Lutz F. Tietze, Gordon Brasche,
and Kersten M. Gericke

Domino Reactions in Organic Synthesis

WILEY-VCH Verlag GmbH & Co. KGaA

Lutz F. Tietze, Gordon Brasche, and Kersten M. Gericke

Domino Reactions in Organic Synthesis

Related Titles

Berkessel, A., Gröger, H.

Asymmetric Organocatalysis

From Biomimetic Concepts to Applications in Asymmetric Synthesis

2005
ISBN 3–527-30517–3

Zhu, J., Bienaymé, H. (eds.)

Multicomponent Reactions

2005
ISBN 3–527-30806–7

de Meijere, A., Diederich, F. (eds.)

Metal-Catalyzed Cross-Coupling Reactions

2004
ISBN 3–527-30518–1

Beller, M., Bolm, C. (eds.)

Transition Metals for Organic Synthesis, 2 Vol.

Building Blocks and Fine Chemicals

2004
ISBN 3–527-30613–7

Mahrwald, R. (ed.)

Modern Aldol Reactions, 2 Vol.

2004
ISBN 3–527-30714–1

Nicolaou, K. C., Snyder, S. A.

Classics in Total Synthesis II

More Targets, Strategies, Methods

2003
ISBN 3–527-30685–4

Eicher, T., Hauptmann, S.

The Chemistry of Heterocycles

Structure, Reactions, Syntheses, and Applications

2003
ISBN 3–527-30720–6

Lutz F. Tietze, Gordon Brasche,
and Kersten M. Gericke

Domino Reactions in Organic Synthesis

WILEY-VCH Verlag GmbH & Co. KGaA

The Authors

Prof. Dr. Dr. h.c. Lutz Tietze
Inst. f. Organische Chemie
Georg-August-Universität
Tammannstr. 2
37077 Göttingen

Dr. Gordon Brasche
Inst. f. Organische Chemie
Georg-August-Universität
Tammannstr. 2
37077 Göttingen

Dr. Kersten Matthias Gericke
Inst. f. Organische Chemie
Georg-August-Universität
Tammannstr. 2
37077 Göttingen

Library of Congress Card No.:
applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Intern et at <http://dnb.ddb.de>.

Typesetting primustype Robert Hurler GmbH
Printing betz-Druck GmbH, Darmstadt
Binding Litges & Dopf Buchbinderei GmbH, Heppenheim
Cover Design Adam Design, Weinheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN-13: 978-3-527-29060-4
ISBN-10: 3-527-29060-5

Table of Contents

Preface

The ability to create complex molecules in only a few steps has long been the dream of chemists. That such thinking is not unrealistic could be seen from Nature, where complicated molecules such as palytoxin, maitotoxin and others are synthesized with apparent ease and in a highly efficient manner. Now, with the development of domino reactions, the dream has become almost true for the laboratory chemist – at least partly. Today, this new way of thinking represents a clear change of paradigm in organic synthesis, with domino reactions being frequently used not only in basic research but also in applied chemistry.

The use of domino reactions has two main advantages. The first advantage applies to the chemical industry, as the costs not only for waste management but also for energy supplies and materials are reduced. The second advantage is the beneficial effect on the environment, as domino reactions help to save natural resources. It is, therefore, not surprising that this new concept has been adopted very rapidly by the scientific community.

Following our first comprehensive review on domino reactions in 1993, which was published in *Angewandte Chemie*, and a second review in 1996 in *Chemical Reviews*, there has been an "explosion" of publications in this field. In this book we have included carefully identified reaction sequences and selected publications up to the summer of 2005, as well as details of some important older studies and very recent investigations conducted in 2006. Thus, in total, the book contains over 1000 citations!

At this stage we would like to apologize for not including *all* studies on domino reactions, but this was due simply to a lack of space. In this book, the term "domino" is used throughout to describe the reaction sequences used, and we seek the understanding of authors of the included publications if we did not use their terminology. Rather, we thought that for a better understanding a unified concept based on our definition and classification of domino reactions would be most appropriate. Consequently, we would very much appreciate if everybody working in this field would in future use the term "domino" if their reaction fulfills the conditions of such a transformation.

We would like to thank Jessica Frömmel, Martina Pretor, Sabine Schacht and especially Katja Schäfer for their continuous help in writing the manuscript and preparing the schemes. We would also like to thank Dr. Hubertus P. Bell for manifold ideas and the selection of articles, Dr. Sascha Hellkamp for careful over-

seeing of the manuscript and helpful advice, and Xiong Chen for controlling the literature. We also like to thank the publisher Wiley-VCH, and especially William H. Down, Dr. Romy Kirsten and Dr. Gudrun Walter, for their understanding and help in preparing the book.

Göttingen, summer 2006

Lutz F. Tietze
Gordon Brasche
Kersten M. Gericke

Abbreviations

)))	Sonification
18-C-6	18-Crown-6 ether
A-3CR (A-4CR)	Asinger three(four)-component reaction
Ac	acetyl
acac	acetylacetonato
ACCN	1,1'-azobis(cyclohexanecarbonitrile)
AcOH	acetic acid
Ac_2O	acetic anhydride
AIBN	2,2'-azobisisobutyronitrile
ALA	δ-amino levulinic acid
ALB	AlLibis[(*S*)-binaphthoxide] complex
All	allyl
Ar	aryl
BB-4CR	Bucherer–Bergs four-component reaction
BEH	bacterial epoxide hydrolase
$BF_3 \cdot OEt_2$	boron trifluoride–diethyl ether complex
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	2,2'-dihydroxy-1,1'-binaphthyl
[bmim]BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
[bmim]PF_6	1-butyl-3-methylimidazolium hexafluorophosphate
BMDMS	bromomethyldimethylsilyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
BOXAX	2,2'-bis(oxazolin-2-yl)-1,1'-binaphthyl
BP	1,1'-biphenyl
BS	*p*bromophenylsulphonyloxy
BTIB	bis(trifluoroacetoxy)-iodobenzene
Bu	*n*-butyl
Bz	benzoyl
CALB	*Candida antarctica* lipase
CAN	ceric ammonium nitrate
cat.	catalytic; catalyst
Cbz	benzyloxycarbonyl

