Houben-Weyl

Methods of Organic Chemistry

Additional and Supplementary Volumes to the 4th Edition

Vol. E 21 c

Stereoselective Synthesis:

C—C Bond Formation by Addition to C=C, Cycloaddition Reactions, Ene Reactions

Publication Year
1995

ISBN (Print)
978-3-13-798004-9

Thieme

Overview of Contents

Volume E 21 c

For Contents to all Volumes see p VII
For Detailed Table of Contents to Volume E 21 c see p XI
For List of Abbreviations see inside back cover

METHODS OF
ORGANIC CHEMISTRY

METHODS OF ORGANIC CHEMISTRY

(HOUBEN-WEYL)

ADDITIONAL AND SUPPLEMENTARY VOLUMES TO THE 4TH EDITION

GEORG THIEME VERLAG STUTTGART · NEW YORK

VOLUME E 21c

STEREOSELECTIVE SYNTHESIS

Editors

Günter Helmchen
Heidelberg / Germany

Reinhard W. Hoffmann
Marburg / Germany

Johann Mulzer
Frankfurt / Germany

Ernst Schaumann
Clausthal / Germany

Authors

T. Bauer
Warszawa / Poland

P. Binger
Mülheim, Ruhr / Germany

C. Chapuis
Geneva / Switzerland

M. Cinquini
Milano / Italy

R. Conrads
Arnsberg / Germany

D. Craig
London / Great Britain

F. Cozzi
Milano / Italy

P. Eilbracht
Dortmund / Germany

D. Fox
Kent / Great Britain

B. Giese
Basel / Switzerland

T. Göbel
Basel / Switzerland

R. Hoffmann
Münster / Germany

J. Jurczak
Warszawa / Poland

B. Kopping
Basel / Switzerland

T. Lübbers
Basel / Switzerland

J. Mattay
Kiel / Germany

P. Metz
Münster / Germany

U. Nubbemeyer
Berlin / Germany

W. Sander
Bochum / Germany

H.-U. Reißig
Dresden / Germany

B. B. Snider
Waltham / USA

J. K. Whitesell
Austin / USA

M. Zaidlewicz
Torun / Poland

H. Zipse
Basel / Switzerland

19 95

GEORG THIEME VERLAG STUTTGART · NEW YORK

Die Deutsche Bibliothek – CIP-Einheitsaufnahme

Methoden der organischen Chemie / (Houben-Weyl). –
Stuttgart ; New York : Thieme
Teilw. begr. von Eugen Müller und Otto Bayer. – Teilw. begr. von Eugen Müller ... Fortgef. von Heinz Kropf. – Erw.- und Folgebd. zur 4. Aufl. hrsg. von K. H. Büchel ... – Teilw. u. d. T.: Methods of organic chemistry
NE: Müller, Eugen [Hrsg.]; Houben, Josef [Hrsg.]; Kropf, Heinz [Hrsg.]; Büchel, Karl H. [Hrsg.]; Methods of organic chemistry

Additional and suppl. vol. of the 4. ed.
Vol. E 21c. Stereoselective synthesis / ed. Günter Helmchen ... Authors H. Ahlbrecht ... – 1995
NE: Helmchen, Günter [Hrsg.]; Bauer, Tomasz

Library of Congress Card No.: applied for

Date of publication 27. 10. 1995

Typesetting: Konrad Triltsch, Druck- und Verlagsanstalt GmbH, D-97070 Würzburg

Printing: Tutte Druckerei GmbH, D-94119 Salzweg-Passau

ISBN 3-13-798004-6

Preface

There was a time when stereoselectivity of a reaction was mostly of mechanistic interest and reactions that could result in the formation of stereoisomers were considered a nuisance and had to be avoided at best. However, this situation has changed over the past two decades, during which stereoselective synthesis has grown into a reliable methodology. This development began with the remodelling of readily available chiral compounds from nature. More recently, these "ex-chiral-pool" synthetic strategies have been complemented and, in many cases, surpassed by the powerful techniques of asymmetric synthesis.

Originally, only a few laboratories were concerned with the design of routes to enantiomerically pure compounds. Since the demand for nonracemic chiral drugs and pesticides has enormously increased, methods of asymmetric synthesis are now bound to be applied by almost every practising chemist. However, newcomers to the field soon find themselves confronted with a confusing vocabulary, with no guidance as to the appropriate method to solve their problem, and with lack of well-documented procedures. This situation frequently leads to frustration or at least to unnecessary work.

This called for the present volume set of the HOUBEN-WEYL series *Methods of Organic Chemistry*. Since the 1950s HOUBEN-WEYL has served the synthetic community by giving comprehensive critical reviews of the existing synthetic methods in a consistent style and with high reliability. The editors, authors and publisher of HOUBEN-WEYL "Stereoselective Synthesis" have worked together to confer this philosophy to the field of asymmetric synthesis. Thus, we hope to supply a treatise which should become the standard reference in the field.

"Stereoselective Synthesis" gives a comprehensive treatment of chemical transformations in which a new stereocenter is created, i.e., all enantio- and those diastereodifferentiating reactions which allow the absolute and relative configuration of a new stereogenic unit to be controlled. Consequently, mechanism-controlled reactions (e.g. S_N2 displacements), "ex-chiral-pool" syntheses which do not lead to new stereogenic units, and *E*/*Z* selective formation of alkenes are not covered.

Following the general introductory chapters covering principles, nomenclature, separation and analysis, the chapters on individual synthetic methods are organized by the type of bond that is broken or formed. Only starting material and products are considered as a basis for the classification, not the reaction mechanism. In the typical HOUBEN-WEYL style, the scope of the most important methods is illustrated with tables of selected examples. Insight into the practical application of the methods can be obtained from the experimental procedures provided.

The wealth of material forced us to break up the work into five volumes (E21a through e). Access to and properties of the common chiral auxiliaries, solvents, reagents and catalysts which are used in various different reactions is covered comprehensively in Volume E 21e avoiding duplication of information in the individual chapters.

The transition of HOUBEN-WEYL from German to English brought about changes in the layout and in the style of presentation without, however, sacrificing the high standard of quality and reliability that is the hallmark of HOUBEN-WEYL.

Special thanks go to our 101 authors who have spent a great deal of time and effort to achieve the goals we have set. We are also indebted to the editorial staff in Stuttgart, who had to cope with the special challenges of editing and publishing a gigantic amount of complex material.

