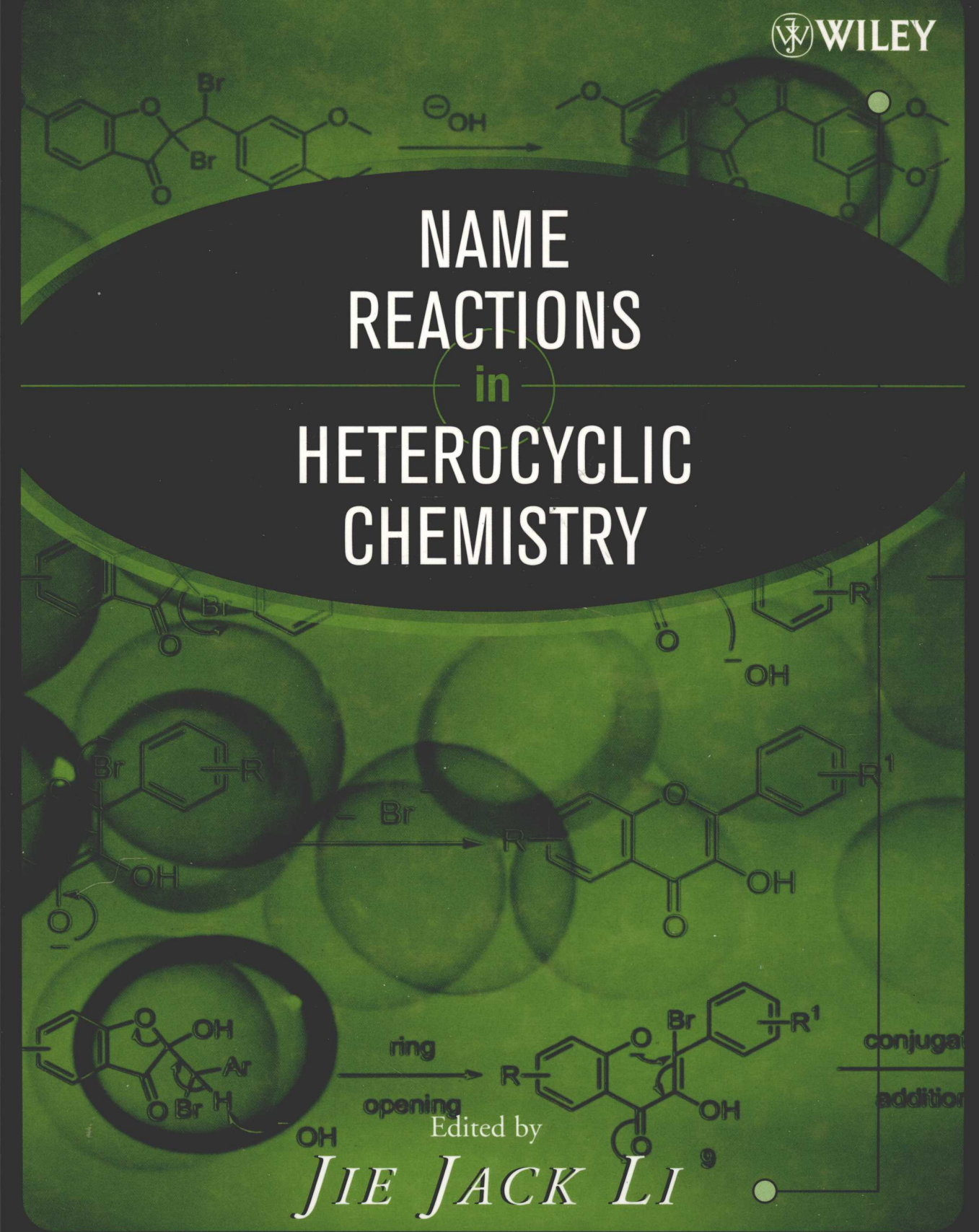
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Name Reactions in Heterocyclic Chemistry

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Name Reactions in Heterocyclic Chemistry

To Alexandra

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

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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 ($\mu\nu$) ..... 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

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