CHEMICAL REVIEWS

REVIEW

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The Vinylogous Aldol and Related Addition Reactions: Ten Years of Progress†

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CONTENTS

1. INTRODUCTION

> *When, in a compound of the type A−E_1=E_2 or A−E_1≡E_2, a structural unit of the type −(RC=CR)$_n$− is interposed between A and E_1 the function of E_2 remains qualitatively unchanged but that of E_1 may be usurped by the carbon atom attached to A.*[1]
>
> Reynold C. Fuson

Rephrasing Fuson's original formulation, the principle of vinylogy explains how the influence of a functional group may be relayed to a distant point in the molecule when these two sites are connected to by conjugated unsaturated linkages, such as double and triple bonds or aromatic moieties.

This principle has been applied, over the years, to the majority of polar carbon−carbon bond-forming reactions of various repute, including the venerable Michael addition reaction, where the electrophilic −**C**=X site (1,2-addition) is "usurped" by a remote conjugated −R**C**=CR−C=X position (1,4-addition) (Scheme 1, eq 1). The aldol addition reaction and the related Mannich process, both fundamental pillars of organic synthesis (Scheme 1, eq 2), have not escaped this fate, and both of their vinylogous extensions have emerged as extremely valuable synthetic methodologies (Scheme 1, eqs 3 and 4).[2−16]

The structural motives arising from reactions involving "vinylogated" donor and/or acceptor components are intrinsically more adorned than their "normal" counterparts, as they embody extended carbon skeletons, additional functionality, and increasing stereochemical complexity. All of these attributes qualify the vinylogous aldol, the vinylogous Mannich, and the vinylogous Michael addition reactions as immensely useful, strategic maneuvers in the art of contemporary organic synthesis.

Since our first comprehensive review in 2000 on the application of the vinylogous aldol and related reactions in organic synthesis,[7] tremendous progress has been achieved in this field. Consultation

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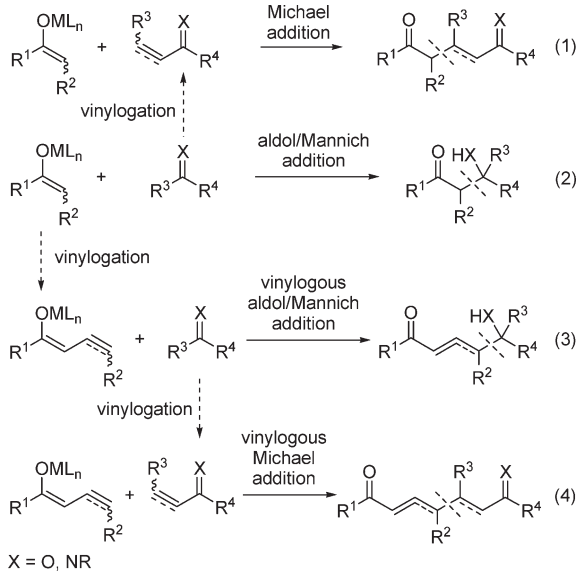
Scheme 1. Showing the Vinylogous Evolution of the Aldol/Mannich/Michael Chemistry



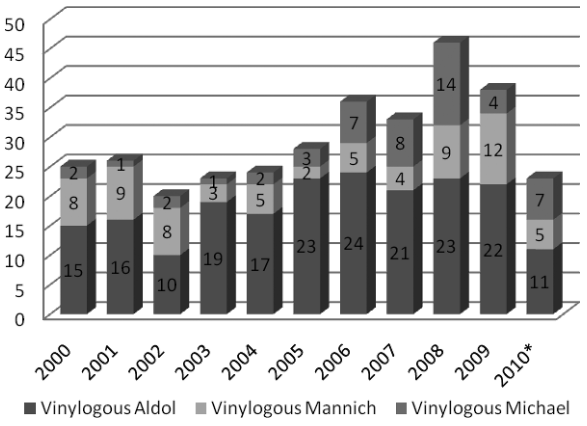


Figure 1. Peer-reviewed research articles published in 2000−2010 (*first quarter): vinylogous aldol vs vinylogous Mannich vs vinylogous Michael reactions.

of leading organic chemistry literature over the past decade testifies and justifies the continual renewal of interest in the vinylogous aldol and related processes that form the theme of this review article. A range of statistical figures offers an overall picture of the state of the art of this research domain and allows the reader to appreciate its thriving evolution. Out of a total of 322 peer-reviewed research articles in the last decennium, 201 were devoted to the aldol reaction, while 70 were centered upon the Mannich reactions and 51 were centered on the Michael reactions. With an increase from 51 in 2000−2001 to 84 in 2008−2009, the number of publications has displayed a constant growth, with a positive progression registered in each field of research (Figure 1).

Over the past decade, the distinction in methodology (diastereoselective vs enantioselective processes) has favored those processes that are highly stereocontrolled, with metal- and nonmetal-based asymmetric catalytic methodologies rising to the ranks of the high-impact research contributions. This growth is expected to continue in 2010, in line with the wave of tendency

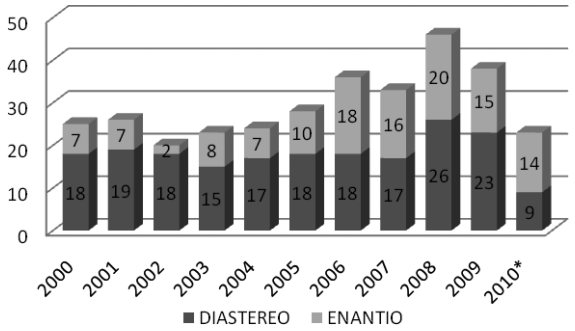


Figure 2. Peer-reviewed research articles published in 2000−2010 (*first quarter): diastereoselective vs enantioselective processes.

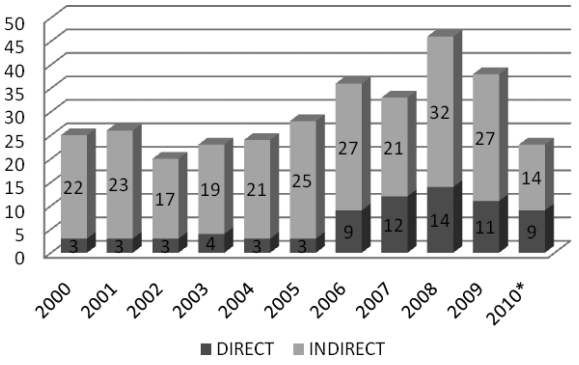


Figure 3. Peer-reviewed research articles published in 2000−2010 (*first quarter): direct vs indirect methodologies.

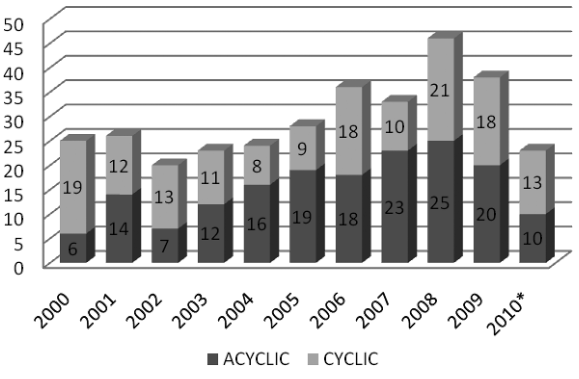


Figure 4. Peer-reviewed research articles published in 2000−2010 (*first quarter): cyclic vs acyclic dienolate donors.

that has steeped the entire ambit of contemporary organic synthesis (Figure 2). On the contrary, studies discussing unselective and racemic procedures, which covered the bulk of pre-2000 research, occupy ever marginal positions and are destined to decline.

Because of brilliant achievements in the last biennium, the direct addition procedures, where the nucleophilic vinylogous reaction components are generated in situ, are able to stand their ground and fully compete with the most traditional and tested indirect procedures based on preformed dienolates. Moreover, this favorable progression is likely to advance further due to operational simplification and overall atom economy of the direct techniques (Figure 3).

A last glance at the statistics shows how works exploring open chain dienolate donors have virtually equal contributions involving alicyclic and heterocyclic dienolates, at least in the

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methodology-oriented papers (Figure 4), even if, in truth, total synthesis practitioners seem to continue to prefer working with linear synthons originating from acyclic diene matrices.

2. ABOUT THIS REVIEW

This review—the sequel to our comprehensive manuscript compiled in *Chemical Reviews* in 2000[7]—summarizes and updates methodology-oriented and target-oriented researches focused on the various aspects of the vinylogous aldol addition reaction (here and hereafter VAR) as well as studies devoted to the related Mannich (VMnR) and Michael (VMcR) processes. The manuscript comprehensively condenses 10 years of research, covering the period 2000−2009, with a 4 month digression in 2010.

The review opens with a first main chapter, which analyzes and confronts studies dedicated to VAR. The chapter is divided in two sections based on the nature of the reaction stereocontrol (unselective and diastereoselective processes vs enantioselective processes), and each section is split further into two subsections summarizing indirect and direct addition procedures. The second main chapter is devoted to VMnR, while the third summarizes VMcR studies. As with the aldol chapter, there are divisions and subdivisions, which mirror the previous choice in organization. For easy comparison, contributions in each section are grouped by similarity, rather than by chronology.

The object of this review is strictly confined to VAR, VMnR, and VMcR addition processes; therefore, eliminative condensation reactions and other nonaldol forming procedures are not exhaustively covered in this review even if vinylogous or potentially vinylogous nucleophilic substrates are involved. This choice led us to exclude a weighty group of works in which the vinylogous diene substrates are destined toward cycloaddition or condensation/cyclocondensation processes.

After our own compilation in 2000,[7] several authoritative reviews, accounts, and commentaries appeared in the literature, partially covering this subject area. These include contributions by Martin devoted to the Mannich reactions[8,9] and Scettri and Soriente,[10] Kalesse,[11,14] and Hosokawa,[13,16] centered upon acyclic dienolate donors. We direct the reader to these works for supporting information on this topic.

3. VINYLOGOUS ALDOL REACTIONS

The VAR represents the vinylogous evolution of the aldol addition reaction, one of the most solid pillars in the art of forming carbon−carbon bonds. Since the pioneering reports by Yoshii,[17] Takei,[18] Ricci,[19] Pelter,[20] Brown,[21] Jefford,[22] and ourselves[23] in the heterocyclic dienolate domain, as well as by Mukaiyama,[24] Chan,[25] and Sato[26] in the acyclic dienolate domain, the VAR process has established itself as a gold standard for the site-selective construction of densely adorned δ-hydroxylated α,β-unsaturated carbonyl compounds and related polyketide networks. Its efficacy is particularly increased by employing prochiral donor and/or acceptor components, where an internal (substrate-controlled) or an external (catalyst-controlled) chiral guidance may orchestrate the stereochemical outcome of the addition process (diastereo- and enantiocontrol).

Both methodology-oriented achievements and target-oriented works of varying complexity are confronted herein, where VAR is the underlying common factor and one of the focal issues in the entire molecule construction. Because of the large body of work devoted to target-oriented VAR (and related VMnR and VMcR), the choice here is to emphasize and comment crucial vinylogous maneuvers, to provide a snapshot, albeit a fleeting image, of the remaining transformations leading to the targeted structures.

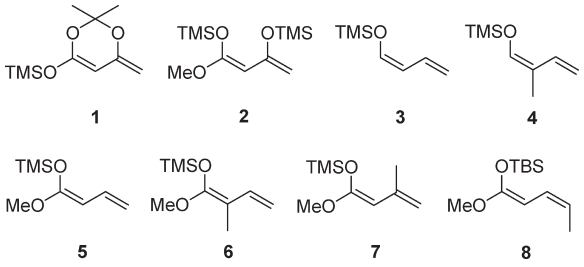
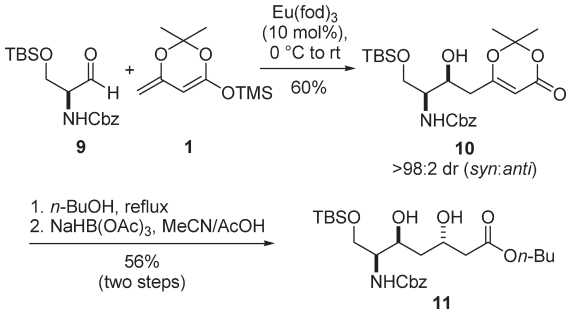


Figure 5. Representative members of the acyclic d_4 silyl butadiene family.

Scheme 2. Synthesis of *N*-(*Z*)-Galantinic Acid Butyl Ester 11[28]



3.1. Diastereoselective and Unselective Processes

In organic synthesis, when a new carbon−carbon bond is created, diastereoselection is often a decisive issue. In principle, with two approaching pro-stereogenic carbons, four stereoisomeric adducts form, the distribution of which strictly depends upon the inherent bias of the complementary coupling components and/or the presence of a pre-existing chiral information within them.

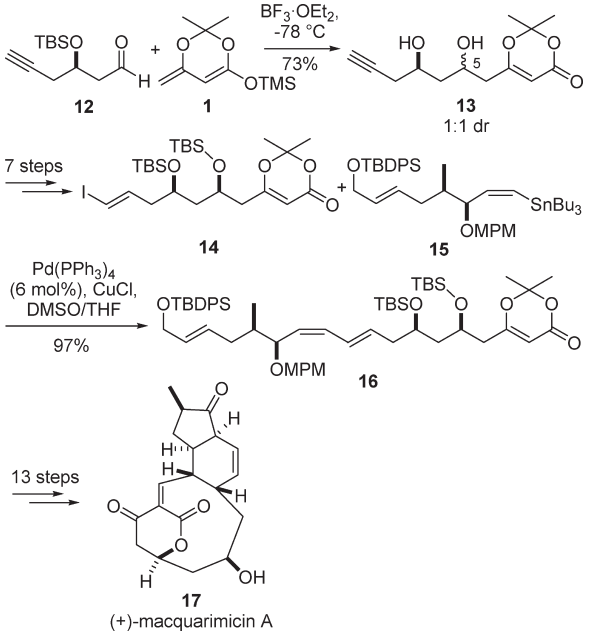
In this section, we will analyze diastereocontrolled VAR processes (simple and/or facial diastereoselection), and only a minor emphasis will be laid on those reactions that evolve in the absence of steric guidance or produce condensation and elimination educts.

For the readers' benefit, indirect and direct methodologies are covered separately. Hence, Mukaiyama type reactions involving preformed silicon-based dienolate synthons are chronicled first (indirect additions), followed by those processes where the vinylogous donor reactant is created in situ according to one-pot/one-step or one-pot/two-step protocols (direct additions).[27]

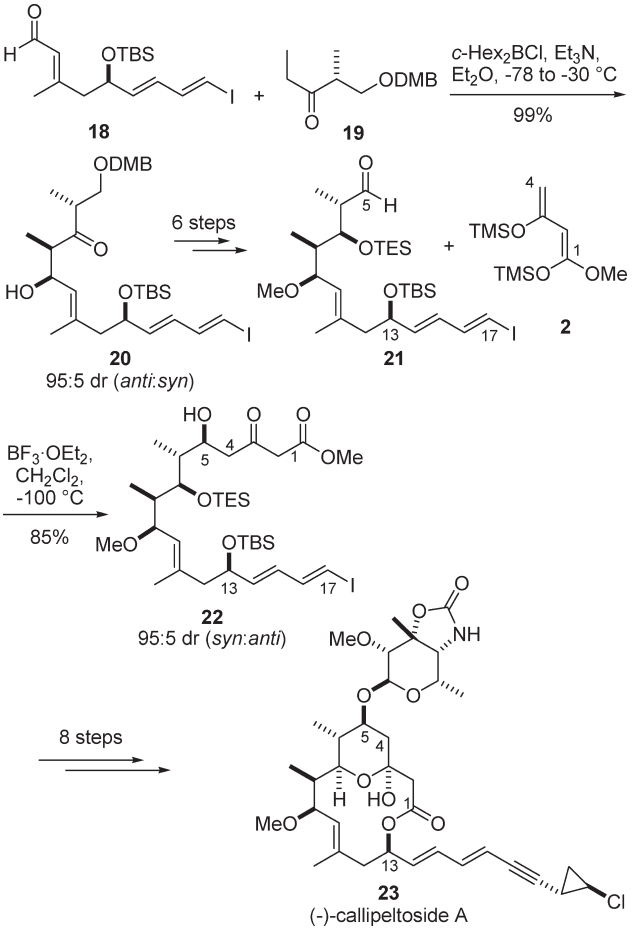
Because of amount of work to be analyzed, a further subdivision has been adopted for reactions involving vinylogous enolates whose diene function may or may not be part of a ring system (acyclic vs cyclic dienolates).

3.1.1. Indirect, Mukaiyama Type Additions of Silicon Dienolates *3.1.1.1. Acyclic Silicon Dienolates.* Open chain, butadiene-based silyl dienol ethers and silyl dienol ketene acetals of type **1**−**8** (Figure 5) cleverly served to implement butenoate

Scheme 3. Total Synthesis of (+)-Macquarimicin A (17)[30,31]



Scheme 4. Total Synthesis of (−)-Callipeltoside A (23)[34]



and acetoacetate fragments into diverse, structurally complex polyketide frameworks and targets via Mukaiyama type VAR protocols (VMAR). Pioneering works utilizing these d_4 nucleophiles during the last quarter of the past century have been reviewed,[10−14] which paved the way for a number of excellent achievements in highly diastereocontrolled total (and partial) syntheses in this millennium first decade.

In designing a short diastereocontrolled synthesis of *N*-(*Z*)-galantinic acid, a key constituent of the potent peptide antibiotic galantin I, Moreau and Campagne[28] exploited dioxinone **1**, which was coupled to serine aldehyde **9** (Scheme 2). The key VMAR proceeded well under $Eu(fod)_3$ catalysis affording *syn*-configured amino alcohol **10** in a 60% isolated yield and >98:2 diastereoselectivity. Finally, **10** was advanced to protected galantinic ester **11** via acetonide deblocking and stereoselective ketone reduction under Evans conditions.

More recently, by exploiting exactly the same chemistry, Gademann et al.[29] constructed stereoisomeric seven carbon long galantinic acid substructures during a biomimetic total synthesis of anachelin H, an iron chelator isolated from the cyanobacterium *Anabaena cylindrica*. As a result, the relative and absolute configuration of the naturally occurring siderophore was firmly established.

The same vinylogous d_4 nucleophile **1** served Tadano and coworkers[30,31] in a multistep total synthesis of natural macquarimicins A−C and certain analogues. The first total synthesis of (+)-macquarimicin A (**17**) is displayed in Scheme 3. The opening key move was a VMAR between dioxinone **1** and chiral nonracemic alkynal **12**, which was in turn accessed from (*R*)-epichloridrin. Under the assistance of $BF_3 \cdot OEt_2$, a 1:1 mixture of diastereoisomers **13** was formed, which was then elaborated to **14** via selective ox-red adjustment of the C5 carbinol chirality.

Optimized Stille coupling between vinyl iodide **14** and (*Z*)-vinylstannane **15** provided the linear 18 carbon long polyene compound **16**, which was manipulated to the final macquarimicin product **17**.

In 1996, Minale and co-workers at Naples University isolated small quantities of callipeltoside A (**23**) from the shallow water sponge *Callipelta* sp.[32] Since this discovery, additional members of callipeltoside family were isolated, all sharing a common aglycon macrolacton moiety. Because of the biological relevance of this substance and its extraordinary structural appeal, numerous synthetic studies toward this natural molecule have been launched, including those recently reported by the Paterson[33,34] and Evans[35] groups, both utilizing the VMAR methodology as a pivotal carbon−carbon bond-forming maneuver. After a preliminary insightful investigation directed to stereodivergent construction of diverse callipeltoside substructures, including the aglycon portion of *ent*-callipeltoside A,[33] Paterson succeeded in completing the construction of (−)-callipeltoside A (**23**), the natural enantiomer of this important compound (Scheme 4).[34]

The opening gambit employed iodide matrix **18**, which was assembled via a catalytic enantioselective VMAR using silyl ketene acetal **7** (to be discussed, Scheme 78, eq 1). Application of boron-mediated *anti*-aldol reaction to (*R*)-configured ethyl ketone **19** produced the elongated adduct **20** in high isolated yield and excellent diastereoselectivity. After ketone reduction, protecting group manipulation, and terminal hydroxyl oxidation, aldehyde **21** was then assembled, which was coupled to Chan ketene acetal **2** under the agency of $BF_3 \cdot OEt_2$ at −100 °C. In the event, polyketide fragment **22** was obtained in 85% yield and

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95:5 dr. Finally, iodide **22** was advanced to the target **23** by a sequence involving, inter alia, a Yamaguchi macrolactonization and a Sonogashira type sp^2-sp cross-coupling. Overall, the entire sequence, including two stereoselective VMAR, encompassed 23 steps for the longest linear sequence, producing **23** in 4.8% overall yield.

To assemble the aglycon portion of **23**, Evans employed two diverse approaches, both utilizing VMAR protocols to elongate suitable chiral nonracemic polypropionate precursors by four carbon atoms.[35,36] According to the improved second-generation approach (Scheme 5), α,β-unsaturated aldehyde **25**—in turn assembled through an enantioselective VMAR coupling using a protected glycolic aldehyde (vide infra, Scheme 80)—was reacted with the boron enolate of β-ketoimide **24** to furnish lactone **26** (86% for three steps) with a good level of diastereoselection (92:8 dr).

Lactone **26**, the C5−C14 portion of the target, was then elaborated to aldehyde **27**, ready for the projected VMAR elongation. Thus, exposure of a mixture of **27** and Chan diene **2** to $BF_3\cdot OEt_2$ in toluene at −90 °C cleanly furnished linear C1−C14 fragment **28** in 88% yield and >20:1 dr. Completion of the synthesis was finally ensured in a convergent manner by sequential connection of the carbohydrate portion and the ene−yne tail. All in all, this improved synthesis of (−)-callipeltoside (**23**) entailed 25 steps for the longest linear sequence, with an acceptable 4% yield. On the basis of the spectral data and optical rotation measurements, this total synthesis confirmed the relative and absolute configuration of the marine macrocycle.

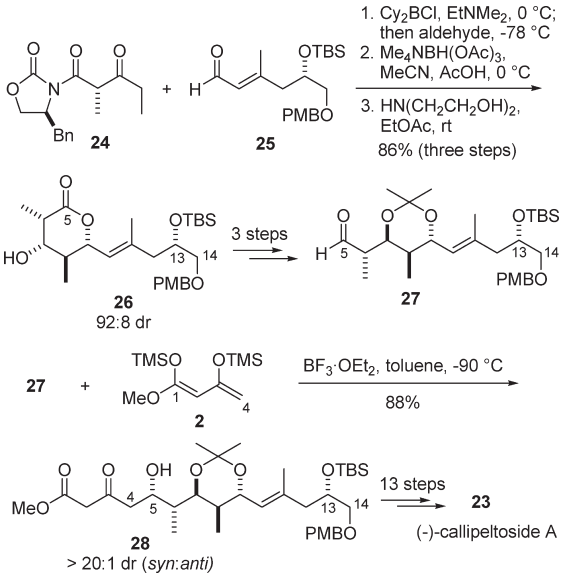
Targeting the macrolide core **33** of (−)-zampanolide (**29**), a structurally intriguing natural product isolated in the Okinawan sponge *Fasciospongia rimosa*, Porco, Jr. et al.[37] planned to start with readily available L-serine methyl ester **30**, utilizing acyclic dienoxy silane **7** (Scheme 6).

The VMAR coupling was efficiently carried out via a three-step, one-pot protocol, where **30** was first reduced in situ to aldehyde **31** according to a racemization-free operation [DIBAL-H and $TiCl_2(Oi\text{-}Pr)_2$ mix]. *syn*-Disposed vinylogous aldol product **32** was thus accessed, with a 16:1 dr (68% yield). Substrate **32** was then advanced to **33** utilizing, as key steps, sequential silyl-modified Sakurai reaction, intermolecular Hoveyda−Grubbs ene−ene metathesis, and a highly optimized sp^2-sp^3 Stille macrocyclization followed by DBU-promoted *exo* to *endo* double bond isomerization. The target macrolide **33** was isolated as a 1:1 mixture of *E*,*Z*- and *E*,*E*-isomers.

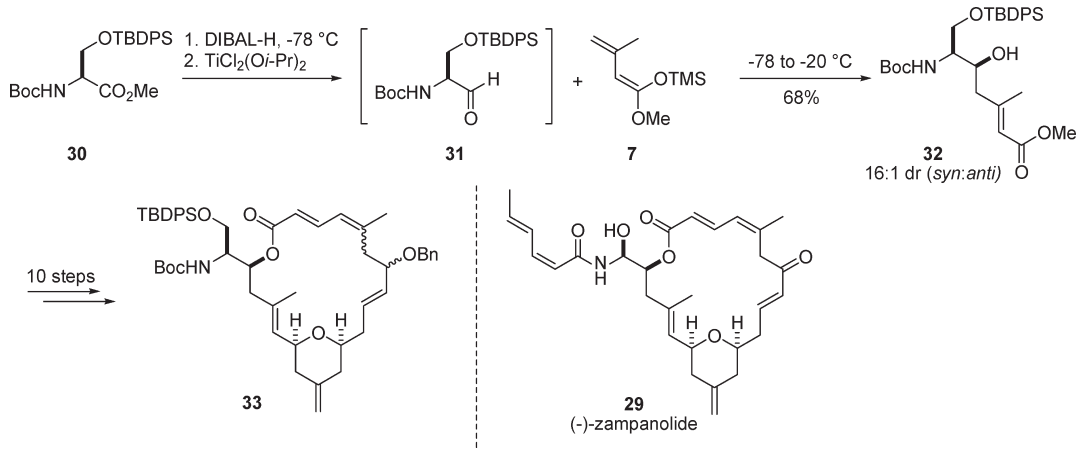
Constanolactones A and B are a class of oxidized fatty acid metabolites, the so-called oxylipins, first isolated from the red alga *Constantinea simplex* in 1990. To assemble these constructs, Pale et al.[38] devised a sequential bilateral functionalization of a central latent chiral cyclopropane dialdehyde by employing d_4 silyl ketene acetal **35** to install the right side portion and vinyl iodide **38** to implement the left side moiety. At first, $ZnCl_2$-mediated VMAR between **35** and cyclopropane aldehyde **34** resulted in the formation of a 3:1 mixture of *anti* and *syn* vinylogous adducts from which the major pure *anti*-isomer **36** was isolated in 50−55% yield (Scheme 7). Simple elaboration conducted to aldehyde lactone **37**, which was coupled to vinyl iodide **38** via the Kishi−Nozaki procedure. This furnished the targeted oxylipins **39** and **40** as an unseparable 1.2:1 mixture of C8-epimers.

Aurilide (**41**) and kulokekahilide-2 (**42**) are cytotoxic marine depsipeptides showing considerable biological interest. Both macrocyclic structures embody a variable peptide portion

Scheme 5. Second Generation Synthesis of (−)-Callipeltoside A (23)[35]



Scheme 6. Synthesis of 33, a Macrocyclic Core of (−)-Zampanolide (29)[37]



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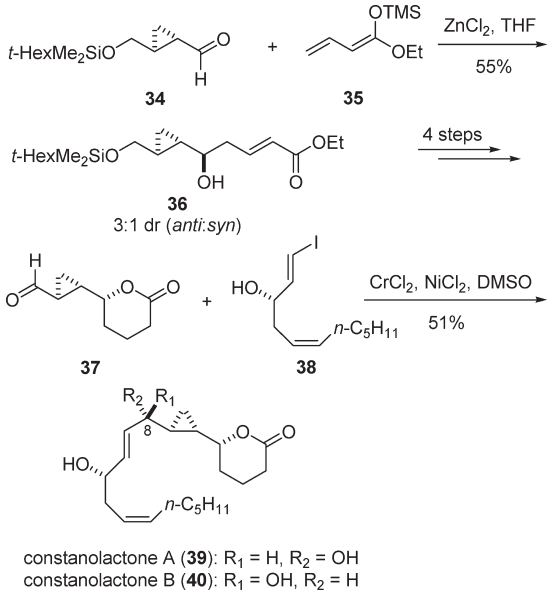
connected to a very similar polyketide subunit. In 2004, Suenaga, Kigoshi, and co-workers[39] and Nakao et al.[40] independently isolated and fully characterized minute quantities of such natural products, unambiguously confirming the structures by synthesis.

Equations 1 and 2 in Scheme 8 highlight the pivotal VMAR maneuvers that ensured the stereocontrolled implementation of the polyketide moieties **44** and **46** within the two metabolites. Both research groups utilized the same chemistry ($BF_3 \cdot OEt_2$) to connect aldehyde fragments **43** or **45** to a common d_4 silyloxy donor, namely, 1-methoxy-2-methyl-1-trimethylsilyloxy-1,3-butadiene (**6**). In truth, Suenaga and Kigoshi completed their journey to aurilide (**41**) (16 steps, 12% global yield), while Nakao terminated the synthesis effort at the polyketide frame stage.

Scheme 7. Total Synthesis of Constanolactones A and B (39 and 40)[38]



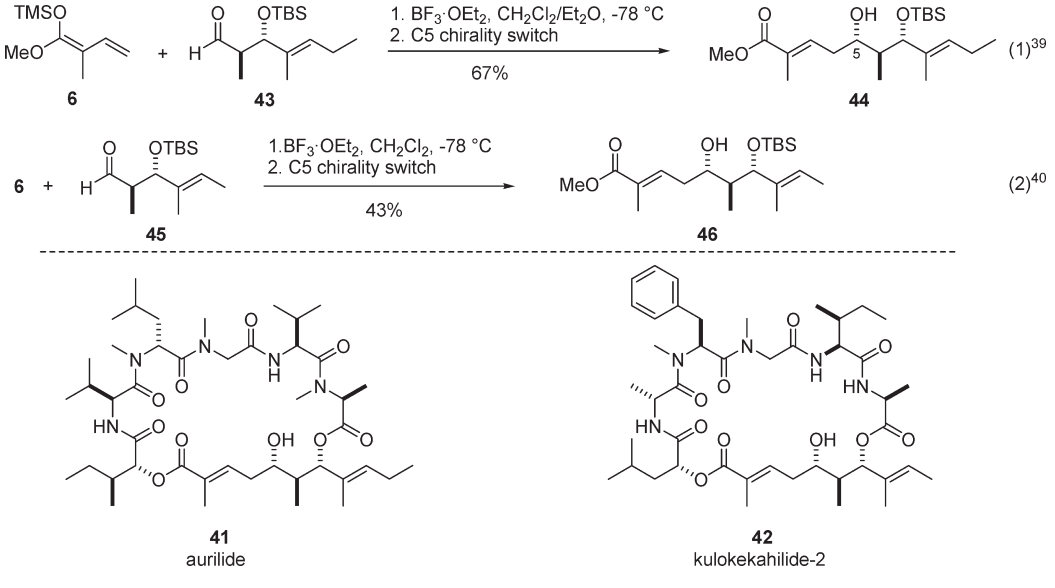
A further couple of cytotoxic natural occurring depsipeptides, Palau'amide (**47**) and cryptophycin-1 (**48**), were targeted by Ma and co-workers[41] and Sewald et al.,[42] respectively, both exploiting VMAR protocols to assemble the proper polyketide precursor skeletons. In the first approach (Scheme 9, eq 1)[41] aldehyde **49**, quickly accessed via the Oppolzer *anti*-aldolization strategy, was coupled to dienol ether **4** ($BF_3 \cdot OEt_2$), providing *syn*-configured enal **50**, which was advanced to the final depsipeptide **47** by a multistep procedure involving conventional peptide chemistry techniques. Unexpectedly, while the synthetic material matched the alleged structure of Palau'amide as proposed by Moore and co-workers,[43] both the rotation value and the NMR data of the synthetic sample did not match the data obtained for the natural product, thus suggesting that the previous assignments for stereochemistry of Palau'amide were improper.

In a recent contribution, Suenaga and co-workers[44] thoroughly reinvestigated the stereostructure of Palau'amide (**47**) by total synthesis, utilizing a VMAR addition as the key step of the entire construction. In the event, the authors synthesized four C37,C38 stereoisomers of the natural product, confirming that stereostructure **47** (37*S*,38*R*) was indeed identical to that of natural Palau'amide.

In a clever approach to a tetracyclic C20 quassinoid intermediate, namely, condensed racemic tetracycle (±)-**56a**, Spino and Perreault[45] utilized a diastereoselective VMAR procedure as one of the key reactions in the overall synthesis plan (Scheme 10).

After a highly productive sequence of three diene-transmissive Diels–Alder cycloadditions, bicyclic aldehyde (±)-**54**, requested for VMAR elongation, was first implemented and then connected to prochiral silyloxy diene **8** under the guidance of the Lewis acid $B(C_6F_5)_3$ following an improved protocol proposed by Kalesse et al. (vide infra). Two *syn*-disposed diastereoisomers eventually formed, (±)-**55a** and (±)-**55b**, which were recovered as an inseparable mixture. After protection of the free hydroxyl as TBS ether, the mixture was heated to 295 °C, which resulted in exclusive formation of two separable tetracyclic cycloadducts (±)-**56a** and (±)-**56b** in 68% combined yield. The tetracyclic

Scheme 8. Chemical Structures of Aurilide (41) and Kulokekahilide-2 (42) and the Key VMAR Producing the South Polyketide Portion of These Metabolites[39,40]



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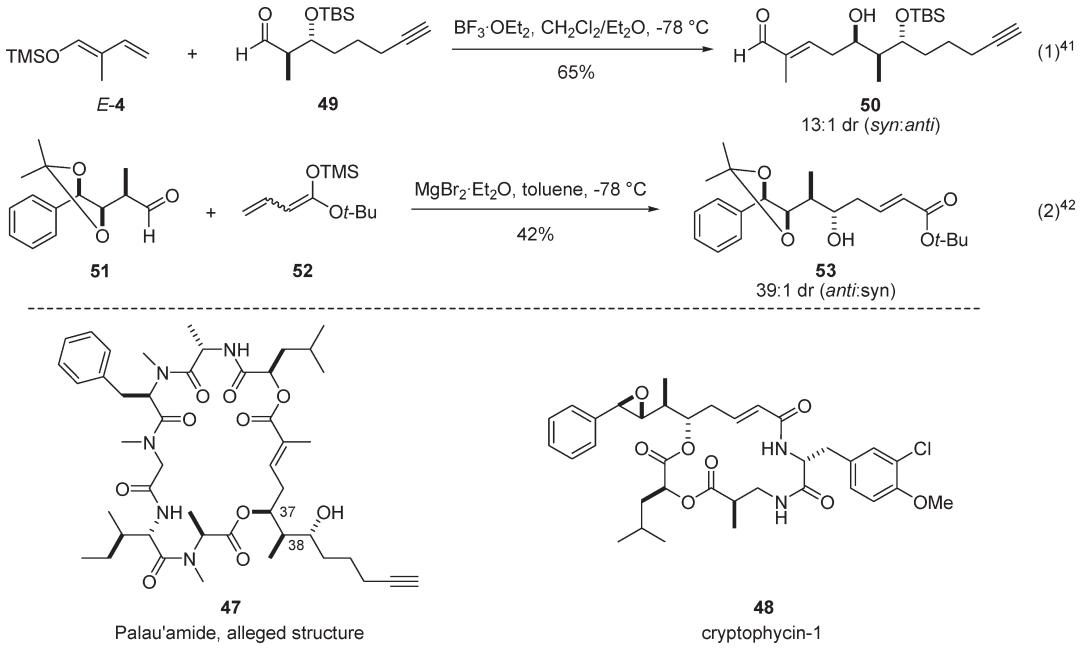
Scheme 9. Chemical Structures of Palau'amide (47) (Alleged Structure) and Cryptophycin-1 (48) and the Key VMAR Producing Polyketide Precursors 50 and 53[41,42]



compound (±)-**56a** so formed indeed contains sufficient chemical complexity around its carbon skeleton to be advanced to a number of naturally occurring quassinoids.

In a preparatory study toward C19 quassinoids, Donahue and Hart[46] envisaged a divergent plan to assemble racemic tricyclic advanced precursors (±)-**61** and (±)-**62** (Scheme 11).

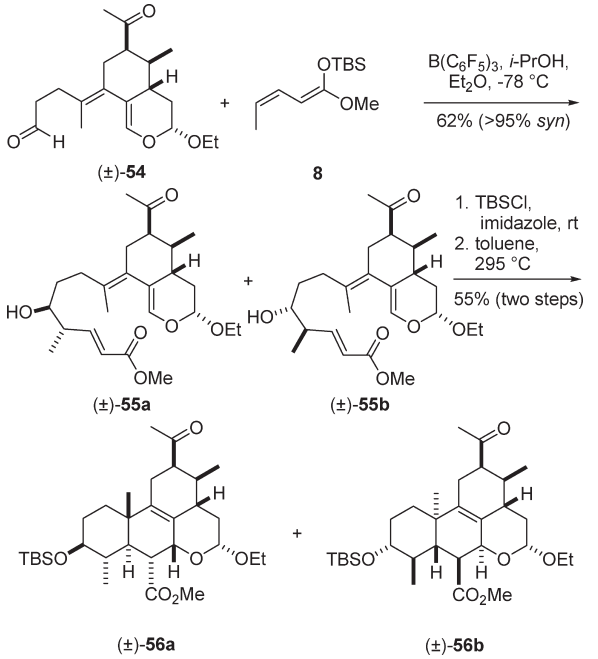
Briefly, the key VMAR between bromoaldehyde (±)-**57** and β-methyl- or β-allyl-substituted silyl ketene acetals **7** or **58** was carried out in the presence of $TiCl_4$ to produce *anti*-configured (with respect to the C8−C14 bond) aldols (±)-**59** and (±)-**60**, preferentially. In this instance, the nature of the chelating Lewis acid and the presence of a bromine atom in (±)-**57** played a central role in governing the observed diastereoselectivity. Tributylstannane/AIBN-promoted radical cyclization then ensured formation of the targeted tricycles (±)-**61** and (±)-**62**.

During 10 years of studies focused on the exploitation of nonracemic polyketide frameworks derived from diastereocontrolled VMAR processes as pivotal building blocks in total synthesis, Kalesse et al.[47−57] built up a judicious body of work that elects VMAR as one of the most powerful and reliable methodologies in polyketide chemistry realm.

In a remarkable contribution,[47,49] the first total synthesis of ratjadone (**66**), a cytotoxic polyketide isolated from *Sorangium cellulosum*, was completed, which featured VMAR as the crucial maneuver in implementing the pyran substructure of the target (Scheme 12).

The opening stratagem was the construction of chiral aldehyde **64** via Evans *syn*-aldolization methodology. Next, an optimized VMAR was conducted[50] between dienolate **63** and aldehyde **64** in the presence of substoichiometric quantities of commercially available (hydrated, vide infra) $B(C_6F_5)_3$ (TPPB) in a 9:1 CH_2Cl_2/Et_2O solvent mixture, to produce all-*syn* silylated aldol **65** in 80% yield and with more than 19:1 dr. Interestingly, under such conditions, complete TBS group transfer to the hydroxyl

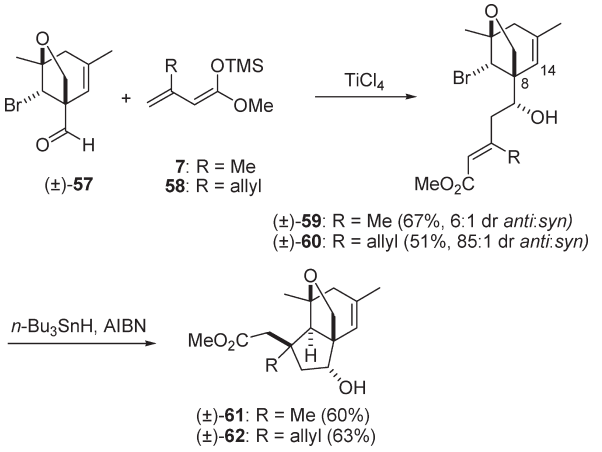
Scheme 10. *syn*-Selective VMAR Protocol in a Convergent, Racemic Synthesis of C20 Quassinoids Intermediates 56a,b[45]



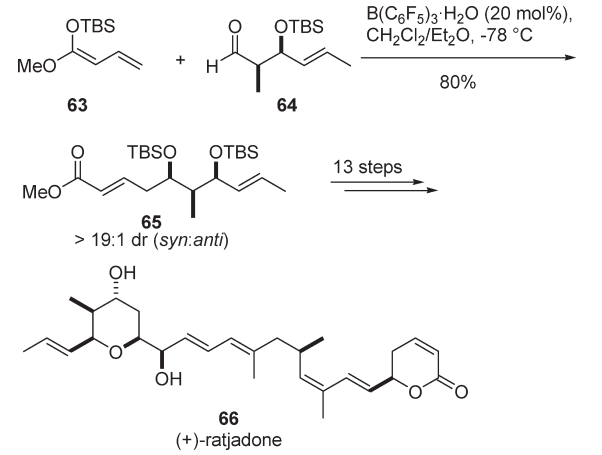
function of the aldol occurred, thus rendering subsequent hydroxyl protection unnecessary. At this point, 10 carbon long intermediate **65** was elaborated into the final ratjadone structure by a sequence of 13 steps.

In continuing efforts toward improvement of the VMAR methodology, Kalesse and co-workers[48] showed how both regioselectivity (γ vs α attack) and diastereoselectivity (*syn* vs

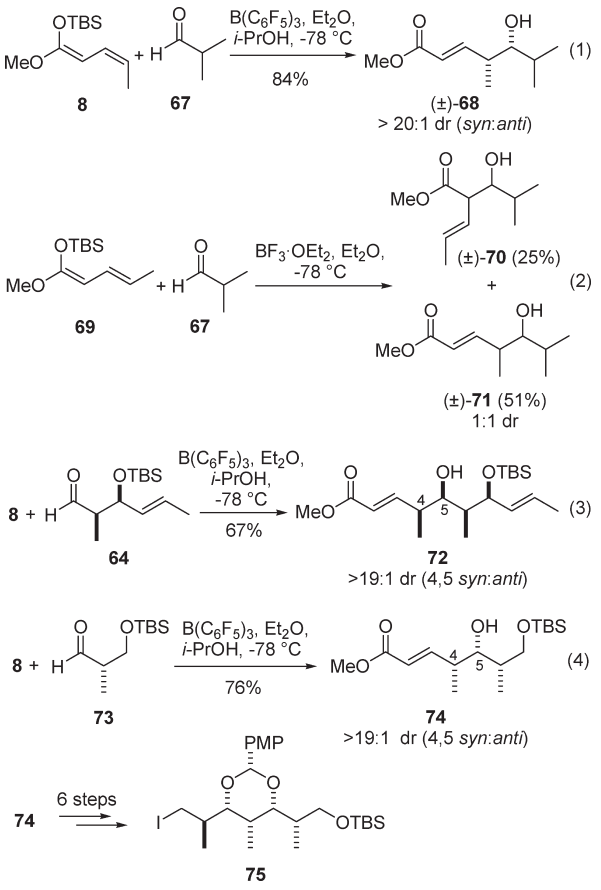
Scheme 11. Diastereoselective VMAR Leading to C19 Quassinoid Precursors (±)-61 and (±)-62[46]



Scheme 12. Total Synthesis of (+)-Ratjadone (66) Featuring a Diastereoselective VMAR[47,49]



Scheme 13. Diastereoselective VMAR Procedures Using Achiral and Chiral Aldehydes and Application in the Synthesis of the C1−C7 Fragment 75 of Oleandolide by Kalesse[48,51]



anti aldols) could be deeply affected by the geometry of the dienolate component, as well as the solvent/cosolvent combination. Indeed, reaction of (*Z*)-configured ketene acetal **8** (3,4-*Z*:*E* > 20:1) with isobutyraldehyde (**67**) in the presence of TPPB, Et_2O, and *i*-propanol resulted in almost exclusive formation of *syn*-configured vinylogous aldol (±)-**68** with a >20:1 dr and <1% α-aldol adduct (Scheme 13, eq 1). On the other hand, use of isomeric (*E*)-configured dienolate **69** (3,4-*Z*:*E* < 1:20) produced either no reaction (with TPPB) or a 1:2 mixture of α- and γ-aldol products (±)-**70** and (±)-**71** when $BF_3 \cdot OEt_2$ was employed (no diastereoselectivity observed).

The use of isopropyl alcohol proved to be necessary to overcome the undesired activation of the electrophile by cationic silicon species; in fact, when a silicon-involving catalytic pathway is operative (with silylated aldol products mainly formed), a dramatic drop in diastereoselection was generally observed. To evaluate the stereoinduction by neighboring asymmetric centers, a series of chiral nonracemic aldehydes were reacted with ketene acetal **8** (e.g., **64** and **73** in eqs 3 and 4) under the previously optimized VMAR conditions. In these instances, all-*syn* vinylogous aldol products **72** and **74** were obtained in good yields and with high facial Felkin type diastereocontrol.

The efficiency of such VMAR procedure was then cleverly demonstrated by the same authors during the asymmetric synthesis of the C1−C7 fragment **75** of oleandolide, the polyketide portion of macrolide antibiotic oleandomycin (eq 4).[51]

Tedanolide (**81**) is a highly cytotoxic marine natural product, whose challenging 18-membered polyketide macrolactone architecture committed Kalesse's group during a 5 year endeavor aimed at the asymmetric total synthesis of useful quantities of tedanolide itself and altered analogues thereof.[52−54] Retrosynthetic analysis revealed that the C1−C12 hemisphere of the target could be accessed by VMAR using the usual ketene acetal **8** and chiral nonracemic polyketide aldehyde **76** (Scheme 14). Thus, aldehyde **76** was first synthesized via three sequential carbon−carbon bond-forming reactions—namely, crotylboration, Wittig olefination, and Evans aldolization—which was then reacted with **8** in the presence of hydrated TPPB and *i*-PrOH. Interestingly, it was found that it was not the TPPB itself, but rather a hydrated species present in most commercially available sources, which actually acted as the Lewis acid. The *syn* vinylogous aldol product **77** formed in a good 91% isolated yield and with >20:1 dr. Routine chemistry

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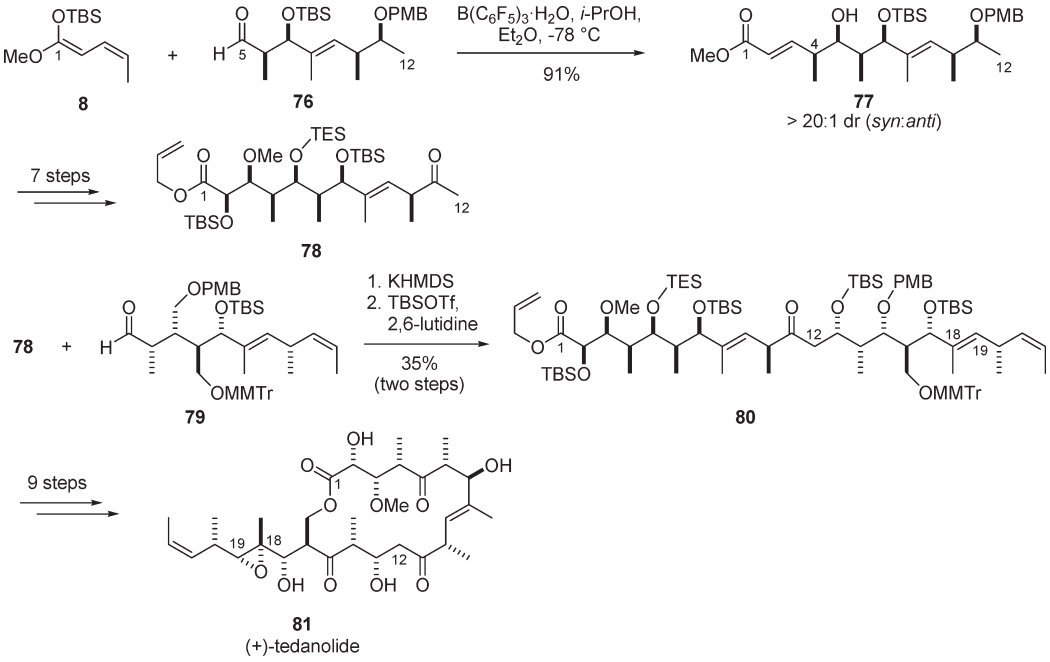
Scheme 14. Total Synthesis of (+)-Tedanolide (81) Featuring a Diastereoselective VMAR[52−54]

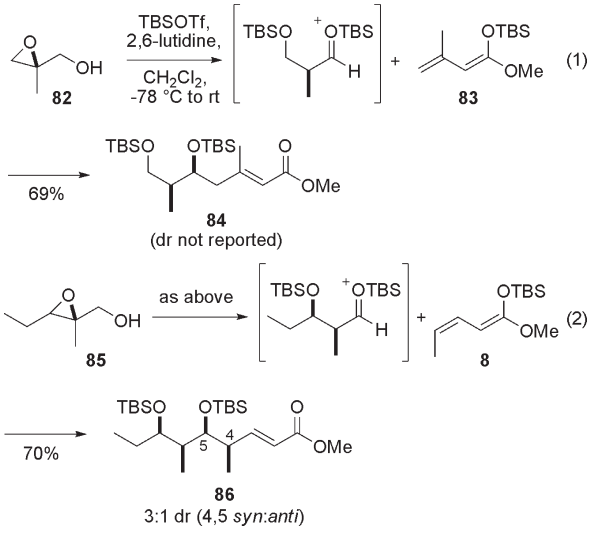


transformed **77** into linear polyketide **78**, ready for aldol coupling with aldehyde **79**. The Felkin type aldol product **80** thus obtained was finally elaborated into the targeted tedanolide (**81**) via, inter alia, Mitsunobu type macrolactonization and Δ^{18} allylic alcohol epoxidation.

A catalytic version of the TPPB·H_2O-promoted acyclic VMAR was exploited by Kalesse et al.[55,56] during the asymmetric synthesis of the northern hemisphere of amphidinolide H2 (not shown). In that case, extended enolate **8** coupled to 2,3-*O*-isopropylidene-L-glyceraldehyde in the presence of 0.7 mol equiv *i*-PrOH and as little as 1 mol % of hydrated tris(pentafluorophenyl)borane giving the expected *syn*-Felkin vinylogous aldol product in a respectable 61% yield and excellent diastereoselectivity (14:1:1 dr).

A remarkable one-pot nonaldol−aldol VMAR protocol was utilized by Kalesse and Rahn[57] to assemble various polyketide segments by starting with chiral nonracemic epoxy alcohols **82** and **85** (masked forms of β-hydroxy aldehyde species). Thus, as shown in Scheme 15, addition of methyl-substituted dienolates **83** and **8** to in situ-generated aldehyde acceptors derived from epoxides **82** and **85** provided polyketide fragments **84** and **86**, respectively, with a good preference for all-*syn* aldol products.

Scheme 15. One-Pot Nonaldol−Aldol VMAR[57]



In aldol chemistry, substrate control via chirality transfer from a chiral auxiliary has been emerging over the years as a viable complement to the so-called chironic approach, where chirality propagates from the inherent chirality of the substrate. This concept translated well to the VMAR domain by equipping acyclic dienolates with proper chiral auxiliaries such as, for example, the popular Evans' oxazolidinone moieties.

Along these lines, Kobayashi and co-workers introduced a series of acyclic vinyl ketene silyl *N*,*O*-acetals of type **87** as chiral d_4 donor substrates in VMAR processes.[58−63] At first,[58] aldolization reactions were analyzed using differently substituted vinyl ketene acetals **87**, **92**, and **94**, which were coupled to a panel of aliphatic and aromatic aldehydes (Scheme 16). Choosing the reaction between L-valine-derived α-methyl-substituted acetal **87** and hexanal (**88**) as a model example, it was found that $TiCl_4$ was the most effective promoter in terms of both yield and stereoselectivity (eq 1). Indeed, the reaction took place at the γ-position solely, affording δ-hydroxy-α-methyl-α,β-unsaturated imide **89** in 97% yield and 42:1 diastereoselectivity. Chirality transfer from the auxiliary to the newly formed stereogenic carbon is remarkable and represents a rare example of remote 1,7-asymmetric induction in an acyclic carbon−carbon bond-forming reaction. Benzaldehyde (**90**) reacted equally well,

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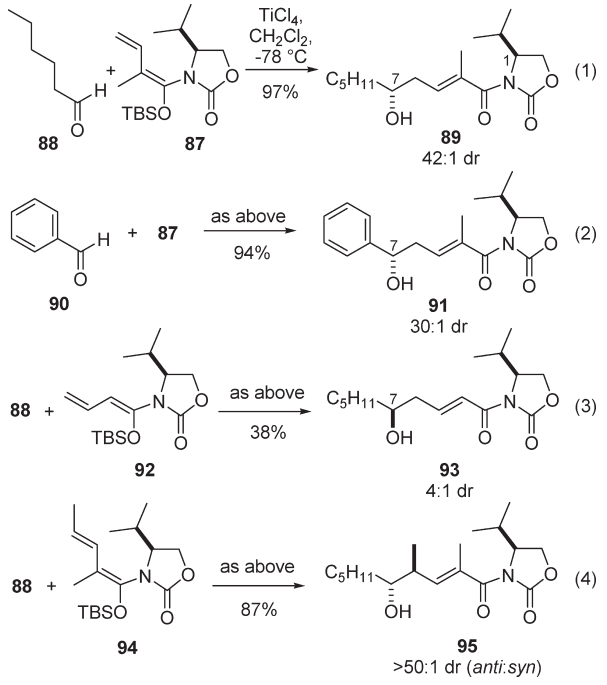
Scheme 16. VMAR Additions with Chiral Vinylketene Silyl *N,O*-Acetals 87, 92, and 94[58]



providing compound **91** in 94% yield and 30:1 diastereoselectivity (eq 2). On the contrary, VMAR involving *Z*-disposed unsubstituted silyl ketene acetal **92** (eq 3) gave rise to unsaturated lactam **93**, predominantly (4:1 dr), having an absolute configuration at C7 carbon opposite to that of compounds **89** and **91**. Furthermore, when chiral prochiral ketene acetal **94** was employed (eq 4), reaction with hexanal (**88**) gave the *anti*-aldol adduct **95** in high isolated yield, as an almost single *anti*-stereoisomer.

Indeed, the α-methyl group in such vinyl ketene *N,O*-acetals proved to be crucial in achieving high levels of stereoselectivity in these VMAR processes. Careful in-solution investigations[58] and solid-state X-ray crystallography[59] of substituted and unsubstituted silyloxy dienes **87**, **92**, and **94** proved decisive in establishing their actual configurational and conformational arrangements, as shown in Figure 6.

In the proposed transition state A, with compounds of type **87** (R = H) and **94** (R = Me), the auxiliary ring is almost perpendicular to the diene plane, and the L-valine isopropyl group blocks the upper face of the donor. Because of restricted rotation of the oxazolidinone moiety by the enolate TBS group, an axial chirality generates between the diene plane and the auxiliary ring. This arrangement would likely force the incoming aldehyde to approach the less hindered face of the nucleophile from the bottom. In this model, the aldehyde carbonyl is located antiperiplanar with respect to the diene (R′-*exo*) and liberates its Si face, giving rise to aldols **89** or **91** that possess the same C7 hydroxyl location (7*R* for **89** and 7*S* for **91**). With chiral prochiral diene **94** (R = Me), this favorable arrangement translates into an almost exclusive formation of (6*S*,7*R*)-configured *anti*-stereoisomer **95**. Conversely, the α-Me-free diene **92** was assumed to possess a *trans* relationship between the terminal olefin and the chiral auxiliary, and the much lower diastereoselectivity observed

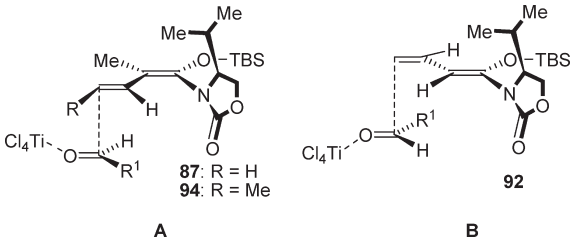


Figure 6. Proposed transition state models for the $TiCl_4$-promoted VMAR involving α-methyl vinyl ketene *N,O*-acetals (A) or unsubstituted vinyl ketene *N,O*-acetals (B).[58]

using this diene (Scheme 16, eq 3), giving aldol **93**, is possibly due to the longer distance between the stereogenic center of the valine auxiliary and the terminal olefinic γ-carbon (transition state B, Figure 6). Interestingly, the absolute configuration of the C7 in the adduct **93** was opposite to that of **89** (Scheme 16, eq 1 vs eq 3).

The viability and stereochemical predictability of this auxiliary-driven diastereoselective VMAR technique, pioneered by the Kobayashi group, paved the way to a general exploitation in asymmetric synthesis, as highlighted in the several publications hereafter analyzed and condensed.

Exactly the same chemistry was exploited during the total synthesis of both enantiomers of convolutamydines E and B **98** and **99** where *N,O*-silyl ketene acetals **87** and *ent*-**87** reacted in parallel with dibromoisatin **96** (Scheme 17).[60] With both enantiomers of **98** in hand, determination of the absolute configuration of the natural products was unambiguously established.

