# Name Reactions in Heterocyclic Chemistry

# Name Reactions in Heterocyclic Chemistry

This Page Intentionally Left Blank

# Name Reactions in Heterocyclic Chemistry

Edited by

**Jie-Jack Li**

Pfizer Global Research & Development

Scientific Editor:

**E. J. Corey**

Harvard University


A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.
Published simultaneously in Canada.



***Library of Congress Cataloging-in-Publication Data is available.***

ISBN 0-471-30215-5

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

*To Alexandra*

This Page Intentionally Left Blank

# Table of Contents

This Page Intentionally Left Blank

# Foreword

Part of the charm of synthetic organic chemistry derives from the vastness of the intellectual landscape along several dimensions. First, there is the almost infinite variety and number of possible target structures that lurk in the darkness, waiting to be made. Then, there is the vast body of organic reactions that serve to transform one substance into another, now so large in number as to be beyond credibility to a non-chemist. Further, there is the staggering range of reagents, reaction conditions, catalysts, elements and techniques that must be mobilized in order to tame these reactions for synthetic purposes. Finally, it seems that new information is being added to the science at a rate that outstripped our ability to keep up with it. In such a troubled setting any author, or group of authors, must be regarded as heroic if, through their efforts, the task of the synthetic chemist is eased.

The field of heterocylic chemistry has long presented a special problem for chemists. Because of its enormous information content and variety, it is not well taught to chemistry undergraduate or graduate students, even in simplified form. There is simply too much material for the time available. And yet, the chemistry of heterocyclic compounds and methods for their synthesis form the bedrock of modern medicinal chemical and pharmaceutical research. It is important for medicinal chemists to be broadly knowledgeable across a wide swath of heterocyclic chemistry. Those who specialize narrowly do so at their own peril. If you grant me the accuracy of all of the above, you likely will share my conviction that there is a need for high-quality, up-to-date, and authoritative books on heterocyclic synthesis that are helpful for the professional research chemist and also the advanced student. This volume, *Name Reactions in Heterocyclic Chemistry* is a model of what such books should be. Written concisely and with great skill and care by Dr. Jie Jack Li and a distinguished group of experts in the field of heterocyclic chemistry, this is a book that will be tremendously useful and helpful to synthetic and medicinal chemists, on whose shelves it will surely find a place. On behalf of these users, myself included, I send thanks and congratulations.

E. J. Corey
May 1, 2004

## Preface

Since the infancy of organic chemistry, the practitioners in the field have often associated reactions with the chemists who discovered it. Even with the advent of IUPAC nomenclature, name reactions are still intimately intertwined with our profession, becoming a part of our daily language. Therefore, getting acclimated with this jargon is an integral part of the training to earn proficiency in organic chemistry.

On the other hand, heterocycles are of paramount importance to medicinal and agricultural chemists. This comprehensive and authoritative treatise provides a one-stop repository for name reactions in heterocyclic chemistry. Each name reaction is summarized in seven sections:

1. Description;
2. Historical Perspective;
3. Mechanism;
4. Variations and Improvements;
5. Synthetic Utility;
6. Experimental; and
7. References.

I also have introduced a symbol [R] to highlight review articles, book chapters and books dedicated to the respective name reactions.

I have incurred many debts of gratitude to Prof. E. J. Corey of Harvard University, who envisioned this project in the summer of 2002. What he once told me:—"*The desire to learn is the greatest gift from God.*"—has been a true inspiration. Furthermore, it has been my greatest privilege as well as a pleasure to work with a stellar collection of contributing authors from both academia and industry. Some of them are world-renowned scholars in the field; some of them have worked intimately with the name reactions that they have written; some of them even took part in the discovery of the name reactions that they authored in this manuscript. As a consequence, this book truly represents the state-of-the-art for *Name Reactions in Heterocyclic Chemistry.* We will follow up with the second volume to complete the series on heterocyclic chemistry.

Jack Li
April 24, 2004

## Contributing authors:

Nadia M. Ahmad
School of Chemistry
University of Nottingham
University Park
Nottingham
NG7 2RD, UK

Dr. Dawn A. Brooks
Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Prof. James M. Cook
Department of Chemistry
University of Wisconsin—Milwaukee
3210 North Cramer Street
Milwaukee, WI 53211-3029

Dr. Timothy T. Curran
Department of Chemical R&D
Pfizer Global Research & Development
2800 Plymouth Road
Ann Arbor, MI 48105

Dr. Paul Galatsis
Department of Chemistry
Pfizer Global Research & Development
2800 Plymouth Road
Ann Arbor, MI 48105

Prof. Gordon W. Gribble
Department of Chemistry
6128 Burke Laboratory
Dartmouth College
Hanover, NH 03755

Dr. Daniel D. Holsworth
Department of Chemistry
Pfizer Global Research & Development
2800 Plymouth Road
Ann Arbor, MI 48105

Dr. Andrew Hudson
Ligand Pharmaceuticals
10275 Science Center Road
San Diego, CA 92121

Prof. Jeffrey N. Johnston
Department of Chemistry
Indiana University
800 East Kirkwood Avenue
Bloomington, IN 47405-7102