*c*Hx	cyclohexyl
CM	cross-metathesis
COD	cycloocta-1,5-diene
COX	cyclooxygenase
CuTC	copper thiophene-2-carboxylate
Cy	cyclohexyl
d	day(s)
DAIB	(diacetoxy)iodobenzene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCTMB	1,4-dicyano-tetramethylbenzene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIBAL	diisobutylaluminum hydride
diglyme	diethyleneglycol dimethylether
dimeda	N,N'-dimethylethylenediamine
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N*,*N*'-dimethylpropylene urea
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,2-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDDA	ethylenediamine-*N*,*N*'-diacetic acid
ee	enantiomeric excess
Et	ethyl
FVP	flash-vacuum pyrolysis
h	hour(s)
H-4CR	Hantzsch four-component reaction
HFIP	hexafluoroisopropanol
HIV	human immunodefficiency virus
HLE	human leukocyte elastase
HMG	hydroxymethylglutamate
HMPA	hexamethylphosphoric triamide
HOMO	highest occupied molecular orbital
HTX	histrionicotoxin
HWE	Horner–Wadsworth–Emmons or Horner–Wittig–Emmons
IBX	2-iodoxybenzoic acid

IMCR	isocyanide MCR
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium 2,2',6,6'-tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
M-3CR	Mannich-three-component reaction
MCR	multicomponent reaction
Me	methyl
MEM	(2-methoxyethoxy)methyl
MeOH	methanol (methyl alcohol)
min	minute(s)
MOB	masked *o*-benzoquinones or *o*-benzoquinoid structures
MOM	methoxymethyl
MPEG	polyethyleneglycol monomethylether
MPV	Meerwein–Ponndorf–Verley
Ms	mesyl/methanesulfonyl
MS	molecular sieves
Mts	2,4,6-trimethylphenylsulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
N,N-DEA	*N,N*-Diethylamine
P-3CR	Passerini three-component reaction
PBG	porphobilinogen
PEG	poly(ethylene glycol)
PET	photo-induced electron transfer
PGE	prostaglandin E_1
PIDA	phenyliodine(III) diacetate
PLE	pig liver esterase
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PNA	peptide nucleic acid
Pr	propyl
PrLB	(Pr = Praseodymium; L = lithium; B = BINOL)
PTSA	*p*-toluenesulfonic acid
Py	pyridine
r.t.	room temperature
RAMP	(*R*)-1-amino-2-(methoxymethyl)pyrrolidine
RCM	ring-closing metathesis
RDL	*Rhizopus delemar* lipase
RNR	ribonucleotide reductase
ROM	ring-opening metathesis
S-3CR	Strecker three-component reaction
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine

SAWU-3CR	Staudinger reduction/aza-Wittig/Ugi three component reaction
SEM	2-trimethylsilylethoxymethoxy
SET	single-electron transfer
SHOP	Shell Higher Olefin Process
TADDOL	(–)-(4*R*,5*R*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBABr	tetrabutylammonium bromide
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TDMPP	tri(2,6-dimethoxyphenyl)phosphine
TEMPO	tetramethylpiperidinyl-1-oxy
TES	triethylsilyl
tetraglyme	tetraethyleneglycol dimethylether
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl
TMANO	trimethylamine-*N*-oxide
tmeda	N,N,N'N'-tetramethylethylenediamine
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPAP	tetrapropylammonium perruthenate
TPS	*tert*-butyldiphenylsilyl
triglyme	triethyleneglycol dimethylether
Ts	tosyl/*p*-toluenesulfonyl
TTMSS	tris(trimethylsilyl)silane
U-4CR	Ugi four-component reaction
UDC	Ugi/De-Boc/Cyclize strategy
UV	ultraviolet
μSYNTAS	miniaturized-SYNthesis and Total Analysis System

Introduction

During the past fifty years, synthetic organic chemistry has developed in a fascinating way. Whereas in the early days only simple molecules could be prepared, chemists can now synthesize highly complex molecules such as palytoxin [1], brevetoxine A [2] or gambierol [3]. Palytoxin contains 64 stereogenic centers, which means that this compound with its given constitution could, in principle, exist as over 10^{19} stereoisomers. Thus, a prerequisite for the preparation of such a complex substance was the development of stereoselective synthetic methods. The importance of this type of transformation was underlined in 2003 by the awarding of the Nobel Prize to Sharpless, Noyori and Knowles for their studies on catalytic enantioselective oxidation and reduction procedures [4]. Today, a wealth of chemo-, regio-, diastereo- and enantioselective methods is available, which frequently approach the selectivity of enzymatic process with the advantage of a reduced substrate specificity.

The past decade has witnessed a change of paradigm in chemical synthesis. Indeed, the question today is not only what can we prepare – actually there is nearly no limit – but how do we do it?

The main issue now is the efficiency of a synthesis, which can be defined as the increase of complexity per transformation. Notably, modern syntheses must obey the needs of our environment, which includes the preservation of resources and the avoidance of toxic reagents as well as toxic solvents [5]. Such an approach has advantages not only for Nature but also in terms of economics, as it allows reductions to be made in production time as well as in the amounts of waste products.

