Some New Nazarov Chemistry

Marcus A. Tius*[a]

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The Nazarov cyclization is a 4π-electron conrotatory cyclization of a pentadienyl cation that leads to a five-membered ring, typically a cyclopentenone. Because the mechanism is well defined, it is often possible to make accurate and useful stereochemical predictions regarding the course of the reaction. Because the reaction intermediates are carbocations, it is also possible to devise tandem processes whereby the initial cyclization is followed by one or more C–C bond forming processes. In recent years, a number of advances have been made in the asymmetric version of the Nazarov cyclization, adding to its usefulness in total synthesis. It is the goal of this review to introduce the reader to some of the newer methodological advances roughly spanning the past ten years, and to do so within a mechanistic framework.
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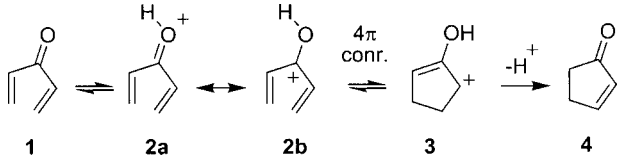
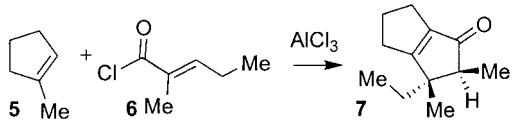
1. Introduction and General Concepts

In the years since the publication of Habermas, Denmark and Jones' 1994 review of the Nazarov reaction[1] a number of new developments have been described. It is the goal of this microreview to introduce the reader to some of these newer discoveries.

The Nazarov reaction is classically formulated as a 4π-electron conrotation of pentadienyl cation **2**, which is formed by proton transfer to the dienone **1** [Equation (1)]. The allyl cation **3** is formed as an intermediate. Proton loss from **3** terminates the reaction and leads to cyclopentenone **4**. Since the reaction proceeds through carbocationic intermediates, there is an opportunity to perform C–C bond forming reactions subsequent to cyclization. It is sometimes the case that adventitious Wagner–Meerwein rearrangements of the cyclic cation (cf. **3**) may frustrate synthetic planning. An example of such a rearrangement from the work of Santelli and co-workers is shown in Equation (2).[2,3] Friedel–Crafts acylation of methylcyclopentene (**5**) with the chloride **6** led to the enone **7** through successive 1,2-hydride and alkyl shifts.



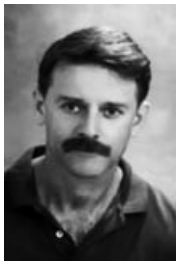
(1)



(2)

Although the example of Equation (1) is symmetrical and does not reveal the issue, it is often useful to be able to control the location of the α,β-unsaturation during the

[a] Department of Chemistry, University of Hawaii,
2545 The Mall, Honolulu, HI 96822, USA
Fax: +1-808-956-5908
E-mail: tius@gold.chem.hawaii.edu



Marc Tius was born in 1953 in Izmir, on the Aegean coast of Turkey. He moved to Greece with his father and mother when he was 5 years old. He attended elementary school for six years in Kavala, a town in Eastern Macedonia, and gymnasium for another six years in Thessaloniki, a larger city in northern Greece. In 1971 he enrolled as an undergraduate at Dartmouth College in Hanover, New Hampshire, where he majored in Mathematics and Chemistry. His first research experience was in Professor Gordon Gribble's labs. In 1975 he moved south from Hanover to Cambridge and started graduate studies at Harvard, where he joined Professor E. J. Corey's group. For his thesis he completed the synthesis of aphidicolin, working with Larry Blaszczak first, and then with Jagabandhu Das. After a brief postdoc in the Corey group, he moved to Hawaii in August, 1980, where he has been ever since. He currently has a joint appointment in the Chemistry Department of the University of Hawaii, and at the Cancer Research Center of Hawaii.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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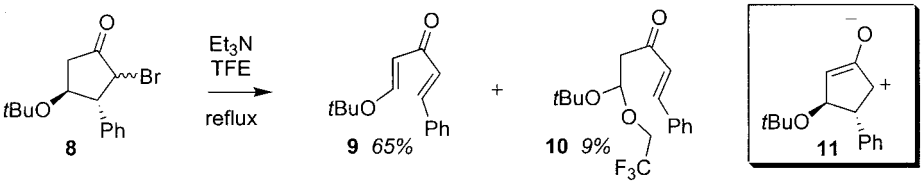


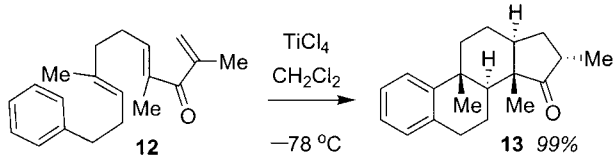
(3)

termination event. As will be discussed in section 4 of this microreview, judicious placement of a heteroatom, typically silicon or tin, but also fluorine, on the acyclic precursor to the pentadienyl cation offers a means of controlling the location of the double bond in the cyclic product by influencing the termination step.

Although the Nazarov reaction is formulated as the cyclization of an acyclic cation, the retro-Nazarov cleavage is now also known through the efforts of Harmata and coworkers,[4,5] and others.[6] For example, exposure of cyclopentanone **8** to a small excess of triethylamine in trifluoroethanol at reflux led to a mixture of acyclic enones **9** and **10** [Equation (3)].[4] The reaction presumably takes place through conrotatory ring opening of **11**, which is formed from **8** through sequential deprotonation and solvolytic loss of bromide in the polar reaction medium. A single β-alkoxy group is sufficient to allow the retro-Nazarov reaction to proceed, since the reaction is driven by the stabilization of the acyclic product that is conferred by the electron donating alkoxy group and the conjugating phenyl.

2. Interrupted Nazarov Reactions and Other Tandem Processes

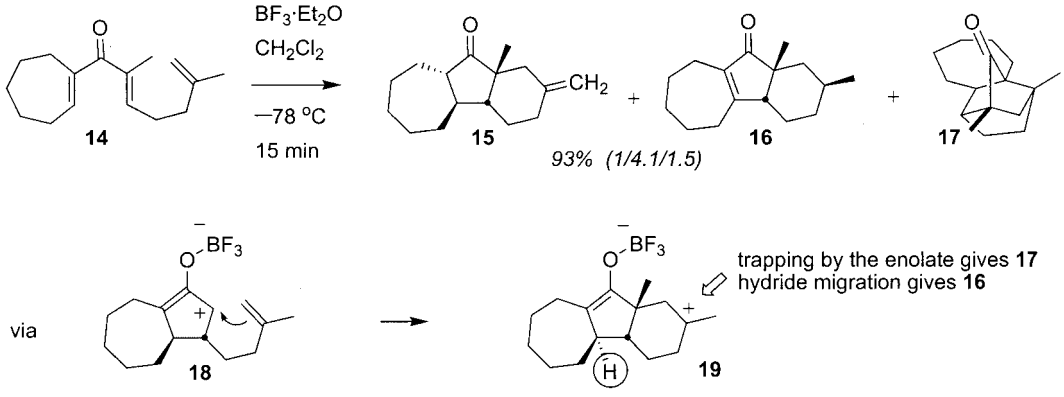
The potential for coupling a Nazarov reaction with additional C–C bond forming steps is illustrated by West's spectacular synthesis of steroid-like compound **13** [Equation (4)].[7–11] The Nazarov cyclization of keto olefin **12** generates an intermediate carbocation that triggers a polyolefin cyclization cascade leading to **13** in nearly quantitative yield. Three rings and five stereocenters are formed in the process.



(4)

West has explored a number of variations on this general theme. For example, exposure of enone **14** to $BF_3{\cdot}Et_2O$ leads to a mixture of the ketones **15**, **16** and **17** in excellent yield [Equation (5)].[12] The three products reflect the different fates of the common intermediate, tertiary cation **19**, which is formed by intercepting **18**. Proton loss from **19** leads to **15**, whereas **16** results from hydride migration. Intramolecular trapping by the boron enolate gives bridged product **17**. This chemistry gives an indication of the large degree of molecular complexity that results from linking the Nazarov reaction to another C–C bond forming process.

The Nazarov intermediate can also be trapped by dienes in an intra- or intermolecular process leading to [4+3] cycloadducts. An example of the intramolecular process is summarized in Equation (6)].[13,14] Treatment of a mixture of enone **20** and 2 equiv. furan with $BF_3{\cdot}Et_2O$ leads to *exo* adduct **22** in 70% yield. Significantly, none of the simple, monocyclic Nazarov product was isolated from this reaction, suggesting that trapping of the cation was quantita-



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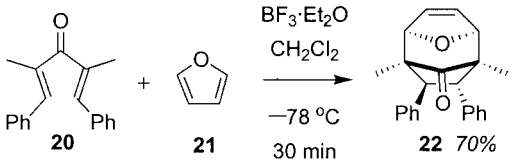
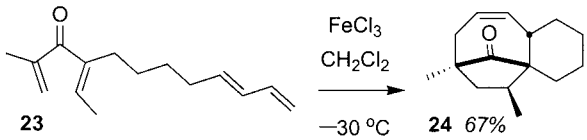
tive. In the case of unsymmetrical dienes, cycloaddition proceeds with unexpected regiocontrol, and provides a one-step synthesis of substituted keto-bridged cyclooctenes.



