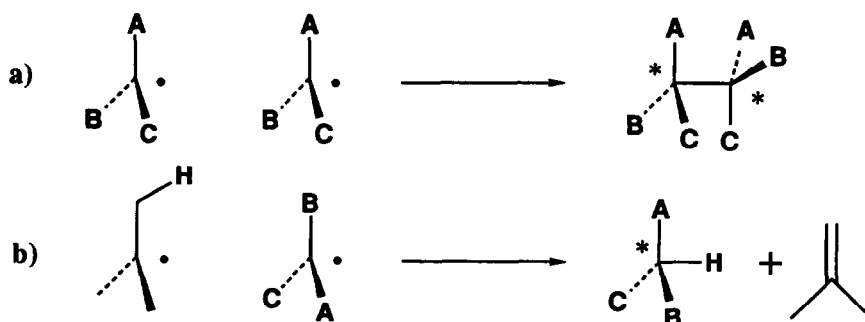
Summary: Radicals α to the carbonyl of ethyl 3,4,4-trimethylpentanoate couple with little stereoselectivity while analogous tertiary radicals derived from ethyl 2,3,4,4-tetramethylpentanoate disproportionate at 25 °C to give the corresponding alkene and alkane. The alkane is formed by disproportionation with a diastereoselectivity of greater than 20:1.

Recent reports indicate that radical-molecule reactions can be highly stereoselective.¹ Radical additions to alkenes with amide auxiliary groups occur with significant diastereofacial selectivity as does addition to alkenes of radicals having the same auxiliary groups. Stereoselectivity in these radical reactions governed by "auxiliary control" can be understood based on transition states for reaction that reflect ground state alkene or radical conformational preferences. Radicals with ground-state conformations that are fixed by allylic strain also react with stereoselectivity. Several examples that have been termed "substrate controlled" reactions have been reported for these radicals.^{2,3}

We have begun a study of auxiliary and substrate controlled stereoselectivity of radical-radical termination reactions, including coupling and disproportionation (Scheme 1). The stereoselectivity of radical-radical coupling processes has been the focus of several investigations⁴ with very high simple

Scheme 1. Stereochemistry and Radical-Radical Termination Processes.

a.) Coupling, b.) Disproportionation.

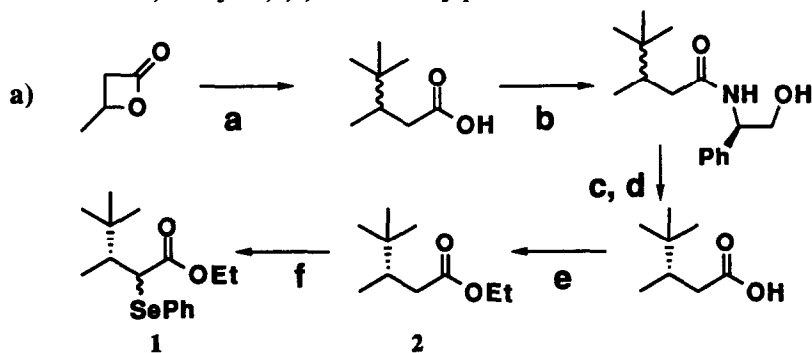


diastereoselection being observed by Rüchardt and coworkers in some cases.⁵ Stereoselective coupling is the exception rather than the rule, however, and most radicals couple with little stereochemical control. One radical bearing a chiral oxazolidine auxiliary group that adds to alkenes with substantial stereoselectivity, gives coupling products with little stereochemical preference in authentic radical processes while oxidative coupling of the corresponding enolate with I₂ or CuCl₂ gave dimer with very

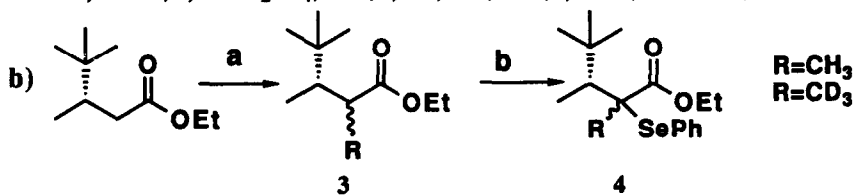
high selectivity.⁶ It was concluded in these studies that enolate oxidation does not proceed by an authentic radical-radical coupling process. We have now examined the termination reactions of chiral radicals derived from 3,4,4-trimethylpentanoic acid (substrate control) and we report here an unprecedented diastereoselective disproportionation reaction in solution.