Aiming at construction of the AB ring moiety of fomitellic acids of type **100**, potent inhibitors of calf DNA polymerase and human DNA topoisomerases, the same research group extended the utility of auxiliary-driven VMAR by using prochiral aldehyde **101** as the starting substrate (Scheme 18).[61] At the outset, VMAR between D-valine-derived *ent*-**87** and enal **101** was examined under the standard conditions previously established ($TiCl_4$ in CH_2Cl_2, −50 °C). In this instance, however, poor yields of the expected vinylogous aldol were attained. After thorough optimization, the authors found that by adding a catalytic amount of water (10 mol %), the reaction proceeded quite efficiently in a reproducible manner using toluene as the solvent. Thus, with useful quantities of chiral material **102** at hand, the synthesis was advanced to fomitellic acid AB ring subunit **103** by auxiliary removal and Ti(III)-mediated radical cascade cyclization. In a subsequent paper,[62] Kobayashi attempted to rationalize the unexpected effect of water addition during the $TiCl_4$-mediated VMAR, suggesting that, although the exact role of catalytic water remains unclear, two scenarios could be operative: (1) water might coordinate to $TiCl_4$, resulting in partial dissociation of $TiCl_4$ aggregates, or (2) both the proton and the $TiCl_4$ of a $TiCl_4 \cdot H_2O$ complex may coordinate to the aldehyde carbonyl, resulting in double activation, according to the Brønsted acid-assisted Lewis acid acceleration principle.

A convergent total synthesis of the antifungal agent khafrefungin (**112**) was devised by Kobayashi et al.,[63] exploiting two highly diastereoselective homologative VMAR to implement the polypropionate *seco*-acid segment of the natural product. As illustrated in Scheme 19, the opening move was the VMAR between chiral/prochiral aldehyde **104** and L-valine-based

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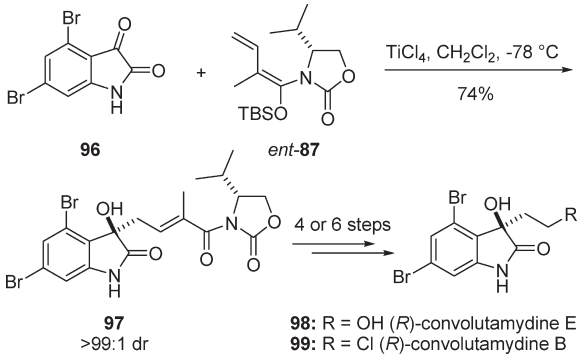
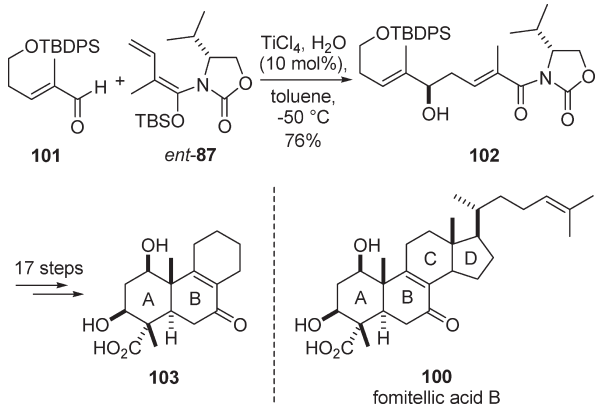
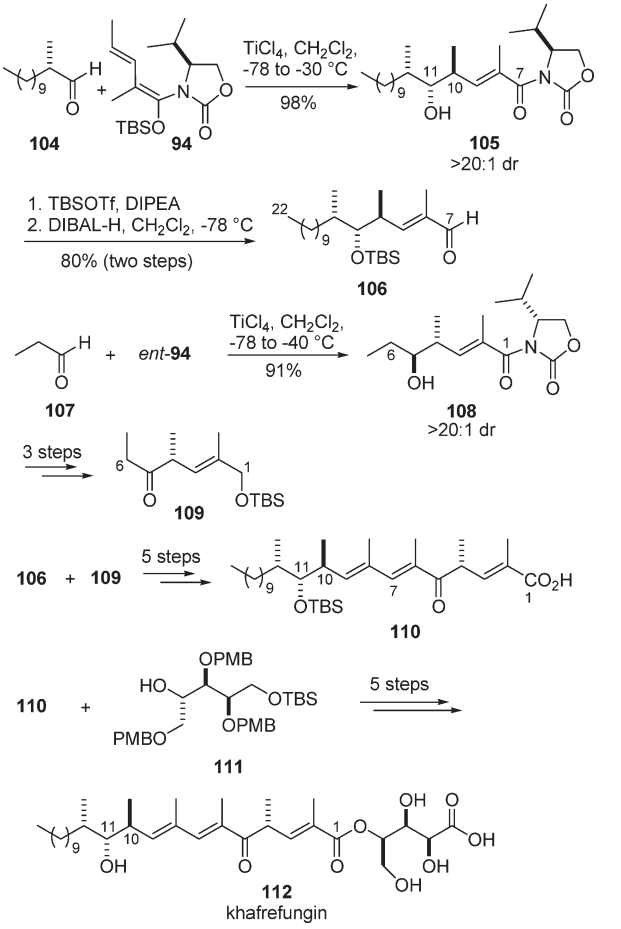
Scheme 17. Diastereoselective Synthesis of (*R*)-Convolutamydines E and B (98 and 99)[60]



Scheme 18. Auxiliary-Driven VMAR Leading to the AB Ring Subunit 103 of Fomitellic Acids[61]



Scheme 19. Convergent Auxiliary-Driven Total Synthesis of Khafrefungin (112)[63]



chiral/prochiral silyl *N*,*O*-acetal **94**. Under standard conditions ($TiCl_4$, CH_2Cl_2), the reaction proceeded in the matched manifold, affording the corresponding C10−C11 *anti*-aldol **105** (target numbering) in 98% yield, with a remarkable >20:1 diastereoselectivity. Then, auxiliary removal and protecting group manipulation converted **105** to aldehyde **106**, the C7−C22 fragment of the target. In a parallel fashion, VMAR homologation of propanal (**107**) with the enantiomer of **94** provided aldol **108**, which was soon elaborated to complementary C1−C6 ketone fragment **109**, ready for the final fragment assembly. Thus, aldol coupling between **106** and **109** proceeded uneventfully, giving rise to *seco*-acid **110**, which was esterified with L-xylose-derived alcohol **111**, providing khafrefungin (**112**) in synthetically useful yields (23% overall yield along 14 steps for the longest linear sequence from **107**).

To demonstrate the practicality and versatility of the chiral auxiliary-governed VMAR using silyl ketene *N*,*O*-acetals, Kobayashi explored in detail the potential of the reaction with regards to the aldehyde substrates (Scheme 20, eqs 1−5).[64] Initially, the remote asymmetric induction during VMAR between *E*,*E*-configured acetal **94** and nonheterosubstituted aldehyde **113** was investigated (eq 1; $TiCl_4$, CH_2Cl_2). Good yields of the expected vinylogous aldol **114** were obtained with a marked preference for the *anti*-configured isomer. Conversely (eq 2), an almost complete switch to *syn*-selectivity was witnessed with α-heteroatom-substituted aldehydes of type **115**, giving rise to *syn*-configured adduct **116**. Turning to nonracemic aldehyde substrates, it was shown that (2*R*)-α-methyldodecanal *ent*-**104** (eq 3) gave rise to 4,5-*anti*-5,6-*anti*-disposed isomer **117** with (4*S*,5*R*) absolute configuration. When using (2*R*)-α-silyloxy-substituted aldehyde **118** (eq 4), reversal of facial diastereoselectivity was attained, producing 4,5-*syn*-5,6-*syn*-adduct **119** with a (4*S*,5*R*) absolute configuration. Importantly, extension of the reaction to (2*S*)-α-silyloxy aldehyde *ent*-**118** resulted in preferential formation of 4,5-*syn*-5,6-*anti*-configured adduct **120**, possessing the same (4*S*,5*R*) absolute configuration (eq 5). This result shows that while the *syn*-stereochemistry would be dictated by the relative location of the two reactants in the transition state, the absolute stereocontrol at the 4,5-carbon sites would mainly depend on the chirality resident in the L-valine auxiliary, not the aldehyde chirality.

The above disclosed reliable auxiliary-driven VMAR methodology introduced and developed by the Kobayashi group was admirably utilized by several authors to target biologically relevant natural occurring compounds. This chemistry, for example, was independently exploited by Lipshutz[65] and Hosokawa and Tatsuta,[66] targeting piericidin A1 (**123**) and actinopyrone A (**124**), respectively (Scheme 21). In particular, both authors focused on preparation of intermediary polypropionate *anti*-aldol **122**, which was accessed via $TiCl_4$-promoted VMAR between ketene acetal *ent*-**94** and tiglic aldehyde **121**.

Again, the Hosokawa and Tatsuta group succeeded in synthesizing agents benzopyrenomycin (**127**)[67] and trichostatin D (**130**)[59] by

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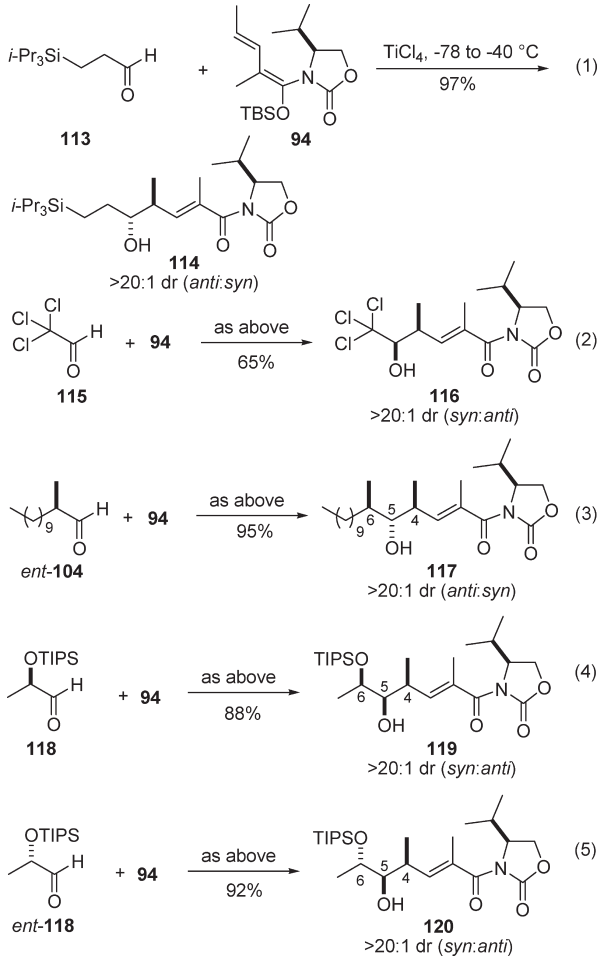
Scheme 20. Diastereoselective VMAR of (*S*)-Valine-Based Vinylketene Acetal 94 with Various Achiral and Chiral Aldehydes[64]

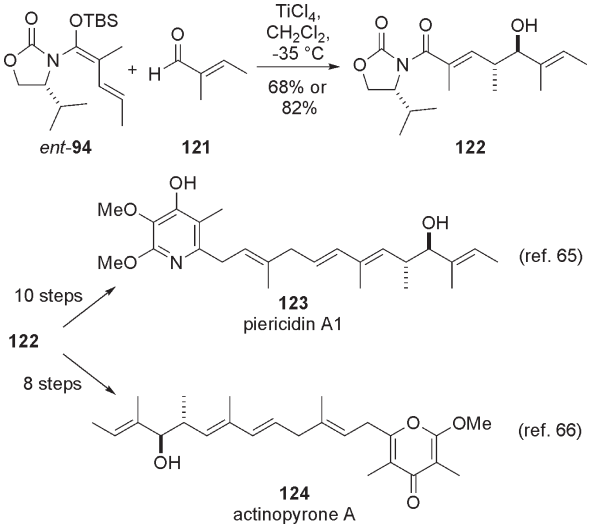


employing VMAR involving *ent*-**94** and suitable aromatic aldehydes **125** and **128** (Scheme 22). In the first instance, $BF_3 \cdot OEt_2$ in CH_2Cl_2 was the promoter of choice, while in the latter case, $TiCl_4$ in CH_2Cl_2 was used. Interestingly, while the reaction involving condensed tetracyclic aldehyde **125** predominantly gave rise to *syn*-configured adduct **126**, VMAR utilizing *p*-bromobenzaldehyde (**128**) produced the expected *anti*-configured vinylogous aldol **129** (96:4:<1:<1 dr). Because chirality of the auxiliary in the nucleophile was the same and the stereoselection issue was not dependent upon the Lewis acid employed, it was probably the nature of the aromatic aldehyde that made the difference.

This elegant chemistry was further implemented by Maier and co-workers[68] to elaborate various stereoisomeric fragments of chondramides to delineate their definite stereostructures. Scheme 23 (eq 1) illustrates, as an example, the key VMAR maneuver between L-valine-based dienolate **94** and acetaldehyde (**131**) ($TiCl_4$, CH_2Cl_2). The resulting *anti*-aldol **132**—the exclusive VMAR product—was then manipulated to **133** via a further elongation using the "normal" Evans aldol chemistry.

In a study directed to the formal total synthesis of *N*-methylmaysenine, the 19-membered macrolide **137** was targeted (Scheme 23, eq 2).[69] After preliminary work intended to profile the conditions to improve the diastereoselectivity of the crucial VMAR addition, it was

Scheme 21. Total Syntheses of Piericidin A1 (123)[65] **and Actinopyrone A (124)**[66]



found that treatment of L-Phe-derived *N*,*O*-acetal **135** with masked malondialdehyde **134** in the presence of 1 mol equiv $TiCl_4$ at ambient temperature resulted in formation of majorly *syn*-disposed adduct **136** in 79% yield, albeit in moderate 3.5:1 diastereoselectivity. A multistep sequence including a highly productive ene−ene RCM macrocyclization then afforded macrolactam **137**, the targeted precursor in the 1980 Corey total synthesis of *N*-methylmaysenine.[70]

The unique natural product palmerolide A (**138**), a polyketide metabolite, was first isolated from the antarctic marine tunicate *Synoicum adareanum* in 2006.[71] The structure and absolute stereochemistry of **138** were finally solved by two independent total syntheses by De Brabander et al.[72] and Nicolaou and Chen[73,74] in 2007−2008. According to the Kobayashi protocol, both research groups initiated their journey with a very similar opening move, a VMAR between vinyl iodide aldehyde **139** and D-Val- (De Brabander) or D-Phe-derived (Nicolaou) silyl ketene *N*,*O*-acetals *ent*-**94** or *ent*-**135** (Scheme 24). In both events, very good yields and excellent levels of diastereoselectivity were attained using $TiCl_4$ as the Lewis acid promoter. It is worth noting that both VMAR led to C19−C20 *anti*-stereoisomers (palmerolide numbering) while the final target required a C19−C20 *syn*-geometry. Therefore, both authors had to face reversal in the stereochemistry of C19 to *syn*-isomers, prior to completing their goal. The two approaches relied on highly stereodivergent planning, and this stereodivergence allowed the researchers to access diverse palmerolide A stereoisomers, thus permitting firm revision of the originally proposed structure of palmerolide A.

A few research articles utilizing acyclic silyl dienolates of type **1** and **2** in nonstereoselective and/or racemic processes appeared in the literature, including simple VMAR addition processes and multicomponent cascade procedures. As an example, Clarke and Martin investigated the VMAR between Chan diene **2** and arylpropanal **142**, giving rise to pyrane intermediate **143**, a key fragment in the total synthesis of (±)-centrolobine (Scheme 25, eq 1)[75,76] The same diene **2** was also exploited by Scettri et al. in a $SiCl_4$-catalyzed VMAR with diverse aromatic, heteroaromatic, and α,β-unsaturated aldehydes.[77]

A couple of examples are given in Scheme 25 (eqs 2 and 3). Interestingly, while reaction involving aromatic and heteroaromatic

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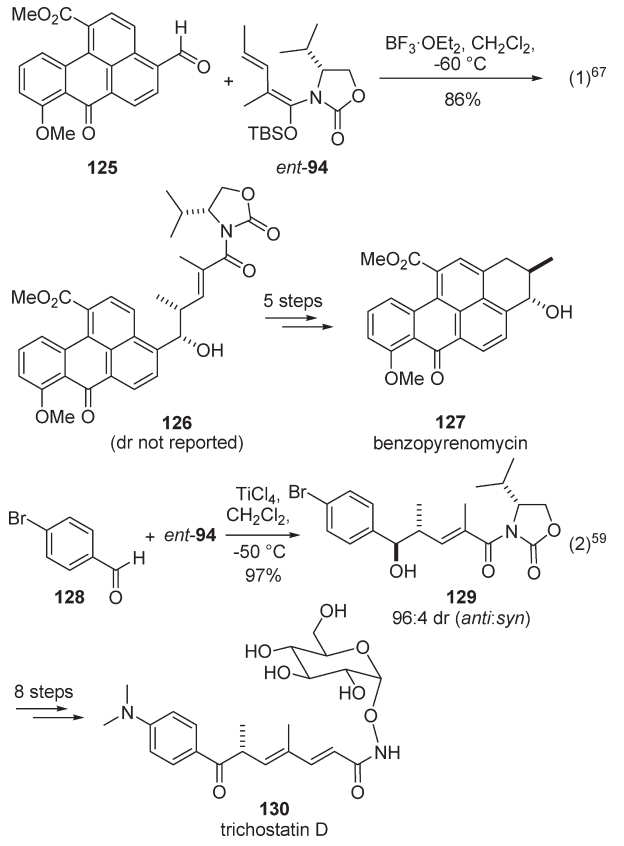
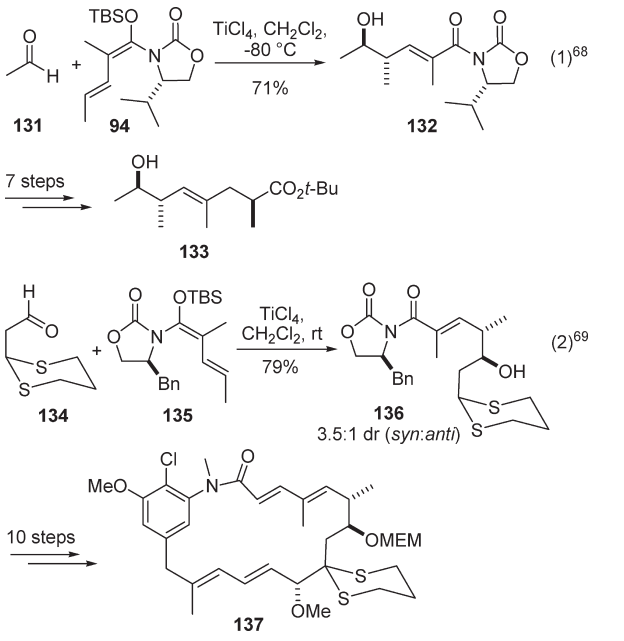
Scheme 22. Total Syntheses of Benzopyrenomycin (127)[67] and Trichostatin D (130)[59]



Scheme 23. Auxiliary-Driven VMAR to Intermediary Compounds 133[68] and 137[69]



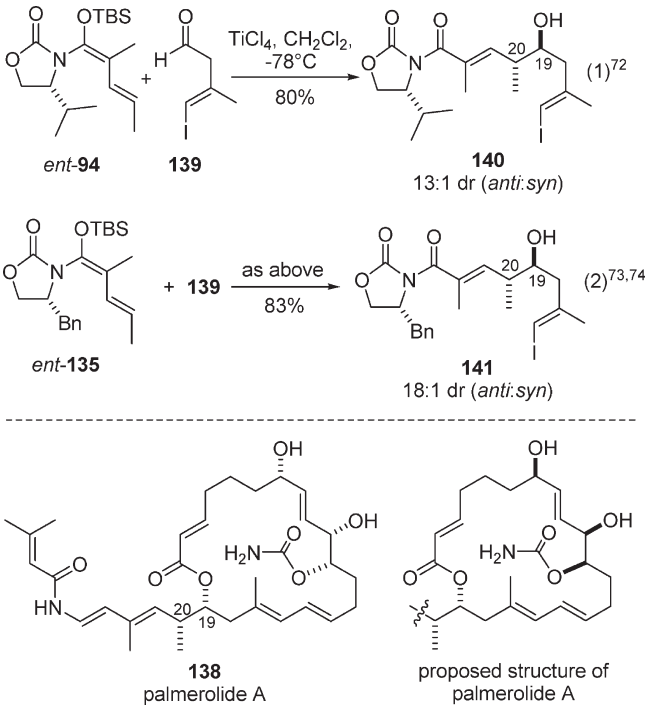
aldehydes performed well (e.g., eq 2), only scarce amounts of vinylogous aldol adducts formed with aliphatic aldehydes (eq 3), emphasizing once more the reluctant reactivity of aliphatic substrates in these VMAR processes.

The same authors also investigated VMAR using dioxinone substrates of type **1** and **148** under solvent-free reaction conditions. Indeed, the vinylogous addition easily occurred in the presence of catalytic benzoic acid, and with prochiral dienolate **148**, *syn*/*anti* diastereoselectivity was attained (Scheme 26, eqs 1 and 2).[78] Also, dioxinone substrate **1** was assayed by Bach and Kirsch in VMAR with a series of aldehyde acceptors under $TiCl_4$ assistance.[79] In all cases, the expected racemic aldols formed in good to excellent yields, as exemplified by eq 3 in Scheme 26.

Exactly the same reaction was investigated by Ollevier et al.,[80] introducing $Bi(OTf)_3 \cdot 4H_2O$ as the Lewis acid VMAR catalyst (eq 4, Scheme 26). In these catalytic conditions, the VMAR proceeded efficiently with various aromatic aldehydes, and vinylogous aldol adducts were solely detected, with no contamination of *O*-silylated aldols.

More recently, Cossy et al. exploited dioxinone **1** during a short synthesis of the C1−C13 fragment of lyngbouilloside, one of the first glycosidic macrolides of cyanobacterial origin.[81] The pivotal carbon−carbon bond-forming maneuver was a $TiCl_4$-catalyzed VMAR between **1** and 4-pentenal (**150**) that produced racemic aldol adduct (±)-**151**. The pure (*R*)-enantiomer **151** was subsequently obtained via resolution of the racemic mixture by preparative chiral HPLC and further advanced to **152**. Target

Scheme 24. Total Syntheses of Palmerolide A (138)[72−74]



fragment **154** was finally obtained by intermolecular cross-metathesis between **152** and chiral nonracemic-protected ene triol **153**, followed by 1,3-*anti*-reduction (Scheme 27).

3.1.1.2. Cyclic Silicon Dienolates. Cyclic dienoxy silane d_4 nucleophiles, including the widely exploited furan-, pyrrole-, and thiophene-based prototypes **155**−**164** in Figure 7, have been largely explored during the last 20 years of the past century in VMAR processes to enter a variety of highly functionalized

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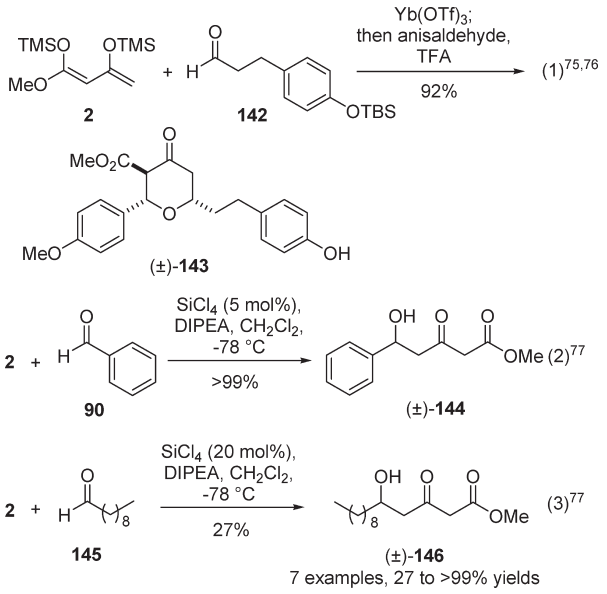
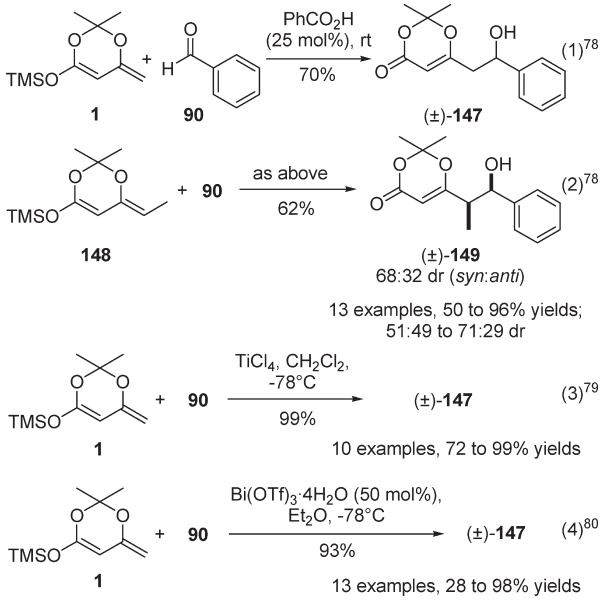
Scheme 25. Utilizing Chan Diene 2 in the Synthesis of VMAR Products (±)-143, (±)-144, and (±)-146[75−77]



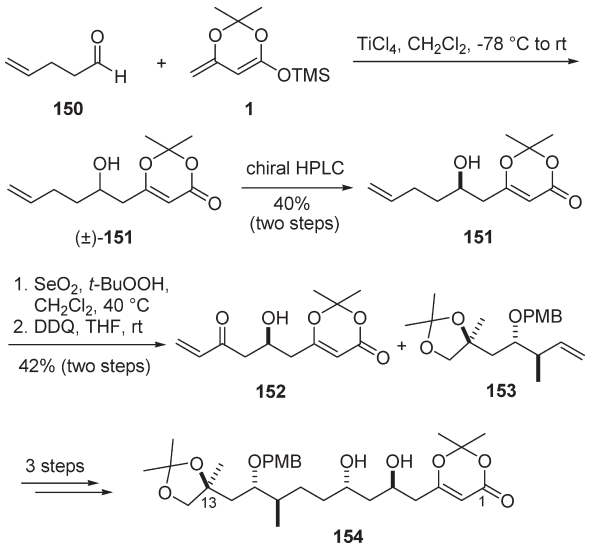
Scheme 26. Brønsted Acid-Catalyzed and Lewis Acid-Promoted VMAR to Racemic Products (±)-147 and (±)-149[78−80]



butenolide type frameworks.[2−7,15] In 2000−2010, VMAR utilizing this compound family continued to be a flourishing area of research with enormous potential for both methodology-oriented and target-oriented investigations.

Following their own initial pre-2000 studies centered on the exploitation of the silyloxy reagent triad TBSOF (**157**), TBSOP (**163**), and TBSOT (**164**) in organic synthesis,[2−7] Casiraghi et al. launched a program at the beginning of 2000, directed at the asymmetric synthesis of variously shaped cyclitols and carbasugars, which exploited much of the potential that this heterocyclic silyloxydiene-based methodology had to offer.[82] Scheme 28

Scheme 27. Synthesis of the C1−C13 Fragment of Lyngbouilloside (154)[81]



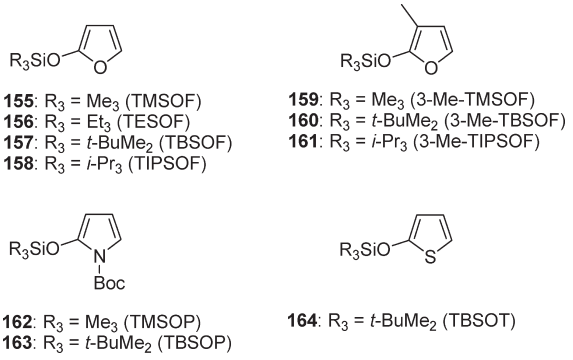


Figure 7. Representative members of heterocyclic silyloxy diene d_4 donors.

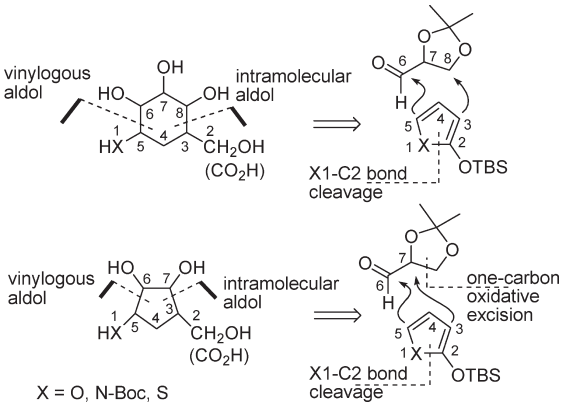
depicts the corresponding synthetic strategies for cyclohexane and cyclopentane polyols exploiting **157**, **163**, and **164** as common nucleophilic matrices, at both the C3 and the C5 positions and using protected D- and L-glyceraldehyde as common electrophilic, chiral nonracemic sources.

In particular, construction of the carbocycle targets entailed two carbon−carbon bond formations, that is, a vinylogous aldol addition installing the C5−C6 connection, followed by an intramolecular aldol addition to connect C3 to C8 (for pseudopyranose rings) or C3 to C7 (for pseudofuranose rings). Finally, fission of the C2-X1 linkages, either reductively or hydrolytically, unveiled monocyclic polyol or hydroxylated carboxylic acid targets. Following a preparative work aimed at optimizing the crucial intermolecular vinylogous aldolization and the intramolecular ring-forming aldolization,[83] total syntheses of 5a-carbapyranose, 4a-carbafuranose, 1-sulfanyl-5a-carbapyranose, and 1-sulfanyl-4a-carbafuranose compounds **165**−**168** were realized by using 2,3-*O*-isopropylidene-D-glyceraldehyde (**169**) as the common three-carbon synthon (Schemes 29 and 30).[84,85]

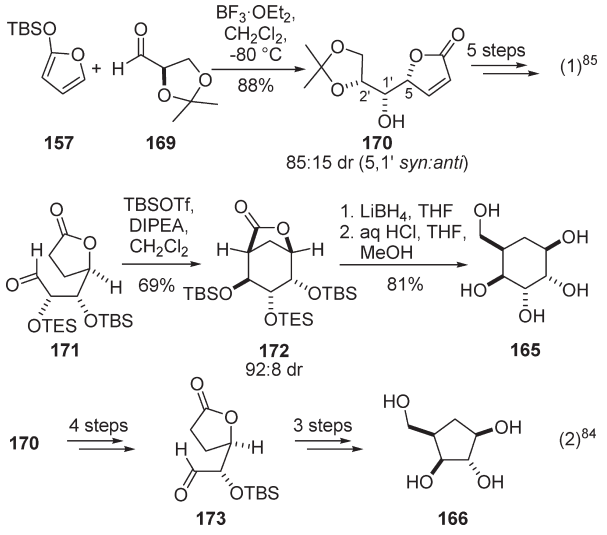
For β-D-*gulo*-carbapyranose **165** (Scheme 29, eq 1), the opening ploy was a highly diastereoselective $BF_3 \cdot OEt_2$-promoted VMAR between silyloxy furan **157** and (*R*)-glyceraldehyde

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

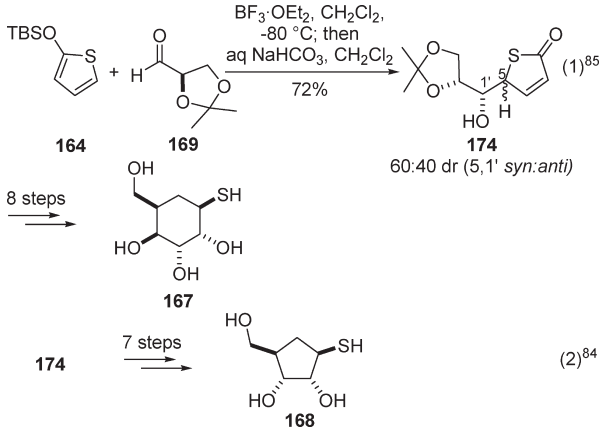
Scheme 28. First-Generation Strategy towards Cyclohexane and Cyclopentane Polyols[82]



Scheme 29. Diastereoselective Synthesis of 5a-Carbapyranose 165 and 4a-Carbafuranose 166[84,85]



Scheme 30. Diastereoselective Synthesis of 1-Sulfanyl-5a-carbapyranose 167 and 1-Sulfanyl-4a-carbafuranose 168[84,85]



169, producing butenolide adduct **170** in 75% isolated yield and 85:15 diastereoselectivity in favor of the 5,1′-*syn*-1′,2′-*anti*-configured isomer (5*R*,1′*S*,2′*R*). Conventional chemistry transformed **170** to aldehyde **171** that was advanced to bicyclic compound **172** by using a direct, highly productive, and silylative cycloaldolization maneuver assisted by the TBSOTf/DIPEA Lewis acid/Lewis base mixture. Finally, carbasugar **165** was unmasked via reductive lactone excision and acidic deprotection. Paralleling this chemistry, a sequence of four transformations including an oxidative one-carbon shortening step afforded aldehyde **173**, which was soon elaborated to carbafuranose **166** in high isolated yield.

By following exactly the synthesis protocols in Scheme 29 and simply changing the heteroatom in the diene component from oxygen to sulfur, 1-sulfanyl-analogues **167** and **168** were also constructed, as highlighted in Scheme 30. Thus, VMAR between **164** and **169** first produced aldol **174**, as a stereoisomeric mixture, from which the required 5,1′-*syn*-configured isomer was advanced to either pyranose **167** or furanose **168** (Scheme 30).

To assess the flexibility of this asymmetric, full-aldol methodology leading to cyclitols and congeners, several variants of this strategy were realized by simply changing the size and stereochemistry of the aldehyde component and/or the nature of the vinylogous silyloxy diene nucleophile.

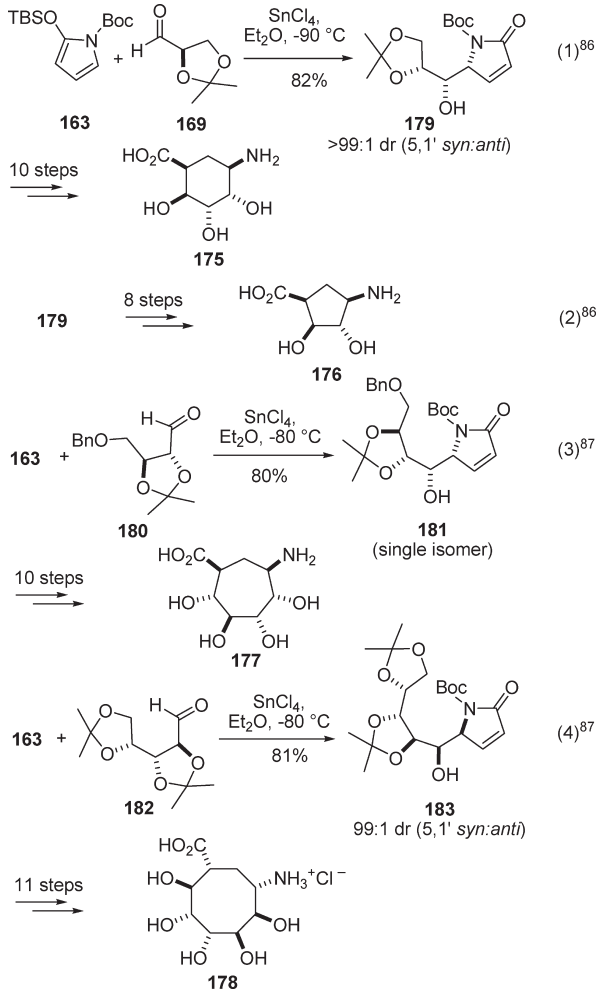
As an example, total syntheses of aminocyclohexane-, aminocyclopentane-, aminocycloheptane-, and aminocyclooctanecarboxylic acid polyols **175**−**178** are synthetically grouped in Scheme 31.[86,87]

Because the essential chemistry was similar, only a slight variation of the protocols was required, with marginal adaptation to the targets. Thus, six- and five-membered carbocyclic γ-amino acids **175** and **176** were selectively accessed via VMAR between TBSOP **163** and three-carbon aldehyde **169** (eqs 1 and 2), while seven-membered and eight-membered ring amino acids **177** and **178** (eqs 3 and 4) derived from VMAR, again involving TBSOP **163**, but changing four carbon and five carbon long sugar aldehydes **180** and **182** for glyceraldehyde **169**.

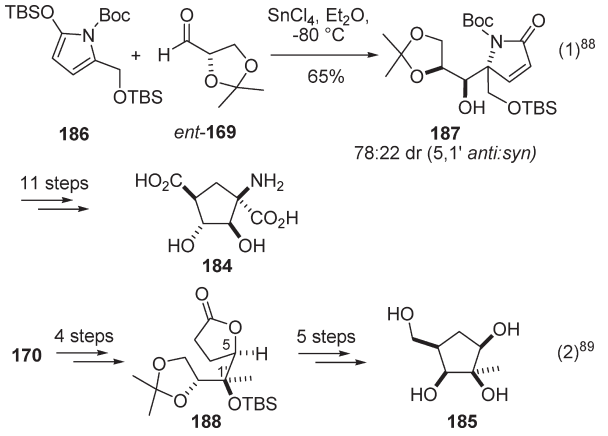
The efficiency and variability of the vinylogous aldol addition/silylative ring-forming aldolization technique for the synthesis of carbasugars then fueled a project aimed at the asymmetric synthesis of carbocyclic structures bearing quaternary stereocenters.[88,89] The enantioselective total syntheses of a constrained 2,4-disubstituted L-glutamate **184** and a novel C2-methyl-branched 4a-carbafuranose **185** are displayed in Scheme 32.

To access cyclopentane dicarboxylic acid **184**,[88] a $SnCl_4$-promoted VMAR between L-glyceraldehyde *ent*-**169** and γ-substituted silyloxy pyrrole **186**—in turn obtained via vinylogous aldolization between **163** and formaldehyde—was planned. In the event, a diastereoselective reaction took place giving the γ,γ-disubstituted stereoisomer **187** preferentially (78:22 dr). Conventional chemistry allowed the authors to convert **187** into the targeted amino acid **184** via a multistep sequence including, inter alia, selective unmasking of the terminal acetonide functionality, oxidative diol fission, and a remarkable silylative cycloaldolization. For **185** (Scheme 32, eq 2), a rare member of C2-methyl-branched carbasugar family, the same reaserch group first synthesized enantiopure butenolide **170** via VMAR between furan **157** and aldehyde **169** (see Scheme 29, eq 1) and then installed the C1′-quaternary stereocenter (hydroxyl oxidation plus Grignard addition) to **188**. Finally, they converted this

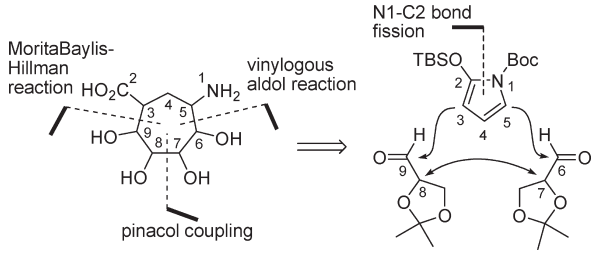
Scheme 31. Diastereoselective Synthesis of Aminocycloalkanecarboxylic Acids 175−178[86,87]



Scheme 32. Diastereoselective Syntheses of Carbafuranoses 184 and 185[88,89]



Scheme 33. Second-Generation Strategy to Amino Acid Polyols[90]



intermediary compound to carbasugar **185**, by using the previously disclosed silylative cycloaldolization/lactone reductive opening protocol.

The unique synthetic potential of the dienoxy pyrrole scaffolds was recently explored by Casiraghi et al. during a new generation synthesis of a series of cycloheptane amino acid polyols.[90] This approach complements the previously analyzed first-generation route and inherently possesses an even superior level of flexibility. As shown in Scheme 33, a generic cycloheptane amino acid is disconnected along three bonds, C5−C6, C3−C9, and C7−C8, unveiling the three corresponding building subunits, namely, the pyrrole skeleton, and the two aldehyde components, be they identical or different. In the synthetic direction, three sequential carbon−carbon bond-forming reactions were planned as follows: (a) a VMAR operation installing the C5−C6 connection, (b) a Morita−Baylis−Hillman reaction forming the C3−C9 bond, and (c) an intramolecular pinacol coupling closing the ring at C7−C8.

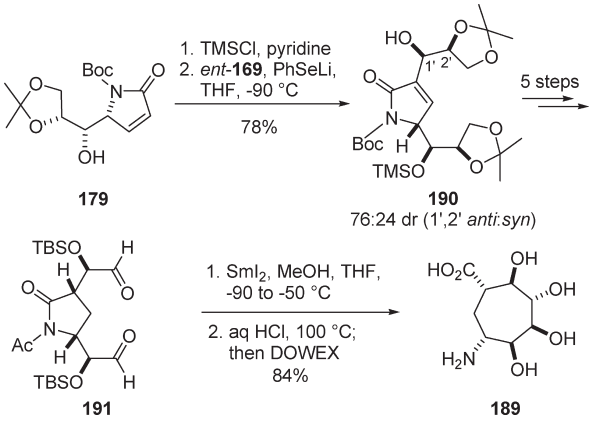
From the perspective of diversity-oriented synthesis, this new scheme seems to possess an added asset in that it not only provides access to stereochemically diverse congeners by variation of the stereochemistry of the starting chiral components, but it also permits a unified approach to differently sized cycloalkane structures by simply varying the size of the aldehyde synthons. This concept was demonstrated by the asymmetric synthesis of *β*-D-*glycero*-D-*gulo*-configured **189** (Scheme 34).

The authors began the construction of **189** by using dienoxy silane **163** and exploiting *R*-configured glyceraldehyde acetonide **169** in the opening VMAR and its enantiomer *ent*-**169** in the Morita−Baylis−Hillman reaction. Thus, **163** was first coupled to **169**, leading to pyrrolinone **179** in a remarkable 82% yield (see Scheme 31, eq 1). Installation of the second polyol appendage at the α-position of the unsaturated lactam moiety was carried out by a variant of the Morita−Baylis−Hillman reaction. After temporary hydroxyl silylation, treatment of a 1:2 mixture of the silylated lactam and *ent*-**169** with a solution of lithium benzeneselenolate led directly to the formation of adduct **190**, contaminated with some amounts of a second 1′,2′-*syn*-isomer. A sequence of five simple operations gave the dialdehyde **191** via protecting group manipulation and bilateral oxidative fragmentation. Exposure of **191** to samarium(II) iodide in methanol-tetrahydrofuran produced a bicyclic intermediate, which was finally advanced to amino acid **189** via lactam opening and full deprotection.

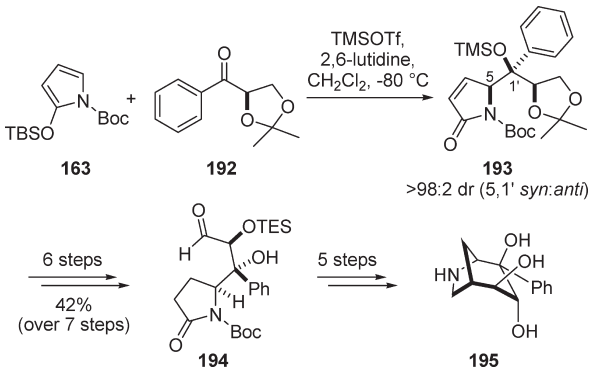
With a library of structurally and stereochemically diverse cycloalkane *γ*-amino acid structures at hand, the same research group utilized selected compounds of this repertoire (mainly cyclopentane amino acids) to implement RGD-containing 14-membered cyclic pseudotetrapeptide analogues, which showed one-digit nanomolar binding affinity toward the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ human integrin receptors.[91]

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 34. Diastereoselective Synthesis of Cycloheptane Amino Acid Polyol 189[90]



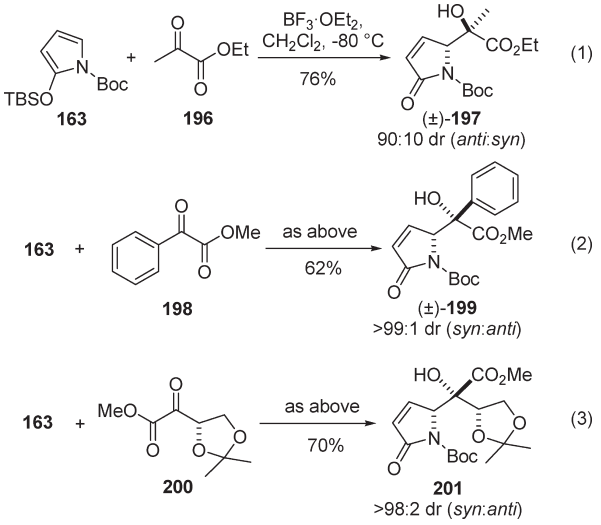
Scheme 35. Diastereoselective Synthesis of Normorphan Triol 195[93]



Also, exploiting unsaturated lactam **179** (see Scheme 31, eq 1), Zambrano et al.[92] succeeded in developing a short diastereoselective synthesis of 1-deoxy-7,8-di-*epi*-castanospermine, which served to revise a previously misassigned structure of this alkaloid.

Unlike aldehydes, ketones are not very disposed to act as acceptors in aldol and VARs, even though they readily give rise to quaternary carbon stereocenters during these processes. To investigate the ability of pyrrole-based dienoxy silane **163** to couple to ketone acceptors in a vinylogous scenario, the Casiraghi group faced the synthesis of a series of azabicyclo-[x.2.1]alkane systems, using VMAR as the initial construction step.[93] As an example, the synthesis of densely functionalized chiral nonracemic normorphan **195** is portrayed in Scheme 35. After considerable experimentation, coupling of aryl ketone **192** to TBSOP **163** was best achieved by employing TMSOTf as the Lewis acid combined with 2,6-lutidine. The silylative vinylogous addition proceeded well, furnishing the unsaturated lactam intermediate **193** in good yield and remarkable diastereoselectivity (>98:2 5,1′ *syn*/*anti* ratio). This material was then advanced to aldehyde **194**, which was cyclized to the azabicycle skeleton **195** as usual (silylative carbocyclization followed by carbonyl lactam reduction).

Scheme 36. VMAR between TBSOP 163 and Keto Esters 196, 198, and 200[93]

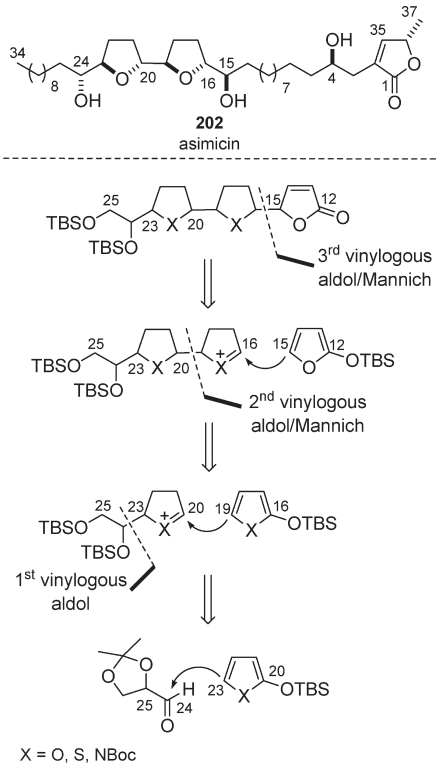


Also, VMARs between TBSOP **163** and prochiral α-keto ester compounds **196**, **198**, and **200** were investigated with the results grouped in Scheme 36. All coupling reactions performed well under the guidance of BF_3 etherate at −80 °C, giving rise to the respective vinylogous aldols (±)-**197**, (±)-**199**, and **201** with exquisite levels of diastereoselectivity. Remarkably, a clear diastereoselective switch was witnessed depending on the nature of the substituents in the ketone substrates, with *N,O-anti*-configured isomer (±)-**197** obtained with pyruvate ester **196**, and *N,O-syn*-disposed isomers (±)-**199** and **201** formed with glyoxylate **198** and dioxolanyl oxoacetate **200**.

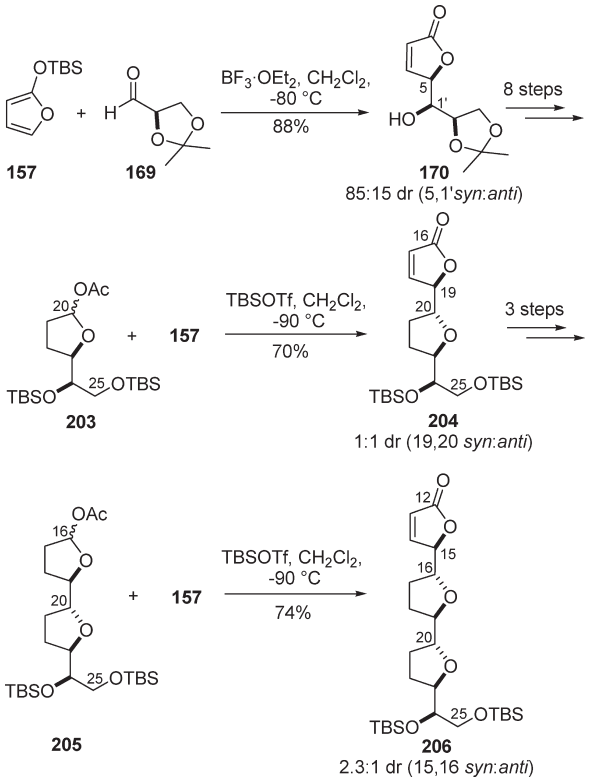
The annonaceous acetogenins are a class of C35 or C37 plant metabolites isolated from the archaic family of the *Annonaceae*. Of special interest is the anticancer activity of certain members of this compound class that, in some instances, is several orders of magnitude greater than that of currently used chemotherapeutics. In 2000, Casiraghi et al.[94] planned to build up a library of adjacently linked trinuclear structures, which cover the C12−C25 carbon segment of bis-THF annonaceous acetogenins, as well as related unnatural aza and thia analogues. Scheme 37 shows a representative member of bis-THF annonaceous acetogenins, asimicin (**202**), along with the modular, step-growth homologative plan to C12−C25 acetogenin type core units.

The chemistry involved features three sequential vinylogous aldol (or Mannich, vide infra) processes where heterocyclic dienoxy silane synthons TBSOF (**157**), TBSOT (**164**), and TBSOP (**163**) can be installed as wished during the stepwise elongation sequence. As an example, the synthesis of the C12−C25 bis-THF segment of asimicin (**202**), one of the most potent members of this family, is shown in Scheme 38. Thus, the first VMAR between furan **157** and aldehyde **169** produced aldol adduct **170**, which was transformed to **203**, the electrophilic substrate of the second VMAR homologation. TBSOTf-promoted VMAR between the oxonium ion from **203** and **157** then afforded dinuclear C16−C25 fragment **204**, which was advanced to **205**, ready for the third and final VMAR coupling. Again, the vinylogous reaction was promoted by TBSOTf and produced a

Scheme 37. Retrosynthetic Step-Growth Homologative Plan to C12−C25 Segments of Adjacently Linked Bis-THF Annonaceous Acetogenins and Unnatural Aza and Thia Analogues Featuring Three Sequential VMAR[94]



Scheme 38. Synthesis of the C12−C25 Adjacently Linked Bis-THF Segment 206 of Asimicin (202)[94]



mixture of trinuclear adducts, where the requisite C12−C25 asimicin candidate **206** prevailed. According to this flexible plan, eight isomeric bis-tetrahydrofuran units, four bis-thiolane units, and two bis-pyrrolidine units were assembled in a parallel fashion.

In the same year, Figadère et al.[95] reported the synthesis of the C10−C34 bis-THF segment of (−)-4-deoxygigantecin (**207**) by using a very similar linking strategy (Scheme 39). The initial move was the VMAR type addition between **155** and natural muricatacin-derived acetal **208** under $TrClO_4$ catalysis that allowed preparation of dinuclear intermediate **209**.

In this instance, the reaction occurred with moderate diastereoselectivity giving a 3:2 *anti*:*syn* mixture of isomeric products; however, base-catalyzed epimerization of the unwanted *anti*-configured isomer to *syn*-**209** was easily attained. Conventional chemistry was used to transform **209** into aldehyde **210**, which was finally advanced to the target compound **211** via a further VMAR with furan **155** ($BF_3 \cdot OEt_2$; 1:1 dr).

This reliable VMAR type technique was also successfully applied by Hanessian and co-workers[96] in the total synthesis of (+)-longicin (**212**), a monotetrahydrofuran polyketide compound of the annonaceous acetogenin family (Scheme 40). There, the key maneuver was a $BF_3 \cdot OEt_2$-promoted VMAR between the furan silyloxy diene **155** and the chiral nonracemic acetal **213**, readily obtained from D-glutamic acid. A 1:1 mixture of the desired isomer **214** and its C13 epimer was obtained, from which pure **214** was isolated by flash chromatography. A multistep bifurcated sequence involving an asymmetric Racherla−Brown allylation and Grubbs ene−ene RCM converged to an advanced THF intermediate **215**, which was finally elaborated to (+)-longicin (**212**), whose structure was thus unambiguously confirmed.

Nakiterpiosin (**216**) and nakiterpiosinone (**217**) are two related C-nor-D-homosteroids isolated from the sponge *Terpios hoshinota* that show promise as anticancer agents. The asymmetric total synthesis of these structurally complex natural products was addressed in 2009−2010 by Chen et al.[97,98] with a clever, extensive investigation that also permitted revision of the originally proposed structure of both metabolites and provided evidence of their biological effects. Scheme 41 delineates how diastereoselective VMAR impacted the initial stages of the synthesis sequences that arrived at the target compounds through a laborious, yet elegant pathway. For nakiterpiosin (**216**) (eq 1), stannous triflate-promoted VMAR between brominated aldehyde **219** and 3-Me-TIPSOF (**161**) afforded all-*syn*-configured butenolide adduct **220** in 80% yield as a single distereoisomer (90% ee). Indeed, in an accurate screening of 14 different Lewis acid promoters, $Sn(OTf)_2$ emerged as the best performer in terms of both conversion and stereoselectivity. For example, using $BF_3 \cdot OEt_2$, a 100% conversion was attained, with a moderate 4:1 diastereomeric ratio, while with $Bi(OTf)_3$, an improved 11:1 dr was reached albeit at the expense of both reaction efficiency (56% conversion) and product enantiopurity (60% ee, due to partial racemization of the precious starting aldehyde **219**). The key aryl stannane **222** was then synthesized via intermediate **221** through a sequence that involved *trans*-selective double bond saturation within **220** and ox-red adjustment of the carbinol at C22. Finally, a modified Stille

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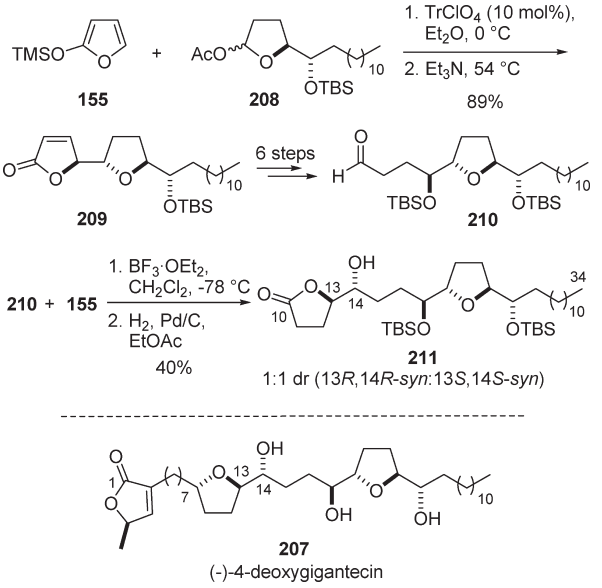
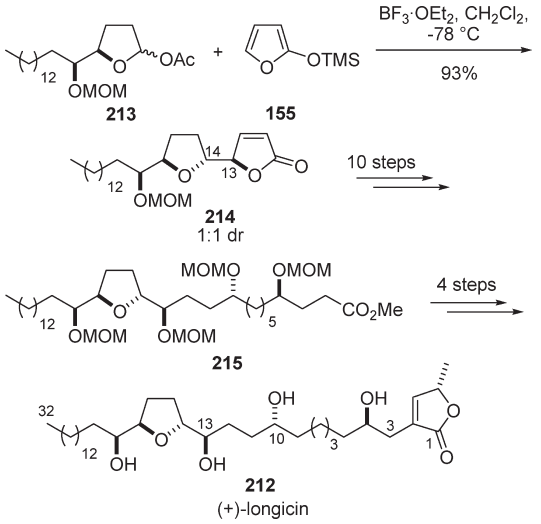
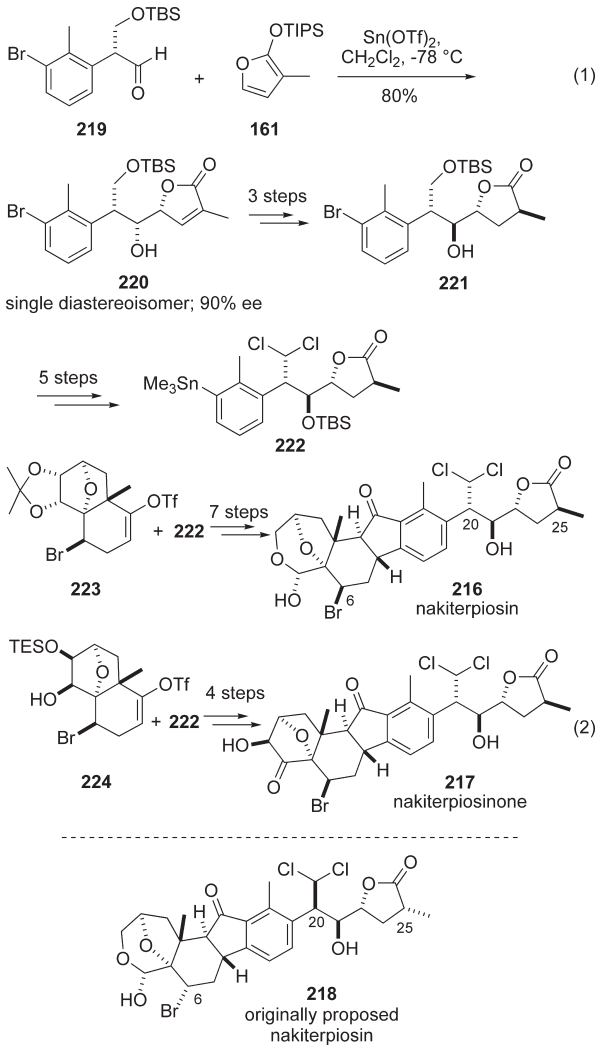
Scheme 39. Synthesis of C10−C34 Bis-THF Segment 211 of (−)-4-Deoxygigantecin (207)[95]



Scheme 40. Total Synthesis of (+)-Longicin (212)[96]



Scheme 41. Total Synthesis of Nakiterpiosin (216), and Structurally Related Compounds 217 and 218[97,98]

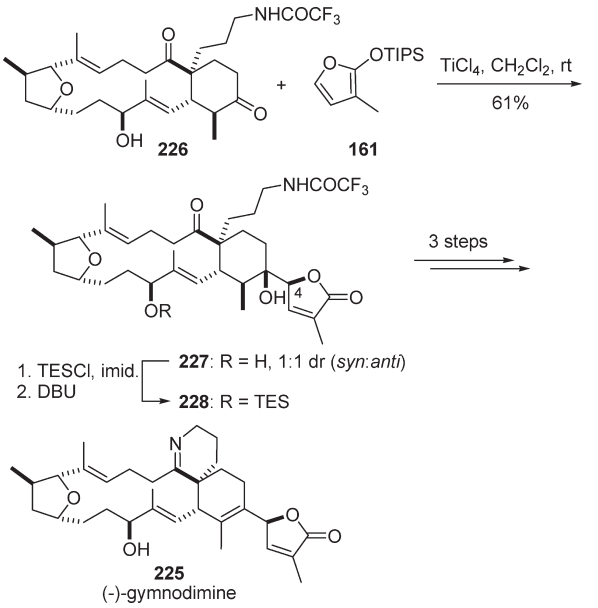


carbonylative coupling of stannane **222** with triflate **223**, followed by a skillful multistep manipulation, completed the synthesis of **216** (actual, revised structure), whose relative and absolute configuration was unambiguously determined by single crystal X-ray analysis. Furthermore, the same stannane precursor **222** was employed in a carbonylative coupling to triflate **224**, to provide access to nakiterpiosinone (**217**) (Scheme 41, eq 2). The important work of Chen finally culminated with the synthesis of the originally proposed nakiterpiosin (**218**; 6,20,25-tri*epi*-nakiterpiosin) that utilized, once more, a VMAR protocol to assemble the crucial butenolide intermediate.