Dr. Jie Jack Li
Department of Chemistry
Pfizer Global Research & Development
2800 Plymouth Road
Ann Arbor, MI 48105

Dr. Jin Li
Research Technology Center
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340

Dr. Chris Limberakis
Department of Chemistry
Pfizer Global Research & Development
2800 Plymouth Road
Ann Arbor, MI 48105

Christopher M. Liu
Department of Chemistry
University of Michigan
930 North University Avenue
Ann Arbor, MI 48109-1055

Dr. Adrian J. Moore
School of Sciences
Fleming Building
University of Sunderland
UK SR1 3SD

Prof. Richard J. Mullins
Department of Chemistry
Xavier University
3800 Victory Parkway
Cincinnati, OH 45207-4221

Prof. Brian J. Myers
Department of Chemistry
and Biochemistry
Ohio Northern University
525 South Main Street
Ada, OH 45810

Peter A. Orahovats
Department of Chemistry
University of Michigan
930 N. University Avenue
Ann Arbor, MI 48109-1055

Dr. Michael Palucki,
Department of Process Research
Merck & Co., Inc.
Rahway, NJ 07065-0900

Dr. Derek A. Pflum
Department of Chemical R&D
Pfizer Global Research & Development
2800 Plymouth Road
Ann Arbor, MI 48105

Prof. Christian M. Rojas
Department of Chemistry
Barnard College
3009 Broadway
New York, NY 10027

Dr. Subas Sakya
CNS Chemistry
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340

Prof. Kevin M. Shea
Department of Chemistry
Clark Science Center
Smith College
Northampton, MA 01063

Jennifer M. Tinsley
Department of Chemistry
University of Michigan
930 North University Avenue
Ann Arbor, MI 48109-1055

Prof. David R. Williams
Department of Chemistry
Indiana University
800 East Kirkwood Avenue
Bloomington, IN 47405-71020

Prof. John P. Wolfe
Department of Chemistry
University of Michigan
930 N. University Avenue
Ann Arbor, MI 48109-1055

# Acronyms and Abbreviations

| | |
|---|---|
| ))))) | ultrasound |
|  | polymer support |
| Ac | acetyl |
| AcOH | acetic acid |
| ADP | adenosine diphosphate |
| AE | asymmetric epoxidation reaction |
| AFO | Algar–Flynn–Oyamada |
| AIBN | 2,2'-azobisisobutyronitrile |
| Alpine-borane® | *B*-isopinocamphenyl-9-borabicyclo[3.3.1]-nonane |
| AME | acetyl malonic ester |
| AMNT | aminomalononitrile *p*-toluenesulfonate |
| Ar | aryl |
| ATP | adenosine triphosphate |
| AUC | area under curve |
| B: | generic base |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BFO | benzofurazan oxide |
| TBHP | *tert*-butyl hydrogen peroxide |
| BINAP | 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| BOP | benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate |
| BPO | benzoyl peroxide |
| Bu | butyl |
| BZ reaction | Barton–Zard reaction |
| CAN | ceric ammonium nitrate (ammonium cerium(IV) nitrate) |
| CTAB | cetyl trimethylammonium bromide |
| CB-1 | cannabinoid receptor-1 |
| Cbz | benzyloxycarbonyl |
| CNS | central nervous system |
| COX-2 | cyclooxygenase II |
| CSA | camphorsulfonic acid |
| CuTC | copper thiophene-2-carboxylate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCB | dichlorobenzene |
| DCC | 1,3-dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | diethyl azodicarboxylate |
| DEPC | diethyl phosphorocyanidate |
| DET | diethyl tartrate |
| Δ | solvent heated under reflux |

DIC ..... diisopropylcarbodiimide
DHPM ..... 3,4-dihydropyrimidin-2(1*H*)-one
$(DHQ)_2$-PHAL ..... 1,4-bis(9-*O*-dihydroquinine)-phthalazine
$(DHQD)_2$-PHAL ..... 1,4-bis(9-*O*-dihydroquinidine)-phthalazine
DHT ..... 5α-dihydrotestosterone
DIBAL ..... diisobutylaluminum hydride
DMA ..... *N,N*-dimethylacetamide
DMA ..... *N,N*-dimethylaniline
DMAP ..... *N,N*-dimethylaminopyridine
DME ..... 1,2-dimethoxyethane
DMF ..... dimethylformamide
DMFDMA ..... dimethylaminoformaldehyde dimethyl acetal
DMS ..... dimethylsulfide
DMSO ..... dimethylsulfoxide
DMSY ..... dimethylsulfoxonium methylide
DMT ..... dimethoxytrityl
*DNA* ..... deoxyribonucleic acid
DNP ..... 2,4-dinitrophenyl
*L*-DOPA ..... 3,4-dihydroxyphenylalanine
dppb ..... 1,4-bis(diphenylphosphino)butane
dppe ..... 1,2-bis(diphenylphosphino)ethane
dppf ..... 1,1′-bis(diphenylphosphino)ferrocene
dppp ..... 1,3-bis(diphenylphosphino)propane
E1 ..... unimolecular elimination
E2 ..... bimolecular elimination
E1cb ..... 2-step, base-induced β-elimination *via* carbanion
EDG ..... electron donating group
*ee* ..... enantiomeric excess
EMME ..... ethoxymethylenemalonate
*ent* ..... *enantiomer*
EPP ..... ethyl polyphosphate
Eq ..... equivalent
Et ..... ethyl
EtOAc ..... ethyl acetate
EPR (= ESR) ..... electron paramagnetic resonance spectroscopy
ESR (= EPR) ..... electronic spin resonance
EWG ..... electron withdrawing group
FMO ..... frontier molecular orbital
FVP ..... flash vacuum pyrolysis
GABA ..... γ-aminobutyric acid
GC ..... gas chromatography
GC reaction ..... Gabriel–Colman reaction
H ..... hours
His ..... histidine
HIV ..... human immunodeficiency virus
HMDS ..... hexamethyldisilazine