May 1995

Günter Helmchen
Reinhard W. Hoffmann
Johann Mulzer
Ernst Schaumann

Contents to all Volumes

Table of Contents

Volume E 21c

1.5.4. Formation of C – C Bonds by Addition of Free Radicals to Olefinic Double Bonds

B. Giese, T. Göbel, B. Kopping and H. Zipse

1.5.4.1. Intermolecular Reactions

1.5.4.1.1. Chiral Radicals

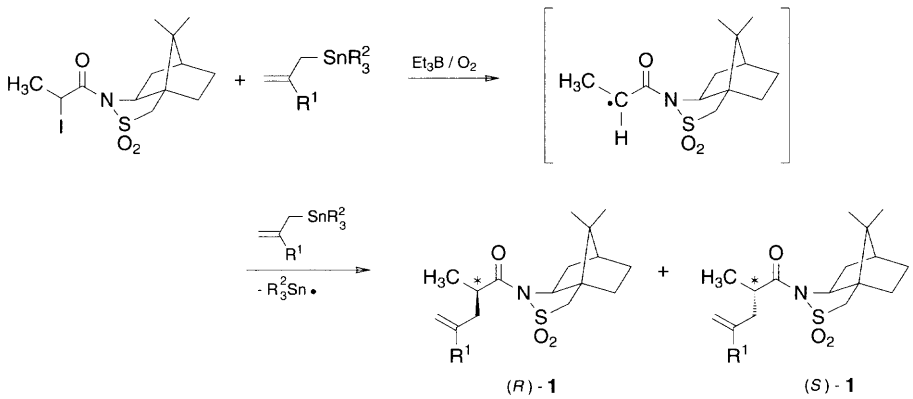
1.5.4.1.1.1. With Auxiliary Control

1.5.4.1.1.1.1. Auxiliaries

For the auxiliaries employed see Section D.2.2.

1.5.4.1.1.1.2. Addition to Alkenes

Radicals bearing a chiral amide group, derived from Oppolzer's camphor sultam, are intermediates in radical reactions with allylstannanes[1]. The allylations yield the two isomeric products with high selectivities.

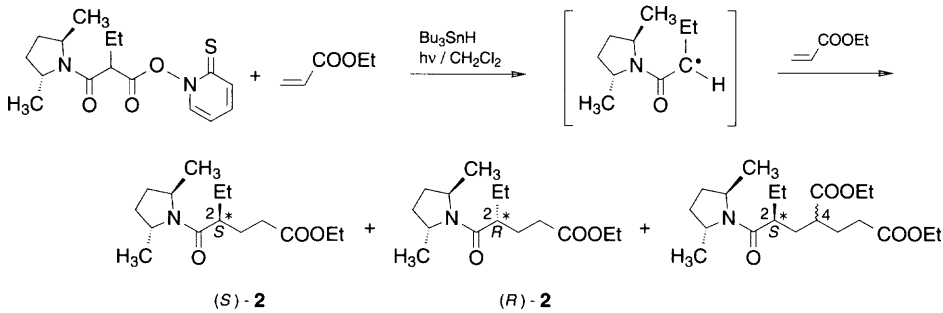


R^1	R^2	Temp (°C)	Solvent	d.r. [(*R*)/(*S*)]	Yield (%)
CH_3	Bu	25	C_6D_6	93:7	95
$COOCH_3$	C_6H_5	25	C_6D_6	94:6	95
H	Bu	25	C_6D_6	93:7	95
H	Bu	0	CH_2Cl_2	95:5	95
H	Bu	−20	CH_2Cl_2	96:4	95

***N*-(4-Substituted 2-Methyl-1-oxo-4-pentenyl)-10,2-camphanesultams; General Procedure[1]:**
A mixture of 1.0 equiv of the chiral α-iodoamide, 1.5 equiv of allyl(tributyl)stannane and 0.05–0.2 equiv of triethylborane in C_6H_6 or CH_2Cl_2 (0.5 M) is stirred under a very slow stream of air until all the starting iodide is consumed (GC control). The solution is diluted with Et_2O, followed by 2 to 5 drops of DBU. After 5 min the solution is filtered through a layer of silica gel and washed with dry Et_2O. The residue is concentrated in vacuo and purified by flash chromatography.

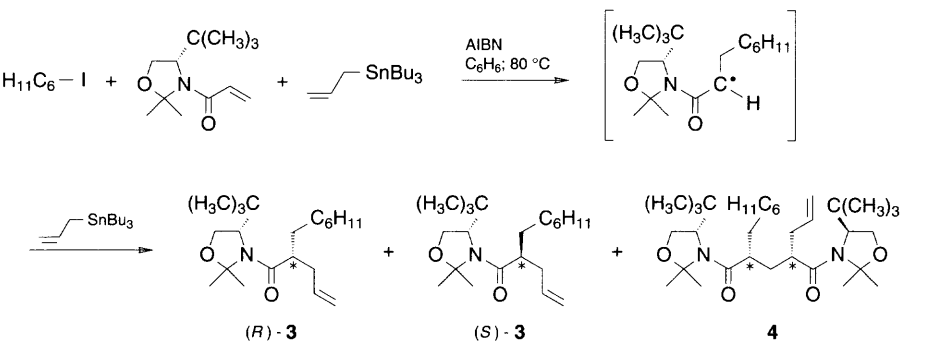
for references see p 2248

Stereoselective C–C bond formation also occurs in the addition of chiral dimethylpyrrolidine amide substituted radicals to ethyl acrylate[2]. The radicals are generated via irradiation of alkyl thiohydroxamates ("Barton method")[3]. Reactions at different temperatures yield isomeric mixtures of monoadducts (35–50%) and diadducts (15–25%). High levels of asymmetric induction are observed in the production of the monoadduct. The diadduct is a 1:1 mixture of C-4 diastereomers, presumably possessing the *S* configuration at C-2.



2: *ethyl 4-[(2R,5R)-2,5-dimethyl-1-pyrrolidinylcarbonyl]hexanoate*
At 80 °C; yield: not reported; d.r. [(*S*)-**2**/(*R*)-**2**] 92:8
At 25 °C; yield: 55%; d.r. [(*S*)-**2**/(*R*)-**2**] 96:4
At −24 °C; yield: 30%; d.r. [(*S*)-**2**/(*R*)-**2**] 97:3

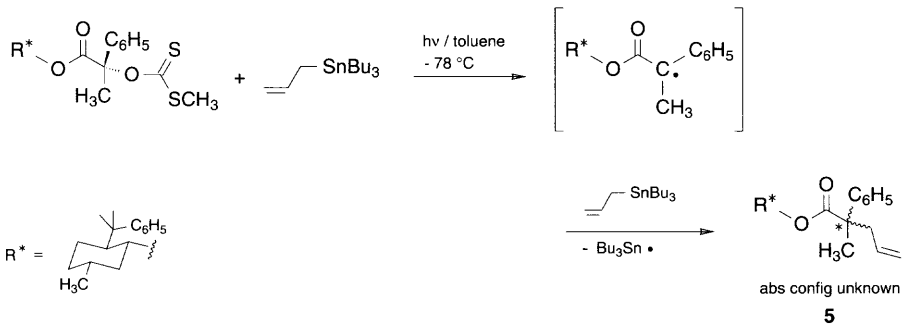
In a similar reaction, chiral oxazolidine amides are used as chiral auxiliaries[92]. The amide-substituted radical, generated via the addition of cyclohexyl radicals to the corresponding alkene, undergoes addition to tributyl(2-propenyl)stannane with significant diastereoselectivity. The monoadduct is formed in a ratio of 96:4 and for the diadduct only one major diastereomer is observed.