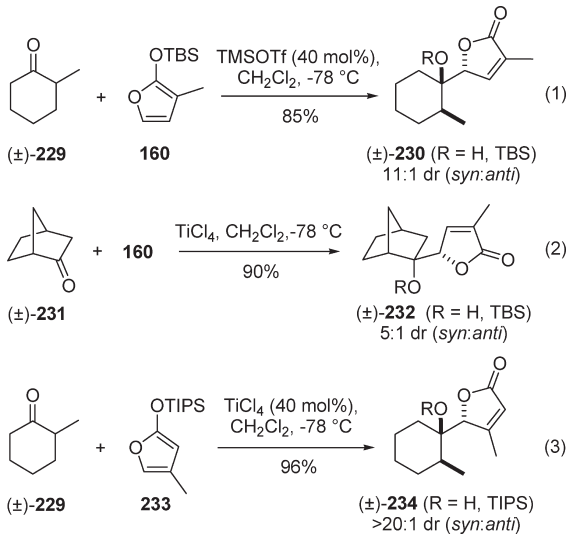
During a remarkable enantioselective total synthesis of the marine toxin (−)-gymnodimine (**225**), Romo et al. envisaged a Lewis acid-catalyzed VMAR to append the butenolide framework to macrolidic hydroxyketone **226** using 3-Me-TIPSOF **161** as the nucleophilic reaction component.[99] Indeed, under $TiCl_4$ assistance, the reaction performed well at ambient temperature, giving rise to the butenolide construct **227** as a 1:1 mixture of two diastereoisomers, epimeric at the C4 position. The lack of diastereoselectivity at the C4 during this transformation was not a problem, since, after silylation and base-promoted epimerization, predominant formation of the proper diastereomeric compound **228** was attained (Scheme 42). Dehydration of the tertiary alcohol **228**, followed by temporary protection of the amine group and careful acidic deprotection, finally advanced **228** to the (−)-gymnodimine target **225**. The appendage of the delicate butenolide framework to highly functionalized ketone **226** through a VMAR addition is noteworthy, since this late-stage maneuver provides a convenient route for the synthesis of varied gymnodimine congeners for further mode-of-action studies.

In a preparative paper, Romo and Kong[100] deeply investigated VMAR between furan-based silyloxy dienes and unsymmetric cyclic ketones to test the viability of this maneuver as a reliable tool to append butenolide arrays to ketone substrates. In general, 2-substituted cyclohexanones and bicyclic ketones of type

Scheme 42. Final Steps of the Total Synthesis of (−)-Gymnodimine (225) Showing Butenolide Incorporation via VMAR[99]



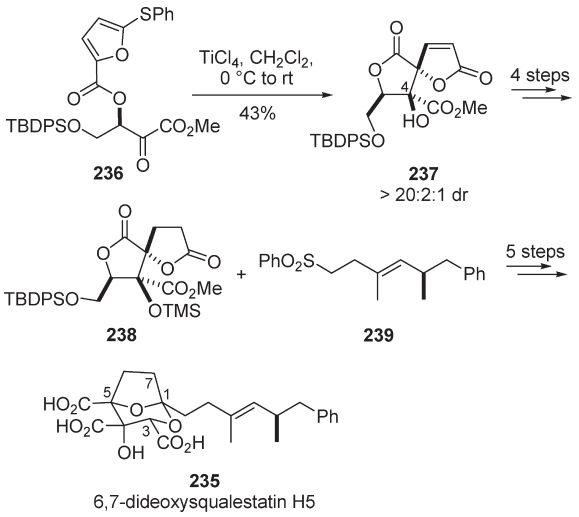
Scheme 43. Diastereoselective VMAR between Substituted Silyloxy Furans and Cyclic Ketones[100]



(±)-**229** and (±)-**231** (Scheme 43) provided the corresponding vinylogous products (±)-**230**, (±)-**232**, and (±)-**234** as separable mixtures of nonsilylated and silylated aldols in good yields and with fair to good levels of diastereoselectivity. Notably, the $TiCl_4$-catalyzed addition of γ-Me-TBSOF to ketone (±)-**229** (not shown) occurred at the nonvinylogous α-position, probably due to heavy steric effects preventing attack at the nucleophile γ-position.

A rather elegant, rarely exploited intramolecular VAR involving chiral furoic acid methyl ester **236** was adopted by Martin et al. to obtain 6,7-dideoxysqualestatin H5 (**235**), a

Scheme 44. Total Synthesis of 6,7-Dideoxysqualestatin H5 (235)[101]



member of the natural zaragozic acid family (Scheme 44).[101] Thus, the $TiCl_4$-induced cyclization proceeded well, giving the desired spirocyclic adduct **237** with an exquisite level of diastereoselectivity. To stabilize this delicate intermediate, **237** was promptly silylated at the free hydroxyl and then advanced to bicyclic lactone **238**. Coupling of **238** to dianion of sulfone **239** followed by four simple transformations finally completed the synthesis of **235** (17 steps from commercially available erythronolactone).

In a recent study directed toward the synthesis of highly hydroxylated γ-substituted butenolides, Boto and Hernández[102] utilized varied sugar-derived acetoxy acetal substrates as oxonium ion precursors in $BF_3 \cdot OEt_2$-assisted VMAR additions with TMSOF **155**. Regrettably enough, while the butenolide segment was indeed embodied into the sugar, only modest levels of γ-site selectivity and diastereoselectivity were attained, thus penalizing the synthetic applicability of this procedure.

TMSOF **155** was also employed by Tadano et al.[103] to introduce a butenolide frame into an oxabicyclo[4.2.1]nonadiene aldehyde skeleton, in a route directed toward the synthesis of (−)-1893A, a cytotoxic metabolite of a marine endophytic fungus.

The chiral auxiliary technique cleverly exploited by Kobayashi and colleagues to embody chirality into acyclic dienolates (vide supra), was translated by Royer et al. in the cyclic dienolate domain, by introducing a number of temporarily chiral silyloxy pyrrole vinylogous nucleophiles. In line with this concept, the total stereoselective synthesis of (−)-cephalotaxine (**240**) and some C7 alkylated analogues was designed, based on the VMAR between chiral nonracemic pyrrole **242** and cyclobutanone **241** (Scheme 45, eq 1).[104,105] Thus, $BF_3 \cdot OEt_2$-assisted VMAR produced the aldol adduct **243** in 77% yield but only 4% diastereomeric excess. Remarkably, subsequent acidic treatment of this mixture furnished spiro compound **244** in a quantitative yield with a good de in favor of the requisite stereoisomer. A series of transformations, including dismantling of the auxiliary moiety in the nitrogen ring and adopting previously disclosed chemistry, finally concluded the synthesis of (−)-cephalotaxine (**240**) in 16 overall steps with a global yield of 9.8%.

The same author further exploited the reactivity of similar chiralized silyloxy pyrroles with aromatic aldehydes to enter

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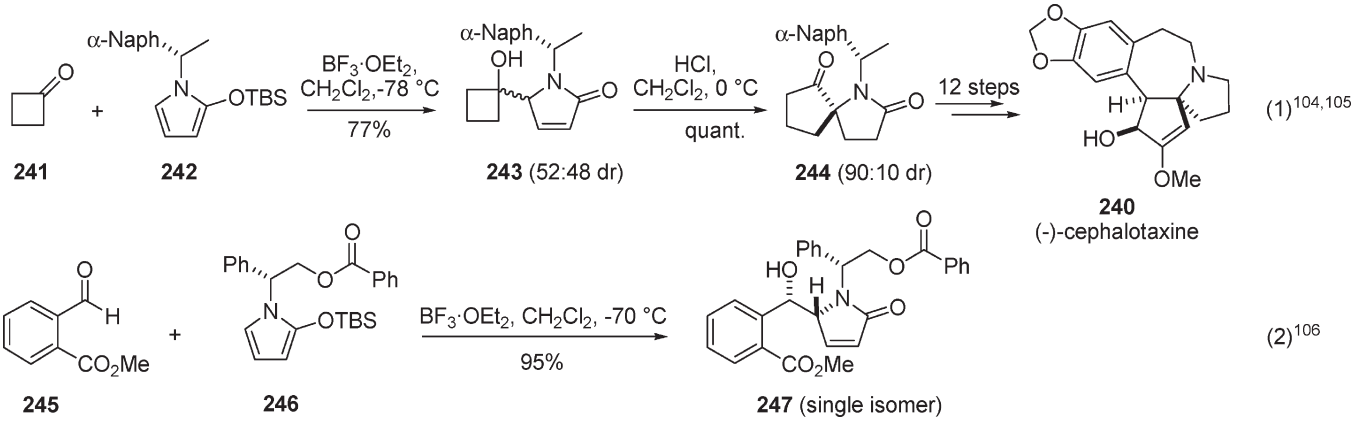
Scheme 45. Chiral Auxiliary Approach to (−)-Cephalotaxine (240) and Functionalized Fragment 247[104−106]



polyfunctionalized pyrrolidine compounds and related alkaloidal systems.[106] Of note, while VMAR with simple benzaldehyde derivatives produced the vinylogous adducts without any diastereoselectivity (under $BF_3 \cdot OEt_2$), use of aldehydes bearing chelating ortho-substituents as in methyl 2-formylbenzoate **245** resulted in a highly diastereocontrolled VMAR, producing the corresponding aldol **247** with excellent yields (Scheme 45, eq 2).

Several papers appeared in the period covered by this review, which were mainly focused on the viability and simple diastereoselectivity control of VMAR involving furan- and pyrrole-based dienoxy silanes and aromatic or aliphatic aldehydes. Scheme 46 lists four representative reactions selected from independent studies where furan-based VMAR was conducted using diverse Lewis acid promoters.[77,107−109] In these instances it is clear how the nature of the Lewis acid impacts simple diastereocontrol with variable results, which are difficult to fully rationalize.

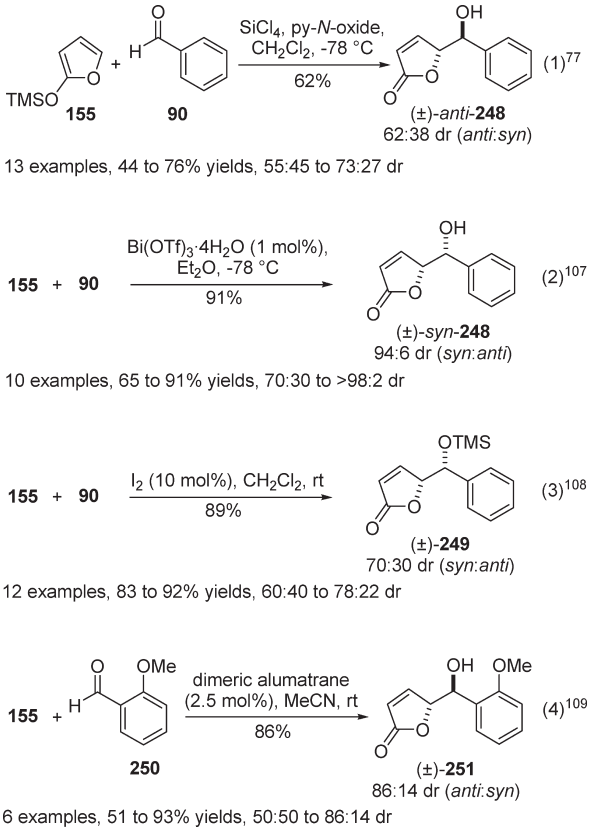
Scheme 47, on the other hand, groups VMAR between unsubstituted and substituted silyloxy furans and aliphatic aldehydes under Lewis acid promotion.[110−113] Here, the stereochemical outcome followed a similar trend, with *syn*-isomers preferentially formed in any case. With γ-substituted furan **256**, reversal of stereochemistry was observed when fluoride ions were used as promoter (eq 4). In this instance, however, isolated yields of the γ-aldols were dramatically reduced by competitive reaction at the less encumbered furan α-site.

A comprehensive scan of the transition state space for the reaction of TMSOF **155** and methacrolein (24 combinations) was conducted in 2005 by de Lera and co-workers,[114] which offered a satisfactory explanation of the *syn* (like) simple diastereoselectivity obtained experimentally in several Lewis acid-promoted VMAR involving these and related partners. It was calculated that the *syn*-adducts are preferentially formed following a g^+ (*gauche*$^+$, that is, "Diels−Alder-like") orientation of the two reactants with the aldehyde in the *s*-trans conformation.

In a series of papers, Soriente and co-workers[115−117] utilized achiral hydrogen bond donors such as calix[4]pyrrole **260** and urea derivative **261** as suitable catalysts in VMAR involving silyloxy furan **155** or silyloxy pyrrole **163** as vinylogous nucleophiles (Scheme 48). Moderate to good yields of the corresponding butenolide type products were obtained with slightly unbalanced mixtures of *syn*- and *anti*-configured isomers.

Quite recently, Stoeckli-Evans and Neier[118] shortly reported a study where unsubstituted and substituted *N*-Boc silyloxy

Scheme 46. Simple Diastereoselection of Lewis Acid-Promoted VMAR Involving Silyloxy Furans and Aromatic Aldehydes[77,107−109]



pyrroles of type **163** and **265** were reacted with aliphatic aldehydes under Lewis acid catalysis, to provide racemic unsaturated lactam compounds (±)-**263** and (±)-**266** (Scheme 49). The synthetic procedure led to *anti*-configuration of the two newly formed stereocenters, and this stereochemical disposition was firmly ascertained via X-ray crystal structure analysis.

To conclude this section, particular emphasis has to be placed on two clever works by Jacobi et al. who exploited rare

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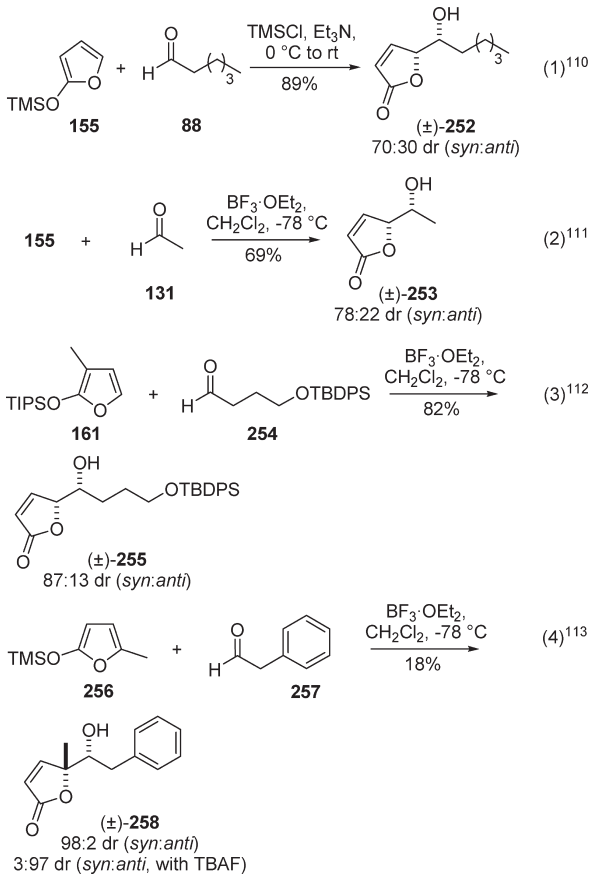
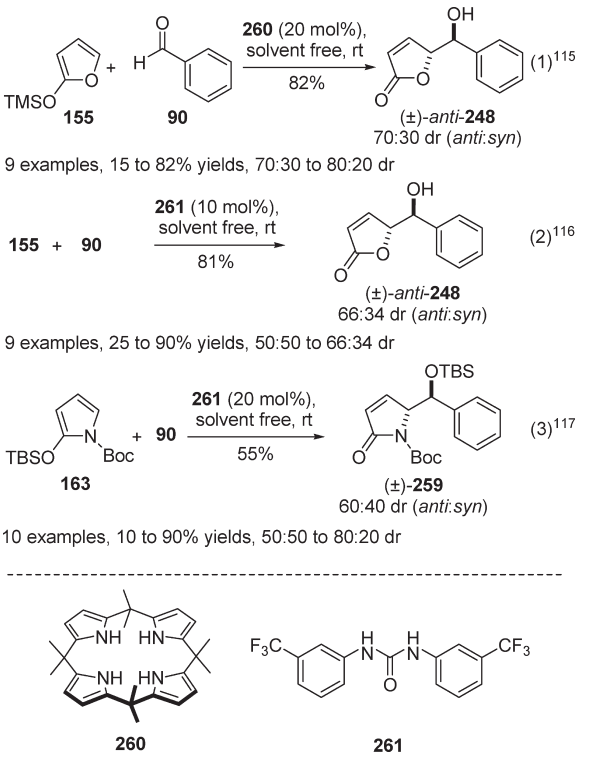
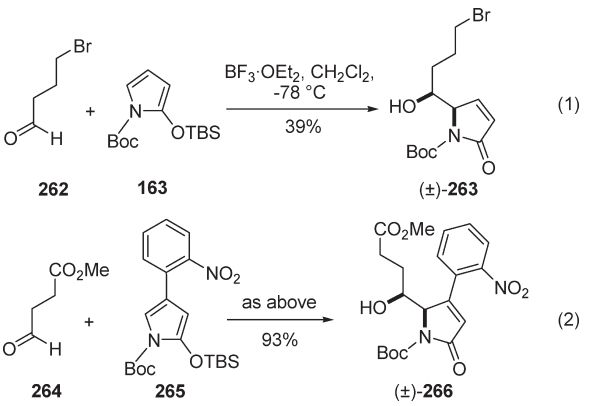
Scheme 47. Simple Diastereoselection of Lewis Acid-Promoted VMAR Involving Silyloxy Furans and Aliphatic Aldehydes[110−113]



Scheme 48. Simple Diastereoselection of Brønsted Acid-Promoted VMAR with Silyloxy Furan and Pyrrole Reactants[115−117]



Scheme 49. $BF_3 \cdot OEt_2$-Promoted Diastereoselective VMAR between Silyloxy Pyrroles 163 and 265 with Aliphatic Aldehydes[118]



phenylogous aldolizations as the pivotal maneuvers during the stereoselective synthesis of two polycyclic core units of furanosteroids related to the viridin (**267**) and wortmannin (**268**) families (Scheme 50).[119,120] In particular, to access the viridin core unit (±)-**270**, an intramolecular Mukaiyama type phenylogous aldolization was carried out on tricyclic *p*-methyl-substituted silyl phenol **269** under the guidance of $TiCl_4$ in CH_2Cl_2. In the event, dearomatized tetracycle (±)-**270** was formed in good yield with a 4:1 *syn*/*anti* diastereoselectivity. On the other hand, for wortmannin core (±)-**274**, the crucial move—that was optimized through a meticulous preparative work—was a phenylogous cross aldol reaction between silyl phenol **271** and ethylglyoxylate **272**. There, intermediate (±)-**273** was obtained, which directly underwent clean lactonization to provide α-configured lactone (±)-**274** solely.

3.1.2. Direct Additions of in situ-Generated Dienolates.

As with the normal aldol additions, the VAR may be adapted to a direct modality with the vinylogous nucleophilic species generated in situ, thus bypassing time-consuming isolation of stable, preformed nucleophiles. This may be an added asset vis-à-vis the indirect procedure, provided acceptable chemo-, regio-, and stereoselectivity are equally attained.

Herein disclosed are direct VARs involving both acyclic and cyclic in situ-generated donor components, which are triggered by either Lewis/Brønsted acids, Lewis/Brønsted bases, or mixtures thereof.

Using his own remote aldolization technique of α,β-unsaturated carbonyl compounds based on bulky aluminum tris(2,6-diphenylphenoxide) (**275**, ATPH), Yamamoto et al.[121,122] investigated direct VARs en route to a variety of densely functionalized δ-hydroxy-α,β-unsaturated linear frameworks. Selected examples using this technique are grouped in Scheme 51.

Thus, sequential treatment of a toluene solution of ATPH (**275**) or Me-ATPH (**276**) with α,β-unsaturated carbonyl compounds **277**−**280** and aldehydes **90** and **281** at −78 °C

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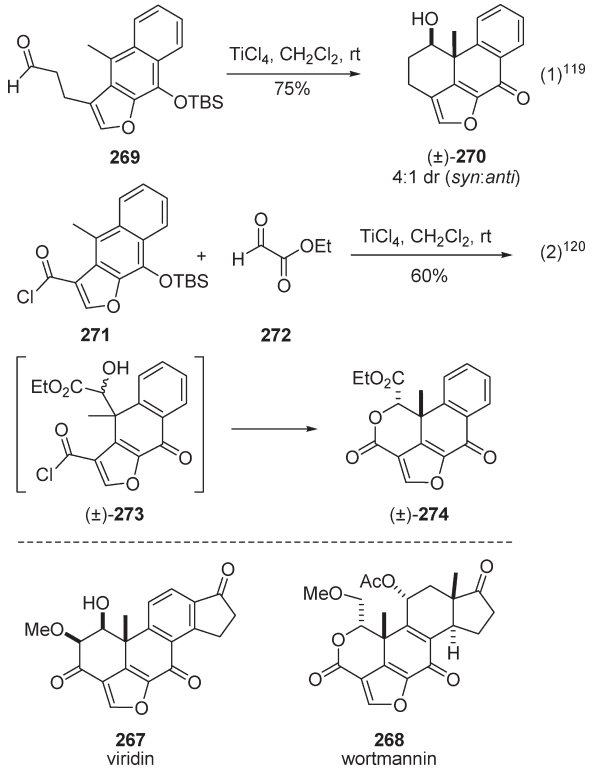
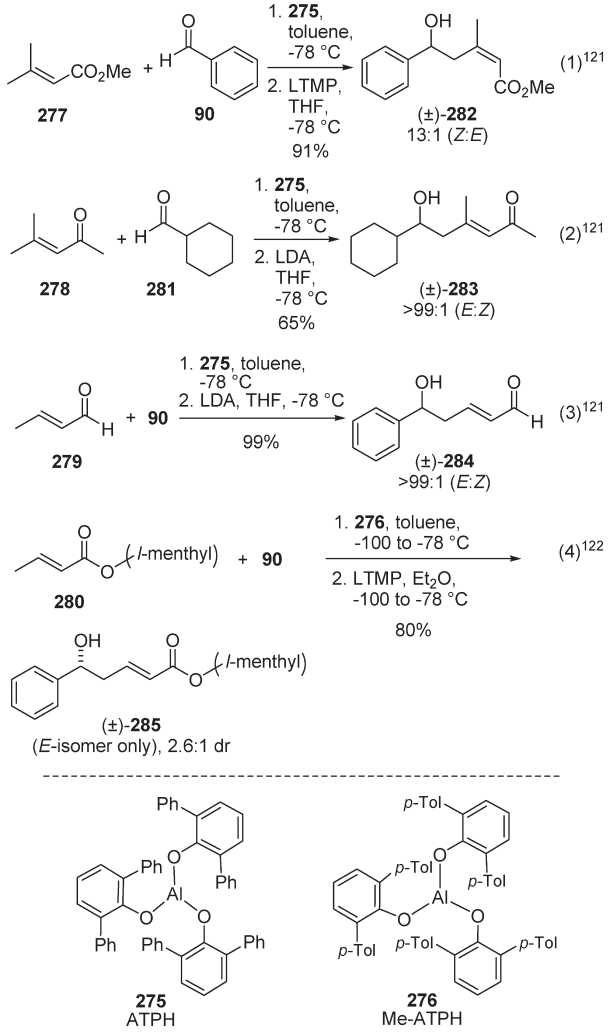
Scheme 50. Phenylogous Aldol Moves during the Synthesis of Viridin/Wortmannin Models (±)-270 and (±)-274[119,120]



Scheme 51. Aldolization of α,β-Unsaturated Carbonyl Compounds with Aldehydes Using ATPH (275) and Me-ATPH (276)[121,122]



was followed by deprotonation with an ethereal solution of LTMP or LDA. After quenching with aqueous NH_4Cl, the expected homoallyl alcohols **282**−**285** were obtained in high isolated yields, complete γ-site selectivity, and, in most cases, high *E*:*Z* selectivities. When chiral *l*-menthyl ester **280** was used (eq 4), adduct **285** was isolated as a diastereomeric mixture (72% de) with *R*-configured carbinol predominating.

Analogous chemistry was also exploited by Paterson et al.[33] during his skillful total synthesis of the callipeltoside aglycon (vide supra, chapter 3.1.1.1). In this instance, β-methylcrotonaldehyde **286** was treated sequentially with ATPH (**275**) followed by LDA and then coupled with (*E*,*E*)-iodopentadienal (**287**) to afford, after quenching, aldehyde (±)-**288**, which represents the C9−C17 portion of the callipeltoside aglycon (Scheme 52, eq 1).

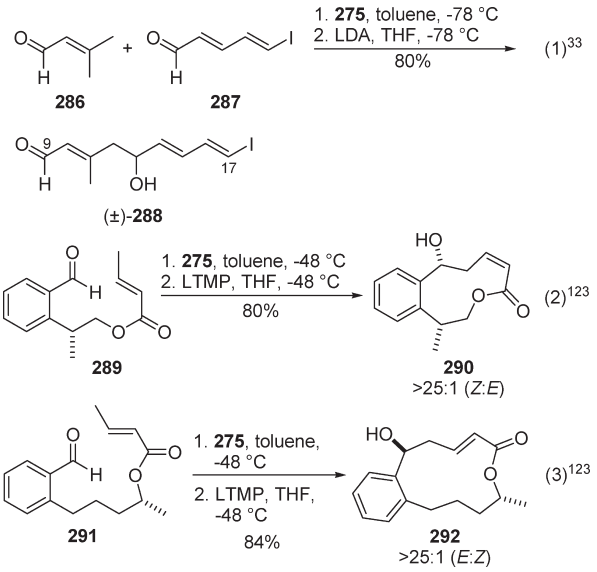
An intramolecular version of the same Yamamoto VAR methodology was applied by Sammakia and Abramite to construct differently sized macrolides.[123] Two chiral examples are shown in Scheme 52 (eqs 2 and 3). In both cases, good yields and high margins of diastereoselectivity were reached, with *syn* compounds (e.g., **290**) or *anti* adducts (e.g., **292**) formed, depending upon the size of the target macrocycles.

Isoprostanes are cyclic derivatives of arachidonic acids and are diastereomeric to prostaglandins. Quite recently, Jahn and Dinca[124] succeeded in synthesizing racemic 15-F_{2t}-isoprostane [(±)-**293**] employing a direct base-promoted VAR as the opening move. Thus (Scheme 53), vinylogous addition of the dianion of methyl acetoacetate **294** to (*E*,*E*)-decadienal (**295**) resulted in formation of oxoester (±)-**296** with a 94% isolated yield. Then, diene (±)-**296** was advanced to cyclopentane (±)-**297** via a multistep sequence involving a remarkable radical anion cyclization/oxidation methodology. Finally, a rather conventional chemistry allowed the authors to complete their route to isoprostane (±)-**293**, which occurred in 12 steps with a 14% overall yield.

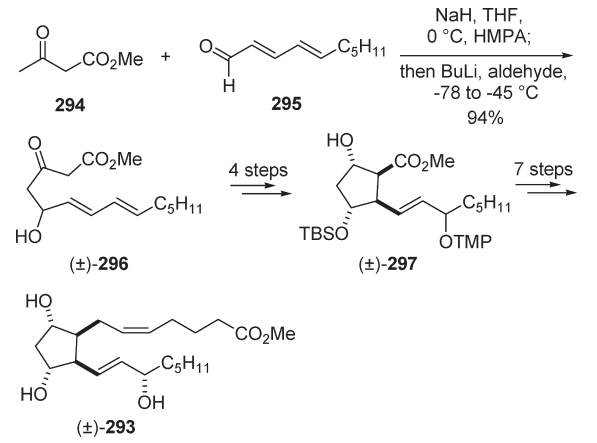
The Henry or nitroaldol reaction is one of the important reactions in organic chemistry; however, its vinylogous extension has been only scantly investigated. Adamo and Suresh[125] recently adopted this methodology by introducing 3,5-diethyl-4-nitroisoxazole (**298**) to create the vinylogous donor in situ. As an example, treatment of **298** with a methanolic triethylamine solution in the presence of aldehyde acceptors did produce the expected nitroaldol adducts (±)-**299** and (±)-**300** in high yields but modest diastereoselectivity (Scheme 54, eqs 1 and 2).

The activated aldehyde derived from Jung's nonaldol/aldol methodology was further employed by Kalesse and Rahn[57] in a direct one-pot Mukaiyama type VAR for rapid construction of polyketide fragments (vide supra, Scheme 15). Thus, treatment of a mixture of methyl crotonate and chiral epoxy alcohol **85** with 8 mol equiv of 2,6-lutidine and 4 mol equiv of TBSOTf triggered a tandem aldol sequence involving in situ generation of the

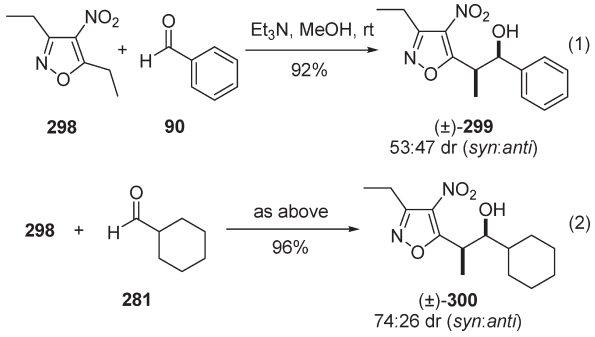
Scheme 52. Application of Inter- and Intramolecular Yamamoto VAR[33,123]



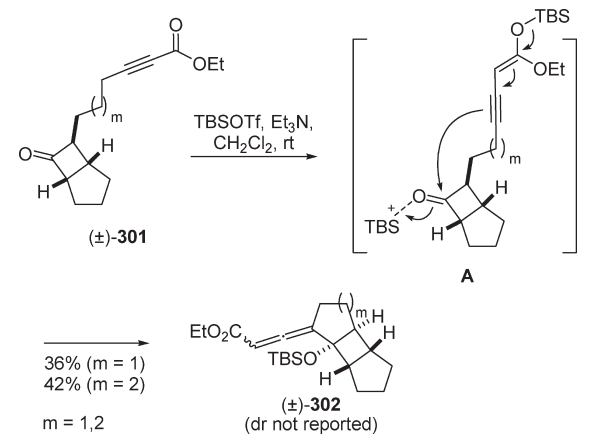
Scheme 53. Total Synthesis of 15-F_{2t}-Isoprostane [(±)-293][124]



Scheme 54. Direct Vinylogous Nitroaldol (Henry) Reaction using Nitroisoxazole 298[125]



Scheme 55. Direct Intramolecular Alkynylogous Mukaiyama Aldol Type Reactions[126]



activated aldehyde species, as well as γ-enolization of the crotonate ester (not shown). In such cases, excellent facial and simple diastereocontrol were witnessed, giving rise to useful chiral non racemic all-*syn* aldol fragments.

A similar silicon Lewis acid/amine base system also mediated direct intramolecular alkynylogous aldol type reactions of chiral bicyclic propargylic esters of type (±)-**301** (Scheme 55).[126] Thus, exposure of propargylic ester-tethered bicyclo[3.2.0]-heptanones (±)-**301** to a TBSOTf/Et_3N mixture resulted in a cascade process whose driving force is a dual activation of the substrate leading to transient silyl ene−yne structures of type A, which smoothly closed to tricyclic allenoate esters (±)-**302** with remarkable diastereoselectivity.

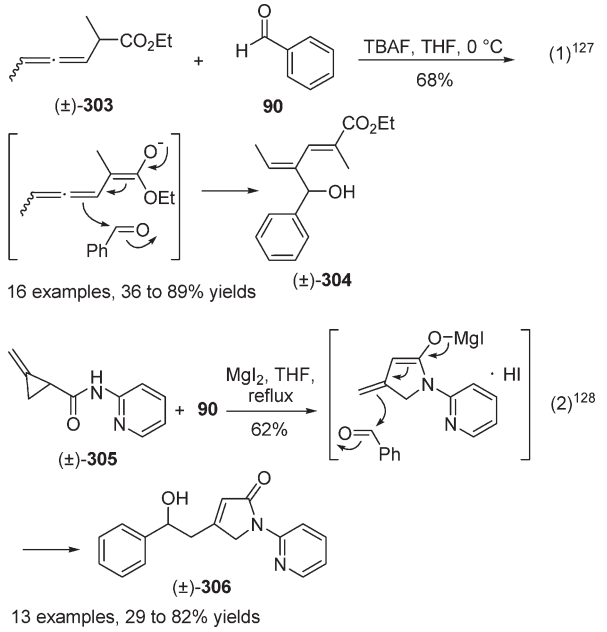
Two further investigations in the acyclic VAR domain are worth mentioning: the first pertaining to the use of allenyl enolates[127] and the second involving heterocyclic magnesium dienolates (Scheme 56).[128] As an example (eq 1),[127] TBAF-mediated reaction of ethyl allenoate (±)-**303** with benzaldehyde (**90**) directly produced racemic vinylogous aldol (±)-**304** via the intermediacy of a transient allenyl enolate. Interestingly, the reaction occurred in a totally vinylogous fashion, with no detection of any isomers derived from α-attack.

In the second contribution by Lautens et al.,[128] a remarkable MgI_2-mediated ring expansion of secondary methylene cyclopropyl amides of type (±)-**305** was investigated (eq 2), which gave rise to a magnesium dienolate species. Intercepting benzaldehyde (**90**), this activated species clearly afforded the aldol product (±)-**306** featuring a synthetically useful α,β-unsaturated lactam moiety.

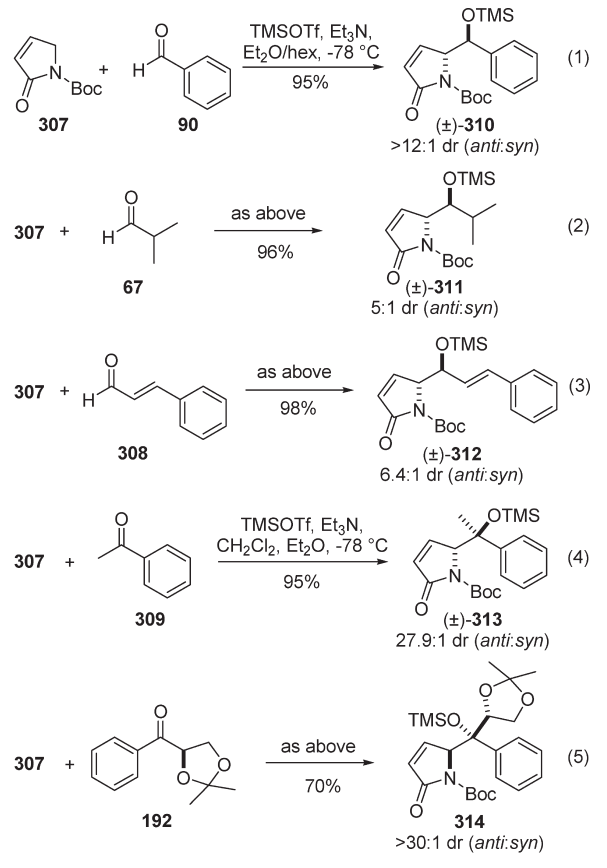
A number of papers on the subject area covered in this section appeared, dealing with direct VAR involving in situ-generated heterocyclic dienolates (mainly furan- and pyrrole-based). To begin, a vinylogous, silylative, and direct variant of the Mukaiyama aldol reaction has been developed by Casiraghi and Zanardi[129] by exploiting *N*-Boc-pyrrolin-2-one **307** as the d_4 donor precursor. After an initial work, targeted at optimizing the experimental procedure, reliable conditions were found according to which the aldol coupling reaction with both aldehyde and ketone acceptors proceeded in a silylative manner with high levels of chemo-, site-, and diastereoselectivity. For example (Scheme 57), treatment of **307** with achiral and chiral carbonyl acceptors **90**, **67**, **308**, **309**,

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

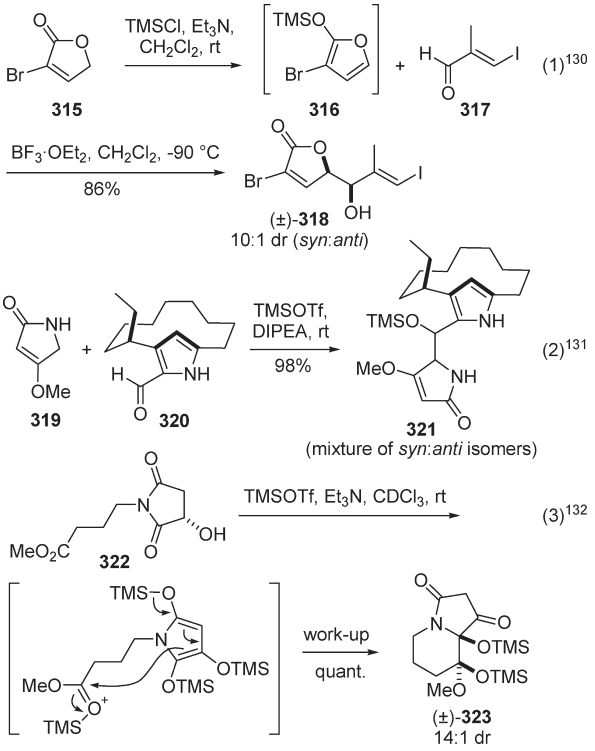
Scheme 56. Further Examples of Direct Vinylogous Aldolizations Involving Allenoate or Methylenecyclopropyl Starters (±)-303 and (±)-305[127,128]



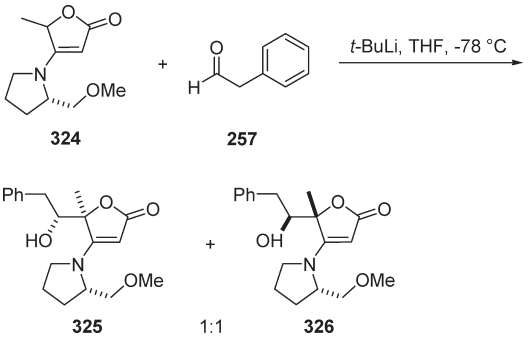
Scheme 57. Direct Silylative VAR Using *N*-Boc-Pyrrolin-2-one 307[129]



Scheme 58. Direct VAR Assisted by Silicon Lewis Acid/Amine Base Pairs[130−132]



Scheme 59. Chiral Auxiliary Approach to Nonracemic Butenolides[134]



and **192** comediated with the TMSOTf/Et_3N dual activator system directly produced the expected vinylogous silylated aldols **310**−**314** in preparative useful yields, complete γ-site selectivity, and marked *anti*/*syn* diastereoselectivity. A tandem mechanistic pathway was proposed, which involves the Et_3N/TMSOTf-driven generation of a dienoxy silane pyrrole intermediate that, in turn, couples to the silicon Lewis acid-activated carbonyl acceptor in a strictly vinylogous and silylative manner.

In a study directed toward the synthesis of carotenoid butenolides, de Lera and co-workers[130] adopted a direct VAR between bromofuranone **315** and 3-iodomethacrolein (**317**) promoted by the dual silicon Lewis acid/amine base TMSCl/Et_3N system in combination with $BF_3 \cdot OEt_2$ (Scheme 58, eq 1). There, racemic *syn*-configured adduct (±)-**318** formed in high isolated yield with a 10:1 *syn*/*anti* diastereomeric ratio.

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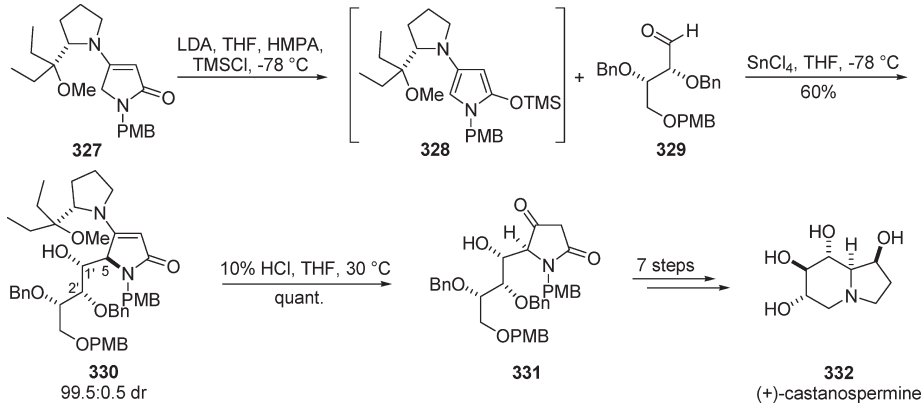
Scheme 60. Total Synthesis of (+)-Castanospermine (332) Featuring a Diastereoselective Direct VAR[135,136]

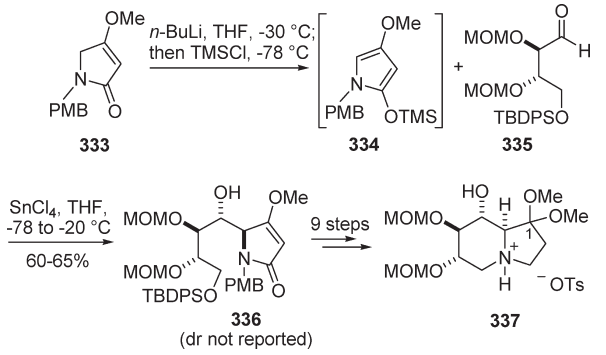


Analogous Lewis acid/amine base system was also exploited by Thomson and Clift[131] during the enantioselective total synthesis of metacycloprodigiosin and prodigiosin R1 (Scheme 58, eq 2). The key reaction was the direct VAR addition between tetramate **319** and chiral nonracemic pyrrole aldehyde **320**, giving rise to **321** as a mixture of diastereoisomers. Again, the TMSOTf/Et_3N mix was chosen by Hoye et al.[132] in a silylative Dieckmann-like cyclization of ester imide **322**, derived from L-malic acid (Scheme 58, eq 3). Following an initial *O*-silylation step, rapid cyclization occurred to give silylated bicycle (±)-**323**, possibly via the intermediacy of a persilylated pyrrole structure. Isolation of (±)-**323** embodying two contiguous chiral *O*,*O*- and *N*,*O*-acetal centers is noteworthy, and it is likely favored by stabilization of the labile acetal functions by double silylation.

Temporary embodiment of a chiral nonracemic pyrrolidine component into unsaturated 2-furanone or 2-pyrrolinone structures to be used in VAR procedures is a largely utilized technique to access enantiomerically enriched lactone and lactam products. First introduced and exploited by Schlessinger in 1988−1998,[133] this technique was also applied by Royer et al. in 2003[134] in a direct VAR between tetronic acid-derived furanone **324** and phenylacetaldehyde (**257**) (Scheme 59). Thus, γ-deprotonation of **324** with *t*-BuLi followed by aldehyde addition afforded a 1:1 mixture of *anti*-configured isomers **325** and **326**. While the simple diastereoselection was complete (no *syn* products were detected), facial selectivity was not, proving that the presence of the chiral auxiliary is not able to discriminate between the two lactone diastereofaces.

The above chiral auxiliary technique was central to the Huang synthesis of (+)-castanospermine (**332**) and two related epimeric compounds (Scheme 60).[135,136] The venture started with VMAR between chiral **327** and L-threose **329** according to a one-pot two-step reaction protocol; that is, enol silylation of **327** with LDA/TMSCl followed by $SnCl_4$-promoted aldehyde Mukaiyama type coupling. In this instance, the vinylogous aldol coupling led to 5,1′-*anti*-1′,2′-*syn*-configured product **330** as the sole detectable stereoisomer, with a 60% isolated yield. Here, both the inherent substrate chirality and the reagent auxiliary chirality matched well in directing both the aldehyde facial and simple diastereoselection. Acidic dismantling of the auxiliary moiety produced tetramic acid **331**, which was advanced to the target **332** by a number of functional group manipulations and final Mitsunobu-like annulation. Overall, the synthesis took nine steps with a 14% global yield from the initial chiral building block **327**. Synthesis of (+)-1-*epi*-castanospermine and

Scheme 61. Total Synthesis of Castanospermine C1-Ketal Derivative 337[137,138]



7-deoxy-6-*epi*-castanospermine was also attained with almost equal efficiency and stereoselectivity.

In a closely related investigation, Hunter et al.[137,138] explored a direct one-pot two-step VAR methodology to assemble certain polyhydroxylated pyrrolinone compounds en route to castanospermine congeners. As an example (Scheme 61), the reaction between PMB-protected methoxypyrrolinone **333** and L-threose aldehyde **335** was especially investigated during a diastereoselective synthesis of castanospermine-related C1 ketal **337**. There, the diastereocontrolled VAR utilized in situ-generated silyloxy pyrrole **334**, which was directly coupled to aldehyde **335**, leading to adduct **336** with good margins of γ-selectivity, as well as simple and facial diastereoselectivity. Then, elaboration of **336** into **337** comprised nine individual steps and involved double bond saturation, C1 ketalization, lactam carbonyl reduction, and cyclization.

In a work directed to the preparation and biological evaluation of lambertellols—fungal metabolites involved in the mycoparasitism by *Lambertella* species—Hashimoto and colleagues[139] exploited an intramolecular base-induced direct VAR to form spirocyclic butenolides of type (±)-**339** (Scheme 62, eq 1). Thus, for example, exposure of a diastereomeric mixture of acetonide-protected aldehyde (±)-**338** to NaHMDS triggered an intramolecular vinylogous aldolization that installed the desired spirocyclic butenolide moiety within (±)-**339** (86:14 dr). Subsequent acidic removal of the acetonide blockage followed by MnO_2 oxidation finally provided racemic lambertellol B (±)-**340** in 55% isolated yield. This material, along with several analogues in this series, were subjected to optical

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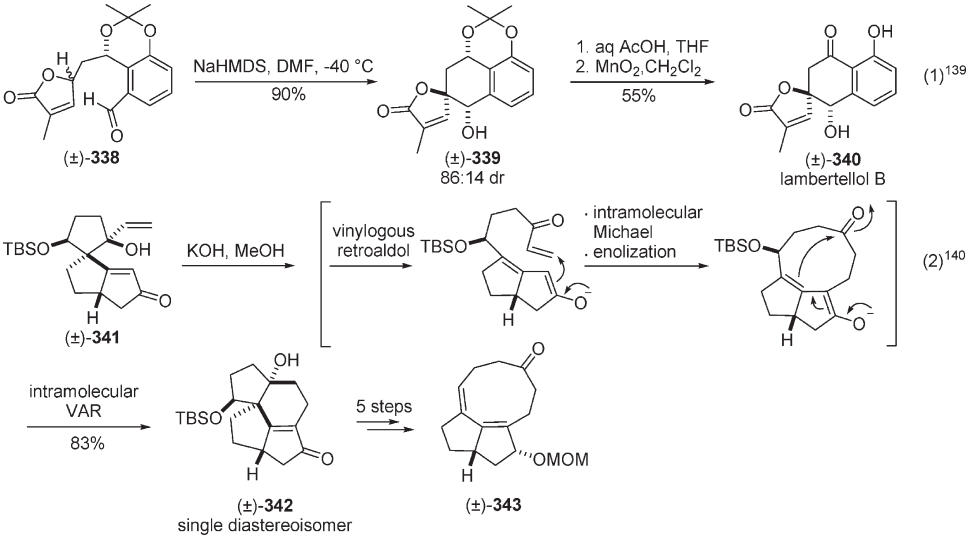
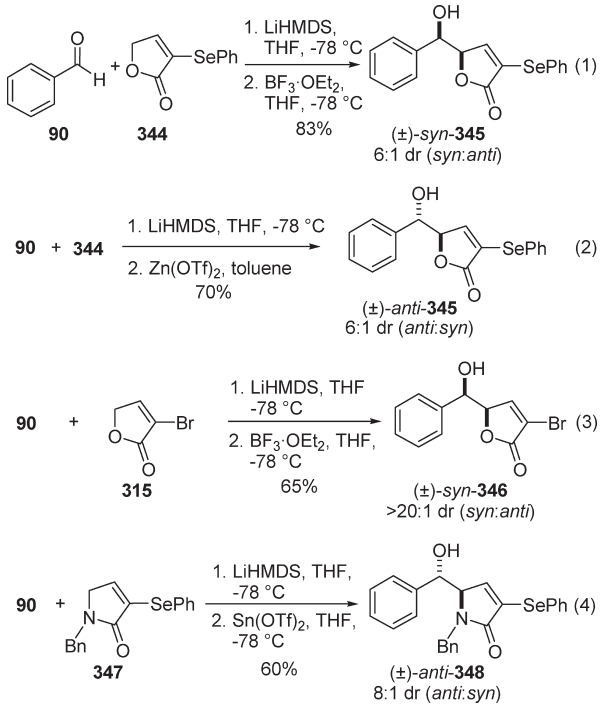
Scheme 62. Intramolecular Base-Induced VAR to Lambertellol B [(±)-340] and Aquariane Ring System [(±)-343][139,140]

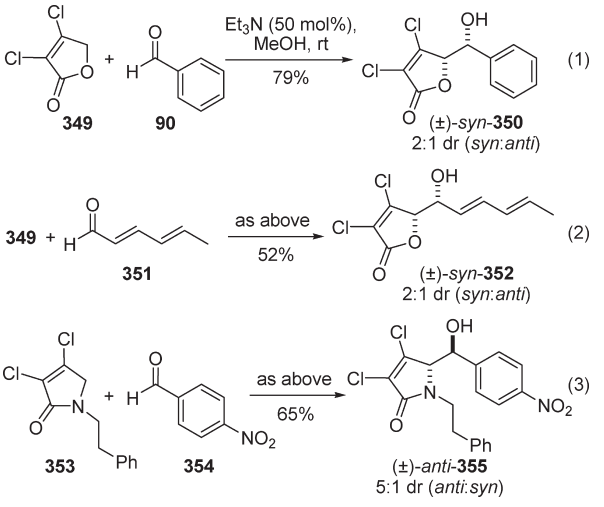


Scheme 63. Direct VAR in Preparation of γ-Substituted Furan-2(5*H*)-ones and Pyrrol-2(5*H*)-ones[141,142]



18 examples; 50 to 95% yields; 1:1 to 50:1 dr

Scheme 64. Direct Et_3N-Catalyzed VAR in Preparation of Mucochloric Acid-Based Butyrolactone and Butyrolactam Derivatives[143]



23 examples; 30 to 86% yields; 1.1:1 to 10:1 dr

resolution via chiral HPLC and individually assayed for their activity against *Monilinia fructigena* and other pathogenic fungi.

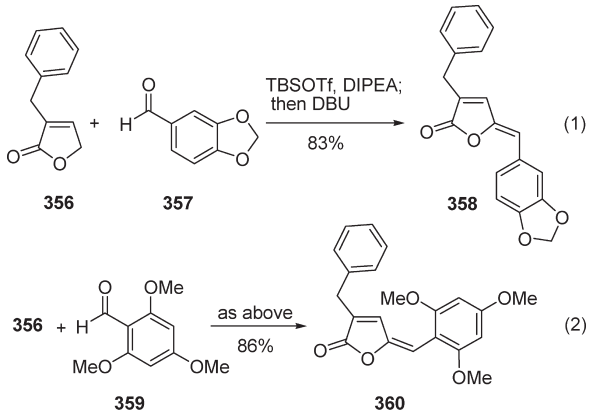
A related intramolecular base-induced VAR was efficiently implemented by Burnell and Thornton[140] in a synthetic approach to the aquariane diterpene ring system (Scheme 62, eq 2). In this effort, tricyclic ketone (±)-**341**, resulting from a multistep sequence involving a remarkable diastereoselective Pauson–Khand reaction, was treated with a methanolic solution of KOH, conditions that triggered an elegant reaction cascade comprising a vinylogous retro-aldolization, followed by a Michael addition–enolization step and subsequent intramolecular vinylogous aldolization. The maneuver resulted in the formation of tetracyclic (±)-**342**, accompanied by only marginal amounts of a second isomer. Further manipulation of the tetracyclic core in (±)-**342** and base-catalyzed Grob fragmentation afforded (±)-**343**, the carbocyclic fused ring system of the aquariolide diterpene family.

The direct VAR addition between furanone and pyrrolinone systems and carbonyl compounds as a mean to construct butenolide-related molecular fragments was thoroughly investigated by the Piancatelli[141,142] and Zhang[143] groups, with the respective results displayed in Schemes 63 and 64.

In particular, Piancatelli and Bella studied direct one-pot two-step VAR additions between a series of 3-heterosubstituted

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 65. Synthesis of Nostoclide Analogues 358 and 360[147−149]



lactone and lactam precursors with aromatic, aliphatic, and α,β-unsaturated aldehydes. It was shown that the *syn*/*anti* diastereoselectivity could be efficiently modulated, based on the nature of the heteroatom component in the donor and/or the Lewis acid involved (Scheme 63).

In searching for an alternative VAR methodology suitable for large-scale synthesis of mucochloric acid-derived γ-butenolide and γ-lactam compounds, Zhang[143] established a direct procedure that utilized substoichiometric quantities of Et_3N in MeOH to propel and direct the vinylogous processes (Scheme 64).

A wide number of aromatic aldehydes, α,β-unsaturated aldehydes, and ketones were reacted with 3,4-dihalo-substituted lactone and lactam substrates of type **349** and **353** to afford the corresponding butenolides **350** and **352** or lactam derivative **355**. Interestingly, a switch in diastereoselectivity was observed by Zhang that was directed by the nature of the heteroatom embodied in the vinylogous donor component.

β-Elimination of activated δ-hydroxy-α,β-unsaturated γ-lactone and γ-lactam compounds is one of the most utilized way to access γ-alkylidene butenolides, a largely encountered progeny of biologically relevant natural and natural-like frameworks.[144−146] Controlling the *Z* vs *E* stereochemistry during elimination is a major issue in these transformations, and only scant reports exist where strict geometry-control is successfully addressed. During the period 2007−2010, in a series of papers, Barbosa et al.[147−149] synthesized several γ-alkylidene butenolides that were designed using the naturally occurring toxins nostoclides as a lead structure (Scheme 65).

Thus, for example, a direct, one-pot/two-step Mukaiyama type VAR/β-elimination procedure was adopted with furanone **356**, which was reacted with piperonal **357** or trimethoxybenzaldehyde **359** to afford high yields of *Z*-disposed butenolide **358** or *E*-disposed congener **360**, respectively. The stereochemistry switch from *Z*- to *E*-isomers in the case of bulky aldehyde **359** is remarkable and was attributed by the authors to a destabilizing steric repulsion between the lactone oxygen lone pair and the methoxy groups in the *ortho*,*ortho*′-positions of the acceptor. With a number of synthetic nostoclide analogues in hand, the same authors[150] performed a rigorous QSAR study to correlate the molecular descriptors of these butenolides with their in vitro ability to interfere with the light-driven reduction of ferricyanide by isolated chloroplasts.

In about the same manner, Boukouvalas et al.[151−153] introduced a highly productive protocol to access important naturally occurring furanone metabolites as, for example, cadiolide B (**364**), (*S*)-melodorinol (**368**), and rubrolide L (**372**), all of which display interesting biological profiles (Scheme 66). To these goals, sequential VMAR/β-elimination maneuvers were adopted using a TBSOTf/tertiary amine Lewis acid−Lewis base mix to generate the active silyldienolate species, followed by base-assisted dehydration. Thus, starting with sterically congested furanone donors **361**, **365**, and **369** and suitable aldehyde acceptors **362**, **169**, and **370**, the expected γ-alkylidene butenolides **363**, **367**, and **371** were formed in good isolated yields, with excellent levels of *Z*-selectivity for the newly formed exocyclic double bond.