HMPA ..... hexamethylphosphoric triamide
HOMO ..... highest occupied molecular orbital
HPLC ..... high performance liquid chromatography
IBCF ..... isobutylchloroformate
Imd ..... imidazole
IPA ..... isopropanol
*i*-Pr ..... isopropyl
KCO ..... potassium channel opener
KHMDS ..... potassium hexamethyldisilazide
KR ..... Kostanecki–Robinson
LAH ..... lithium aluminum hydride
LDA ..... lithium diisopropylamide
LHMDS ..... lithium hexamethyldisilazide
LiHMDS ..... lithium hexamethyldisilazide
LTMP ..... lithium 2,2,6,6-tetramethylpiperidine
LUMO ..... lowest unoccupied molecular orbital
M ..... metal
M ..... moles per liter (molar)
MCR ..... multi-component reaction
*m*-CPBA ..... *m*-chloroperoxybenzoic acid
Me ..... methyl
Mes ..... mesityl
mL ..... milliliters
MMPP ..... magnesium monoperoxyphthalate hexahydrate
mmol ..... millimoles
MO ..... molecular orbital
MOA ..... mechanism of action
MOM ..... methoxymethyl
MRSA ..... methicillin-resistant *Staphylococcus aureus*
MVK ..... methyl vinyl ketone
MWI (μν) ..... microwave irradiation
$NAD^+$ ..... nicotinamide adenine dinucleotide (oxidized form)
NADH ..... nicotinamide adenine dinucleotide
NBS ..... *N*-bromosuccinimide
NCS ..... *N*-chlorosuccinimide
NIS ..... *N*-iodosuccinimide
NMDA ..... *N*-methyl-D-aspartate
NMO ..... *N*-methylmorpholine-*N*-oxide
NMP ..... 1-methyl-2-pyrrolidinone
NMR ..... nuclear magnetic resonance
Nu ..... nucleophile
NPY ..... neuropeptide Y
NSAIDs ..... non-steroidal anti-inflammatory drugs
OA ..... osteoarthritis
PCC ..... pyridinium chlorochromate
PDC ..... pyridinium dichromate

PDE ..... phosphodiesterase
PG ..... prostaglandin
pGlu ..... pyroglutamic acid
Ph ..... phenyl
PK ..... pharmacokinetics
pKa ..... –Log acidity constant
PKC ..... protein kinase C
PPA ..... polyphosphoric acid
PPE ..... polyphosphate ester
PPI ..... proton pump inhibitor
4-PPNO ..... 4-phenylpyridine-*N*-oxide
PPP ..... 3-(3-hydroxyphenyl)-1-*n*-propylpiperidine
PPSE ..... polyphosphoric acid trimethylsilyl ester
PPTS ..... pyridinium *p*-toluenesulfonate
Pro ..... proline
PSI ..... pounds per square inch
PTC ..... phase transfer catalyst
PTSA ..... paratoluenesulfonic acid
Py ..... pyridine
Pyr ..... pyridine
RA ..... rheumatoid arthritis
RNA ..... ribonucleic acid
rt ..... room temperature
Salen ..... *N,N'*-disalicylidene-ethylenediamine
SET ..... single electron transfer
$S_NAr$ ..... nucleophilic substitution on an aromatic ring
$S_N1$ ..... unimolecular nucleophilic substitution
$S_N2$ ..... bimolecular nucleophilic substitution
*t*-Bu ..... *tert*-butyl
TBAF ..... tetrabutylammonium fluoride
TBD ..... 1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDMS ..... *tert*-butyldimethylsilyl
TBDPS ..... *tert*-butyldiphenylsilyl
TBHP ..... *tert*-butylhydroperoxide
TBS ..... *tert*-butyldimethylsilyl
TEA ..... triethylamine
Tf ..... trifluoromethanesulfonyl (triflic)
TFA ..... trifluoroacetic acid
TFAA ..... trifluoroacetic anhydride
TfOH ..... triflic acid
TFP ..... tri-*o*-furylphosphine
TFSA ..... trifluorosulfonic acid
THF ..... tetrahydrofuran
THIP ..... 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol
TIPS ..... triisopropylsilyl
TLC ..... thin layer chromatography