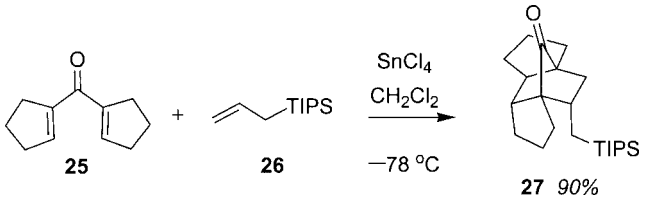
(6)

The rearrangement of enone **23** to the *exo* adduct 24 [Equation (7)] illustrates the intramolecular case.[15] The single stereocenter formed during the conrotation leading to the Nazarov product determines the stereochemical outcome of this reaction.



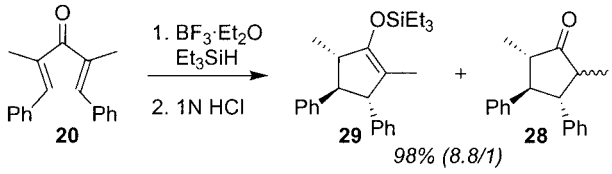
(7)

The nucleophilicity of allylic silanes has been exploited in a large number of synthetic applications, so it should come as no surprise that the intermediate allylic cation from a Nazarov process can be intercepted efficiently as well. Exposure of the enone **25** [Equation (8)] and a ten-fold excess of allyl triisopropylsilane (**26**) to Lewis acid leads to a tandem Nazarov-[3+2] cycloaddition reaction.[16] The bridged product **27** with four rings and five stereocenters is isolated as a single isomer in high yield.



(8)

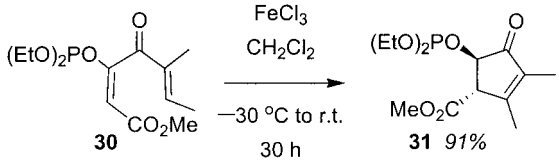
The Nazarov intermediate can be trapped efficiently with triethylsilane as well [Equation (9)].[17,18] Exposure of enone **20** to a small excess of BF_3·Et_2O and 2 equiv. triethylsilane, followed by workup with aqueous acid leads to cyclopentanone **28** in nearly quantitative yield. Reducing the proportion of the Lewis acid makes it possible to isolate silyl enol ether **29** as the major reaction product. Through this variant of the basic reaction, control can be exercised over three stereocenters of the enol ether **29**.



(9)

3. Polarized Alkenes

A special case of the Nazarov reaction that takes place under exceptionally mild conditions is the process involving polarized enones. Mikolajczyk reported the cyclization of phosphonate **30** to the cyclopentenone **31** [Equation (10)].[19] Kocienski has demonstrated the cyclization of the enol ether **32** to **33** [Equation (11)].[20] Both reactions take place readily under very mild reaction conditions, so it would appear that substitution by either electron withdrawing groups, as in **30**, or by electron releasing groups, as in **32**, lowers the barrier to cyclization.



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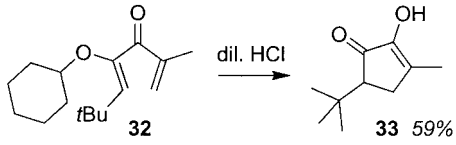
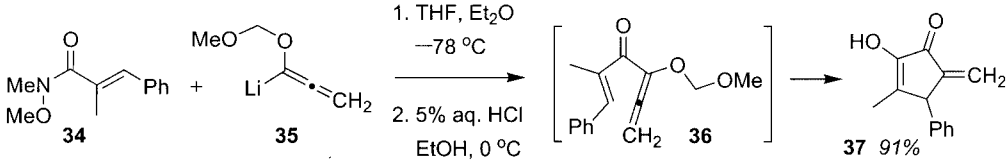


(11)

In 1994 we disclosed the unusual (at the time) reaction that is summarized in Equation (12).[21] Addition of lithioallene **35** to Weinreb enamide **34**, followed by workup with dilute HCl, led in high yield to cross-conjugated cyclopentenone **37**. The presumed intermediate, allenyl ketone **36**, was never observed. We had attributed the ease with which this type of cyclization takes place to favorable polarization of enol ether **36** and also to the small steric requirement of the sp hybridized allene carbon atom. It should be noted that in the case of Equation (12) the Nazarov reaction is terminated through loss of methoxymethyl carbo-



(12)

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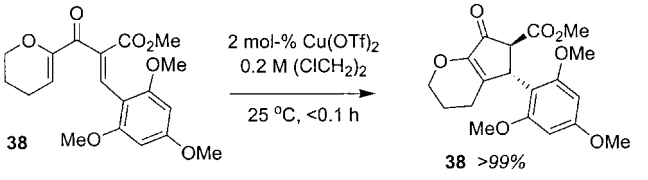
cation, rather than through loss of a proton. This places a restriction on the allene ethers that can be used in the reaction: they must be substituted by a group that can depart as a stable carbocation.

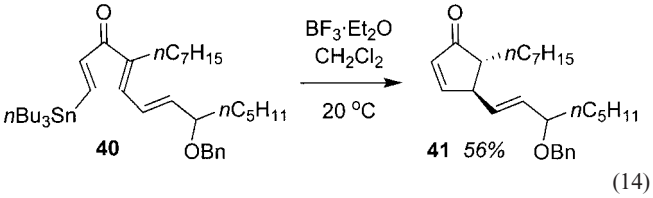
Frontier and co-workers were the first to conduct a systematic investigation into the effects on the ease of Nazarov cyclization of polarizing the alkene. The cyclization of dienone **38**, which has a donor and an acceptor group on each of the respective α carbon atoms, is catalyzed by $Cu(OTf)_2$ and takes place quantitatively [Equation (13)].[22–24] As is the case of the Diels–Alder cycloaddition, the polarized system cyclizes more rapidly than the system lacking polarization. Replacing the carbomethoxy group in **38** by hydrogen, or the oxygen atom by a methylene group, leads to a slower reaction. It is also significant that the double bond in the product is localized on the side of the five-membered ring that bears the electron donating oxygen atom. There are a number of ways with which to control the locus of the unsaturation in the product that will be discussed in the section that follows.



(13)

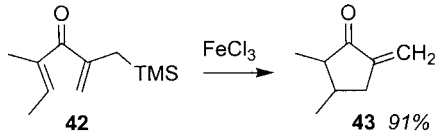
4. Localizing the Double Bond in the Product

Being able to control the termination event of the Nazarov reaction has important consequences for synthetic planning. An early example is provided by Johnson's ingenious prostaglandin synthesis [Equation (14)].[25] Placement of the β-tri-*n*-butylstannyl group in the acyclic enone **40** assures that the process will be terminated by loss of tri-*n*-butylstannyl cation, to provide the kinetic product **41**. Similar use of a trimethylsilyl group has been made by Denmark and by others.[26–30]



(14)

Placement of the directing group need not be at the β carbon atom that is destined to become part of the five-membered ring. Kang and co-workers have shown that ferric chloride effectively catalyzes the rearrangement of keto silane **42** to the exocyclic enone **43** [Equation (15)].[31,32] Incorporating a chlorine atom in the acyclic enone **44** makes it possible to access the cross-conjugated cyclopentenone **45**, the product that results from dehydrochlorination subsequent to the cyclization [Equation (16)].



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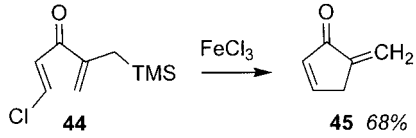
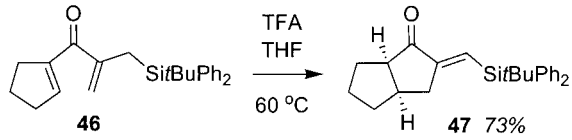


(16)

Pulido and co-workers have exploited the diminished tendency of the *tert*-butyldiphenylsilyl group to undergo protiodesilylation to demonstrate a different kind of control [Equation (17) and Equation (18)].[33] For example, treatment of the dienone **46** with trifluoroacetic acid (TFA) leads to exocyclic silyl enone **47** in 73% yield. In this example, following cyclization the silicon atom stabilizes the adjacent positively charged carbon atom, selectively stabilizing one of the two resonance tautomers of the allylic cation (cf. **3**), leading to proton loss to form the exocyclic product. The example of dienone **48** [Equation (18)] is similar, except that proton loss in this case leads to **49**, presumably due to more favorable energetics for the formation of the endocyclic enone in the bicyclo[4.3.0]nonanone case.