In several instances (e.g., eq 2), to control the fate of the aldol dehydration toward the requisite *Z*-isomers, a steric directing group stratagem was implemented, based on a temporary installation of a removable bromine directing group at the β-position of the furanone donor substrate.[152] Earlier work from the same laboratory had shown that a bulky β-substituent, such as an *i*-propyl group, leads exclusively to the formation of the *Z*-isomers, presumably via an E1cB mechanism.[154]

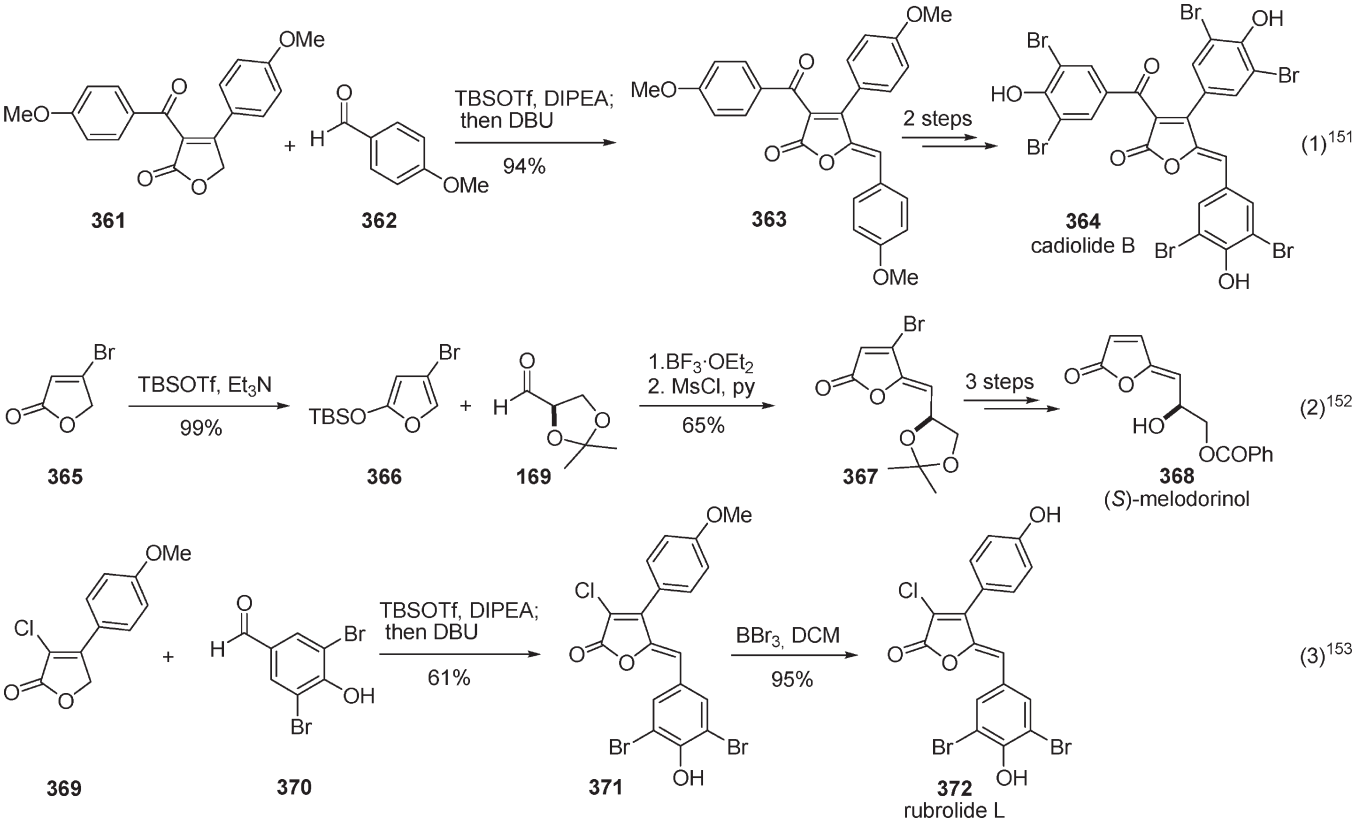
Targeting the 6′-epimer of the natural carotenoid butenolide peridinin **375**, a quite sophisticated structure embodying a *Z*-disposed γ-alkylidene butenolide ring subunit, de Lera et al.[130] equally adopted a sequential VMAR/dehydration procedure to prepare the central all-*Z* butenolide segment of the target, compound **373**, which was then elongated at the halogenated C14 position with the proper stannane unit **374**, and then to C9, to forge the entire skeleton of 6′-*epi*-peridinin (**375**) (Scheme 67). Of note, the key requisite intermediate **373** was delivered as a 7:1 *Z*/*E* mixture likely arising from a stereoselective β-elimination of a *syn*-configured aldol intermediary compound (not shown).

Pulvinic acids and vulpinic acids are yellow or orange pigments found in lichens and in mushrooms, which display a variety of interesting biological activities. With these candidates as targets, Antane et al.,[155] Mansour et al.,[156] and Le Gall et al.[157] independently developed very close strategies to construct the γ-alkylidene butenolide portion of these compounds (Scheme 68). The authors adopted either one-pot/two-step or two-step protocols to install the γ-alkylidene butenolide frames, which were subsequently transformed into the targets via Suzuki−Miyaura cross-coupling of halogenated unsaturated intermediates.

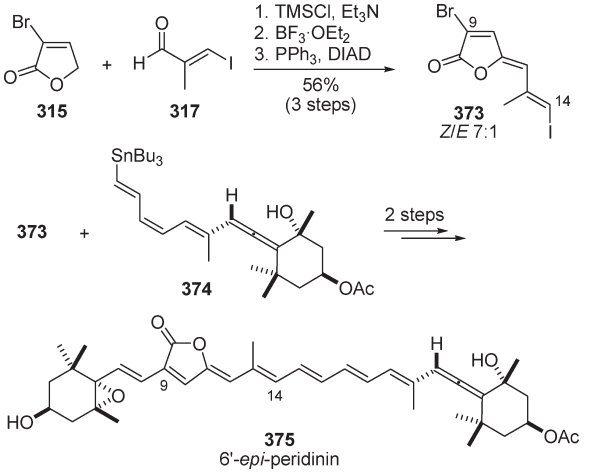
VARs followed by dehydration were further employed by several authors as a key maneuver to implement additional γ-alkylidene butenolides of biological interest. Noticeable reports include short syntheses of racemic pandamarilactonines A−D and ellipsoidones A and B by Argade and Gogoi,[158,159] as well as preparation of a wide series of andrographolide derivatives by Liu et al.[160] Often, the vinylogous aldol adducts were isolated as *syn*/*anti* mixtures and soon subjected to β-elimination, giving rise to the corresponding vinylene butenolides with poor *E*/*Z* selectivities.[158] At the contrary, when one-pot protocols were in place, stereocontrol was easily reached, as exemplified for the synthesis of ellipsoidone A (**389**) (Scheme 69).[159] In the event, *Z*-configured butenolide adduct **388** was preferentially formed in 75% yield based on a vinylogous condensation between furanone **386** and 5-methylfurfurale (**387**).

Similar chemistry was also applied to α,β-unsaturated γ-lactams (aza-butenolides) to arrive at nitrogenous γ-alkylidene butenolide congeners. Miyazaki et al.,[161] for example, synthesized a series of vinylene pyrrolinones of type **393** (Scheme 70,

Scheme 66. Synthesis of Cadiolide B (364), (*S*)-Melodorinol (368), and Rubrolide L (372)[151−153]



Scheme 67. Total Synthesis of 6′-*epi*-Peridinin (375)[130]



eq 1) by KHDMS-driven direct condensation of *N*-Boc lactams of type **390** with aromatic aldehydes (e.g., **391**). The reactions proceeded with good *Z*-selectivity, and several candidates were evaluated for their antithrombotic activity in a rat arterial thrombosis model. Adaptation of this dual VAR/elimination procedure to a soluble polymer-supported execution was described by Li et al.,[162] targeting *Z*-pulchellalactam (**395**), a CD45 protein tyrosine phosphatase inhibitor. Indeed, when pegylated lactam **394** was reacted with isobutyraldehyde (**67**) in the presence of sodium hydride in THF, *Z*-pulchellalactam (**395**) was directly accessed in high purity via vinylogous addition and formal E1cB dehydration (Scheme 70, eq 2).

3.2. Enantioselective Processes

In paralleling the trend of the most experienced carbon−carbon bond-forming reactions, the use of chiral metal- and nonmetal-based catalysts in the VAR has become a major area of study, with a number of salient achievements obtained, in the past decade, in both methodology-oriented studies and target-oriented investigations.

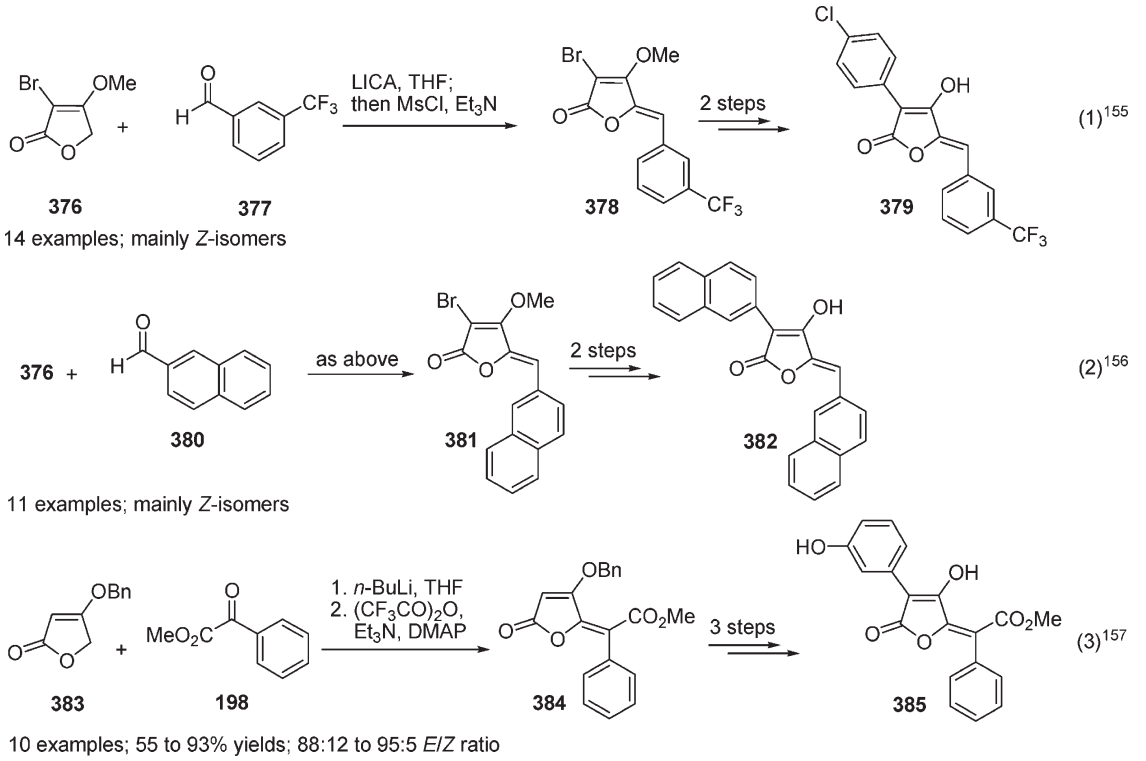
In this chapter, indirect methodologies exploiting preformed silicon dienolates, as well as direct additions of in situ-generated extended enolates are analyzed separately, with reactions utilizing similar enantio-inducing systems grouped together.

3.2.1. Indirect, Mukaiyama Type Additions of Silicon Dienolates *3.2.1.1. Acyclic Silicon Dienolates.* Acyclic silicon dienolates derived from readily available α,β-unsaturated carbonyl compounds, or β-keto esters and β-diketones (see Figure 5), have been extensively explored in recent years in a number of catalytic enantioselective vinylogous Mukaiyama type aldol processes (VMAR). A panel of the most representative members of the chiral metal-based catalysts usually utilized in VMAR is depicted in Figure 8, comprising complexes **396**−**401**.

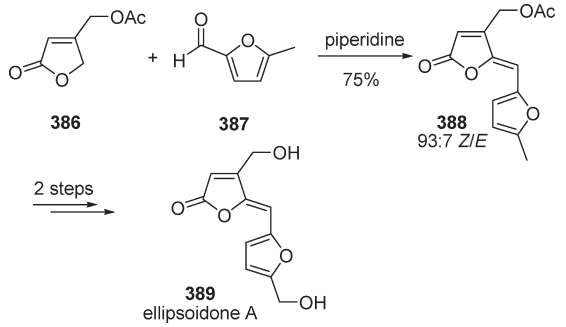
In 2002−2003, Carreira and Fettes[163,164] reported an elegant, convergent strategy for the synthesis of leucascandrolide A (**402**) (Scheme 71). The Carreira plan envisaged an enantioselective VMAR addition between dioxinone **1** and crotonaldehyde (**279**), which was catalyzed by the copper(I) fluoride complex **396**. The product formed, compound **403**, was then advanced to

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

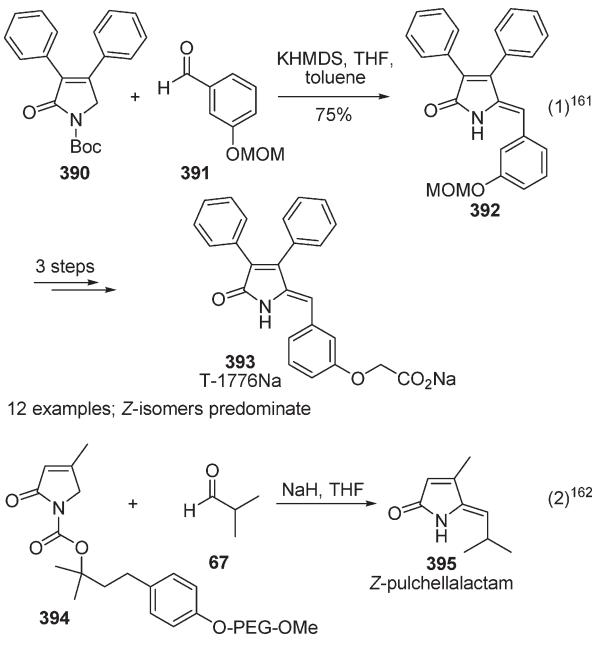
Scheme 68. Synthesis of Vulpinic Acid-Related γ-Alkylidene Butenolides 379, 382, and 385[155−157]



Scheme 69. Synthesis of Ellipsoidone A (389)[159]



Scheme 70. Synthesis of γ-Alkylidene Lactam Compounds 393 and 395[161,162]



methylketone **404**, which was coupled to aldehyde fragment **405** according to the Evans aldolization protocol. Finally, aldol adduct **406** was transformed to macrolactone **407**, which constitutes the C1−C22 fragment of leucascandrolide A. Because macrolide **407** had already been synthesized and transformed to the natural compound **402** by Leighton[165] in 2000, Carreira utilized the same chemistry to transform **407** into **402**, thus completing a new total synthesis of this marine metabolite.

In closely related papers that appeared in the period 2000−2007, Campagne et al.[166−173] utilized the skillful Tol-BINAP·CuF complexes **396** and *ent*-**396** to promote catalytic enantioselective VMAR between acyclic vinyl silyl ketene acetals and carbonyl acceptors. Both linear and lactonized vinylogous aldol products were attained, as shown in Schemes 72 and 73. Initially,[166−168] this asymmetric strategy was optimized using both aliphatic and aromatic aldehydes, resulting in the preparation of enantiomerically enriched linear δ-hydroxy-α,β-unsaturated esters **409**, **410**, and **412**, in good yields and 70−81% ee (Scheme 72). Interestingly, aminated fragment **412** was advanced to the C9−C23 subunit of the group A streptogramin antibiotics in nine steps.[168]

The same research group targeted several chiral nonracemic α,β-unsaturated δ-lactone compounds by employing the Carreira CuF·Tol-BINAP catalysts **396** or *ent*-**396**. The results are

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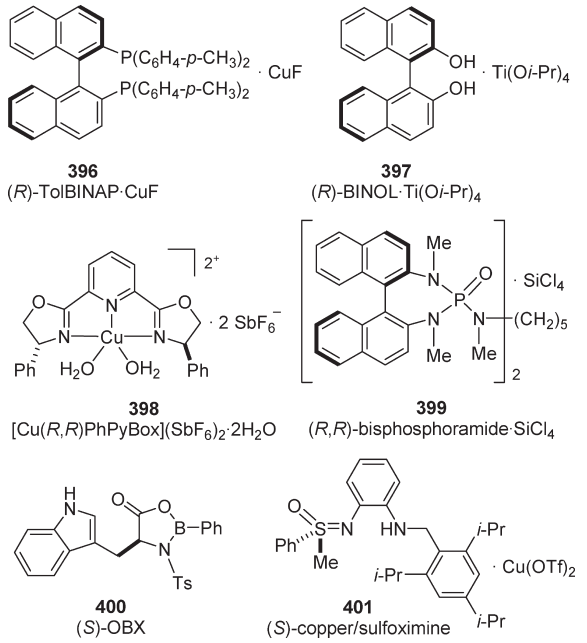
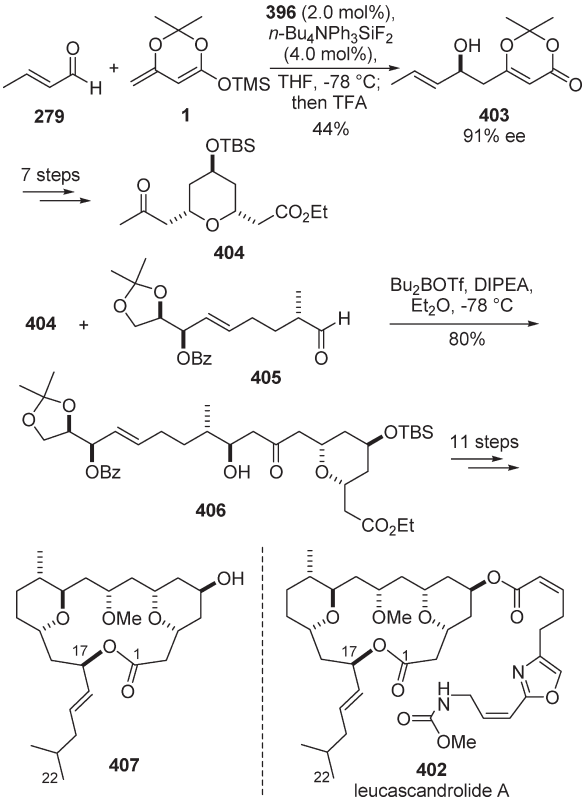


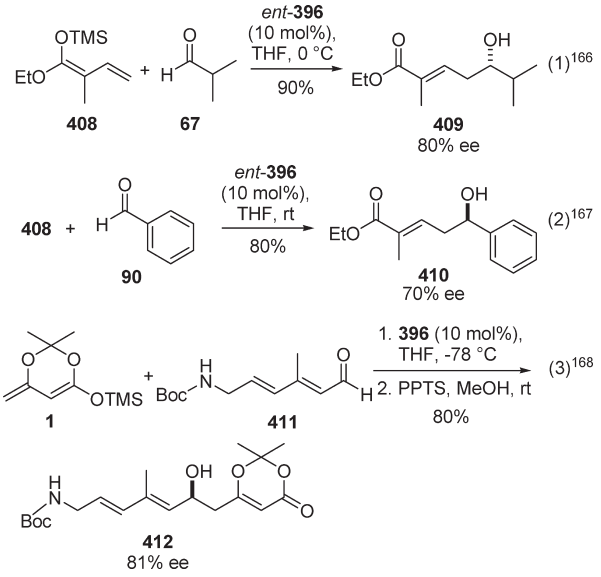
Figure 8. Representative metal-based chiral nonracemic complexes used in catalytic enantioselective VMAR.

Scheme 71. Total Synthesis of C1−C22 Macrolactone Fragment of Leucascandrolide A (402)[163,164]

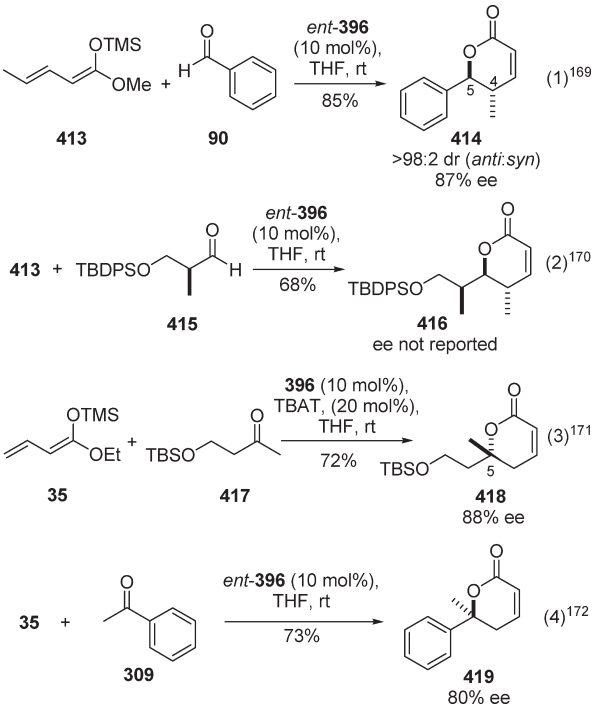


grouped in Scheme 73. With γ-methyl-substituted dienolate **413**, lactones **414** (with benzaldehyde **90**) or **416** (with chiral nonracemic propanal **415**) were obtained in good yield,

Scheme 72. Asymmetric Synthesis of Linear Aldol Fragments via Copper(I)-tol-BINAP Catalyzed VMAR[166−168]



Scheme 73. Asymmetric Synthesis of Lactone Fragments via Copper(I)-tol-BINAP Catalyzed VMAR[169−172]



optimum 4,5-*anti*-diastereoselectivity, and good enantiomeric excesses with little, if any, linear vinylogous adducts formed (Scheme 73, eqs 1 and 2).[169,170] Importantly, enantioenriched lactone **416** was employed as the initial chiral building block to synthesize the Prelog−Djerassi lactone,[169] as well as the C1−C5, C7−C15, and C17−C24 fragments of (+)-discodermolide,[170]

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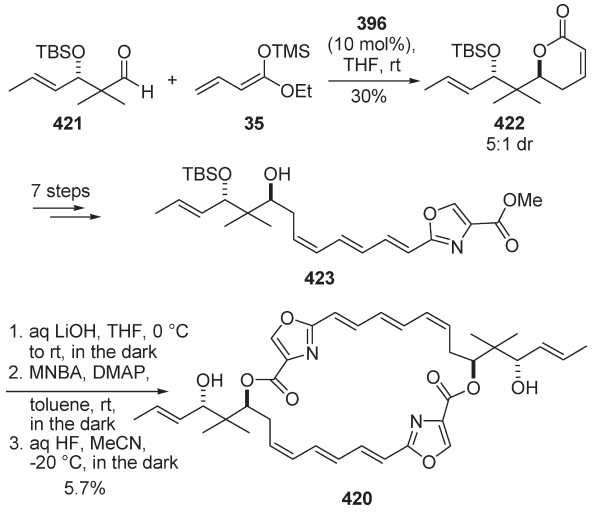
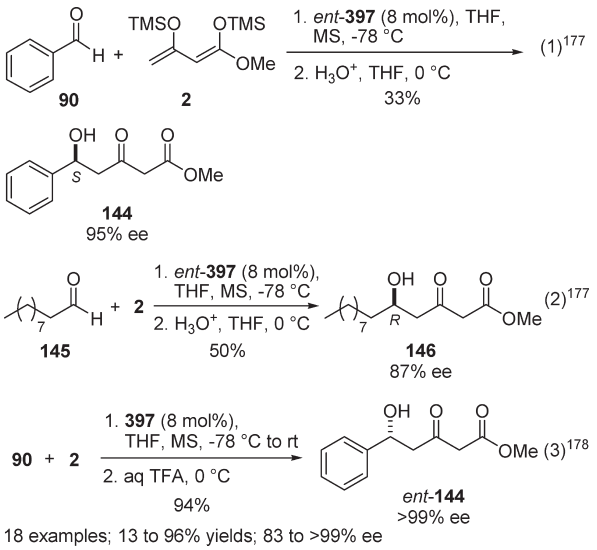
Scheme 74. Asymmetric Synthesis of Simplified Disorazole 420[174]



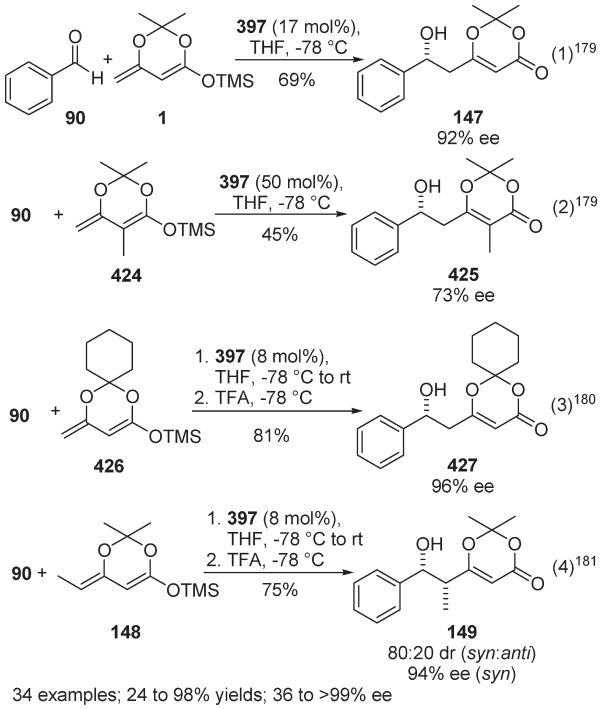
Scheme 75. Asymmetric VMAR Additions Involving Chan Diene 2[177,178]



thus highlighting once more the utility of these vinylogous aldol products in asymmetric synthesis. Furthermore, unsubstituted silyl dienolate **35** reacted with methyl ketones **417** or **309** under the above-mentioned catalytic, asymmetric procedure, producing lactone derivatives **418** or **419**, respectively (Scheme 73, eqs 3 and 4).[171,172] Lactone **418**, bearing a quaternary stereocenter at C5, was then utilized by the same authors as the starting building block in a formal asymmetric synthesis of taurospongin A.[171]

In 2006, Campagne reinvestigated the previously disclosed chemistry, thoroughly extending the scope of his copper-catalyzed asymmetric VMAR.[173] In particular, the study assayed how the dienolate structure, the chiral ligand, and the precatalyst additives impact VMAR diastereo- and enantiocontrol. On the basis of a number of experimental evidence, it was surprisingly

Scheme 76. Asymmetric VMAR Additions of Dioxinone-Derived Dienes 1, 424, 426, and 148[179−181]



concluded that a classical vinylogous Mukaiyama copper Lewis acid-governed reaction involving an eight-membered transition state can probably be ruled out in favor of a mechanism where a racemic "regular" α-aldol reaction occurs, followed by an asymmetric copper(I)-catalyzed allylation.

The Carreira catalyst and the Campagne protocol were quite recently exploited by Kalesse et al.[174] during a clever total synthesis of novel simplified disorazoles of type **420** (Scheme 74). The starting move was an enantioselective VMAR between ketene acetal **35** and aldehyde **421**, in turn obtained via the known Kiyooka aldol reaction.[175] In the event, using copper(I)-BINAP catalyst **396**, the planned VMAR occurred well, giving rise to the wanted lactone **422** in 30% isolated yield (5:1 dr), accompanied by a 25% yield of the corresponding linear adduct (not shown). To advance the synthesis, lactone **422** was separated from the reaction mixture and transformed to polyene carboxylate **423**, ready for the crucial cyclodimerization. After several abortive attempts, conditions were found to perform dimerization, which was conducted by base-catalyzed liberation of the carboxylic function and subsequent cyclization using the Shiina protocol.[176] Remarkably enough, the cyclodimerization solely occurred when the process was carried out with complete exclusion of light, allowing completion of the synthesis and isolation of pure disorazole **420**.

Chiral BINOL, BINAP, and their derivatives are used extensively as ligands in metal-catalyzed asymmetric organic synthesis. On this line, Scettri and colleagues applied, in a series of methodological works, Ti(IV)−BINOL catalysts in VMAR, utilizing either acyclic acetoacetic ester-derived silyl dienolates or dioxinone dienolates as d_4 donor substrates.[177−185] Scheme 75 groups selected examples of BINOL−Ti(IV)-catalyzed asymmetric VMAR involving acyclic silyloxy diene **2** and aliphatic or

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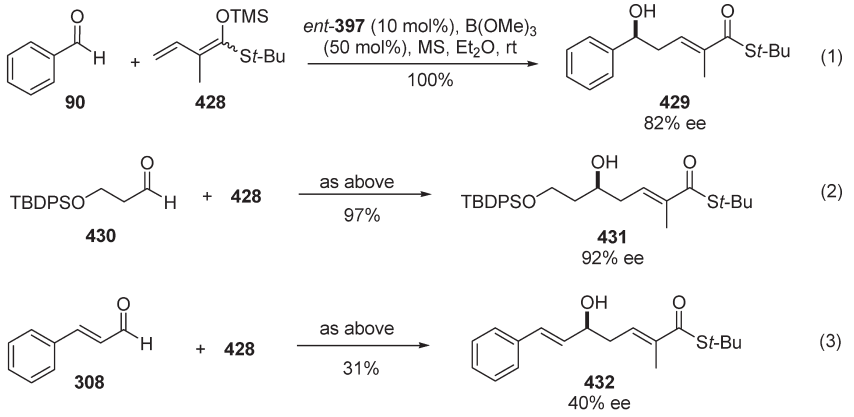
Scheme 77. (*S*)-BINOL−Ti(IV)-Catalyzed VMAR between *O,S*-Ketene Acetal 428 and Various Aldehydes[186]



aromatic aldehydes.[177,178] Indeed, using only minute quantities of (*R*)- or (*S*)-configured BINOL−Ti(IV) reagents **397** or *ent*-**397**, VMAR proceeded in moderate to good efficiency, with the respective enantioenriched adducts recovered in either silylated or silicon-free forms, depending upon the quenching procedure used. Along with the examples shown in Scheme 75, several aliphatic, aromatic, and heteroaromatic aldehydes proved to be competent substrates in these reactions, allowing preparation of the expected adducts in variable yields with high to excellent levels of enantioselectivities.

Dioxinone type silyl ketene acetals of type **1**, **424**, **426**, and **148** also served as suitable donors in a number of asymmetric VMAR additions with Ti(IV)−BINOL catalysts.[179−181] Scheme 76 lists a choice of reactions utilizing either nonprochiral dienes **1**, **424**, and **426**, or prochiral γ-methyl-substituted analogue **148**. Using benzaldehyde (**90**) as the VMAR acceptor, highly enantioenriched adducts formed in moderate to good yields, with ee values rising to >90%. Also in this case, along with the examples here displayed, a wide number of reactions were carried out to evaluate the full scope of these catalytic, enantioselective VMAR procedures.

In a series of parallel experiments, Scettri et al.[182−185] also focused on nonlinear effects and autoinduction in the above disclosed asymmetric VMAR involving dioxinone- and acetoacetic ester-derived dienolates. It was discovered that Ti(IV)−BINOL-mediated additions often proceed through an autoinductive process with amplification of the enantiomeric excess of the resulting aldol addition products. For readers interested in a detailed overview on this matter, a review was published by Scettri et al. in 2004.[10]

More recently, Keck and Heumann[186] reported an improved technique for catalytic asymmetric VMAR between thioester-derived silyl dienolate **428** and several aldehydes. After considerable optimization work, the authors found that a catalyst mixture consisting of 10 mol % (*S*)-BINOL/Ti(O*i*-Pr)$_4$ complex *ent*-**397** (1:1 stoichiometry) in the presence of 4 Å molecular sieves and 50 mol % B(OMe)$_3$ effectively propelled the reaction at room temperature affording enantioenriched vinylogous products of type **429**, **431**, and **432** in moderate to excellent yields (Scheme 77). The collected data suggest that participation of molecular sieves and borate additives is not limited to promoting formation of the active catalyst but may also play a pivotal role in the progress of the reaction and asymmetric induction.

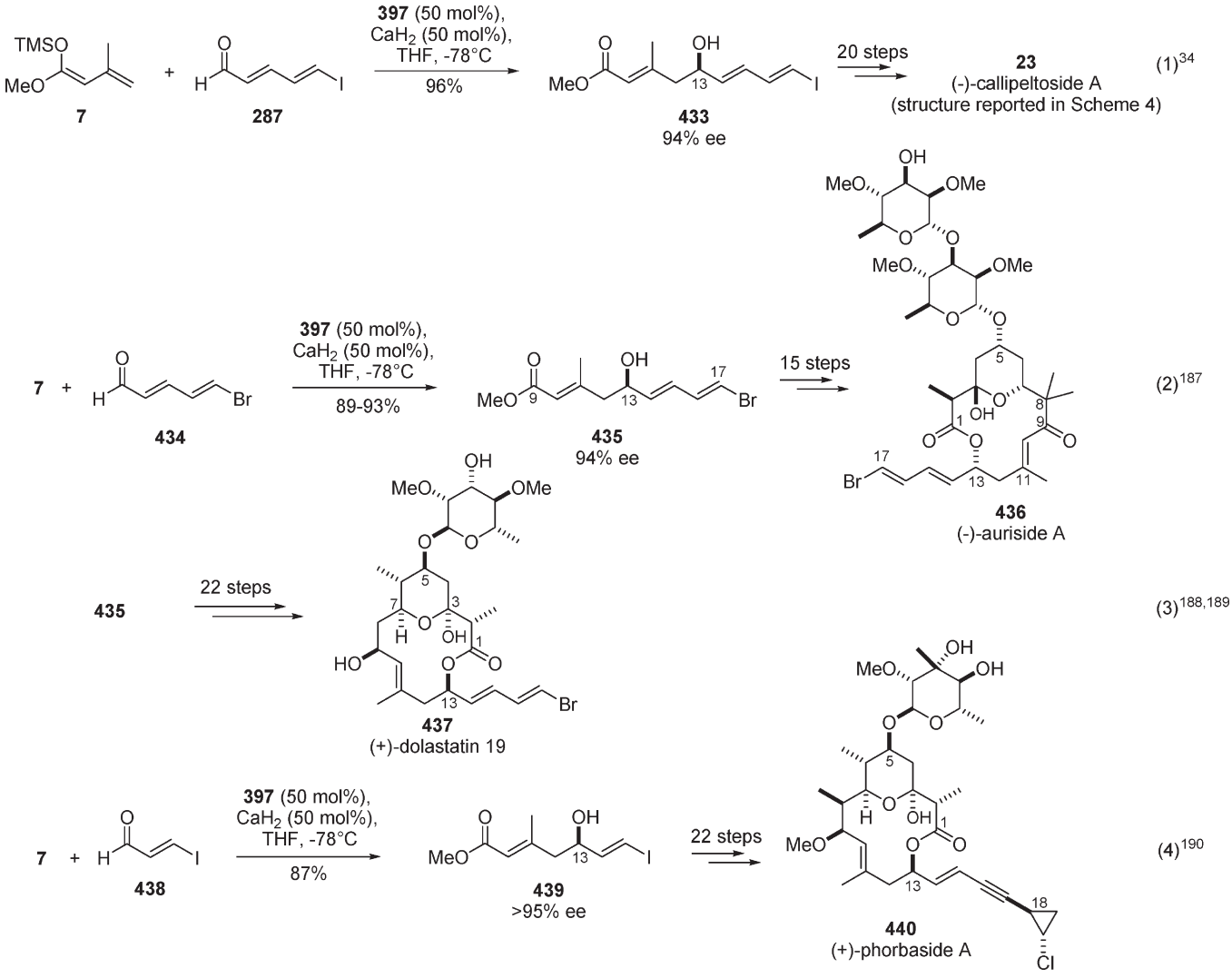
A decisive improvement of the asymmetric VMAR using the BINOL/Ti(O*i*-Pr)$_4$ catalyst system was reached by Paterson during the optimization of the opening move of stereocontrolled total synthesis of (−)-callipeltoside A (**23**) (vide supra, chapter 3.1.1.1.).[34] The methodology consisted of treatment of the selected dienolate donor (e.g., silyl ketene acetal **7**) with the proper aldehyde partner (e.g., iododienal **287**) in the presence of 0.5 equiv each of Ti(O*i*-Pr)$_4$ and (*R*)-BINOL, with 0.5 equiv of CaH_2 as an additive in place of the usual molecular sieves (Scheme 78, eq 1). There, high isolated yield, complete γ-site selectivity, and excellent levels of ee were achieved, with the (*R*)-configured *E,E*-polyketide adduct **433** formed on multigram scale. The use of CaH_2 en lieu of 4 Å MS prevented both competing hydrolysis of the silyl ketene acetal and, importantly, the Lewis acid-promoted isomerization of the initial *E,E*-configured vinyl iodide acceptor.

Very similar chemistry was also exploited by the same author in a full program directed at the total synthesis of several marine antibiotics of polyketide origin.[187−190] In these endeavors, Paterson invariably utilized an enantiocontrolled VMAR between acyclic silyl ketene acetal **7** and bromo- or iodo-substituted enals **434** or **438** as the incipit move to install the absolute *R*-chirality at C13 in the corresponding aldol adducts **435** and **439** (eqs 2 and 4).

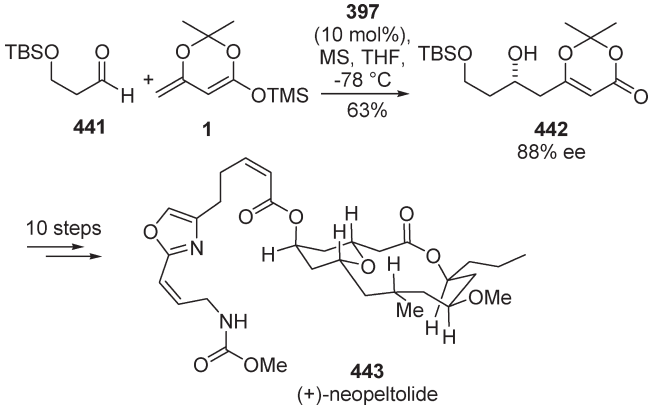
Thus, after completion of the total synthesis of (−)-callipeltoside A (**23**),[34] (−)-auriside A (**436**),[187] (+)-dolastatin 19 (**437**),[188,189] and (+)-phorbaside A (**440**),[190] ambiguities on the relative and absolute stereochemical arrangement of these natural products were fully ruled out. The brilliant chemistry developed in transforming the initial enantioenriched fragments into the final targets is not discussed here, and the interested reader is addressed to the original papers for details.

Successful application of this asymmetric methodology was described by Scheidt and colleagues[191,192] in the total synthesis of the marine macrolide neopeltolide (**443**). As illustrated in Scheme 79, a VMAR coupling between dioxinone **1** and protected hydroxypropanal **441** in the presence of 10 mol % catalyst complex **397** gave β-hydroxy-dioxinone **442** in 63% yield and 88% ee. Seven carbon-long fragment **442**, as well as its enantiomer (parallely obtained by using *ent*-**397** as a catalyst), served to the construction of (+)-neopeltolide (**443**) along with a couple of diastereomeric unnatural variants, thus probing structural assignment of the natural compound.

Scheme 78. Optimized Enantioselective VMAR in the Total Synthesis of Marine Polyketides 23, 436, 437, and 440[34,187−190]



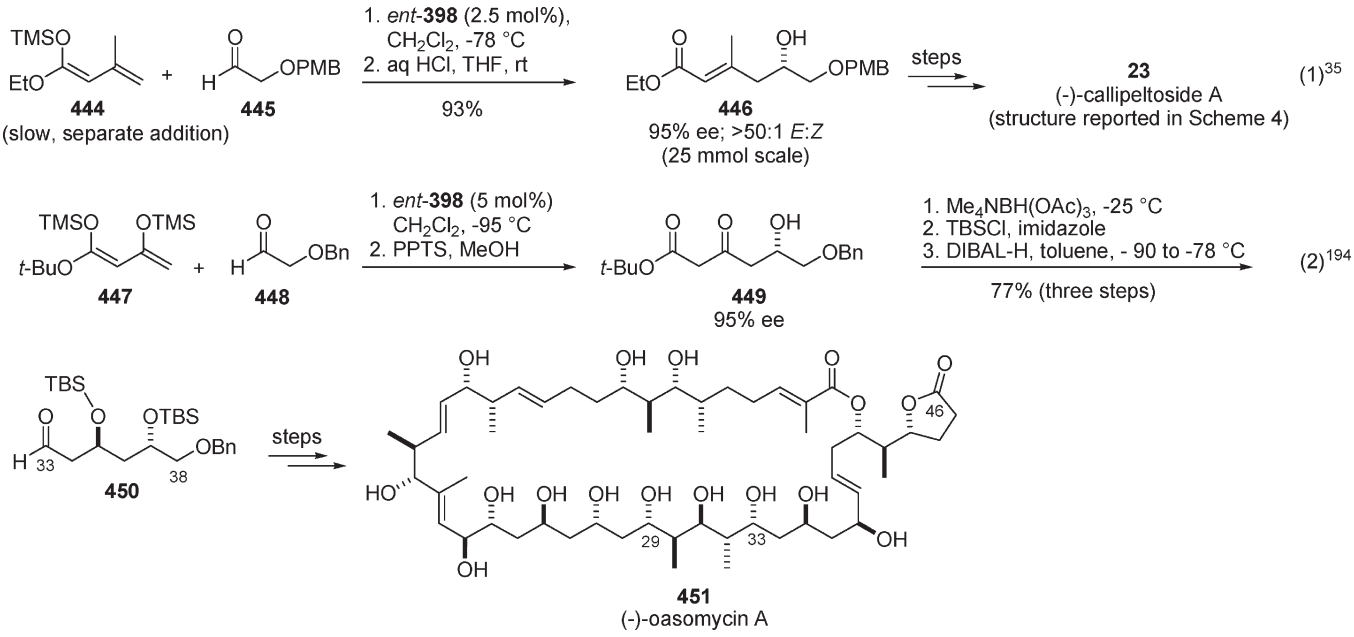
Scheme 79. Further Use of BINOL−Ti(IV) Catalyst System in Asymmetric VMAR[191,192]



Since 1999, Evans and co-workers have shown that C_2-symmetric chiral bis(oxazolinyl)pyridine copper(II) complexes are competent catalysts for the asymmetric VMAR of dienol silanes and (benzyloxy)acetaldehyde.[193] The air stable

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 80. Enantioselective Synthesis of the Fragments 446 and 449 via VMAR Catalyzed by Lewis Acidic Copper(II)-PyBox Complex *ent*-398[35,194]



copper(II) catalyst variant, *ent*-**398**, was conveniently exploited by Evans himself in the VMAR reaction between dienolate **444** and protected hydroxyacetaldehyde **445** during the debut of (−)-callipeltoside A synthesis (Scheme 80, eq 1).[35,36] In the event, (*S*)-configured aldol compound **446** was generated in high yield (93%), with almost complete *E* selectivity (*E*/*Z* > 50:1) and excellent enantioselectivity (95% ee). Crucial to the success of this reaction was the optimized operational procedure, which entailed simultaneous slow addition of separate solutions of the two reactants to the preformed catalyst solution. Enantioenriched product **446** was then cleverly elaborated into (−)-callipeltoside A (**23**), according to the multistep procedure that has previously disclosed in chapter 3.1.1.1. (Scheme 5).

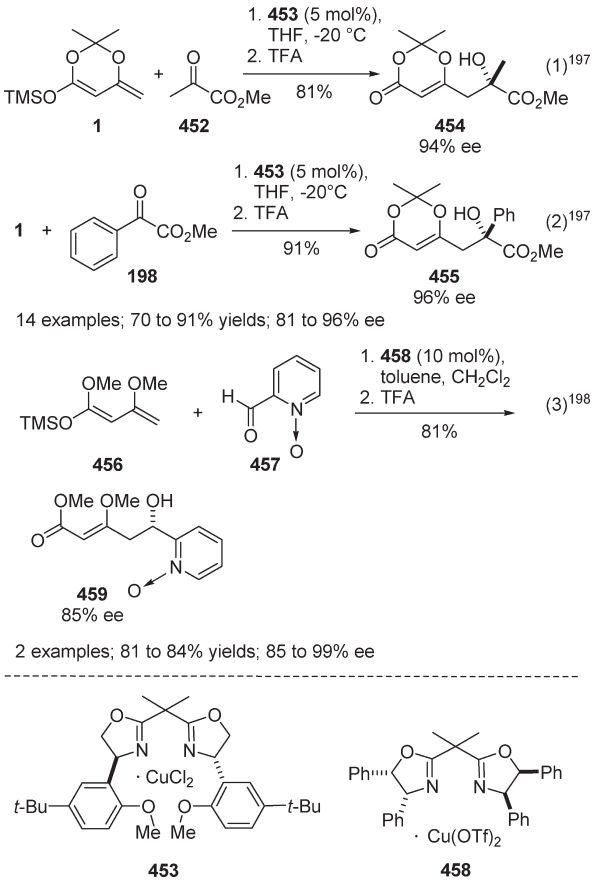
A metal-based asymmetric VMAR also served to Evans and coworkers to prepare the 95% ee-pure polyacetate aldehyde **450**, the C33−C38 subunit of natural macrolide (−)-oasomycin A (**451**) (Scheme 80, eq 2).[194] Starting from Chan diene **447**, reaction with bidentate benzyloxyacetaldehyde (**448**) in the presence of Cu(II) complex *ent*-**398** followed by acidic treatment furnished (*R*)-configured keto ester **449** in good yield and high enantiomeric excess (95% ee). Diastereoselective reduction of the ketone moiety and ester-to-aldehyde transformation provided the requisite fragment **450**, which was utilized in the successful total synthesis of the challenging 42-membered macrolide target **451**.[195,196]

Slightly modified box-based copper(II) complexes **453** and **458** were used by Pagenkopf[197] and Jørgensen[198] in asymmetric VMAR involving keto esters or *N*-oxy-carboxyaldehyde acceptors, respectively. As shown in Scheme 81,[197] dioxinone **1** reacted with methyl pyruvate (**452**) or phenylglyoxylate (**198**) (eqs 1 and 2) in the presence of catalyst **453**, giving rise to the expected linear adducts **454** or **455** in high isolated yields and excellent ee. The scope of this efficient enantioselective technique was also successfully explored with a variety of keto esters, demonstrating the ability of the new catalytic system of type **453** to positively address these transformations.

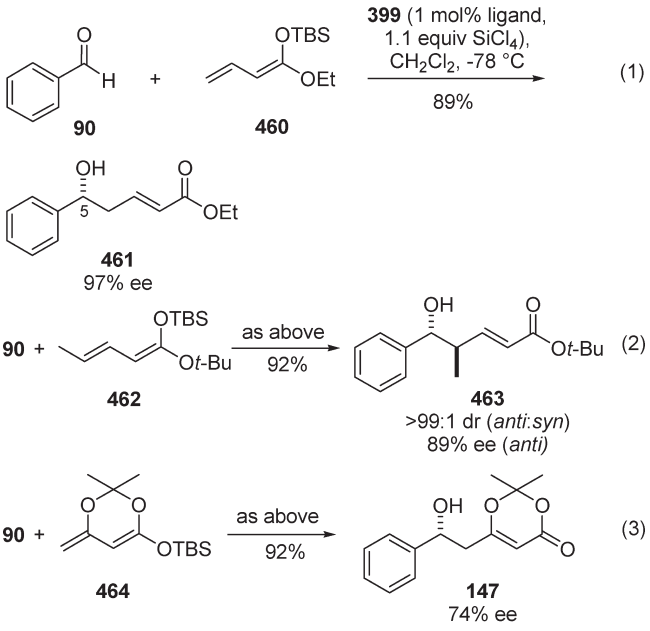
During an extensive work aimed at investigating asymmetric hetero-Diels−Alder reactions of *N*-oxy-pyridine aldehyde (**457**) with electron-rich dienes including Brassard diene (**456**) and Danishefsky diene (not shown), Jørgensen[198] explored the catalytic potential of several chiral copper(II)−box complexes. The authors showed that use of the Danishefsky diene invariably resulted in the formation of HDA adducts, while diene **456** gave only the linear VMAR adduct of type **459** in high yields and enantioselectivity, with no trace of the cyclic HDA adduct (Scheme 81, eq 3). As with aldehyde **457**, pyridine ketones also proved excellent substrates in VMAR additions to diene **456**, providing the corresponding open-chain vinylogous adducts with excellent enantioselectivities. A possible explanation for the isolation of VMAR adducts en lieu of HDA products could be the stability of the formed linear methyl esters due to hydrogen bond stabilization between the *N*-oxide and the aldol hydroxyl group.

On the basis of a series of sound investigations on enantio- and diastereocontrolled Mukaiyama type aldol reactions involving acetate- and propionate-derived silyl ketene acetals and employing Lewis base−Lewis acid combinations of chiral phosphoramide ligands and silicon tetrachloride, the viability of this asymmetric technique was assayed by Denmark et al. in the vinylogous aldol realm.[199−203] In this endeavor, the catalyst of choice was the dimeric bisphosphoramide·$SiCl_4$ complex **399**, which governs the reaction through a phosphoramide-catalyzed and $SiCl_4$-mediated catalytic cycle. Scheme 82 shows a few examples, among many, involving VMAR between benzaldehyde (**90**) and ester-derived silyl dienol ethers **460** and **462** or dioxinone-based dienolate **464**.[199−201] All reactions performed well in site selectivity, as well as in diastereo- and enantiocontrol, producing the expected δ-hydroxy-α,β-unsaturated esters **461**, **463**, and **147** in high isolated yields. It should be noted that, irrespective of the donor structure, all products emerged with 5*R* absolute configuration as a consequence of the preferential attack of the nucleophile to the *Re* face of the aldehyde component.

Scheme 81. Enantioselective Copper-Catalyzed VMAR Using C_2-Symmetric Bis(oxazoline) Complexes 453 and 458[197,198]



Scheme 82. Bisphosphoramide-Catalyzed Enantioselective VMAR of Ester- or Dioxinone-Derived Silyl Dienol Ethers[199−201]



This versatile methodology was next extended to involve VMAR additions of silyl dienol ethers derived from ketones, β-diketones, and amides.[202,203] Scheme 83 lists three out of 75 examples of enantioselective VMAR between aromatic and aliphatic aldehydes **90** and **469** and simple or prochiral dienolates **465**, **467**, and **470** catalyzed by **399** that was obtained by combining 1−5 mol % (*R*,*R*)-bisphosphoramide ligand and 1.1−1.5 equiv of $SiCl_4$. Inspection of the whole results reveals several important points: (1) when the reactions were quenched with a 1:1 mixture of saturated aqueous KF and aqueous $NaHCO_3$, the expected vinylogous aldol adducts of type **466**, **468**, and **471** solely emerged in high yields and with exquisite margins of site-, diastereo-, and enantioselectivities; (2) when the diastereocontrol applied (e.g., eq 2), strict preference for the *anti*-configured isomers occurred; (3) the acceptor enantiofacial discrimination was neatly controlled by the chiral catalyst, which was reflected in preference for C5(*R*)-configured isomers **466** and **468**, or C5(*S*)-isomer **471**; and (4) use of morpholine-derived dienolates overcame the well-known lethargy involving aliphatic aldehydes, with optimal results obtained in several cases (e.g., eq 3).

Paralleling this chemistry, enantioselective VMAR additions catalyzed by the above disclosed Denmark bisphosphoramide/$SiCl_4$ system **399** were also investigated by Scettri et al.[204] involving Chan diene **2**. Under the reported conditions, additions to aromatic, heteroaromatic, and α,β-unsaturated aldehydes were screened, with the expected products obtained in acceptable yields and moderate to good enantioselectivities.

The synthetic potential of catalyst **399** in asymmetric VMAR was cleverly explored by several research groups as a key tool in both total and partial synthesis of biologically relevant natural products of polyketide origin. Thus, Denmark and Fujimori[205] applied this chemistry to the total synthesis of RK-397 (**472**), a member of the large family of polyene macrolides (Scheme 84, eq 1). The synthesis highlights the enantioselective VMAR between ester-derived silyl ketene acetal **460** and silyl-2-propenal **473** that produces (*R*)-configured ester **474** in good yield (75%) and excellent γ-selectivity and enantioselectivity (96% ee). This represents the C19−C25 portion of RK-397 and the chirality in this building block establishes 8 of 10 stereogenic centers in the target by substrate control.

In 2005, Floreancig et al.[206] reported a convergent total synthesis of (+)-dactylolide (**475**), which entails a multistep sequence where stereogenicity is derived from asymmetric catalysis via VMAR between dioxinone-derived silyl dienolate **1** and aldehyde **476** (Scheme 84, eq 2). Indeed, VMAR addition occurred efficiently through Denmark (*S*,*S*)-bisphosphoramide *ent*-**399** catalysis, affording (*S*)-configured vinylogous adduct **477** (83% yield, 93% ee), which represents the C3−C13 east-portion of (+)-dactylolide (**475**). As both enantiomers of the catalyst that were used to establish stereogenicity into the target are available, this sequence is also applicable to the synthesis of the enantiomer of **475**, the macrolactone core of (−)-zampanolide.

Also, the Denmark variant of the asymmetric VMAR was employed by Kirschning et al.[207] and Yang et al.[208] in the synthesis of the C6−C24 fragment **481** of ripostatins A and B and the construction of the C1−C12 fragment **487** of iriomoteolide 1a, respectively (Schemes 85 and 86).

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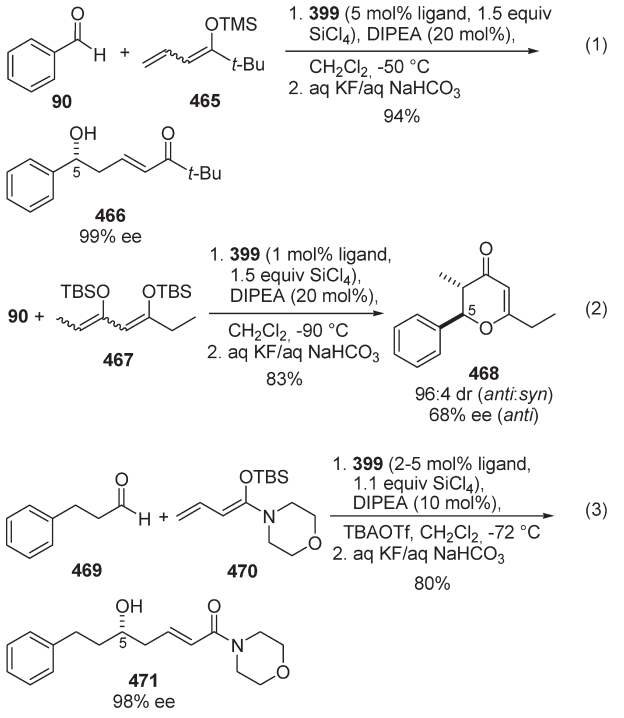
Kirschning[207] coupled chiral aldehyde **478** to β-methyl-substituted silyl ketene acetal **479** arriving at adduct **480** in moderate yield and good 93:7 diastereoselectivity. Of note, the neighboring OPiv group within **478** was beneficial in VMAR coupling, the corresponding OTBS-group giving only poor stereocontrol.

On the other hand, Yang[208] exploited two consecutive asymmetric VMAR to arrive at the targeted fragment **487** (Scheme 86). Initially, **460** was reacted with aldehyde **482** under Denmark's conditions [(*S*,*S*)-configured *ent*-**399** catalyst] to give adduct **483** in high enantiopurity, which was forwarded to elongated aldehyde **484**, the acceptor component of the subsequent VMAR (Carreira's catalyst **396** employed). This sequence produced unsaturated δ-lactone **486**, which was finally advanced to the C1−C12 fragment **487** of iriomoteolide 1a.