3: (*4*S)-*4*-tert-*butyl-3-(2-cyclohexylmethyl-1-oxo-4-pentenyl)-2,2-dimethyloxazolidine*; yield: 33%; d.r. [(*R*)-**3**/(*S*)-**3**] 96:4

4: syn-*1,5-bis*[(*4*S)-*4*-tert-*butyl-2,2-dimethyl-3-oxazolidinyl*]-*2-cyclohexylmethyl-4-(2-propenyl)-1,5-pentanedione*

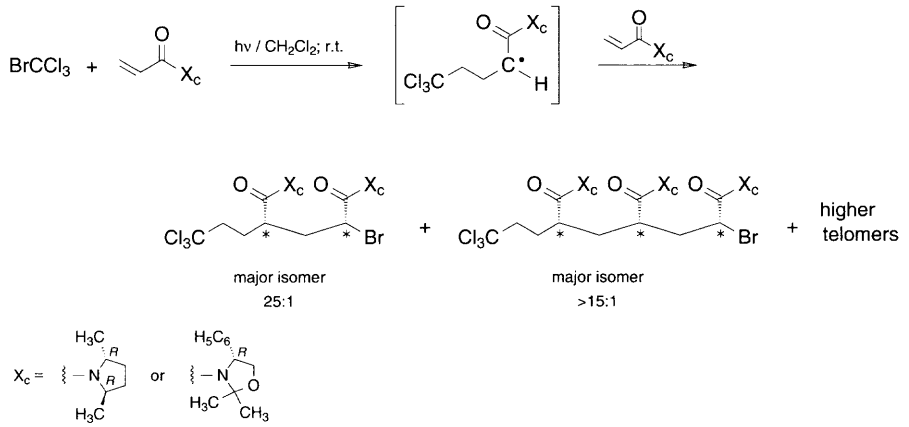
(−)-8-Phenylmenthyl esters are also suitable chiral groups for inducing stereoselectivity in radical addition reactions, as shown in the allylation of phenylmenthyloxycarbonyl-substituted xanthates. The photoinitiated reaction of the radical precursor with tributyl(2-propenyl)stannane at −78 °C affords only one diastereomer[4]. The absolute configuration of (−)-8-phenylmenthyl 2-methyl-2-phenyl-4-pentenoate (**5**) is not known.



5: (−)-*8-phenylmenthyl 2-methyl-2-phenyl-4-pentenoate*; yield: 36%

1.5.4.1.1.1.3. Telomerization

The use of monomers bearing chiral auxiliaries allows the tacticity[5] along the growing chain in radical polymerization to be controlled. The telomerization of acrylamides bearing (2*R*,5*R*)-1-(1-oxo-2-propenyl)-2,5-dimethylpyrrolidine or (4*R*)-2,2-dimethyl-4-phenyloxazolidine as chiral auxiliaries is achieved by a photochemically initiated bromotrichloromethane chain transfer reaction[2, 6, 7]. Both reactions yield mixtures of telomers, with up to ten amide units in different ratios. The observed ratios and the absolute configuration of the main isomers of the di- and triadducts show that the formation of the telomers proceeds with significant control of configuration.



Comparable results are obtained in the telomerization of (1-oxo-2-propenyl)sultams[1].

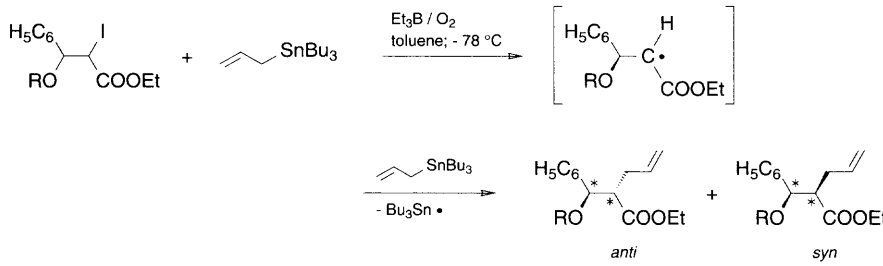
1.5.4.1.1.2. Substrate Control

1.5.4.1.1.2.1. Acyclic Systems

In comparison to stereoselective hydrogen abstraction, diastereoselective C–C bond formation of acyclic radicals often occurs with higher levels of asymmetric induction.

The low temperature (−78 °C) radical allylation of 3-alkoxy-substituted ethyl 2-iodo-3-phenylbutanoates proceeds via an ester-substituted radical that undergoes stereoselective addition across the double bond of tributyl(2-propenyl)stannane[8]. The diastereomeric excess of the products is influenced only to a small extent by the steric bulk of the alkoxy substituent in the 3-position.

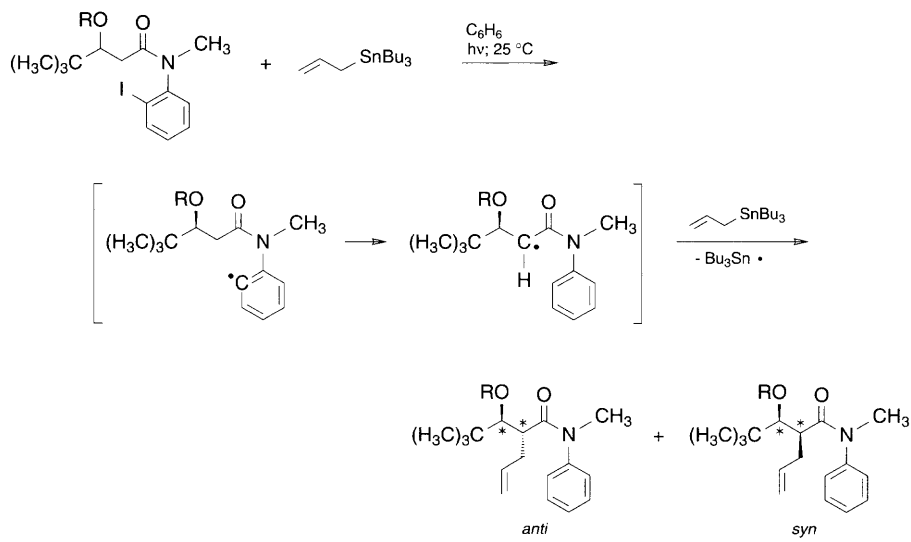
for references see p 2248



R = CH_3; yield: 75%; d.r. (*anti/syn*) 5:95
R = Bn; yield: 87%; d.r. (*anti/syn*) 4:96

The configuration of *β*-oxygen-substituted radicals can be influenced and even reversed by hydrogen bonding[9, 93] or chelation with Lewis acids[94].