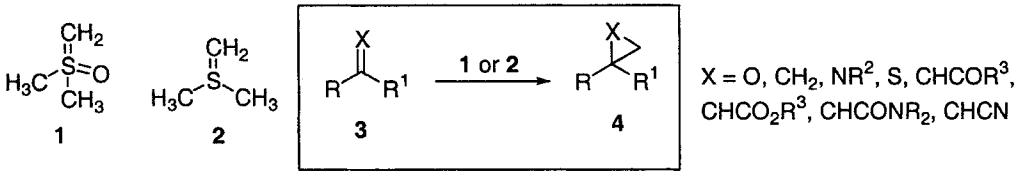
TMEDA ..... *N,N,N′,N′*-tetramethylethylenediamine
TMG ..... tetramethylguanidine
TMP ..... tetramethylpiperidine
TMS ..... trimethylsilyl
TMSCl ..... trimethylsilyl chloride
TMSCN ..... trimethylsilyl cyanide
TMSI ..... trimethylsilyl iodide
TMSOTf ..... trimethylsilyl triflate
Tol ..... toluene or tolyl
Tol-BINAP ..... 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TosMIC ..... (*p*-tolylsulfonyl)methyl isocyanide
TPAP ..... tetra-*n*-propylammonium perruthenate
TRH ..... thyrotropin releasing hormone
Ts ..... *p*-toluenesulfonyl (tosyl)
TSA ..... *p*-toluenesulfonic acid
TsO ..... tosylate

This Page Intentionally Left Blank

## 1.1 Corey–Chaykovsky Reaction

### *1.1.1 Description*

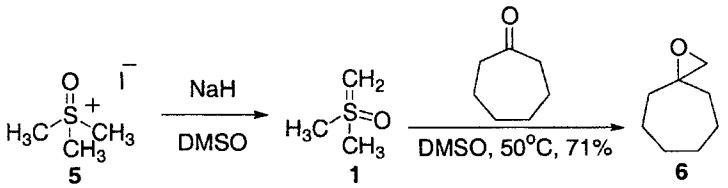
The Corey–Chaykovsky reaction entails the reaction of a sulfur ylide, either dimethylsulfoxonium methylide (**1**, Corey's ylide, sometimes known as DMSY) or dimethylsulfonium methylide (**2**), with electrophile **3** such as carbonyl, olefin, imine, or thiocarbonyl, to offer **4** as the corresponding epoxide, cyclopropane, aziridine, or thiirane.[1–7]

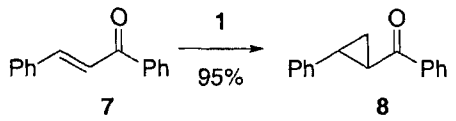



For an α,β-unsaturated carbonyl compound, **1** adds preferentially to the olefin to furnish the cyclopropane derivative, whereas the more reactive **2** generally undergoes the methylene transfer to the carbonyl, leading to the corresponding epoxide. Also due to the difference of reactivities, reactions using **1** require slightly elevated temperature, normally around 50–60°C, whereas reactions using the more reactive **2** can be carried out at colder temperature ranging from –15°C to room temperature. Moreover, while it is preferable to freshly prepare both ylides *in situ*, **2** is not as stable as **1**, which can be stored at room temperature for several days.

### *1.1.2 Historical Perspective*

In 1962, Corey and Chaykovsky described the generation and synthetic utility of dimethylsulfoxonium methylide (**1**) and dimethylsulfonium methylide (**2**).[8–12] Upon treatment of DMSO with NaH, the resulting methylsulfinyl carbanion reacted with trimethylsulfoxonium iodide (**5**) to produce dimethylsulfoxonium methylide (**1**). The subsequent reaction between **1** and cycloheptanone rendered epoxide **6**. Similar results were observed for other ketones and aldehydes as well, with a limitation where treatment of certain ketones (e.g. desoxybenzoin and $\Delta^4$-cholestenone) with **1** failed to deliver the epoxides possibly due to their ease to form the enolate ions by proton transfer to **1**. Interestingly, Michael receptor **7** reacted with **1** to provide access to the "methylene insertion" product, cyclopropane **8**. Meanwhile, thiiranes were isolated in good yields from the reaction of thiocarbonyls and **1**, and methylene transfer from **1** to imines took place to afford aziridines.