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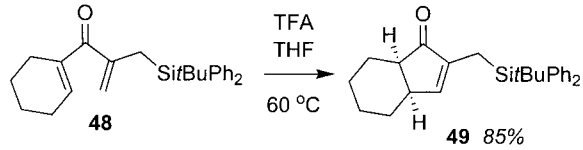

(18)

Silicon and tin are not the only heteroatoms that can be exploited to control the locus of unsaturation in the product. Ichikawa and co-workers have shown that fluorine can also be used in this context. The difluoroenone **50** when exposed to an equivalent of trimethylsilyl triflate leads in good yield to cross-conjugated cyclopentenone **51** [Equation (19)].[34] This reaction offers an alternative to Equations (12) and (16) as a means of accessing cross-conjugated cyclopentenones. Ichikawa has gone on to define conditions for selective addition of nucleophiles either to the exocyclic methylene carbon atom, the β-fluorine bearing carbon atom, or to the carbonyl carbon atom of **51**. This chemistry forms the basis of a very versatile cyclopentenone synthesis.[35]

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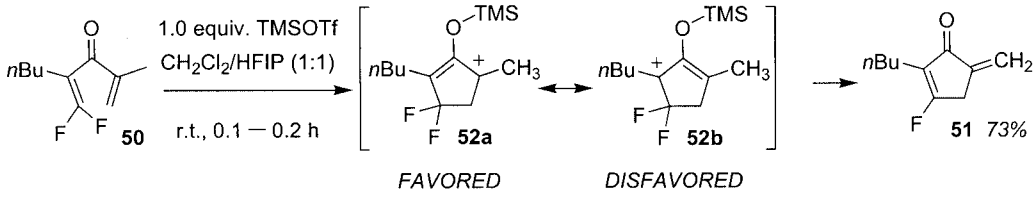

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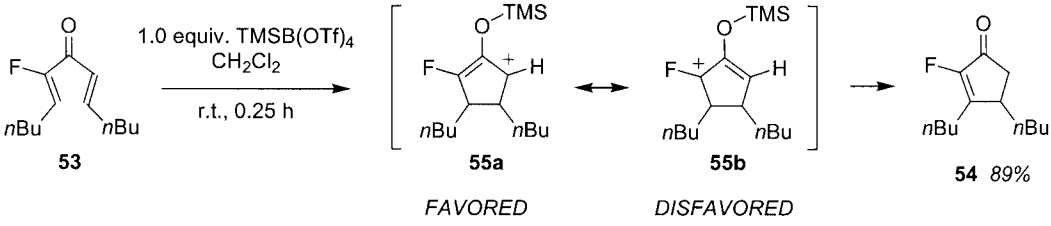
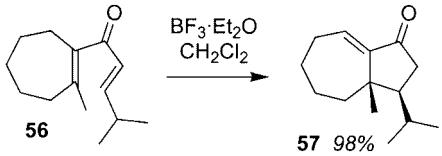


(20)

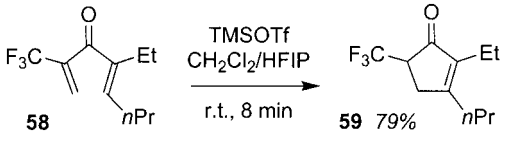
The Nazarov cyclization of **50** is terminated by proton loss from the methyl group, rather than from the *n*-butyl group, because of the influence of the two fluorine atoms that *de*stabilize resonance tautomer **52b**, thus favoring **52a**. The effect of a α-fluorine atom in the acyclic enone has a different consequence on the structure of the product. For example, exposure of **53** to Lewis acid leads exclusively to α-fluoroenone **54** in excellent yield [Equation (20)].[36] Termination of the Nazarov process takes place through completely regiospecific proton loss under the influence of the fluorine atom: the well known ability of a fluorine atom to *stabilize* an adjacent positively charged carbon atom favors resonance tautomer **55b** over **55a**. Proton loss from **55b** leads to **54**.

The key step in Chiu's approach to the synthesis of guanacastepene, summarized in Equation (21), can be understood in the same way. Proton loss from the more stable (tertiary vs. secondary) cationic intermediate leads to exocyclic enone **57** in preference to the alternative endocyclic product.[37,38]



(21)

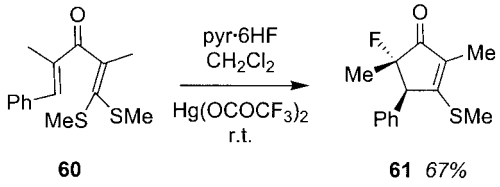
The effect of the α-trifluoromethyl group in **58** [Equation (22)] on the regiochemistry of the termination step is also consistent with the concepts discussed above.[39]



(22)

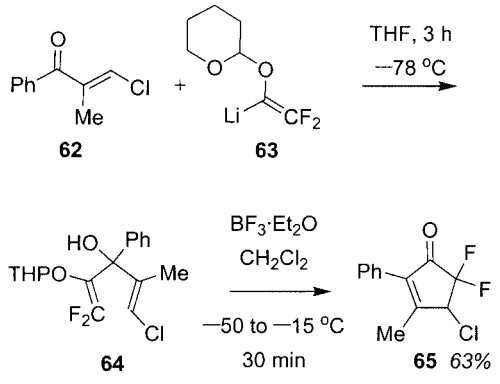
5. Fluorinated Cyclopentanones from the Nazarov Reaction

In addition to the results presented in the preceding section, there are a few other reports of the use of the Nazarov cyclization for the synthesis of fluorinated cyclopentenone products. Hara and co-workers have reported the process summarized in Equation (23).[40] The intermediate allylic cation is trapped by fluoride completely stereoselectively. Mercury(II)-assisted elimination of one of the thiomethoxy groups leads to the observed product **61**.



(23)

A somewhat different reaction type is exemplified in Equation (24). Exposure of the tetrahydropyranyl ether of 2,2,2-trifluoroethanol to *tert*-butyllithium generates difluorovinyllithium species **63** that adds to enone **62**, producing the tertiary alcohol **64**.[41] Following workup and isolation, this material is treated briefly with Lewis acid at low temperature to give the polyhalogenated cyclopentenone **65** in 63% overall yield from **62**. In this example, the reactive pentadienyl carbocation is generated from the irreversible ionization of tertiary alcohol **64**, rather than from reversible protonation of a ketone. Cyclization of the pentadienyl cation must therefore be faster than the competing processes that lead to decomposition of the enol ether function. There



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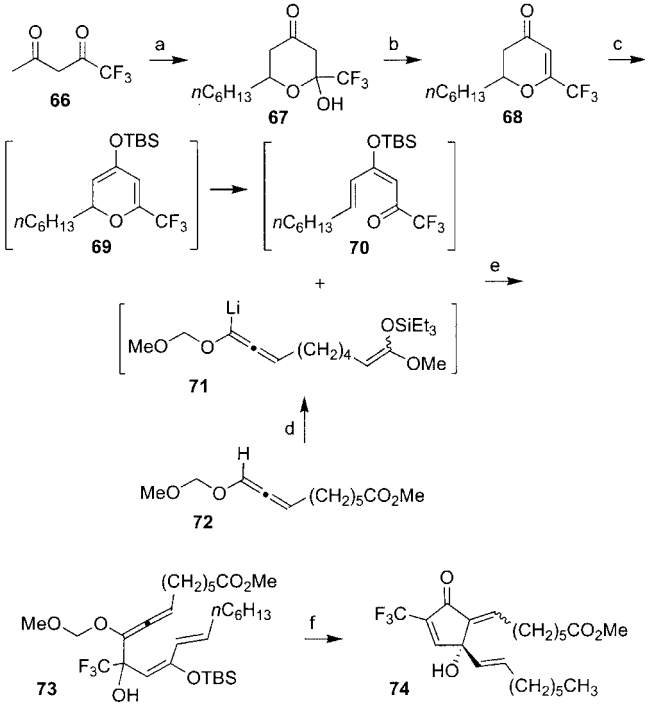
is no ambiguity regarding the position of the double bond in the product. This method provides ready access to products that would be extremely difficult to prepare through alternative means.

The synthesis of a prostaglandin analog bearing a trifluoromethyl group is summarized in Scheme 1.[42] This synthesis illustrates several useful points. Double deprotonation of 1,1,1-trifluoro-2,4-pentanedione (**66**), followed by trapping of the dienolate with heptanal leads to the β-hydroxypyrone **67** in 74% yield. Dehydration of **67** to **68** was easily accomplished by exposure to $BF_3{\cdot}Et_2O$. Conversion of **68** to the *tert*-butyldimethylsilyl enol ether **69** took place upon treatment with *tert*-butyldimethylsilyl triflate and triethylamine at low temperature. Slow warming of the solution of **69** to room temperature yielded **70** through electrocyclic ring opening. It was necessary to use this material quickly, before isomerization of the enol ether double bond had a chance to take place, since isomerization is followed by immediate migration of the silyl group to the oxygen atom of the trifluoromethyl ketone. Addition of the lithioallene **71** to the enone **70** led to the tertiary alcohol **73** in 55% yield. Allene **71** was prepared from ester **72** by sequential treatment with LDA, followed by triethylchlorosilane, and then *sec*-butyllithium. Although the ketene acetal function of **71** does not survive workup, both enol ether functions do. The Nazarov cyclization of **73** is mediated by trifluoroacetic anhydride/2,6-lutidine, and leads to the cyclopentenone **74** as a mixture of *Z* and *E* geometrical isomers at the exocyclic double bond (42% *Z* + 16% *E*). Photochemical isomerization of *Z* to *E* isomers is easily accomplished.

