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Asymmetric Nazarov cyclizations

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Contents

1. Introduction

The Nazarov cyclization[1] is described as the 4π electron conrotatory cyclization of a pentadienyl cation. The past 20 years have brought resurgent interest in this reaction most likely due to the realization that it can provide rapid and efficient access to multi-substituted cyclopentenones with excellent stereochemical control at two (or even three) contiguous ring carbon atoms.[2]

Typically, stoichiometric or super-stoichiometric Brønsted or Lewis acid is used to generate the conjugate acid **2** of pentadienone **1** reversibly (Scheme 1).[3] Electrocyclization subsequently leads to allylic cation **3** in which the *trans* relationship between substituents R^2 and R^4 is dictated by the conrotation. The process is normally terminated through proton loss from cation **3**, leading typically either to cyclopentenone **4** or to **5**, or to a mixture of the two. The *trans* stereochemistry between R^1 and R^2 in **4** or between R^3 and R^4 in **5** reflects the thermodynamically more stable product. The trans relationship between R^2 and R^4 in **3** can be preserved in the final product if loss of an exocyclic proton from R^1 or R^3 terminates the reaction.
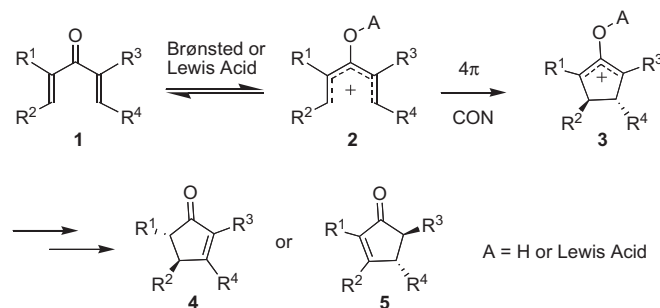
Scheme 1. Acid catalyzed conrotatory cyclization.

Several obstacles must be overcome in order to render such a process general and synthetically useful. Super-stoichiometric strong acids must be avoided so as to suppress undesired competing processes, e.g., Wagner/Meerwein rearrangements. The absolute stereochemistry of the product is determined by the absolute sense of conrotation: the stereochemistry indicated for **3** is a consequence of clockwise conrotation of **2**, viewed from the bottom of the structure as it is shown in Scheme 1. Therefore in an enantioselective
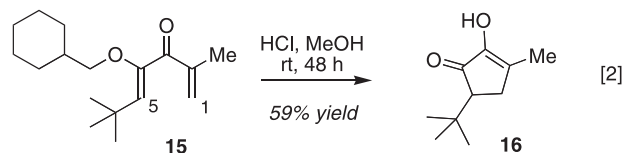
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Nazarov cyclization the absolute sense of conrotation, or the torquoselectivity, must be controlled. The course of the termination step must also be controlled so as to avoid the production of isomeric mixtures of cyclopentenones. Some bias must be present to direct proton loss from **3** so that it does not take place indiscriminately. This Report will examine these constraints in the context of the asymmetric Nazarov cyclization. Enantioselective Nazarov cyclizations that employ asymmetric chiral effectors either catalytically or stoichiometrically will be examined, as well as processes in which transfer of chirality to the cyclic product takes place.
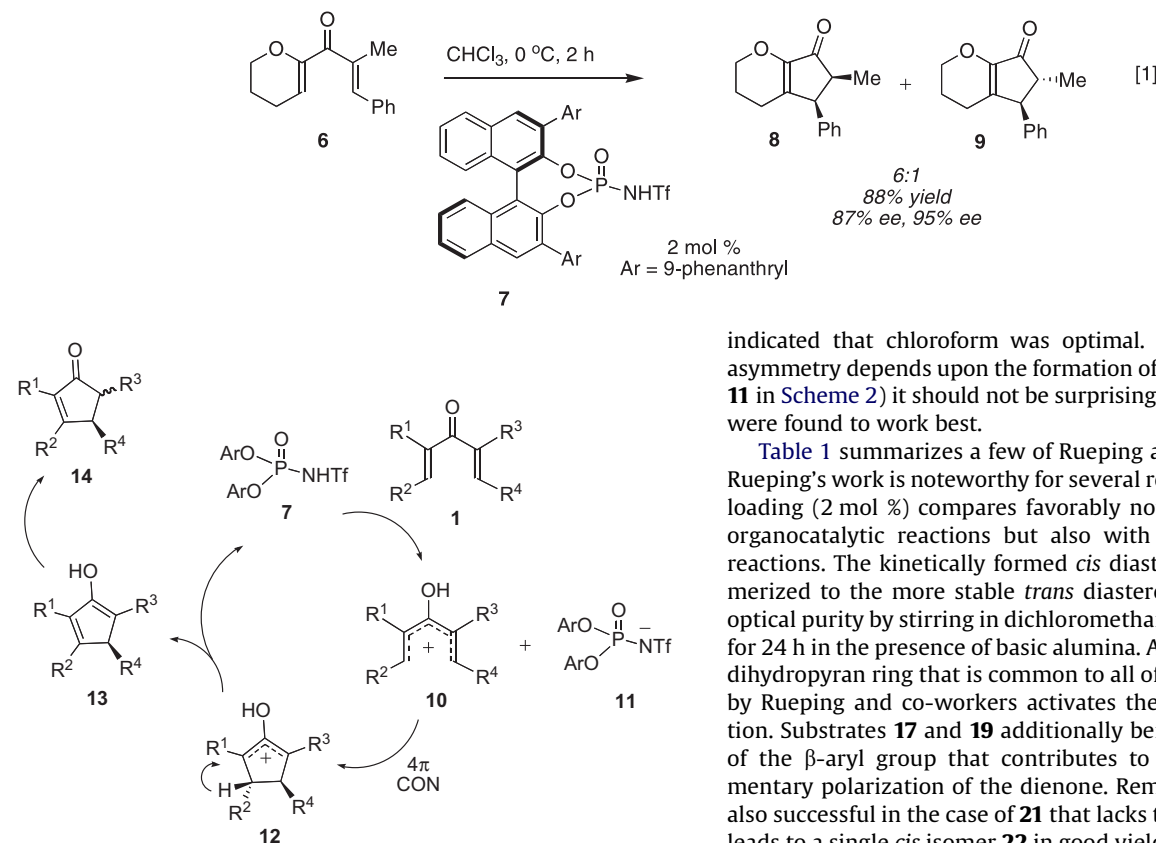
2. Organocatalytic reactions

Rueping and co-workers reported the first enantioselective organocatalytic Nazarov cyclization in 2007.[4] Exposure of a toluene solution of dienone **6** for 2 h at 0 °C to 2 mol % of (*R*)-BINOL-derived *N*-triflylphosphoramide **7** led to the formation of a 6:1 mixture of *cis* and *trans* cyclopentenones **8** (87% ee) and **9** (95% ee), respectively (Eq. 1). The stereochemistry of the phenyl-bearing β-carbon atom is determined by the absolute sense of conrotation, whereas stereochemistry at the α-carbon atom is determined during the final proton transfer step. The preponderance of *cis* product **8** from this reaction indicates that it takes place under kinetic control. The authors proposed a plausible catalytic cycle that is reproduced in Scheme 2. Proton transfer from the chiral Brønsted acid **7** to dienone **1** leads to an ion pair consisting of pentadienyl cation **10** and **11**, the conjugate base of **7**. Conrotatory cyclization of **10** takes place in the counterclockwise direction viewed from the bottom of structure **10** as shown to produce cyclic oxyallyl cation **12**. Proton loss from **12** leads to enol **13** that undergoes successive proton transfer reactions that lead to product **14** with the regeneration of organocatalyst **7**. The regiochemical preference for proton loss from oxyallyl cation **12** is dictated by the presence of the pyranyl ether oxygen atom.

The presence of a pyranyl ether or other α-oxygen atom substituent is a common feature of many substrates for catalytic Nazarov reactions where it plays a dual role. It serves to localize the double bond in the cyclopentenone product, but it also lowers the activation energy for the cyclization by polarizing the dienone. The pyranyl ether substrates utilized by Rueping and co-workers had been used to good effect by Trauner and Liang in the catalytic asymmetric Nazarov some years earlier (vide infra, Eq. 6). The beneficial effect of an α-ether oxygen atom on the rate of Nazarov cyclizations had been demonstrated by Kocienski,[5] Frontier,[6] and others.[7] For example (Eq. 2) dienone **15** has been shown to undergo Nazarov cyclization to **16** upon treatment at ambient temperature with dilute hydrochloric acid. Frontier and co-workers have shown that polarization of the dienone in the opposite sense through the substitution of an α-electron withdrawing group also lowers the barrier for cyclization. Dienones that are polarized in a complementary sense at both the β-carbon atoms (i.e., C1 and C5 in **15**) are predictably the most reactive of all.

indicated that chloroform was optimal. Since the induction of asymmetry depends upon the formation of a tight ion pair (e.g., **10**/**11** in Scheme 2) it should not be surprising that non-polar solvents were found to work best.

Table 1 summarizes a few of Rueping and co-workers' results. Rueping's work is noteworthy for several reasons. The low catalyst loading (2 mol %) compares favorably not only with most other organocatalytic reactions but also with many metal-catalyzed reactions. The kinetically formed *cis* diastereomers could be isomerized to the more stable *trans* diastereomers with no loss of optical purity by stirring in dichloromethane at room temperature for 24 h in the presence of basic alumina. As mentioned above, the dihydropyran ring that is common to all of the examples reported by Rueping and co-workers activates the substrates for cyclization. Substrates **17** and **19** additionally benefit from the presence of the β-aryl group that contributes to the favorable complementary polarization of the dienone. Remarkably, the reaction is also successful in the case of **21** that lacks the β-phenyl group, and leads to a single *cis* isomer **22** in good yield and enantioselectivity (Table 1).

As is commonly the case, Rueping and co-workers determined the optimal catalyst structure empirically. The BINOL-derived phosphates were examined with good results; however, both reactivity and enantioselectivity were highest with the *N*-triflylphosphoramide organocatalysts. A screen of reaction solvents

Scheme 2. Catalytic cycle with chiral Brønsted acid.

Table 1
Examples of the organocatalyzed asymmetric Nazarov cyclization[a]

Entry	Substrate	Product	t (h)	Yield (%)	cis/trans	ee (cis), ee (trans)
1	**17**	**18**	1	85	3.2:1	93, 91
2	**19**	**20**	2	92	9.3:1	88, 98
3	**21**	**22**	4.5	68	cis	86, —

[a] Compound **7** (2 mol %), CHCl$_3$, 0 °C.
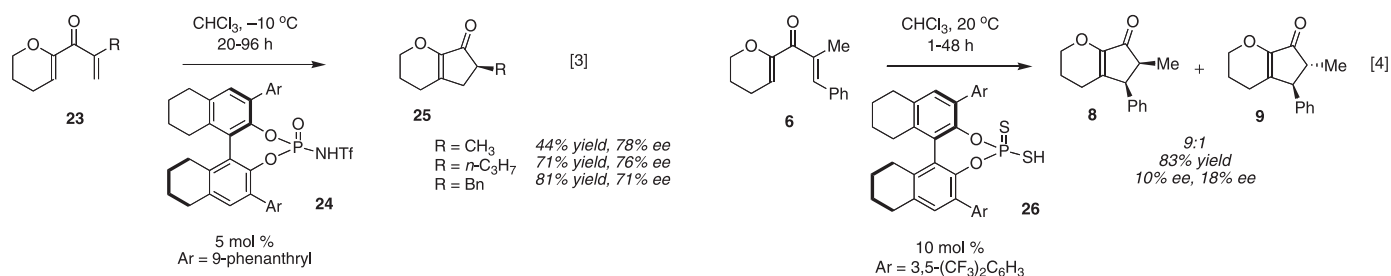
Rueping and Ieawsuwan used the same approach to develop the first organocatalyzed asymmetric electro-cyclization–protonation process,[8] although Trauner and Liang had demonstrated this concept in a metal-catalyzed process (vide infra, Eq. 6). Exposure of enones **23** that lack β-substitution to 5 mol % of phosphoramide **24** at −10 °C leads to products **25** in yields varying between 49% and 93% and ees between 67% and 78% (Eq. 3). The catalytic cycle of this reaction is presumably the same in its essential features as the one that has been summarized in Scheme 2. The key difference between the reactions of Eqs. 1 and 3 is that in Eq. 1 the electrocyclization step takes place enantioselectively and is followed by a diastereoselective kinetic protonation, whereas in Eq. 3 enantioselective protonation of the reaction intermediate is the key step.