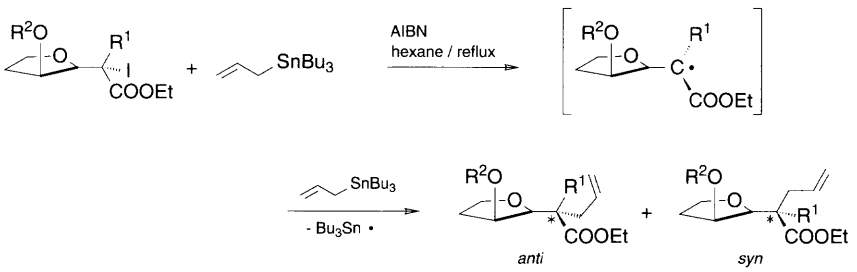
Closely related amide-substituted radicals are intermediates in the allylation of both protected and unprotected *N*-(2-iodophenyl)-4,4,*N*-trimethyl-3-hydroxypentanamides[9]. At 25 °C the *anti/syn* ratios of the allylated products are moderate.



R = H; yield: 64%; d.r. (*anti/syn*) 93:7
R = Ac; yield: 41%; d.r. (*anti/syn*) 15:85

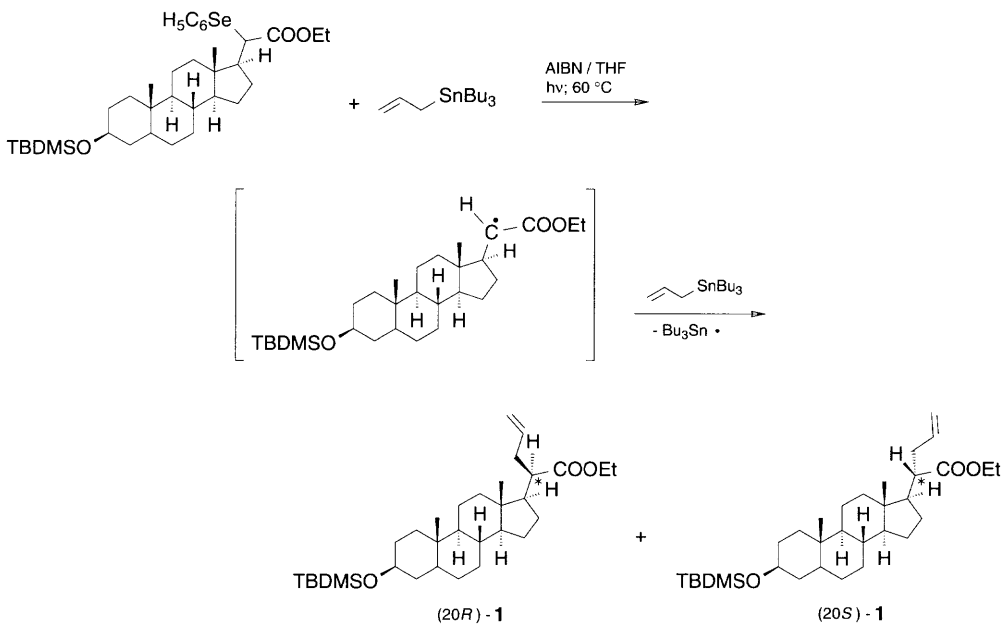
***anti*-3-Hydroxy-4,4,*N*-trimethyl-*N*-phenyl-2-(2-propenyl)pentanamide; Typical Procedure[9]:**
198 mg (0.55 mmol) of *N*-(2-iodophenyl)-4,4,*N*-trimethyl-3-hydroxypentanamide and 343 µl (1.10 mmol) of tributyl(2-propenyl)stannane are mixed in 1.1 mL of C_6H_6 in a NMR tube under argon. The reaction mixture is photolyzed (sunlight lamp) for 48 h at r.t. and concentrated under reduced pressure (GC analysis at this time gives a *anti/syn* ratio of 93:7). Purification by HPLC (hexane/EtOAc 80:20) gives the *anti*-isomer; yield: 97 mg (64%).

Excellent diastereoselectivity in C–C bond formation is observed if chirality is induced by cyclic substituents. For example, the allylation of 1-iodo-1-tetrahydrofuranyl esters affords only one diastereomer[8].



R^1 = H; R^2 = $SiBu_3$; yield: 67%; d.r. (*anti/syn*) >97: <3
R^1 = CH_3; R^2 = $SiBu_3$; yield: 55%; d.r. (*anti/syn*) >97: <3

In the C–C bond formation of more complex cyclic systems, such as the steroid derivative ethyl 3β-(*tert*-butyldimethylsilyloxy)-20-phenylseleno-5-pregnen-21-oate, 1,2-induction is also effective[10]. Reaction with tributyl(2-propenyl)stannane yields the diastereomeric steroids in a ratio of 90:10.

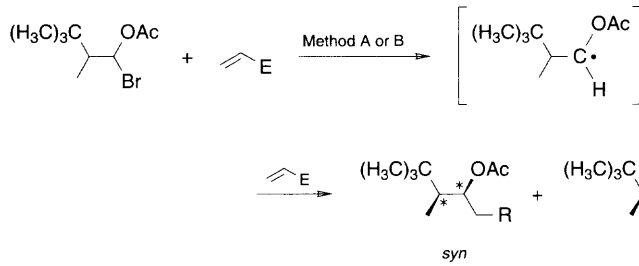


1: *ethyl 3β-*(tert-*butyldimethylsilyloxy*)*-20-*(*2-propenyl*)*-5-pregnen-21-oate*; yield: 90%; d.r. [(20*R*)/(20*S*)] 90:10

The diastereoselectivity of the ester- or amide-substituted radicals is rationalized, and can also be predicted, by invoking the concept of allylic strain (see Section D.2.2.1.2.1.). This concept is also valid for amino-substituted radicals[95].

Acetoxy-substituted chiral radicals are generated via halogen abstraction from 1-acetoxy-1-bromo-2,3,3-trimethylbutane[11]. Addition across the double bond of a variety of different alkenes proceeds with very similar diastereoselectivity.

for references see p 2248

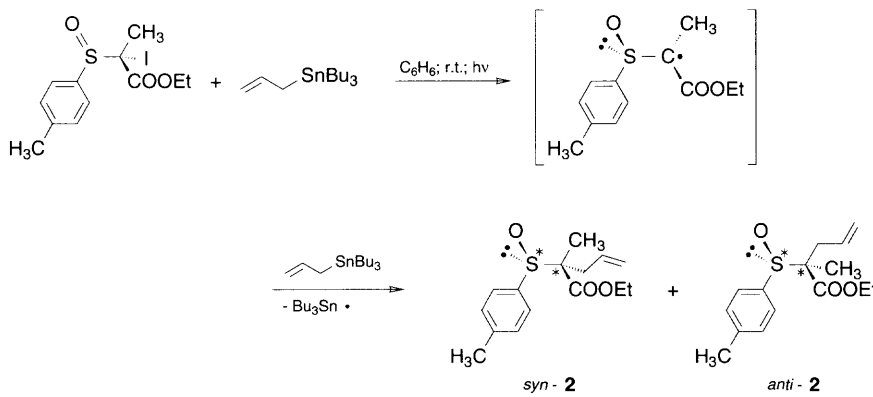


E	Method[a]	R	d.r. (*syn*/*anti*)	Yield (%)
CH_2SnBu_3	A	$CH=CH_2$	81:19	–
CN	B	CH_2CN	80:20	63
COOEt	B	CH_2COOEt	79:21	38

[a] Method A: AIBN, C_6H_6, 80 °C. B: Bu_3SnH, AIBN, C_6H_6, 80 °C.