Scheme 83. Bisphosphoramide-Catalyzed Enantioselective VMAR of Ketone-, β-Diketone-, or Amide-Derived Silyl Dienolates[202,203]



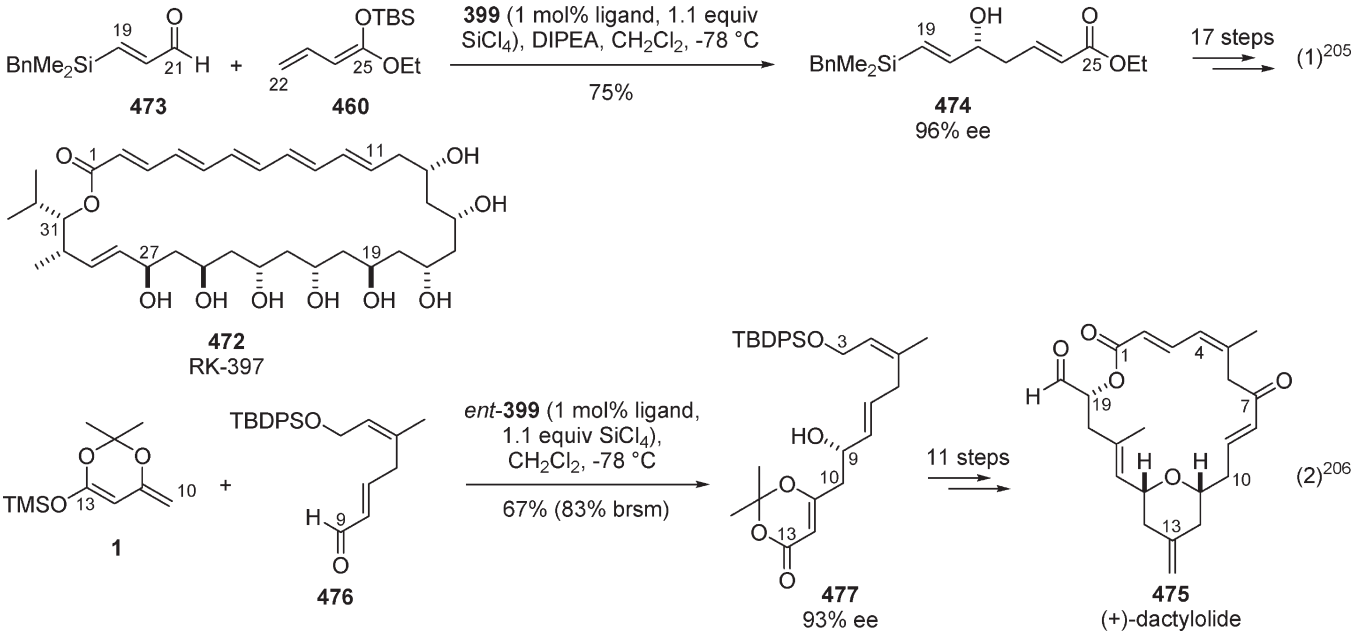
75 examples; 24 to 98% yields; γ:α > 98%; 82:18 to 97:3 dr; 50 to 99% ee

Amino acid-derived chiral 1,3,2-oxazaborolidinone and borolidine catalysts of type **400** (Figure 8) have been extensively employed in asymmetric VMAR by several authors aiming at synthesizing varied enantioenriched polyketide segments. In 2007, Kalesse et al.[209] introduced tryptophane-based *B*-phenyloxazaborolidinone **400** to perform enantioselective VMAR between unsubstituted silyl ketene *O*,*O*-acetal **488** and various aldehydes. A couple of examples are reported in Scheme 87 (eqs 1 and 2). Optimum results were obtained when 100 mol % boron promoter was employed, with *i*-PrOH as an additive. With α-chiral silyloxyaldehydes (e.g., *ent*-**73** in eq 2), VMAR proceeded equally well in both the matched and the mismatched sense, indicating that the chiral Lewis acid overrides the inherent substrate Felkin selectivity. In these cases, however, the aldehyde hydroxyl protecting group did bare a strong influence on the diastereoselectivity, with TBS performing better than PMB.

Extension of this methodology to prochiral γ-substituted dienolate **8** proved problematic, and proper adaptation of the boron catalyst structure was required to attain synthetically useful results.[210] After wide experimentation, Kalesse turned to proline-derived oxazaborolidines of type **491** (Scheme 87), the superior catalyst in this family. Two selected examples are shown in eqs 3 and 4. It can be seen that aliphatic aldehydes, in particular, provided very good selectivities with a 50 mol % catalyst loading.

Valine-based oxazaborolidinone catalyst **496** was employed by Kiyooka and co-workers[211] in the synthesis of a key fragment of the polyol portion of filipin III (**494**), a polyene macrolide antibiotic that selectively binds cholesterol (Scheme 88). Here,

Scheme 84. Enantioselective VMAR in Total Synthesis of RK-397 (472)[205] and (+)-Dactylolide (475)[206]



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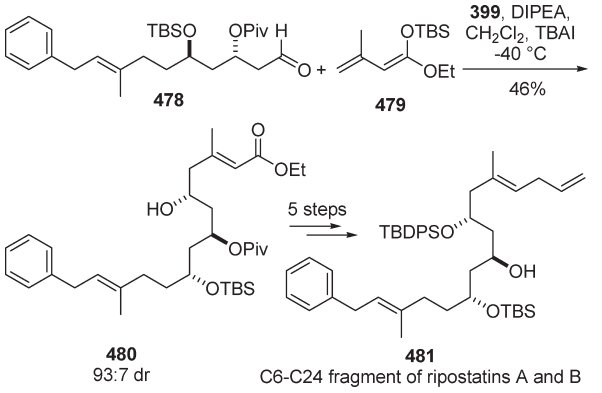
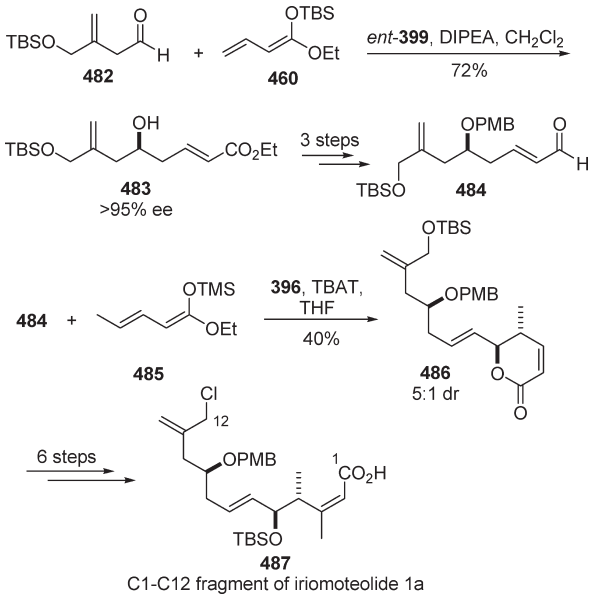
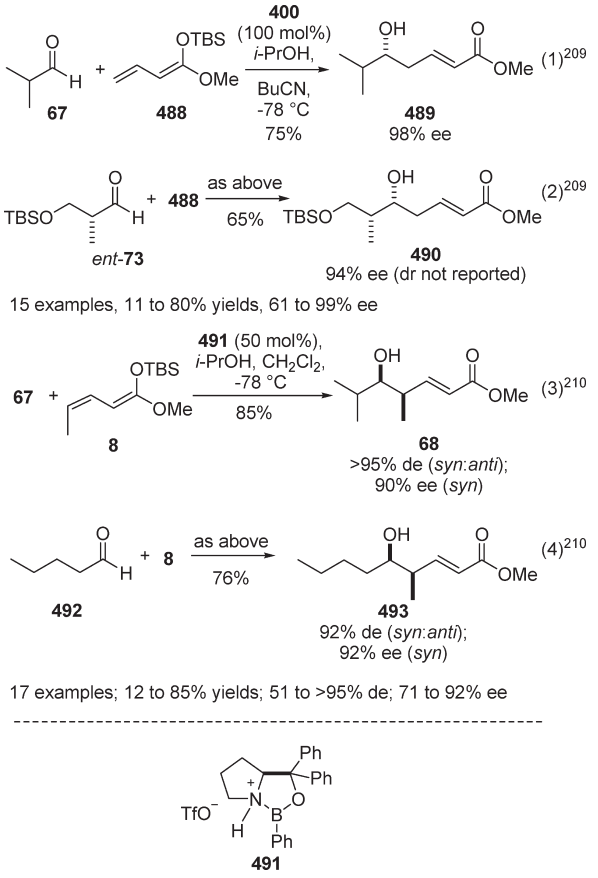
Scheme 85. Asymmetric VMAR in the Synthesis of Ripostatin Fragment 481[207]



Scheme 86. Sequential Asymmetric VMAR in the Synthesis of Iriomoteolide 1a Precursor 487[208]



Scheme 87. Use of Chiral Oxazaborolidine Catalysts in Asymmetric VMAR[209,210]



VMAR between chiral aldehyde **495** and Chan diene **2** afforded hydroxy keto ester **497** in a 92% *syn*-diastereoselectivity. Then, **497** was elaborated into aldehyde **498**, which constitutes the C1−C9 segment of filipin III (**494**).

In 2008, Smith III and colleagues[212] published a brilliant total synthesis of (+)-psymberin (**499**), alias irciniastatin A, featuring a reagent controlled VMAR as the strategic step (Scheme 89). From the strategic perspective, installation of the four stereogenic centers at C8, C9, C11, and C13 took advantage of an initial asymmetric VMAR between aldehyde **500** and dienolate **488** in the presence of 120 mol % boron promoter **400**. The yield of the vinylogous aldol product **501** was 66%, with an almost complete enantiocontrol in favor of the desired *R*-isomer. Once the first stereogenic center was created, the whole sequence proceeded along a further 18 steps in a convergent pathway and culminated in the total synthesis of the natural target.

In a clever investigation aimed at exploring the catalytic potential of copper(II) complexes of type **401** (Figure 8) based on chiral C_1-symmetric aminosulfoximine ligand, Bolm and co-workers studied the asymmetric VMAR between dienoxy silanes of type **502** and α-keto ester acceptors.[213] A series of additions were investigated, two of which are displayed in Scheme 90. High isolated yields and excellent enantioselectivities were obtained for all synthesized adducts (e.g., **503** and **505**).

A group of tridentate Schiff base ligands and metal Lewis acids was examined by Feng et al.[214] as catalysts for HDA/VMAR involving Brassard diene of type **456** and a wide variety of aromatic and aliphatic aldehydes. On the basis of experimental evidence, the authors claimed that when Brassard diene and benzaldehyde are involved, reactions using Ti(IV)−Schiff base complexes occurred via either a concerted hetero-Diels−Alder path (0 to −20 °C) or a stepwise vinylogous Mukaiyama aldol mechanism (−78 °C).

Titanium(IV) complexes of various chiral calix[4]arene derivatives were also tested by Soriente and Neri[215] as catalysts in enantioselective VMAR between Chan silyloxy diene **2** and *p*-nitrobenzaldehyde. Regrettably, while the reaction yields of the corresponding vinylogous adducts were acceptable, the enantioselectivities were extremely low, with a maximum value of 28% ee.

Hydrogen bonding represents a central issue in governing many enzyme-catalyzed reactions, and this concept has been recently put into practice by organic chemists to catalyze important symmetric and asymmetric carbon−carbon bond-forming processes. Along this line, Rawal et al.[216] examined the

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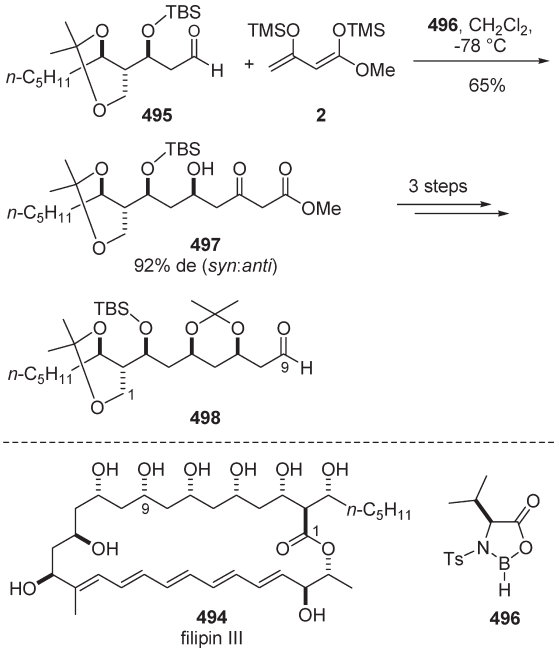
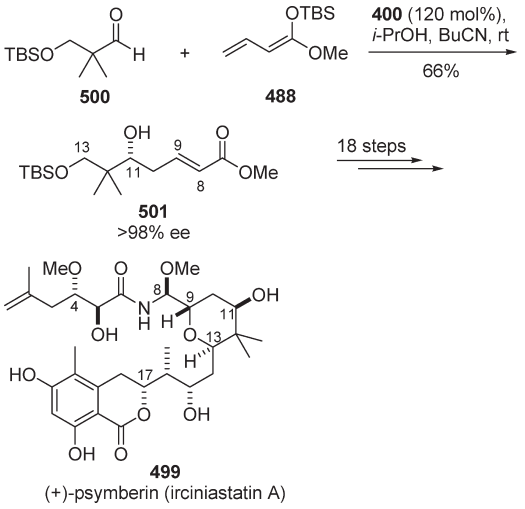
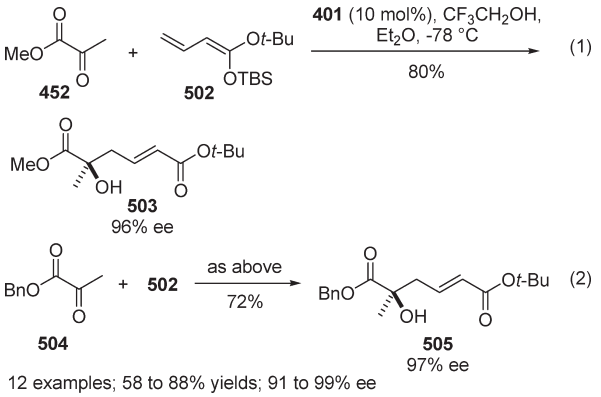
Scheme 88. Oxazaborolidinone-Promoted Asymmetric VMAR in Partial Synthesis of Filipin III (494)[211]



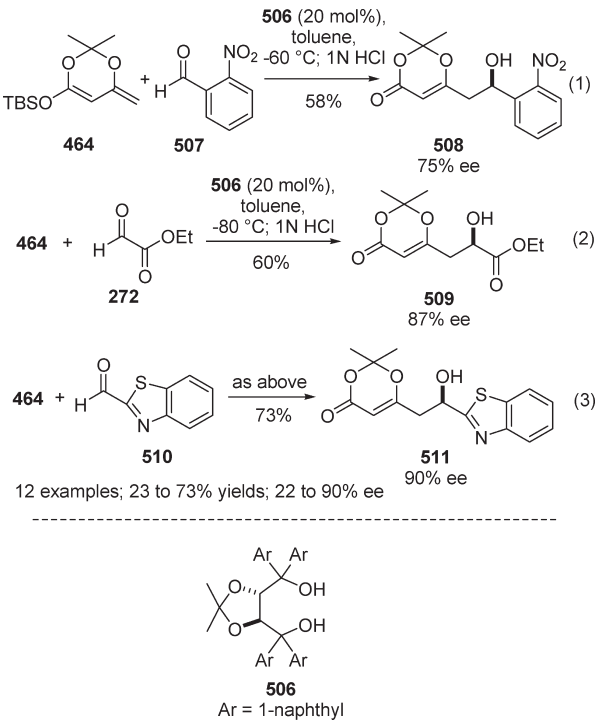
Scheme 89. Oxazaborolidinone-Promoted Asymmetric VMAR in the Total Synthesis of (+)-Psymberin (499)[212]



Scheme 90. Asymmetric VMAR Using Cu(II) Complexes of C_1-Symmetric Aminosulfoximines[213]



Scheme 91. Hydrogen Bond-Catalyzed Asymmetric VMAR of Dioxinone 464 and Various Aldehydes[216]



effectiveness of several common chiral alkaloids and diols as organocatalysts in VMAR additions involving dioxinone-based dienolate **464** and several aldehyde acceptors. Paradigmatic results are listed in Scheme 91 showing TADDOL **506**-catalyzed VMAR additions to aldehydes **507**, **272**, and **510**. After an extensive preparative work aimed at optimizing the protocol, conditions were found to propel the reaction effectively, where TADDOL governed a transition state with aldehyde activation via cooperative hydrogen bonding. VMAR proceeded in moderate to good yields, with ee values ranging from poor (aliphatic aldehydes, not shown) to excellent (aromatic, heteroaromatic aldehydes and α-oxo esters).

Similar enantioselective VMAR additions of acyclic silyl dienolates of type **2** (Chan diene) and **456** (Brassard diene) with a variety of aromatic aldehydes were assayed by Scettri et al.[217,218] to enter diverse δ-hydroxy-β-keto esters and cyclized pyrone compounds. Indeed, all VMAR produced mixtures of open-chain and cyclic adducts in a ratio that depended on the reactivity of the aldehyde component. The authors surmised that two competitive reaction paths were operative, with VMAR giving linear adducts and HDA leading to pyrone derivatives. Nevertheless, the authors did not attempt to rationalize the product distribution nor the mechanisms involved.

Enantioselective Cr(salen)-catalyzed VMAR additions between dioxinone silyl dienolates **1** or **424**, and several aldehydes

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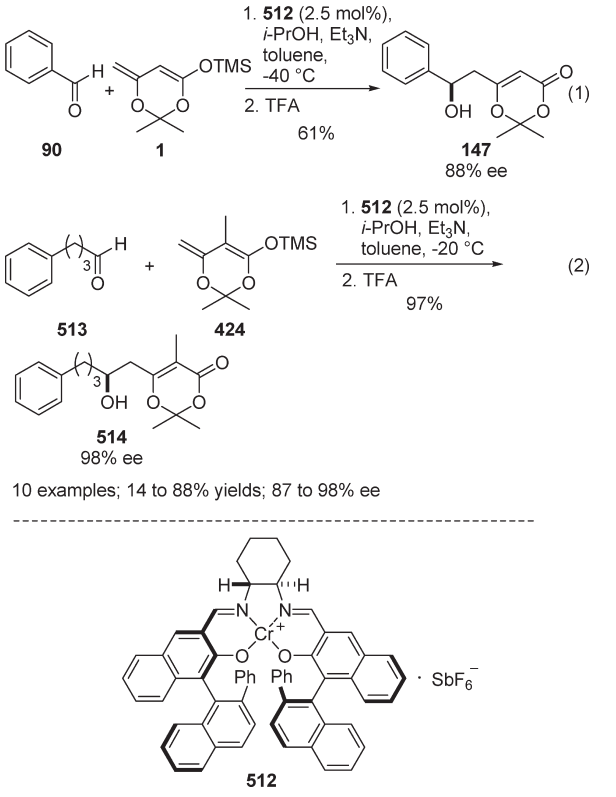
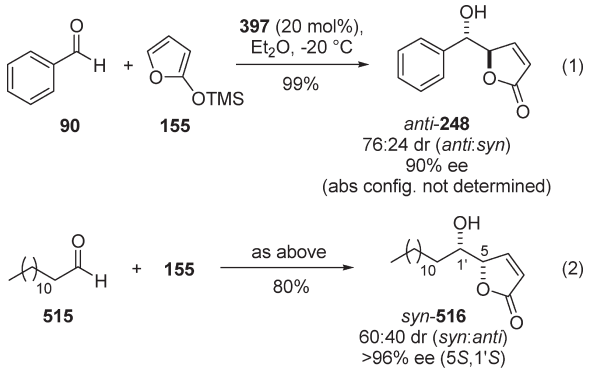
Scheme 92. Enantioselective Cr(salen)-Catalyzed VMAR[219]



were also investigated by Katsuki et al.[219] as a valuable route to access enantioenriched δ-hydroxy-β-keto ester derivatives of type **147** and **514** (Scheme 92). Several examples were reported involving aromatic, aliphatic, and α,β-unsaturated aldehydes. In almost all cases, the reaction ran efficiently (50−88% isolated yields) to afford the respective adducts with outstanding enantioselectivities. The addition of *i*-PrOH was essential for achieving high enantioselectivity; however, the addition of alcohol caused diminished yields probably due to decomposition of the delicate silyl dienolate donor.

3.2.1.2. Cyclic Silicon Dienolates. Most of the chiral metal-based catalysts employed to govern the stereochemical course of VMAR involving acyclic silyl dienolates (chapter 3.2.1.1) were also successfully exploited in VMAR with furan- and pyrrole-based heterocyclic dienoxy silanes. Following initial studies on the Ti(IV)−BINOL-catalyzed asymmetric VMAR between trimethyl silyloxy furan **155** and tridecanal,[220] Figadère and coworkers thoroughly reinvestigated this pioneering work in 2000, by broadening the scope of the reaction and exploring the possibility of an autoinductive aldol process.[221,222] The methodology was applied to VMAR involving aromatic, aliphatic, and olefinic aldehydes using 20 mol % Ti(IV) catalyst **397** that afforded adducts with good to excellent enantioselectivities and modest diastereoselectivities (Scheme 93). For example, VMAR between **155** and benzaldehyde (**90**) gave rise to *anti*-configured adduct *anti*-**248** as the major isomer, accompanied by a minor amount of *syn*-isomer in 99% global yield and 90% ee for the *anti*-isomer. In this case, however, the absolute configuration of the major adduct was not determined (eq 1). Also, VMAR using tridecanal (**515**) performed well giving rise to *syn*-configured (5*S*,1′*S*)-isomer *syn*-**516** preferentially, whose absolute

Scheme 93. Ti(O*i*-Pr)$_4$/(*R*)-BINOL Catalyzed VMAR of Silyloxy Furan 155[221,222]



configuration was ascertained by chemical correlation to natural (+)-muricatacin. The substrate determines which product is formed as the major diastereoisomer, with aliphatic aldehydes leading to the *syn*-isomers and aromatic or olefinic aldehydes giving *anti*-isomers.

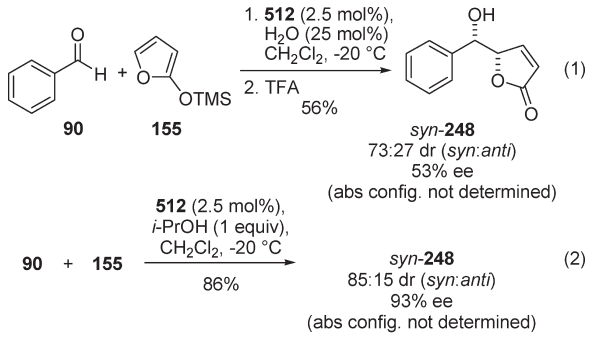
Nonlinear effects, as well as autoinduction phenomena, were also investigated by Figadère in a set of complex experiments.[221] Interestingly, a positive deviation from linearity was detected after a chiral aldol product was added to the mixture of Ti(O*i*-Pr)$_4$/BINOL. This amplification of ee was explained through the occurrence of an autoinductive process involving the formation of a multicomponent titanium catalyst by self-organization of the chiral ligands, that is, the original BINOL and the newly formed aldol adduct. The authors also discovered that replacement of the expensive BINOL ligand in the Ti(IV) catalyst with an achiral phenol (e.g., 2,4,6-trimethyl phenol) in the presence of (+)- or (−)-TADDOL allowed for preparation of the desired butenolide compounds with excellent enantiomeric excess, albeit in moderate dr.

By adopting a very similar catalyst system, the same authors synthesized *iso*-cladospolide B, a hexaketide natural product of marine origin featuring a butenolide core unit.[223] In such an endeavor, several butenolide compounds were prepared by starting with enantiopure 7-silyloxy octanal, and their configurations were assessed by chiro-optical measurements. This allowed the authors to ascertain the absolute configuration of the natural compound. Also, preparation of the C13−C29 fragment of caribenolide I, a potent antitumor marine macrolide, was performed, again using an enantioselective VMAR between silyloxy furan **155** and pentanal.[224] In this instance, an excellent control of the absolute configuration of the various stereogenic centers in the target was exerted by the chirality of the initial butenolide aldol product, in turn obtained via Ti(O*i*-Pr)$_4$/(*R*)-BINOL catalyzed VMAR.

VMAR additions of furan **155** and various aldehyde acceptors were investigated by Katsuki et al.[225,226] by adopting the chiral cationic Cr(salen) complex **512** previously studied in VMAR with acyclic dienolates (chapter 3.2.1.1). As in the case for the reaction with dioxinone dienolate **1**, the addition of a protic cosolvent to the reaction mixture (water or *i*-PrOH) proved to be essential for high and reproducible selectivities to be attained. The authors proposed that the protic medium suppresses the retroaldolization reaction by converting the aldolate into the

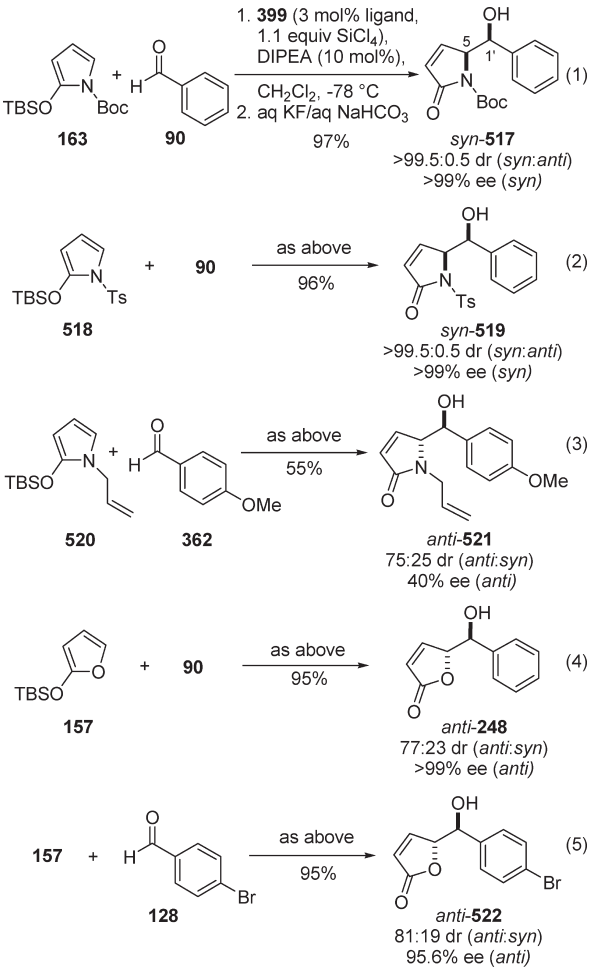
dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 94. Enantioselective Cr(salen)-Catalyzed VMAR of 2-(Trimethylsilyloxy)furan (155) and Aldehydes[225,226]



11 examples; 44 to 98% yields; 48:52 to 89:11 dr; 53 to 97% ee (*syn*)

Scheme 95. Enantioselective and Diastereoselective VMAR of Pyrrole- and Furan-Based Dienoxy Silanes Using Denmark Bisphosphoramide/$SiCl_4$ Catalyst[227,228]



27 examples; 55 to 99% yields; 74:26 to >99.5:0.5 dr; <10 to >99% ee (*syn* and *anti*)

hydroxylactone product, thus enabling the isolation of the adduct formed under kinetic control. As an example, VMAR additions between **155** and **90** giving butenolide *syn*-**248** were investigated with either water (Scheme 94, eq 1) or isopropanol (eq 2) as additives. While both cosolvents served to activate the reaction through coordination to the chromium ion, isopropanol proved to be superior to water in terms of reaction yield and selectivity.

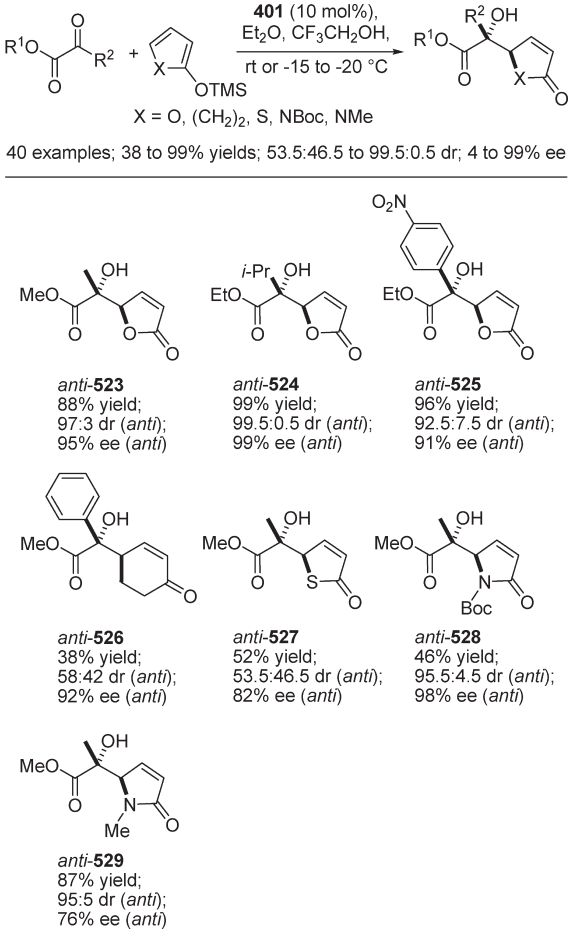
In their continuing efforts to exploit heterocyclic silyloxy dienes as d_4 donor reagents in vinylogous aldol and related processes, the Casiraghi group carefully investigated VMAR of pyrrole- and furan-based dienoxy silanes in a catalytic, asymmetric format.[227,228] After an initial survey of a prototypical reaction between TBSOP **163** and benzaldehyde (**90**) in the presence of a set of several chiral metal-based catalysts, it was discovered that the previously disclosed Denmark bisphosphoramide/$SiCl_4$ couple **399** was a superior catalyst candidate, with the expected (5*S*,1′*S*)-configured vinylogous aldol product *syn*-**517** obtained in high yield and outstanding levels of site-, diastereo-, and enantioselectivities (Scheme 95, eq 1).

Swapping of the pyrrole *N*-protecting group to tosyl (or Cbz) also reflected the behavior of the control reaction with the *N*-Boc substituent, resulting in no substantial erosion of either efficiency or stereocontrol (e.g., eq 2). To the authors' expectations, the VMAR process proved discretely tolerant with respect to the nature of the aldehyde component with both electron-rich and electron-poor aldehydes behaving equally well. On the other hand, strong influence of the electronic nature of the diene heteroatom on diastereo- and enantioselectivity was not anticipated. Indeed, as shown in eqs 3−5, a switch of simple diastereoselectivity from *syn* to *anti* aldols was observed when *N*-alkyl/alkenyl pyrrole or furan dienes were employed; in these cases, (5*R*,1′*S*)-*anti*-configured adducts were obtained as the major reaction products in moderate to good chemical conversions. With furan-based dienolate donors of type **157**, the enantiopurities of the aldol products raised exquisite levels (eqs 4 and 5), whereas those of *N*-alkyl/alkenyl pyrroles were substantially eroded (eq 3) possibly due to strong acceleration of the competitive achiral background pathway.

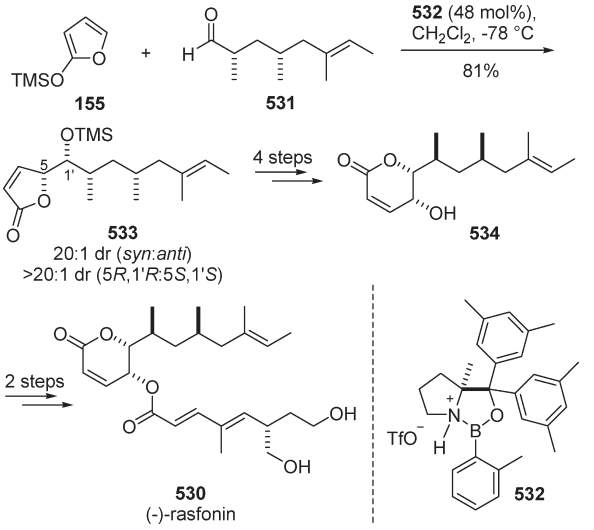
The ability of the Denmark bisphosphoramide catalyst was also tested by Palombi et al. in VMAR additions between furan **155** and a series of aldehydes.[229] The results matched those reported by Casiraghi (vide supra), with *anti*-disposed vinylogous adducts of type **248** preferentially formed, with ee ranging from 50 to >99% (*anti*-isomers, absolute configuration not determined). Overall, these studies, along with the fundamental works by Denmark himself,[199−203] elect the Lewis base-activated, hypervalent silicon chiral Lewis acids of type **399** as privileged catalytic systems in VMAR chemistry, foreseeing these reagents earning a secure place in the repertoire of contemporary asymmetric synthesis.

Productive C_1-symmetric amino sulfoximine copper complex **401** utilized by Bolm and colleagues as asymmetric catalysts in acyclic VMAR (vide supra, chapter 3.2.1.1), was also applied in the cyclic VMAR domain by the same authors.[230−232] Scheme 96 displays a panel of enantioenriched *anti*-configured vinylogous adducts **523**−**529** bearing a quaternary stereogenic center that were produced by starting with alicyclic and heterocyclic dienoxy silanes and α-keto esters via catalytic enantioselective and diastereoselective VMAR. Many substrate combinations were scrutinized that afforded *anti*-configured VMAR products preferentially, with variable levels of diastereo- and enantioselectivities. A detailed study of the variation of the ligand backbone of the catalyst was also carried out, which revealed that the applied sulfoximines are highly modular and that they can perfectly be adjusted to donor and acceptor substrate requirements for optimum performance.

Scheme 96. Enantio- and Diastereoselective VMAR Catalyzed by Aminosulfoximine Copper Complex 401[230−232]



Scheme 97. Enantioselective Total Synthesis of (−)-Rasfonin (530)[233]



The utility of the enantioenriched butenolide type aldols arising from asymmetric VMAR did not go unnoticed to organic synthesis practitioners, due to their malleability and structural diversity. Boeckman Jr. et al.,[233] for example, employed Corey chiral oxazaborolidine **532** to fuel the asymmetric VMAR between silyloxy furan **155** and chiral nonracemic aldehyde **531** (Scheme 97). The use of the chiral boron catalyst was mandatory, since achiral $BF_3 \cdot OEt_2$ provided the requisite (*R*,*R*)-butenolide **533** with poor 1.3:1 diastereofacial control, albeit with good *syn*/*anti* simple diastereoselectivity. Thus, with more hindered chiral oxazaborolidine **532**, VMAR occurred with excellent diastereocontrol, favoring (*R*,*R*)-*syn*-isomer **533** [20:1 *syn*/*anti*; >20:1 (*R*,*R*)/(*S*,*S*)]. Five- to six-membered ring expansion was then performed via lactone-to-lactol reduction and subsequent DBU-promoted enlargement, providing *δ*-lactone **534** in acceptable yield. Finally, the complete carbon skeleton of (−)-rasfonin (**530**) was assembled, via Yamaguchi coupling of free alcohol **534** to the suitable diene acid fragment.

A brilliant application of asymmetric VMAR in total synthesis has been exhibited by Evans and co-workers[234,235] during the construction of the FG ring fragment (C27−C34) of (+)-azaspiracid-1 (**535**), as documented in Scheme 98. In contrast to previous studies by the same authors[193] where bis(aquo) copper−PyBox complex of type **398** (Figure 8) had been successfully used in VMAR involving unsubstituted trimethyl silyloxy furan donor, the choice here was to employ the Sn(II) complex **537** to trigger the desired VMAR transformation. Thus, 3-methylsubstituted silyloxy furan **159** underwent stereoselective aldol addition with *N*-phenyl glyoxamide **536** to furnish lactone **538** in a 94% conversion, with a >40:1 dr and 97% ee. The resulting lactone could easily be recrystallized to enantiopurity prior to the subsequent transformations, resulting in a 67% isolated yield and 99% ee. Compound **538** was next elaborated to **539**, which constitutes the C27−C34 FG ring portion of (+)-azaspiracid-1 (**535**), the enantiomer of the natural marine neurotoxin (−)-azaspiracid-1.

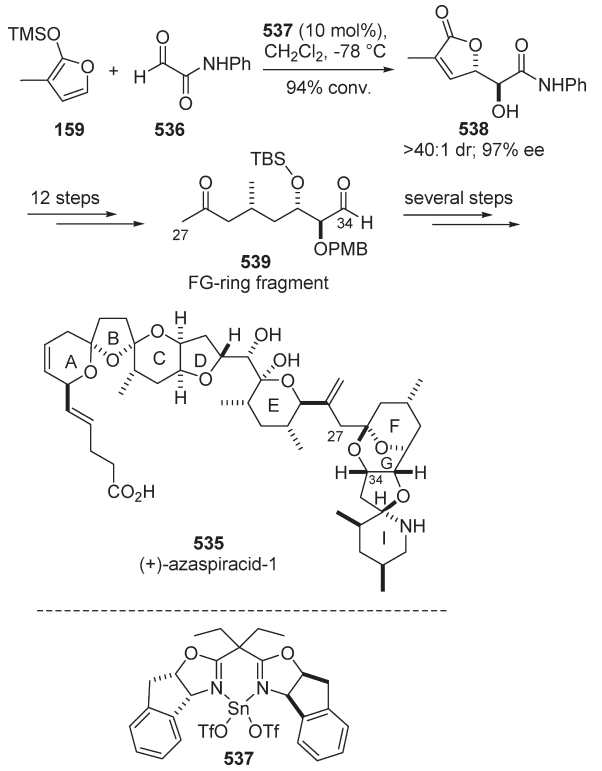
When compared to asymmetric metal catalysis, use of organocatalytic systems in VMAR processes received only marginal attention. However, in recent years, this subject matter is being developing as a useful alternative to biocatalysis and metal catalysis.

Cinchonidine-derived quaternary ammonium phenoxides of type **540** were first employed by Mukaiyama and colleagues as chiral Lewis base catalysts in VMAR of variously substituted silyloxy furan donors.[236] As detailed in Scheme 99, for example, VMAR addition of unsubstituted furan **155** to benzaldehyde (**90**) in the presence of 10 mol % catalyst **540** afforded *anti*-configured butenolide **248** in 92% yield, 88:12 *anti*/*syn* ratio, and 76% ee.[236] Extension of this reaction to 3- and 4-methyl substituted furans was next investigated (e.g., eqs 2−4), with best results obtained with 4-methyl-TMSOF **542**. It is important to notice that the substitution pattern of the silyloxy furan substrate heavily impacts enantiocontrol, as highlighted in eq 2 with 3-methyl-substituted furan **159** where a poor 31% ee of aldol adduct **541** was attained.

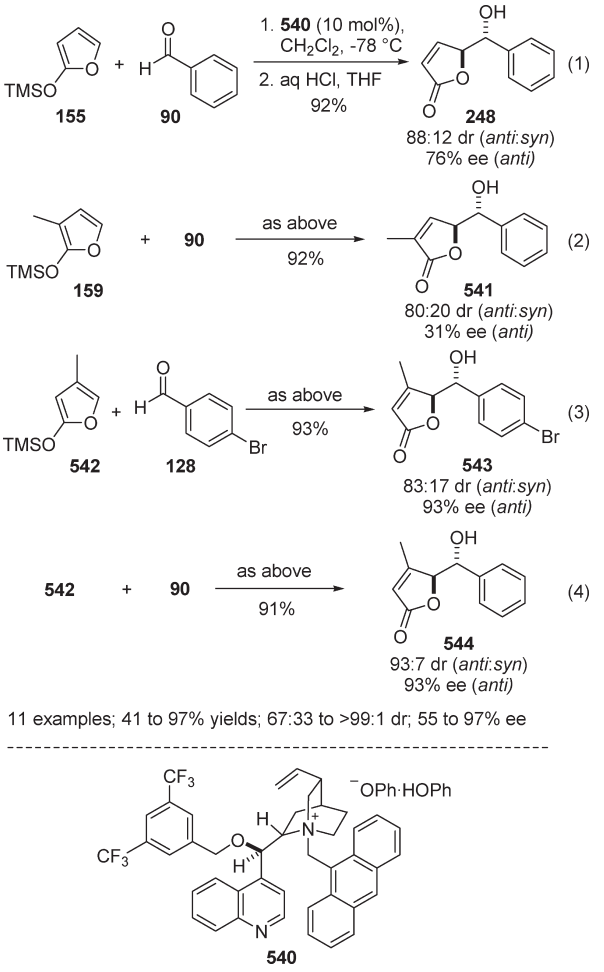
The first example of the use of bifunctional alkaloid thiourea catalyst as H-bond donors in asymmetric VMAR between silyloxy furan **155** and aromatic aldehydes was very recently communicated by Wang and colleagues.[237] In particular, in this work, the quinine-thiourea catalyst **545** proved to be an excellent bifunctional catalyst in governing VMAR reactions, resulting in the formation of a variety of butenolide products in high yields

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 98. Asymmetric VMAR in the Total Synthesis of (+)-Azaspiracid-1 (535)[234,235]



Scheme 99. Enantioselective VMAR Using Cinchonidine-Derived Quaternary Ammonium Salt Catalyst 540[236]



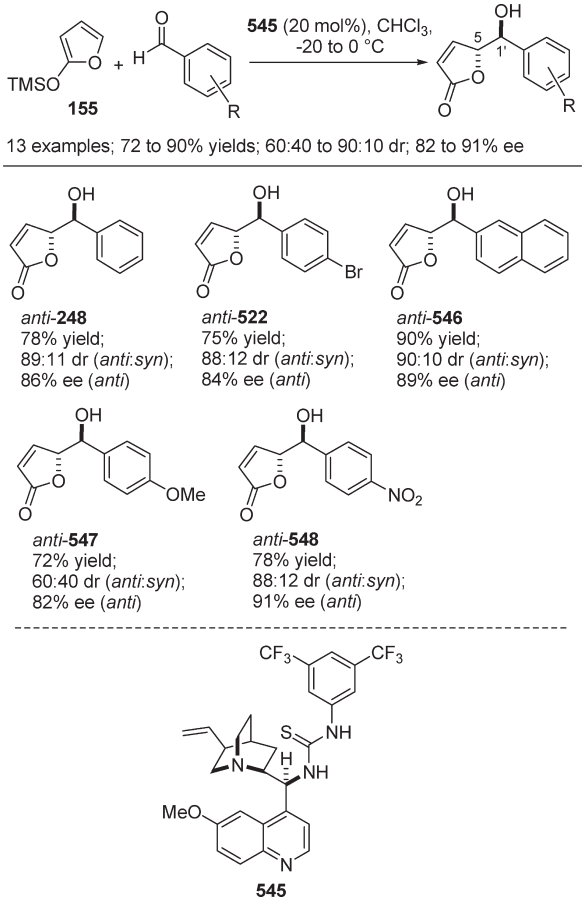
and valuable levels of diastereo- and enantioselectivity. Selected examples are listed in Scheme 100 showing that, in all cases, formation of *anti*-configured adducts of type **248**, **522**, and **546**−**548** was preferentially attained. During optimization of the procedure, the authors found that adding small amounts of water or alcohols to the reacting mixture was beneficial to the reaction yield, possibly due to inactivation of the silyl cationic species responsible for parasitic racemic reactions. Of note, the major products displayed in the original paper (and herein) are (5*R*,1′*S*)-*anti*-configured, although the absolute configurations of the newly formed butenolide stereocenters were not clearly justified.

3.2.2. Direct Additions of in situ-Generated Dienolates. Within the vinylogous aldol realm, direct, reagent-controlled enantioselective processes have been only scantly represented, in spite of the innate advantages that they offer in terms of simplicity and atom economy. In this context, a skillful methodology for performing such vinylogous transformations was introduced in 2006−2007 by Shibasaki et al. by extending the reductive/alkylative aldol protocol of α,β-unsaturated carbonyl compounds to allenic esters.[238−240] In fact, when a nucleophilic species (e.g., hydride or alkyl anion source) attacks an allenyl ester substrate in a conjugative way, an ambident dienolate forms that may add to a carbonyl acceptor at either the γ- (vinylogous addition) or the α-position. Shibasaki, Kanai, and co-workers[238,239] reported a remarkable ligand effect in Cu(I)-catalyzed, asymmetric reductive VAR between allenic esters and diverse ketones, where the product constitution (α- vs γ-aldol) can be switched depending on the nature of the chiral diphosphine ligand employed in the catalytic system. In particular, when (*R*)-DTBM-SEGPHOS **549** was employed, γ-additions preferentially occurred, whereas Taniaphos (diphosphine ferrocene ligands, not shown) effected α-additions exclusively. Scheme 101 groups γ-*cis*-selective asymmetric reductive VAR of ethyl allenoate **550** to ketones, catalyzed by chiral copper catalyst **549**·Cu(OAc) in conjunction to achiral phosphine additive PCy_3. The reaction proved to be applicable to various methyl ketones including aromatic, aliphatic, and α,β-unsaturated candidates giving rise to the expected vinylogous aldol adducts **551**−**554** in very good isolated yields and exquisite levels of site- and enantioselectivities.

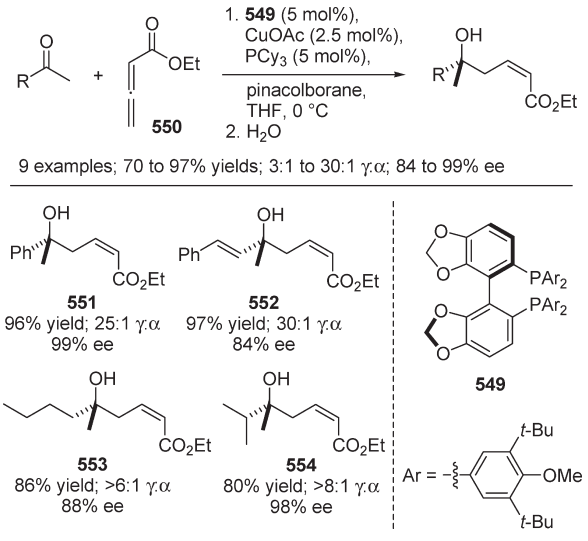
The same group also reported a detailed study of the asymmetric alkylative VAR of ketones that assembles dialkylzincs, allenic esters, and ketones to produce δ-lactones of type **556**−**559** bearing tetrasubstituted stereocenters at C5 (Scheme 102).[240] In these reactions, $Cu(OAc)_2$/DIFLUORPHOS system **555** proved to be the best choice of catalyst, providing the expected enantioenriched lactones in high isolated yields and enantioselectivities. The use of a Lewis base additive, such as HMPA, DMSO, or Ph_2SO, combined with molecular sieves, was effective in suppressing formation of unwanted α-adducts and improving the yields of the vinylogous compounds. Control and crossover experiments suggested that addition of the Lewis base triggered a retro-aldolization of the kinetically favored α-aldolates, leading to cyclized adducts through a vinylogous

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 100. Enantioselective VMAR Using Quinine-Thiourea Catalyst 545[237]

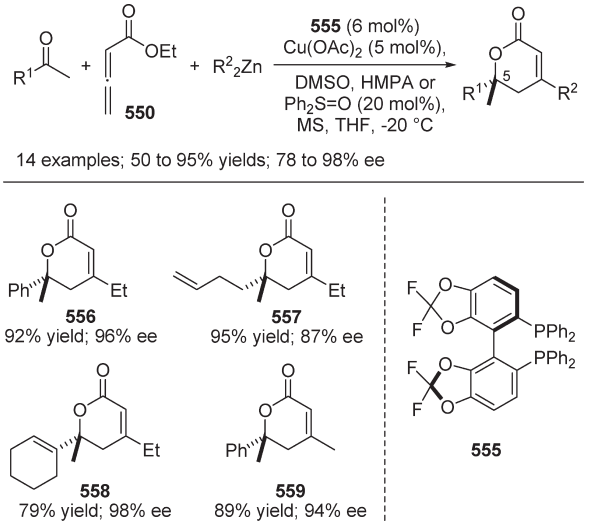


Scheme 101. Asymmetric Reductive VAR of Allenic Esters to Ketones[238,239]



aldolization path, followed by irreversible lactonization of the resulting γ-aldolates.

Scheme 102. Asymmetric Alkylative VAR of Allenic Esters to Ketones[240]



A special case of direct Lewis acid/Lewis base-catalyzed asymmetric reaction leading to enantioenriched δ-lactones was recently reported by Tiseni and Peters, which possibly evolved through a VAR mechanism involving in situ-generated dienamide d_4 donor species.[241] A complex formed in situ from $Er(OTf)_3$ and commercially available norephedrine type ligands of type **560** triggered a formal hetero-Diels−Alder reaction between acyl chlorides (e.g., **561**) and aromatic, heteroaromatic, and alkenyl aldehydes, leading to the corresponding lactone products of type **562** (Scheme 103). The authors claimed that a highly organized transition state involving a tetracoordinate erbium complex is operative, leading to the lactone products via a vinylogous aldol addition reaction.

A unique example of direct, enantioselective VAR between 2-(5*H*)furanone derivatives and aldehydes catalyzed by an axially chiral guanidine base was reported by Terada's group in 2010.[242] After an extensive optimization of the organocatalyst, guanidine **563** was elected as the catalyst of choice to guide the reaction between dichlorofuranone **349** and benzaldehyde (**90**), to provide butenolide *syn*-**350** with satisfactory levels of diastereoselection and excellent enantioselectivity (Scheme 104, eq 1). To improve diastereocontrol, sterically demanding dibromo furanone **564** was employed, which provided *syn*-**565** with enhanced diastereoselectivity (eq 2). Interestingly, with 3-phenylthiofuranone **566**, a decline in the overall performance of the reaction did not occur, and the expected butenolide *syn*-**567** was isolated in a nearly quantitative yield, with good diastereoselectivity and virtually complete enantioselectivity (eq 3). Of note, unsubstituted furan-2(5*H*)-one was not an appropriate substrate in these reactions, and this slightly obscures the generality of the guanidine catalyst to drive these important transformations.

The domino reaction of salicylaldehydes with γ-enolizable α,β-unsaturated aldehydes has been independently investigated by Bräse[243−245] and Woggon[246,247] groups in light of its useful exploitation in total synthesis of natural products. Careful choice of the reaction conditions may foster a cascade reaction where an intermolecular vinylogous aldolization process is followed by an intramolecular oxa-Michael closure. Along these lines, Woggon

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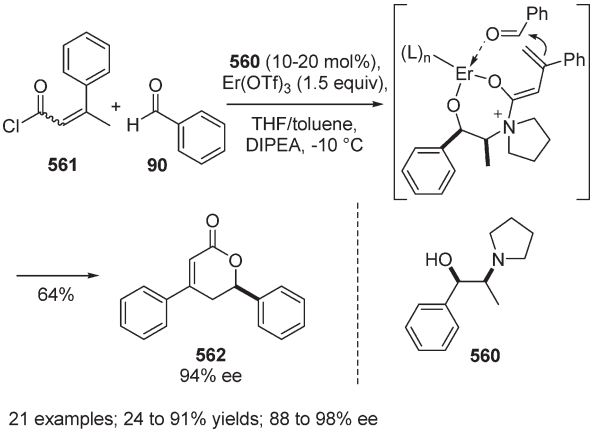
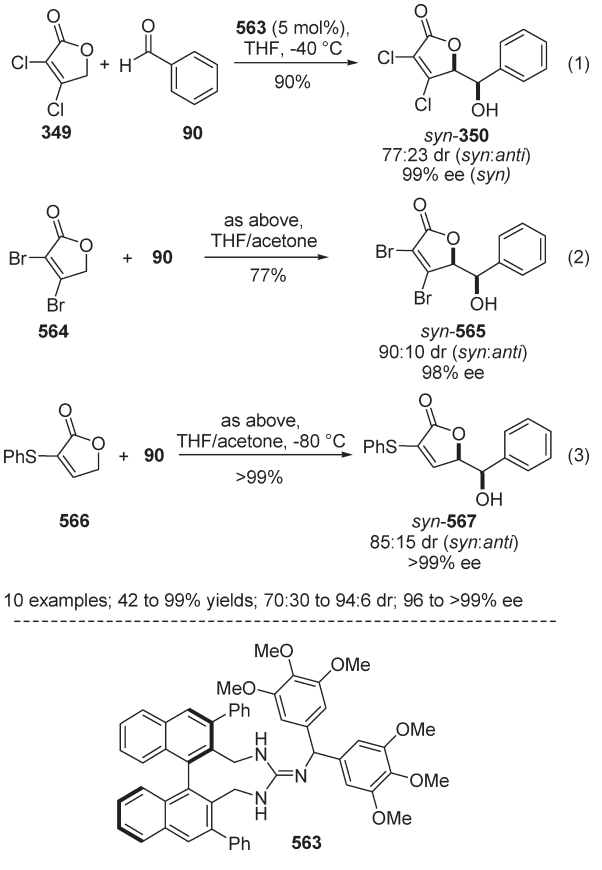
Scheme 103. Direct Lewis Acid/Lewis Base-Catalyzed Enantioselective VAR to δ-Lactones[241]

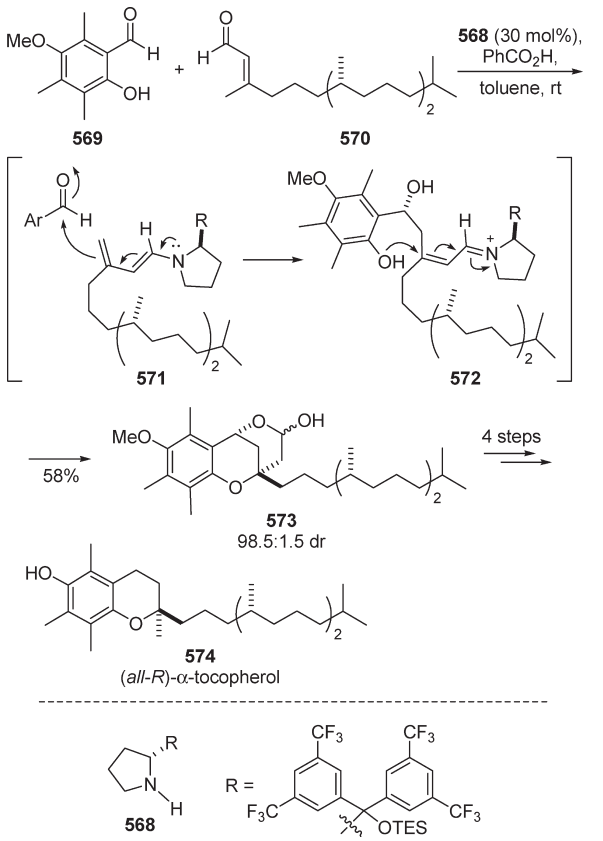


Scheme 104. Enantioselective Direct VAR of 2-(5*H*)-Furanone Derivatives Catalyzed by the Chiral Guanidine Organocatalyst 563[242]



et al.[246] elaborated an asymmetric organocatalytic procedure, which culminated in the elegant total synthesis of α-tocopherol (**574**) (Scheme 105). The synthesis commenced with reaction of salicylaldehyde **569** with phytenal (**570**) in the presence of the Jørgensen (*R*)-proline-derived organocatalyst **568**. In the event, tricyclic lactol **573** was obtained in satisfying 58% yield and with

Scheme 105. Synthesis of α-Tocopherol (574) Highlighting a Direct Asymmetric VAR Using Dienamine Organocatalysis[246]



excellent diastereoselectivity (97% de) via a domino cascade sequence involving (i) amine-triggered γ-enolization of aldehyde **570** to dienamine d_4 donor **571**, (ii) vinylogous aldol addition between **571** and **569** to intermediate **572**, and (iii) oxa-Michael closure with release of the amine organocatalyst. Consequently, tricyclic acetal **573** was transformed in natural (all-*R*)-α-tocopherol **574** by a short four-step reaction sequence.

Very similar chemistry was employed by Bräse and colleagues[245] to assemble enantiomerically enriched tricyclic acetal **576**, the key intermediate in the formal synthesis of 4-dehydroxydiversonol (Scheme 106, eq 1). Thus, salicylaldehyde **575** was reacted with senecialdehyde (**286**) in the presence of catalytic amounts of the Jørgensen organocatalyst *ent*-**568** to give lactol **576** in a good 74% isolated yield and 87% ee. Facile chemistry then allowed transformation of **576** to xantone **577**, the Tietze[248] precursor of 4-dehydrodiversonol.

Furthermore, Woggon[247] very recently reported on the enantioselective synthesis of confluentin (**580**) and daurichromenic acid (**581**), which capitalized on the above disclosed direct asymmetric VAR (Scheme 106, eq 2). In this case, the same salicylaldehyde utilized by Bräse was reacted with farnesal (**578**) under Jørgensen prolinol organocatalysis, to afford tricyclic compound **579**, the common precursor of both targeted compounds **580** and **581**.

4. VINYLOGOUS MANNICH REACTIONS

The vinylogous Mannich addition reaction (VMnR)—the conjugate extension of the nucleophilic addition of carbon enolate

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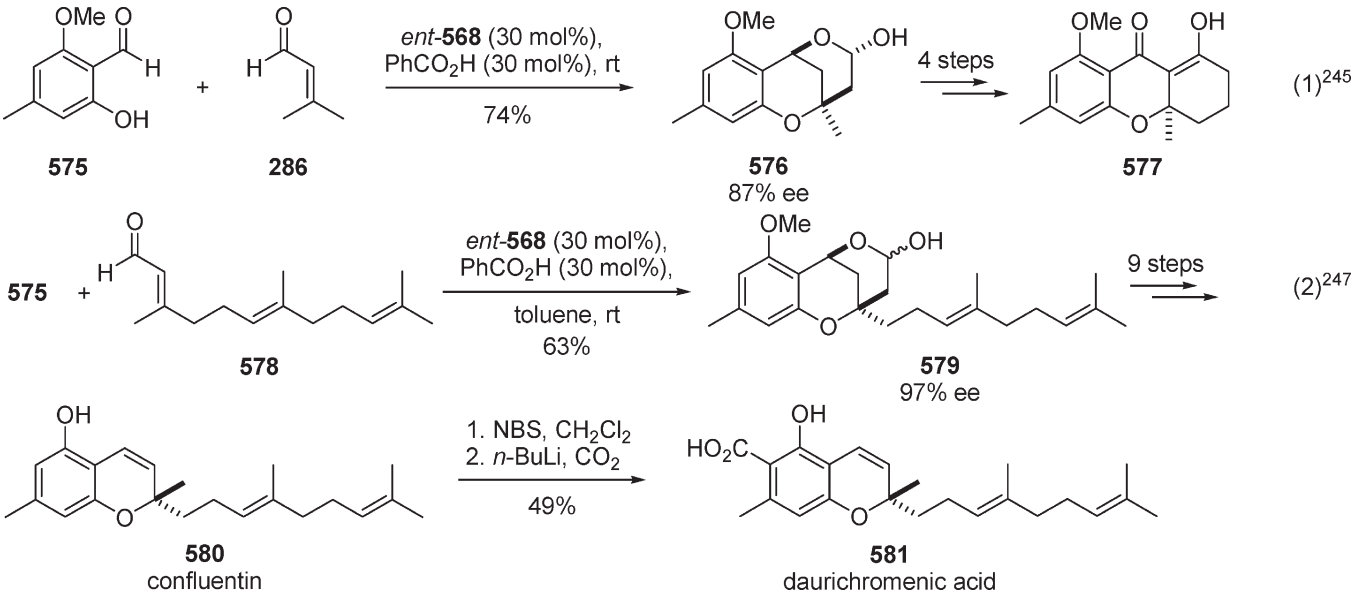
Scheme 106. Direct Asymmetric VAR Using Dienamine Organocatalysis[245,247]



donors to imines or iminium salts—although less exploited than the cognate aldol addition, has attracted ever increasing attention in recent years, with outstanding results in both methodology- and target-oriented endeavors.[8,9] The δ-amino-α,β-unsaturated carbonyl compounds arising from this vinylogous coupling represent versatile synthons that can be converted into a variety of useful derivatives including simple pyrrolidine and piperidine heterocycles, as well as complex naturally occurring alkaloidal compounds.