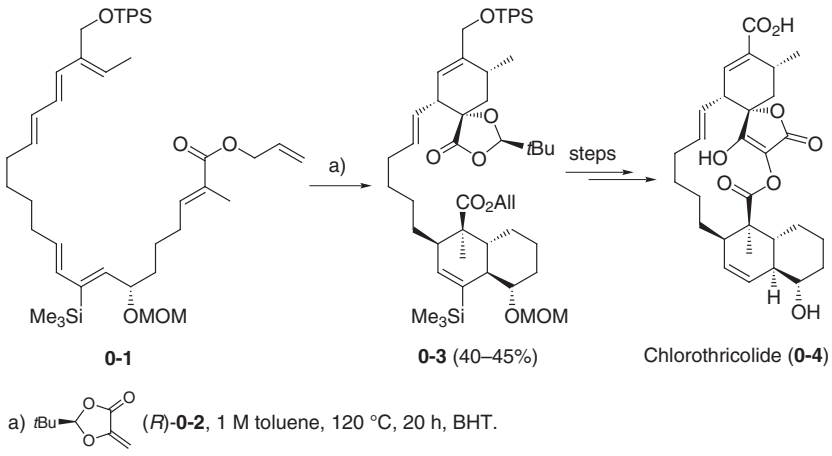
Until now, the "normal" procedure for the synthesis of organic compounds has been a stepwise formation of individual bonds in the target molecules, with work-up stages after each transformation. In contrast, modern synthesis management must seek procedures that allow the formation of several bonds, whether C–C, C–O or C–N, in one process. In an ideal procedure, the entire transformation should be run without the addition of any further reagents or catalysts, and without changing the reaction conditions. We have defined this type of transformation as a "domino reaction" or "domino process" [6]. Such a process would be the transformation of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former-bond forming reactions.

Thus, domino processes are time-resolved transformations, an excellent illustration being that of domino stones, where one stone tips over the next, which tips the

next, and the next… such that they all fall down in turn. In the literature, although the word "tandem" is often used to describe this type of process, it is less appropriate as the encyclopedia defines tandem as "locally, two after each other", as on a tandem bicycle or for tandem mass spectrometers. Thus, the term "tandem" does not fit with the time-resolved aspects of the domino reaction type; moreover, if three or even more bonds are formed in one sequence the term "tandem" cannot be used at all.

The time-resolved aspect of domino processes would, however, be in agreement with "cascade reactions" as a third expression used for the discussed transformations. Unfortunately, the term "cascade" is employed in so many different connections – for example, photochemical cascades, biochemical cascades or electronic cascades – on each occasion aiming at a completely different aspect, that it is not appropriate; moreover, it also makes the database search much more difficult! Moreover, if water molecules are examined as they cascade, they are simply moving and do not change. Several additional excellent reviews on domino reactions and related topics have been published [7], to which the reader is referred.

For clarification, individual transformations of independent functionalities in one molecule – also forming several bonds under the same reaction conditions – are not classified as domino reactions. The enantioselective total synthesis of (–)-chlorothricolide **0-4**, as performed by Roush and coworkers [8], is a good example of tandem and domino processes (Scheme 0.1). In the reaction of the acyclic substrate **0-1** in the presence of the chiral dienophile **0-2**, intra- and intermolecular Diels–Alder reactions take place to give **0-3** as the main product. Unfortunately, the two reaction sites are independent from each other and the transformation cannot therefore be classified as a domino process. Nonetheless, it is a beautiful "tandem reaction" that allows the establishment of seven asymmetric centers in a single operation.



Scheme 0.1. Synthesis of chlorothricolide (**0-4**) using a tandem process.

Domino reactions are not a new invention – indeed, Nature has been using this approach for billions of years! However, in almost of Nature's processes different enzymes are used to catalyze the different steps, one of the most prominent examples being the synthesis of fatty acids using a multi-enzyme complex starting from acetic acid derivatives.

There are, however, also many examples where the domino process is triggered by only one enzyme and the following steps are induced by the first event of activation.

The term "domino process" is correlated to substrates and products without taking into account that the different steps may be catalyzed by diverse catalysts or enzymes, as long as all steps can be performed under the same reaction conditions.

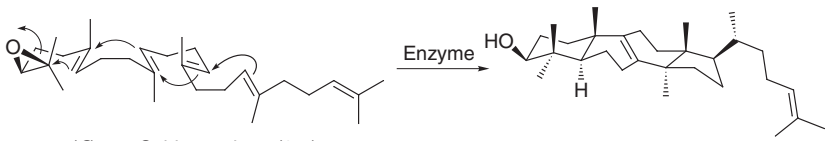
The quality of a domino reaction can be correlated to the number of bond-forming steps, as well as to the increase of complexity and its suitability for a general application. The greater the number of steps – which usually goes hand-in-hand with an increase of complexity of the product, the more useful might be the process.

An example of this type is the highly stereoselective formation of lanosterol (**0-6**) from (*S*)-2,3-oxidosqualene (**0-5**) in Nature, which seems not to follow a concerted mechanism (Scheme 0.2) [9].

Knowledge regarding biosyntheses has induced several biomimetic approaches towards steroids, the first examples being described by van Tamelen [10] and Corey [11]. A more efficient process was developed by Johnson [12] who, to synthesize progesterone **0-10** used an acid-catalyzed polycyclization of the tertiary allylic alcohol **0-7** in the presence of ethylene carbonate, which led to **0-9** via **0-8** (Scheme 0.3). The cyclopentene moiety in **0-9** is then transformed into the cyclohexanone moiety in progesterone (**0-10**).

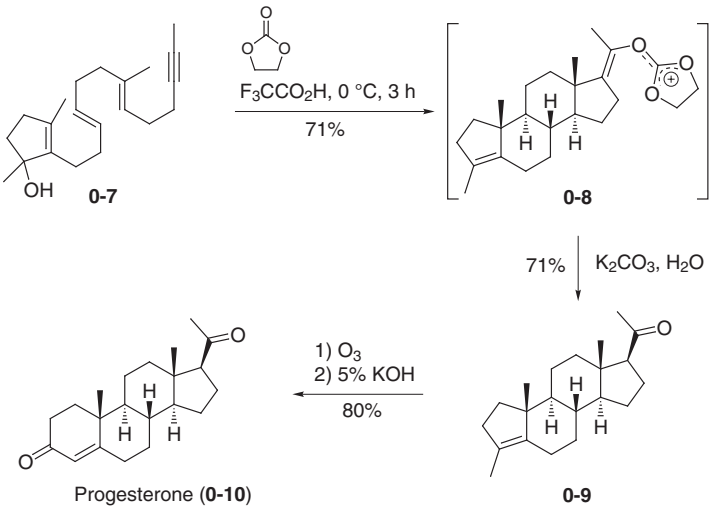
In the biosynthesis of the pigments of life, uroporphyrinogen III (**0-12**) is formed by cyclotetramerization of the monomer porphobilinogen (**0-11**) (Scheme 0.4). Uroporphyrinogen III (**0-12**) acts as precursor of inter alia heme, chlorophyll, as well as vitamin B_{12} [13].