Implicit in the preceding discussion is the fact that the optimal catalyst structure is determined empirically through a process of trial and error. To the extent that the changes at two or more sites of the catalyst structure exercise their effects on the optical purity of the product independent of one another, progress toward identifying the optimal catalyst can be rapid. Given the successes of the Rueping group in optimizing the phosphoramide organocatalysts it is somewhat surprising that phosphorodithioic acids were found by Blanchet and co-workers to be poor catalysts for the Nazarov cyclization of **6** and not amenable to optimization (Eq. 4).[9] For example, exposure of dienone **6** to 10 mol % of phosphorodithioic acid **26** in chloroform at 20 °C led to a 9:1 mixture of **8** and **9** in only 10% ee and 18% ee, respectively.
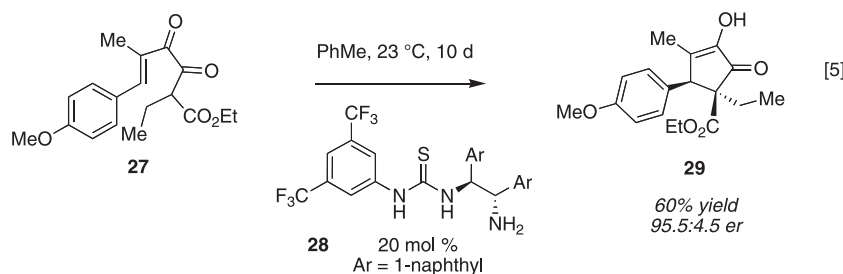
Tius and co-workers developed a mechanistically distinct organocatalytic Nazarov cyclization. Treatment of diketoester **27** with 20 mol % of bifunctional organocatalyst **28** in toluene at 23 °C for 10 days led to cyclopentenone **29** in 60% yield and in an enantiomeric ratio of 95.5:4.5 (Eq. 5).[10] The product was formed as a single diastereomer. A noteworthy feature of this reaction is the formation of products bearing two adjacent asymmetric carbon atoms one of which is an all-carbon quaternary stereocenter. The relative and absolute stereochemistry of both stereogenic carbon atoms is determined during the electrocyclization. The mechanistic hypothesis that accounts for the catalytic action that was proposed by the authors is indicated by structure **30** (Fig. 1). A cooperative process whereby the thiourea engages the ketone carbonyl oxygen atom in a double hydrogen bonding interaction while the primary amine engages the enol form of the β-ketoester as a Brønsted base rationalizes the observation that thiourea organocatalysts lacking a basic amine do not convert substrate to cyclic product. This raises the question of how stereochemical information is transmitted from the organocatalyst to the substrate since several bond lengths separate the stereogenic carbon atoms of the catalyst from the developing carbon–carbon bond. If the mechanism implicit in structure **30** is valid, as it appears to be, the catalyst may be exercising its effect through the imposition of helicity from torsion of the C3–C4 bond.
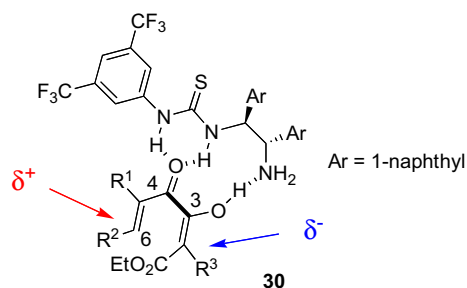

Fig. 1. Cooperative mechanism.

This catalytic system was designed to induce complementary polarization at each of the terminal carbon atoms of the diketoester as indicated in **30**. Exploiting the tendency of the substrate to form only *E* enol so as to minimize electron pair–electron pair repulsions from the enol hydroxyl and ester carbonyl oxygen atoms made it unnecessary to control the geometry of a tetrasubstituted alkene. The product yields varied between 58% and 95%, whereas enantiomeric ratios varied between 90:10 and 98.5:1.5 (Fig. 2). The long reaction times are very likely an indication of strong product inhibition of the catalyst. Since the starting material and the product are both α-hydroxyenones, the organocatalyst can likely engage the product through interactions that are analogous to those indicated for **30**. A limitation of this reaction is the requirement for aryl substitution at C6 that is common for many substrates for the Nazarov reaction.
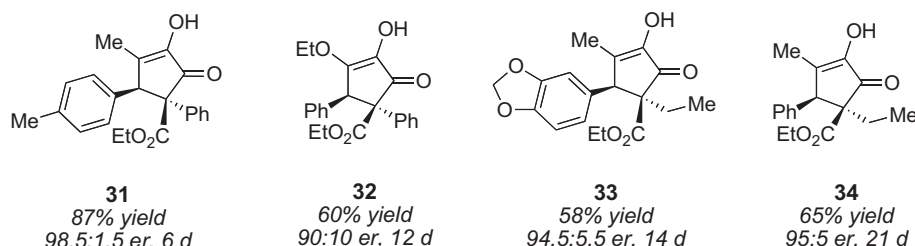
3. Metal catalyzed cyclizations

A larger body of work describes transition metal salt-catalyzed asymmetric Nazarov cyclizations. Trauner and Liang used Sc(OTf)$_3$–PYBOX complex (1*S*,2*R*)-**35** to catalyze the cyclization of dienones **23** to cyclopentenones *ent*-**25** in good yields and optical purities (Eq. 6).[11] As was the case in Eq. 3, the absolute stereochemistry of the products was not determined during the electrocyclization step, but instead during the protonation of the scandium enolate. Sterically more demanding α-substituents R in **23** generally led to products of higher optical purity, as might be expected given the closer proximity of the bulky indane–PYBOX to the α-carbon atom. The influence of the PYBOX ligand is not felt strongly at the β-carbon atoms of the dienone as revealed by the result that is summarized in Eq. 7. A comparison of the results of Eqs. 6 and 7 suggests that the presence of a β methyl group of either configuration in the cyclic enolate reverses the stereochemical outcome of the protonation step. The Nazarov cyclization of **36** is only moderately diastereoselective, leading in 62% yield to *syn* product **37** (40% ee) and in 18% yield to *anti* isomer **38** (79% ee). Trauner has interpreted this result by invoking double diastereoselection during the protonation of the enolate following the electrocyclization. This limitation notwithstanding, Trauner's work represents the first example of catalytic asymmetric Nazarov reactions that proceed with high levels of enantioselectivity. It should also be noted that when the issue of diastereoselectivity was circumvented through the use of **39** (the five membered ring precludes the formation of *anti* product), then a reasonable yield and modest enantioselectivity was observed for product **41** (Eq. 8) under the influence of scandium(III)–PYBOX catalyst **40**.[12]

Fig. 2. Examples of cyclizations catalyzed by **28**.

[8]

39

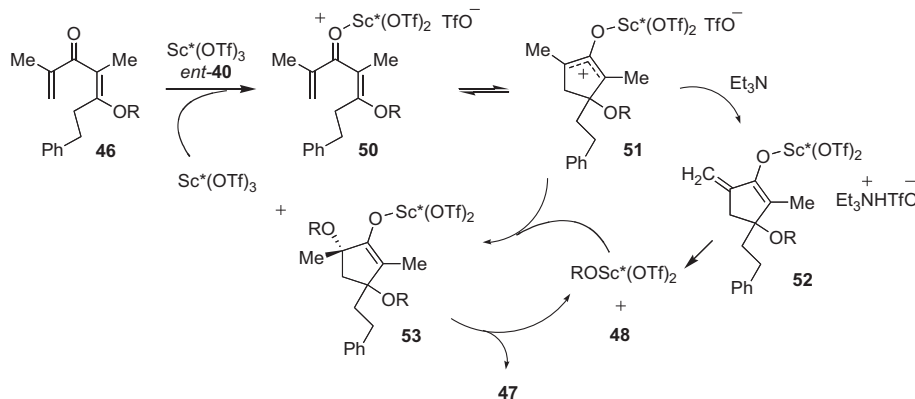**40**   20 mol %

41

53% yield
61% ee
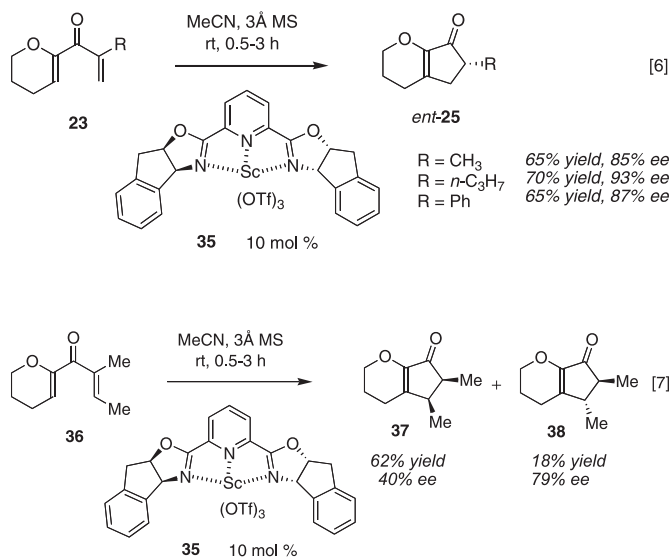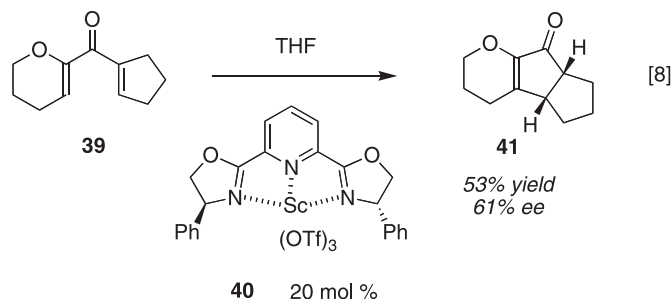
Transition metal BOX and PYBOX complexes are attractive structural motifs for catalysts, providing the substrate can offer an opportunity for bidentate chelation with the metal. Ma and co-workers have described a tandem enantioselective Nazarov cyclization–electrophilic fluorination sequence that leads to fluoroindanones (Eq. 9).[13] Development of a tandem process introduces another element of complexity to the process. In Ma and co-workers' reaction, fluorination of the enolate represents the termination step of the process. Exposure of phenone **42** to *N*-fluorobenzenesulfonimide **43** and 10 mol % Cu(II)–BOX complex **44** for 8 h at 80 °C in 1,2-dichloroethane led to fluoroindanones **45**. Although it is difficult to make generalizations on the basis of the three examples of the asymmetric version of the process that Ma and co-workers have reported, it appears that all reactions show excellent *trans* selectivity and that the optical purity of the product is highest in the case in which the β-aryl group in **42** is 2,4,6-trimethoxyphenyl. The synthesis of a fluorine-substituted quaternary carbon atom in high optical purity that has been described in this work is noteworthy.
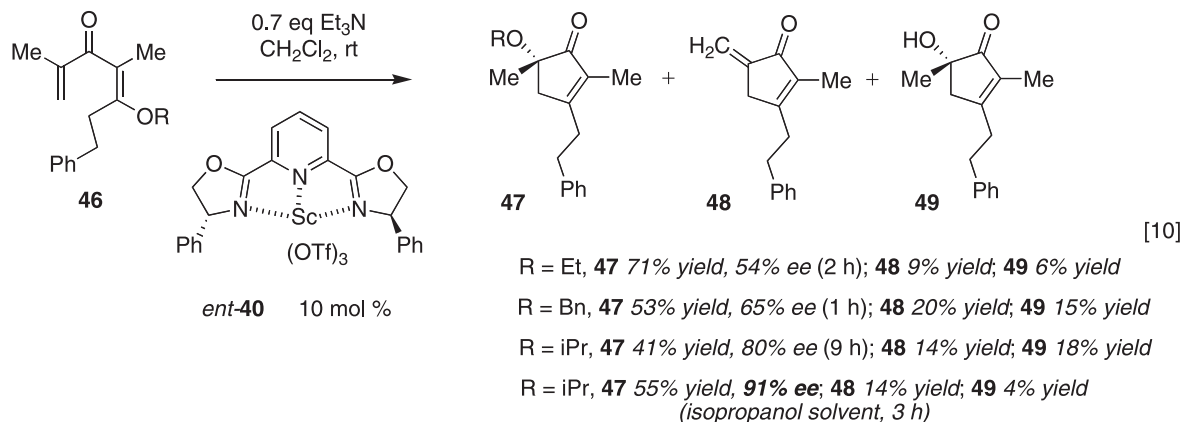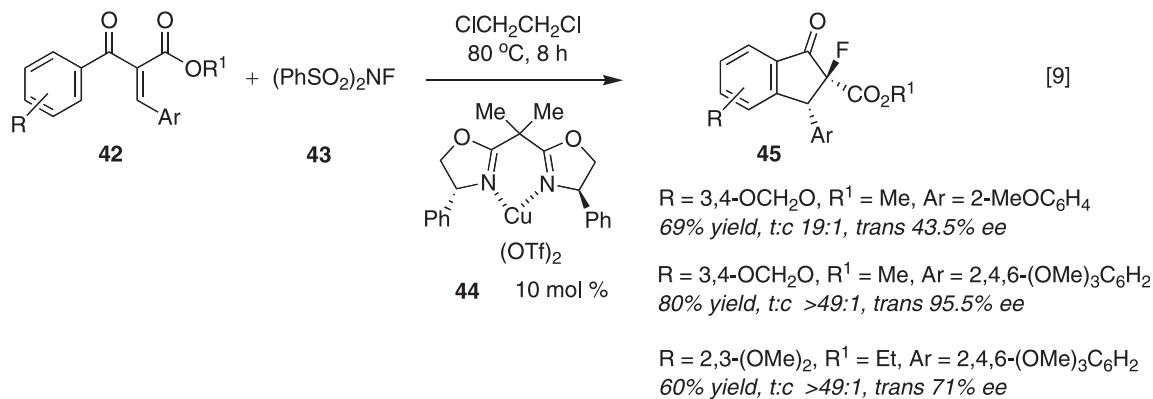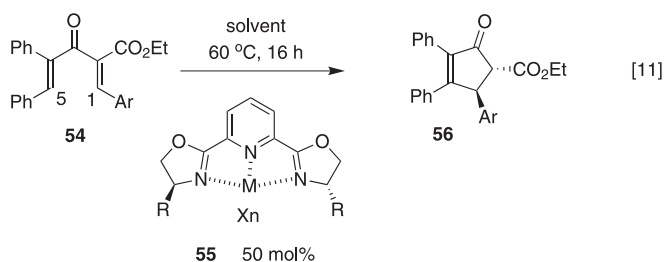
Shindo and Yaji have reported a Sc(OTf)$_3$–PYBOX catalyzed asymmetric Nazarov reaction that appears to proceed through a unique mechanism.[14] Exposure of dienone **46** to 10 mol % of *ent*-**40** and 0.7 equiv of triethylamine in dichloromethane at room temperature led to a mixture of optically enriched cyclopentenone **47** and byproducts **48** and **49** (Eq. 10). Triethylamine was found to be necessary so as to reduce the catalyst loading. The apparent migration of the alkoxy group from the β-carbon atom in **46** to the α-tertiary carbon atom in **47** is at first glance puzzling, but the appearance of byproducts **48** and **49** leave little doubt concerning the mechanism, which corresponds to an interrupted Nazarov cyclization. Scheme 3 summarizes the catalytic cycle proposed by Shindo and Yaji. Complexation of *ent*-**40** with **46** leads to pentadienyl cation **50** that undergoes electrocyclization to oxyallylic cation **51**. This intermediate partitions between elimination that proceeds via **52** leading ultimately to cross-conjugated cyclopentadienone **48** and nucleophilic trapping of **51** by alkoxide leading through **53** to major product **47**. By means of crossover experiments intermolecular alkoxy migration was also shown to occur, providing an alternative pathway for the conversion of **51** to **47**. Byproduct **49** is presumably the result of trapping of **51** by adventitious water. According to this mechanism, the absolute sense of the electrocyclization step is probably not under catalyst control, whereas the termination step that leads from **51** to **53** is. In this sense the process resembles the reactions of Eqs. 6 and 9. The yields for the α-alkoxycyclopentenones varied from 34 to 71%, whereas ees varied between 0% and 91%. Controlling the stereochemical outcomes of both electrocyclization and trapping steps using a single catalyst would make it possible to form two stereogenic carbon atoms during the reaction, a process that would be very valuable in synthesis.