Optically pure 3,4,4-trimethylpentanoic acid was obtained as outlined in Scheme 2. The diastereomeric amides of this acid derived from *R*-phenylglycinol could be separated by HPLC on silica with 10% isopropanol in hexane. The first-eluting amide derives from the *S*-(-) acid.⁷ Hydrolysis of the separated diastereomers gave the resolved acids that were converted to the phenyl selenides by procedures developed by Hart.^{2c} The selenide **1** was isolated as a 7:1 mixture of diastereomers while **3** is formed as a 18:1 mixture and **4** is isolated as a 14:1 mixture.^{2c}

Scheme 2. Preparation of Optically Pure Phenylselenides of a.) Ethyl 3,4,4-trimethylpentanoate and b.) Ethyl 2,3,4,4-tetramethylpentanoate



a) $t\text{-BuMgCl}$, CuCl_2 , 70%;⁸ b) isobutyl chloroformate, *N*-methylmorpholine, (*R*)-phenylglycinol, 67%;
c) HPLC; d) 2M H_2SO_4 , 96%; e) EtI , CsF , 69%; f) LDA; PhSeSePh , 82%

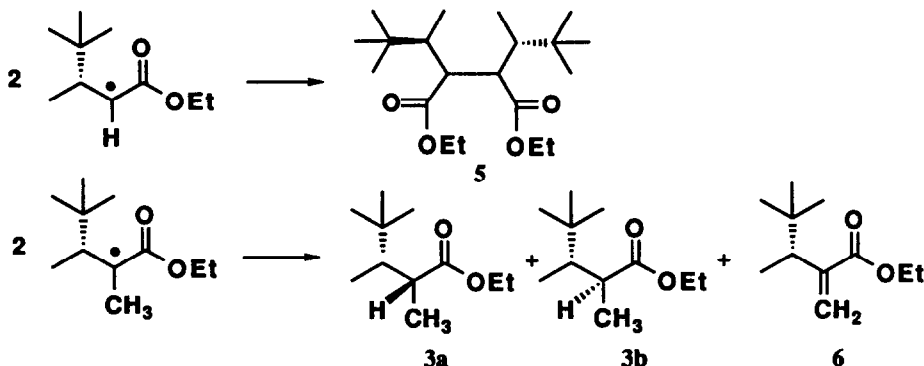


a) LDA; CH_3I (or CD_3I), 81%; b) LDA; PhSeSePh , 28%

Enolate oxidative coupling of **2** was performed by formation of the enolate of the ester with 1.1 equivalents of lithium diisopropylamide followed by reaction of the enolate with 1.1 equivalents of CuCl_2 at -78°C (solvent THF). Of the three possible diastereomeric coupling products **5**, only two were formed but the ratio of these two diastereomers was only 1:1.5.⁹ These products were fully characterized but because of the low stereoselectivity that was obtained in the coupling reactions, no attempt was made to rigorously assign their stereochemistry.¹⁰ Photolysis of the selenide **1** also gives radical-radical coupling products with little diastereoselectivity. Thus, irradiation of optically pure (*S*)-**1** (0.4M) and bis(tributyltin) (0.4M) through Pyrex with a medium pressure mercury lamp gives tributyltin phenylselenide and the same two coupling products, **5**, that were obtained from the enolate oxidation reaction of the ester. The product

ratio of these diastereomers is 1:1.84 at 80°(benzene solvent) but drops slightly to 1.75 at 25° (solvent benzene) and 1.2 at -78°C (solvent methylene chloride).⁹