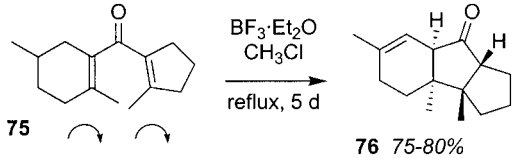


Scheme 1. (a) LDA, THF, –78 °C; heptanal; 74%; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp.; 95%; (c) Et_3N, TBSOTf, Et_2O, –78 °C, 1 h; 0 °C, 0.5 h; room temp. 4 h; (d) LDA, Et_3SiCl, THF, –78 °C to room temp.; *s*BuLi, THF, –78 °C; (e) add solution of **70** to **71**, –78 °C; 55% from **72**; (f) 2,6-lutidine, TFAA, –78 °C to –40 °C; 42% *Z* + 16% *E*.

The Nazarov cyclization of **73** is initiated by ionization of the tertiary alcohol to a heptatrienyl cation that undergoes 4π conrotatory ring closure. Even through the cation is destabilized by the trifluoromethyl group, its formation is facilitated by the silyloxy group, as well as by the extended conjugation. It is significant that cyclization competes successfully with hydrolytic cleavage of the two enol ether functions. The preference to form the thermodynamically disfavored *Z* isomer of the exocyclic double bond will be discussed later in this review.

6. Control of Absolute Stereochemistry

In general there are three ways to control absolute stereochemistry: Through use of asymmetric catalysts, or chiral auxiliaries, or through asymmetry transfer. All three approaches have shown promise in the Nazarov reaction, and examples of each will be discussed. Before doing so, it is useful to review the key step in Harding's trichodiene synthesis [Equation (25)].[43] Exposure of the ketone **75** to $BF_3{\cdot}Et_2O$ in refluxing chloroform for five days leads to product **76** in excellent yield. Under the vigorous conditions required for cyclization of (±)-**75**, C–C double bond migration takes place. Whereas the relative stereochemistry of the two methyl-bearing quaternary carbon atoms in (±)-**76** is a consequence of the conrotatory mechanism, the stereochemistry at the carbon atoms α to the carbonyl is determined during protonation. In order to control the absolute stereochemistry at the β carbon atom(s) of a Nazarov product, it is necessary to control the sense of the conrotation, clockwise or counterclockwise. In order to control stereochemistry at the α carbon atom(s), it is necessary to control the facial selectivity for enol protonation.



(25)

Examples of the Nazarov reaction involving asymmetry transfer will be discussed first. Denmark and co-workers have used a stereogenic trimethylsilyl-bearing carbon atom to control the sense of conrotation of **77** [Equation (26)].[44] Exposure of the homochiral ketone **77** to ferric chloride at low temperature led in excellent yield and with complete transfer of asymmetry to enone **78**. In this example, clockwise conrotation maximizes overlap of the C–Si bond with the allylic carbocation all along the reaction coordinate. The stereochemistry of the β carbon atoms of **78** reflect the sense of conrotation, whereas the stereochemistry α to the carbonyl group is determined during a proton transfer step, and reflects a thermodynamic preference.

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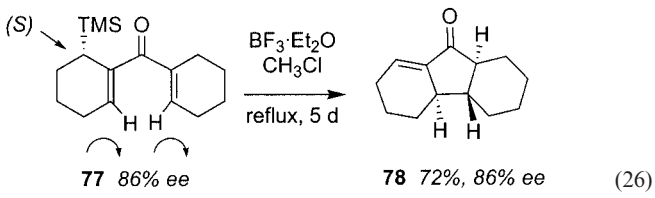
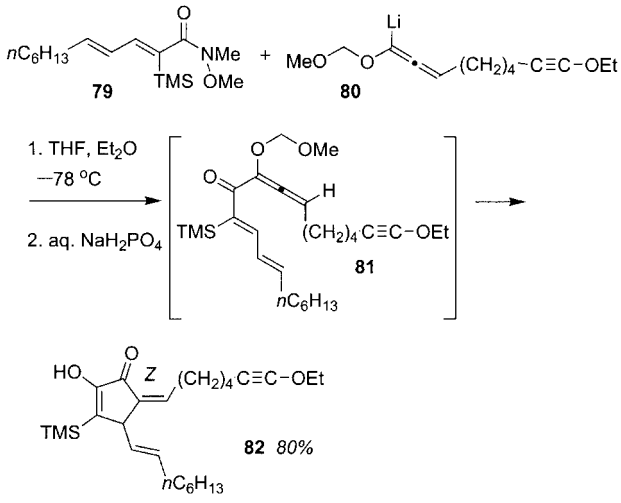


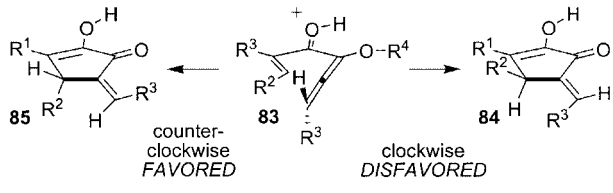
(26)

Transfer of asymmetry need not be from a sp^3 hybridized carbon atom. In the discussion that accompanies Scheme 1, mention was made of the preference for **73** to cyclize to *Z*-**74**. We first noticed this effect during our synthesis of **82** [Equation (27)].[45] When we added the lithioallene (±)-**80** to the Weinreb amide **79**, we noticed a pronounced preference (ca. 6:1) for formation of the *Z* exocyclic bond isomer of cyclic product (±)-**82**. We were fortunate that cyclization of **81** took place spontaneously during workup with aqueous NaH_2PO_4. Had the cyclization of **81** required strong acid, it is likely that rapid *Z* to *E* isomerization of the kinetically formed product would have obscured the effect.



(27)

The *Z* isomer of **82** is probably preferred for steric reasons. If one considers the general case of cation **83** [Equation (28)], the allene function is stereogenic, therefore the two modes of conrotation, clockwise or counterclockwise as viewed by the reader, lead to diastereomeric cyclopentenones **84** or **85**, respectively. Counterclockwise conrotation is favored in this example because it allows the two large groups, R^2 and R^3, to move away from each other as the reaction proceeds. This being the case, if one were to proceed from a homochiral allene, axial to tetrahedral chirality transfer would be expected to take place. Moreover, the larger the allene substituent R^3, the more effective the transfer of chirality would be. This has been shown to be the case. Combining homochiral allene amide **86** with vinyllithium **87** at low temperature, followed by aqueous workup led to cyclopentenone **89** in 64% yield with >95% chirality transfer [Equation (29)].[46] The *tert*-butyl substituent in **88** forces counterclockwise (as viewed by the reader) conrotation to take place.



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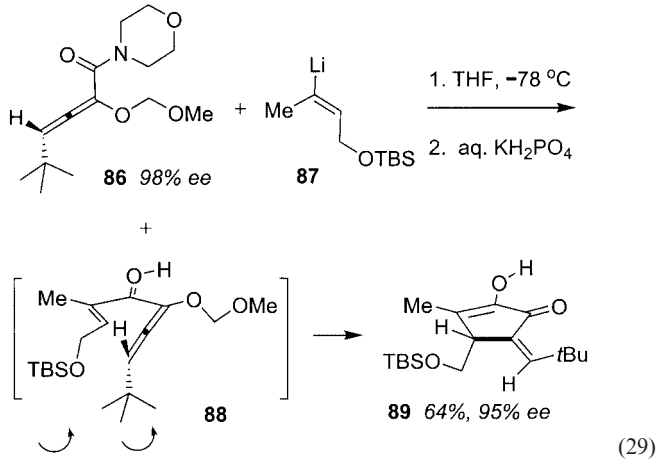
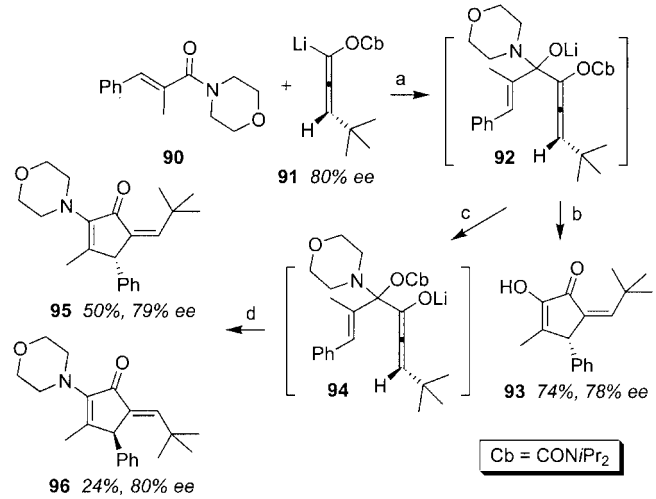


(29)

Related results by Hoppe and co-workers reveal an unanticipated mechanistic complexity in these systems (Scheme 2).[47] Enantiomerically enriched lithioallenyl carbamate **91** was added to enamide **90** at low temperature. Rapid transfer of the reaction mixture to ethanolic HCl led to the cyclopentenone **93** in 74% yield and with 98% chirality transfer. However, when the reaction mixture was warmed to room temperature before being exposed to acid, the diastereomeric products **95** and **96** were formed, both with approximately 98% chirality transfer. It appears that upon warming, migration of the carbamoyloxy group in **92** produces allenolate **94** in situ. The carbamoyloxy group



Scheme 2. (a) PhMe, –78 °C, 30 min; (b) rapid transfer to 5% HCl in EtOH; **93** 74%, 78% *ee*; (c) PhMe, 1 h, –78 °C; 1 h room temp.; (d) 2 N HCl; **95** 50%, 79% *ee*; **96** 24%, 80% *ee*.