The domino approach is also used by Nature for the synthesis of several alkaloids, the most prominent example being the biosynthesis of tropinone (**0-16**). In this case, a biomimetic synthesis was developed before the biosynthesis had been disclosed. Shortly after the publication of a more than 20-step synthesis of tropinone by Willstätter [14], Robinson [15] described a domino process (which was later improved by Schöpf [16]) using succinaldehyde (**0-13**), methylamine (**0-14**) and acetonedicarboxylic acid (**0-15**) to give tropinone (**0-16**) in excellent yield without isolating any intermediates (Scheme 0.5).

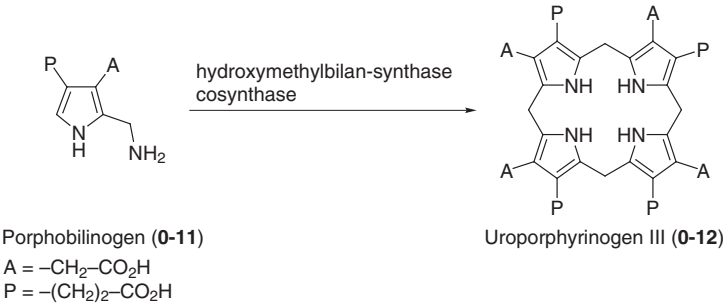


(*S*)-2,3-Oxidosqualene (**0-5**) Lanosterol (**0-6**)

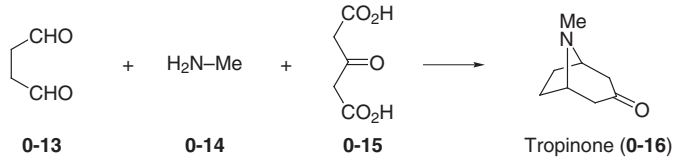
Scheme 0.2. Biosynthesis of lanosterol (**0-6**).



Scheme 0.3. Biomimetic synthesis of progesterone (**0-10**).

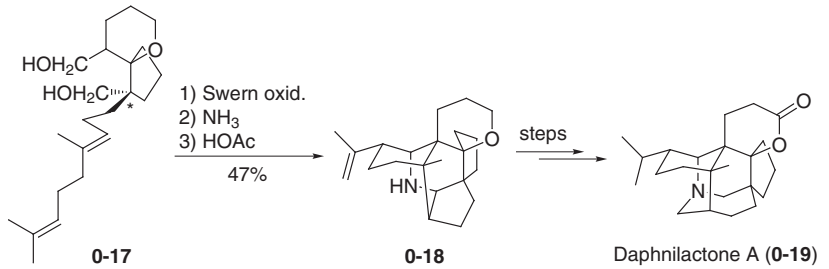


Scheme 0.4. Biosynthesis of uroporphyrinogen III (**0-12**).

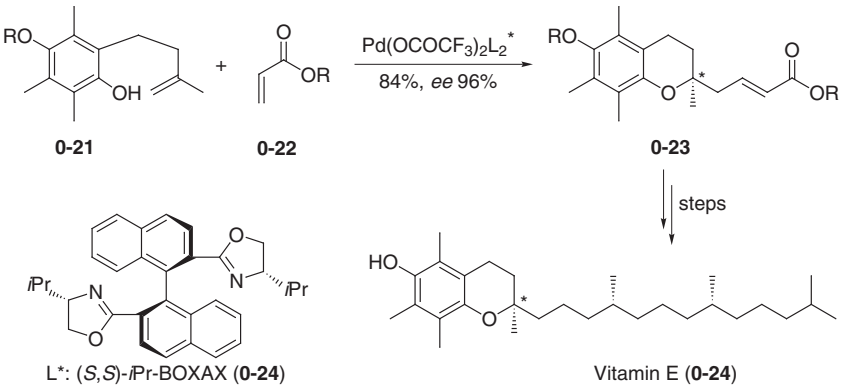


Scheme 0.5. Domino process for the synthesis of tropinone (**0-16**).

Tropinone is a structural component of several alkaloids, including atropine. The synthesis is based on a double Mannich process with iminium ions as intermediates. The Mannich reaction in itself is a three-component domino process, which is one of the first domino reactions developed by humankind.



Scheme 0.6. Total synthesis of the daphnilactone A.

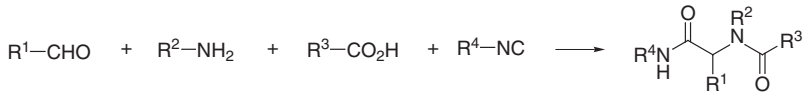


Scheme 0.7. Enantioselective Pd-catalyzed domino reaction for the synthesis of Vitamin E (**0-24**).

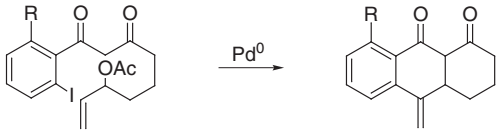
Another beautiful example of an early domino process is the formation of daphnilactone A (**0-19**), as described by Heathcock and coworkers [17]. In this process the precursor **0-17** containing two hydroxymethyl groups is oxidized to give the corresponding dialdehyde, which is condensed with methylamine leading to a 2-azabutadiene. There follow a cycloaddition and an ene reaction to give the hexacycle **0-18**, which is transformed into daphnilactone A (**0-19**) (Scheme 0.6).