The steric outcome of C–C bond formation is rationalized by assuming a Felkin–Anh like transition state (see Section D.2.2.1.2.3.).

The reaction of ethyl 1-iodo-1-(4-methylphenylsulfinyl)propanoate with tributyl(2-propenyl)stannane is highly stereoselective[12]. Only a trace amount of a second diastereomer is formed.



2: *ethyl 2-methyl-2-(4-methylphenylsulfinyl)-4-pentenoate*; yield: 87%; d.r. (*syn*/*anti*) >98: <2

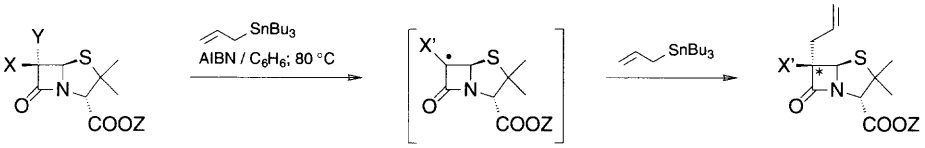
This essentially absolute stereocontrol is rationalized by presuming a stable conformation of the intermediate radical due to dipole–dipole interactions of the sulfinyl and the ester groups. 1,2-Induction is not restricted to ester-substituted radicals. It can also be observed with a trifluoromethyl group[96].

1.5.4.1.1.2.2. Cyclic Systems

Cyclobutyl Radicals

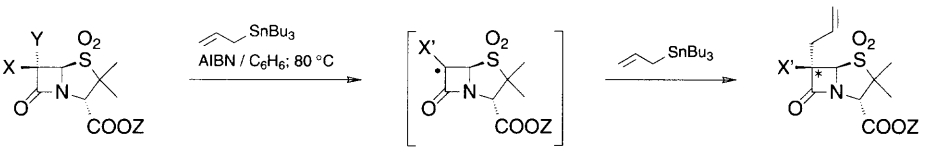
The selectivity in addition reactions of cyclobutyl radicals to alkenes has been investigated in reactions of β-lactam derivatives[31–33]. 6-Bromopenicillanic acid esters were used as precursors in reductive addition reactions with alkenes[31,32] or with allylstannanes[30,31]. Addition to the intermediate penicillanic acid-6-yl radical occurred exclusively from the α-face of the β-lactam ring.

Table 1. Allylation of 6-Bromopenicillanic Acid Derivatives with Tributyl(2-propenyl)stannane



Substrate		Product		Yield (%)	Ref
X	Y	Z	X'		
H	Br	CH_3	H	87	30, 31
H	Br	$CH_2CH=CH_2$	H	85	30
H	Br	4-$CH_3OC_6H_4$	H	81	30
Br	Br	CH_3	Br	53	30, 31
Br	Br	$CH_2CH=CH_2$	Br	55	30
	Br	CH_3		82	30, 31
	Br	CH_3		75	30, 31
H	Br	$CH(C_6H_5)_2$	H	95	32
Br	H	$CH(C_6H_5)_2$	H	95	32

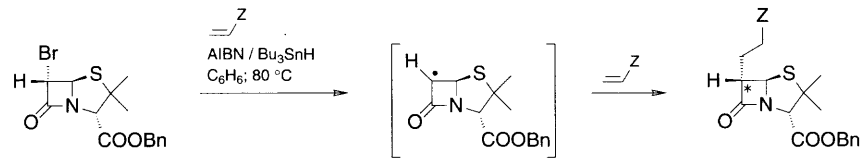
Table 2. Alkylation of 6-Bromopenicillanate 1,1-Dioxides with Tributyl(2-propenyl)stannane



Substrate		Product		Yield (%)	Ref
X	Y	Z	X'		
H	Br	CH_3	H	93	30, 31
H	Br	$CH_2CH=CH_2$	H	69	30
H	Br	4-$CH_3OC_6H_4$	H	76	30
Br	Br	$CH_2CH=CH_2$	Br	59	30

Methyl 6α-(2-Propenyl)penicillanate (Table 1); Typical Procedure[30]:
2.0 g (6.04 mmol) of tributyl(2-propenyl)stannane and 100 mg (0.61 mmol) of AIBN are added to a solution of 1.2 g (4.08 mmol) of methyl 6α-bromopenicillanate in 50 mL of C_6H_6. The resulting mixture is refluxed under argon for 5 h. Flash chromatography (silica gel, hexane, then hexane/EtOAc) of the crude mixture allows the isolation of a colorless oil; yield: 905 mg (87%).

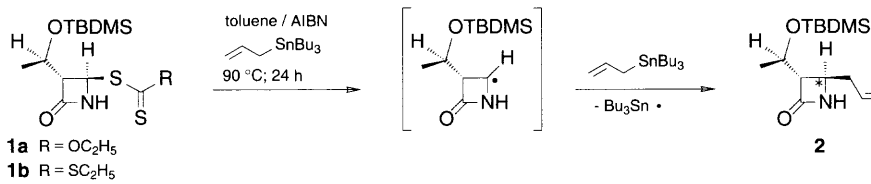
for references see p 2248



Z = CN; yield: 67%
Z = $COOCH_3$; yield: 55%
Z = OAc; yield: 43%

Benzyl 6α-(2-Methoxycarbonylethyl)penicillanate; Typical Procedure[32]:
200 mg (0.45 mmol) of benzyl 6α-bromopenicillanate, 5 mL of dry benzene and 580 mg (6.7 mmol) of methyl 2-propenoate are refluxed under nitrogen. To this mixture are added 157 mg (0.54 mmol) of tributyltin hydride, 2 mg of AIBN and 380 mg (4.4 mmol) of methyl 2-propenoate in 2 mL of C_6H_6 over a period of 5–6 h (syringe pump). After the addition is complete the mixture is refluxed for 2 h and then cooled to r.t. The solvent and excess methyl 2-propenoate are removed. The residue is dissolved in 50 mL of CH_3CN and washed with three 50-mL portions of hexanes. The solvent is then removed and the residue purified by chromatography (EtOAc/hexanes 1:4); yield: 132 mg (65%); mp 84–85 °C.