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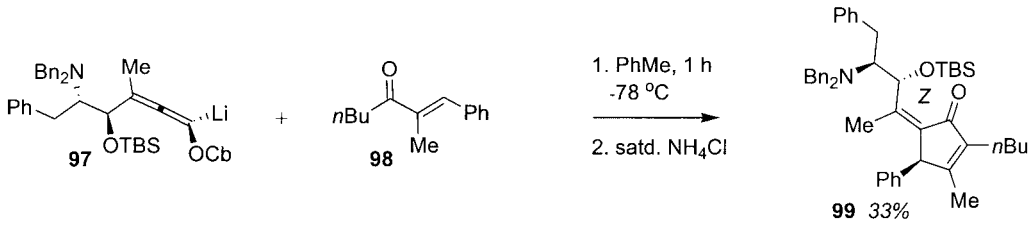

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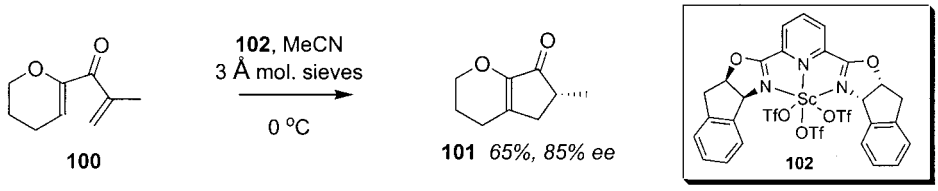
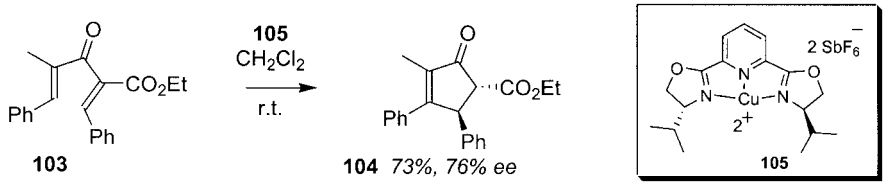


(31)



(32)

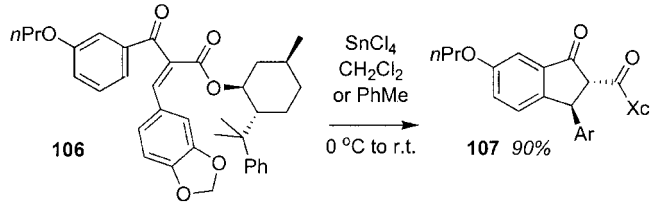
then acts a leaving group during a cyclization in which product stereochemistry is determined by the chirality of the carbon atom bearing the leaving group. Notice that in products **95** and **96**, the influence of the axial chirality of the allene on the product is overridden.

Hoppe has observed similar chemistry in the case of allene adducts to ketones [Equation (30)].[48,49] For example, addition of the lithioallene **97** to the ketone **98** leads to the cyclopentenone **99** following cyclization. The *E* geometrical isomer of the exocyclic double bond was not observed for reasons that are not yet understood. The reaction of Equation (30) demonstrates that a large degree of stereochemical complexity can be introduced through such processes.

The use of asymmetric catalysis arguably provides the most attractive and elegant approach to the control of absolute stereochemistry in the Nazarov cyclization, as well as in other areas of synthesis. The first successful result is due to Trauner and co-workers [Equation (31)].[50] Exposure of the enone **100** to PYBOX·$Sc(OTf)_3$ catalyst **102** leads to the cyclopentenone **101** in 65% yield and 85% *ee*. The step that determines the product stereochemistry is the proton transfer to the chelated metalloenolate. Highest levels of enantioselection were realized when the substrate bore a sterically demanding α substituent.

Aggarwal and co-workers reported related results using cationic Cu^{II}·PYBOX catalyst **105** [Equation (32)].[51] Cyclization of **103** led to β-keto ester **104** in 73% yield and 76% *ee*. The reaction apparently works best when there is a phenyl group β to the ester. The ester carbonyl group in **103** and the ether oxygen atom in **100** probably provide sites for bidentate chelation to the ligated metal, and may be critical to the success of both reactions.

A third way to control the absolute stereochemical course of the Nazarov cyclization is through the use of a chiral auxiliary. Pridgen and co-workers reported the chiral auxiliary controlled indanone synthesis summarized in Equation (33).[52] The reaction is catalyzed by $SnCl_4$ and produces **107** as the major product, along with a small amount of the diastereomer at the β carbon atom.



(33)

Pridgen showed that the Evans chiral oxazolidinones were also effective auxiliaries, and good diastereomeric ratios were observed even in reactions catalyzed by *protic acid*. In light of Trauner's and Aggarwal's results, that have been summarized above in Equations (31) and (32), this is surprising, and suggests that at least in the examples studied

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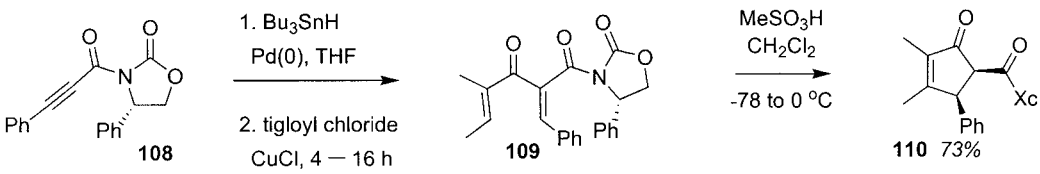
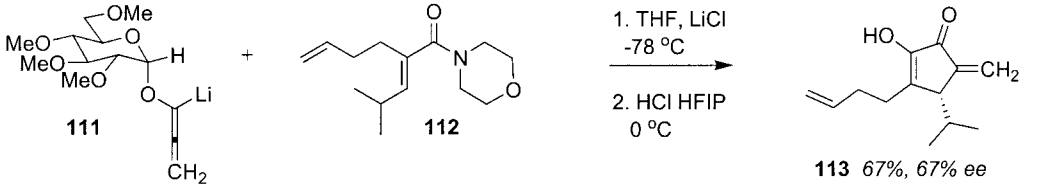


(34)



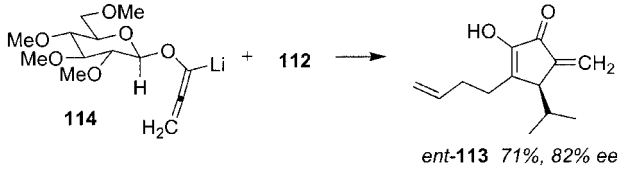
(35)

by Pridgen, the conformational restriction on the starting material that is imposed by bidentate chelation of the 1,3-dicarbonyl system to tin (or other metal) is not a prerequisite for high optical purity of the products. Flynn's work [Equation (34)] confirms this.

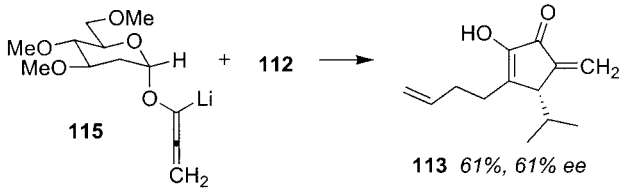
Flynn and co-workers also examined the oxazolidinone chiral auxiliaries [Equation (34)].[53] Regio- and stereoselective Pd(0)-catalyzed hydrostannation of alkyne **108** was followed by acylation with tigloyl chloride to produce **109**. Treatment of **109** with methanesulfonic acid at –78 °C, followed by warming to 0 °C and quenching into hydrogencarbonate led to the kinetic *cis* substituted product **110** in 73% yield. As was the case in Aggarwal's work [Equation (32)], Pridgen and Flynn's both report results for cyclopentenones bearing a β aryl group. It is not yet clear whether their methods are general, and whether they will deliver products in high diastereomeric excess in the absence of a β aryl.

A different use of chiral auxiliaries for stereochemical control in the Nazarov reaction is illustrated in Equation (35).[54] Lithioallene **111** is easily derived from D-glucose. Its addition to morpholino enamide **112** takes place in the presence of a few equiv. LiCl. Workup with HCl in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) leads to the cyclopentenone **113** in 67% yield and in 67% *ee*.[55] Loss of the chiral auxiliary from the cyclic allylic cation intermediate terminates the process. The optical purity of products was higher when the reaction was quenched into HFIP rather than ethanol, suggesting that a fast termination step favors more efficient transfer of stereochemical information. Since the auxiliary is cleaved during the cyclization and no separate step for its removal is required, it is traceless.

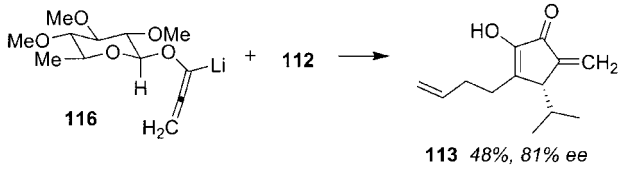
The question naturally arises whether other sugar-derived chiral auxiliaries on the allene ether can also offer opportunities for the asymmetric Nazarov. The issue was probed by performing the reactions summarized in Equations (36), (37), and (38).[54] Lithioallene **114**, derived from the β anomer of D-glucose, when combined with **112** leads to the *enantiomer* of **113** in 71% yield and 82% *ee*. Since L-glucose is far too expensive to be used as the starting material for a chiral auxiliary synthesis, it is highly significant that both enantiomeric series can be accessed from D-glucose-derived auxiliaries **111** and **112**. Lithioallene **115**, derived from the α anomer of 2-deoxy-D-glucose, leads to **113** in 61% yield and 61% *ee*, not significantly different from **111**, whereas lithioallene **116** gives the same product in 48% yield and 81% *ee*. It is a bit puzzling that the absence of the methoxy substituent at C-2 of **115** and at C-6 of **116** has little effect on the optical purity of the product, whose absolute stereochemistry correlates with the stereochemistry of the anomeric carbon atom.