One of the first enantioselective transition metal-catalyzed domino reactions in natural product synthesis leading to vitamin E (**0-23**) was developed by Tietze and coworkers (Scheme 0.7) [18]. This transformation is based on a Pd^{II}-catalyzed addition of a phenolic hydroxyl group to a C–C-double bond in **0-20** in the presence of the chiral ligand **0-24**, followed by an intermolecular addition of the formed Pd-species to another double bond.

One very important aspect in modern drug discovery is the preparation of so-called "substance libraries" from which pharmaceutical lead structures might be selected for the treatment of different diseases. An efficient approach for the preparation of highly diversified libraries is the development of multicomponent reactions, which can be defined as a subclass of domino reactions. One of the most



Scheme 0.8. Ugi four-component (U-4CR) approach.



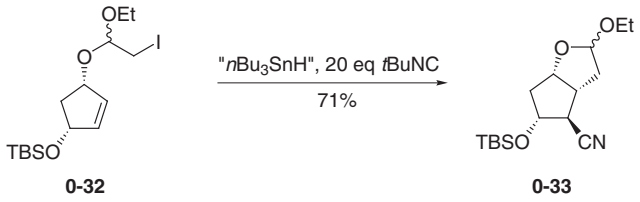
Scheme 0.9. Pd-catalyzed domino reaction.

widely used transformations of this type was described by Ugi and coworkers using an aldehyde **0-25**, an amine **0-26**, an acid **0-27**, and an isocyanide **0-28** to prepare peptide-like compounds **0-29** (Scheme 0.8) [7c]. This process could be even enlarged to an eight-component reaction.

As a requisite for all domino reactions, the substrates used must have more than two functionalities of comparable reactivity. They can be situated in one or two molecules or, as in the case of multicomponent domino reactions, in at least three different molecules. For the design and performance of domino reactions it is of paramount importance that the functionalities react in a fixed chronological order to allow the formation of defined molecules.

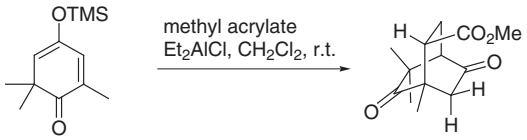
There are several possibilities to determine the course of the reactions. Thus, one must adjust the reactivity of the functionalities, which usually react under similar reaction conditions. This can be done by steric or electronic differentiation. An illustrative example of the latter approach is the Pd^0-catalyzed domino reaction of **0-30** to give the tricyclic compound **0-31**, as developed by the Tietze group (Scheme 0.9) [19]. In this domino process a competition exists between a Pd-catalyzed nucleophilic allylation (Tsuji–Trost reaction) and an arylation of an alkene (Heck reaction). By slowing down the oxidative addition as part of the latter reaction, through introducing an electronic-donating moiety such as a methoxy group, substrate **0-30b** could be transformed into **0-31b** in 89 % yield, whereas **0-30a** gave **0-31a** in only 23 % yield.

Another possibility here is to use entropic acceleration. In this way, it is possible to use a substrate that first reacts in an intramolecular mode to give an intermediate, which then undergoes an intermolecular reaction with a second molecule. An impressive older example is a radical cyclization/trapping in the synthesis of prostaglandin $F_{2\alpha}$, as described by the Stork group [20]. A key step here is the radical transformation of the iodo compound **0-32** using nBu$_3$SnH formed *in situ* from



0-32 **0-33**

Scheme 0.10. Radical reaction in the synthesis of prostaglandine $F_{2\alpha}$.



0-34 **0-35**

Scheme 0.11. Twofold Michael reaction in the synthesis of valerianandoid A.

nBu$_3$SnCl and NaBH$_3$CN in the presence of tBuNC and AIBN. The final product is the annulated cyano cyclopentane **0-33** (Scheme 0.10).

However, it is also possible to avoid an intramolecular reaction as the first step, for example if the cycle being formed in this transformation would be somehow strained, as observed for the formation of medium rings. In such a case, an intermolecular first takes place, followed by an intramolecular reaction.

On the other hand, many reactions are known where in a first intermolecular step a functionality is introduced which than can undergo an intramolecular reaction. A nice example is the reaction of dienone **0-34** with methyl acrylate in the presence of diethylaluminum chloride to give the bridged compound **0-35** (Scheme 0-11). The first step is an intermolecular Michael addition, which is followed by an intramolecular Michael addition. This domino process is the key step of the total synthesis of valerianandoid A, as described by Hagiwara and coworkers [21].

A different situation exists if the single steps in a domino process follow different mechanisms. Here, it is not normally adjustment of the reaction conditions that is difficult to differentiate between similar transformations; rather, it is to identify conditions that are suitable for both transformations in a time-resolved mode. Thus, when designing new domino reactions a careful adjustment of all factors is very important.

Classification

For the reason of comparison and the development of new domino processes, we have created a classification of these transformations. As an obvious characteristic, we used the mechanism of the different bond-forming steps. In this classification, we differentiate between cationic, anionic, radical, pericyclic, photochemical, transition metal-catalyzed, oxidative or reductive, and enzymatic reactions. For this type

Table 0.1 A classification of domino reactions.

I. Transformation	II. Transformation	III. Transformation
1. Cationic	1. Cationic	1. Cationic
2. Anionic	2. Anionic	2. Anionic
3. Radical	3. Radical	3. Radical
4. Pericyclic	4. Pericyclic	4. Pericyclic
5. Photochemical	5. Photochemical	5. Photochemical
6. Transition metal	6. Transition metal	6. Transition metal
7. Oxidative or reductive	7. Oxidative or reductive	7. Oxidative or reductive
8. Enzymatic	8. Enzymatic	8. Enzymatic

of classification, certain rules must be followed. Nucleophilic substitutions are always counted as anionic processes, independently of whether a carbocation is an intermediate as the second substrate. Moreover, nucleophilic additions to carbonyl groups with metal organic compounds as MeLi, silyl enol ethers or boron enolates are again counted as anionic transformations. In this way, aldol reactions (and also the Mukaiyama reaction) as well as the Michael addition are found in the chapter dealing with anionic domino processes. A related problem exists in the classification of radical and oxidative or reductive transformations, if a single electron transfer is included. Here, a differentiation according to the reagent used is employed. Thus, reactions of bromides with nBu$_3$SnH follow a typical radical pathway, whereas reactions of a carbonyl compound with SmI_2 to form a ketyl radical are listed under oxidative or reductive processes. An overview of the possible combinations of reactions of up to three steps is shown in Table 0.1.