42   **43**

ClCH$_2$CH$_2$Cl
80 °C, 8 h

44   10 mol %

45

[9]

R = 3,4-OCH$_2$O, R^1 = Me, Ar = 2-MeOC$_6$H$_4$
69% yield, t:c 19:1, trans 43.5% ee

R = 3,4-OCH$_2$O, R^1 = Me, Ar = 2,4,6-(OMe)$_3$C$_6$H$_2$
80% yield, t:c >49:1, trans 95.5% ee

R = 2,3-(OMe)$_2$, R^1 = Et, Ar = 2,4,6-(OMe)$_3$C$_6$H$_2$
60% yield, t:c >49:1, trans 71% ee

46

0.7 eq Et$_3$N
CH$_2$Cl$_2$, rt

ent-**40**   10 mol %

47   +   **48**   +   **49**

[10]

R = Et, **47** *71% yield, 54% ee* (2 h); **48** *9% yield*; **49** *6% yield*

R = Bn, **47** *53% yield, 65% ee* (1 h); **48** *20% yield*; **49** *15% yield*

R = iPr, **47** *41% yield, 80% ee* (9 h); **48** *14% yield*; **49** *18% yield*

R = iPr, **47** *55% yield, **91% ee***; **48** *14% yield*; **49** *4% yield*
(isopropanol solvent, 3 h)

Scheme 3. Catalytic cycle of the Sc(OTf)$_3$–PYBOX catalyzed process.

Ar = 2-naphthyl, R = *t*-Bu, solvent = PhMe; *40% yield, **93% ee***
MX$_n$ = Fe(OTf)$_2$

Ar = Ph, R = iPr, solvent = CH$_2$Cl$_2$:hex (1:2); *76% yield, 78% ee*
MX$_n$ = Co(ClO$_4$)$_2$·6H$_2$O

Ar = 4-CF$_3$C$_6$H$_4$, R = *t*-Bu, solvent = CH$_2$Cl$_2$:hex (1:2); *23% yield, 61% ee*

MX$_n$ = Fe(ClO$_4$)$_2$·6H$_2$O

Asymmetric Nazarov cyclizations catalyzed by Fe(II)- and Co(I)–PYBOX complexes have been described by Itoh and co-workers.[15] Exposure of triaryl pentadienone **54** to 50 mol % of the Fe(II) or Co(I) catalyst **55** led to the expected product **56** (Eq. 11). It appears that the C5 phenyl group in **54** is required and that electron poor aryl groups at C1 lead to low yields of cyclized product. Yields varied between 13% and 85%, whereas ees varied from 0 to 93%. It appears that this protocol may be limited to the subset of strongly polarized acyclic dienones. The high catalyst loadings may discourage its widespread adoption in synthesis.

A relatively small number of structural motifs of the metal ligand have been explored. The limitations of the BOX and PYBOX catalysts that are manifest in the earlier discussion led Tang and co-workers to develop a tris(oxazoline) ligand for Cu(II).[16] They had hypothesized that incorporating a capping group into the structure of the BOX ligand would improve the enantiocontrol by extending the influence of the complex to the distal carbon atoms of the pentadienyl cation. A series of DFT calculations were not definitive, so the precise role of the capping group remains unknown. Nevertheless, the catalysts derived from the tris(oxazolines) proved to be highly effective both in terms of yield as well as enantioselectivity. All of the tris(oxazoline) ligands that were evaluated led to higher yields and far better optical purities of product than could be obtained from **35** or **55** (R=iPr, MX$_n$=Cu(SbF$_6$)$_2$). For example, following treatment of divinyl β-ketoester **57** (Eq. 12) at 25 °C with the cationic Cu(II) complex derived from tris(oxazoline) **59**, cyclopentenone **60** was formed in 90% yield and in 92% ee as essentially a single diastereomer (>99:1). A relatively small diminishment in yield and optical purity was observed when the diastereomeric ligand **58** was used in which the stereochemistry of the pendent indane–oxazoline is enantiomeric to that in **59**.

Catalyst loadings were modest (10 mol %) but the reaction times varied according to the electronic nature of the aryl substituent: cyclization of dienones bearing electron poor aryl groups were much slower than substrates bearing electron rich aryl rings. It is very significant that the aryl group in the substrate is not required and that the cyclization of **57** to **60** (R=cyclohexyl) in the presence of **59** took place in 88% yield (at 50% conversion) and 78% ee after 10 days at 40 °C in 1,2-dichloroethane. The complementary activation that is provided by the enol ether and the ester groups in **57** is sufficient to ensure that reaction takes place at a reasonable rate.
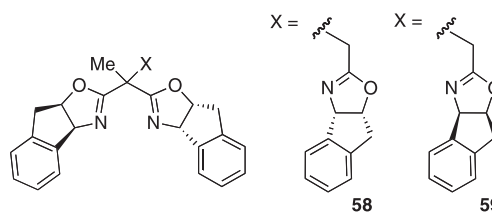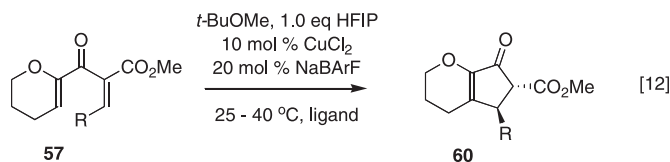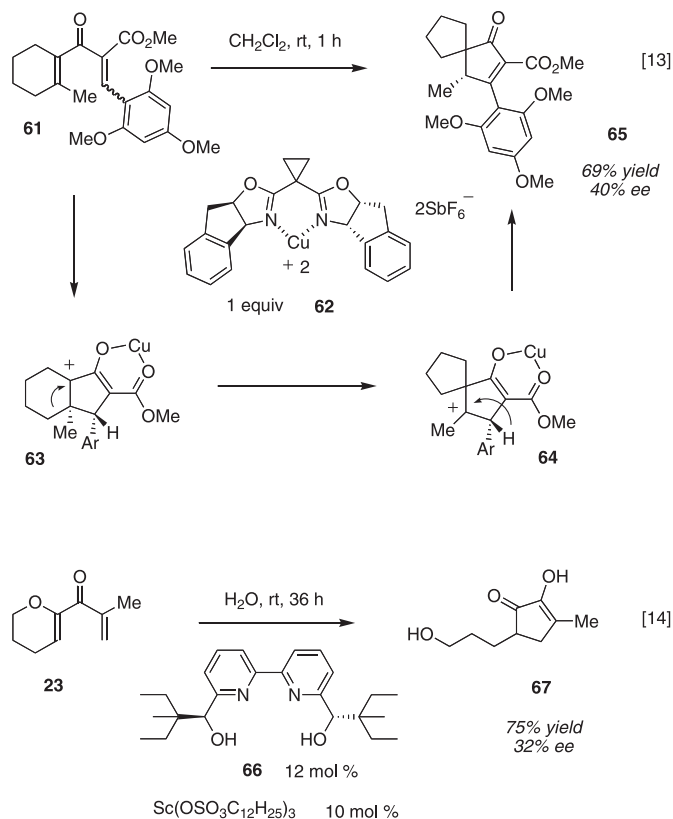

R = Ph, ligand = **59**, 20 h; *90% yield, 92% ee, dr >99:1*

R = Ph, ligand = **58**, 20 h; *73% yield, 85% ee, dr >99:1*

R = cyclohexyl, ligand = **59**, 10 d; *88% yield, 78% ee*

Since the Nazarov cyclization proceeds through the intermediacy of carbocations it should not be surprising that Wagner/Meerwein rearrangements can take place prior to the termination step. Indeed, such rearrangements are most often seen when the cyclization generates a quaternary carbon atom. Frontier and Huang have reported an interesting example of this chemistry (Eq. 13).[17] Treatment of ketoester **61** with stoichiometric Cu(II) complex **62** led to spirocyclic product **65** in 69% yield in 40% ee. The initial cyclization to **63** is presumably followed by C–C bond migration to produce carbocation **64**. [1,2]-Hydride migration converts **64** to **65**.

Kobayashi and Kokubo have described a radically different catalyst system.[18] Dodecylsulfate scandium (Sc(DS)$_3$) was developed as a water-compatible Lewis acid as a part of a broader exploration of the use of water as a solvent for chemical reactions. This surfactant catalyst creates a hydrophobic environment in water in which reaction takes place. When dienone **23** was treated for 36 h in water at room temperature with a catalyst prepared from 10 mol % Sc(DS)$_3$ and homochiral bipyridine **66**, Nazarov cyclization took place
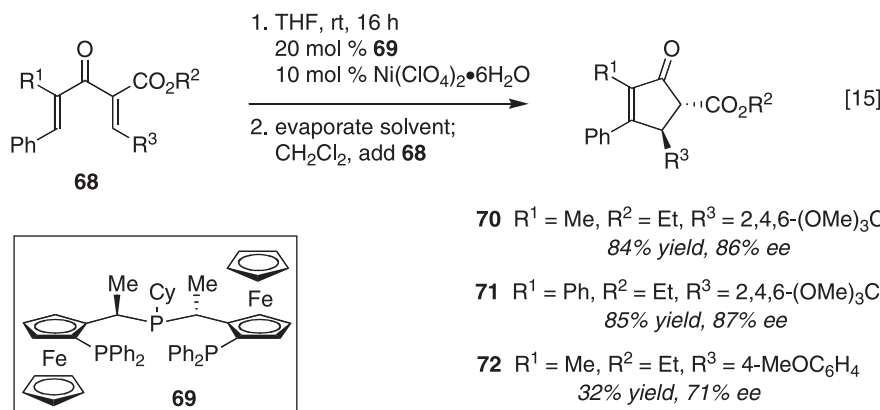
the substrate. Likewise, exposure of **68** (R^1=Ph, R^2=CH_2CH_3, R^3=2,4,6-trimethoxyphenyl) led to **71** in 85% yield and 87% ee. However, **68** (R^1=CH_3, R^2=CH_2CH_3, R^3=4-methoxyphenyl) led to product **72** in only 32% yield and in 71% ee after 9−15 days reaction time. Erosion of both yield and optical purity of the product was also observed for the cases in which R^2=Bn or R^2=1-naphthyl (both R^1=CH_3, R^3=2,4,6-trimeth-oxyphenyl). In the case of R^2=1-naphthyl no reaction took place after 1 month.