As for the previous VARs, this VMnR chapter is organized into two main sections dealing with substrate-controlled diastereoselective processes (4.1) and reagent/catalyst-controlled enantioselective processes (4.2); each is further divided into indirect Mukaiyama type additions (4.1.1 and 4.2.1) and direct additions (4.1.2 and 4.2.2). Further grouping of reactions involving acyclic vs cyclic dienolate species has been occasionally applied for a better grasp on this subject. Those interested in this research area are also encouraged to consult appropriate review articles by Martin, which appeared in 2001−2002.[8,9]

4.1. Diastereoselective and Unselective Processes

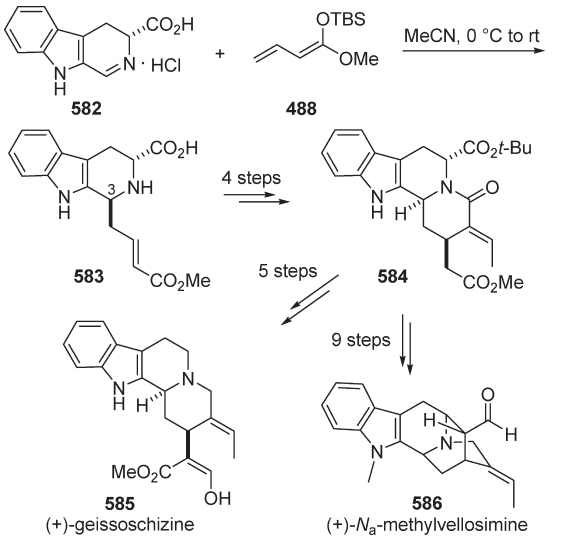
The contributions describing VMnR involving prochiral donor/acceptor reaction components (chiral or achiral) to give enantiopure (or racemic) *syn*/*anti* Mannich bases, with diastereocontrol dictated by the intrinsic bias of the substrates (substrate-controlled), are taken into particular consideration in this section. Unselective VMnR affording racemic Mannich bases where simple and facial stereocontrol issues do not apply are also included.

4.1.1. Indirect Mukaiyama Type Additions of Silicon Dienolates

4.1.1.1. Acyclic Silicon Dienolates. The VMnR addition of acyclic dienol derivatives with cyclic iminium ions, extensively exploited by Martin and colleagues,[8,9] has played a strategic role in the design of diastereocontrolled entries to a variety of indole alkaloids, in both racemic and enantiomerically pure formats.

For example, Martin reported in 2003[249] a biomimetic total synthesis of (+)-geissoschizine (**585**) and (+)-N_a-methylvellosimine (**586**), two polycyclic indole alkaloids of natural origin.

Scheme 107. Total Synthesis of (+)-Geissoschizine (585) and (+)-N_a-Methylvellosimine (586)[249]



Scheme 107 highlights the crucial Mukaiyama type VMnR (VMMnR) utilized to assemble the carboline intermediate **583**. In the event, dihydrocarboline **582** was allowed to react with vinyl ketene acetal **488** to produce the expected adduct **583** as the sole isolable product. The nucleophilic attack of silyloxy diene **488** onto iminium ion **582** occurred with high diastereoselectivity from the *Si*-face, establishing the correct absolute stereochemistry at the C3 carbon of the two indole alkaloid targets. Crude adduct **583** was then elaborated to tetracycle **584**, the divergent building block for both alkaloids **585** and **586**.

A biogenetically inspired approach to *Strichnos* alkaloids akuammicine (±)-**589** and strychnine (±)-**592** was also designed and executed by the same author in 2001,[250] featuring a VMMnR between acyclic unsubstituted silyloxy diene *E*-**3** and

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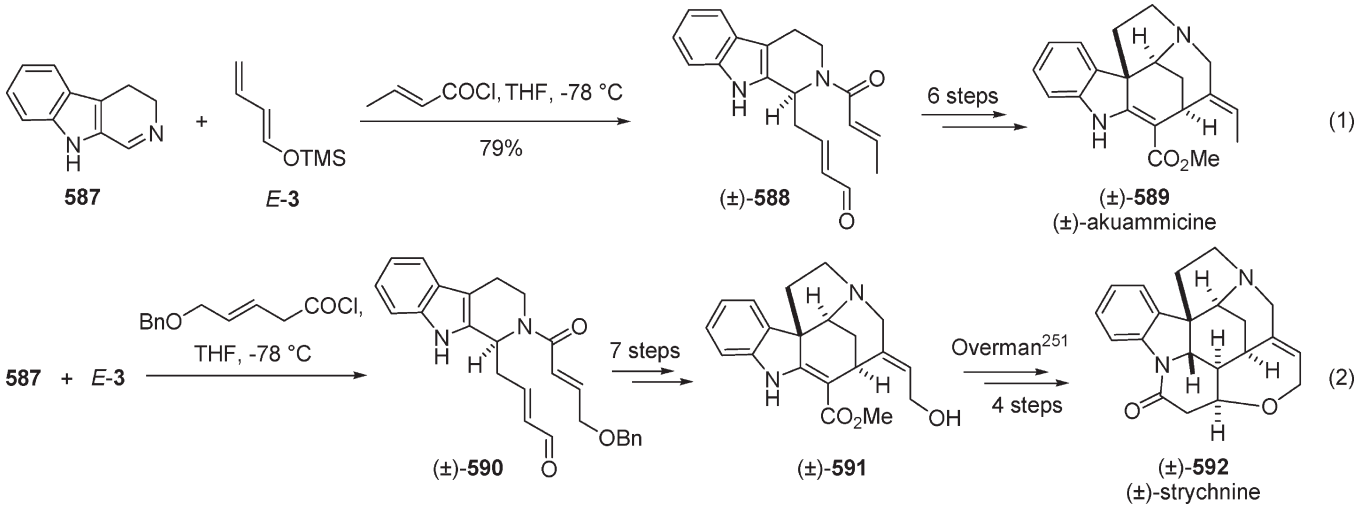
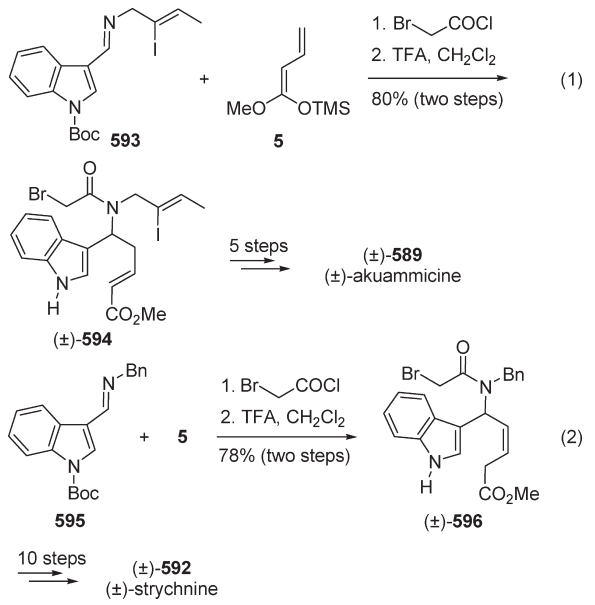
Scheme 108. Concise Total Synthesis of Akuammicine (±)-589 and Strychnine (±)-592 (Formal Synthesis)[250]



carboline **587**, which was activated by crotonyl chloride or benzyloxy crotonyl chloride (Scheme 108, eqs 1 and 2). There, VMMnR between linear silyloxy diene *E*-**3** and **587**, previously activated in situ with the proper acyl chloride reactant, provided the respective vinylogous adducts (±)-**588** and (±)-**590**, which were in turn elaborated to the final alkaloids via multistep sequences involving hetero-Diels−Alder reactions followed by biomimetically patterned transformations and skeletal reorganizations. For strychnine (±)-**592**, the authors stopped the synthesis at pentacycle (±)-**591**, the same precursor envisioned by Overman[251] during his clever synthesis of this challenging alkaloid.

In 2010, concise total syntheses of the same *Strychnos* alkaloids (±)-**589** and (±)-**592** were communicated by Andrade at al.[252] Inspired by the previously disclosed investigations of Martin, Andrade syntheses included, as key steps, an initial VMMnR addition followed by sequential spirocyclization/intramolecular aza-Baylis−Hillman reaction and Heck cyclization. Scheme 109 highlights the key VMMnR, which utilized in situ-generated acyl iminium chlorides from imines **593** and **595** and open-chain silyl ketene acetal **5**. Thus, VMMnR between imine **593** and silyloxy diene **5** in the presence of bromoacetyl chloride afforded, after acidic treatment, vinylogous adduct (±)-**594**, which was in turn elaborated to (±)-akuammicine by a five-step reaction sequence (Scheme 109, eq 1). The same VMMnR protocol was employed by Andrade in the reaction between imine **595** and vinyl silyl ketene acetal **5** affording, after acidic treatment, the vinylogous Mannich adduct (±)-**596**, which was advanced to strychnine (±)-**592** in a 10-step reaction sequence (Scheme 109, eq 2).

Scheme 109. Concise Total Synthesis of Akuammicine (±)-589 and Strychnine (±)-592[252]



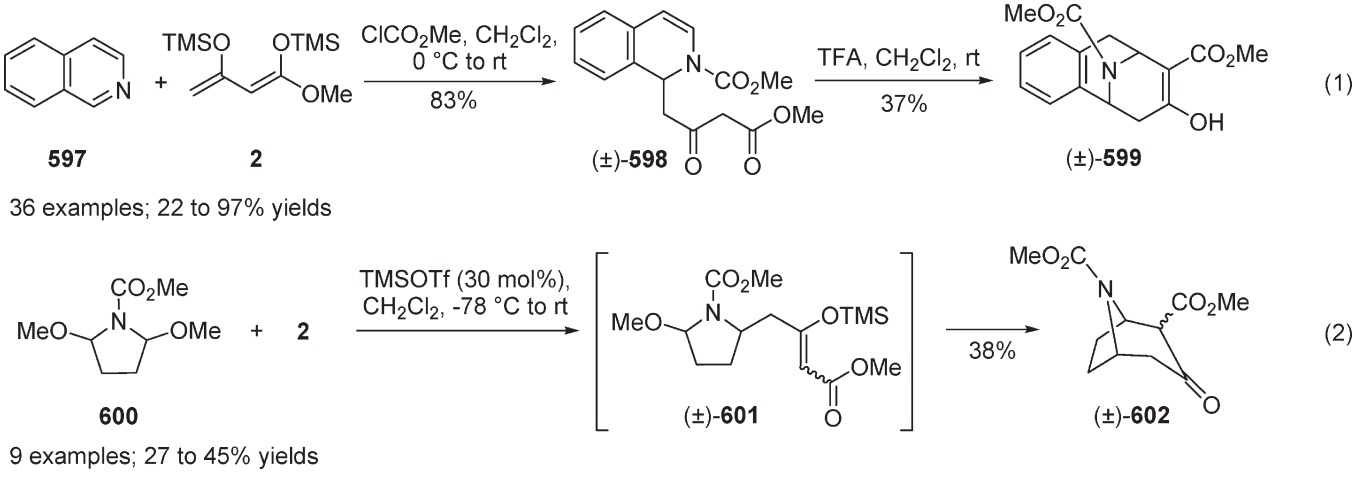
Quinolinium and isoquinolinium salts, generated in situ by acylation of quinoline and isoquinoline, are important synthetic building blocks in the synthesis of complex alkaloids including benzomorphan and isobenzomorphan skeletons. In 2008, Langer[253] reported a direct two-step synthesis of functionalized isobenzomorphans exploiting, as a key move, a VMMnR between methyl chloroformate-activated isoquinoline **597** and Chan diene **2** (Scheme 110, eq 1). Racemic enamine (±)-**598** formed via regioselective attack of the terminal carbon of ketene acetal **2** and was converted to isobenzomorphan (±)-**599** by a TFA-triggered intramolecular Mannich reaction. In the same manner, the scope of the reaction was investigated, with variation of both the donor silyl diene component and the isoquinoline acceptor, invariably producing the expected isobenzomorphans in synthetically useful yields.

The same author[254] succeeded in synthesizing various tropinones via sequential Me_3SiOTf-catalyzed vinylogous Mukaiyama−Mannich/Mukaiyama−Mannich reactions by starting with two ambident complementary reaction partners, that is, bissilyl dienolate **2** and dimethoxy pyrrolidine **600** (Scheme 110, eq 2). In this instance, however, tropinone compounds of type (±)-**602** were isolated in modest yields as mixtures of stereoisomers and keto−enol tautomers.

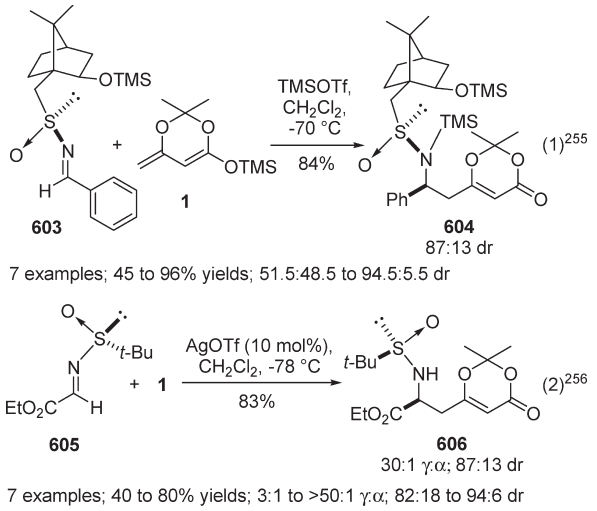
Auxiliary-driven approaches to δ-amino-α,β-unsaturated esters utilizing chiral sulfinilimines of type **603** or **605** were

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

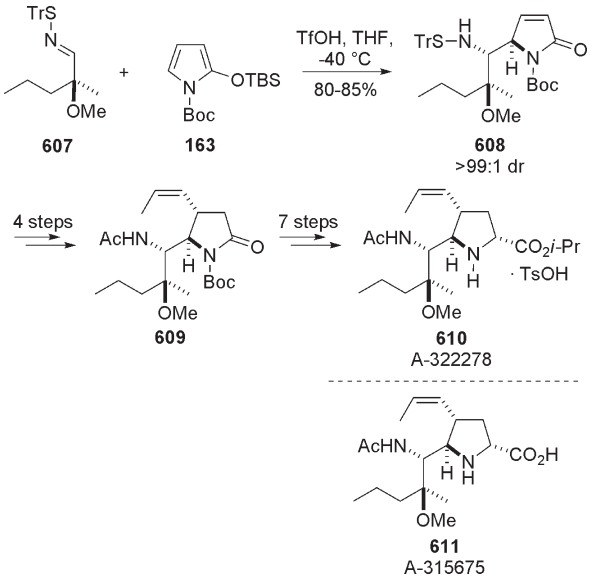
Scheme 110. Synthesis of Isobenzomorphans of Type (±)-599 and Tropinones of Type (±)-602[253,254]



Scheme 111. Auxiliary-Driven VMMnR Using Sulfinilimines 603 and 605[255,256]



Scheme 112. Total Synthesis of A-322278 (610)[259−261]



exploited by Kawecki[255] and Chen[256] in diastereoselective VMMnR with dioxinone **1**. As shown in Scheme 111, both reactions performed well in the presence of TMSOTf (eq 1) or AgOTf (eq 2), giving the expected γ-substituted adducts **604** or **606** in good yields, complete γ-selectivity, and acceptable diastereomeric ratios. Of note, Chen reported that changing the silver catalyst from triflate to acetate or trifluoroacetate salts resulted in a dramatic site selectivity switch, with α-adducts solely formed in good yields and excellent levels of diastereocontrol.

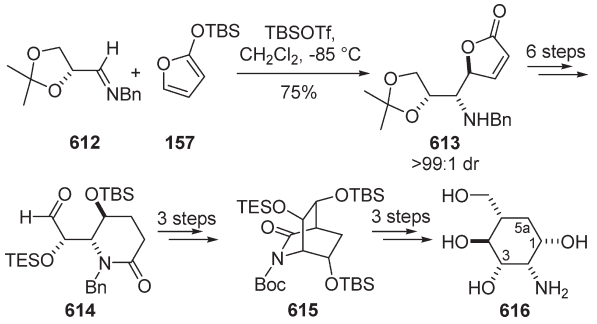
Achiral *N*-tosyl and *N*-aryl imines were further employed by Chen[257] and Scettri[258] during VMMnR investigations involving dioxinone-derived silyloxy dienes of type **1** or **148**. While Scettri utilized a $SiCl_4$/DIPEA catalyst mixture to propel the reaction, no catalyst was adopted by Chen, who claimed that when the reaction occurred at room temperature in toluene or CH_2Cl_2 (or even without a solvent), good yields of isolated adducts were attained.

4.1.1.2. Cyclic Silicon Dienolates. As compared to the corresponding reactions with acyclic silyl dienolates, VMMnR using heterocyclic dienolate synthons of type **155**−**164** (Figure 7) have been more frequently investigated. Often the products of these transformations (butenolide type adducts) cleverly served as suitable building blocks in diverse synthesis endeavors, usually targeting alkaloids, imino-, and amino-sugar compounds, or variously shaped nitrogen heterocycles.

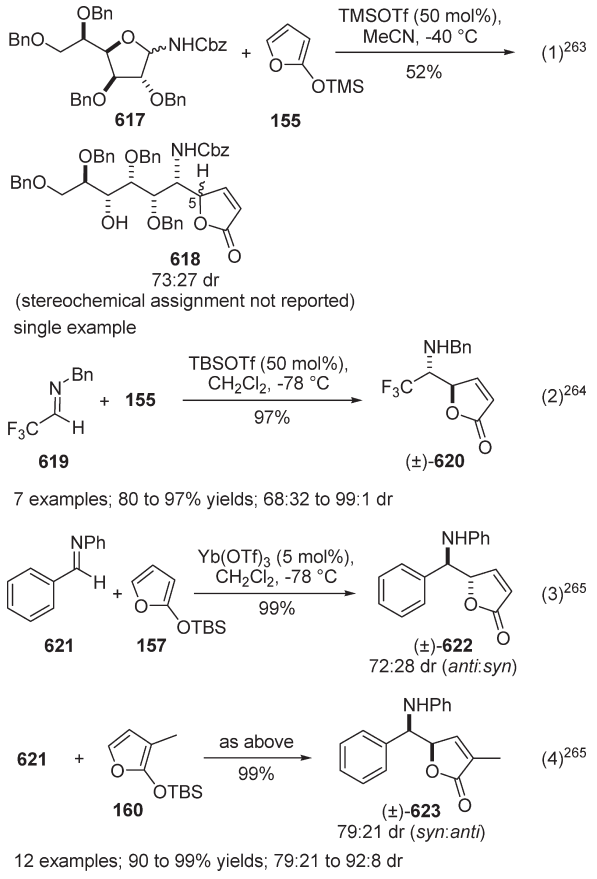
In 2002−2003, researchers at Abbott laboratories[259−261] exploited a crossed VMMnR between silyloxy pyrrole **163** and chiral trityl sulfenimine **607** during a kilogram scale synthesis of A-322278 (**610**), a pro-drug of the potent influenza virus neuraminidase inhibitor A-315675 (**611**) (Scheme 112). After extensive preparatory work aimed at optimizing the VMMnR protocol, practical conditions were found for the reaction to be scaled up in a reproducible manner. In particular, treatment of **163** with imine **607** in the presence of triflic acid in THF at −40 °C furnished the

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

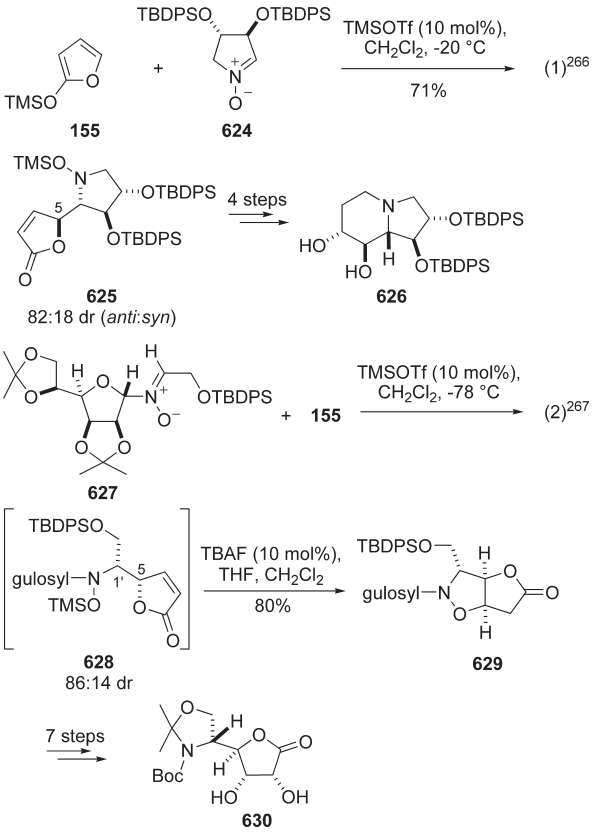
Scheme 113. Diastereoselective Synthesis of 5a-Carba-β-L-Mannopyranose (616)[262]



Scheme 114. Lewis Acid-Catalyzed Diastereoselective VMMnR Using Silyloxy Furans 155, 157, and 160[263−265]



Scheme 115. Synthesis of Indolizidine Alkaloid 626 and Nikkomycin-Related Furanose 630 via Diastereoselective VMMnR Involving Nitrone Acceptors 624 and 627[266,267]



desired amino lactam **608** in 80−85% isolated yield and >99:1 *anti*/*syn* diastereomeric ratio. Conjugated addition of bromomagnesium di[(*Z*)-1-propenyl]cuprate and subsequent adjustment of the amine protecting group resulted in the formation of pyrrolidinone **609**, which was then manipulated to give the target pro-drug **610** in a high degree of purity and good yield (16 steps, 13% overall yield). Interestingly, the synthesis was used by the Abbott group to deliver more than 1 kg of **610** for preclinical and clinical investigations.

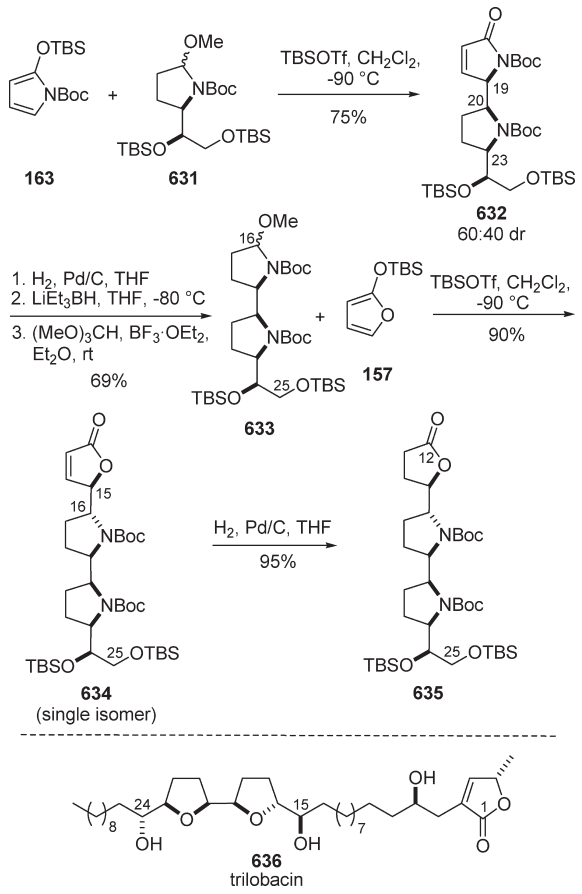
In a continuing program devoted to the asymmetric synthesis of densely hydroxylated carbocycles (carbasugars), Rassu and Casiraghi[262] completed a further contribution in this realm, which featured, as the crucial operation, a vinylogous Mukaiyama−Mannich reaction between furan **157** and protected D-glyceraldehyde *N*-benzylimine **612** (Scheme 113). Targeting validamine-related 5a-carba-β-L-mannopyranose (**616**), reaction of **157** with imine **612** promoted by TBSOTf gave unsaturated aminobutenolide **613** as a single diastereoisomer, which was promptly elaborated to **614** via double bond reduction, DBU-assisted γ-lactone to δ-lactam enlargement, and terminal hydroxyl oxidation. Direct silylative aldol carbocyclization then afforded bicyclic compound **615**, which was finally dismantled to **616** by reductive lactam opening and deprotection.

In a work directed to investigate the addition of various silylated nucleophiles to D-glucose-derived *N*,*O*-acetal **617**, Martin and Desvergnes[263] reported a VMMnR utilizing furan **155** as the silylated donor species (Scheme 114, eq 1). There, butenolide amine **618** was obtained as a 73:27 mixture of C5 epimers in a 52% yield. The same furan **155** was also utilized by Bonnet−Delpon and Crousse[264] in Lewis acid-catalyzed VMMnR with diverse trifluoromethyl acetaldehyde imines. As an example, eq 2 in Scheme 114 reports the addition involving imine **619** that furnished *anti*-configured (±)-**620** in 97% yield and >98% de.

In an engaging investigation, Royer et al.[265] studied the Yb(OTf)$_3$-catalyzed VMMnR of silyloxy furans **157** and **160**, which were conducted with either preformed or in situ-generated imines (Scheme 114, eqs 3 and 4). Interestingly, depending on the furan substitution and irrespective of the reaction protocol, a

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 116. Diastereoselective Synthesis of 635, the C12−C25 Bis-Pyrrolidine Segment of the Aza Analogue of Trilobacin (636)[94]



diastereoselectivity switch from *anti* to *syn* products was witnessed, when passing from unsubstituted furan **157** to 3-methyl-substituted analogue **160**. However, a mechanistic rationale accounting for this unpredictable result was not provided by the authors.

Summarizing the stereochemical results in this section centered upon the VMMnR of furan silicon dienolates with acyclic imines, one can notice that, as a rule, *anti*-configured Mannich products highly predominate with unsubstituted furans, while 3-substituted furans revert this behavior giving *syn*-adducts preferentially, and this paradigm applies also to catalyzed asymmetric versions of these transformations (see infra, section 4.2.1.2, Schemes 135−137).

Chiral, five-membered cyclic nitrone **624**, shortly derived from (*R,R*)-tartaric acid, was employed by Trombini and Lombardo[266] as the Mannich acceptor in a VMMnR with silyloxy furan **155** (Scheme 115, eq 1). The reaction, catalyzed by 10 mol % TMSOTf, displayed complete facial selectivity and afforded *anti*-configured butenolide **625** as the major isomer, accompanied by a minor amount of its C5-epimer in 71% overall yield (82:18 dr). The bulky TBDPS-protecting group in nitrone **624** proved to be an optimum choice forcing the attack of the γ-carbon of **155** only on the less encumbered *Si*-face of the nitrone. Simple chemistry was then applied to transform **625** into protected indolizidine **626**, which was recovered in a 24% overall yield over five steps.

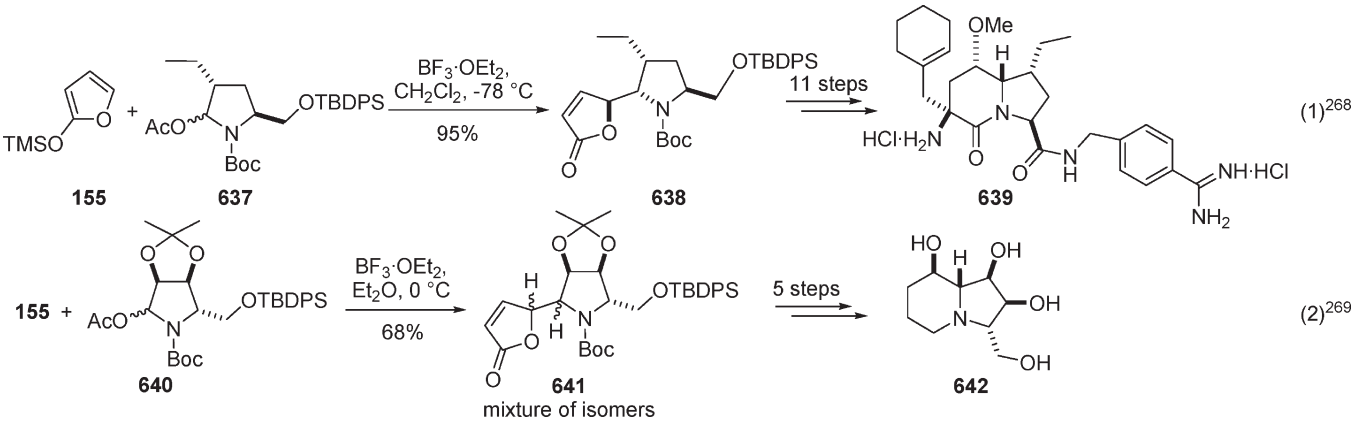
The VMMnR addition between silyloxy furan **155** and chiral nitrone **627** was exploited by Tamura and Sakamoto[267] during a synthetic approach to polyoxin C (Scheme 115, eq 2). The TMSOTf-catalyzed process took place smoothly, giving unstable vinylogous product **628**, which was readily converted to the stable bicyclic product **629** upon TBAF treatment. Of note, good stereoselectivity was obtained in favor of the (5*S*,1′*R*)-*anti*-isomer **628** (86:14 dr) due to optimal control by the *N*-gulosyl auxiliary substituent as well as the bulkiness of *C*-substituent of the nitrone acceptor. Bicyclic compound **629** was then applied to the synthesis of **630**, the *C*-terminal amino acid component of polyoxin C.

According to the previously disclosed retrosynthetic plan in Scheme 37 (chapter 3.1.1.2), portraying the route with which varied, adjacently linked binuclear acetogenin targets were assembled, Casiraghi et al.[94] expanded this chemistry to the VMMnR domain. In particular, two sequential VMMnR additions were carried out, which involved in situ-generated iminium acceptors derived from suitable pyrrolidine *N,O*-acetal precursors. Thus, as shown in Scheme 116, the first vinylogous Mannich addition between pyrrole **163** and *N,O*-acetal **631** was promoted by TBSOTf and furnished C19−C20-*anti*−C20-C23-*cis*-configured lactam **632**, along with minor amounts of an *anti*−*trans*-isomer (not shown, 60:40 dr). Carbon−carbon bond saturation and lactam-to-lactol reduction provided *N,O*-acetal **633** ready for the conclusive vinylogous Mannich maneuver. Thus, elongation of **633** with furan-based **157** (TBSOTf again as the promoter) proved highly diastereoselective, with C15−C16-*syn*−C16-C19-*trans*-disposed trinuclear butenolide **634** solely produced in a good 90% isolated yield. Simple catalytic hydrogenation of **634** furnished trinuclear compound **635**, which may be regarded as the C12−C25 fragment of the unnatural aza-analogue of trilobacin (**636**), a highly potent bis-THF annonaceous acetogenin.

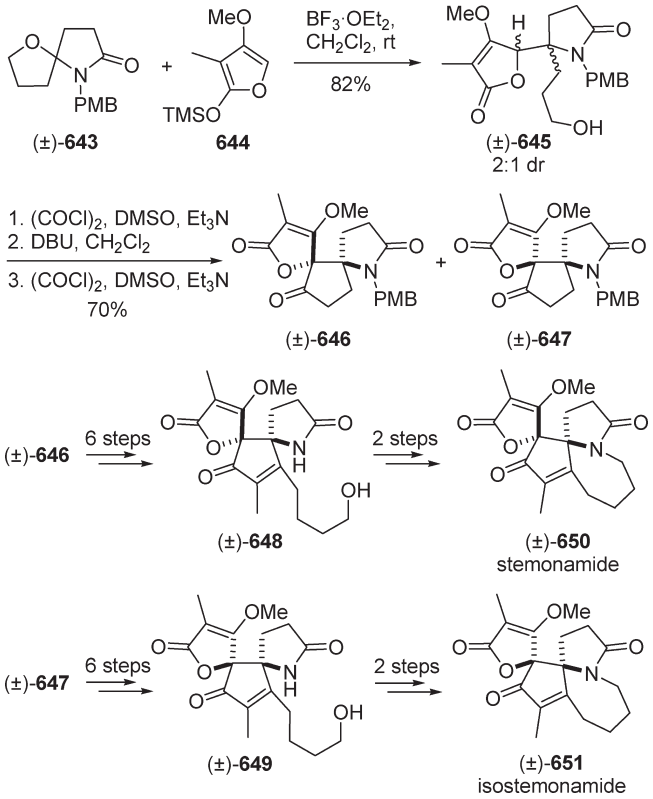
The same powerful VMMnR technique was also successfully applied by Hanessian and co-workers[268,269] in the total synthesis of functionally relevant indolizidinones of type **639** and polyhydroxylated indolizidines of type **642** (Scheme 117). In both instances, $BF_3\cdot OEt_2$-triggered diastereoselective VMMnR between furan **155** and pyroglutamic acid-derived **637** or **640** proceeded well, affording the expected binuclear butenolide structures **638** or **641** in high isolated yield and acceptable diastereocontrol. Intermediates **638** and **641** were then advanced to the respective targets **639** and **642** with simple chemistry, involving double bond reduction, γ-lactone to δ-lactam ring enlargement, functional groups manipulation, and deprotection.

N-Acyliminium-based chemistry was exploited by Kende and colleagues[270,271] in the total synthesis of racemic stemonamide and isostemonamide alkaloids (±)-**650** and (±)-**651** (Scheme 118). Thorough and careful preparatory work allowed the authors to delineate a successful approach where the tetracycle core of both target alkaloids could be constructed via (i) an intermolecular VMMnR of a silyloxy furan (e.g., **644**) to a cyclic *N*-acyliminium ion [e.g., from (±)-**643**] to create the first quaternary center and (ii) a direct VAR spirocyclization [e.g., (±)-**645** to (±)-**646**/(±)-**647**] to construct the tricyclic core of stemonamine group. Thus, *N*-PMB-protected succinimide-derived *N,O*-aminal (±)-**643** was reacted with silyloxy furan **644** in the presence of $BF_3\cdot OEt_2$ affording a 2:1 mixture diastereoisomers (±)-**645** in 82% yield. Oxidation of the mixture (±)-**645** under Swern conditions gave the corresponding aldehydes, which were used in the DBU-promoted direct VAR to produce the corresponding spirocyclic compounds (±)-**646** and

Scheme 117. Diastereoselective VMMnR in the Total Synthesis of Indolizidine Compounds 639 and 642[268,269]



Scheme 118. Total Synthesis of *Stemona* Alkaloids Stemonamide (±)-650 and Isostemonamide (±)-651[270,271]



(±)-**647**. After chromatographic separation of the two diastereoisomers, it was found that the former possessed the relative stereochemistry of stemonamide (±)-**650**, while the latter corresponded to isostemonamide (±)-**651**. In a parallel way, (±)-**646** and (±)-**647** were converted to the targeted alkaloids through a multistep sequence including—inter alia—final ring closure involving the respective advanced intermediates (±)-**648** and (±)-**649**.

Following notable achievements in the late 1990s in the field of VMMnR additions of silyloxy furans to cyclic *N*-acyl iminum ions,[8,9] Pilli and colleagues[272−275] exhaustively investigated this chemistry expanding the scope of both the donor and the acceptor components. In particular, unsubstituted and γ-methyl-substituted silyloxy furans were used in combination with achiral or chiral five-, six-, and seven-membered *N*-acyl iminium ions in Lewis acid-catalyzed VMMnR additions. Scheme 119 enlists a selection of results from these studies. Irrespective of the Lewis acid employed and the size of the acceptor component (5−7-membered iminium ions), silyloxy furan **157** reacted with the iminium ions generated in situ from *N*,*O*-acetals (±)-**652** or (±)-**654** giving the corresponding 5,2′-*syn*-configured products (±)-**653** and (±)-**655** in acceptable/good yields and good

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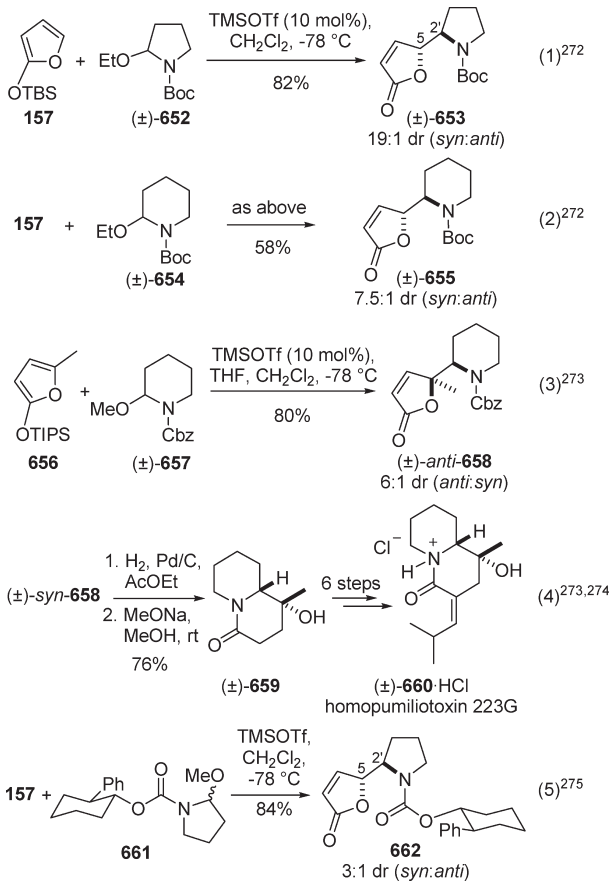
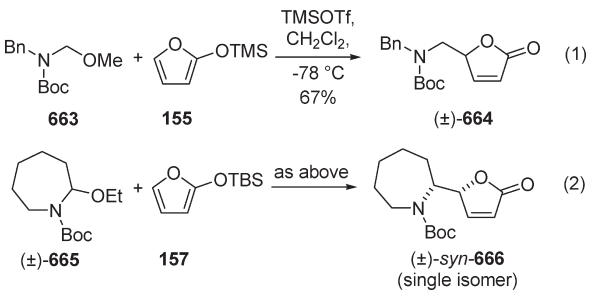
Scheme 119. Diastereoselective VMMnR Additions of Silyloxy Furans to Variously Sized in situ-Generated *N*-Acyl Iminium Ions by[272−275]



Scheme 120. VMMnR Additions of Silyloxy Furans to Acyclic and Cyclic in situ-Generated *N*-Acyl Iminium Ions[277]



syn/*anti* diastereoselectivities (eqs 1 and 2).[272] Preferential formation of the *syn*-configured isomers did not come as a surprise, as these results perfectly matched those obtained in similar works from previous studies.

Martin and Bur[276] drew conclusions consistent with these experiments through ab initio calculations (RHF/3-21G* level) of the transition state geometries associated with the addition of 2-methoxyfuran to 5-membered *N*-carbomethoxy-*N*-acyliminium ion. In this case, it was found that a Diels−Alder arrangement was preferred for the limiting transition state, leading to the *threo* (*syn*)-isomer.

On the other hand, when Pilli employed γ-methyl-substituted silyloxy furan **656** under TMSOTf catalysis, reversal in diastereoselectivity was witnessed, with *anti*-configured isomers obtained preferentially (e.g., eq 3).[272−274] Although a convincing mechanistic rationale could not be proposed even after DFT calculations, the authors claimed such unexpected preference for the *anti*-isomers to be due to some unpredictable steric hindrance posed by the γ-methyl group of the nucleophile, which could not be properly taken into account in the DFT calculations.

The minor *syn*-isomer (±)-*syn*-**658** [optimally produced under $TiCl_4$ promotion from reaction of **656** with (±)-**657**] served to Pilli and co-workers in the construction of the quinolizidine skeleton of racemic homopumiliotoxin 223G (±)-**660**, via the intermediacy of expanded bicyclic lactam (±)-**659** (eq 4).[273,274] The same authors exploited chiral *N*,*O*-acetals of type **661** (eq 5) during VMMnR additions of certain silyloxy furans.[275] As an example, **157** was reacted with **661** under Lewis acid catalysis, furnishing (5*R*,2′*R*)-configured *syn*-isomer **662** preferentially, along with minor amounts of its C5-epimer (3:1 *syn*/*anti* dr). As expected, the simple diastereoselectivity favoring the *syn*-isomers followed the same *syn*-selective trend observed with the corresponding achiral prochiral substrates (eq 1 vs 5).

Variously shaped amino alkyl furanones of type (±)-**664** and (±)-**666** were also addressed by Aurrecoechea and colleagues in a study aimed at construction of diverse pyrrolidine and piperidine derivatives (Scheme 120).[277] Thus, the TMSOTf-promoted VMMnR between silyloxy furans **155** or **157** and acyclic or cyclic iminium ion precursors of type **663** and (±)-**665** provided multigram quantities of the corresponding vinylogous products (±)-**664** and (±)-**666**. High diastereoselectivity favoring *syn*-configured isomers was generally observed (when applied), which was in line with previous reports by Pilli (vide supra). These mono- and binuclear amino alkyl butenolide products provided expeditious entry to a panel of azacyclic compounds via either radical or enamine type ring closures.

The efficient in situ preparation of cyclic *N*-acyl iminium ions from readily available lactam or amino acid starters and subsequent interception with diverse silyloxy furan nucleophiles constitutes the fil rouge of three independent works that appeared over the 2000−2002 period.[278−280] In the first example (Scheme 121, eq 1),[278] the iminium ion generated in situ from 2-ethoxypiperidine (±)-**654** (under TIPSOTf catalysis) reacted with γ-allyl-substituted silyloxy furan **667** to afford γ,γ-disubstituted butenolide (±)-**668** preferentially (4:1 *anti*/*syn* dr), accompanied by minimal amounts of an unwanted isomer deriving from α-attack. Bicyclic compound (±)-**668** was then readily converted to racemic alkaloid securinine (±)-**669** via a short synthesis sequence featuring, inter alia, a novel RCM protocol (nine overall chemical steps).

In the second contribution (eq 2),[279] Hernández exploited a DIB/I_2-triggered radical decarboxylation−oxidation of *N*-Cbz-L-proline (**670**) to create an *N*-acyl iminium ion, which then reacted with silyloxy furan **155** in the presence of $BF_3 \cdot OEt_2$ (one-pot/two-step procedure). In the event, *syn*-configured pyrrolidinyl furanone (±)-**671** mainly formed (6:1 *syn*/*anti* dr), which was transformed into hydroxyindolizidinone (±)-**672** by simple catalytic hydrogenation.

In the third contribution, Suh et al.[280] reported on the facile nucleophilic addition of silyloxy furan to medium- or large-sized iminium ions (7−9-membered), generated from the corresponding

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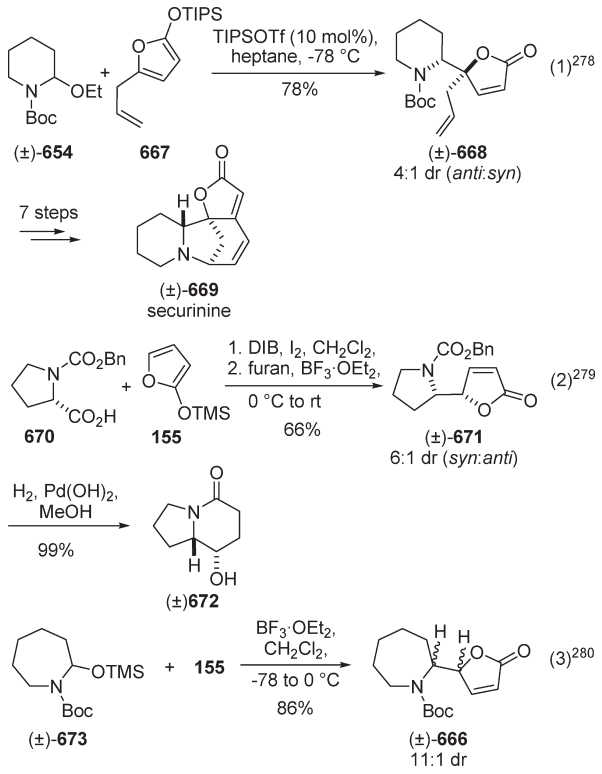
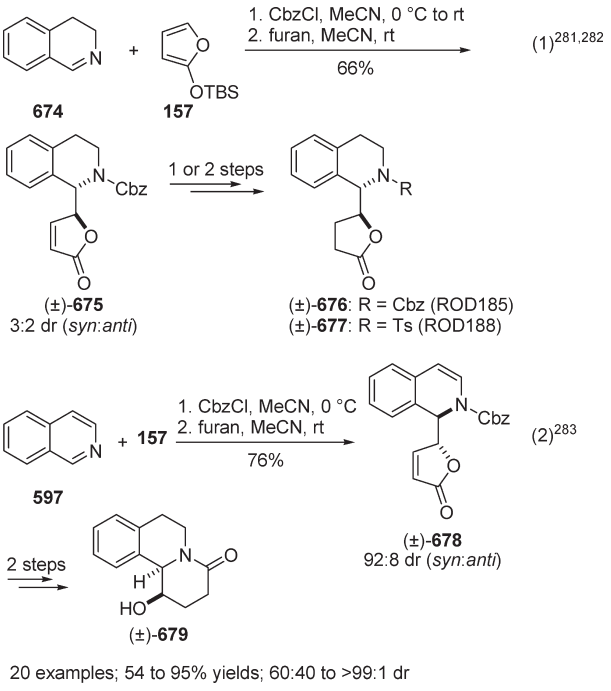
Scheme 121. Lewis Acid-Promoted VMMnR between Silyloxy Furans and in situ-Generated *N*-Acyl Iminium Ions[278−280]



Scheme 122. VMMnR Additions of Silyloxy Furan 157 to 3,4-Dihydroisoquinoline- and Isoquinoline-Derived *N*-Acyl Iminium Ions[281−283]



N,O-acetal trimethylsilyl ethers under BF_3 etherate assistance. As an example (eq 3), the seven-membered *N*-acyl iminium ion derived from (±)-**673** reacted well with silyloxy furan **155**, affording butenolide adduct (±)-**666** in good yield (86%) as an inseparable 11:1 mixture of diastereoisomers, whose relative configuration was not ascertained.

In 2000 Dodd and co-workers[281,282] described the first VMMnR addition of 2-trialkyl silyloxy furans with 3,4-dihydroisoquinolinium salts. Thus, as shown in Scheme 122 (eq 1), treatment of 3,4-dihydroisoquinoline (**674**) with benzyl chloroformate gave an acyl iminium salt, which reacted in situ with silyloxy furan **157** to afford *syn*-configured (±)-**675** along with its *anti*-isomer (3:2 dr).

The major *syn*-isomer (±)-**675** served to construct a panel of *N*-acyl- and *N*-arylsulfonyl isoquinolyl furanones of type (±)-**676** and (±)-**677**, which constitute new classes of positive allosteric modulators of the $GABA_A$ receptor.

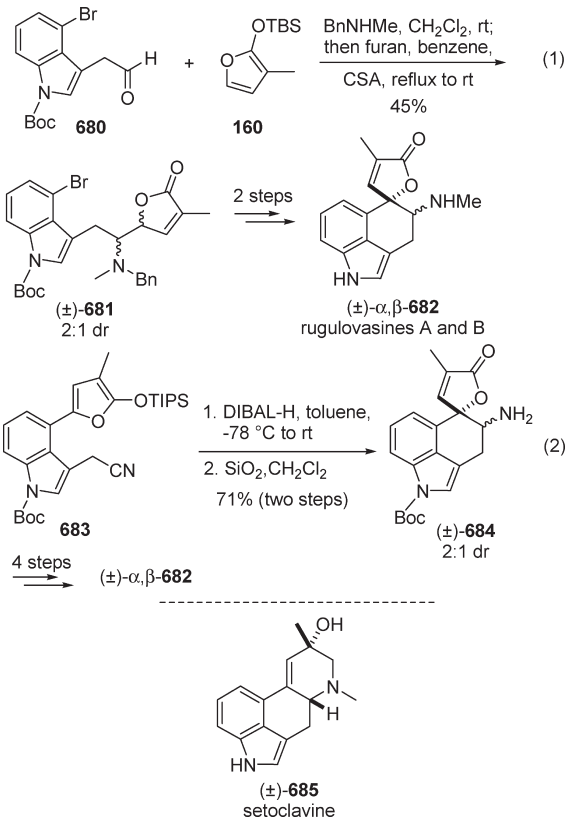
In a subsequent work, the same author[283] extended this procedure to completely aromatic isoquinoline iminium acceptors and showed that VMMnR proceeded well using a variety of silyloxy furans and acylating/sulfonylating agents. As an emblematic example (1 out of 20, eq 2), three-component VMMnR involving isoquinoline **597**, silyloxy furan **157**, and benzyl chloroformate provided easy access to isoquinolino-butenolide (±)-**678** in high yield and good 92:8 *syn*/*anti* dr. The potential of such a strategy in synthesis was demonstrated by the short transformation of (±)-**678** to (±)-**679**, which represents the central unit of tetrahydroisoquinoline-bearing alkaloids and pharmaceutical products as well.

By grouping the examples in this section dealing with the addition between silyloxy furans and cyclic iminium ions, one can notice a uniform *syn*-preference with unsubstituted silyloxy furans, with the exception of only two examples involving γ-methyl-substituted donors (e.g., Scheme 119, eq 3, and Scheme 121, eq 1). Although a decisive mechanistic rationale is hard to construct in the absence of additional experimental and computational data, one can argue that, for these reactions, the reactants approach in the transition state usually favors a *syn*-directed trajectory, but this bias is somehow perturbed by the steric hindrance of the substituents within the furan moiety, giving rise to a reversal in simple diastereoselection.

The power of the vinylogous Mukaiyama−Mannich reaction in total synthesis has been rarely demonstrated best than in the 2001 work by Martin and co-workers dealing with the synthesis of the *Ergot* alkaloids rugulovasines A and B and setoclavine.[284] Central to the construction of these natural alkaloids was VMMnR, performed between suitable silyloxy furan donors and in situ-generated imine/iminium ion acceptors in either intermolecular or intramolecular fashion. Thus, as shown in Scheme 123 (eq 1), for the intermolecular VMMnR approach to racemic rugulovasine A [(±)-β-**682**] and rugulovasine B [(±)-α-**682**], crude aldehyde **680** (derived from the corresponding nitrile) was reacted with benzyl methylamine to give an iminium ion intermediate, which easily underwent reaction with silyloxy furan **160** (in the presence of camphorsulfonic acid) to furnish an inseparable diastereomeric mixture (2:1) of adducts (±)-**681**. Subsequent intramolecular $S_{RN}1$ reaction on (±)-**681** and global deprotection guaranteed formation of the targeted alkaloids as a 1:2 β/α mixture. According to a second intramolecular VMMnR variant (eq 2), tricyclic nitrile **683** was first accessed, which was subjected to the crucial VMMnR by

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

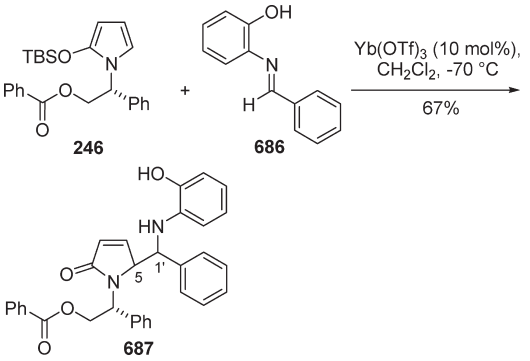
Scheme 123. Total Syntheses of Rugulovasines A and B [(±)-α,β-682] and Setoclavine [(±)-685] Featuring Inter- or Intramolecular VMMnR[284]



DIBAL-H reduction (with anhydrous SiO_2 added prior to workup) to a delicate imine intermediate promptly intercepted by addition of the silyloxy furan γ-carbon. Vinylogous Mannich product (±)-**684** formed in 71% yield as a 2:1 diastereomeric mixture, which was forwarded to rugulovasines A and B via simple chemistry (2:1 β/α mixture). Finally, a similar procedure was applied to the *N*-tosyl variant of **683** to construct the fully fused tetracyclic alkaloid setoclavine (±)-**685** via intramolecular VMMnR and lactone-to-lactam rearrangement.

Silyloxy pyrroles in VMMnR addition have been investigated to a much lesser extent than the silyloxy furan relatives, although they offer the undoubtable benefit of using the *N*-pyrrole site as an anchoring point for chiral auxiliary appendages. Capitalizing on the experience in the use of chiral silyloxy pyrroles in VMAR additions, in 2000, Royer[285] demonstrated that these nucleophiles could serve admirably in the ytterbium triflate-catalyzed additions to various aldimines deriving from aromatic or heteroaromatic aldehydes (Scheme 124). Best performances were achieved with silyloxy pyrrole **246**, which reacted with aldimines (e.g., **686**) to afford the corresponding adducts of type **687** as separable mixture of diastereoisomers. Good *anti*/*syn* diastereoselectivity was generally observed, with increasing dr values arising in the presence of a coordinating hydroxyl group in the imine; however, precise structural assignment of the major *anti*-configured products (5,1′-*S*,*R* and 5,1′-*R*,*S*) was not given. The *anti*-selectivity with chiral *N*-benzyl pyrrole **246** is in contrast to the *syn*-diastereopreference generally observed using

Scheme 124. Auxiliary-Driven Diastereoselective VMMnR Employing Chiral Silyloxy Pyrrole Vinylogous Donors[285]



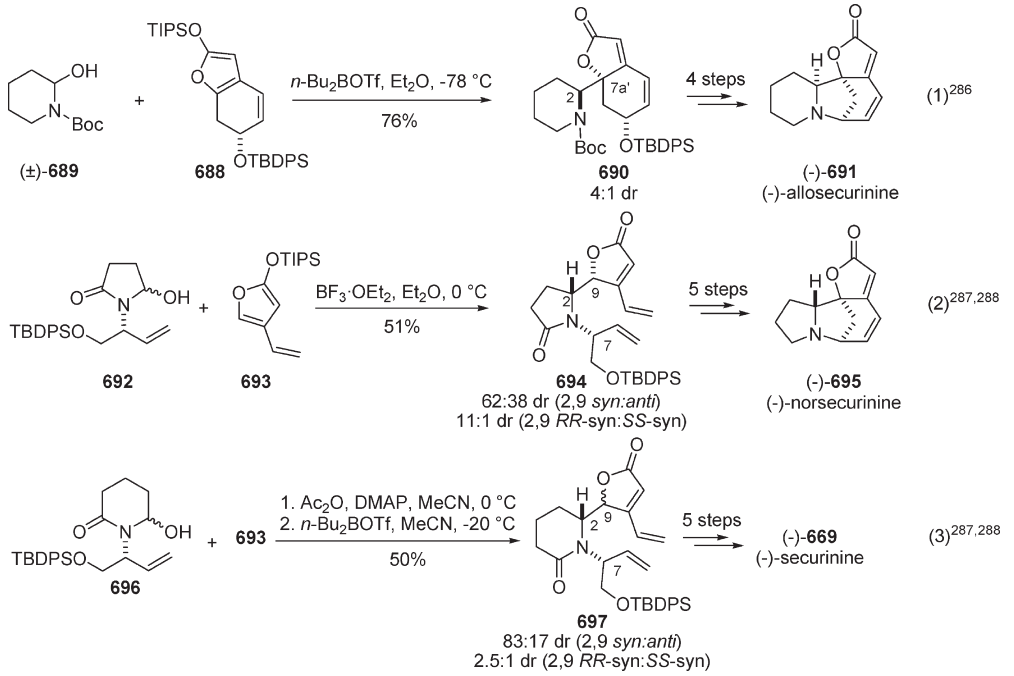
7 examples; 18 to 90% yields; 65:35 to 100:0 dr

silyloxy furans (vide infra); yet, a possible explanation accounting for this reversal of selectivity was not reported by the authors.

For the total synthesis of *Securinega* alkaloids, Figueredo and colleagues envisaged a novel stereoselective entry to allosecurinine (−)-**691** and its enantiomer viroallosecurinine (not shown), which featured a VMMnR as the key maneuver (Scheme 125, eq 1).[286] Thus, chiral nonracemic silyloxy furan **688** [in turn obtained from (+)-menisdaurilide] was used as a crude material in the VMMnR addition to the piperidinium ion generated in situ from (±)-**689** in the presence of *n*-Bu_2BOTf as the Lewis acid promoter. (2*S*,7a′*S*)-*N*,*O*-*syn*-Adduct **690** (target numbering) preferentially formed (4:1 dr) in a good 76% isolated yield. Deprotection and ring closure finally completed the synthesis of (−)-allosecurinine (−)-**691** in a five-step sequence and 47% overall yield from **688**.

