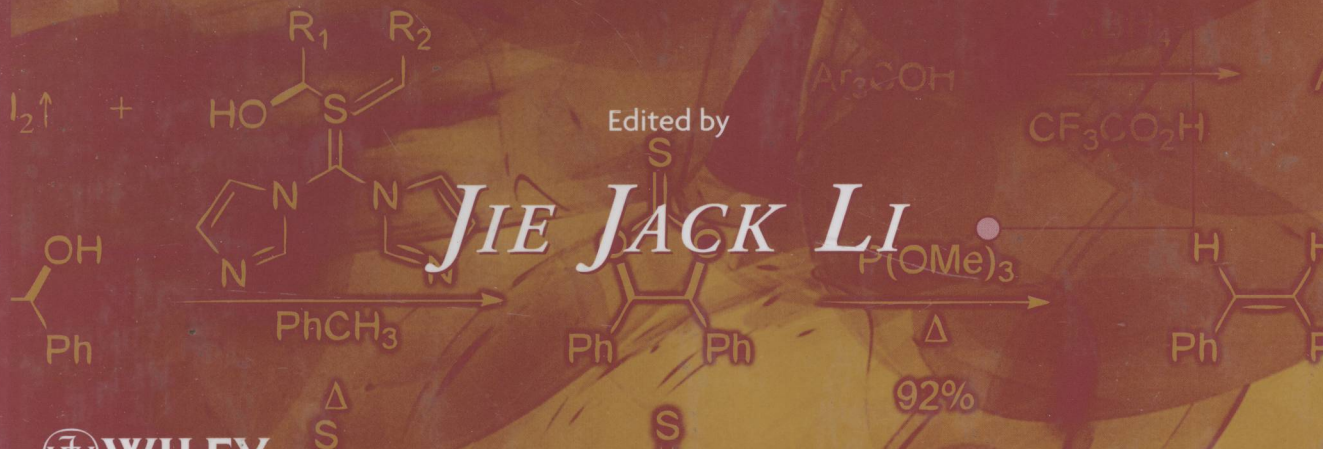
Foreword by
E. J. Corey

NAME REACTIONS for HOMOLOGATIONS

Part II



Edited by

Jie Jack Li

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Bristol-Myers Squibb Company

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E. J. Corey

Harvard University

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Name Reactions for Homologations
Part II

Dedicated to

Prof. E. J. Corey

On occasion of his eightieth birthday

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. 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 that landscape at a rate that exceeds the ability of a normal person 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.

These two volumes on methods for the extension of carbon chains by the use of coupling reactions brings to the attention of practicing synthetic chemists and students of chemistry a wide array of tools for the synthesis of new and useful molecules. It is a valuable addition to the literature by any measure and surely will prove its merit in years to come. The new knowledge that arises with its help will be impressive and of great benefit to humankind.

E. J. Corey
October 1, 2008

Preface

This book is the fourth volume of the series *Comprehensive Name Reactions*, an ambitious project conceived by Prof. E. J. Corey of Harvard University in the summer of 2002. Volume 1, *Name Reactions in Heterocyclic Chemistry*, was published in 2005 and was warmly received by the organic chemistry community. Volume 2, *Name Reactions for Functional Group Transformations* was published in 2007. After publication of the current Volumes 3 and 4 on homologations in 2009, we plan to roll out Volume 5, *Name Reactions on Ring Formation* in 2010; and Volume 6, *Name Reactions in Heterocyclic Chemistry-2*, in 2011, respectively.

Continuing the traditions of the first two volumes, each name reaction in Volume 4 is also reviewed in seven sections:

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

I also 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. 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 great privilege and a pleasure to work with a collection of stellar 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 reviewed; some of them even discovered the name reactions that they authored in this series. As a consequence, this book truly represents the state-of-the-art for *Name Reactions for Homologations*.

I welcome your critique.