Togni's work highlights several of the challenges that are commonly encountered. The lack of reactivity of the ligated Lewis acidic metal makes it necessary to use highly activated substrates, such as **68**, thereby limiting the reaction scope. Even with reactive substrates a complete reaction requires 1−2 weeks with 10 mol % catalyst. A ^{31}P NMR study showed that the major Ni(II)−Pigiphos species that was observed during the reaction corresponded to the catalyst−product adduct. This provides an indication that the concentration of active catalyst remained very low and identifies the problem as product inhibition. These two problems, low catalyst reactivity and product inhibition, have contributed to the difficulty in defining a general and efficient catalytic asymmetric Nazarov cyclization.

4. Stoichiometric reactions

There are a small number of Nazarov reactions that make use of stoichiometric or nearly stoichiometric chiral effectors again underscoring the problem of product inhibition of the catalytic cycle. Aggarwal and Belfield have described one such stoichiometric (or nearly stoichiometric) process (Eq. 16).[20] Treatment of ketoester **73** (R=CH_3) with 1 equiv of the Cu(II) hexafluoroantimonate adduct of PYBOX ligand **74** at room temperature in dichloromethane led to product **75** in 73% yield and 76% ee. Yield and enantioselectivity both improved for the reaction leading to **76** (98% yield, 86% ee). As anticipated, the presence of the additional phenyl group resulted in activation of the acyclic substrate. This
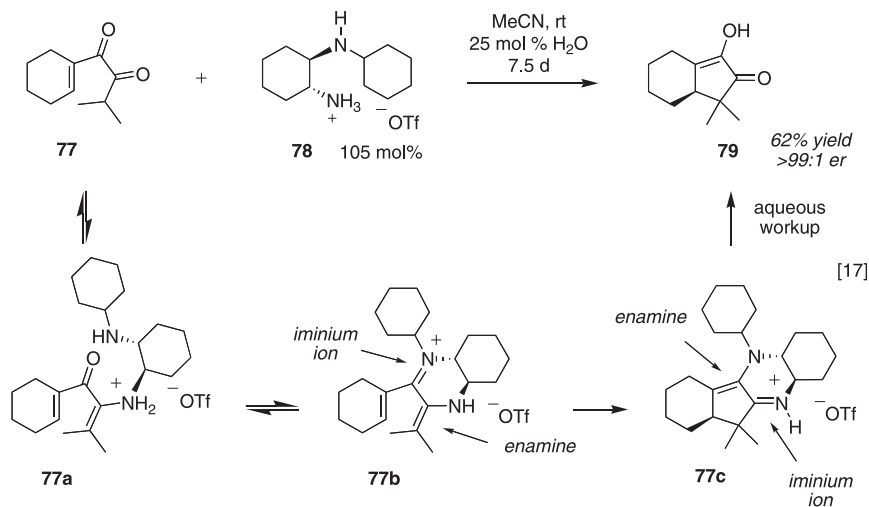
followed by trapping of the intermediate cation by water (Eq. 14). This resulted in cleavage of the dihydropyran ring and the formation of α-diketone **67** that was isolated in 75% yield in 32% ee.

68

70 R^1 = Me, R^2 = Et, R^3 = 2,4,6-$(OMe)_3C_6H_2$
84% yield, 86% ee

71 R^1 = Ph, R^2 = Et, R^3 = 2,4,6-$(OMe)_3C_6H_2$
85% yield, 87% ee

72 R^1 = Me, R^2 = Et, R^3 = 4-$MeOC_6H_4$
32% yield, 71% ee

Togni and Walz have reported a thorough exploration of an asymmetric Ni(II)-catalyzed Nazarov cyclization (Eq. 15).[19] Togni had demonstrated through his earlier efforts the Lewis acidic properties of dicationic Ni(II)−Pigiphos (**69**) in diverse reactions, therefore the application of this catalyst system to the Nazarov cyclization represented a logical extension of his earlier work. A preliminary solvent screen indicated that dichloromethane was optimal and furthermore that the strongly coordinating acetonitrile completely suppressed the reaction. Exposure of **68** (R^1=CH_3, R^2=CH_2CH_3, R^3=2,4,6-trimethoxyphenyl) to 10 mol % Ni(II)−Pigiphos in dichloromethane led to **70** in 84% yield in 86% ee after 6−8 days reaction time. The catalyst was prepared in tetrahydrofuran but the solvent was evaporated and replaced with dichloromethane prior to the addition of

became clearer from the results of the reaction that used substoichiometric Cu(II) complex. When **73** (R=CH_3) was treated with 0.5 equiv of reagent the yield of **75** dropped to 42%, whereas the

75 R = Me *73% yield, 76% ee*
76 R = Ph *98% yield, 86% ee*
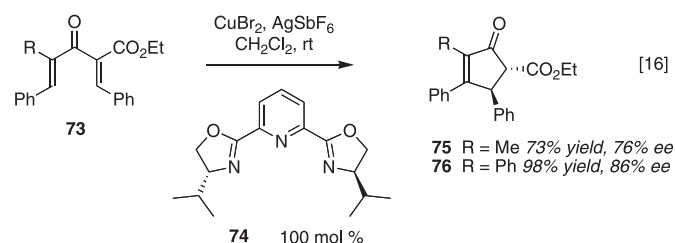
optical purity of product increased slightly to 78% ee. By contrast when **73** (R=Ph) was treated with 0.5 equiv of the Cu(II) complex the optical purity of **76** was unaltered (86% ee) and the yield was essentially the same (96%), indicating that the catalyst had turned over once. This reaction is subject to the same limitations that have been disclosed earlier in this review: in the absence of phenyls at both distal carbon atoms of **73**, erosion of either the yield or the optical purity, or both, is observed. Aggarwal and Belfield observed similar trends with substrates bearing the N,N-diethylamide group in place of the carboethoxy group in **73**. Their work is noteworthy as it represents the first asymmetric Nazarov cyclization that is promoted by a chiral non-racemic Lewis acid complex and that achieves high levels of enantioselectivity.

Tius and co-workers adopted a different approach making use of iminium ion catalysis that provides an attractive strategy for controlling the absolute stereochemical outcome of the Nazarov cyclization.[21] Unfortunately, absent some compensating factor, the acyclic iminium ion that is derived from the pentadienone is energetically favored over the cyclic allylic cation. This problem of unfavorable energetics was overcome through the use of diamine mono-triflate **78** (Eq. 17). Exposure of α-diketone **77** to 1.05 equiv of **78** in wet acetonitrile at room temperature led to slow consumption of the starting material with the formation of cyclic product **79** in 62% yield in >99:1 er after a reaction time of 7.5 days. The diamine could be isolated and reused without erosion of the optical purity of the product. This reaction presumably succeeds by engaging both carbonyl groups of **77** with reagent **78** to form enamine–iminium species **77b**. Following cyclization, enamine–iminium species **77c** is formed, rendering the energetics of the cyclization favorable. Cyclopentenone **79** is liberated from the complex with **78** during aqueous workup. Notably this Nazarov cyclization leads to products in very high optical purity and in moderate yield even in the absence of activating aryl substituents. Shortcomings of the process are that it is not completely general and it is very slow.

separation of diastereomeric carbamates derived from (S)-(1-phenylethyl)isocyanate. This reaction took place with no erosion of optical purity, indicating that the trimethylsilyl group in **80** directed the electrocyclization in an anti-$S_{E'}$ sense with essentially perfect control. The observed absolute sense of the conrotation is the one that allows continuous overlap of the C–Si bond with the developing allyl cation. The trimethylsilyl substituent is lost during the termination step of the cyclization leading to the exocyclic (with respect to the five membered ring) double bond in **81**.

Tius and co-workers first demonstrated axial to tetrahedral chirality transfer from an allene during the Nazarov cyclization

[18]

80   86% ee

81

72% yield
86% ee
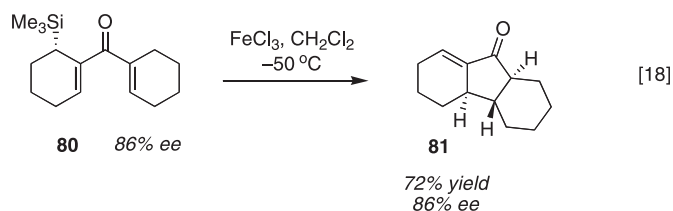
(Eq. 19).[23] The enantiomers of morpholino enamide **82** were separated by semi-preparative HPLC. Exposure of **82** (93% ee) to vinyllithium species **83** in tetrahydrofuran at −78 °C provided a mixture of cyclopentenones **84** (R=n-Bu, 50% yield, 78% ee) and **85** (R=n-Bu, 9% yield, 64% ee). The tetrahedral intermediate **83a** was presumably converted to allenyl ketone **83b** during workup with aqueous potassium dihydrogen phosphate. Cyclization of **83b** to a mixture of diastereomers **84** and **85** took place spontaneously. Major product **84** was formed with 84% asymmetry transfer. As predicted, asymmetry transfer of >95% was observed when allenamide **86** was used as the starting material: the preferred sense of conrotation is the one that maintains the greatest

[17]

77 + **78** 105 mol%   →   **79**   62% yield   >99:1 er

77a ⇌ **77b** → **77c**

5. Asymmetry transfer

There are a few examples that demonstrate transfer of asymmetry during the Nazarov cyclization. The first example was provided by Denmark and co-workers who showed that cyclization of optically active β′-silyldivinyl ketone **80** (Eq. 18) under the influence of ferric chloride led to conrotatory ring closure to provide tricyclic ketone **81** in 72% yield.[22] The optically enriched starting material for the synthesis of **80** was prepared by chromatographic

distance between the substituent on the exocyclic methylene carbon atom (n-Bu or t-Bu) and the substituent on the sp³-hybridized ring carbon atom. This preference for the Z exocyclic double bond isomer is kinetic, since complete isomerization to the E isomer could be induced to take place. The lower optical purity of **85** (R=n-Bu) is a consequence of Z to E isomerization of **84** (R=n-Bu) that took place during column chromatography of the product mixture on silica gel.