(36)



(37)



(38)

Cyclopentenone **113** was the key intermediate in the asymmetric synthesis of roseophilin, therefore we made a

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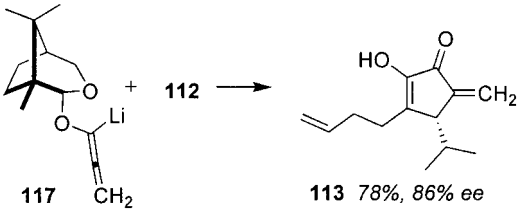
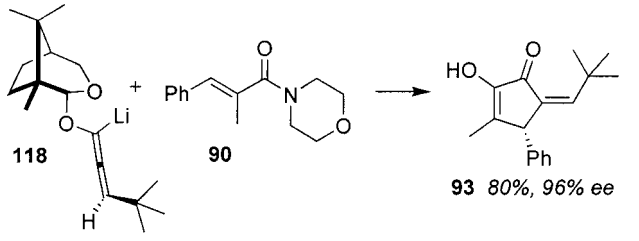
significant effort to optimize its yield and optical purity.[55] An improved preparation of **113** was realized through the use of camphor-derived lithioallene **117** [Equation (39)].[56] The optimized yield and *ee* were 78% and 86%, respectively. Yields and optical purities of cyclopentenone products are uniformly higher with **117** than with sugar-derived allenes **111**, **114**, **115** or **116**. In none of these is the allene function stereogenic, however, by introducing a substituent at the distal carbon atom, one can render it so. Since the chirality of the allene also influences the stereochemical course of cyclization [see Equations (29), (30), and Scheme 2], a matched-mismatched issue arises. For example, lithioallene **118** [Equation (40)] represents the matched case, and since the *tert*-butyl substituent on the distal allene carbon atom is large, one would predict that its influence on the *ee* of the product would be substantial. This is the case. Combining **118** with enamide **90** leads to cyclopentenone **93** in 80% yield and 96% *ee*. The effect of the *tert*-butyl group can be appreciated by noting that the reaction of lithioallene **117**, which lacks the *tert*-butyl substituent, with enamide **90** leads to the cyclopentenone product in 71% yield, but in only 77% *ee*.



(39)

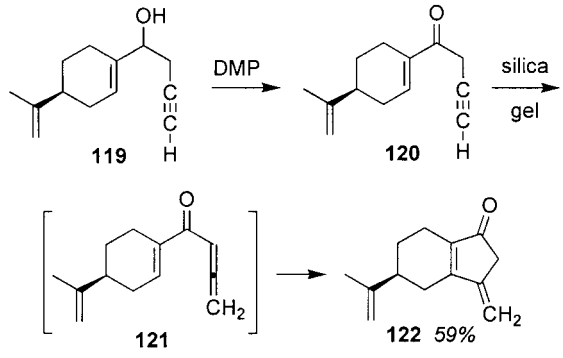


(40)

7. Other Developments

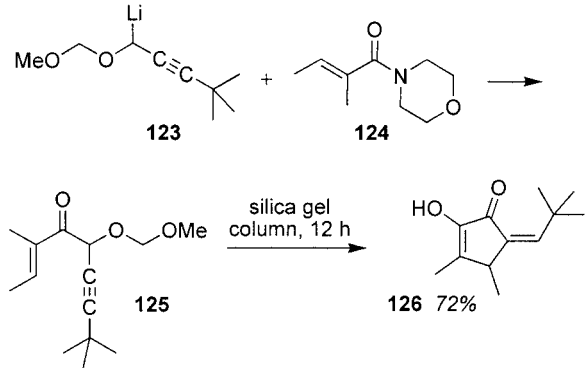
What follows is a partial listing of some of the developments that have been disclosed during the years following the Habermas, Denmark and Jones review of the Nazarov reaction.[1]

Hashmi and co-workers have reported that the oxidation of propargyl vinyl alcohols such as **119** [Equation (41)] with the Dess–Martin periodinane, followed by silica gel column chromatography led to cyclic products, e.g. **122**.[57] This process can be understood to take place through silica gel catalyzed isomerization of initially formed propargyl enone **120** to allenyl ketone **121**, followed by cyclization. Small amounts of **121** could be isolated, but the Nazarov cyclization was strongly catalyzed by the silica gel. The beneficial effect of silica gel for the catalysis of recalcitrant Nazarov reactions had been noted some years earlier.[58]

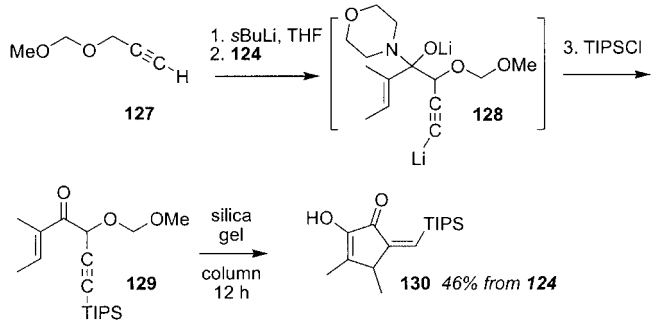


(41)

Inspired by Hashmi's results, we explored the reaction summarized in Equation (42).[59] Addition of **123** to the enamide **124** to give the propargyl enone **125** following workup. This material was loaded onto a silica gel chromatography column which was eluted ca. 12 h later to produce the cyclic enone **126** in 72% yield. Isomerization of **125** to the allene doubtless preceded the cyclization. The advantage of this variant of the reaction of Equations (27) and (29) is that it avoids having to preform and store the sensitive allene. There is another advantage as well. The dianion of methoxymethyl propargyl ether (**127**) is easily prepared [Equation (43)]. Its addition to enamides takes place regiospecifically to give, in the case of **124**, O,C-dianion **128**



(42)



(43)

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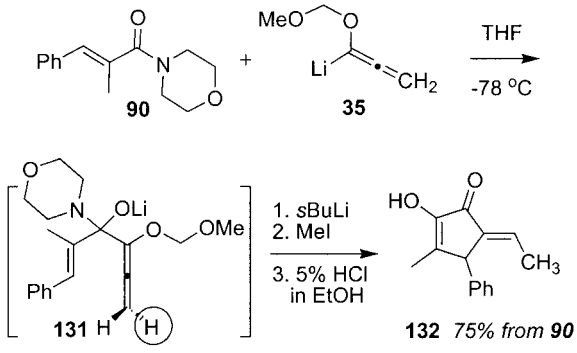
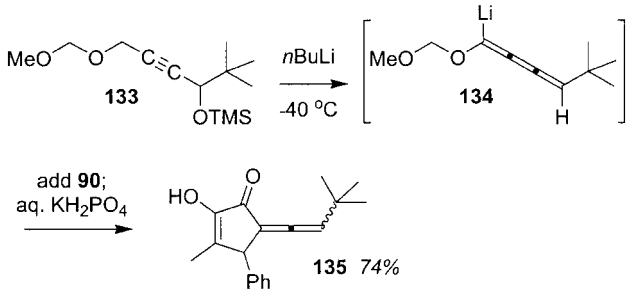
as an intermediate. Exposure of this material to a suitable electrophile, such as TIPS chloride, leads to the propargyl enone **129** which undergoes cyclization to **130** upon exposure to silica gel column chromatography, as described previously. This demonstrates a highly convergent protocol for the synthesis of cross-conjugated cyclopentenones that are substituted at the β exocyclic sp^2 carbon atom.

An alternative approach to the synthesis of compounds like **130** is summarized in Equation (44). Addition of lithioallene **35** to enamide **90** leads to tetrahedral intermediate **131**.[60] The allene protons of **131** are acidic, therefore treatment of **131** with *sec*-butyllithium leads to the O,C-dianion (cf. **128**) that is trapped with iodomethane. Cyclization to **132** (75% yield) takes place during workup with acid. The *E* isomer of the exocyclic olefin corresponds to the thermodynamic reaction product. The *Z* kinetic isomer can be accessed either by using milder acid for workup (e.g. aq KH_2PO_4) or by limiting the contact time with HCl. As is the case of Equation (43), this protocol allows for rapid access to multi-substituted cyclopentenones.



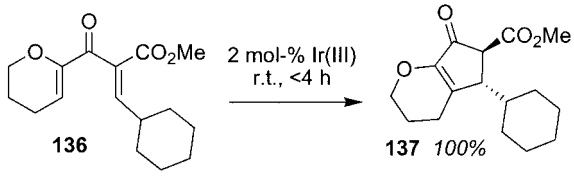
(44)

There are undoubtedly many useful tandem processes such as the ones summarized in Equations 43 and 44 that remain to be discovered. A different sort of Nazarov reaction is shown in Equation (45). Exposure of propargyl ether **133** to slightly more than 2 equiv. *n*-butyllithium leads to the formation of butatrienyl anion **134**, which is trapped by enamide **90** and worked up with aqueous phosphate to give the *exo* allenyl cyclopentenone **135** in 74% yield following column chromatography.[61] The allene function in **135** is stereogenic, therefore the product is isolated as a mixture of diastereomers. The method appears to be quite general, and works for terminally disubstituted butatrienes as well.