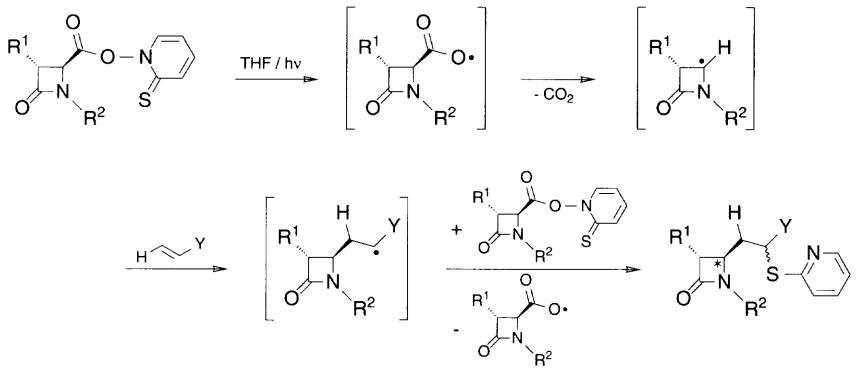
trans Addition relative to the other ring substituents is also observed in reactions of 3-substituted azetidinone-4-yl radicals with allylstannanes[33]. Here, ethylthio or ethoxycarbonylthio groups are used as precursor functionalities. Addition of tributyl(2-propenyl)stannane to the intermediate radicals proceeds such that (4*R*)-4-(2-propenyl)-2-azetidinones are obtained exclusively.



1a R = OC_2H_5
1b R = SC_2H_5

2: (*3S,4R*)-*3*-[(R)-*1*-(tert-*butyldimethylsilyloxy*)*ethyl*]-*4-propenyl-2-azetidinone*; yield: from **1a**, 72%; from **1b**, 79%

1,2-Dihydro-2-thioxo-1-pyridinyl 4-oxo-2-azetidinecarboxylates are used in addition reactions of 4-azetidinyl radicals to electron-deficient alkenes[78]. After the primary addition step, the adduct radical abstracts the 2-thiopyridinyl group from the precursor, which regenerates after decarboxylation the azetidinone-4-yl radicals and forms terminally difunctionalized addition products. Again, addition of alkenes to the azetidinone-4-yl radical occurs exclusively *trans* to the substituent in 3-position.



R^1	R^2	Y	Time (h)	Config. of New Stereogenic Center	Yield (%)
CH_3	TBDMS	$SO_2C_6H_5$	1	*R*	77
CH_2TBDMS	TBDMS	$SO_2C_6H_5$	1	*R*	54
	3,4-$(CH_3O)_2C_6H_3$	$COOCH_3$	17	*R*	54
		$SO_2C_6H_5$	18	*R*	44

Addition of 1,2-Dihydro-2-thioxo-1-pyridinyl 4-Oxo-2-azetidinecarboxylates to Electron-Deficient Alkenes; General Procedure[78]:

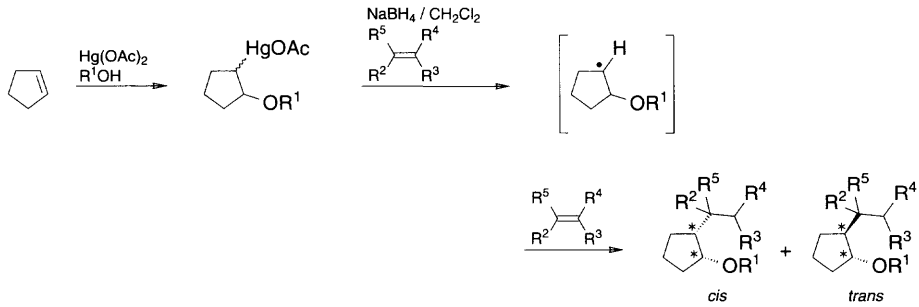
To a solution of 1 mmol of the 2-oxo-4-azetidine carboxylic acid in 7 mL of anhyd THF (7 mL) at −20 °C are added 1.1 mmol of *N*-methylmorpholine and 1.1 mmol of isobutyl chloroformate under argon. The solution is stirred for 30 min at −20 °C and 1.2 mmol of the sodium salt of *N*-hydroxy-2-thiopyridone is added. The mixture is stirred at −20 °C under argon for 45 min in the dark, then rapidly filtered, and the solids washed with 3 mL of anhyd THF. The yellow filtrate is irradiated in the presence of 5 mmol of the alkene with a 250-W tungsten lamp at r.t. under argon. Concentration of the mixture and purification of the residue by flash chromatography gives the adducts. In the case of nitroethylene, 2 mmol of camphorsulphonic acid are added after filtration of the salts, and the filtrate is cooled again to −20 °C, before adding the nitroalkene and irradiation.

Cyclopentyl Radicals

The stereoselectivity in addition and abstraction reactions of cyclopentyl radicals has been reviewed recently[37]. It has been concluded that β-substituents at the radical, as well as the alkene substituents, have a large influence on the selectivity, however only small solvent effects have been found.

Cyclopentyl radicals substituted in the β-position relative to the radical center are formed during the solvomercuration/reductive alkylation reaction of cyclopentene[34]. The organomercurial produced in the first solvomercuration step is reduced by sodium borohydride and yields free cyclopentyl radicals in a radical chain mechanism. Addition of alkenes can then occur *trans* or *cis* to the β-alkoxy substituent introduced during the solvomercuration step. The adduct radical is finally trapped by hydrogen transfer from mercury hydrides to yield the *trans*- and *cis*-addition products. The *trans*/*cis* ratio depends markedly on the alkene employed and it appears that the addition of less reactive alkenes occurs with higher *trans* selectivity. In reactions of highly substituted alkenes, this reactivity control is compensated for by steric effects. Therefore, only the *trans*-addition product is observed in reactions of tetraethyl ethenetetracarboxylate. The choice of alcohol employed in the solvomercuration step has, however, only a small influence on the stereoselectivity.

for references see p 2248



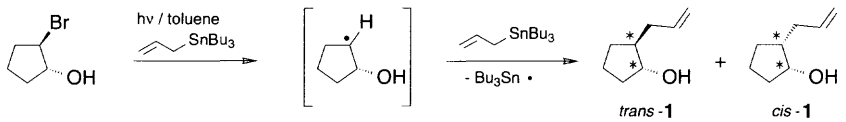
Alcohol	Alkene				d.r. (*trans*/*cis*)	Yield (%)[a]
R^1	R^2	R^3	R^4	R^5		
CH_3	H	H	CN	H	77:23	50
Et	CN	H	CN	H	77:23	65
Et	H	H	CN	H	72:28	66
Et	H	Cl	CN	H	60:40	60
Et	H	CH_3	CN	H	77:23	43
Et	H	H	Ac	H	87:13	51
Et	H	H	$COOCH_3$	H	88:12	60
Et	H	H	C_6H_5	H	90:10	15
Et	$COOCH_3$	H	$COOCH_3$	H	88:12	–
Et	$COOCH_3$	$COOCH_3$	$COOCH_3$	$COOCH_3$	>98:2	–
i-Pr	H	H	CN	H	77:23	50
t-Bu	H	H	CN	H	80:20	8[b]

[a] Overall yield for the solvomercuration/reductive alkylation one-pot procedure.
[b] Low yield due to solvomercuration step.