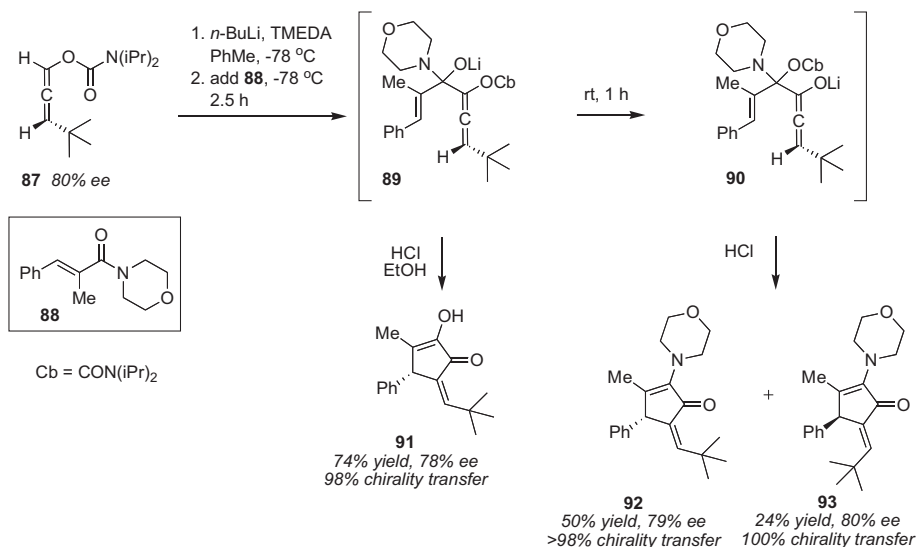An indication of mechanistic complexity that can be encountered in these reactions was manifested in work of Hoppe

[19]
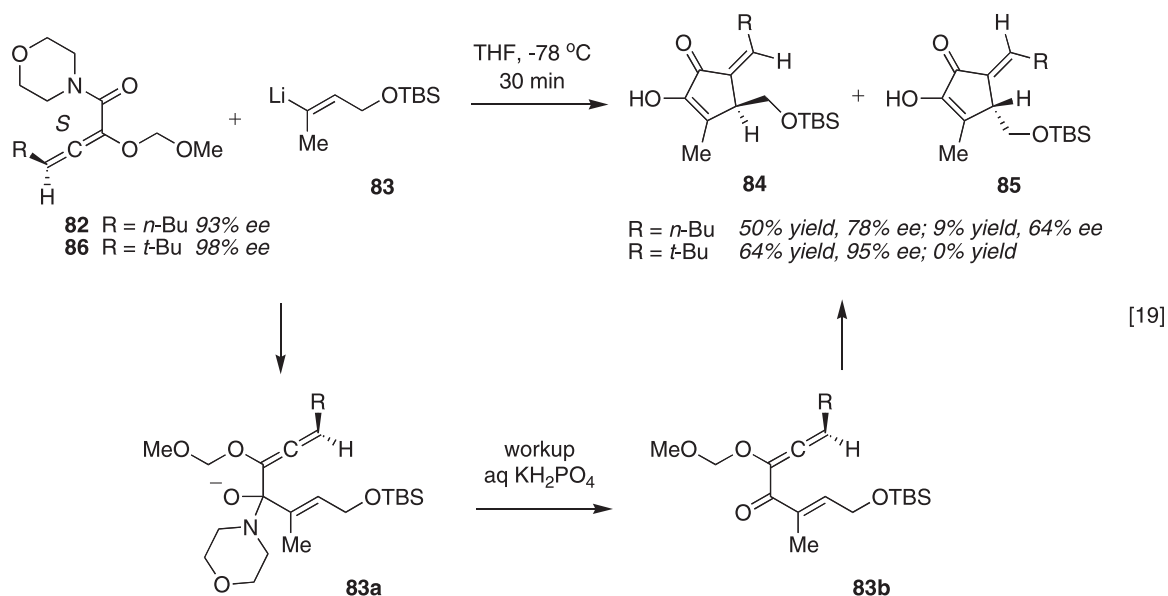
and co-workers (Scheme 4).[24] Although there is at present no effective asymmetric synthesis of allenamides, such as **82** or **86**, Hoppe and co-workers had demonstrated a highly efficient asymmetric synthesis of enantiomerically enriched allenyl carbamates based on the (−)-sparteine-mediated isomerization of propargylic carbamates. Allenyl carbamate **87** (80% ee) was deprotonated with *n*-butyllithium/TMEDA in toluene. Deprotonation took place regiospecifically, directed by the carbamoyl group. The lithioallene is internally chelated and is configurationally stable. Addition of the lithioallene to morpholino enamide **88** at −78 °C led to presumptive intermediate **89**. When the solution of **89** at −78 °C was transferred to ethanolic HCl solution at low temperature, Nazarov product **91** was isolated in 74% yield and 78% ee, representing 98% asymmetry transfer from **87**. This is the product that one would have predicted based on the results shown in Eq. 19. If, however, the solution of **89** was allowed to warm to room temperature over the course of an hour before quenching with HCl, the outcome of the reaction was quite different. α-Morpholino cyclopentenones **92** and **93** were isolated in 50% yield (79% ee) and 24% yield (80% ee),

respectively. Complete or nearly complete asymmetry transfer was observed in both products. Hoppe and co-workers suggested that upon warming the solution of **89**, 1,2-migration of the carbamoyloxy group took place to produce a mixture of diastereomers of **90**. Each diastereomer produced a single product, either **92** or **93**. Whereas the stereochemical outcome of the cyclization that led to **91** was determined only by the axial chirality of the allene, in the case of **92** and **93** it was the stereochemistry of the tetrahedral carbon atom in **90** that controlled the reaction outcome. Hoppe and co-workers interpreted these results to suggest that the cyclization of **90** corresponds to a conrotatory process.

Hoppe and co-workers have demonstrated that this process is general. For example, enantiomerically pure carbamoyloxy allene **94** was deprotonated at −78 °C and was added to enone **95** (Eq. 20).[25] After 1 h, the reaction mixture was warmed to room temperature for 1 h and was subsequently quenched with saturated aqueous ammonium chloride. This led to cyclopentenone **96** in 33% yield as the major product. None of the *E* geometrical isomer of **96** was observed, although other reaction products were


Scheme 4. Mechanistic complexity in the carbamoyloxy allene Nazarov cyclization.

[20]

94

Cb = CON(i-Pr)$_2$

95

96
33% yield
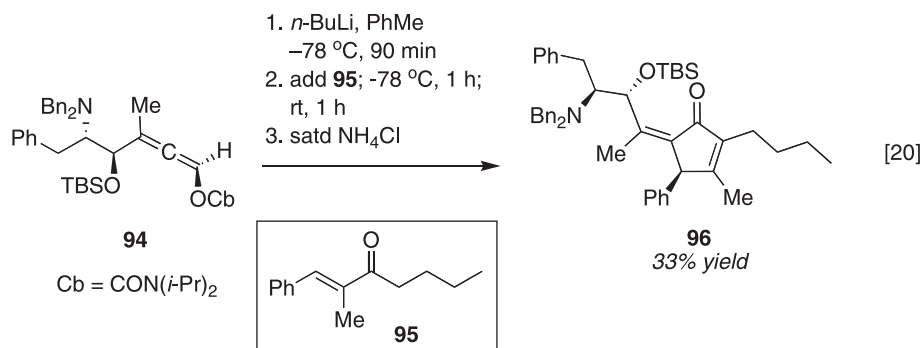
formed. It seems unlikely that the addition of the lithioallene derived from **94** to enone **95** took place with complete diastereoselectivity. The isolation of a single isomer in moderate yield suggests that only one of the tetrahedral intermediates was able to undergo cyclization. This reaction is noteworthy not only because of the structural complexity of allene **94**, but also because it demonstrates simultaneous control of the absolute stereochemistry of the ring carbon atom and control of the geometry of the exocyclic double bond.

6. Diastereoselective Nazarov cyclizations of non-racemic precursors

A modest number of examples have been reported in which a Nazarov cyclization has been performed on a chiral, non-racemic substrate. Williams and co-workers[26] have reported the total synthesis of (+)-fusicoauritone that makes use of a diastereospecific Nazarov cyclization in the key step. The cyclization of α-diketone **97** took place in the presence of boron trifluoride etherate in 1,2-dichloroethane at reflux to produce cyclic product **98** in 77% yield (Eq. 21).[27]

[21]

97

98
77% yield

99
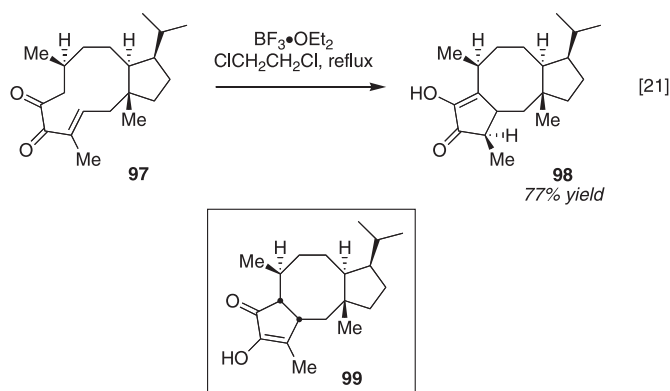
Williams and co-workers reported that their early efforts had led to mixtures of **98** and isomeric α-diketone **99**. Exposure of **99** to boron trifluoride etherate led to **98** suggesting that **99** was the kinetic product, whereas **98** was the result of thermodynamic equilibration of **99**. For the purposes of the (+)-fusicoauritone synthesis, divinyl ketone **100** was prepared (Eq. 22) and was exposed to catalytic tosic acid in 1,2-dichloroethane to produce enone **101** in 92% yield as a mixture of C6 diastereomers. Epimerization at C6 took place readily through the formation of the extended enol. This reactivity was exploited in the fusicoauritone synthesis. Autoxidation of chloroform solutions of the enol led to the C6 hydroperoxide that was reduced to the alcohol in 95% overall yield for the two steps from **101**.
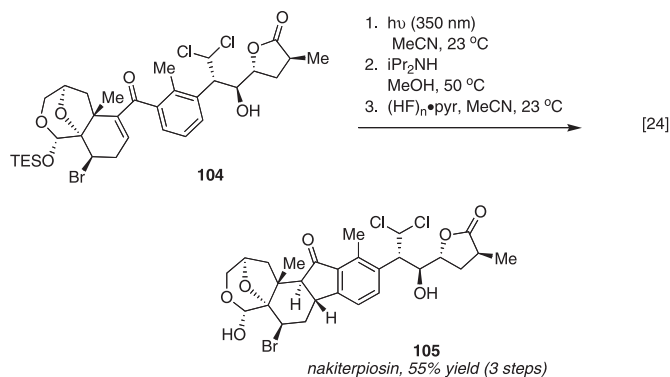

[22]

100

101
92% yield
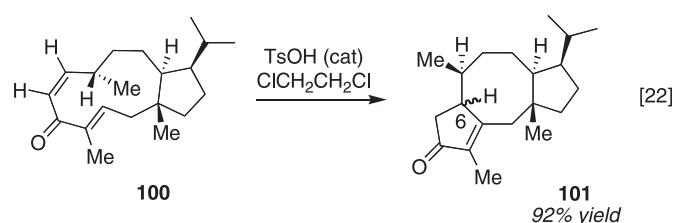
The synthesis of marine sponge metabolite nakiterpiosin made use of a rarely utilized photochemical Nazarov reaction of a phenone. Gao and co-workers prepared phenone **102** through a carbonylative Stille reaction (Eq. 23).[28]

[23]

102
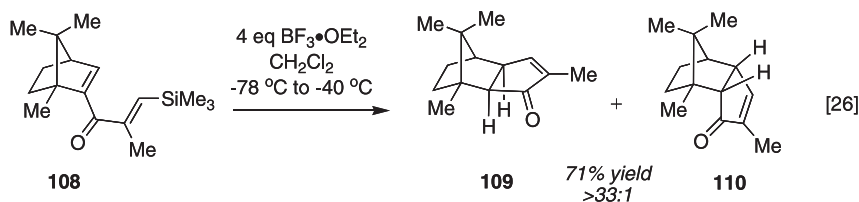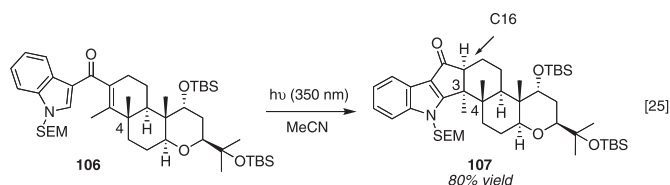
103
60% yield (2 steps)
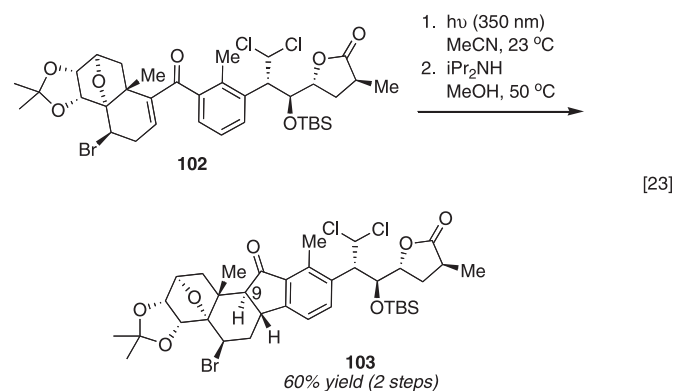
Irradiation of a solution of **102** in acetonitrile at 350 nm led to a 1:1 mixture of C9 epimers of the desired Nazarov product. Brief exposure of this mixture to Hünig's base in methanol at 50 °C led to the *trans* ring fused product **103** in 60% yield for the two steps. In subsequent work, Chen and co-workers improved their original nakiterpiosin synthesis by deferring the photochemical step to the very end of the synthesis.[29] Irradiation of phenone **104** at 350 nm (Eq. 24) under the same conditions as were used for **102**, followed by epimerization and fluorodesilylation led to nakiterpiosin **105** in 55% yield for the three steps. The success of this stereospecific photochemical Nazarov cyclization in the context of the polyfunctional nakiterpiosin precursor **104** testifies to the mildness of the conditions.