Clearly, the list can be enlarged by introducing additional steps, whereas the steps leading to the reactive species at the beginning (such as the acid-catalyzed elimination of water from an alcohol to form a carbocation) are not counted.

The overwhelming number of examples dealing with domino processes are those where the different steps are from the same category, such as cationic/cationic or transition metal/transition metal-catalyzed domino processes, which we term "homo domino processes". An example of the former reaction is the synthesis of progesterone (see Scheme 0.3), and for the latter the synthesis of vitamin E (Scheme 0.7).

There are, however, also many examples of "mixed domino processes", such as the synthesis of daphnilactone (see Scheme 0.6), where two anionic processes are followed by two pericyclic reactions. As can be seen from the information in Table 0.1, by counting only two steps we have 64 categories, yet by including a further step the number increases to 512. However, many of these categories are not – or only scarcely – occupied. Therefore, only the first number of the different chapter correlates with our mechanistic classification. The second number only corresponds to a consecutive numbering to avoid empty chapters. Thus, for example in Chapters 4 and 6, which describe pericyclic and transition metal-catalyzed reactions, respectively, the second number corresponds to the frequency of the different processes.

In our opinion, this approach provides not only a clear overview of the existing domino reactions, but also helps to develop new domino reactions and to initiate ingenious independent research projects in this important field of synthetic organic chemistry.

References

1 (a) R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter, Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J.-i. Uenishi, J. B. White, M. Yonaga, *J. Am. Chem. Soc.* **1989**, *111*, 7525–7530; (b) E. M. Suh, Y. Kishi, *J. Am. Chem. Soc.* **1994**, *116*, 11205–11206.

2 K. C. Nicolaou, Z. Yang, G. Q. Shi, J. L. Gunzner, K. A. Agrios, P. Gärtner, *Nature* **1998**, *392*, 264–269.

3 (a) I. Kadota, H. Takamura, K. Sato, A. Ohno, K. Matsuda, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 46–47; (b) I. Kadota, H. Takamura, K. Sato, A. Ohno, K. Matsuda, M. Satake, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 11893–11899.

4 (a) K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032; (b) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; (c) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1999–2007.

5 (a) R. A. Sheldon, *C. R. Acad. Sci., Ser. IIc: Chim.* **2000**, *3*, 41–551; (b) R. A. Sheldon, *Chem. Ind. (London, U. K.)* **1997**, 12–15; (c) R. A. Sheldon, *Pure Appl. Chem.* **2000**, *72*, 1233–1246; (d) R. A. Sheldon, *Russ. Chem. J.* **2000**, *44*, 9–20; (e) R. A. Sheldon, *Green Chem.* **2005**, *7*, 267–278.

6 (a) L. F. Tietze, U. Beifuss, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 137–170; (b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; (c) L. F. Tietze, F. Haunert, Domino Reactions in Organic Synthesis. An Approach to Efficiency, Elegance, Ecological Benefit, Economic Advantage and Preservation of our Resources in Chemical Transformations, in: M. Shibasaki, J. F. Stoddart and F. Vögtle (Eds.), *Stimulating Concepts in Chemistry*, Wiley-VCH, Weinheim, **2000**, pp. 39–64; (d) L. F. Tietze, A. Modi, *Med. Res. Rev.* **2000**, *20*, 304–322; (e) L. F. Tietze, M. E. Lieb, *Curr. Opin. Chem. Biol.* **1998**, *2*, 363–371; (f) L. F. Tietze, *Chem. Ind. (London, U. K.)*, **1995**, 453–457; (g) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967–1983.

7 (a) H. Pellissier, *Tetrahedron* **2006**, *62*, 1619–1665; (b) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; (c) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; (d) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley, Weinheim, **2005**; (e) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831–844; (f) T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York; **1992**; (g) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103–13159; (h) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195–206; (i) H. Waldmann, *Nachr. Chem. Tech. Lab.* **1992**, *40*, 1133–1140

8 W. R. Roush, R. J. Sciotti, *J. Am. Chem. Soc.* **1998**, *120*, 7411–7419.

9 K. U. Wendt, G. E. Schulz, E. J. Corey, D. R. Liu, *Angew. Chem. Int. Ed.* **2000**, *39*, 2812–2833.

10 (a) E. E. van Tamelen, J. D. Willet, R. B. Clayton, K. E. Lord, *J. Am. Chem. Soc.* **1966**, *88*, 4752–4754; (b) E. E. van Tamelen, M. A. Schwartz, E. D. Hessler, A. Storni, *Chem. Commun.* **1966**, 409–411; (c) E. E. van Tamelen, *Acc. Chem. Res.* **1975**, *8*, 152–158; (d) E. E. van Tamelen, *J. Am. Chem. Soc.* **1982**, *104*, 6480–6481.

11 (a) E. J. Corey, W. E. Russey, P. R. Ortiz de Montellano, *J. Am. Chem. Soc.* **1966**, *88*, 4750; (b) E. J. Corey, S. C. Virgil, *J. Am. Chem. Soc.* **1991**, *113*, 4025–4026; (c) E. J. Corey, S. C. Virgil, S. Sashar, *J. Am. Chem. Soc.* **1991**, *113*, 8171–8172; (d) E. J. Corey, S. C. Virgil, D. R. Liu, S. Sashar, *J. Am. Chem. Soc.* **1992**, *114*, 1524–1525.

12 W. S. Johnson, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9–17.

13 (a) L. F. Tietze, H. Geissler, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1038–1040; (b) L. F. Tietze, H. Geissler, G. Schulz, *Pure Appl. Chem.* **1994**, *66*, 10–11.