Ethoxymercuration/Reductive Alkylation of Cyclopentene; General Procedure[34]:
A suspension of 4.1 g (13 mmol) of mercury(II) acetate in 10 mL of EtOH is mixed with 1.36 g (20 mmol) of cyclopentene at 20 °C. After the mercury(II) acetate has dissolved, 1.5 g (7.0 mmol) of mercury(II) oxide are added in four portions. The colorless solution is diluted with 100 mL of CH_2Cl_2 and 60 mmol of the alkene. The mixture is cooled to 0 °C, 1.5 g (40 mmol) of $NaBH_4$ are added quickly and stirring is continued for 1 h. The excess $NaBH_4$ is destroyed with 30 mL of water and the liquid layers are decanted and separated. The water layer is extracted with three 30-mL portions of CH_2Cl_2 and the combined organic phases are filtered through a funnel filled with anhyd $MgSO_4$. After evaporation of the solvent, distillation of the residue yields the addition products.

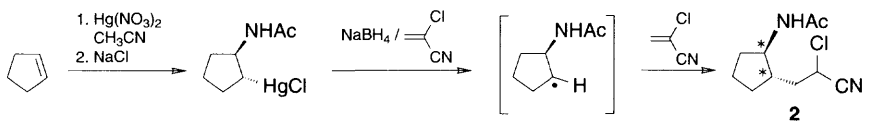
The influence of the solvent has been studied in the addition reaction of the β-ethoxycyclopentyl radical to 2-propenenitrile[37]. It is found that the preference for *trans* addition is increased by using more polar solvents, e.g., d.r. (*trans*/*cis*), cyclohexane 68:32, tetrahydrofuran 76:24, dichloromethane 77:23, acetonitrile 81:19.

Preference for *trans* addition is observed to a similar extent in reactions of the β-hydroxycyclopentyl radical[35]. After bromine abstraction from the precursor by stannyl radicals, addition to allylstannane occurs such that the *trans*-adduct radical is formed with high selectivity. Final elimination of the stannyl radical continues the chain mechanism and forms the allylation product.



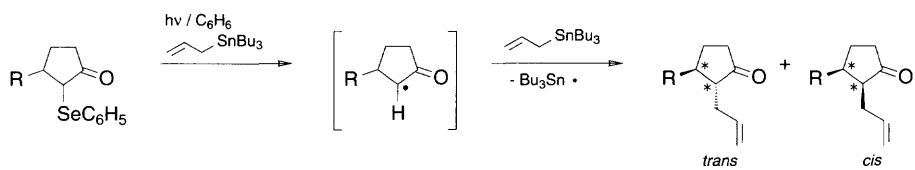
1: *2-(2-propenyl)cyclopentanol*; yield: 67%; d.r. (*trans*/*cis*) 91:9

β-Acetamidocyclopentyl radicals give very high *trans* selectivity in addition reactions to 2-chloro-2-propenenitrile[38]. This is found in the amidomercuration/reductive alkylation reaction of cyclopentene, in which only the *trans*-product is found.



2: (*1S*,2R*)-2-acetylamino-α-chlorocyclopentanepropanenitrile*; yield: 75%

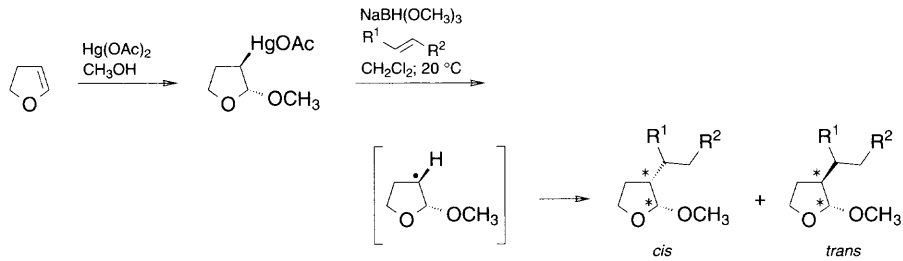
Cyclopentyl radicals flanked with β-substituents on both sides are formed in reactions of 3-alkyl-2-phenylselenocyclopentanones[36]. After photochemical initiation, the cyclopentyl radical is formed through abstraction of the phenylseleno group. Addition to tributyl(2-propenyl)stannane occurs preferentially *trans* to the β-alkyl substituent and consecutive elimination of the stannyl radical gives the final allylation product. It has also been reported[37] that addition of the β-methyl cyclopentyl radical to 2-propenenitrile occurs with d.r. (*trans*/*cis*) 92:8, hence it seems likely that the carbonyl group adjacent to the radical center reduces the selectivity.



R = CH_3; yield: 98%; d.r. (*trans*/*cis*) 78:22
R = Bu; yield: 95%; d.r. (*trans*/*cis*) 79:21

for references see p 2248

Heterocyclic cyclopentyl radicals formed in the solvomercuration/reductive alkylation reaction of dihydrofuran give products with *trans* selectivity in a slightly higher ratio than the corresponding carbocyclic analogs[34]. This is attributed to anomeric effects, which lead to a more pronounced axial orientation of the β-alkoxy substituent in the tetrahydropyranyl radical.

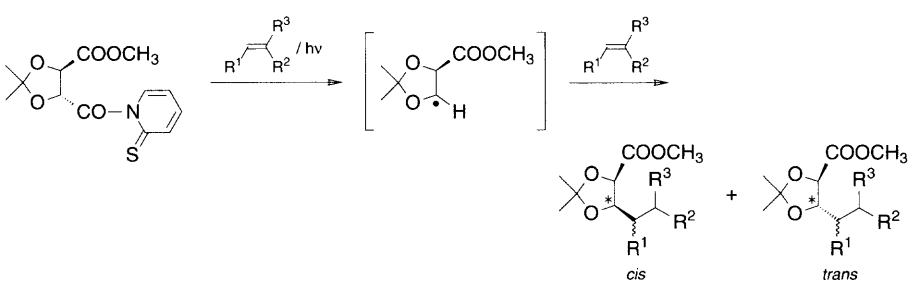


R^1	R^2	d.r. (*trans*/*cis*)	Yield (%)[a]
CN	CN	64:36	20
H	CN	86:14	45
H	Ac	82:12	40
H	$COOCH_3$	93:7	48

[a] Overall yield for the solvomercuration/reductive alkylation procedure.