Giannis and co-workers reported a conceptually related photochemical Nazarov cyclization in their recent synthesis of terpendole E analogues.[30] Protected 3-indole ketone **106** (Eq. 25) was irradiated at 350 nm in acetonitrile to produce cyclopentenone **107** in 80% yield as a single diastereomer. The angular methyl group at C4 probably determines the stereochemistry of the product of Eq. 25, ring closure taking place so as to move the
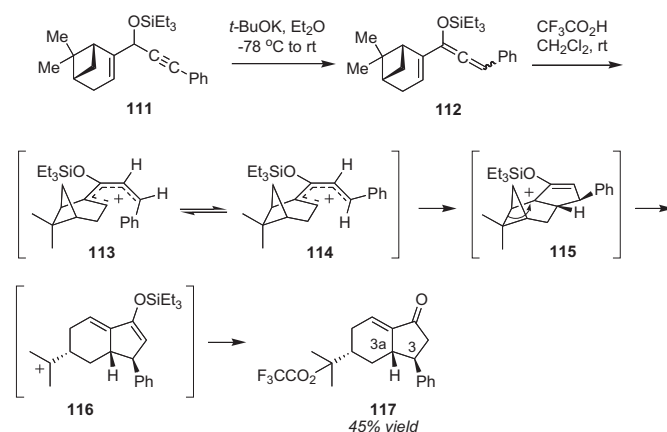
[24]

104

105
nakiterpiosin, 55% yield (3 steps)

When one of the alkene groups of the dienone is part of a bridged, bicyclic system, conrotation is inevitably driven to minimize steric interactions. This was clearly seen in West and co-workers' results with bornenyllithium-derived dienone **108** (Eq. 26) that cyclized to produce *exo* cyclopentenone **109** as the nearly exclusive reaction product.[35] The trimethylsilyl group in **108** controls the location of the double bond in the enone product. The strong preference for *exo* diastereomer **109** is consistent with the observed preference for *exo* addition of electrophiles to norbornene. West and co-workers pointed out that although the interactions of the distal carbon atoms of the pentadienyl cation that is derived from **108** are not completely analogous to an electrophilic addition to norbornene, the process should be subject to the same constraints and should therefore be expected to lead to the same stereochemical outcome. This was certainly the case.

Under the appropriate reaction conditions it is sometimes possible to couple the Nazarov cyclization with subsequent reactions that exploit the reactivity of the intermediate cation. West and Wu have demonstrated the Nazarov/Wagner/Meerwein cascade process that is summarized in Scheme 5.[36] Propargyl silyl ether **111** was derived in a straightforward sequence of steps from (−)-myrtenal. Base-catalyzed isomerization of **111** to allenyl ether **112** was followed by exposure to trifluoroacetic acid in dichloromethane at room temperature. This led to the production of enone **117** in 45% overall yield from **111**. The *cis* relative stereochemistry of the phenyl group at C3 and the hydrogen atom at C3a indicates that sterically controlled protonation of the allenyl ether to produce pentadienyl cation **113** as the initially formed product was
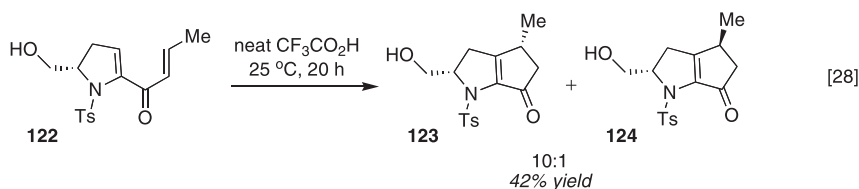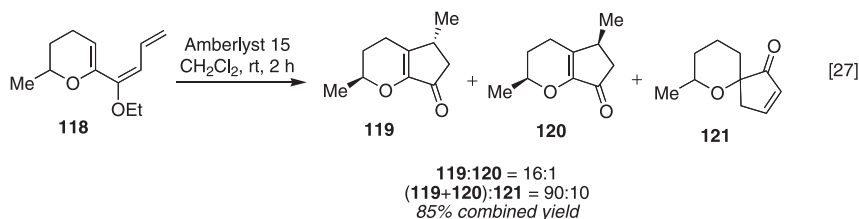
methyl group at C3 away, leading to the *trans* relationship of the two adjacent angular methyl groups in **107**. The stereochemistry at C16 was determined during the proton transfer step that took place following cyclization.

[25]

106

107
80% yield

[26]

108

109 71% yield >33:1

110

The mechanism of the photochemical Nazarov cyclizations of Eqs. 23–25 deserves some comment. It is known that in the case of cyclic cross-conjugated dienones ring size influences the mechanism.[31,32] In 4,4-disubstituted 2,5-cyclohexadienones the photochemical Nazarov cyclization takes place from an electronically excited state by means of a disrotation, as predicted by the orbital symmetry rules. However, medium-sized ring cross-conjugated dienones have been shown to follow a different pathway in which photochemical *Z* to *E* isomerization of one of the two double bonds of the dienone leads to a highly strained ground state intermediate that undergoes a thermal Nazarov electrocyclization. Both the disrotatory ring closure from the excited state of the dienone as well as the conrotatory process from the strained *E* isomer of the ground state would lead to the same stereoisomer of the product.[33] 1-Cyclohexenyl(phenyl) methanone has been shown to undergo photochemical *Z* to *E* isomerization followed by thermal ring closure.[34] This suggests that irradiation of ketones **102**, **104**, and **106** also results in thermal, conrotatory ring closure from a highly distorted ground state intermediate. The sense of conrotation cannot be ascertained from the structures of the respective products **103**, **105** or **107**. The unique advantage of the photochemical Nazarov cyclization is that it makes it possible to selectively activate the enone function under neutral conditions within a large, polyfunctional molecule.

111 **112**

113 **114** **115**

116 **117**
45% yield

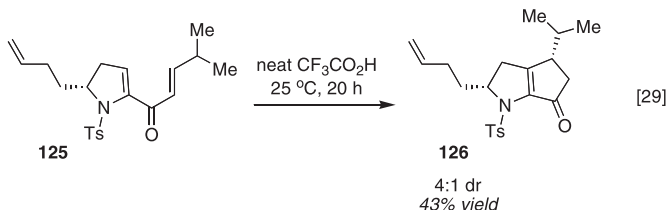**Scheme 5.** Nazarov/Wagner/Meerwein cascade process.

followed by *Z* to *E* isomerization to give cation **114**. Conrotatory ring closure of **114** took place to produce cation **115** that rearranged to **116** in order to relieve the strain of the cyclobutane ring. Trapping of **116** with trifluoroacetate and silyl enol ether hydrolysis led to **117**. The sense of conrotation of **114** was apparently controlled by the *gem*-dimethyl substituted bridge and took place so as to move the phenyl group away from the methyl. The

counterintuitive consequence of this is that the cyclization then occurs from the same side of the pentadienyl cation as the *gem*-dimethyl substituted bridge.

There are significant ambiguities that render the incorporation of such diastereoselective reactions into synthetic planning a challenge. Prandi and co-workers have nonetheless marked some significant accomplishments in the area. The protonation of racemic triene **118** led to a pentadienyl cation that underwent Nazarov cyclization to a mixture of diastereomeric enones **119** and **120** in a 16:1 ratio (Eq. 27).[37] Spiroenone **121** is the product of an alternative Nazarov cyclization and accounted for 10% of the total product mixture. Major product **119** is the result of conrotation toward the pyran ring and does not correspond to the isomer that one would have predicted from the example of Scheme 5. Prandi and Occhiato do not offer an explanation for this observation beyond a suggestion that the sense of conrotation in this example may result from the interplay of steric and stereoelectronic factors. This is apparently also the case for the Nazarov cyclization of homochiral dienone **122** (Eq. 28); however, in this example it is the *syn* diastereomer **123** that is the major reaction product.

7. Chiral auxiliaries in the Nazarov cyclization

Pridgen and co-workers reported the first asymmetric Nazarov cyclization controlled by a chiral auxiliary group in 1999.[39] Their work was motivated by the need for a practical and scalable asymmetric synthesis of indane endothelin receptor antagonists. The synthesis of starting materials **127a**−**c** followed a conventional strategy that made use of a Knoevenagel condensation with piperonal (Table 2). The phenyl- and isopropyl oxazolidinones **127a** and **127b** both underwent cyclization in dichloromethane or toluene at 0 °C in the presence of tin tetrachloride to produce **128a** or **128b**, respectively, as the major reaction product in good yield. The reasonable assumption that the stereochemical course of the cyclization was controlled through bidentate chelation of the Lewis acid with the carbonyl oxygen atoms of the oxazolidinone and the amide is probably not correct in this case. Cyclization of **127c** that lacks the oxazolidinone ring takes place with even higher selectivity for **128c**, and cyclization of **127a** to **128a** is catalyzed by methanesulfonic acid, arguing against a bidentate interaction of the substrate with the acid. These two results strongly suggest that bidentate metal−carbonyl complexation is not a prerequisite for

119:**120** = 16:1
(**119**+**120**):**121** = 90:10
85% combined yield

[27]

10:1
42% yield

[28]

Although the reasons for the observed diastereoselectivity for these reactions may be opaque, Prandi and co-workers have used remote stereocontrol in a Nazarov cyclization that was directed toward a total synthesis of roseophilin (Eq. 29).[38] Treatment of dienone **125** in neat trifluoroacetic acid for 20 h led to cyclopentenone **126** in 43% yield as a 4:1 diastereomeric mixture. The structure of the minor component of the mixture was not confirmed, but the authors proposed that it might be derived from an interrupted Nazarov process in which the pendent alkene group has intercepted the intermediate allylic cation. Cyclizations of the type shown in Eqs. 28 and 29 lead to enantiopure products in moderate yield but with excellent control of relative stereochemistry.

high diastereoselectivity in this particular reaction. The authors suggest on the basis of computational work an unconventional model in which the two carbonyl groups in **127** adopt a *transoid* conformation in the reactive intermediate. The lack of an aromatic group in the chiral auxiliary group of **127b** and the lack of a carbonyl group in the chiral auxiliary group of **127c** preclude π-stacking interactions as the source of asymmetric induction.

Flynn and co-workers have described a very useful extension of this work that introduces a one-pot palladium catalyzed tandem hydrostannylation−cross coupling process to prepare the oxazolidinone starting materials (Scheme 6).[40] Palladium catalyzed *syn* hydrostannation of **130** was followed by coupling in situ with tigloyl chloride **131** to produce dienone **132** in 88% yield. Cyclization of **132** in the presence of methanesulfonic acid at low temperature led to the isolation of *cis* diastereomer **133** in 73% yield. This is evidently the kinetic product, since exposure of **132** to methanesulfonic acid in dichloromethane at 18 °C led to *trans* diastereomer **134**. *trans* Product **134** was also isolated in 76% yield following treatment of **132** with Cu(II) triflate in dichloromethane at 18 °C. These are convenient protocols for forming the two isomeric series of products.

In subsequent and more extensive work Flynn and co-workers explored the full scope of these reactions and were able to extend

4:1 dr
43% yield

[29]