Jack Li
October 1, 2008

Contributing authors:

Dr. Nadia M. Ahmad
Takeda Cambridge
418 Cambridge Science Park
Cambridge
CB4 0PA
United Kingdom

Dr. Marudai Balasubramanian
Research informatics
Pfizer Global Research & Development
Eastern Point Rd
Groton, CT 06340

Dr. Marco A. Biamonte
Medicinal Chemistry
BIOGEN IDEC
5200 Research Place
San Diego, CA 92122

Prof. Sherry Chemler
618 Natural Sciences Complex
Department of Chemistry
University at Buffalo
The State University of New York
Buffalo, NY 14260-3000

Dr. Daniel P. Christen
Transtech Pharma
4170 Mendenhall Oaks Pkwy, Suite 110
High Point, NC 27265

Dr. Timothy T. Curran
Chemical Development
Vertex Pharmaceuticals
130 Waverly Street
Cambridge, MA 02139

Dr. Paul Galatsis
Department of Chemistry
Pfizer Global Research & Development
Eastern Point Rd
Groton, CT 06340

Prof. Brian Goess
Department of Chemistry
Plyler Hall
Furman University
Greenville, SC 29613

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

Dr. Paul Humphries
Department of Chemistry
Pfizer Global Research & Development
Eastern Point Rd
Groton, CT 06340

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

Prof. Subbu Perumal
School of Chemistry
Madurai Kamaraj University
Madurai 625021, India

Dr. Jeffrey A. Pfefferkorn
Pfizer Global Research & Development
Eastern Point Rd
Groton, CT 06340

Dr. Jeremy M. Richter
Discovery Chemistry
Bristol–Myers Squibb Company
311 Pennington–Rocky Hill Road,
Pennington, NJ 08534

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

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

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 Ave.
Ann Arbor, MI 48109

Dr. Yong-Jin Wu
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Dr. Ji Zhang
Process Research & Development
Pharmaceutical Research Institute
Bristol-Myers Squibb
Princeton, NJ 08543-4000

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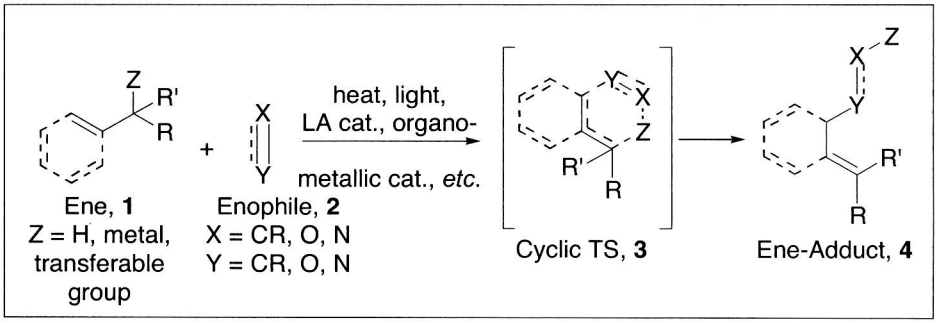
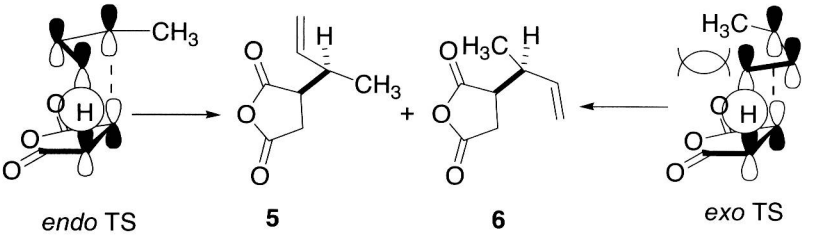
1.1.1 Alder–Ene Reaction