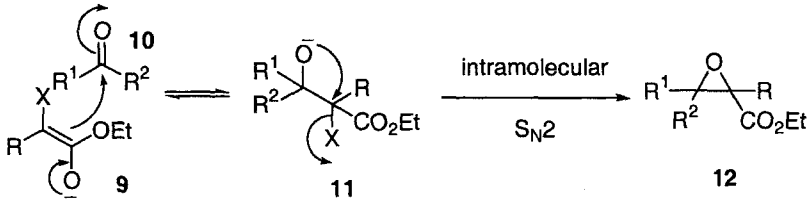



### *1.1.3 Mechanism*

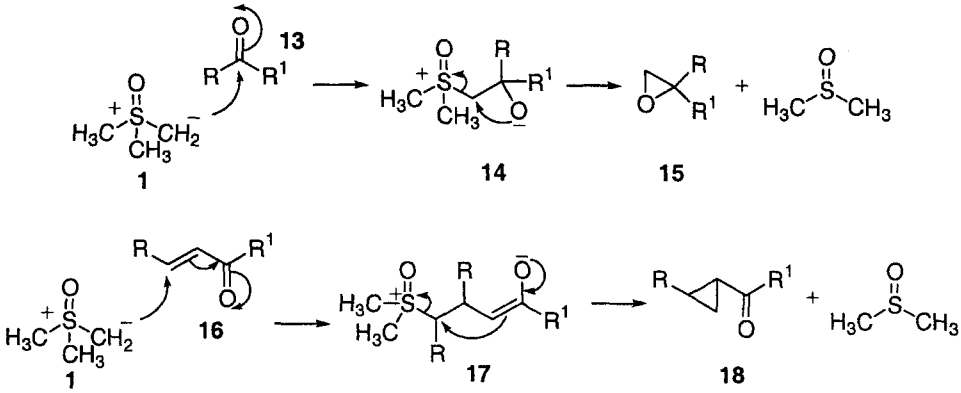
Similar to phosphur ylides, sulfur ylides **1** and **2** possess the nucleophilic site at the carbon atom and the pendant leaving group at the heteroatom (sulfur). Different from the Wittig reaction, the Corey–Chaykovsky reaction does not lead to olefins.

The mechanism of epoxide formation using sulfur ylides[13] is analogous to that of the Darzens condensation. In the Darzens condensation, enolate **9** adds to ketone **10**, forming alkoxide **11**, which undergoes an internal $S_N2$ to give epoxide **12**. In a parallel fashion, addition of dimethylsulfoxonium methylide (**1**) to ketone **13**, led to betaine **14**, which also undergoes an internal $S_N2$ to secure epoxide **15**. On the other hand, Michael addition of **1 to** enone **16** gives betaine **17**, which subsequently undergoes an internal $S_N2$ to deliver cyclopropyl ketone **18**.[14]

Darzens condensation:



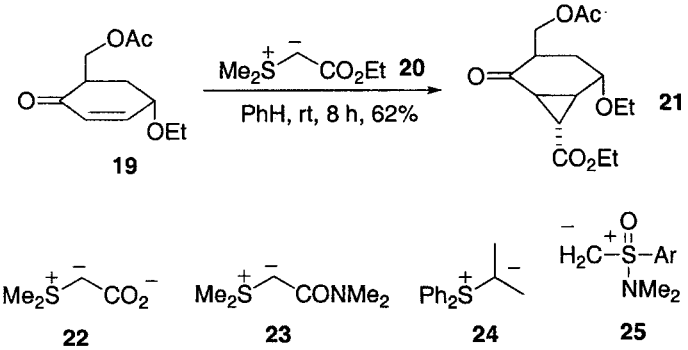

Corey–Chaykovsky reaction:




### *1.1.4 Variations and Improvements*

Sulfur ylides **1** and **2** are usually prepared by treatment of either trimethylsulfoxonium iodide (**5**) or trimethylsulfonium iodide, respectively, with NaH or *n*-BuLi.[12] An improvement using KO*t*Bu[13,15] is safer than NaH and *n*-BuLi for large-scale operations.

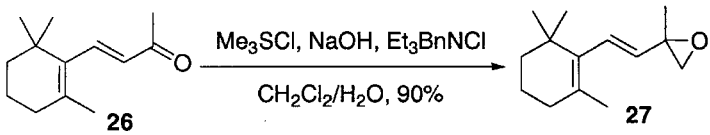
In addition, NaOMe, and $NaNH_2$, have also been employed. Application of phase-transfer conditions with tetra-*n*-butylammonium iodide showed marked improvement for the epoxide formation.[16] Furthermore, many complex substituted sulfur ylides have been synthesized and utilized. For instance, stabilized ylide **20** was prepared and treated with α-D-*allo*-pyranoside **19** to furnish α-D-cyclopropanyl-pyranoside **21**.[17] Other examples of substituted sulfur ylides include **22–25**, among which aminosulfoxonium ylide **25**, sometimes known as Johnson's ylide, belongs to another category.[18] The aminosulfoxonium ylides possess the configurational stability and thermal stability not enjoyed by the sulfonium and sulfoxonium ylides, thereby are more suitable for asymmetric synthesis.