The same research group planned a general and enantioselective route to assemble medicinally important norsecurinine and securinine type alkaloids.[287,288] In a parallel fashion (Scheme 125), chiral hemiaminals **692** and **696** were prepared via enantioselective allylation of succinimide or glutarimide precursors, ready for the key VMMnR with vinyl silyloxy furan **693**. Five-membered precursor **692** produced a mixture of diastereoisomers by direct exposure to BF_3 etherate from which pure (*R*,*R*,*R*)-configured *syn*-isomer **694** could be isolated by simple crystallization in 51% yield (eq 2). For piperidinone series **697**, a slightly modified protocol was implemented, which consisted of acetylation and exposure to *n*-Bu_2BOTf. In this instance, two isomers were formed in predominance, namely, epimeric (2*R*,7*R*,9*R*)-*syn*- and (2*R*,7*R*,9*S*)-*anti*-isomers **697**, and each proved to be a suitable precursor of the targeted securinine (eq 3). To account for the observed diastereoselectivity of VMMnR, density functional theory calculations were carried out for a strictly related model reaction.[288] These calculations anticipated the preferential formation of the *syn*(*threo*)- over *anti*(*erythro*)-isomers, in partial agreement with the above experimental results, as they probably underestimated the influence of the stereogenic center external to the ring on the *syn*/*anti* selectivity. Finally, compounds **694** and **697** were converted to the targeted alkaloids via RCM maneuver and intramolecular vinylogous nucleophilic alkylation.

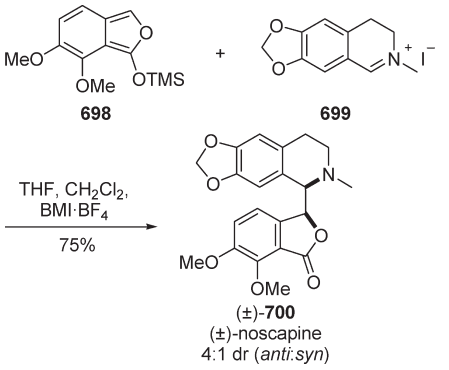
Scheme 125. Stereoselective Total Syntheses of *Securinega* Alkaloids (−)-691, (−)-695, and (−)-669, Featuring Intermolecular VMMnR Additions[286−288]



A clever example of "phenylogous" Mukaiyama−Mannich addition reaction involving phthalide-derived silyloxy dienes of type **698** was recently reported by Santos et al.[289] during a study directed toward the synthesis of a series of racemic phthalide tetrahydro-isoquinoline alkaloids. As an example, the concise synthesis of noscapine (±)-**700** is shown in Scheme 126. Thus, unstable silyloxy diene **698**, in turn obtained from the corresponding phthalide by γ-deprotonation and *O*-silylation, was coupled to in situ-generated *N*-methyl isoquinolinium ion **699** under the assistance of butyl methyl imidazolinium tetrafluoroborate (BMI·BF_4) additive. Remarkably, the phenylogous addition proved to be diastereoselective, unexpectedly producing the *anti*-configured (*erythro*) adduct (±)-**700** in a 75% isolated yield, and 4:1 diastereomeric ratio. Despite detailed investigation on the possible mechanism involved in this transformation (theoretical calculations at DFT level), the authors were unable to rationalize the stereochemical reversal observed with this reaction with respect to the normal behavior of similar VMMnR involving silyloxy furan analogues.

4.1.2. Direct Additions of in situ-Generated Dienolates. A direct variant of the previously analyzed Mukaiyama type phenylogous Mannich addition involving phthalide-related d_4 nucleophiles (vide supra, chapter 4.1.1.2) was developed in 2007 by Couture et al.[290] as the key transformation in a short total synthesis of narceine imide **704**, a strong inhibitor of aldehyde reductase and liver alcohol dehydrogenase. In the event (Scheme 127), dimethoxy-isoindolinone **701** was reacted with *N*-methyl-dihydroisoquinolinium iodide **702** in the presence of KHMDS in THF at −78 °C to afford racemic adduct (±)-**703**, which was isolated as a 1:1 mixture of diastereoisomers. Quaternaryzation of this mixture with methyl iodide followed by deprotonation and acidic treatment, finally produced *Z*-configured narceine imide **704** in a high isolated yield.

Scheme 126. Total Synthesis of Noscapine Alkaloid (±)-700[289]



A concise, enantioselective synthesis of angiotensin converting enzyme inhibitor (−)-A58365A (**709**) has been achieved by Martin et al.[291] following a direct VMMnR addition and a lactone-to-lactam rearrangement as the key transformations (Scheme 128). Thus, butenolide **705** was directly treated with a TMSOTf/Et_3N mixture followed by L-pyroglutamic acid-derived aminal **706** to form adduct **707**, which was soon deprotected to binuclear butenolide **708** (mixture of four isomers). Finally, lithium methoxide in methanol triggered the desired lactone-to-lactam rearrangement, giving rise to the targeted indolizidine **709** after acidic methyl ester hydrolysis.

Vinyloxiranes are valuable and highly reactive species that have found wide applications in organic synthesis. Remarkable transformations include ring-opening and/or rearrangement processes

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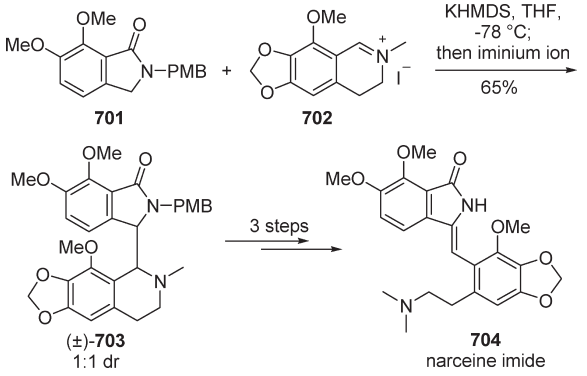
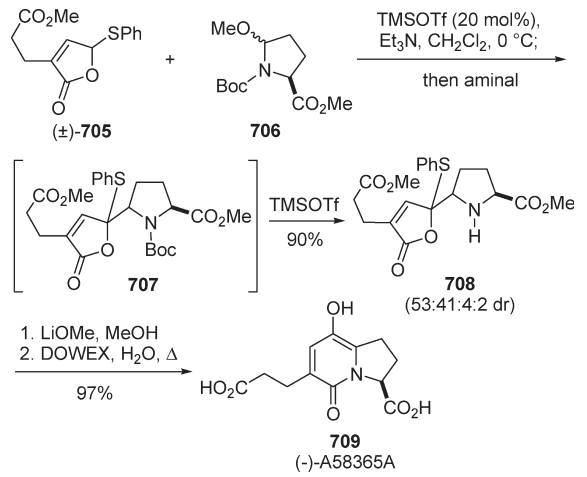
Scheme 127. Total Synthesis of Narceine Imide 704[290]



Scheme 128. Direct VMMnR in the Total Synthesis of ACE Inhibitor (−)-A58365A (709)[291]



promoted by Lewis acids or transition metal catalysts. In 2004−2006, Lautens et al.[292−294] widely exploited a series of racemic vinyloxiranes of type (±)-**711**, (±)-**714**, and (±)-**717** as masked vinylogous enolates in direct Mannich additions (Scheme 129). Thus, for example, treatment of vinyloxirane (±)-**711** with catalytic $Sc(OTf)_3$ resulted in the formation of an open chain, active dienolate species via 1,2-hydride shift, which in turn reacted with imine **710** to give the vinylogous addition product (±)-**712** in high isolated yields (eq 1). Interestingly, when an aryl-substituted oxirane of type (±)-**714** was involved, 1,2-migration of the aryl group occurred, with α-aryl-substituted α,β-unsaturated aldehyde (±)-**715** formed as the sole reaction product (eq 2). In a similar manner, several oxyrane vinylogous donors were screened for direct Lewis acid-catalyzed VMnR additions to imine acceptors (eqs 3 and 4), for the preparation of useful unsaturated aldehyde candidates with high efficiency and reproducibility.

A clever variant of this strategy was applied by the same authors[295] to monoactivated methylenecyclopropanes, which, under MgI_2 treatment, served as synthetic equivalents of acyclic vinylogous magnesium enolates in Mannich reactions with imine species.

A direct VMnR with α,α-dicyanolefins and *N*-Boc protected α-amidosulfones—synthetic equivalents of imine acceptors—was devised by Chen and Li,[296,297] which was applied to forge a series of racemic dicyanomethylene bicyclic products (Scheme 130). When treated with K_2CO_3 under ultrasound irradiation, dicyanoalkylidene compounds of type **721**, **724**, and **726** formed the corresponding activated dienolate species in situ, via deprotonation at the C-γ carbon. Subsequent reaction with α-amido sulfone (±)-**722** then produced the expected Mannich products (±)-**723**, (±)-**725**, and (±)-**727** in good yields, although the relative configuration of the products and diastereomeric ratios were not assessed.

Chiral sulfinimine **603**, previously disclosed in Mukaiyama type VMnR (chapter 4.1.1.1), was also utilized by Kawecki[255] in the analogous direct additions with acetoacetate **728** and dioxinone **730** (Scheme 131). The in situ-generated lithium dienolates cleanly underwent the vinylogous addition to imine **603** giving an intermediary Mannich product that was converted to auxiliary-free piperidines **729** and **731** in moderate yield and appreciable enantioselectivity. It should be noted that lowering the temperature below −50 °C resulted in the formation of the α-coupling product, while at −30 °C only the γ-coupling product was observed in the reaction mixture.

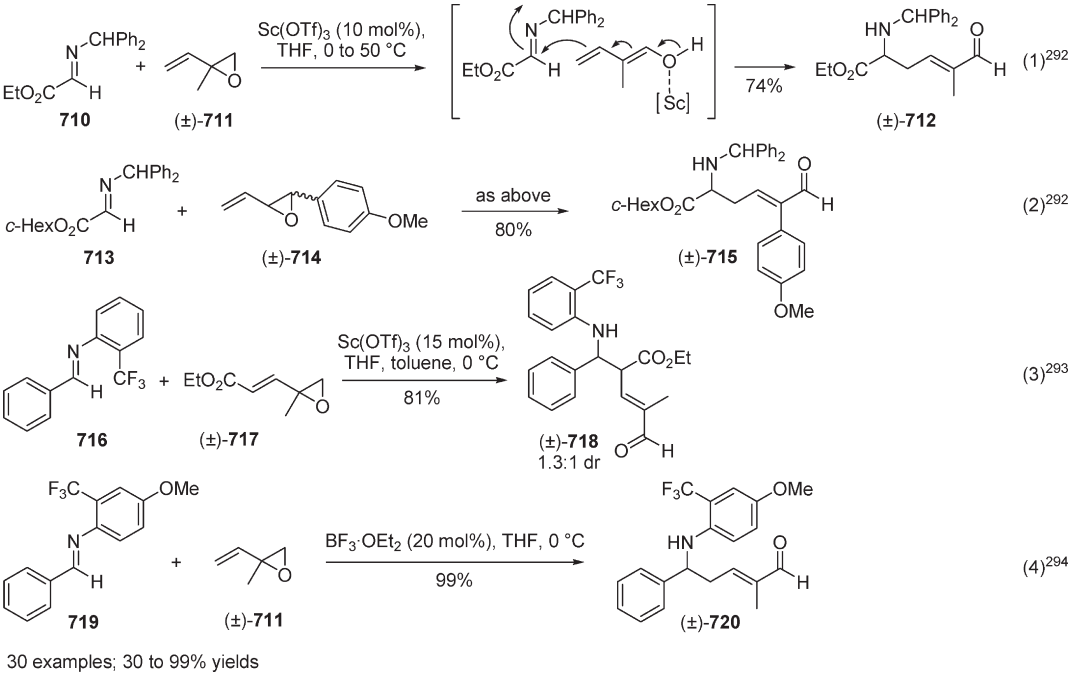
4.2. Enantioselective Processes

As with the vinylogous aldol chemistry, the enantioselective versions of the vinylogous Mannich reactions have only experienced a marked fluorishing in recent years, with outstanding achievements reached in both metal-based catalysis and organocatalysis domains. For ease, the current chapter has also been divided into two sections dealing with indirect and direct additions. Furthermore, the indirect process section has been subdivided into reactions involving acyclic dienolate synthons and cyclic counterparts.

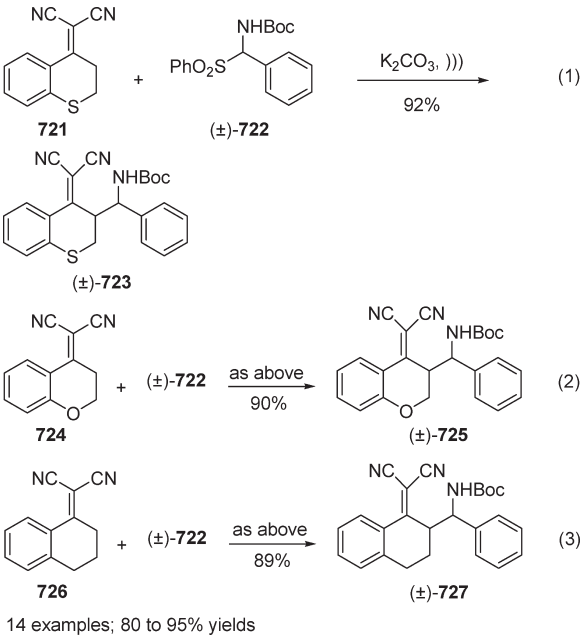
4.2.1. Indirect Mukaiyama Type Additions of Silicon Dienolates *4.2.1.1. Acyclic Silicon Dienolates.* Chiral Brønsted acid organocatalysis—the exploitation of catalytic amounts of low molecular weight chiral organic molecules to drive and control an organic transformation via a protic acid functionality—was recently applied by Schneider and coworkers[298−301] in the vinylogous Mannich realm, by devising BINOL-based phosphoric acids of type **732**, **733**, and **734** as the catalysts of choice. In a series of papers over the period 2008−2010,[298−301] Schneider investigated VMMnR between extended silyl ketene acetals or aminals and various aromatic and heteroaromatic aldimines, according to either a two-component protocol (preformed aldimines) or a three-component protocol (in situ-generated aldimines). A picture displaying seven (out of 70) vinylogous Mannich products obtained by this asymmetric technique is portrayed in Scheme 132 summarizing product yields, as well as diastereo- and enantioselectivities. Optimized catalysts **732**−**734** invariably produced compounds with exquisite levels of enantioselectivity and *anti*-diastereoselectivity, if applicable. Although all contributions were basically methodology-oriented, a clever exploitation in synthesis was attained for a selected candidate **741**, which was shortly elaborated to naturally occurring pyridine alkaloid (*S*)-anabasine (**742**).

In applying the same (*R*)-BINOL-based organocatalytic technique to Brassard diene **456** and imine acceptors, Akiyama et al.[302] performed a direct asymmetric synthesis of diverse dihydropyridone derivatives. Of the two possible reaction paths—concerted aza-Diels−Alder reaction vs stepwise vinylogous Mannich/

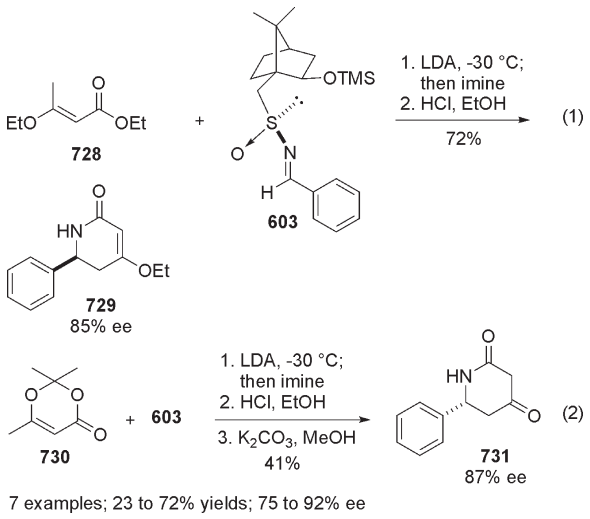
Scheme 129. Direct Vinylogous Mannich Type Reactions via Ring-Opening Rearrangement of Vinyloxiranes[292−294]



Scheme 130. Base-Catalyzed Solvent-Free Direct VMnR Involving Dicyanoalkylidene Donors[296]



Scheme 131. Direct VMnR of Lithium Dienolates to Chiral Sulfinimine 603[255]



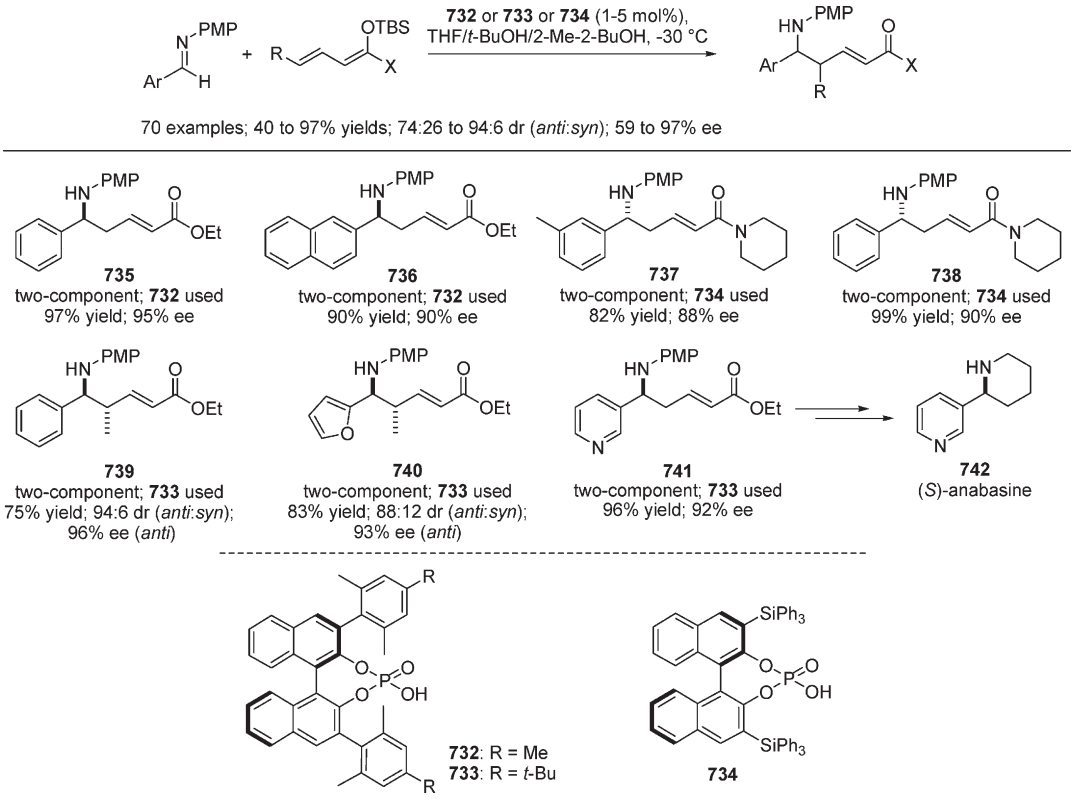
lactamization—the authors sustained that an aza-DA cycloaddition was involved. However, no firm evidence ruling out an alternative two-step mechanism was supplied by the authors.

In a recent communication, Liu and Feng[303] reported a highly efficient asymmetric three-component VMMnR between open chain silyl dienolate **35** and in situ-generated aromatic aldimines (Scheme 133). Crucial for the success of this three-component VMMnR was the use of C_2-symmetric *N*,*N*′-dioxide ligands of type **744** in conjunction with catalytic $Sc(OTf)_3$. Under optimized conditions, all reactions (16 examples) proved highly efficient, giving the expected δ-amino-α,β-unsaturated esters of type **745** and **746** in excellent yields and enantioselectivities. However, several flaws do exist on the face of this otherwise skillful methodology: failure of the procedure involving aliphatic aldehydes and omitted determination of the absolute configuration of the products.

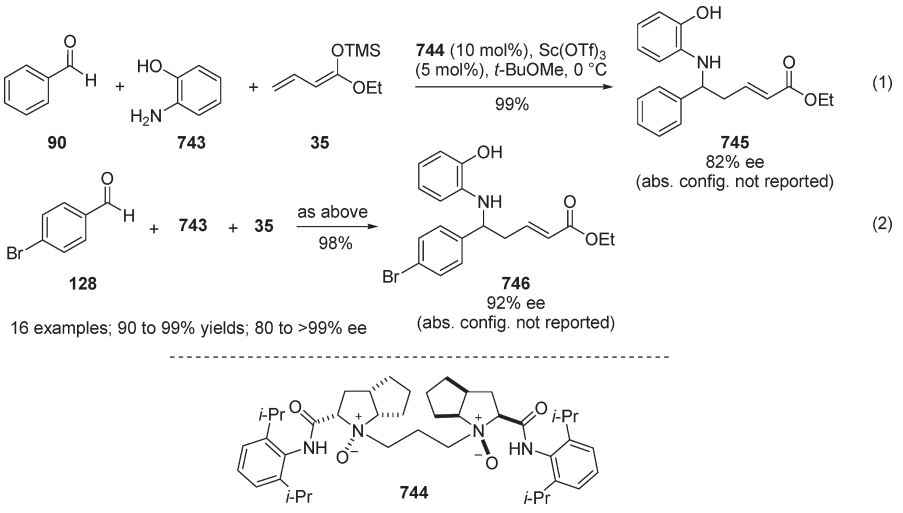
An efficient, metal-catalyzed enantioselective VMMnR procedure compatible with acyclic silyl dienolates of type **3** and **5** was developed by Carretero et al.[304] This reaction relied on the use of

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 132. Brønsted Acid-Catalyzed Enantioselective VMMnR Involving Acyclic Silyloxy Dienes[298−301]



Scheme 133. Asymmetric Three-Component VMMnR of Silyl Dienolate 35 Catalyzed by C_2-Symmetric *N,N′*-Dioxide 744[303]



N-(thienylsulfonyl)imines (e.g., **747** and **749**) as acceptors and copper(I)−Fesulphos complexes of type **751** as catalysts (Scheme 134). The reactions were performed in the presence of silver(I) perchlorate to give δ-amino-α,β-unsaturated carbonyl compounds of type **748** and **750** in good yields and with outstanding enantiocontrol. A relevant advantage of using the 2-thienylsulfonyl group as amine protecting group is its facile removal, which allowed quick elaboration of the formed adducts into valuable chiral nonracemic compounds.

4.2.1.2. Cyclic Silicon Dienolates. Optimizing a catalytic, enantioselective protocol to efficiently control the fate of a reaction involving a number of variables subtly interconnected with each other is one of the hardest tasks faced by a methodology-oriented chemist. To succeed, one has to plan a painstaking work where intellectual rigor, intuition, and fortune are often decisive.

Hoveyda, Snapper, and co-workers[305−307] admirably described, in a series of papers, the development of enantio- and diastereoselective catalytic VMMnR protocols wherein unsubstituted

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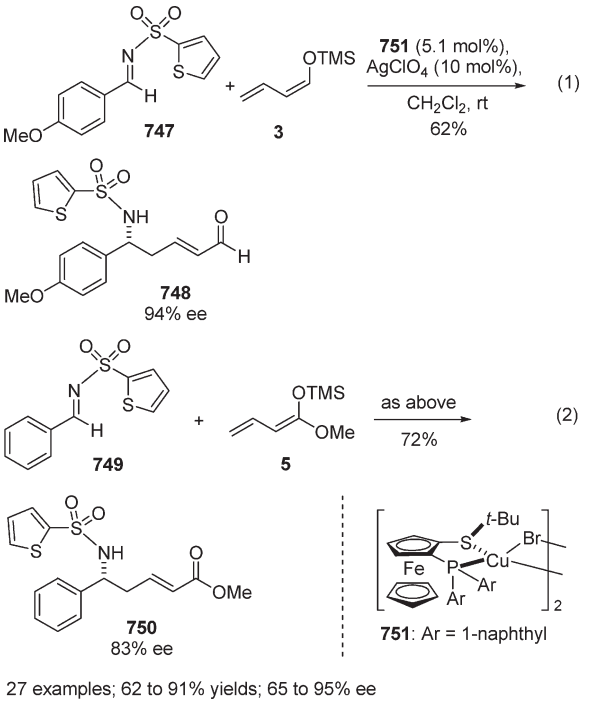
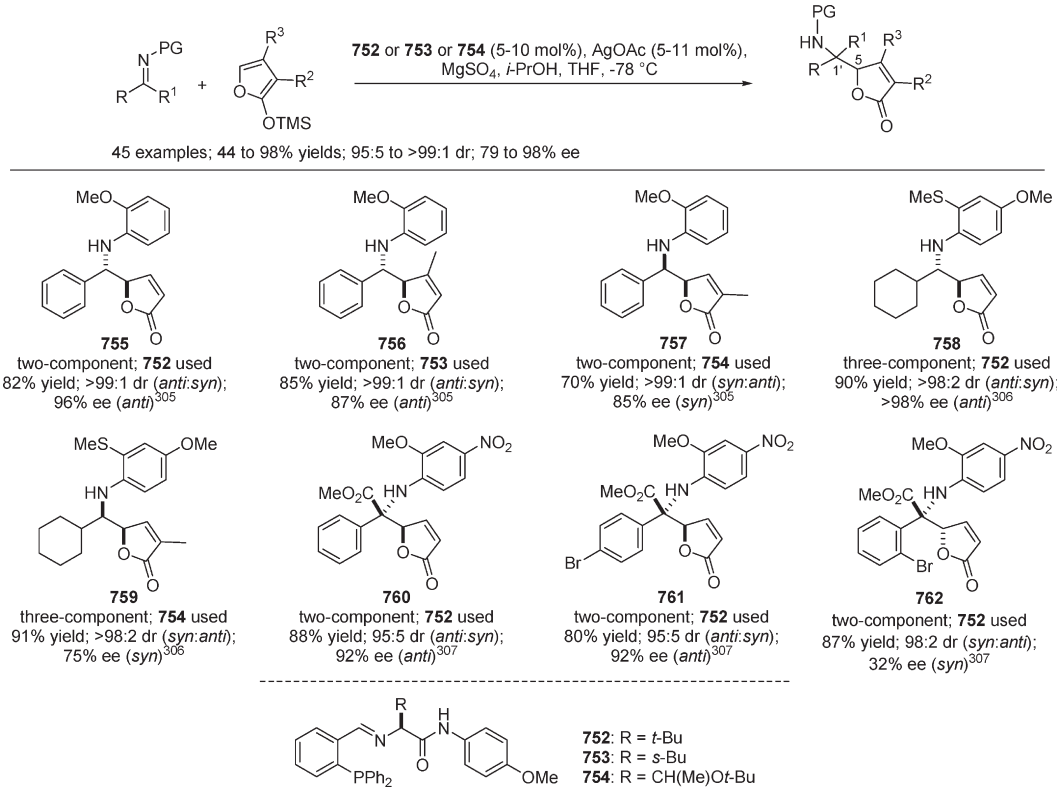
and methyl-substituted 2-silyloxy furans of type **155**, **159**, and **541** reacted with aromatic or aliphatic aldimines to form important aminated butenolide structures. After a thorough preliminary work, optimal conditions were found to govern these processes, with amino acid-derived phosphine ligands of type **752**, **753**, or **754** in complex with AgOAc being the privileged catalyst systems. In particular, VMMnR involving preformed aromatic imines performed well when 5 mol % ligands **752**−**754** in complex with AgOAc were employed as catalysts (Scheme 135). The reactions proceeded to >98% conversion (up to 85% isolated yields) and afforded, in general, the *anti*-disposed butenolide adducts with excellent diastereo- and enantioselectivity (e.g., compounds **755** and **756**). As an exception, with α-methyl-substituted 2-silyloxy furans, reversal in diastereoselectivity was observed in favor of *syn*-configured butenolides (e.g., compound **757**). In a similar manner, aliphatic, in situ-generated aldimines proved to be competent substrates to give rise to the corresponding *anti*-configured adducts in good isolated yields and valuable levels of diastereo- and enantioselectivity (e.g., compound **758**). Also, in this case, reversal of diastereoselectivity was attained when passing from unsubstituted silyloxy furans to α-methyl-substituted congeners (e.g., compound **759**).

The issue of catalyst vs substrate control in reactions involving chiral aldehydes was addressed by the same authors by employing 2-phenylpropanal imine as a chiral probe. It was demonstrated that *anti*-configured Mannich products prevailed, irrespective of the resident imine chirality [(*R*) vs (*S*) vs racem], and this confirmed that the outcome of the reaction is dictated by the identity of the chiral catalyst and not the substrate. Finally, the authors extended the scope of the reaction by turning to activated, preformed α-ketoimine esters. After further optimization of the reaction parameters, VMMnR of ketoimine derived from *p*-nitro-*o*-anisidine was scrutinized, giving rise to a 95:5 *anti*/*syn* mixture of amino butenolides (e.g., compounds **760** and **761**) carrying a quaternary center at C1′. Remarkably, when an

Scheme 134. Asymmetric VMMnR of Acyclic Silyl Dienolates Catalyzed by Copper(I)-Fesulphos Complex 751[304]



Scheme 135. Asymmetric Two- and Three-Component Ag-Catalyzed VMMnRs Involving 2-(Trimethylsilyloxy)furans[305−307]



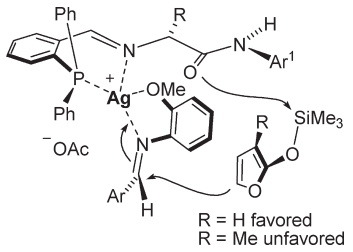
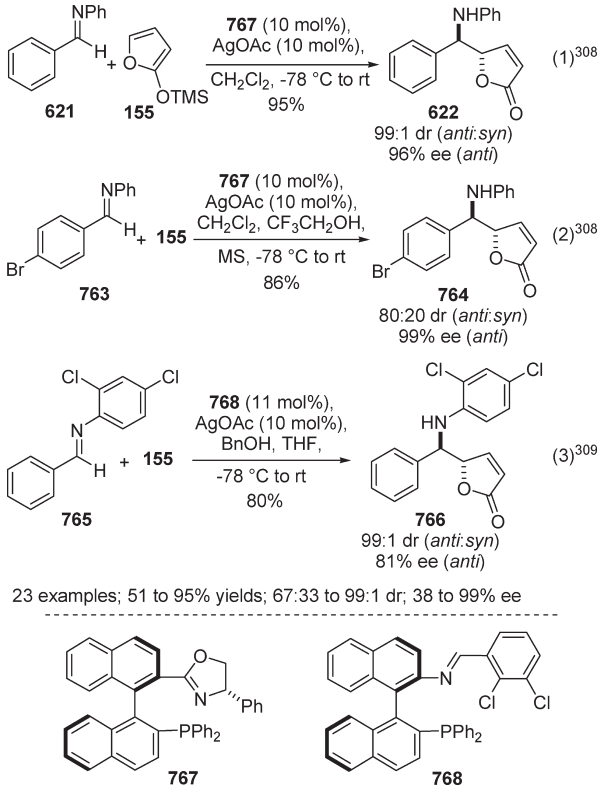
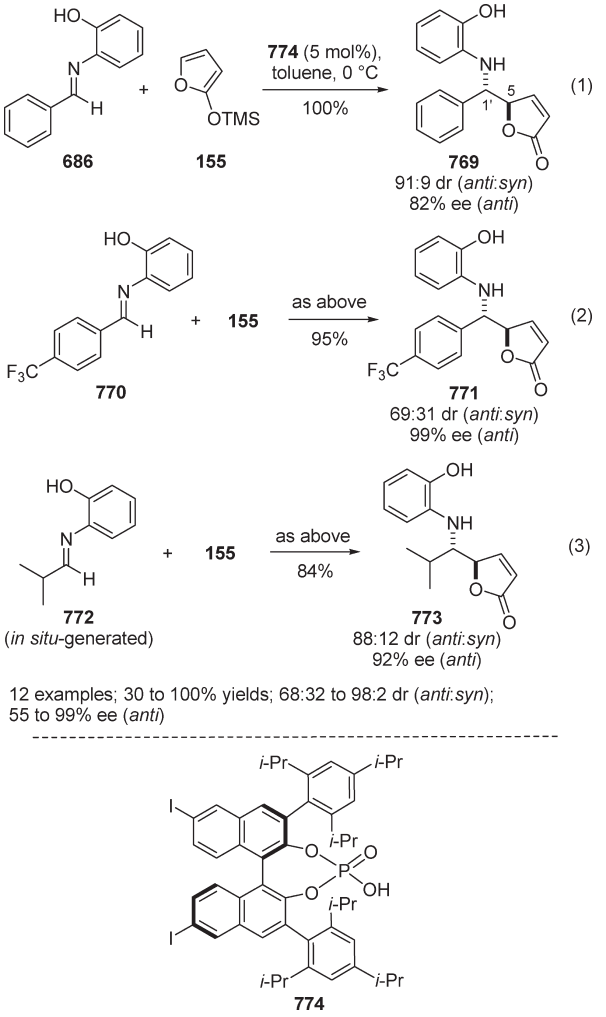


Figure 9. Proposed transition state model for Ag-catalyzed enantioselective VMMnRs involving 2-(trimethylsilyloxy)furans and aromatic aldimines.

Scheme 136. Axially Chiral Phosphine Ligands in Silver(I)-Catalyzed Asymmetric VMMnR Using Silyloxy Furan 155[308,309]



Scheme 137. Asymmetric VMMnR of Silyloxy Furan 155 and Aldimines Catalyzed by Iodine-Substituted Chiral Phosphoric Acid 774[310]



o-bromo-substituted arylimine was employed, reversal in diastereoselectivity was observed along with a marked erosion of the enantioselectivity (e.g., compound **762**).

On the basis of these results and after extensive work directed at identifying the actual nature of the Ag-based catalytic system, possible models were postulated to account for the observed reaction behaviors. In particular, Figure 9 depicts a model that governs the path toward the *anti*-disposed (5*R*,1′*S*)-adducts of type **755** (R = H). Herein, a tightly organized intracomplex scenario is responsible for simultaneous Lewis acid activation of the substrate and Lewis base activation of the enol silane reactant, while providing the proper steric environment for high enantiodifferentiation (*Si*−*Si*-face approach leading to *anti*-diastereoisomers). Such a path should be unfavorable for 3-methylsubstituted furan (R = Me) because of steric repulsion in the catalyst-bound imine, and this justifies the stereochemical switch to *syn*-isomers (e.g., compound **757**).

As previously discussed for the diastereoselective VMMnR additions on acyclic imines (section 4.1.1.2), the same *anti* vs *syn* reversal of simple diastereoselection was observed here, depending on the substitution in the silyloxyfuran component. Indeed, it is the C3 substitution in the furan donor (H vs CH_3) that seems to dictate the mutual location of the two reactants in the transition states, ultimately imparting a definite switch of diastereoselection.

The application of chiral phosphine−Schiff base type ligands in Ag(I)-catalyzed asymmetric VMMnR additions to aldimine using unsubstituted trimethylsilyloxy furan (**155**) as d_4 nucleophile was investigated by Shi et al. in 2009.[308,309] The authors discovered that phosphine-oxazoline ligand **767** and phosphine-imine **768** proved to be excellent catalysts when applied in conjunction with AgOAc to give the expected δ-amino butenolide compounds of type **622**, **764**, and **766** in good yields and acceptable to good margins of enantio- and diastereoselectivities in favor of the *anti*-(*R*,*S*)-diastereoisomers (Scheme 136). Plausible mechanistic models to rationalize both the facial and the

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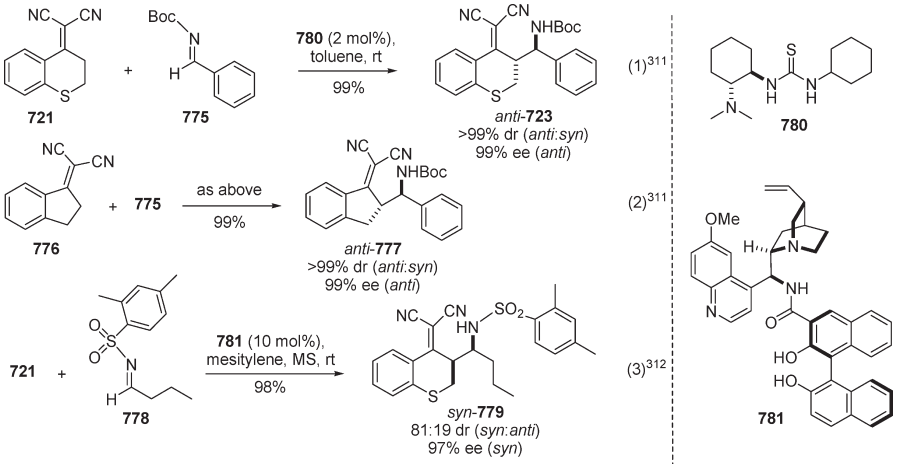
Scheme 138. Asymmetric VMnR of Dicyanoalkylidenes with Aryl and Alkyl Imines[311,312]



simple stereoselectivity in these asymmetric silver-catalyzed transformations were postulated, evoking transition state structures similar to those previously described by Hoveyda and Snapper (vide supra). Once more, these findings show that VMMnR involving unsubstituted furans largely favor *anti*-configured Mannich products.

Utilizing the same copper(I)/Fesulphos chiral complexes of type **751** exploited in asymmetric VMMnR involving acyclic silyl dienolate nucleophiles (vide supra, chapter 4.2.1.1), Carretero et al.[304] expanded this chemistry to unsubstituted silyloxy furan **155**. In this instance, reactions with a number of aromatic and alkenyl *N*-thienylsulfonyl imines were investigated giving rise to (5*S*,1′*S*)-*syn*-configured δ-amino butenolides in good yields and excellent diastereo- and enantioselectivities. The *syn*-diastereopreference here observed with sulfonyl imines is rather surprising and deviates from the usual trend that privileges *anti*-configured isomers when unsubstituted furan donors are used. No comments were provided by the authors about this point.

Akiyama and co-workers[310] extended the chiral BINOL-based Brønsted acid organocatalysis to asymmetric VMMnR of **155** with aromatic and aliphatic aldimines. Once the optimum catalyst was discovered, that is, iodine-substituted phosphoric acid **774**, the reaction outcome was evaluated in terms of the imine component in a panel of 12 experiments (Scheme 137). Invariably, using a 5 mol % catalyst loading in toluene at 0 °C, all reactions went to completion with full γ-site selectivity, excellent isolated yields, and outstanding margins of *anti*/*syn* diastereoselectivity and enantioselectivity (5*R*,1′*S*).

4.2.2. Direct Additions of in situ-Generated Dienolates. A major advancement in this domain was recently reached by Chen[297,311,312] and Jørgensen[313] groups, who independently utilized dicyanoalkylidene nucleophiles as d_4 donors in asymmetric VMnR additions to *N*-Boc or *N*-sulfonyl-protected imines. In particular, Chen et al. introduced a series of chiral bifunctional thiourea-tertiary amine organocatalysts to govern these processes, while Jørgensen and Niess capitalized on varied rigid chiral phase-transfer salts derived from *Cinchona* alkaloids or pyrrolidine analogues.

Scheme 138 displays some examples of direct asymmetric VMnR of dicyanoalkylidenes with selected imines by Chen et al.[297,311,312] exploiting chiral thiourea- or (*S*)-BINOL-derived organocatalysts **780** and **781**. Excellent stereoselectivities have been achieved for a broad spectrum of substrates with *anti*-configured or *syn*-configured adducts being formed according to the nature of the catalyst/imine couple employed. Worth noting is the fact that both the imines derived from aromatic aldehydes and those derived from aliphatic aldehydes could be successfully applied in these versatile and general VMnR procedures.

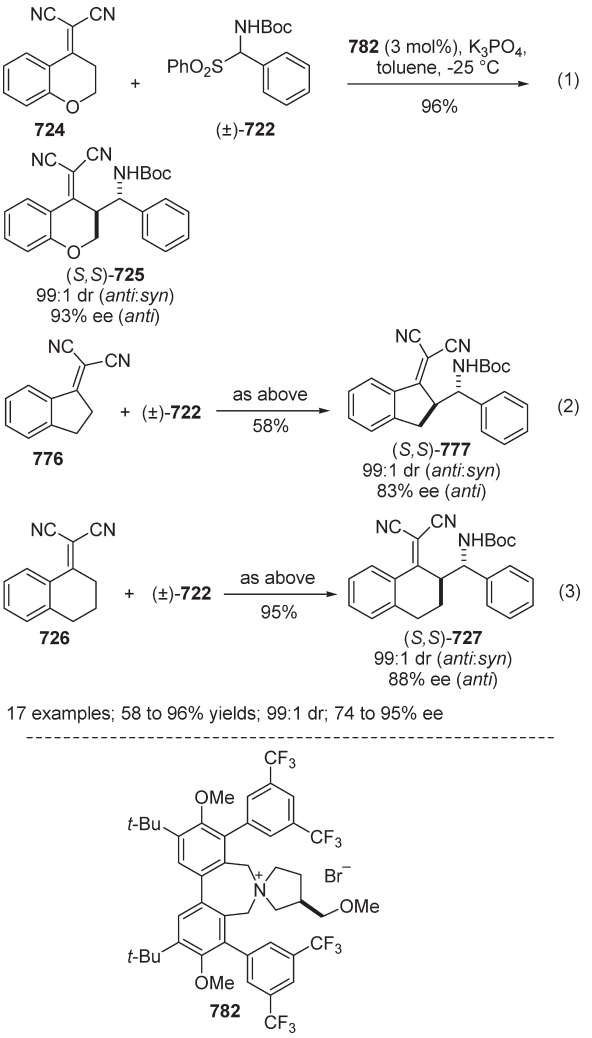
Jørgensen and Niess[313] also investigated a similar asymmetric VMnR using α-amidosulfones of type **722** as the imine precursors, which reacted with α,α-dicyanoalkenes (e.g., **724**, **776**, and **726**) under phase-transfer catalytic conditions (Scheme 139). A rigid pyrrolidinium salt **782** was used, affording the (*S*,*S*)-configured aminoalkylated products (e.g., **725**, **777**, and **727**) in good yields, complete *anti*-diastereoselectivity, and up to 95% ee. The obtained Mannich products proved to be valuable synthetic intermediates that can be utilized for a variety of transformations. With the dicyanomethylene group as a masked ketone, double bond cleavage could deliver corresponding amino-ketone derivatives, important intermediates for diverse natural products.

The same α,α-dicyanoalkylidenes d_4 nucleophiles **724** and **726** were also utilized by Zhou et al.[314] in asymmetric direct VMnR additions to *N*-Boc-arylimines (Scheme 140). Ferrocenyl oxazoline-derived *N*,*P*-ligands of type **783** were employed in complex with AgOAc to promote these asymmetric transformations. After a preliminary optimization study, (*S*)-SynPhos **783** was chosen as the asymmetric catalyst, giving the desired (*R*,*R*)-configured vinylogous adducts of type **725** and **727** in good yields and moderate to good enantio- and diastereoselectivities.

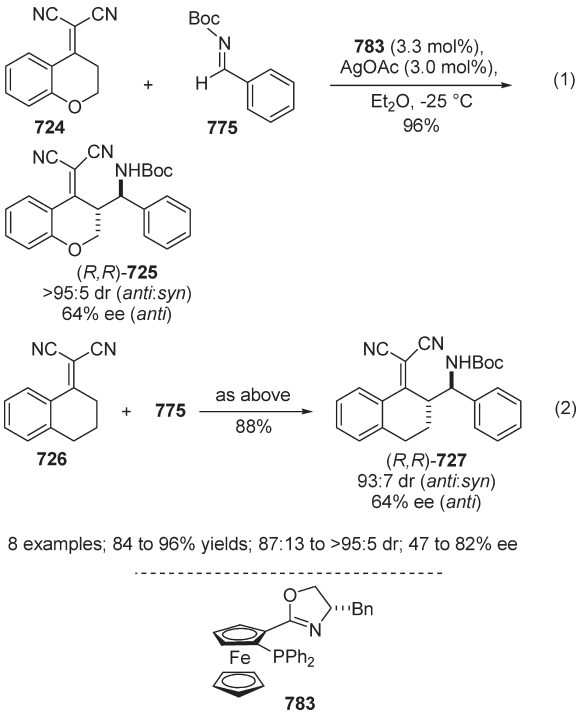
Direct, catalytic, and asymmetric VMnR of γ-butenolides and α,β-unsaturated γ-butyrolactams was the focus of a remarkable piece of work by Shibasaki and Matsunaga et al.[315,316] These authors capitalized on their experience in the use of PyBox-based and BINAP-based Schiff base−metal complexes to access enantioenriched highly functionalized γ-lactone and γ-lactam α,β-unsaturated compounds.

In a first contribution,[315] direct VMnR of γ-butenolides **786** and **788** was described, using *N*-diphenylphosphinoyl imines of type **785** or **790** as Mannich acceptors (Scheme 141). After a thorough optimization screening, it was found that the use of

Scheme 139. Asymmetric VMnR of Dicyanoalkylidenes with α-Amidosulfones[313]



Scheme 140. Asymmetric Direct VMnR of Dicyanoalkylidenes with *N*-Boc-Imines[314]



catalytic TfOH in addition to flame-dried La(OTf)$_3$, Me-PyBox **784**, and TMEDA was important for improving yield, stereoselectivity, and reproducibility. The scope of the reaction was investigated with a number of aromatic and aliphatic phosphinoyl imines and unsubstituted or substituted butenolide donors, with selected results displayed in Scheme 141. Of note, *anti*-diastereoselctivity was invariably observed, although partial loss of enantioselectivity affected reactions involving α-methylsubstituted donors (eq 2). The authors speculated that a ternary La(OTf)$_3$/Me-PyBox/TMEDA 1:1:1 combination was the reactive species in the reaction and that Brønsted acid TfOH was effective to prevent the competitive racemic background reactions.

The second report by the same authors[316] was centered upon bimetallic Ni−Ni BINAM−Schiff base catalyst **797** in direct VMnR with α,β-unsaturated γ-butyrolactam **307**. Optimization of the catalyst and reaction conditions led to the selection of catalyst **797** in THF with added DRIERITE (CaSO$_4$) as the best performing choice (Scheme 142). Control experiments using either heterobimetallic, monometallic, or homobimetallic non-nickel-based catalyst species failed, suggesting that two Ni centers are essential for a chemoselective reaction to occurr. With optimal conditions in hand, the direct, catalytic, and enantioselective VMnR was studied using different *N*-Boc aromatic and heteroaromatic aldimines with outstanding results invariably obtained (e.g., compounds **792**−**796**, Scheme 142).

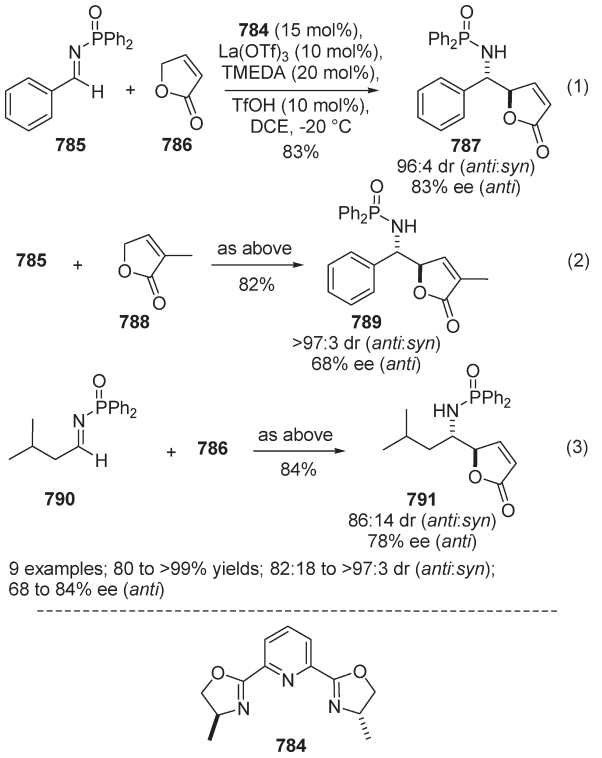
5. VINYLOGOUS MICHAEL REACTIONS

Since its very first appearance, the Michael addition reaction—that is, the 1,4-conjugate addition of carbon nucleophiles to vinylogous carbonyl (or β-electron-poor vinyl compounds) acceptors—has excelled as one of the preeminent synthetic methods of carbon−carbon bond formation. Even more appealing, yet less exploited, is the vinylogous version of the reaction, where the nucleophilic donor component is also vinylogous. When both the Michael donors and the acceptors are carbonyl compounds reacting in a vinylogous sense, precious α,β-unsaturated 1,7-dicarbonyl compounds form, paving the way for further advancement to relevant natural and non-natural target structures. When compared to VAR and VMnR addition processes, the vinylogous Michael reaction (VMcR) has gained minor attention during the decade covered by this review, with about 50 research papers appearing devoted mainly to methodological studies. Nevertheless, significant progress was witnessed in the domain of asymmetric catalytic reactions with both cyclic and acyclic dienolates involved.

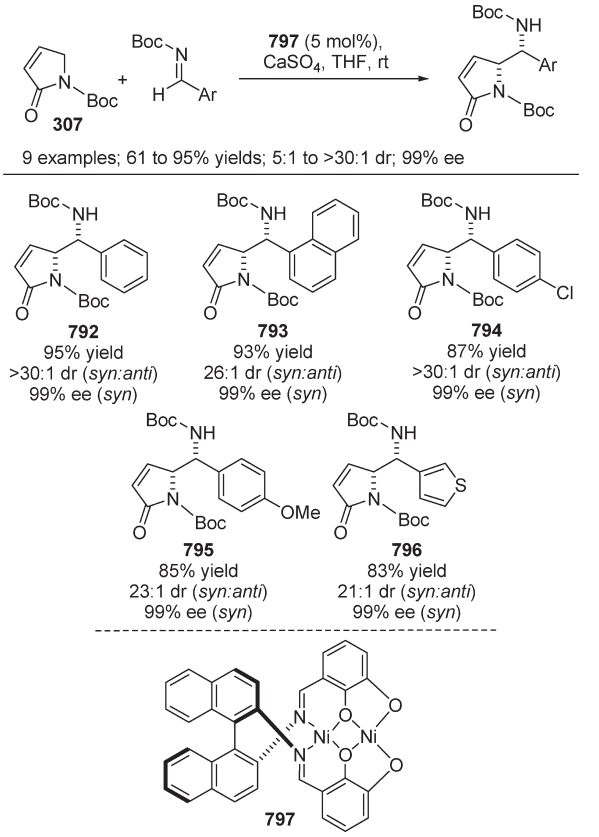
As with the aldol (chapter 3) and Mannich (chapter 4) sections, this chapter is also organized by methodology (diastereoselective vs enantioselective processes; indirect vs direct processes). However, because of the limited number of contributions to be analyzed, further subdivisions between acyclic and cyclic dienolates have been omitted.

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 141. Direct Catalytic and Asymmetric VMnR of γ-Butenolides[315]



Scheme 142. Direct Catalytic and Asymmetric VMnR with α,β-Unsaturated γ-Butyrolactam 307[316]



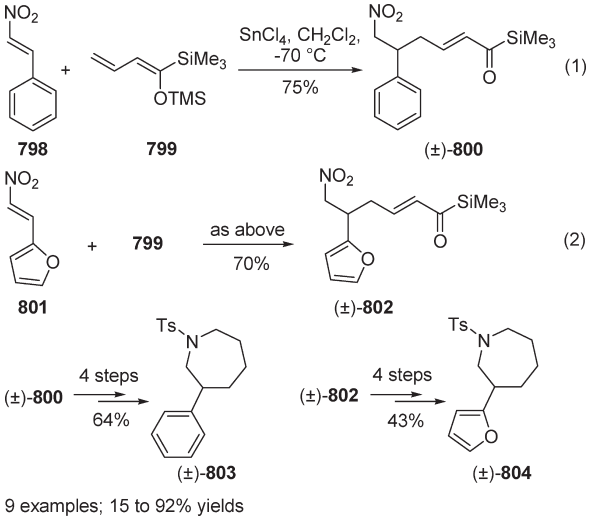
5.1. Diastereoselective and Unselective Processes

5.1.1. Indirect Mukaiyama Type Additions of Silicon Dienolates. In a short study aimed at the synthesis of a variety of three-substituted azepanes, Denmark and Xie[317] developed a racemic Mukaiyama type VMcR (VMMcR) addition of preformed 1-silyl-substituted dienol ethers of type **799** to nitroalkenes **798** or **801** activated by Lewis acids (Scheme 143). Thus, for example, reaction of acyl silane-derived **799** with **798** under $SnCl_4$ assistance afforded racemic α,β-unsaturated acyl silane (±)-**800**, which was then elaborated to azepane (±)-**803** via photoinduced protiodesilylation in a protic solvent followed by double bond saturation, Al−Hg reduction of the nitrogroup, and concomitant intramolecular reductive amination/tosylation. In the same way, (±)-**802** was elaborated into azepane (±)-**804**.

More recently, Scettri, Acocella et al.[318] utilized dioxinone-derived dienol silane **1** in a racemic VMMcR addition to α,β-unsaturated aldehydes under solvent-free conditions and Lewis base catalysis. The expected Michael adducts were obtained in low to moderate yields, accompanied by substantial amounts of the corresponding TMS-protected vinylogous aldols.

During an extensive, continuing program directed toward the synthesis of varied aromatic and heteroaromatic compounds utilizing acyclic Chan type dienes, Langer and colleagues[319−323] envisaged a VMMcR methodology as the initial carbon−carbon bond-forming maneuver. Scheme 144 illustrates three examples selected from a repertoire of several transformations where phenol **807**, xanthone (±)-**811**, and pyrrole **814** were synthesized through the intermediacy of often labile vinylogous Michael adducts [e.g., (±)-**806**, (±)-**810**, and **813**]. In general, isolated yields were only moderate, but the complex nature of the

Scheme 143. Lewis Acid-Promoted VMMcR of Open Chain Dienol Silyl Ethers to Nitroalkenes[317]



products renders this concise methodology appealing to aromatic and heteroaromatic synthesis practitioners.

During the period 2006−2010, several authors[324−328] developed closely related VMMcR of substituted and unsubstituted 2-silyloxy furan nucleophiles with a variety of Michael acceptors

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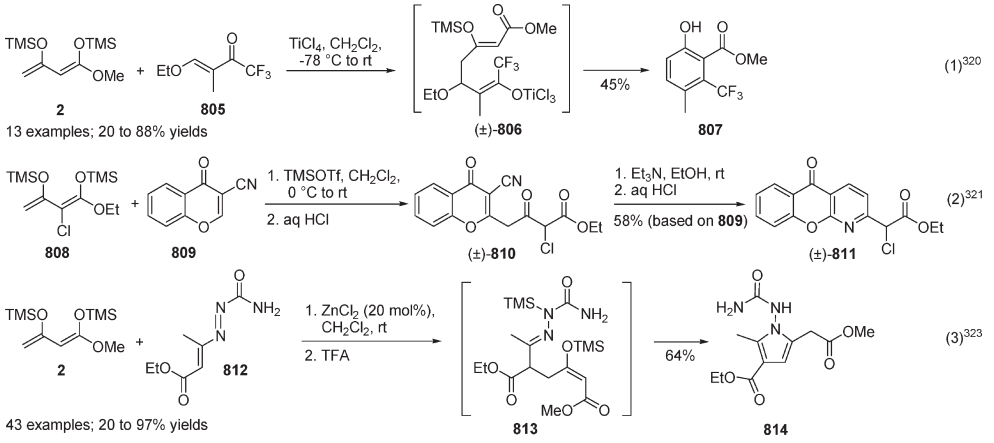
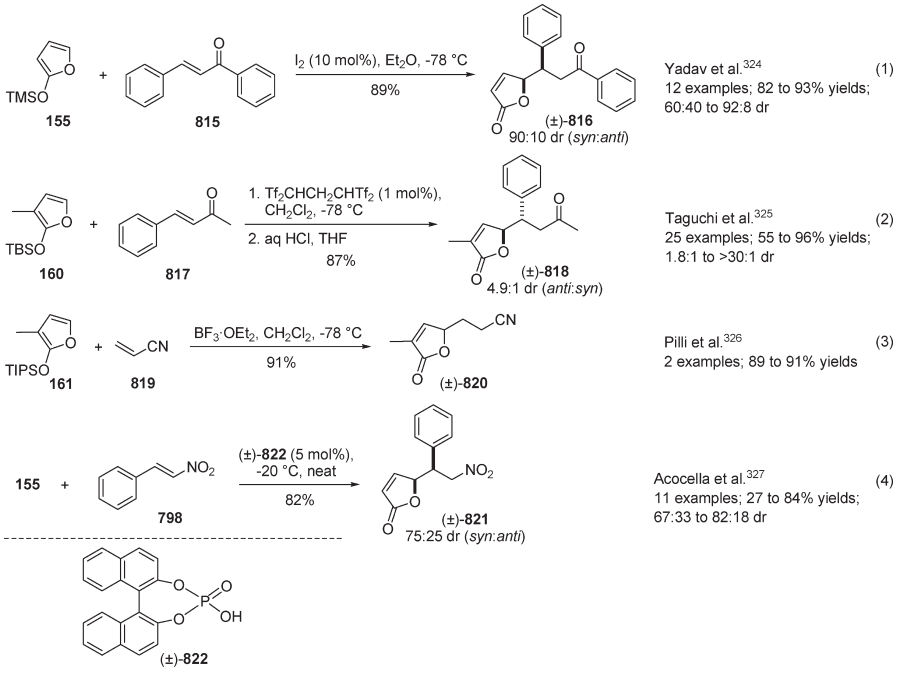
Scheme 144. VMMcR Methodology to Functionalized Aromatic and Heteroaromatic Compounds[319−323]



Scheme 145. Indirect VMMcR Additions of Silyloxy Furans to Diverse Michael Acceptors[324−328]



including α,β-unsaturated ketones, nitroalkenes, and unsaturated nitriles. A summary of these endeavors is given in Scheme 145, with the donor and acceptor components as well as the products displayed. Reactions were driven by either Lewis acid (e.g., eqs 1 and 3) or Brønsted acid catalysts (eqs 2 and 4), and when prochiral acceptors were involved, moderate to good simple diastereoselectivities were attained.