Timothy T. Curran

1.1.1.1 Description



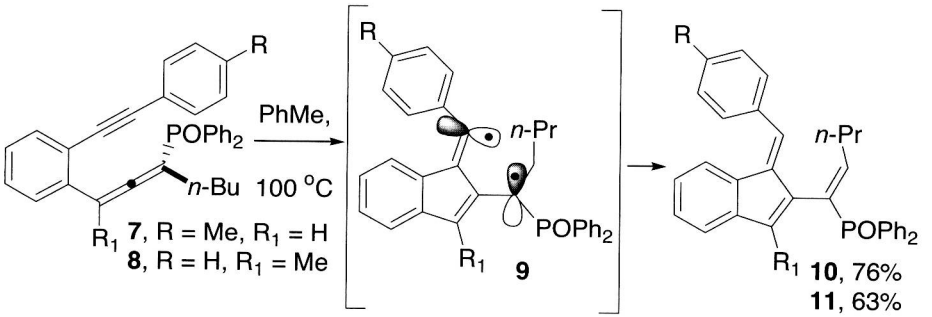
The Alder–Ene reaction is the indirect substitution addition of a compound containing a double or triple bond which also has an allylic, transferable group (typically a hydrogen–ene, **1**) with another multiple bond containing compound (enophile, **2**). The reaction leads to an allylic shift of one double bond and the transfer of the allylically-positioned, transferable group and formation of a new bond.



In the all carbon and hydrogen instance, the Alder–Ene reaction is considered to be concerted and is thermally allowed based on Woodward–Hoffman rules. Thus, the Alder–Ene reaction is proposed to be a six-electron process, like the Diels–Alder reaction, having transition states (*endo* and *exo*) analogous to the Diels–Alder reaction. However, the Alder–Ene reaction is easily modulated by steric effects as secondary electronic stabilizing effects have yet to be clearly identified. For example, Berson reported *cis*-2-butene reacted with maleic anhydride to provide about a 4:1 ratio of *endo*:*exo* adducts **5**:**6**, while *trans*-2-butene provided little selectivity at 43:57 ratio of **5**:**6**. In the reaction of maleic anhydride with *trans*-2-butene, the *exo*-TS encounters a steric interaction that the *endo*-TS does not. Steric effects are

observed for the thermal reaction of *cis*-2-butene and *trans*-2-butene with diethyl azodicarboxylate (DEAD) wherein the *trans*-compound reacts 3.7 times faster. These observations are steric in nature and lack electronic-stabilizing data for the *endo*-TS in comparison to the Diels–Alder reaction.[1,2]

Also, as shown in this example and similar to the Diels–Alder reaction, the "normal" or "traditional mode" of reaction is for the lowest unoccupied molecular orbital (LUMO) of the electron-deficient enophile to react with the highest occupied molecular orbital (HOMO) of the electron-rich ene. However, there are some carbon and hydrogen containing systems that have been proposed to proceed via radical or stepwise pathways. For example, allenyl alkynes **7** and **8** were thermally cyclized using PhMe under relatively mild conditions to provide **10** and **11** in good yield. The authors suggested a radical mechanism for this transformation via the fulvene biradical intermediate **9**.[3]

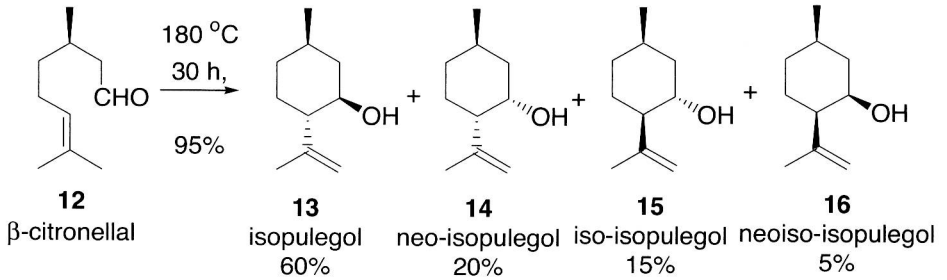


In addition, with the implementation of metals and the use of a variety of enophiles (RCHO, O_2, PTAD, RNO, SeO_2, R^3COR^4, benzyne, *etc.*), there is evidence for many of these reactions to be stepwise and oftentimes very difficult to distinguish concerted reactions from stepwise reactions. The broader definition of a radical, stepwise or concerted process of the Alder–Ene reaction will be utilized here.