14 (a) R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 129–144; (b) R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3163–3165; (c) R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 393–403; (d) R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1896**, 29, 936–947; (e) R. Willstätter, *Justus Liebigs Ann. Chem.* **1901**, *317* 204–265.

15 R. Robinson, *J. Chem. Soc.* **1917**, *111*, 762–768; *J. Chem. Soc.* **1917**, *111*, 876–899.

16 C. Schöpf, G. Lehmann, W. Arnold, *Angew. Chem.* **1937**, *50*, 779–787.

17 (a) C. H. Heathcock, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 665–681; (b) C. H. Heathcock, J. C. Kath, R. B. Ruggeri, *J. Org. Chem.* **1995**, *60*, 1120–1130.

18 L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker, *Angew. Chem. Int. Ed.* **2005**, *44*, 257–259.

19 L. F. Tietze, G. Nordmann, *Eur. J. Org. Chem.* **2001**, 3247–3253.

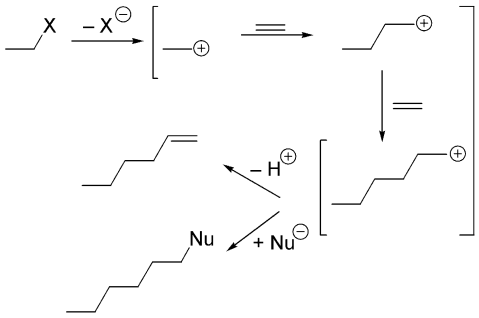
20 (a) G. Stork, P. M. Sher, H.-L. Chen, *J. Am. Chem. Soc.* **1986**, *108*, 6384–6385; (b) G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1986**, *108*, 303–304.

21 H. Hagiwara, A. Morii, Y. Yamada, T. Hoshi, T. Suzuki, *Tetrahedron Lett.* **2003**, *44*, 1595–1597.

1
Cationic Domino Reactions

In this opening chapter, the class of domino reactions that covers processes in which carbocations are generated in the initial step will be discussed. In this context, it should be noted that it is of no relevance whether the carbocation is of formal or real nature. The formation of a carbocation can easily be achieved by treatment of an alkene or an epoxide with a Brønsted or a Lewis acid, by elimination of water from an alcohol or an alcohol from an acetal, or by reaction of carbonyl compounds and imines with a Brønsted or a Lewis acid. It is worth emphasizing that the reaction of carbonyl compounds and imines with nucleophiles or anionic process (e. g., in the case of an aldol reaction) is sometimes ambiguous. They could also be classified under anionic domino reactions. Thus, the decision between a cationic reaction of carbonyl compounds in the presence of a Brønsted or a Lewis acid will be discussed here, whereas reactions of carbonyl compounds under basic conditions as well as all Michael reactions are described in Chapter 2 as anionic domino processes. It is important to note that all transformations which are affiliated to a cationic initiation must be regarded as cationic processes, and those with an anionic initiation as anionic processes, as an alternation between these two classes would require an as-yet not observed two-electron transfer process. As just discussed for the cationic/anionic process, in examples for a cationic/radical domino process, an electron-transfer again must take place, although in this case it is a single electron transfer. Examples of these processes have been described, but the transfer of an electron is a synonym for a reduction process, and we shall discuss these transformations in Section 1.3, which deals with cationic/reductive domino processes. Furthermore, to date no examples have been cited in the literature for a combination of cationic reactions with photochemically induced, transition metal-catalyzed or enzymatic processes. Nevertheless, carbocations are feasible to act in an electrophilic process in either an inter- or intramolecular manner with a multitude of different nucleophiles, generating a new bond with the concomitant creation of a new functionality which could undergo further transformation (Scheme 1.1).

In most of the hitherto known cationic domino processes another cationic process follows, representing the category of the so-called homo-domino reactions. In the last step, the final carbocation is stabilized either by the elimination of a proton or by the addition of another nucleophile, furnishing the desired product. Nonetheless, a few intriguing examples have been revealed in which a succession



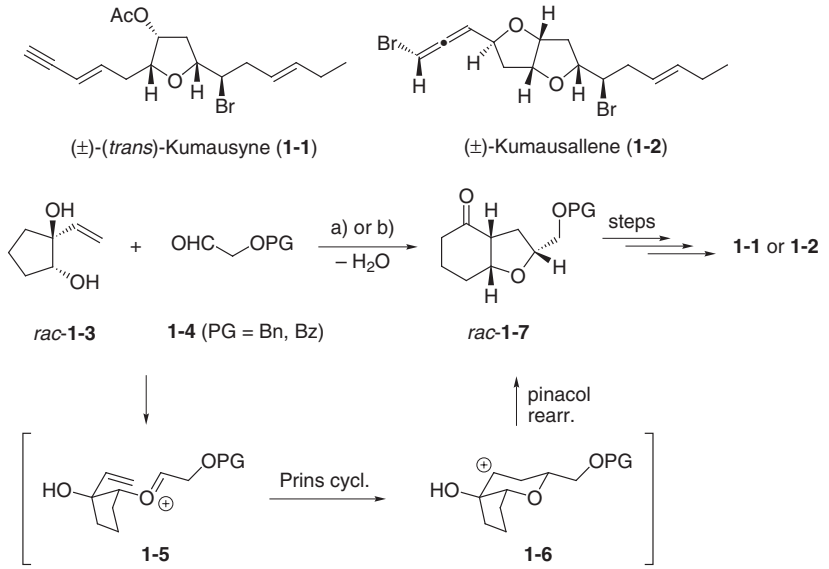
Scheme 1.1. General scheme of a cationic-cationic domino process.

of cationic (by a pericyclic step) or a reduction is also possible, these being categorized as hetero-domino reactions. Furthermore, rearrangements, which traverse several cationic species, are also quite common and of special synthetic interest. Following this brief introduction, we enter directly into the field of cationic domino reactions, starting with the presentation of cationic/cationic processes.