### *1.1.5 Synthetic Utility*

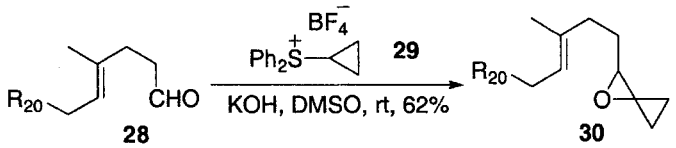
#### *1.1.5.1 Epoxidation*

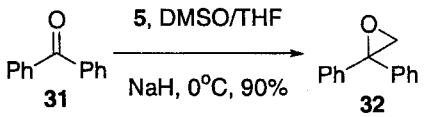
Epoxidation of aldehydes and ketones is the most profound utility of the Corey–Chaykovsky reaction. As noted in section 1.1.1, for an α,β-unsaturated carbonyl compound, **1** adds preferentially to the olefin to provide the cyclopropane derivative. On the other hand, the more reactive **2** generally undergoes the methylene transfer to the carbonyl, giving rise to the corresponding epoxide. For instance, treatment of β-ionone (**26**) with **2**, derived from trimethylsulfonium chloride and NaOH in the presence of a phase-transfer catalyst $Et_4BnNCl$, gave rise to vinyl epoxide **27** exclusively.[19]

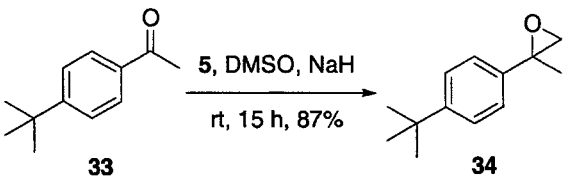


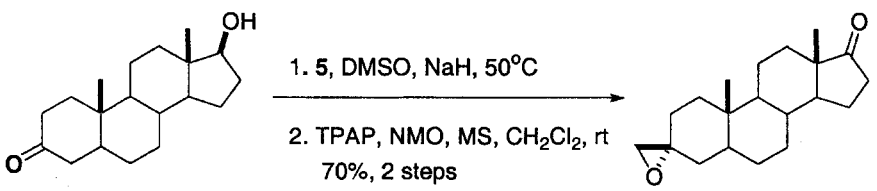

Isolated carbonyls always give epoxides from the Corey–Chaykovsky reaction. Take the aldehyde substrate as an example. Spiro epoxide **30** was produced from the reaction of trisnorsqualene aldehyde **28** ($R_{20}$ represents the polyene side-chain with 20 carbons) with substituted sulfur ylide **29**, prepared *in situ* from cyclopropyldiphenylsulfonium tetrafluoroborate and KOH.[20] For the epoxidation of ketones, the Corey–Chaykovsky reaction works well for diaryl- (**31**),[21] arylalkyl- (**32**),[22]

as well as dialkyl (**33**)[23] ketones. When steric bias exists on the substrate, stereoselective epoxidation may be achieved. For example, treatment of dihydrotestosterone (DHT, **35**) with the Corey ylide **1** followed by TPAP oxidation resulted in only one diastereomeric keto-epoxide **36**.[23]