Scheme 3. Termination Processes of 2-Pentanoate Radicals



The enolate oxidative coupling of the ester 3 was carried out in the same manner as the reaction of 2. Analysis of the crude reaction mixture by gas chromatography/mass spectrometry showed no trace of dimeric coupling products. Instead, the reaction gave only the disproportionation products with a ratio of alkanes 3 to alkene 6 of 1.5:1 (Scheme 3). The ratio of the diastereomers of the alkanes 3a:3b was 22:1.¹¹ This product ratio is in contrast to the starting ratio of 1:18 for the diastereomers of 3.

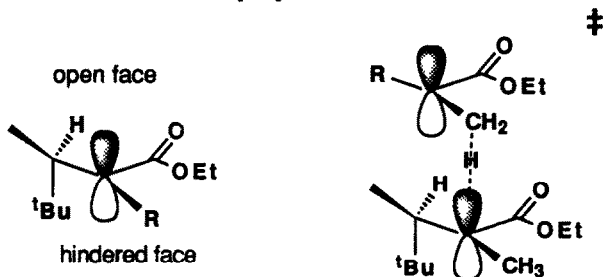
Photolysis of selenide 4 resulted in the production of the disproportionation products by what must be a radical pathway. The photolysis in degassed sealed tubes was done in the presence of one equivalent of bis(tributyltin) at three temperatures, 80° (benzene), 25° (benzene) and -78° (methylene chloride). The only significant product other than the disproportionation products was tributyltin phenylselenide. Over 90% of the starting selenide can be accounted for in the products 3 and 6. The alkane:alkene product ratio was 1:1 and the ratio of alkane products 3a and 3b was 14:1 (80°), 23:1 (25°), and 53:1 (-78°).⁹ That the products of this reaction are formed by disproportionation of a pair of radicals is supported by the observation that reaction of the -CD₃ analog of 4 gave only alkanes 3a-d₄ and 3b-d₄ and the alkene 6-d₂. Furthermore, photolyses of 4 (-CH₃) in benzene-d₆ with 5 eq. methanol-d₄ gave products with no deuterium incorporation, eliminating an enol intermediate from consideration.

The reaction of radicals derived from 3,4,4-trimethylpentanoic acid can be understood by the structures shown in Figure 1. The 2° radical derived from 2 couples with some selectivity, reaction on the hindered face of two such radicals apparently being avoided. A statistical coupling would have given a 1:2:1 product mixture but only two of the three possible dimer products are formed. The 3° radical does not terminate by coupling, however, and the major alkane disproportionation product is identical to the major product observed by Hart and Krishnamurthy in the reduction of the radical by tin hydride.^{2c} This suggests that disproportionation occurs *via* a transition state in which hydrogen is transferred to the less hindered face of the second radical (Figure 1). The selectivity of this reaction is remarkable in light of the fact that termination processes are normally thought to be diffusion controlled.¹² The effect of temperature on product selectivity suggests that enthalpy contributes significantly to the competing transition states for disproportionation.

The reactions reported here initiated by photolysis of phenylselenides give product distributions

similar to mixtures obtained by oxidation of the enolates. This is in contrast to the results of studies on amide enolates where enolate oxidation gave much more selectivity than phenylselenide photolyses.⁶

Figure 1. Conformations and Disproportionation Transition State of α Ethylpentanoate Radicals



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9. Triplicate analyses of duplicate runs were carried out.
10. Coupling of the radical having the *3-S* configuration potentially gives two products with C-2 symmetry (*S,S,S,S*) and (*S,R,R,S*) while the (*S,R,S,S*) has no such symmetry. The minor product formed in the coupling reaction has no symmetry by NMR and we assign it as the (*S,R,S,S*) compound. Based upon coupling of the less hindered face of both radicals, we tentatively assign the major diastereomer as (*S,R,R,S*).
11. We cannot rule out some reprotonation of unreacted enolate during workup in this reacton.
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