1.1 Cationic/Cationic Processes

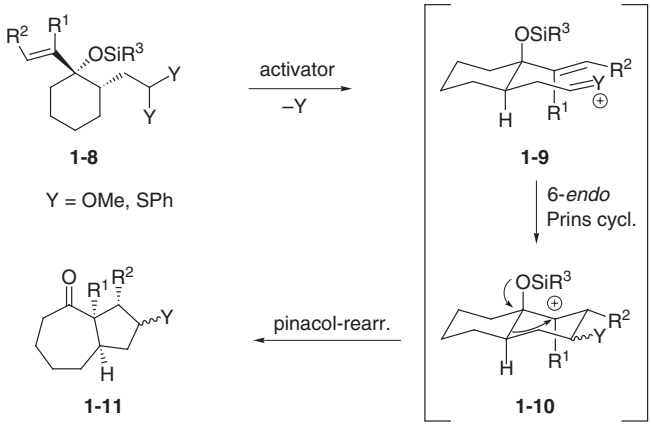
The termination of cationic cyclizations by the use of pinacol rearrangements has shown to be a powerful tool for developing stereoselective ring-forming domino reactions. During the past few years, the Overman group has invested much effort in the design of fascinating domino Prins cyclization/pinacol rearrangement sequences for the synthesis of carbocyclic and heterocyclic compounds, especially with regard to target-directed assembly of natural products [1]. For example, the Prins/pinacol process permits an easy and efficient access to oxacyclic ring systems, often occurring in compounds of natural origin such as the *Laurencia* sesquiterpenes (±)-*trans*-kumausyne (**1-1**) [2] and (±)-kumausallene (**1-2**) [3] (Scheme 1.2). For the total synthesis of these compounds, racemic cyclopentane diol *rac*-**1-3** and the aldehyde **1-4** were treated under acidic conditions to give the oxocarbenium ion **1-5**. Once formed, this subsequently underwent a Prins cyclization affording the carbocationic intermediate **1-6** by passing through a chairlike, six-membered transition state. Further interception of carbocation **1-6** by pinacol rearrangement furnished racemic *cis*-hydrobenzofuranone *rac*-**1-7** as the main building block of the natural products **1-1** and **1-2** in 69 % and 71 % yield, respectively.

The Prins/pinacol approach to ring formations is not limited to the assembly of oxacyclic ring systems; indeed, carbocyclic rings can also be easily prepared [4, 5]. A nice variant of this strategy envisages the Lewis acid-induced ring-expanding cyclopentane annulation of the 1-alkenylcycloalkanyl silyl ether **1-8** (Scheme 1.3) [1d]. Under the reaction conditions, the oxenium ion **1-9** produced performed a 6-*endo* Prins cyclization with the tethered alkene moiety, giving cyclic carbocation **1-10**. Gratifyingly, the latter directly underwent a pinacol rearrangement resulting in the



a) *p*TsOH, $MgSO_4$, CH_2Cl_2, 0 °C → r.t., 69%, PG = Bn.
b) BF_3•OEt_2, CH_2Cl_2, –23 °C, 71%, PG = Bz.

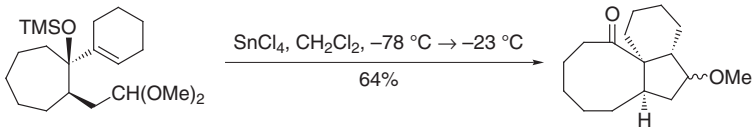
Scheme 1.2. Synthesis of annulated furans for an access to the terpenes kumausyne and kumausallene.



Scheme 1.3. Domino Prins/pinacol rearrangement process.

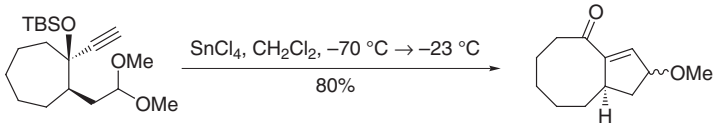
formation of cycloalkanone **1-11**, which correlates to a one-carbon expansion of the substrate **1-8.**

This process allowed, for example, formation of the angulary fused tricycle **1-13** containing a five-, six-, and eight-membered ring from precursor **1-12** in 64 % yield (Scheme 1.4) [1d].



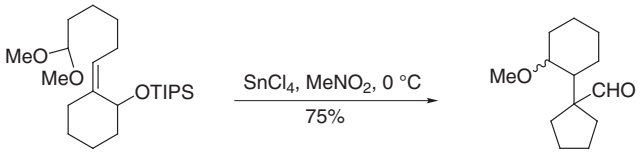
1-12 **1-13**

Scheme 1.4. Synthesis of annulated tricyclic compounds.



1-14 **1-15**

Scheme 1.5. Ring-enlarging cyclopentene annulation.



1-16 **1-17**

Scheme 1.6. Synthesis of cyclopentylcyclohexanes.

In a similar manner, terminal alkynes such as **1-14** participate in a Prins/pinacol reaction, resulting in a ring-expanding cyclopentene annulation to give compounds such as **1-15** in high yield (Scheme 1.5) [5].

The Prins cyclization can also be coupled with a ring-contraction pinacol rearrangement, as illustrated in Scheme 1.6. This allows a smooth conversion of alkylidene-cyclohexane acetal **1-16** to single bond-joined cyclohexane cyclopentane aldehyde **1-17** [1e].

It should be mentioned at this point that the strategy for ring construction is not restricted to being initiated by a Prins cyclization. The first step can also be triggered by preparing allylcarbenium ions from allylic alcohols. One virtue of using this initiator for cationic cyclization is the possibility of installing functionalities in the cyclopentane ring that can be employed readily to elaborate the carbocyclic products. Thus, treatment of precursor **1-18** with triflic anhydride led to a cyclization-rearrangement with concurrent protodesilylation, delivering hydroazulenone **1-19** in formidable 80% yield (Scheme 1.7) [6].

Finally, a carbocyclic ring formation initiated by a keteniminium cyclization is depicted in Scheme 1.8 [6]. In the presence of triflic anhydride and DTBMP, pyrrolidine amide **1-20** was converted into the keteniminium ion **1-22**, traversing inter-