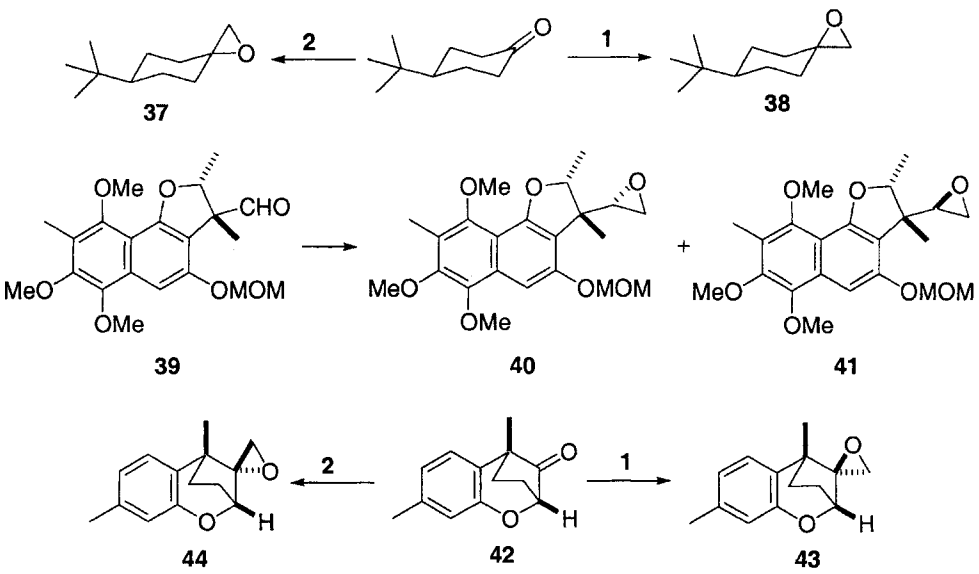


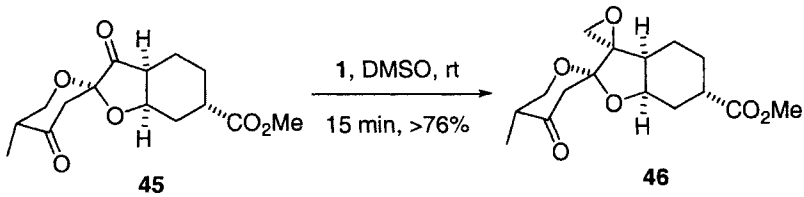



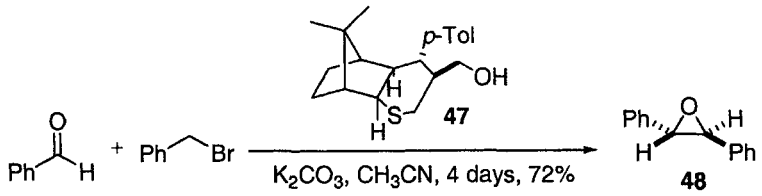

Stereoselective epoxidation can be realized through either substrate-controlled (e.g. **35** → **36**) or reagent-controlled approaches. A classic example is the epoxidation of 4-*t*-butylcyclohexanone.[12] When sulfonium ylide **2** was utilized, the more reactive ylide irreversibly attacked the carbonyl from the axial direction to offer predominantly epoxide **37**. When the less reactive sulfoxonium ylide **1** was used, the nucleophilic addition to the carbonyl was reversible, giving rise to the thermodynamically more stable, equatorially coupled betaine, which subsequently eliminated to deliver epoxide **38**. Thus, stereoselective epoxidation was achieved from different mechanistic pathways taken by different sulfur ylides. In another case, reaction of aldehyde **38** with sulfonium ylide **2** only gave moderate stereoselectivity (**41**:**40** = 1.5/1), whereas employment of sulfoxonium ylide **1** led to a ratio of **41**:**40** = 13/1.[24] The best stereoselectivity was accomplished using aminosulfoxonium ylide **25**, leading to a ratio of **41**:**40** = 30/1. For ketone **42**, a complete reversal of stereochemistry was observed when it was treated with sulfoxonium ylide **1** and sulfonium ylide **2**, respectively.[25]



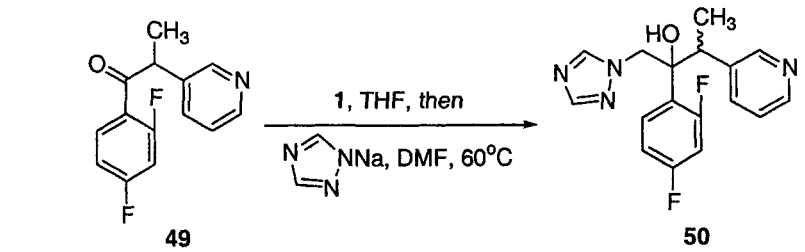

In transforming bis-ketone **45** to keto-epoxide **46**, the elevated stereoselectivity was believed to be a consequence of the molecular shape — the sulfur ylide attacked preferentially from the convex face of the strongly puckered molecule of **45**. Moreover, the pronounced chemoselectivity was attributed to the increased electrophilicity of the furanone versus the pyranone carbonyl, as a result of an inductive effect generated by the pair of spiroacetal oxygen substituents at the furanone α-position.[26]

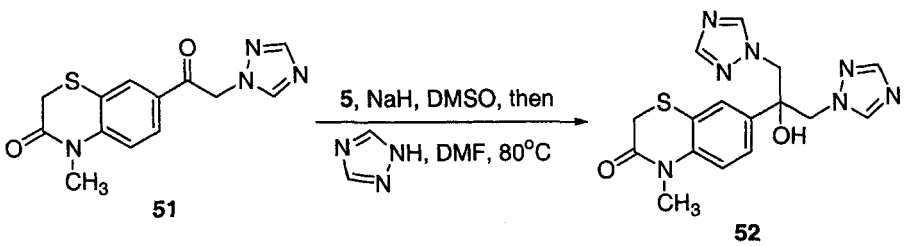



Since chiral sulfur ylides racemize rapidly, they are generally prepared *in situ* from chiral sulfides and halides. The first example of asymmetric epoxidation was reported in 1989, using camphor-derived chiral sulfonium ylides with moderate yields and *ee* (< 47%).[27] Since then, much effort has been made in the asymmetric epoxidation using such a strategy without a significant breakthrough. In one example, the reaction between benzaldehyde and benzyl bromide in the presence of one equivalent of camphor-derived sulfide **47** furnished epoxide **48** in high diastereoselectivity (*trans:cis* = 96:4) with moderate enantioselectivity in the case of the *trans* isomer (56% *ee*).[28]



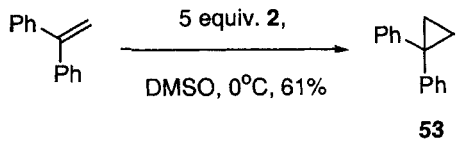

The Corey–Chaykovsky reaction incited some applications in medicinal chemistry. During the synthesis of analogs of fluconazole, an azole antifungal agent, treatment of **49** with **1** led to the corresponding epoxide, which was subsequently converted to **50** as a pair of diastereomers.[29] Analogously, the Corey–Chaykovsky reaction of ketone **51** gave the expected epoxide, which then underwent an $S_N2$ reaction with 1*H*-1,2,4-triazole in the presence of NaH to deliver **52**, another azole antifungal agent.[30]