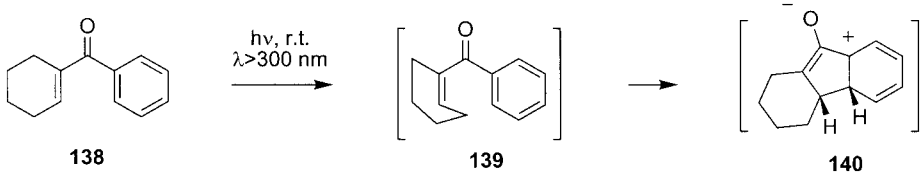
(45)

In all the work that has been discussed up to this point, initiation of the Nazarov cyclization has taken place under the influence of either protic or Lewis acid. Even in the case of the cyclizations mediated by silica gel, it is probably reasonable to assume that acidic sites on the surface of the silica gel grains catalyze the reaction. Frontier and co-workers have demonstrated remarkably efficient catalysis of the reaction summarized in Equation (46) by an Ir^{III} complex.[62] Whereas the enone **136** gives less than 50% yield of **137** after 240 h in the presence of $Cu(OTf)_2$, the presence of [IrMe(CO)dppeDIB](BARF)$_2$ in catalytic quantity leads to a complete reaction in less than 4 h at room temp. {DIB = *o*-diiodobenzene; BARF = [B(3,5-$C_6H_3(CF_3)_2)_4$]}. Remarkably, the reaction kinetics are first order in both ketone and catalyst, so product inhibition apparently does not occur.



(46)

In the case of 1-cyclohexenyl(phenyl)methanone **138** (Equation 47), Leitich and co-workers have shown that the Nazarov reaction can be initiated photochemically.[63] Irradiation of **137** at room temp. leads to the formation of the unstable *trans*-cyclohexene **138** which cyclizes to **139**. This Nazarov intermediate has been intercepted through [4+2], [2+2] and ene reactions. The photochemical approach offers another way to conduct "interrupted" Nazarov reactions.



(47)

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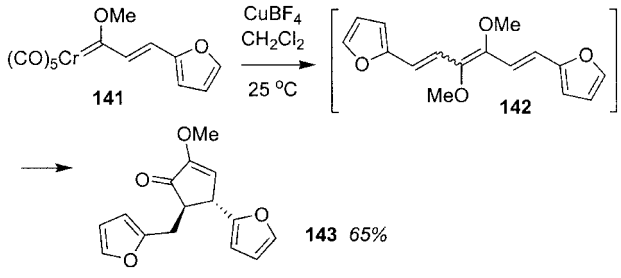
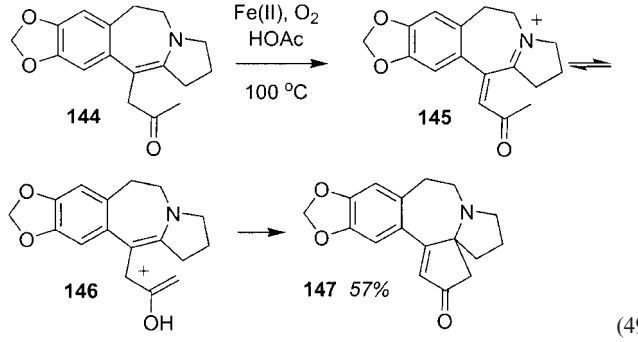
Barluenga and co-workers have reported an unusual method for carrying out the Nazarov reaction. Exposing of the Fisher carbene **141** [Equation (48)] to one equiv. of Cu^{I} tetrafluoroborate initiates a cascade that results in formation of the cyclopentenone **142** in 65% overall yield.[64] The copper salt catalyzes both the dimerization step that leads to **141** as well as the cyclization. Ochiato and co-workers have also used proton transfer to enol ethers to initiate the Nazarov.[65]



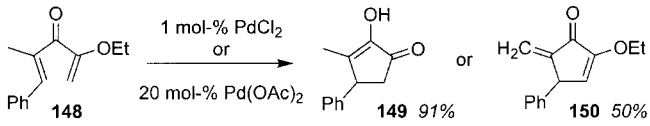
(48)

An interesting and unusual approach to cephalotaxine alkaloids that makes use of a Nazarov reaction is due to Li and co-workers.[66,67] Warming the keto enamine **144** in the presence of Fe^{II} and air in acetic acid leads to the enone **147** in 57% yield [Equation (49)]. This process can be understood as taking place through a series of steps starting with oxidation to **145**. Tautomerization of **145** to enol **146** reveals the pentadienyl cation that undergoes cyclization to **147**.



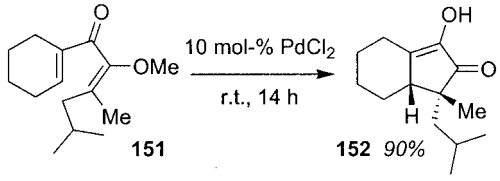
(49)

Finally, there are reactions that produce the same sorts of products as the Nazarov, but that proceed through different mechanisms. For example, exposure of α-ethoxy dienone **148** to 1 mol-% $PdCl_2$ in wet acetone leads to α-hydroxycyclopentenone **149** in high yield [Equation (50)].[68] Control experiments have shown that formation of **148** is not catalyzed by adventitious protic acid. The use of $Pd(OAc)_2$ leads to a different product. Cross-conjugated cyclic dienone **150** results from an oxidative process, suggesting a mechanism whereby the Pd^{II} salt catalyzes the cyclization by activating one of the C–C π bonds toward intramolecular nucleophilic attack by the enol ether. Depending upon the choice of catalyst, simple hydrolysis of an intermediate Pd-enolate leads to **149**, or β-hydride elimination leads to **150**.

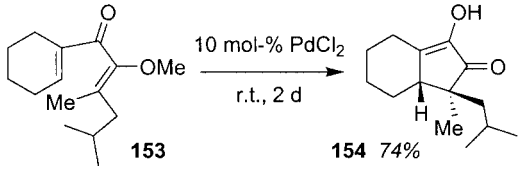


(50)

The $PdCl_2$ reaction follows the same stereochemical course as a conrotatory Nazarov, as revealed by the results of Equations (51) and (52). Enones **151** and **153** are geometrical isomers. Their cyclizations provide diastereomeric products **152** and **154** in high yield, with no crossover products. The ease with which quaternary carbon atoms are incorporated into the products by means of this cyclization is noteworthy.

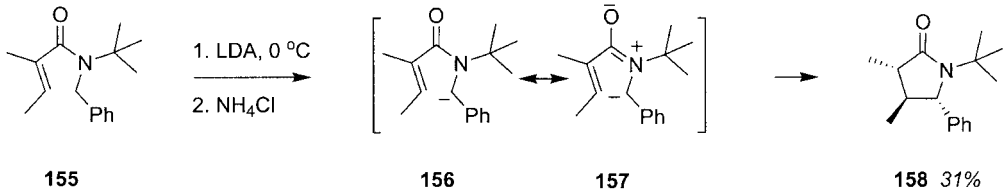


(51)



(52)

Clayden and co-workers have recently disclosed the mechanistically intriguing anionic cyclization of *N*-benzyl acrylamides [Equation (53)].[69] For example, exposure of



(53)

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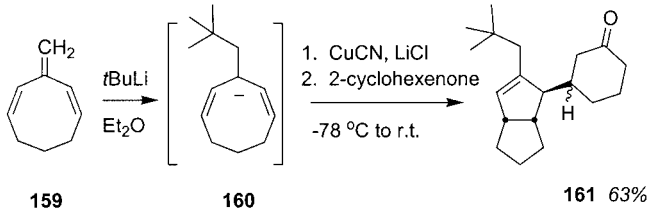
acrylamide **155** to LDA, followed by quenching with weak acid led to γ-lactam **158** in 31% yield. The reaction is apparently initiated by benzylic deprotonation to give **156**. The anion either undergoes stereoelectronically disfavored 5-*endo*-*trig* ring closure, or possibly 6π disrotatory ring closure (consider resonance structure **157**). It will be challenging to design an experiment that will reveal the mechanistic course of this reaction.

On the other hand, Williams and co-workers have demonstrated the first *unambiguous* example of a 6π disrotatory anionic cyclization in the system shown in Equation (54).[70] Addition of *tert*-butyllithium to triene **159** produces pentadienyl anion **160** that undergoes disrotatory closure to a symmetrical allylic anion. Trapping with cyclohexenone gives **161** in 63% overall yield. This method offers opportunities for different modes of C–C bond formation following the cyclization step, and it promises to have great utility in synthesis.



(54)

8. Conclusion

I have attempted to present the reader with an overview of some of the newer advances in Nazarov methodology within a mechanistic framework. The area remains an important and active one for research, with many unmet challenges but also many opportunities for discovery. I have made an attempt to include as much of the new Nazarov chemistry as space allows, and I apologize for anyone's results that I have left out of the pages above.