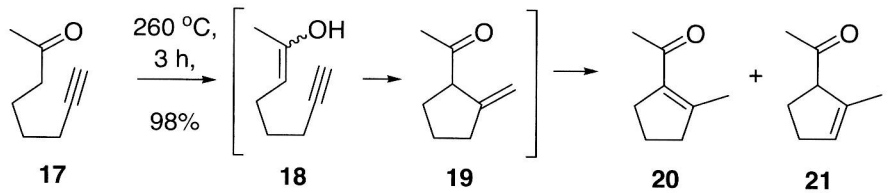
1.1.1.2 Historical Perspective

Until recently, the Alder–Ene reaction was more underdeveloped than other pericyclic reactions like the Diels–Alder reaction. Alder's initial 1943 report on the study of the reaction that bears his name, described reactions of maleic anhydride with simple enes using an autoclave and temperatures in excess of 200 °C.[4] One of the reasons for the slow development may be attributed to the relatively harsh conditions used to promote the reaction thermally and the lack of high selectivity. While intramolecular reactions served to allow the

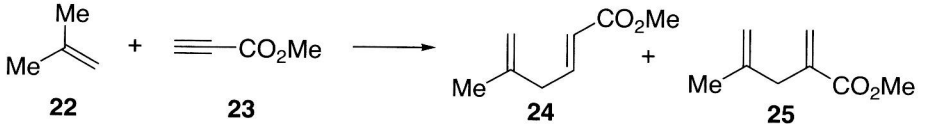
temperature for cyclization to be reduced in some instances, the reaction still lacked selectivity as illustrated in the thermal cyclization of β-citronellal (**12**) forming isopulegol **13** as the major product.[2]



By the time of Hoffmann's first review on the subject in 1969, a variety of enophiles had been used including allenes, alkynes, benzyne, diazodicarboxylates, enones and enoates, ketones with and without electron-withdrawing groups (EWG), aldehydes, triazoline-dione (TAD), singlet oxygen ($^1O_2$), sulphur trioxide and selenium dioxide. Shortly after Hoffmann's review, a review describing enol formation for the ene component and intramolecular reaction with an enophile (Conia type ene reaction) appeared.[5] Subsequent to that review, Oppolzer and Snieckus reviewed the intramolecular Alder–Ene reaction.[6] They noted energetic differences between the intramolecular and intermolecular Alder–Ene reactions and suggested that the participation of non-activated enophiles in the intramolecular ene process is due to the less negative $\Delta S^{\ddagger}$ (–18 to –19 kcal/mol compared to the intermolecular case –36 to –45 kcal/mol) which compensates for the higher $\Delta H^{\ddagger}$ (31–32 kcal/mol for the intramolecular case and 18–22 kcal/mol for the intermolecular case). As shown, the reaction was typically thermally promoted under relatively harsh conditions, and mixtures of products were oftentimes reported.[2] The conversion of keto–alkyne **17** into an 85:15 mixture of **20**:**21** was reported in high yield at 260 °C via the enol intermediate **18** followed by ene reaction providing **19**. Alkene migration provided the two products.



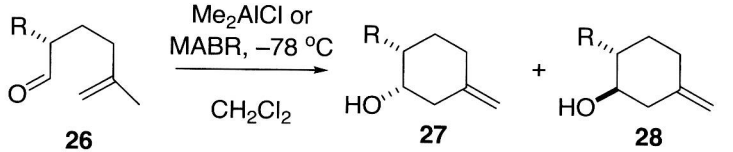
Similar to the Diels–Alder reaction, Lewis acid-catalyzed approaches were applied to intra- and intermolecular ene reactions, which served to diminish the temperatures required to promote the reaction and improved the selectivity. For example, reaction of 2-Me-2-propene with methyl propiolate provided a mixture of **24** and **25** at 220 °C, but proved higher yielding and more regioselective providing exclusively **24** when a Lewis acid was used.[1]