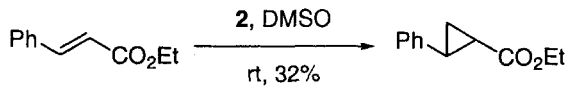



### *1.1.5.2 Cyclopropanation*

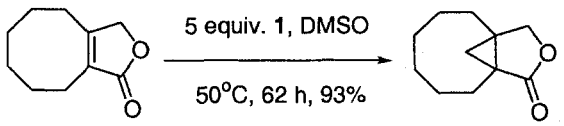
Due to the high reactivity of sulfonium ylide **2** for α,β-unsaturated ketone substrates, it normally undergoes methylene transfer to the carbonyl to give the corresponding epoxides. However, cyclopropanation did take place when 1,1-diphenylethylene[12] and ethyl cinnamate[13] were treated with **2** to furnish cyclopropanes **53** and **54**, respectively.



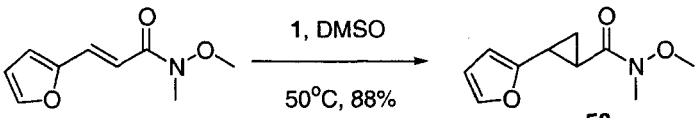



**54**

Dimethylsulfoxonium methylide (**1**) is the reagent of choice for the cyclopropanation of α,β-unsaturated carbonyl substrates. The reaction is generally carried out at more elevated temperatures in comparison to that of **2**, although exceptions exist. The method works for α,β-unsaturated ketones, esters and amides. Representative examples are found in transformations of 2(5*H*)-furanone **55** to cyclopropane **56**[31] and α,β-unsaturated Weinreb amide **57** to cyclopropane **58**.[32]



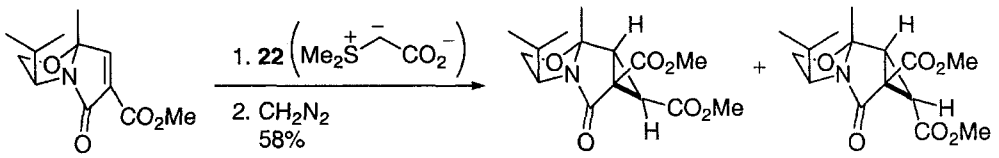

**55** **56**



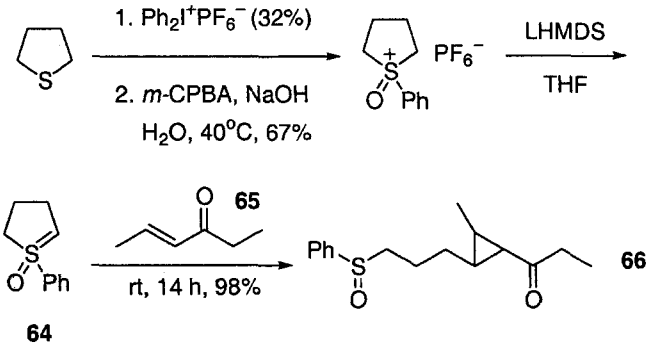

**57** **58**

As in the case of epoxidation, asymmetric cyclopropanation can be accomplished through either substrate-controlled or reagent-controlled approaches. The former approach requires an inherent steric bias in the substrates that often exist in the form of chiral auxiliaries. Substrate **59**, derived from 1-hydroxy pinan-3-one, gave only diastereomer **60** when treated with **1**.[33] Ylide **1** attacked the less shielded face opposite to the *gem*-dimethyl group, and DMSO release with formation of the spirocyclic adduct occurred prior to bond rotation. With regard to chiral α,β-unsaturated bicyclic γ-lactam **61**, the cyclopropanation took place in a highly diasteroselective fashion using anion **22** (dimethylsulfuranylidene acetate), resulting in the *anti*-adduct **62** as the predominant product (**62** : **63** = 99:1).[34]


**59** **60**




Reagent-controlled asymmetric cyclopropanation is relatively more difficult using sulfur ylides, although it has been done.[35] It is more often accomplished using chiral aminosulfoxonium ylides. Finally, more complex sulfur ylides (e.g. **64**) may result in more elaborate cyclopropane synthesis, as exemplified by the transformation **65** → **66**.[36]




### *1.1.5.3 Aziridination*

In the initial report by Corey and Chaykovsky, dimethylsulfonium methylide (**2**) reacted smoothly with benzalaniline to provide an entry to 1,2-diphenylaziridine **67**.[12] Franzen and Driesen reported the same reaction with 81% yield for **67**.[13] In another example, benzylidene-phenylamine reacted with **2** to produce 1-(*p*-methoxyphenyl)-2-phenylaziridine in 71% yield. The same reaction was also carried out using phase-transfer catalysis conditions.[37] Thus aziridine **68** could be generated consistently in good yield (80–94%). Recently, more complex sulfur ylides have been employed to make more functionalized aziridines, as depicted by the reaction between *N*-sulfonylimine **69** with diphenylsulfonium 3-(trimethylsilyl)propargylide (**70**) to afford aziridine **71**, along with desilylated aziridine **72**.[38]