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[1] K. L. Habermas, S. E. Denmark, T. K. Jones, *Org. React.* **1994**, *45*, 1–158.
[2] C. Morel-Fourrier, J. P. Dulcere, M. Santelli, *J. Am. Chem. Soc.* **1991**, *113*, 8062–8069.
[3] J. Motoyoshiya, T. Yazaki, S. Hayashi, *J. Org. Chem.* **1991**, *56*, 735–740.
[4] M. Harmata, D. R. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 14328–14329.
[5] M. Harmata, P. R. Schreiner, D. R. Lee, P. L. Kirchhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 10954–10957.
[6] Z. C. Etheridge, S. Caddick, *Tetrahedron: Asymmetry* **2004**, *15*, 503–507.
[7] J. A. Bender, A. M. Arif, F. G. West, *J. Am. Chem. Soc.* **1999**, *121*, 7443–7444.
[8] C. C. Browder, F. P. Marmsäter, F. G. West, *Can. J. Chem.* **2004**, *82*, 375–385.
[9] C. C. Browder, F. P. Marmsäter, F. G. West, *Org. Lett.* **2001**, *3*, 3033–3035.
[10] J. A. Bender, A. E. Blize, C. C. Browder, S. Giese, F. G. West, *J. Org. Chem.* **1998**, *63*, 2430–2431.
[11] V. Nair, S. Bindu, V. Sreekumar, A. Chiaroni, *Org. Lett.* **2002**, *4*, 2821–2823.
[12] C. C. Browder, F. G. West, *Synlett* **1999**, 1363–1366.
[13] Y. Wang, D. D. Schill, A. M. Arif, F. G. West, *Org. Lett.* **2003**, *5*, 2747–2750.
[14] A. Yungai, F. G. West, *Tetrahedron Lett.* **2004**, *45*, 5445–5448.
[15] Y. Wang, A. M. Arif, F. G. West, *J. Am. Chem. Soc.* **1999**, *121*, 876–877.
[16] S. Giese, L. Kastrup, D. Stiens, F. G. West, *Ang. Chem. Int. Ed.* **2000**, *39*, 1970–1973.
[17] S. Giese, F. G. West, *Tetrahedron* **2000**, *56*, 10221–10228.
[18] S. Giese, F. G. West, F. G. *Tetrahedron Lett.* **1998**, *39*, 8393–8396.
[19] P. Balczewski, M. Mikolajczyk, *Org. Lett.* **2000**, *2*, 1153–1155.
[20] S. Casson, P. Kocienski, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1187–1191.
[21] M. A. Tius, C.-K. Kwok, X.-q. Gu, C. Zhao, *Synth. Commun.* **1994**, *24*, 871–885.
[22] W. He, X. Sun, A. J. Frontier, *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279.
[23] J. F. P. Andrews, A. C. Regan, *Tetrahedron Lett.* **1991**, *32*, 7731–7734.
[24] G. Liang, S. N. Gradl, D. Trauner, *Org. Lett.* **2003**, *5*, 4931–4934.
[25] M. R. Peel, C. R. Johnson, *Tetrahedron Lett.* **1986**, *27*, 5947–5950.
[26] S. E. Denmark, R. C. Klix, *Tetrahedron* **1988**, *44*, 4043–4060.
[27] S. E. Denmark, K. L. Habermas, G. A. Hite, *Helv. Chim. Acta* **1988**, *71*, 168–194.
[28] S. E. Denmark, G. A. Hite, *Helv. Chim. Acta* **1988**, *71*, 195–208.
[29] M. Miesch, L. Miesch-Gross, M. Franck-Neumann, *Tetrahedron* **1997**, *53*, 2103-2110.
[30] M. Miesch, L. Miesch-Gross, M. Franck-Neumann, *Tetrahedron* **1997**, *53*, 2111–2118.
[31] K.-T. Kang, S. S. Kim, J. C. Lee, J. S. U, *Tetrahedron Lett.* **1992**, *33*, 3495–3498.
[32] C. Kuroda, H. Sumiya, A. Murase, A. Koito, *Chem. Commun.* **1997**, 1177–1178.
[33] A. Barbero, P. Castreño, C. García, F. J. Pulido, *J. Org. Chem.* **2001**, *66*, 7723–7728.
[34] J. Ichikawa, S. Miyazaki, M. Fujiwara, T. Minami, *J. Org. Chem.* **1995**, *60*, 2320–2321.
[35] J. Ichikawa, M. Fujiwara, S. Miyazaki, M. Ikemoto, T. Okauchi, T. Minami, *Org. Lett.* **2001**, *3*, 2345–2348.
[36] J. Ichikawa, *Pure Appl. Chem.* **2000**, *72*, 1685–1689.
[37] P. Chiu, S. Li, *Org. Lett.* **2004**, *6*, 613–616.
[38] A. Nakazaki, U. Sharma, M. A. Tius, *Org. Lett.* **2002**, *4*, 3363–3366.
[39] J. Ichikawa, M. Fujiwara, T. Okauchi, T. Minami, *Synlett* **1998**, 927–929.
[40] S. Hara, S. Okamoto, M. Narahara, T. Fukuhara, N. Yoneda, *Synlett* **1999**, 411–412.
[41] P. E. Harrington, L. Li, M. A. Tius, *J. Org. Chem.* **1999**, *64*, 4025–4029.
[42] M. A. Tius, H. Hu, J. K. Kawakami, J. Busch-Petersen, *J. Org. Chem.* **1998**, *63*, 5971–5976.
[43] K. E. Harding, K. S. Clement, *J. Org. Chem.* **1984**, *49*, 3870–3871.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[44] S. E. Denmark, M. A. Wallace, C. B. Walker, Jr., *J. Org. Chem.* **1990**, *55*, 5543–5545.
[45] M. A. Tius, J. Busch-Petersen, M. Yamashita, *Tetrahedron Lett.* **1998**, *39*, 4219–4222.
[46] H. Hu, D. Smith, R. E. Cramer, M. A. Tius, *J. Am. Chem. Soc.* **1999**, *121*, 9895–9896.
[47] C. Schultz-Fademrecht, M. A. Tius, S. Grimme, B. Wibbeling, D. Hoppe, *Ang. Chem. Int. Ed.* **2002**, *41*, 1532–1535.
[48] M. Zimmermann, B. Wibbeling, D. Hoppe, *Synthesis* **2004**, 765–774.
[49] B. K. Tokeshi, M. A. Tius, *Synthesis* **2004**, 786–790.
[50] G. Liang, D. Trauner, *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545.
[51] V. K. Aggarwal, A. J. Belfield, *Org. Lett.* **2003**, *5*, 5075–5078.
[52] L. N. Pridgen, K. Huang, S. Shilcrat, A. Tickner-Eldridge, C. DeBrosse, R. C. Haltiwanger, *Synlett* **1999**, 1612–1614.
[53] D. J. Kerr, C. Metje, B. L. Flynn, *Chem. Commun.* **2003**, 1380–1381.
[54] P. E. Harrington, M. A. Tius, *Org. Lett.* **2000**, *2*, 2447–2450.
[55] P. E. Harrington, M. A. Tius, *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514.
[56] P. E. Harrington, T. Murai, C. Chu, M. A. Tius, *J. Am. Chem. Soc.* **2002**, *124*, 10091–10100.
[57] A. S. K. Hashmi, J. W. Bats, J-H. Choi, L. Schwarz, *Tetrahedron Lett.* **1998**, *39*, 7491–7494.
[58] M. A. Tius, D. J. Drake, *Tetrahedron* **1996**, *52*, 14651–14660.
[59] J. Forest, C. Bee, F. Cordaro, M. A. Tius, *Org. Lett.* **2003**, *5*, 4069–4072.
[60] C. Bee, M. A. Tius, *Org. Lett.* **2003**, *5*, 1681–1684.
[61] E. Leclerc, M. A. Tius, *Org. Lett.* **2003**, *5*, 1171–1174.
[62] M. Janka, W. He, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.* **2004**, *126*, 6864–6865.
[63] J. Leitich, I. Heise, J. Rust, K. Schaffner, *Eur. J. Org. Chem.* **2001**, 2719–2726,. and references therein.
[64] J. Barluenga, P. Barrio, R. Vicente, L. A. López, M. Tomás, *J. Organomet. Chem.* **2004**, *689*, 3793–3799.
[65] E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna, P. Venturello, *J. Org. Chem.* **2003**, *68*, 9728–9741.
[66] W.-D. Z. Li, Y.-Q. Wang, *Org. Lett.* **2003**, *5*, 2931–2934.
[67] S.-H. Kim, J. K. Cha, *Synthesis* **2000**, 2113-2116. See also: M. J. Porter, N. J. White, G. E. Howells, D. D. P. Laffan, *Tetrahedron Lett.* **2004**, *45*, 6541–6543.
[68] C. Bee, E. Leclerc, M. A. Tius, *Org. Lett.* **2003**, *5*, 4927–4930.
[69] J. Clayden, D. W. Watson, M. Helliwell, M. Chambers, *Chem. Commun.* **2003**, 2582–2583.
[70] D. R. Williams, J. T. Reeves, *J. Am. Chem. Soc.* **2004**, *126*, 3434–3435.

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