Table 2
Chiral auxiliary-controlled aromatic Nazarov

	Starting material	Acid (equiv)	Yield (%)	Product ratio (**128a**–**c**/**129a**–**c**/other)
127a X_c =	**127a**	SnCl$_4$ (1.1)	85	88:12:0
	127b	SnCl$_4$ (1.1)	74	71:16:14
127b X_c =	**127c**	SnCl$_4$ (1.1)	90	92:4:4
	127a	MeSO$_3$H (2.0)	88	85:15:0
127c X_c=8-Phenylmenthoxy	**127a**	TiCl$_4$ (1.1)	60	70:30:0
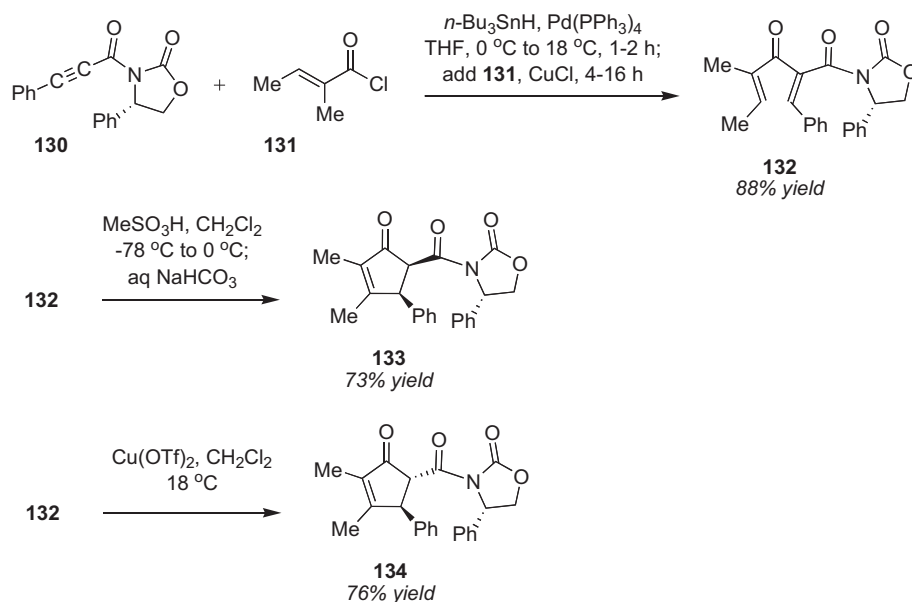
Scheme 6. Hydrostannylation/cross coupling/Nazarov cascade process.
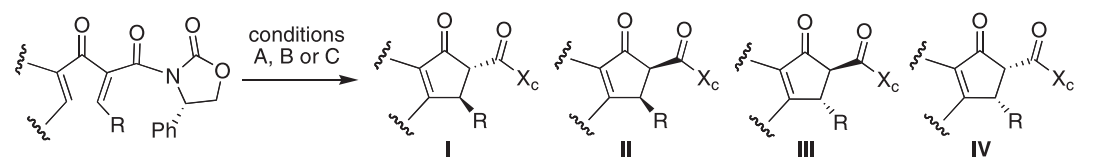
it to the synthesis of cyclopentenones bearing only aliphatic substituents.[41] A comprehensive screen of oxazolidinone chiral auxiliary groups revealed none that were more effective than the phenyloxazolidinone, therefore the (S)-phenyloxazolidinone group was used throughout. A partial listing of their results is summarized in Table 3. Product yields were generally high; however, torquoselectivity was modest. This was offset by the ease with which the diastereomeric products could be separated by chromatography. The sense of asymmetric induction for substrates bearing a β-phenyl (**136**, **132**, and **137**) or a β-n-propyl group (**135** and **138**) was reversed. In at least one case that is not discussed in this Report, reversal of torquoselectivity was observed in changing a Brønsted
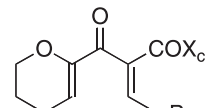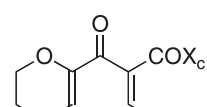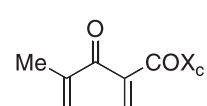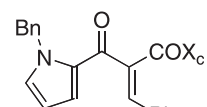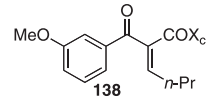
to a Lewis acid catalyst. A mechanistic hypothesis based on the relative sizes of the chiral auxiliary and the substituent groups has been proposed by the authors to rationalize the results. Nevertheless, these results highlight some of the challenges of incorporating these reactions into synthetic planning at this early stage of development.

Harrington and Tius have developed a different type of chiral auxiliary-controlled asymmetric Nazarov cyclization (Scheme 7).[42] Addition of lithioallene **140** to morpholino enamide **139** at −78 °C in THF and in the presence of 4 equiv of lithium chloride, followed by quenching into a solution of hydrochloric acid in hexafluoroisopropanol (HFIP) at 0 °C led to cyclopentenone **141** in 67%

Table 3
Lewis and Brønsted acid catalyzed Nazarov cyclizations

Entry	Substrate	Conditions[a]	I[b]	II[b]	III[b]	IV[b]
1	**135**	A	27 (32)	0	65 (68)	0
2	**136**	B C	48 (70) (7)	(9) 64 (68)	8 (13) (2)	(8) (23)
3	**132**	A B C	(31) 65 (60) 0	(41) (8) 70 (63)	(17) 10 (16) 0	(11) (2) (23)
4	**137**	B	51 (56)	16 (18)	18 (22)	(4)
5	**138**	A	26 (28)	(0)	43 (46)	0

^a A: MeSO₃H (5–10 equiv), −78 °C to rt, CH₂Cl₂; aq NaHCO₃, 1–24 h; B: Cu(OTf)₂ (1.1 equiv), −78 °C to rt, CH₂Cl₂; aq NaHCO₃, 1–48 h; C: MeSO₃H (10 equiv), −78 °C to 0 °C, 0.5–2 h; aq NaHCO₃.

^b Isolated yield (¹H NMR yield).
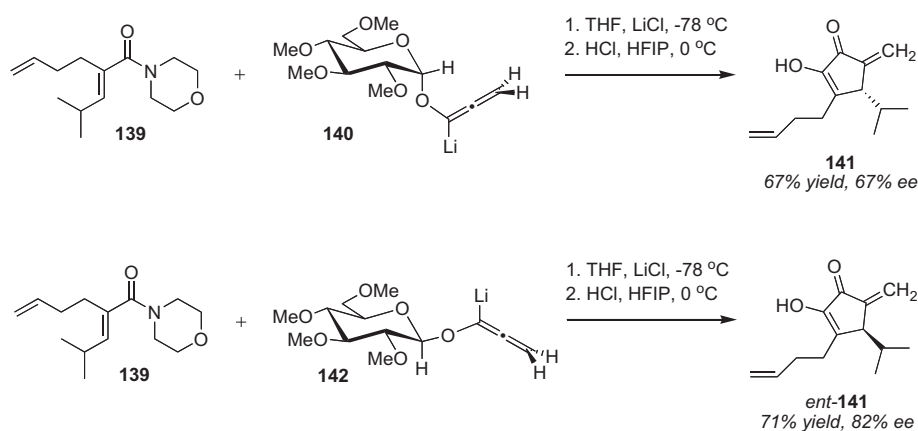
Scheme 7. Glucose derived chiral auxiliaries for the allene ether Nazarov.

yield and 67% ee. In contrast to the oxazolidinone based chiral auxiliaries, the permethylated α-D-glucose derived chiral auxiliary in **140** is lost during the cyclization, so it is traceless. As a consequence, the timing of the cleavage of the chiral auxiliary along the reaction 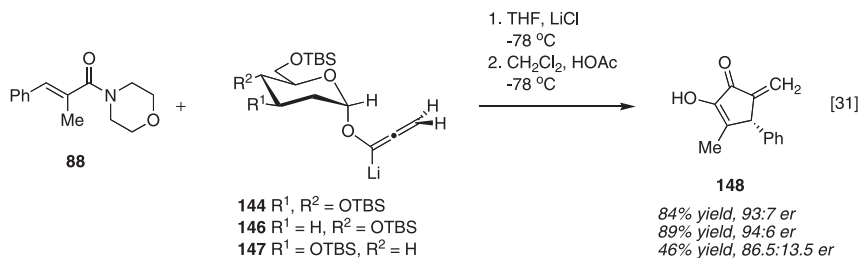coordinate is important: cleavage must take place after the formation of the σ-bond that forms the cyclopentane ring has been initiated, and not before. Sugar derived chiral auxiliaries often suffer from a limitation due to the fact that in general only the D-sugars are available, thereby limiting access to only one enantiomeric series of product. This is not the case for the present example. Lithioallene

142 that is derived from the β-anomer of permethylated D-glucose leads to *ent*-**141** in 71% yield and 82% ee. In this way both enantiomeric series of products are available from cheap D-glucose.

The permethylated D-glucose based reagents of Scheme 7 represent the first generation approach to the problem. Unexpectedly, lithioallene **144** (Eq. 30) that was derived from 2-deoxy-D-glucose proved to be far superior to both **140** and to **142**, but also to the lithioallene that had been prepared from permethylated 2-deoxy-D-glucose.[43] The combination of **144** with morpholino enamide **143** led to cyclopentenone **145** in 66% yield and 90% ee. The counterintuitive conclusion was that substitution at C2 of the chiral auxiliary had little effect on the stereochemical outcome of the cyclization, whereas the nature of the ether protecting groups did have an effect. This observation led to the development of greatly improved second-generation chiral auxiliaries.
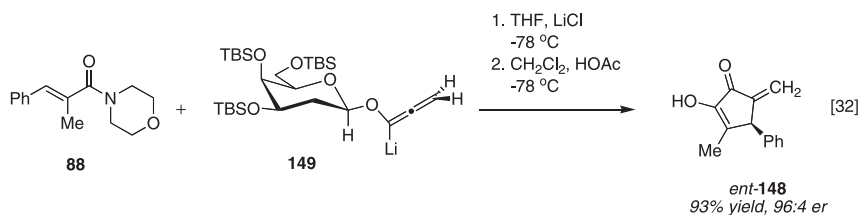
to an axial one that then shields one face of the acyclic pentadienyl cation, thereby strongly biasing the sense of conrotation.

The pyran ring inversion that apparently takes place during the Nazarov cyclizations in the case of α-glycosidic allenyl ethers does not take place in the β-anomeric series. This is revealed by the result of Eq. 32. Lithioallene **149** that was derived from β-2-deoxy-D-galactose when combined with enamide **88** led to cyclopentenone *ent*-**148** in 93% yield and with 96:4 er. This result can be contrasted with the outcome of the reaction of **88** with the lithioallene that was derived from persilylated β-2-deoxy-D-glucose. The yield of *ent*-**148** was 68% yield but the er was only 89:11, suggesting that the C4 axial group in **149** plays the critical role in controlling the absolute stereochemistry of products. Therefore both in the α- and the β-anomer series the prerequisite for high enantioselectivity is the presence of an axial group that blocks one face of the pentadienyl cation.

[30]

145
66% yield, 90% ee

A noteworthy feature of all lithioallenes is their high reactivity. The asymmetric Nazarov cyclizations of the allenyl ethers take place readily at low temperature and they are not limited to substrates bearing aryl groups. The product yields reported for **144** varied between 53% and 85%, whereas ees varied between 86% and 93%.

Lithioallene **150** was designed on the basis of the results presented above. Since conformational flexibility of the pyran ring is not a requirement for an effective chiral auxiliary, **150** was predicted to be an effective reagent for the asymmetric allene ether Nazarov cyclization because the silyloxy group at C3 is held in the axial position (Table 4). The results of Table 4 bear
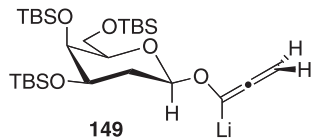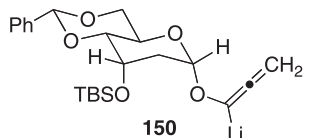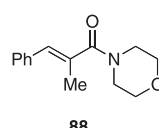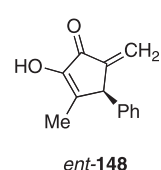

[31]

88

144 R^1, R^2 = OTBS
146 R^1 = H, R^2 = OTBS
147 R^1 = OTBS, R^2 = H

148
84% yield, 93:7 er
89% yield, 94:6 er
46% yield, 86.5:13.5 er

A systematic exploration of the factors that control the stereochemical outcome of the reactions of lithioallene **144** revealed that the silyloxy group at C3 exercised only a minimal effect on the product stereochemistry, whereas the C4 silyloxy group had a significant effect (Eq. 31).[44] For example, the reaction of **144** with morpholino enamide **88** led to cyclic product **148** in 84% yield and 93:7 er. Lithioallene **146** that was derived from 2,3-dideoxy-D-glucose led to **148** in 89% yield and 94:6 er, essentially the identical result that was obtained from **144** within experimental error. On the other hand **147** that was derived from 2,4-dideoxy-D-glucose led to **148** in 46% yield and with reduced er of 86.5:13.5. These results can be explained by postulating inversion of the pyran ring during the cyclization. Ring inversion has the effect of converting the C4 equatorial silyloxy group

this out. It is noteworthy that an all-carbon quaternary center can be incorporated into cyclopentenones **160** and *ent*-**160** with 89:11 and 5:95 er, respectively. Low yields of **158** and *ent*-**158** were observed because of the instability of these products that undergo decomposition through a β-elimination process involving the enol ether with the carbamate acting as a leaving group.

The predictable stereochemical outcome of the allene ether Nazarov cyclizations makes their incorporation into synthetic planning straightforward. Camphor-derived lithioallene **161** was developed during the total synthesis of natural roseophilin (Eq. 33).[45] The reaction of **161** with enamide **139** led to **141** in 78% yield and 86% ee, a significant improvement over the result with
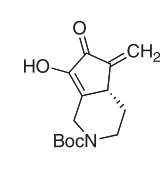

[32]

88   **149**

ent-**148**
93% yield, 96:4 er

Table 4
Sugar derived chiral auxiliaries for the allene ether Nazarov

149   **150**

Entry	Enamide	Product from **149**	yield/er	Product from **150**	yield/er
1	**88**	*ent*-**148**	92% 96.5:3.5	**148**	69% 97:3
2	**151**	*ent*-**152**	57% 96:4	**152**	59% 95:5
3	**153**	*ent*-**154**	93% 93:7	**154**	90% 97:3
4	**155**	*ent*-**156**	83% 91:9	**156**	57% 93:7
5	**157**	*ent*-**158**	59% 95:5	**158**	29% 93:7
6	**159**	*ent*-**160**	78% 95:5	**160**	54% 89:11
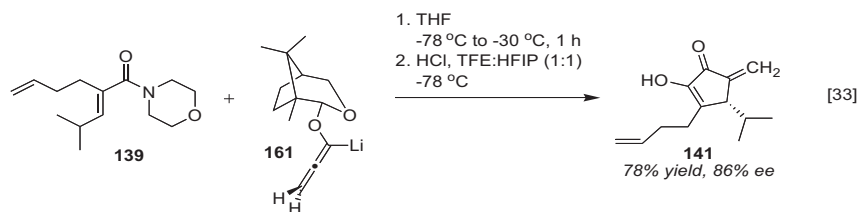
140 (Scheme 7). Because of the array of useful functionality in **141** it was possible to convert it in only eight steps to (22R,23R)-roseophilin.