22 **23** **24** **25**

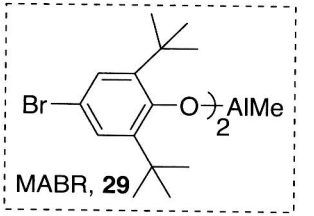
	24	25
220 °C, 45%	93	7
$AlCl_3$, rt, 61%	100	0

With continued study of a variety of Lewis acids, not only was the selectivity improved but was frequently changed. Yamamoto and co-workers developed bis-phenoxy-methyl aluminum catalysts which proved to change the selectivity and provide high stereoselectivities for the Alder–Ene product.[7] In the instance cited, the stereoselectivity was changed due to use of the bulky Lewis acid MABR, **29** which provided mainly *trans*-**28.** In comparison, Me_2AlCl provided predominantly the *cis* product **27**.

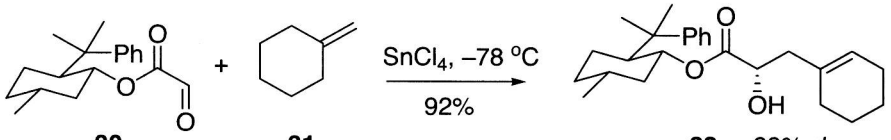


26 **27** **28**

R	Me_2AlCl Yield %, ratio **27**:**28**	MABR Yield %, ratio **27**:**28**
Me	65, 9:1	82, 1:32
i-Pr	70, 33:1	85, 1:17
Ph	95, 26:1	98, 1:62

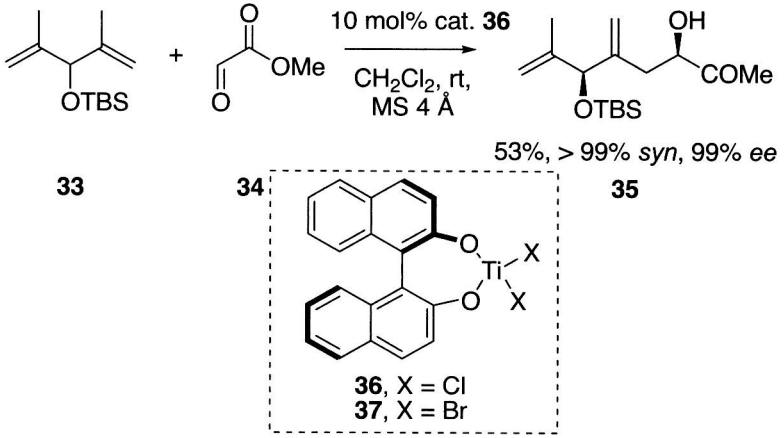


These reactions were, of course, limited to instances in which the enophile could be activated with a Lewis acid. Nevertheless, this was an excellent advancement toward promoting the utility of the Alder–Ene reaction and an asymmetric, Lewis acid-promoted ene reaction was reported by Whitesell using a chiral auxiliary.[8]



30 **31** **32**, > 99% *de*

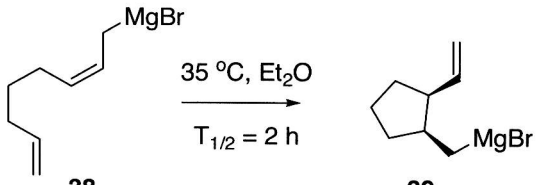
The development and use of optically-enriched Lewis acids toward promoting the Alder–Ene reaction followed. This was elegantly applied to the desymmetrization of *meso*-bis-alkenes like **33** acting as the ene component with catalyst **36** and 4 Å molecular sieves in CH_2Cl_2. Not only were these binapthol-based titanium ligands used for desymmetrization, but catalyst **36** and **37** also proved general in promoting the intermolecular Alder–Ene reaction on a variety of enes with glyoxalate esters in 68–98% yields and 88–97% *ee*.[1]



33 **34** **35**

36, X = Cl
37, X = Br

Metallo-Alder–Ene reactions have been reported in which the transferable group was an organometallic. One such example reported Grignard reagent **38** converting to **39** at room temperature.[9]



38 **39**

Catalytic transition-metals have more recently been utilized to promote reactions which provide formally the Alder–Ene product. Several