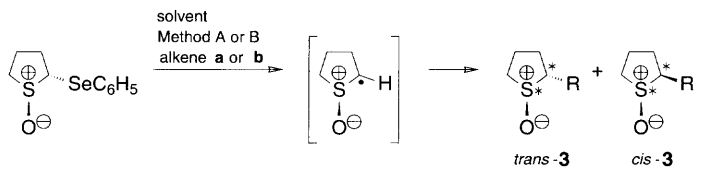
Solvomercuration/Reductive Alkylation of Dihydrofuran; General Procedure[34]:
2.03 g (6.4 mmol) of mercury(II) acetate and 1.27 g (5.8 mmol) of mercury(II) oxide are stirred with 1.05 g (15 mmol) of dihydrofuran in 15 mL of CH_3OH for 1 h. The solvent is removed in vacuo, and after addition of 80 mL of CH_2Cl_2 and 80 mmol of alkene, a solution of sodium trimethoxyborohydride in 40 mL of THF is added over 5–20 min. Stirring is continued for 3 h, the solvent is evaporated and the products isolated by vacuum distillation.

Heterocyclic radicals with two ring heteroatoms, such as the reactions of tartaric acid derivatives, have been investigated[39]. Here, the isopropylidene-protected hydroxy groups define the cyclopentyl unit and one of the carboxy groups is utilized as the precursor functionality. Irradiation leads to a radical chain process, in which addition of alkenes to the intermediate radical occurs preferentially *trans* to the β-carboxy group. Only the *trans*-isomer is observed in the ^{1}H-NMR spectrum of the product in all cases and d.r. (*trans*/*cis*) 25:1 is estimated from HPLC measurements after degradation of the monoadducts to known compounds.



R^1 = H; R^2 = H; R^3 = $COOCH_3$; yield: 70%
R^1 = H; R^2 = H; R^3 = $SO_2C_6H_5$; yield: 70%
R^1, R^2 = $-CON(CH_3)CO-$; R^3 = H; yield: 93%

Larger solvent effects on the *trans/cis* ratio are observed in reactions of 1-oxothiolan-2-yl radicals[40]. Tetrahydro-2-phenylselenothiophene 1-oxide is used as the precursor; addition to alkenes and also deuterium abstraction from deuterostannane have been investigated. The addition reactions proceed with *trans* selectivity, which is improved by using polar, protic solvents and by adding Lewis acids as complexing agents.



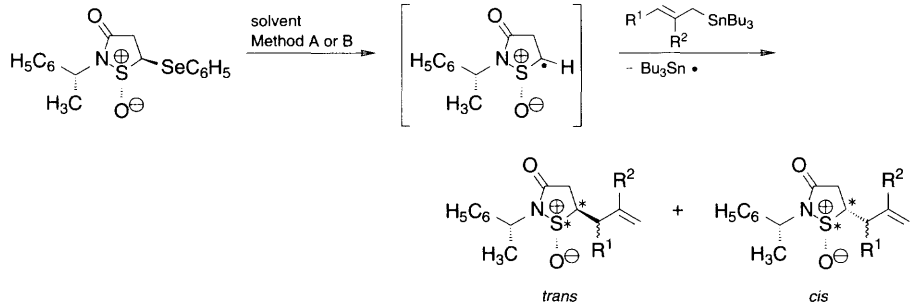
Alkene **a:** CH_2 = CHTMS; alkene **b:** CH_2 = $CHCH_2SnBu_3$
3a: R = CH_2CH_2TMS; *tetrahydro-2-(2-trimethylsilylethyl)thiophene 1-oxide*
3b: R = $CH_2CH{=}CH_2$; *tetrahydro-2-(2-propenyl)thiophene 1-oxide*

Method[a]	Solvent	Complexing Agent	Alkene	Product	d.r. (*trans/cis*)	Yield (%)
A	C_6H_6	–	**a**	**3a**	4.0:1	25
		–	**b**	**3b**	6.0:1	35
B	C_6H_6	–	**b**	**3b**	2.3:1	78
	THF	–			2.3:1	44
	EtCN	–			3.5:1	88
		$LiClO_4$, 0.5 M			9:1	82
	CH_2Cl_2	–			6.3:1	63
		$Eu(dpm)_3$, 0.5 M			8.1:1	54
	EtOH	–			6.4:1	87
	THF	LiCl, 0.5 M			5.3:1	25
		$ZnBr_2$, 0.5 M			7.3:1	62
		$BF_3 \cdot OEt_2$			6.8:1	75

[a] Method A: AIBN, 80 °C. B: AIBN, 15 °C, hν.

The same influence by the solvent on the *trans/cis* ratio is observed in allylation reactions of enantiomerically pure 3-oxo-2-(1-phenylethyl)-5-isothiazolidinyl 1-oxide radicals[41]. The *trans*-addition products are again formed preferentially and the highest selectivities are found in strongly polar, protic solvents.

for references see p 2248

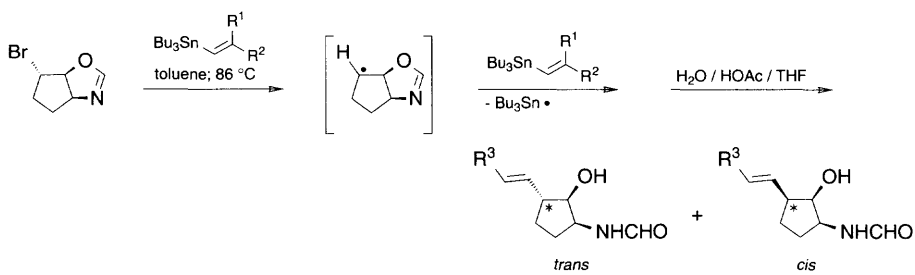


Method[a]	Solvent[b]	R^1	R^2	d.r. (*trans*/*cis*)	Yield (%)
A	C_6H_6	H	H	6.8:1	75
B	C_6H_6			9.6:1	82
	C_6H_{12}/DME			9:1	83
	DME			10:1	79
	EtOH			17.5:1	82
	TFE			50:1	89
A	C_6H_6	H	CH_3	6.8:1	64
B	C_6H_6			12.8:1	69
	C_6H_6	CH_3	H	10:1	40
A	C_6H_6	H	Cbz	3.8:1	62
B	C_6H_6			7.9:1	90
	EtOH			12.6:1	79
	TFE			22.8:1	87
	C_6H_6	H	Bu	9.6:1	79
	i-PrOH			14.4:1	63
	EtOH			17.2:1	82

[a] Method A: AIBN, Δ. B: hν, r.t.
[b] DME = 1,2-dimethoxyethane; TFE = trifluoroethanol.

Heterocyclic ring systems annulated to cyclopentyl radicals can be considered as two simultaneously present substituents. *cis*-Annulated ring systems in the β,γ-position to the radical center are found to give *trans* selectivities which are larger than when a single β-substituent is present. Bicyclic radicals with an overall bend shape are often exclusively attacked by alkenes from the convex face.

Bicyclic oxazolocyclopentyl bromides are employed as precursors in addition reactions to β-stannylalkenes, which give, overall, the stannyl substitution product, through an addition/elimination mechanism[42].



R^1 = COOEt; R^2 = H; R^3 = COOEt; yield: 79%; d.r. (*trans*/*cis*) 89:11
R^1 = H; R^2 = C_6H_5; R^3 = C_6H_5; yield: 70%; d.r. (*trans*/*cis*) 100:0