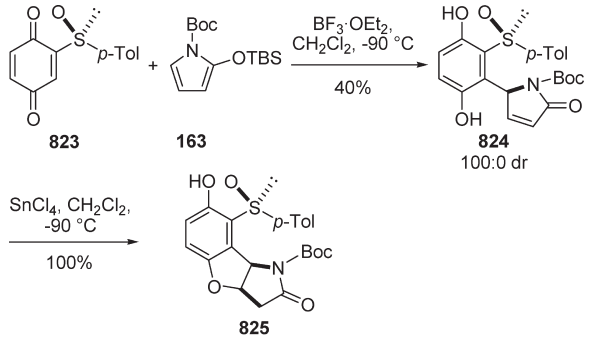
Optically pure sulfinylquinones of type **823** were exploited by García Ruano and Sanz-Tejedor et al.[329] in diastereoselective Michael additions with *N*-Boc-silyloxy pyrrole **163** (Scheme 146). There, $BF_3 \cdot OEt_2$-promoted VMMcR addition was completely stereoselective leading to the Michael type adduct **824** in modest yield. Interestingly, tin(IV) chloride treatment of **824** triggered clean intramolecular oxa-Michael closure to afford tricyclic structure **825**, which was isolated as a single diastereoisomer in quantitative yield.

By adopting very similar chemistry, Brimble et al.[330−332] succeeded in synthesizing pyrrolidinobenzofuran and pyrrolidinonaphthofuran adducts and their thia-analogues, useful intermediates for the synthesis of kalafungin-related quinone heterocycles. In these circumstances, silyloxy pyrrole **163** and silyloxy thiophene **164** were used in coupling reactions with the proper 2-acylquinone substrates (not shown). As for the reaction mechanism involved, however, the authors surmised that the reaction proceeded via a direct electrophilic substitution, rather than a VMMcR pathway, as in the case of the previously disclosed arylsulfinyl quinone analogues of type **823**.

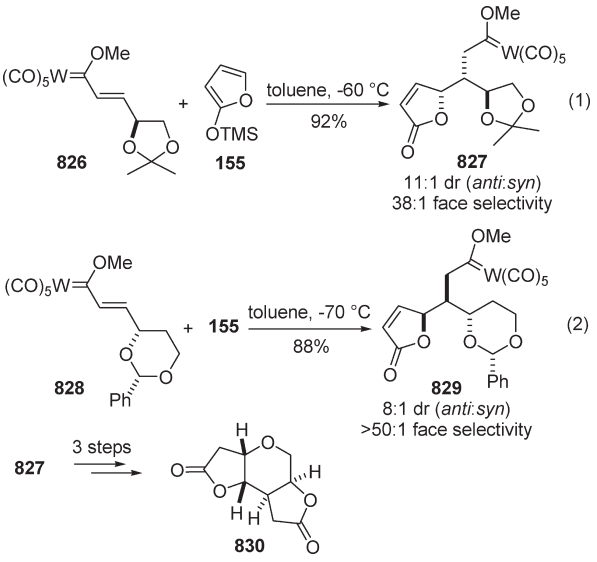
A rare example of uncatalyzed diastereoselective VMMcR between tungsten carbene complexes of type **826** or **828** and silyloxy furan **155** was reported in 2005 by Barluenga et al.[333] as the key move in a short synthesis of enantiopure polycyclic bislactone structures (Scheme 147). In the event, VMMcR

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

Scheme 146. Diastereoselective VMMcR of Silyloxy Pyrrole 163 and 2-(Arylsulfinyl)-1,4-benzoquinones[329]



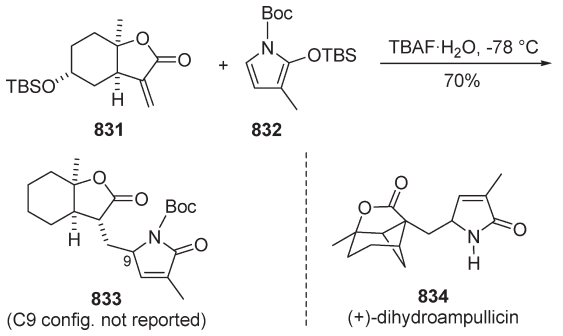
Scheme 147. Uncatalyzed VMMcR Using Tungsten Carbene Complexes 826 and 828[333]



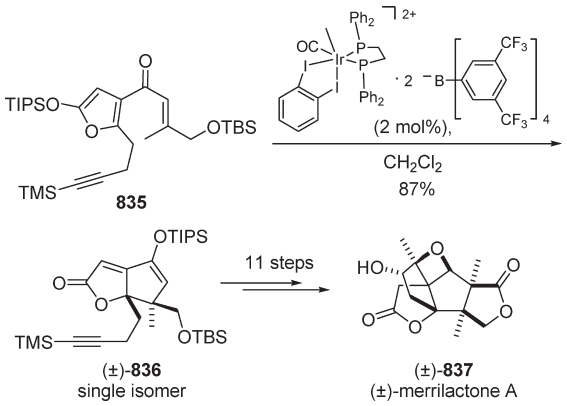
proceeded efficiently to afford the expected vinylogous Michael adducts **827** and **829** with excellent margins of simple and facial diastereoselectivities. Simple deprotection of the ketal functionality in **827** and subsequent intramolecular displacement of the methoxy group resulted in the formation of a bicyclic metal carbine, which was in turn advanced to bislactone **830** in high isolated yields.

(+)-Dihydroampullicin (**834**) is a fungal metabolite exhibiting remarkable root growth activity in lettuce seedings. In addressing the total synthesis of this lactam metabolite, Bermejo et al.[334] targeted the Michael adduct **833**, which was in turn obtained by a VMMcR addition between methyl-substituted *N*-Boc-silyloxy pyrrole **832** and methylene lactone **831** (Scheme 148). Indeed, the planned fluoride ions promoted VMMcR cleanly, producing the expected Michael adduct **833**, which was isolated in 70% yield as the sole reaction product. Although chirality at C9 was not assessed, **833** was devised as a valuable intermediate toward (+)-dihydroampullicin (**834**), thus demonstrating the viability of

Scheme 148. Towards the Total Synthesis of (+)-Dihydroampullicin (834)[334]



Scheme 149. Total Synthesis of (±)-Merrilactone A (±)-837[335,336]



the VMMcR addition to access structurally complex naturally occurring compounds.

A clever application of the asymmetric VMMcR has been implemented by A. J. Frontier and co-workers during a study aimed at the total synthesis of (±)-merrilactone A (**837**) (Scheme 149).[335,336] Merrilactone A is a neurotrophic agent isolated from the pericarps of *Illicium merrilianum* in 2000 by Fukuyama and co-workers.[337] The key reaction employed was an iridium(III)-catalyzed intramolecular Mukaiyama−Michael addition—a sort of Nazarov type cyclization—involving the highly substituted silyloxyfuryl ketone **835**, which led to bicyclic furanone **836** in a high yield and with excellent diastereoselectivity. Regardless as to whether the mechanism of this remarkable cyclization entails a true vinylogous Mukaiyama−Michael ring closure or whether it involves a 4π-Nazarov electrocyclization, this fine result highlights, once more, the value of heterocyclic siloxydiene structures in selective and synthetically relevant operations. Next, bicycle **836** was elaborated into targeted racemic merrilactone A (±)-**837** by a procedure encompassing 11 steps with a respectable 18% global yield for the entire sequence from (±)-**836**.

5.1.2. Direct Additions of in situ-Generated Dienolates. Racemic direct VMcR, be they diastereocontrolled or not, have been only marginally explored in this past decade, with few papers on this subject appearing over the period 2007−2010.

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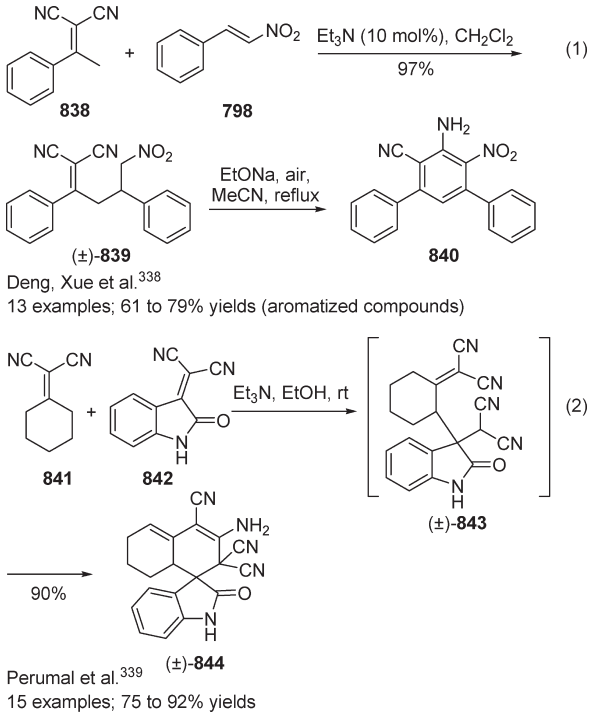
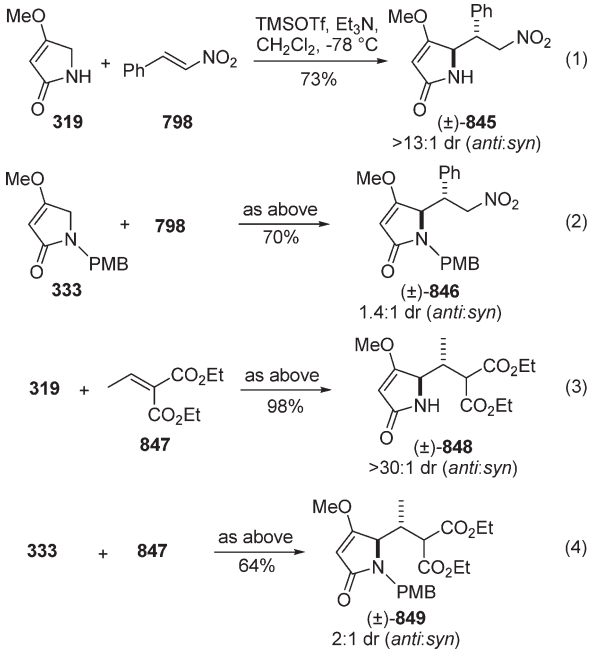
Scheme 150. Direct VMcR of Vinyl Malonitriles[338,339]

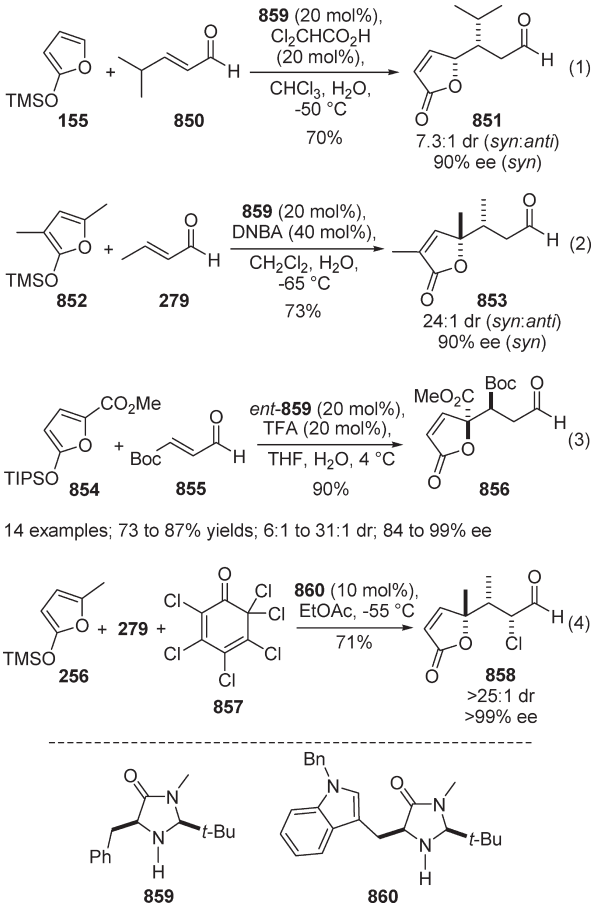


Scheme 151. TMSOTf/Et_3N-Promoted Direct VMcR Using Tetramate Donors 319 and 333[340]



A couple of contributions by Xue et al.[338] and Perumal et al.[339] were centered upon the use of certain vinyl malonitriles as d_4 Michael donors in reactions with activated double bonds such as nitro olefins (e.g., **798**) or dicyanolefins (e.g., **842**). Examples are shown in Scheme 150, highlighting the initial formation of the VMcR adducts **839** or **843**, which were then elaborated into the final products **840** or **844** often by a one-pot tandem transformation.

Scheme 152. Enantioselective Organocatalytic VMMcR of 2-Silyloxy Furans[343,344]



shown in Scheme 150, highlighting the initial formation of the VMcR adducts **839** or **843**, which were then elaborated into the final products **840** or **844** often by a one-pot tandem transformation.

Turning to five-membered heterocyclic vinylogous donor substrates of type **319** or **333**, Zanardi et al.[340] explored in 2008 a direct VMcR with a number of acyclic and cyclic Michael acceptors. The emphasis of the protocol was the in situ formation of an intermediary siloxydiene donor species undergoing a concomitant Michael addition to suitable conjugated acceptors, which included activated α,β-unsaturated esters, nitroalkenes, and conjugated alkynes and ketones. Scheme 151 shows selected examples, with reaction yields and product *anti*/*syn* diastereomeric ratios. In all cases, the reactions were promoted by the TMSOTf/Et_3N system, which governed both the formation of the active dienolate species and the activation of the acceptor component. In these instances, the reactions performed well producing the respective *anti*-configured Michael adducts (±)-**845**, (±)-**846**, (±)-**848**, and (±)-**849** in good yields and moderate to high diastereoselectivities. The diastereocontrol strictly depended upon the N-substitution of the tetramate donor, with the N-free **319** performing better than its protected counterpart **333**.

Similar Lewis acid/Lewis base promoted VMcR between furanone **786** and α,β-unsaturated carbonyl compounds were reported by Malanga et al.[341] to access certain racemic butenolide

dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

compounds. Regrettably, poor diastereocontrol was attained for these transformations, resulting in a 1:1 mixture of *syn*/*anti* diastereoisomers.

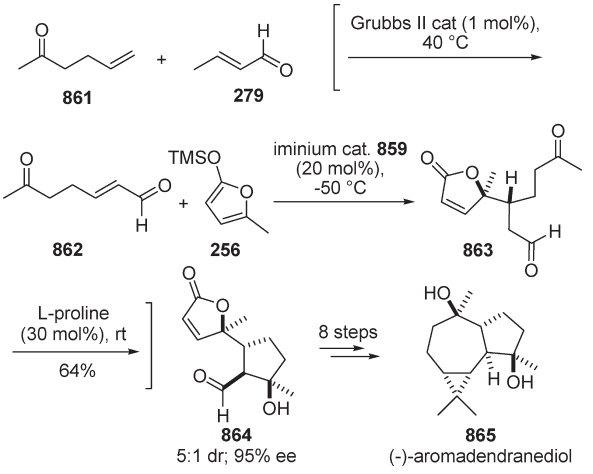
5.2. Enantioselective Processes

5.2.1. Indirect Mukaiyama Type Additions of Silicon Dienolates. The focus in this section is on the catalytic enantioselective Mukaiyama−Michael reactions (VMMcR) involving heterocyclic furan- and pyrrole-based silyloxy dienes. To our knowledge, no reports involving the use of acyclic vinylogous donors have appeared in the period covered by this review.

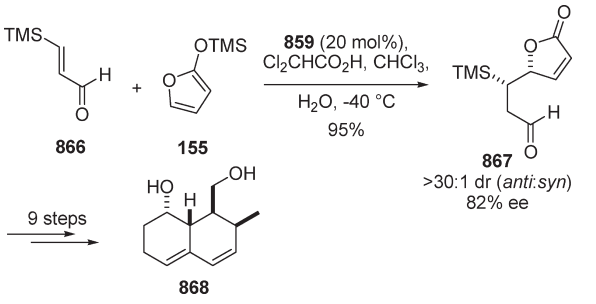
Pioneered by the seminal studies of Katsuki et al. in the late 1990s,[342] the enantioselective catalytic version of the vinylogous Mukaiyama−Michael reaction employing furan and related dienoxy silanes is now an established asymmetric methodology to access chiral nonracemic butenolide type scaffolds.

The organocatalytic enantioselective Mukaiyama−Michael reactions disclosed by MacMillan in 2003 and 2005 are emblematic examples of this.[343,344] In these cases, iminium organocatalysis exploited chiral imidazolidinones in the addition of unsubstituted and substituted silyloxyfuran nucleophiles to α,β-unsaturated aldehyde acceptors to create highly functionalized, enantiomerically enriched butenolide architectures. Scheme 152 lists selected examples emphasizing the efficiency and the adaptability of this asymmetric methodology. Whether simple siloxyfuran **155**, dimethyl siloxyfuran **852**, methoxycarbonyl silyloxy furan **854**, or γ-methyl-substituted siloxyfuran **256** were used, all coupling reactions proved productive, giving rise to the Michael adducts **851**, **853**, **856**, and **858**, respectively, with exquisite margins of regio-, diastereo-, and enantioselectivity. Remarkably, when this organocatalytic procedure was adopted,

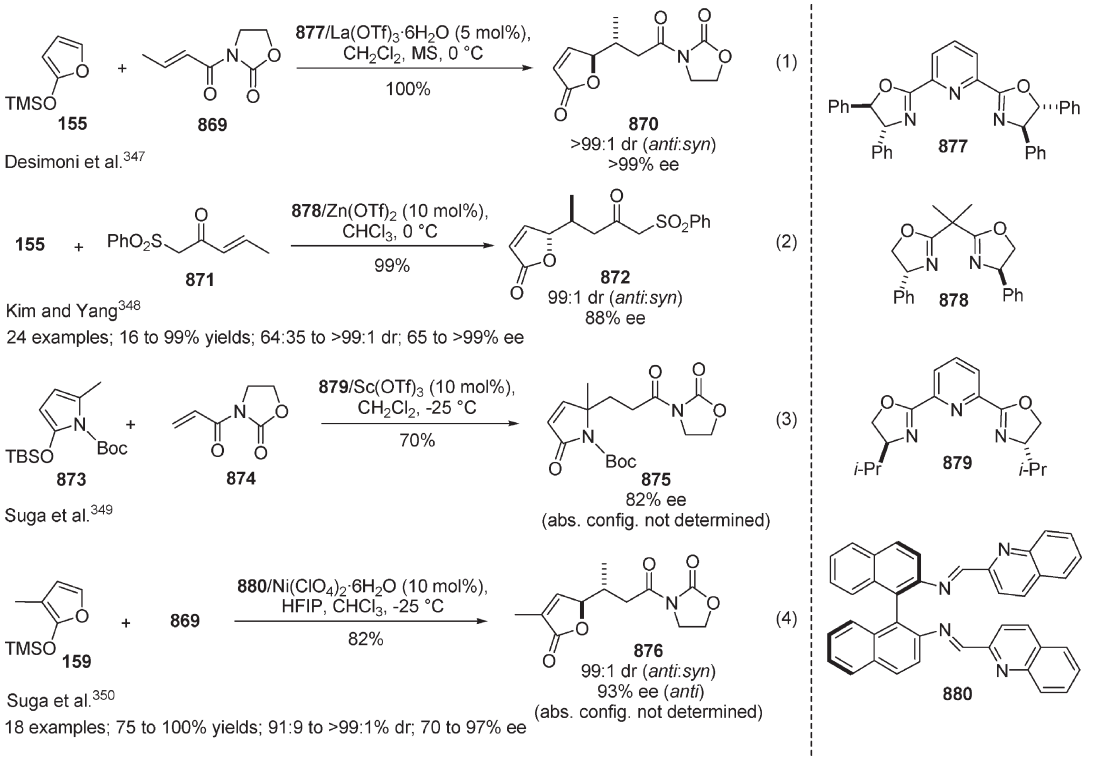
Scheme 153. Total Synthesis of (−)-Aromadendranediol (865) via a Triple Cascade Enantioselective Catalytic Path[345]



Scheme 154. Total Synthesis of (+)-Compactin Decalin Core 868[346]



Scheme 155. Chiral Metal-Based Catalyzed Asymmetric VMMcR of Silyloxy Furan and Pyrrole Donors with Various α,β-Unsaturated Carbonyl Compounds[347−350]



dx.doi.org/10.1021/cr100304n |*Chem. Rev.* 2011, 111, 3076–3154

only conjugate additions were observed at both the furan (γ-attack only) and the aldehyde (no α-attack) components.

As with the reaction in eq 4, intercepting the enamine intermediate initially formed with the electrophilic chlorine source **857** remarkably resulted in the formation of α-chloroaldehyde **858** having an all-*syn* configuration in high yield and almost complete diastereo- and enantioselectivities.

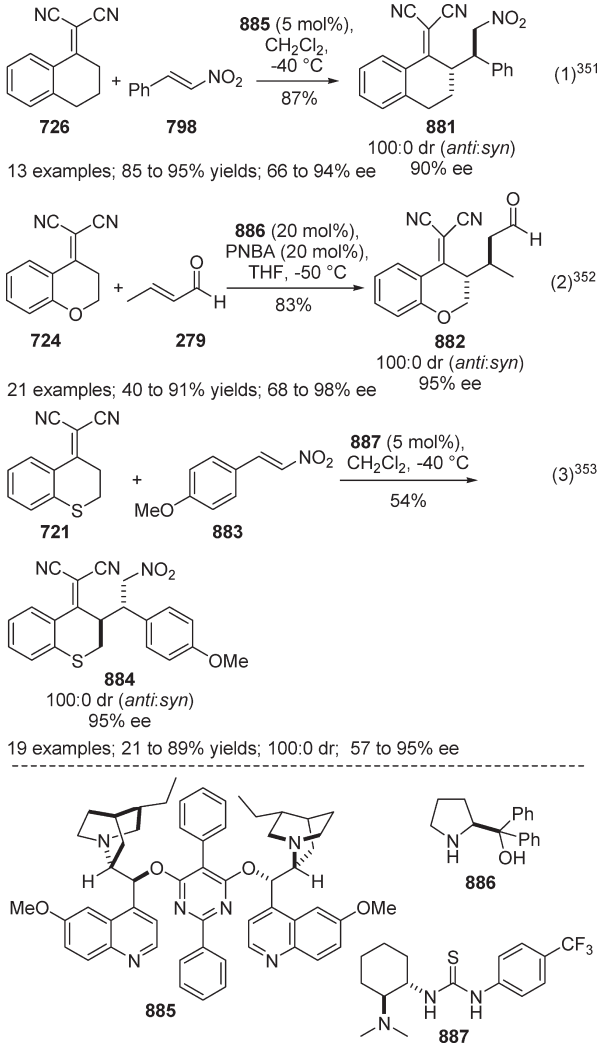
An exciting example of a triple cascade catalysis was reported by the same author in 2009,[345] to generate (inter alia) the carbocyclic core **864** of (−)-aromadendranediol (**865**), a widely distributed sesquiterpene of marine and terrestrial origin (Scheme 153). In brief, a first organometallic cross-metathesis cycle involving unsaturated ketone **861** and crotonaldehyde (**279**) produced ketoaldehyde **862**, which was involved in a second organocatalytic imiunium cycle with γ-methyl-substituted dienoxyfuran **256**, producing butenolide **863** via an intermolecular vinylogous Mukaiyama−Michael addition protocol. Once generated, **863** was exposed, in a third catalytic cycle, to L-proline, finally resulting in production of bicycle **864** via an enamine-based cycloaldolization. Remarkably, **864** was accessed directly from simple and inexpensive carbonyl precursors in 64% overall yield, with 5:1 diastereomeric ratio and 95% enantiomeric excess. Only eight steps separated **864** to the targeted terpene **865**, which proved identical in all respects to the natural isolate.

The powerful organocatalytic enantioselective Mukaiyama−Michael addition methodology launched by the MacMillan group was duly exploited by Robichaud and Tremblay during a formal synthesis of (+)-compactin, a leading HMG-CoA reductase inhibitor with a key role in cholesterol biosynthesis.[346] As shown in Scheme 154, the opening reaction was the vinylogous addition of siloxyfuran **155** to trimethylsilyl-substituted acrolein **866**, to prepare the chiral substrate **867** in a 95% yield and with interesting enantio- and diastereoselectivity (>30:1 *anti*/*syn*, 82% ee). Subsequent conversion of the aldehyde functionality in **867** into the corresponding dibromide (Corey−Fuchs) followed by radical annulation provided a bicycle, which was next progressed to diol **868**, the decalin core of (+)-compactin.

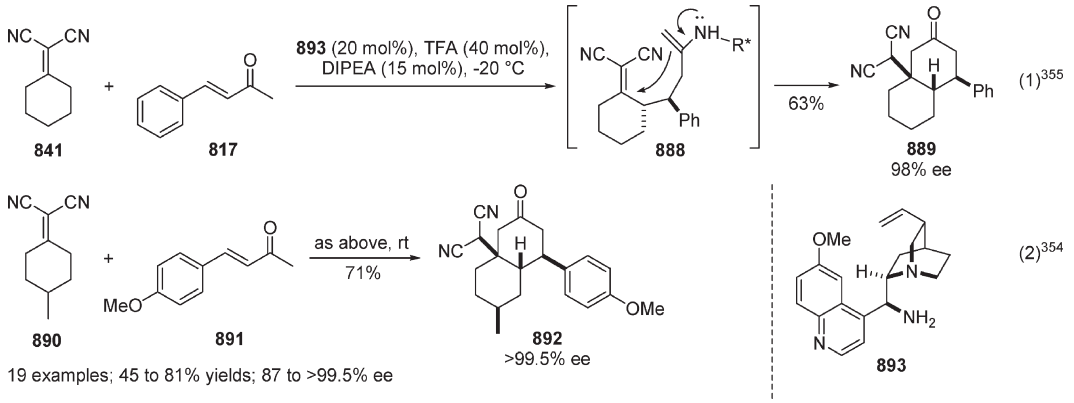
Asymmetric, enantioselective VMMcR of various silyloxy furan and pyrrole donors were also exploited by several authors to access a repertoire of butenolide-related structural frameworks in highly enantioenriched formats using metal-based catalysis. For example, Desimoni et al.[347] succeeded in synthesizing butenolides of type **870** utilizing (*R*,*R*)-diPh-PyBox **877** as a ligand in complex with hydrated lanthanum triflate (Scheme 155, eq 1).

Kim and Yang,[348] on the other hand, explored the VMMcR between furan **155** and α,β-unsaturated ketones of type **871** by adopting (*R*)-Ph-Box **878**·Zn(OTf)$_2$ as a catalyst (eq 2) to enter butenolide Michael adducts of type **872**. In both studies, good

Scheme 156. Direct Asymmetric VMcR of Dicyanolefins to Various Michael Acceptors[351−353]



Scheme 157. Asymmetric Domino VMcR-McR Additions of Dicyanoalkenes Catalyzed by Chiral Primary Amine Organocatalysts[354,355]



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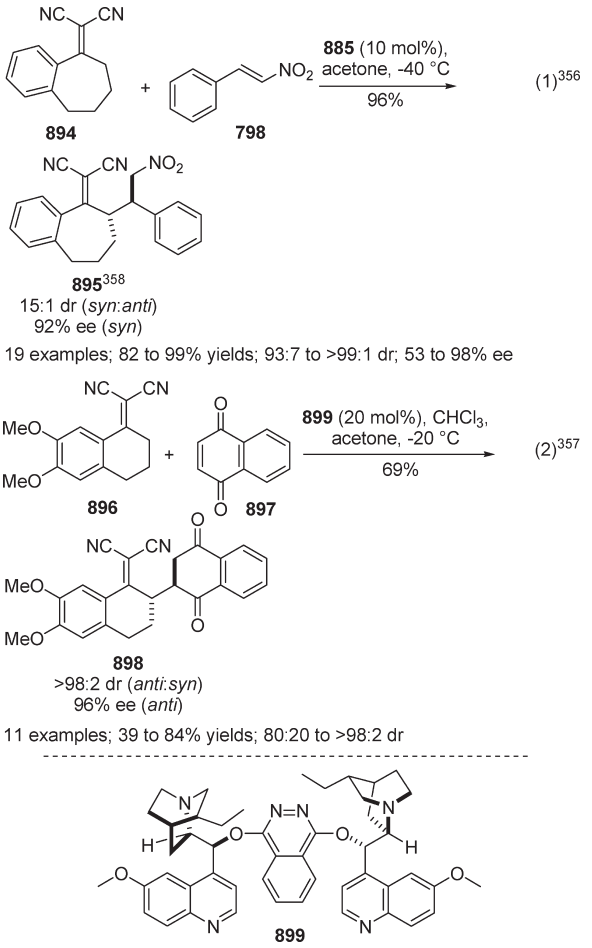
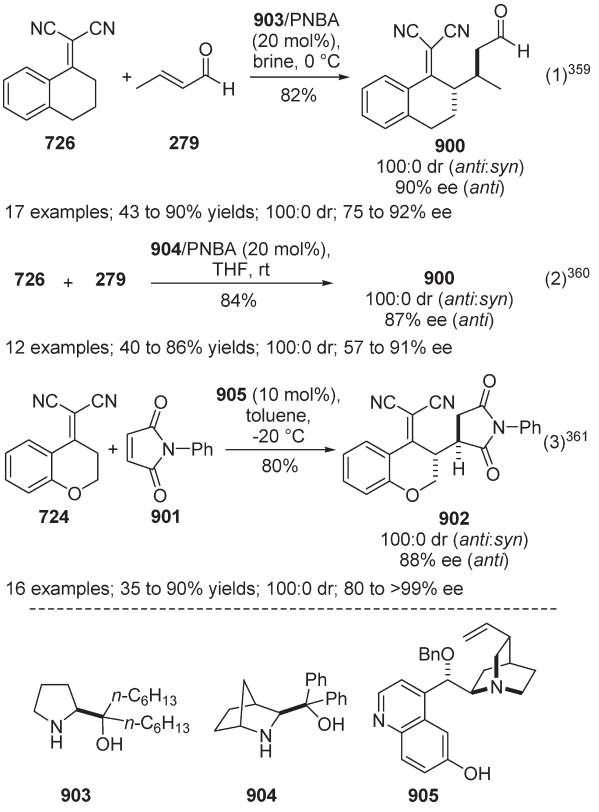
Scheme 158. Direct Asymmetric VMcR of Dicyanolefins with Nitro Olefins or Quinones[356,357]



Scheme 159. Direct Asymmetric VMcR of Dicyanolefins with α,β-Unsaturated Aldehydes and *N*-Substituted Maleimides[359−361]



facial and simple stereocontrols were attained allowing the products to be recovered in high enantiopurities. Turning to pyrrole **873**, Suga et al.[349] adopted similar chemistry to arrive at γ,γ-disubstituted lactams of type **875** (eq 3). In this instance, (*S*, *S*)-*i*-Pr-PyBox **879** was elected as the best ligand in conjunction with rare-earth Lewis acids; however, only moderate enantioselectivity was invariably obtained. A better result was reached by the same author[350] in reactions with silyloxy furan derivatives of type **159** (eq 4). There, axially chiral binaphthyl-diimine ligands, for example, (*R*)-BINIM-2QN **880**, proved to be extremely efficient when complexed with Ni(II) salts. Regrettably, despite the efficiency of such catalytic asymmetric VMMcR methodologies in readily furnishing a repertoire of functionalyzed molecular frames, the utility in total synthesis of this library of chiral building blocks has not yet been fully appreciated.

5.2.2. Direct Additions of in situ-Generated Dienolates.

Organic chemists have currently to pursue the ambitious goal of simultaneously establishing substoichiometric amounts of structurally discrete chemical systems, which embody chirality to promote and govern a given transformation, while also creating substantial quantities of chiral nonracemic substances.

On this note, planning and executing direct, asymmetric VMcR utilizing d_4 pro-nucleophiles—such as dicyanolefins, α,β-unsaturated carbonyl compounds, or furanone, pyrrolinone, and azalactone heterocycles—is a challenging task, requiring development of complex catalytic systems that simultaneously elicit formation of appropriate vinylogous donors, activate acceptors, oversee chemo- and diastereocontrol and, in mimicking nature, perfectly propagate chirality into the products.

This section will focus on recent advances in the area of direct asymmetric VMcR using chiral metal catalysts and, especially, small-molecule organocatalysts. Contributions are grouped together in view of the nature of the Michael d_4 component employed.

In a prolific program focused on the exploitation of symmetric and unsymmetric dicyanolefin substrates in direct VMcR with a series of Michael acceptors, Chen et al.[351−355] utilized a variety of organocatalysts spanning from *Cinchona* alkaloids, proline-derived secondary amines, or thiourea tertiary amines. We have selected only a few of many examples aimed at analyzing the full extent of these organocatalyzed asymmetric VMcR (Scheme 156).[351−353] Indeed, reactions tolerated a wide variety of donor and acceptor substrates (e.g., **726**, **724**, and **721** vs **798**, **279**, and **883** compounds) giving rise to *anti*-configured adducts **881**, **882**, and **884** in good yields, complete diastereoselectivity, and up to 98% ees. The organocatalysts employed included simple prolinol-derivative **886**, thiourea tertiary amine **887**, and C_2-symmetric dihydroquinidine-derived **885**. Remarkably, relative and absolute configurations of all synthesized adducts were firmly ascertained by single-crystal X-ray analysis of suitable candidates.

The same authors[354,355] extended these asymmetric methodologies to direct domino vinylogous Michael/Michael additions for the assembly of highly functionalized enantioenriched decaline

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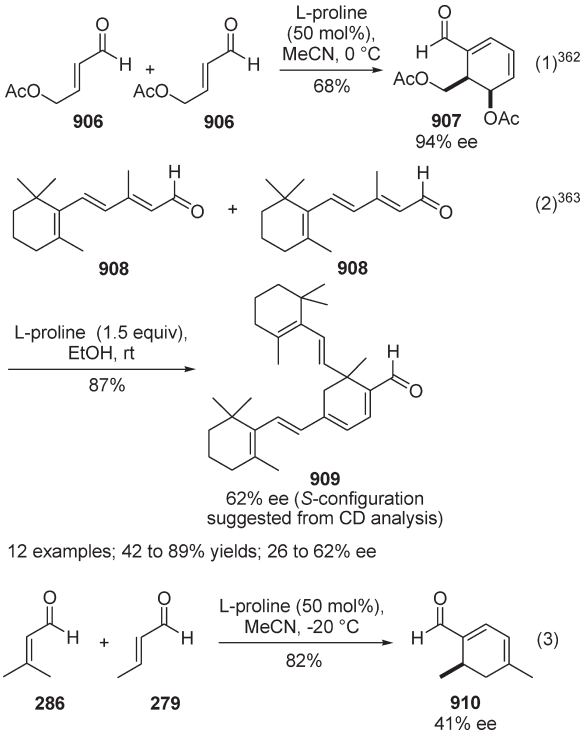
Scheme 160. L-Proline-Catalyzed Homo- and Cross-Dimerizations of Enals[362,363]



systems. *Cinchona*-based primary aminocatalysts (e.g., **893**) were employed, resulting in efficient, diastereo- and enantioselective reactions (Scheme 157). In the event, the initial VMcR addition resulted in the formation of an intermediary enamine adduct **888** (eq 1) that underwent smooth intramolecular enamine−Michael ring closure leading to decaline **889** with complete diastereo- and enantiocontrol.[355] Remarkably, application of this domino addition/ring closure to symmetric prochiral dicyanoalkylidene **890** resulted in desymmetrization of the substrate and formation of a single decaline **892** bearing four stereogenic centers including a quaternary all-carbon stereocenter (eq 2).

Almost the same chemistry was independently adopted by Jørgensen et al.[356,357] in asymmetric direct VMcR of activated dicyanoalkenes with nitro olefins or quinones (Scheme 158). With nitro olefins, all of the reactions scrutinized invariably produced the expected Michael adducts, when $(DHQD)_2PYR$ **885** was used as the organocatalyst. Both the diastereo- and the enantiocontrol proved highly effective with de and ee reaching >99% values.[358] With quinone systems, on the other hand, $(DHQD)_2PHAL$ **899** was selected as the best catalyst, and moderate to good yields, high diastereomeric ratios, and good enantiomeric excess were obtained. The reactions also proceeded well on a large scale, thus providing an opportunity for different derivatization procedures.

The same set of alkylidene dicyanides was exploited in 2008 by Loh et al.[359−361] in direct asymmetric organocatalyzed VMcR with α,β-unsaturated aldehydes and maleimides (Scheme 159). Water-tolerant (*S*)-prolinol derivative **903**, for example, was the catalyst of choice in the asymmetric VMcR between **726** and aldehyde **279** giving rise to *anti*-configured adduct **900** as a single diastereoisomer (eq 1).[359] In this case, brine was used as a reaction medium using only 20 mol % catalyst in conjunction with *p*-nitrobenzoic acid (PNBA). Prolinol/aza-norbornyl compound **904** was also successfully employed (THF as the solvent) to control these asymmetric transformations, with optimum dr and useful ee invariably obtained (eq 2).[360] N-Substituted maleimides of type **901** also proved to be competent Michael acceptors in VMcR additions catalyzed by *Cinchona* organocatalysts of type **905** (eq 3).[361] In this last instance (toluene as the solvent), several conjugated addition examples were scrutinized, which produced diverse Michael adducts in variable yields, excellent diastereoselectivities, and good ee values.

By introducing a new concept in enantioselective amine-based organocatalysis—simultaneous activation of both the donor and the acceptor substrates by a simple organocatalyst—Hong et al.[362] and Watanabe et al.[363] independently investigated the use of L-proline to assist the homodimerization and crossed addition of certain α,β-unsaturated aldehydes, en route to chiral nonracemic and highly functionalized six-membered carbocycles. As an example, reaction of 4-oxobut-2-enyl acetate (**906**) with 50 mol % L-proline in CH_3CN at 0 °C afforded the diene adduct **907** (Scheme 160, eq 1)[362] in 68% yield and with remarkable enantioselectivity (94% ee). Using 1.5 equiv of L-proline in EtOH, polyenal **908** was also a good substrate, giving rise to homodimer **909** in 87% yield and 62% ee (eq 2). Similarly, cross-addition between 3-methyl-2-butenal (**286**) and crotonaldehyde (**279**) afforded aldehyde **910** in 82% isolated yield and 41% ee. In the latter case, the chemoselectivity of the reaction is truly remarkable, with **286** serving as the donor (dienamine catalysis) and **279** as the iminium ion Michael acceptor (iminium catalysis). Equally remarkable is the absence of homocoupling-derived products, which emphasizes the subtle dependence of the reaction course upon substrate substitution.

As for the mechanism involved (Figure 10), both authors proposed a common generalized scheme featuring (i) dienamine to conjugate iminium ion VMcR (A + B → C), (ii) intramolecular enamine/Mannich addition (C → D), and (iii) hydrolysis/β-elimination to release the target E with complete recovery of the proline catalyst. An alternative Diels−Alder pathway was ruled out based on the moderate ee values that these proline-promoted reactions afforded.

Turning to heterocyclic furan and pyrrole-based d_4 nucleophiles, direct asymmetric VMcR to chalcones and α,β-unsaturated aldehydes were very recently investigated by Wang et al.,[364] Ge, Li et al.,[365] and Chen et al.[366] using thiourea tertiary amine catalyst **916**, cyclohexyl diamine **917**, or prolinol **918**, respectively (Scheme 161). In all instances, asymmetric VMcR performed well, invariably producing *syn*-adducts predominantly (**912**, **914**, or **915**) in moderate to good yields and interesting levels of diastereo- and enantioselectivities. In all contributions, the relative and absolute configurations of the products were accurately assessed, and the synthetic potential of some butenolide representatives was demonstrated by important transformations leading to fused bi-, tri-, and polycyclic structures of biological interest.[366]

A very appealing chiral, organic ion pair catalyst assembled through a network of multiple hydrogen bonding, for example, the supramolecular structure **925** (Scheme 162), was introduced in 2009 by Ooi et al.[367] as the optimum catalyst for the direct asymmetric VMcR between azlactone **919** and α,β-unsaturated acyl benzotriazoles **920**. In solution (toluene, −40 °C), minute amounts of complex **925** promoted highly

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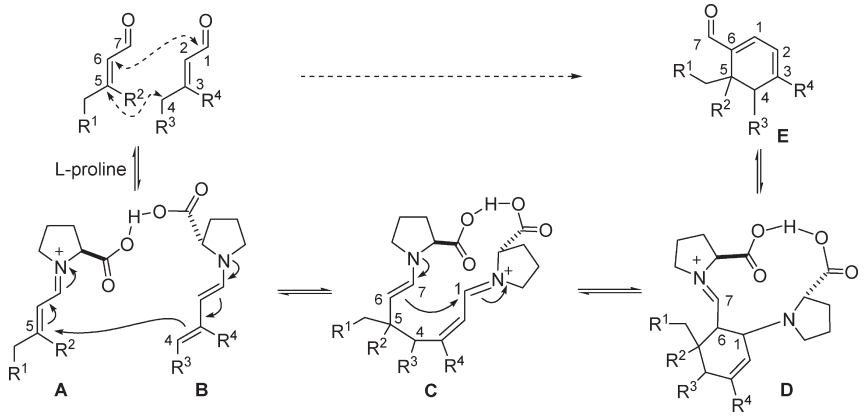
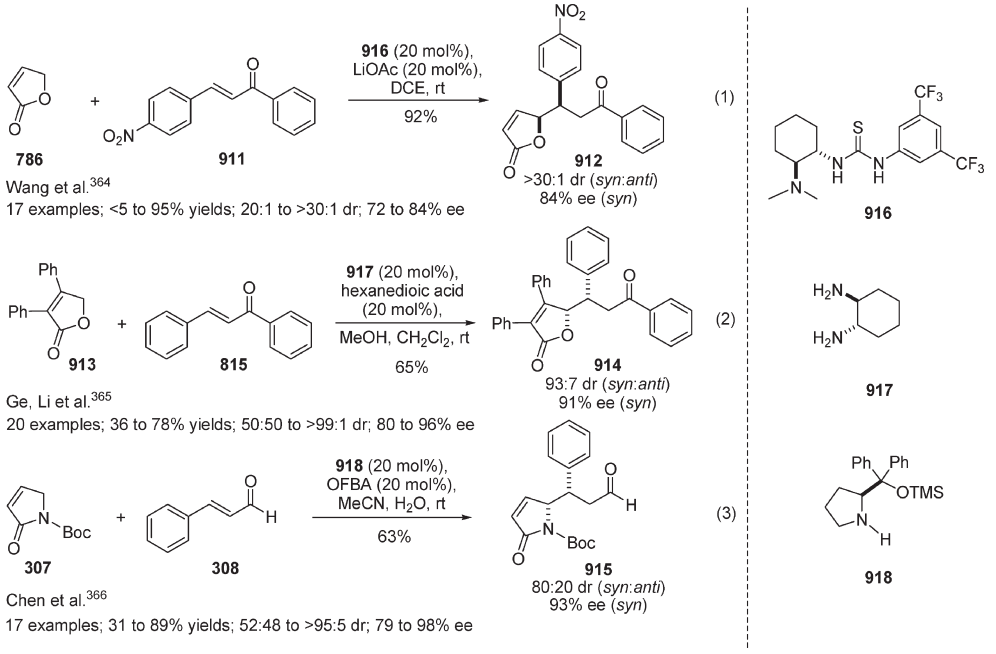


Figure 10. Proposed mechanism of the cascade dimerization of crotonaldehyde substrates.[362]

Scheme 161. Direct Diastereo- and Enantioselective Organocatalytic VMcR of Furanone and Pyrrolinone Donors[364−366]



stereoselective VMcR additions of 2-unsubstituted oxazol-5-(4*H*)one **919**, a pro-*Cγ* nucleophile, to α,*β*-unsaturated benzotriazole ester surrogates **920**, with a broad substrate range. In the event, all products (e.g., compounds **921**−**924**) formed in excellent yields and superb levels of diastereo- and enantioselectivities. While absolute configuration at C3′ was ascertained by chemical correlation to a known succinic acid derivative, the absolute configuration at C2 was not, but this was considered uninfluential due to the role the heterocyclic oxazolone nucleus exert (a CO_2H equivalent).

The dinuclear zinc complex **927**, prepared simply by Trost et al.[368] by mixing commercially available (*S*,*S*)-bis-prolylphenol with 2 equiv of Et_2Zn, which had already proved successful in a variety of direct asymmetric addition reactions and desymmetrization processes,[369] now proved to be an admiral catalyst candidate for the direct asymmetric VMcR of furanone **786** to nitro olefins (Scheme 163, eq 1). Indeed, only vinylogous addition products were obtained (e.g., **821**) in good yields, with excellent diastereoselectivity in favor of *syn*-configured compounds. VMcR tolerated a wide variety of nitroalkenes ranging from nitrostyrene **798** to variously substituted aryl and heteroaryl analogues or aliphatic derivatives, always resulting in excellent performances. Interestingly, simple manipulation, including elaboration of the heterocyclic ring and reduction of the nitro group, demonstrated the utility of the Michael adducts obtained, to serve as versatile chiral building blocks in total synthesis.

A further dinuclear metal catalyst, the homobimetallic Ni_2−Schiff base complex (*S*)-configured **797** previously adopted by Shepherd et al.[316] in direct asymmetric VMnR with imine compounds (vide supra, chapter 4.2.2), was similarly utilized by the same research group[316] to assist direct VMcR to nitro olefins (e.g., **798**) by means of pyrrolinone **307** (Scheme 163, eq 2). Several Michael acceptor candidates were also tested in this study, and these invariably resulted in the formation of the respective *syn*-lactam products with excellent yields, diastereoselectivity, and ees.

The intrinsic appeal and utility of these nonmetal and metal-based direct, asymmetric VMcR, along with the synthetic

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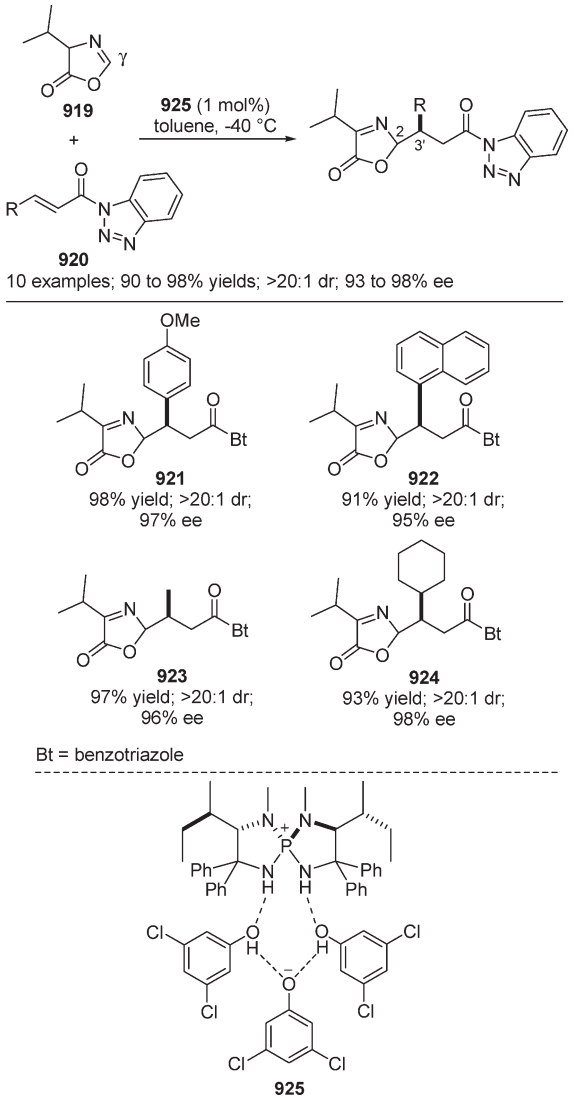
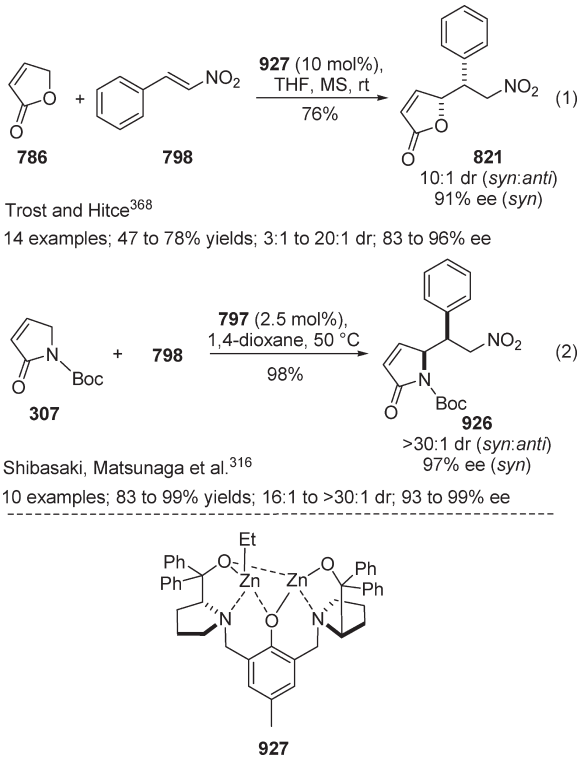
Scheme 162. Direct Asymmetric VMcR of Azlactone 919 to α,β-Unsaturated Acyl Benzotriazoles 920[367]



Scheme 163. Direct, Chiral Metal-Catalyzed VMcR of Furanone and Pyrrolinone Donors with Nitroalkenes[316,368]



potential the formed Michael adducts offer, makes it obvious that these methods will be increasingly exploited in the years to come, and we expect that novel methodology- and target-oriented studies will lead to further advances in this exciting domain.

6. CONCLUDING REMARKS

This review chronicles the flourishing research into the vinylogous aldol and related Mannich and Michael reactions over the 10 year period 2000−2010 (first quarter). The article is directly grafted onto the roots of our first contribution on this subject matter that appeared in this journal in 2000.[7] This initial compendium covered the very first pioneering works of the 1980s through the end of the 1990s. Together, these two reviews present the reader with a truly unique panorama that bridges across the origins of this fascinating area of organic chemistry to its present day status.

As we had foreseen then in our first compendium, the studies since carried out in the methodology and in the synthetic application of the VARs, together with the Mannich and Michael expressions, have indeed opened a new era of reappraisal, where these carbon−carbon bond-forming methodologies have been assigned a pre-eminent place in the repertoire of contemporary organic chemistry.

Close scrutiny of the corpus of this review first reveals a dicotomy between strictly methodological works where emphasis is laid on defining the optimal experimental conditions and target-oriented syntheses where the vinylogous maneuver is central to the construction of a given compound.

In the vinylogous aldol domain, with a reliable and predictable methodology well established, the utility of this important carbon−carbon bond-forming process is demonstrated by outstanding synthetic applications, for example, in the total synthesis of several polyketide natural metabolites.

In the vinylogous Mannich and Michael realms, methodology is experiencing a nascent phase of development with points of evolution in the enantioselective catalytic approaches. As a consequence, only few, yet brilliant synthetic advances have been performed, for example, in the synthesis of alkaloidal molecules. Indeed, if methodology offered general and predictable models, a variety of complex targets and fragments could be accessed via relatively short synthetic routes.

In going with the flow of the current tendency that has permeated the whole of contemporary organic chemistry, the applications of substrate-controlled, auxiliary-controlled, and catalyst-controlled processes leading to stereochemically defined products are constantly increasing, and the appeal of racemic or unstereoselective reactions is consequently and rapidly waning.

While the basic chemistry of the vinylogous aldol and the related Mannich and Michael satellites can be considered an

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established discipline, some areas still require attention if this methodology is to be translated more extensively into synthesis. First, studies of direct, catalytic, asymmetric additions should be attentively investigated because of their intrinsic appeal for rapid, atom-conservative access to chiral building block molecules. Second, mechanistic cycles and transition state geometry invoked to govern the course of metal- and nonmetal-based asymmetric catalyzed reactions warrant closer examination, as their rationale was not often backed up either by precise experimental data nor by rigorous molecular mechanic calculations, except in a few exceptional cases. Third, another serious omission in certain studies involving diastereocontrolled and enantiocontrolled processes is the lack of precise stereochemical assignment (relative and/or absolute) of the vinylogous addition products. This is a crucial issue if a mechanistic insight is to be formulated and for the products themselves to be exploited in synthesis. In prospect, we can anticipate that chiral catalysis will certainly begin to outnumber chiron- and auxiliary-driven approaches, albeit in the construction of small synthons or in the initial phases of a multistep total synthesis of complex organic molecules. Future investigations will continue to demonstrate the ability and utility of these important carbon−carbon bond-forming processes, not only in the VAR area but also in the less exploited VMnR and VMcR domains.

In closing this review, we wish to underline our intent. Our intentions are to convey the synthetic potential of these vinylogous methodologies to the reader and to acknowledge the inspiring contributions of the many colleagues worldwide, the young and not so young, researchers and students, who have furthered VAR, VMnR, and VMcR to the forefront of synthetic organic chemistry.

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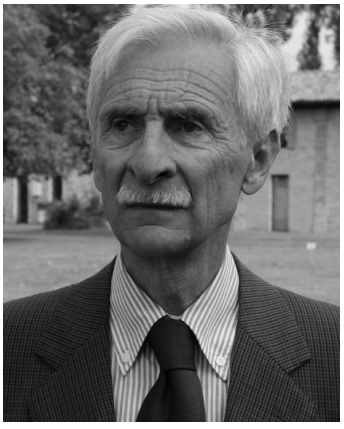
BIOGRAPHIES



Giovanni Casiraghi is currently a Professor of Organic Chemistry at the University of Parma (Italy), Pharmaceutical Department. He received his Laurea degree in Chemistry from the University of Pavia in 1964, after which he carried out postdoctoral research with Professor Silvio Pietra working on the development of vicarious nucleophilic substitutions on phenazine compounds. In 1968, he joined the Department of Organic Chemistry of the University of Parma as an Assistant Professor, where he launched a full research programme focused on regioselective ortho-functionalization of metal phenolate systems. In 1982, he was promoted to Associate Professor, and in 1985, he was promoted to Full Professor of Organic Chemistry. In 1986, he moved to take up the chair of Organic Chemistry at the University of Sassari, and in 1992, he accepted an appointment at the Faculty of Pharmacy of University of Parma, chair in Organic Chemistry. His research interests focus on target- and methodology-oriented synthesis of natural and natural-like molecules, mainly exploiting vinylogous aldol type reactions involving heterocyclic dienoxysilane reagents. A further field of research is concerned with molecular design and recognition and the biological actions of organic molecules and their assemblies.

Lucia Battistini is currently an Assistant Professor of Organic Chemistry at the University of Parma (Italy), Pharmaceutical Department. She was born in 1969 in Parma, Italy, and obtained her Laurea degree in Pharmaceutical Chemistry and Technology from the University of Parma in 1995. In 1999, she received her Ph.D. degree in Bioorganic Chemistry from the University of Torino working on the exploitation of heterocyclic silyloxy dienes in the synthesis of biologically active compounds and their mimics. In 1999, she became a Researcher at the Department of Pharmacy, University of Parma, where she currently holds a position as Assistant Professor of Organic Chemistry. Her current specific interests are focused on the design and synthesis of pseudopeptide ligands for molecular recognition and biomedical applications.

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earned his Laurea degree in Pharmaceutical Chemistry and Technology in 2002 at the Università di Parma, Italy. In 2005, he graduated from the postgraduate School of Chemical Synthesis at the University of Milan, Italy, working on the development of new stereoselective strategies towards the synthesis of polyfunctionalized carbocyclic aminoacids. In 2001, he joined the BioOrganicSynthesiS group (BOSS Group) directed by Prof. Giovanni Casiraghi at the Pharmaceutical Department of the University of Parma, where he obtained a position as a Researcher. His main research interests are in the field of asymmetric synthesis of multifunctional natural and natural-like compounds, including carbasugars, conformationally constrained amino acids, and densely functionalized heterocycles. His current research interests are focused on catalytic, asymmetric vinylogous processes and their development and exploitation under environmentally friendly conditions.

Gloria Rassu is a Research Executive at the Consiglio Nazionale delle Ricerche, Italy (CNR), Istituto di Chimica Biomolecolare. She was born and raised in Sassari, Italy, and earned her Laurea degree in Chemistry at the University of Sassari in 1979. After 5 years of postdoctoral work, she joined the research group of Professor G. Casiraghi, working on the development of a novel vinylogous aldol methodology and its exploitation in the total synthesis of densely functionalized chiral compounds. In 1991, she began her independent research, focusing on the design and application of new stereoselective methods, with predilection toward the synthesis of biologically active natural molecules and their unnatural variants. In 2001, she was promoted to a First Researcher position, and in 2002, she took up the present position at the CNR, Sassari.

Franca Zanardi is currently an Associate Professor of Organic Chemistry at the University of Parma (Italy), Pharmaceutical Department. She received her Laurea degree in Chemistry (1993) and her Ph.D. in Bioorganic Chemistry (1997) from the same university under the direction of Prof. G. Casiraghi. She became an Assistant Professor in 1998 and Associate Professor in 2002. Her research interests concern the exploitation of heteroatom-containing pentacyclic bidentate nucleophiles in the stereoselective synthesis of biologically relevant small organic molecules. A further field of research concerns the synthesis of novel integrin antagonists to be exploited as therapeutic/diagnostic tools in cancer-related diseases.

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ADDITIONAL NOTE

[†]This paper celebrates the 75th anniversary of the seminal review article "The Principle of Vinylogy" by Reynold C. Fuson (*Chem. Rev.* **1935**, *16*, 1).

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