The camphor-derived lithioallene **161** has been shown to be generally useful for the asymmetric Nazarov cyclization, although the optical purity of products is somewhat lower than observed from the reactions of **149** or **150**. The preparation of axially chiral substituted lithioallenes (e.g., **162**, Eq. 34) as single diastereomers is straightforward and their reactivity with enamides follows that of **161**.[46] For example, addition of **162** to enamide **88** led to cyclopentenone **163** in 67% yield and 79% ee. Although **163** was isolated as a single E geometrical isomer at the exocyclic double bond, this was the result of acid catalyzed isomerization of the kinetically formed Z isomer. Substitution on the allene raises a matched–mismatched issue since the axial chirality of the allene also influences the torquoselectivity (see Eq. 18). In the case of methyl substitution at the distal allene carbon atom one would predict only a modest effect on the optical purity of the product. A much larger effect would be expected in the case of the allene that is substituted by a tert-butyl group (**164**, Eq. 35). This is indeed what was observed. Lithioallene **164** reacted with enamide **88** and led to cyclopentenone **165** in 80% yield and 96% ee. The axial stereochemistry of the allene in **164** and in **162** represents the matched case. In the mismatched case the axial chirality of the tert-butyl allene overwhelms the effect of the chiral auxiliary leading to the enantiomeric series of cyclopentenones. The products derived from **164** were much less prone to undergo Z to E isomerization during the reaction, making it possible to isolate the Z isomers as the major reaction products.

yield. Simply stirring **167** with 10 equiv of phenethylamine **168** in the presence of dry Florisil in the absence of solvent leads to α-aminocyclopentenone **169** in 67% yield as a single diastereomer. This is a cascade process in which the first step is the amine-catalyzed isomerization of **167** to the allenyl ketone that then undergoes rapid cyclization. The cyclic cation is intercepted by the amine from the less hindered face of the molecule, leading ultimately to the observed product. There are several unusual features of this reaction. The first concerns the initial step that leads to the allene. The allene is stereogenic and since the distal TIPS substituent is very large, on the basis of the preceding discussion (e.g., Eq. 35) one would have to predict that it exerts a very large if not dominant effect on the torquoselectivity. This further suggests that the isomerization step is highly selective for the matched allene diastereomer and that the role of the chiral auxiliary is to influence the course of this isomerization step. The second unusual feature of this reaction concerns the nucleophilic trapping of the cation by the amine. The lifetime of the highly reactive intermediate cation must be long enough to allow effective trapping by the amine nucleophile in the absence of any solvent.

The asymmetric interrupted Nazarov cyclization is reasonably general, as the examples of Fig. 3 indicate. There appear to be no obvious limitations in terms of the enone starting material and both aliphatic and aromatic substituents are tolerated. It is noteworthy that secondary amines can also be used as nucleophiles as indicated by the examples of **171**, **172**, and **174**. The acid labile acetal function in **170** was tolerated as well.

One example of the intramolecular version of this interrupted Nazarov reaction has been reported (Scheme 9). Reaction of an
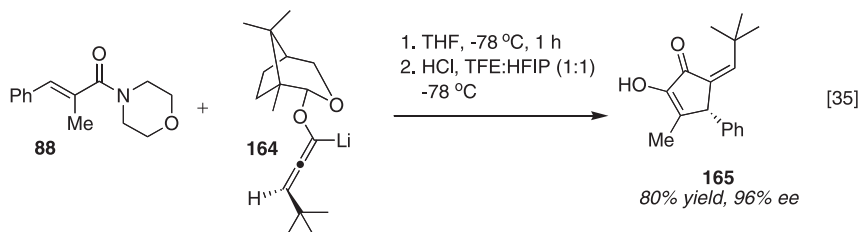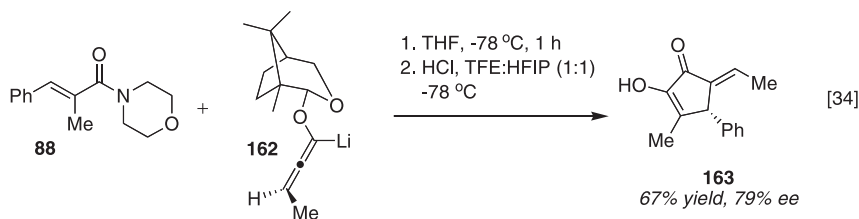
A somewhat different role for the camphor-derived chiral auxiliary group is shown in the diastereoselective interrupted Nazarov reaction that is summarized in Scheme 8.[47] Addition of propargyllithium **166** to enamide **88** leads to enone **167** in 86%

excess of **166** with enamide **175** leads to enone **176**. Exposure of **176** to 10 equiv of triethylamine on dry Florisil in the absence of solvent led to the anticipated product of intramolecular trapping **177** in 50% overall yield for the two steps, propargyllithium
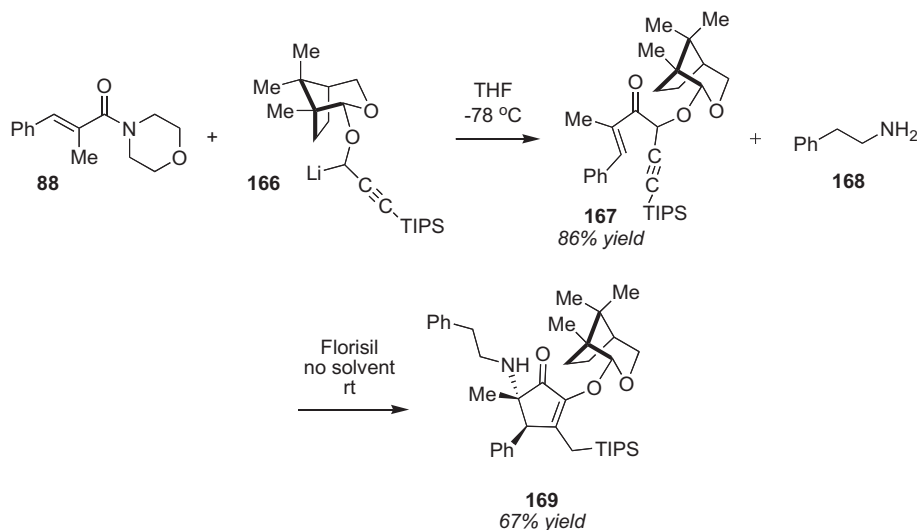
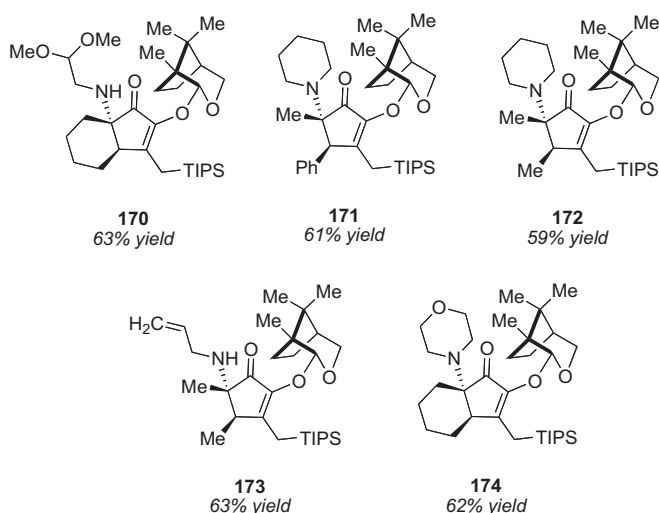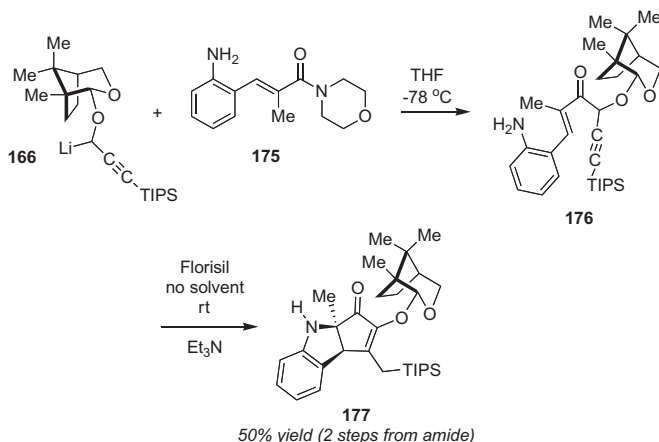**Scheme 8.** Asymmetric interrupted Nazarov.

170
63% yield

171
61% yield

172
59% yield

173
63% yield

174
62% yield

Fig. 3. Examples of the asymmetric interrupted Nazarov reaction.

Scheme 9. Intramolecular asymmetric interrupted Nazarov.

addition to the enamide and cyclization. Because the trapping step that leads to **177** takes place intramolecularly, the relative stereochemistry of the amino and phenyl groups in **177** is opposite that in **169**.

8. Summary and outlook

It is curious that the first efforts to develop asymmetric versions of the Nazarov cyclization, a reaction that was first described in 1941, were reported only within the last 10 years or so. Although a number of imaginative conditions for catalytic asymmetric cyclizations, as well as chiral auxiliary-controlled processes have been described, each is subject to some limitations. At this time a truly general asymmetric Nazarov reaction, either catalytic or chiral auxiliary-controlled has not been described. One of the challenges is the requirement for an activated dienone. For example, in Rueping's seminal work polarization of the dienone by the enol ether is a requirement for the reaction. All the catalytic asymmetric or chiral auxiliary-controlled methods that have been described to date succeed only for dienones that are substituted by either an α-ether or an α-carboxy group, or both. In addition, several of the methods are further limited by requiring β-substitution by one or more aryl groups. Another problem that bedevils the catalytic asymmetric Nazarov reactions is product inhibition.

The chiral auxiliary-controlled allene ether cyclizations do not appear to be subject to any limitations in terms of the dienone, probably because of the activation inherent in the strain energy of the favorably polarized allene. A major shortcoming inherent in these reactions is that four of the five ring carbon atoms in the product are sp^2 hybridized, affording the opportunity to control the absolute stereochemistry of only one ring carbon atom. Although chiral auxiliaries can provide highly practical solutions to problems in asymmetric synthesis, catalytic asymmetric processes have the advantage of atom economy. It seems likely that efforts in the future will focus on developing a truly general catalytic asymmetric Nazarov reaction.

Acknowledgements

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Biographical sketch

Naoyuki Shimada was born in Tokyo, Japan, in 1978. He received his B.Sc. and M.Sc. from Nihon University, where he worked with Professor Shoichi Shimizu. In 2003 he moved to Hokkaido University, where he received his Ph.D. under the supervision of Professor Shuni-chi Hashimoto. He then joined the faculty there as an assistant professor. In 2009 he moved to the University of Hawaii to join the group of Professor Tius. After 2 years of postdoctoral research he returned to Japan. He is currently working as an assistant professor at Kitasato University, where he is developing new catalysts for use in organic synthesis.

Dr. Craig Stewart was born in Greenock, Scotland and raised in Oshawa, Ontario Canada. He obtained his B.Sc. from the University of Western Ontario in 2004 and completed his Ph.D. training at the University of Alberta in 2010 under the supervision of Professor F. G. West. He worked as a postdoctoral researcher at the University of Hawaii at Manoa under the supervision of Professor M. A. Tius through March 2011.
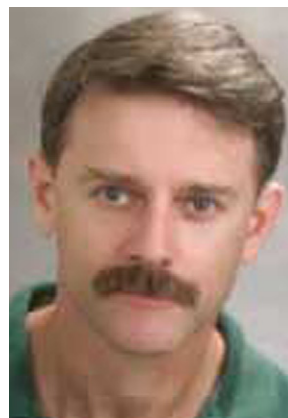
Marc Tius was born in 1953 in Izmir, on the Aegean coast of Turkey. He moved to Greece with his father and mother when he was 5 years old. He attended elementary school for 6 years in Kavala, a town in Eastern Macedonia, and gymnasium for another 6 years in Thessaloniki, a larger city in northern Greece. 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 University of Hawaii Cancer Center.