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Published on Web 08/01/2002

Asymmetric Cyclopentannelation: Camphor-Derived Auxiliary

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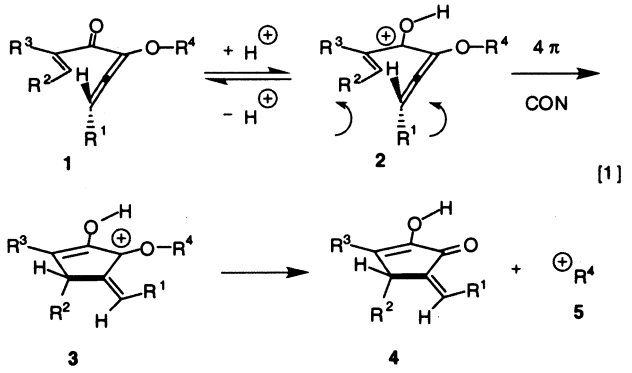
Received April 25, 2002

Abstract: The scope of an enantioselective cyclopentannelation reaction that makes use of allenyl ether-derived nucleophiles has been probed. The enantioselectivity is induced by a traceless chiral auxiliary that is easily derived from camphor. It has been shown that for γ-substituted allene ethers that are axially chiral, very high enantiomeric excesses of cyclopentenone products are observed in the matched cases. Two fundamentally different mechanisms are observed, one for the cyclizations of allenyl ketones (see eq 7), the other for the cyclizations of allenyl alcohols (see eq 11). The methodology is versatile, efficient, and well-suited for applications in synthesis.

Introduction

Some years ago we described a variant of the classical Nazarov cyclization in which an allene ether function participates in the conrotation.[1] In our early efforts, we explored versions of this reaction that provided racemic products, but as the potential of the methodology became clearer to us, we considered adaptations that might provide enantiomerically enriched products.[2,3] We recently reported the first total synthesis of natural (22*R*,23*R*)-roseophilin through an application of the enantioselective version of the cyclopentannelation reaction.[4] There are several aspects of the reaction that are noteworthy, the most startling of which is the ease with which the cyclization takes place. For example, we have been unable to isolate α-allenyl ketones such as **1** (eq 1) because they undergo spontaneous cyclization during workup.[5] This contrasts with the behavior of divinyl ketones, the conventional substrates of the Nazarov reaction,[6] cyclization of which often requires exposure to strong acid.[7] Our mechanistic hypothesis is summarized in eq 1. Reversible protonation of ketone **1** leads to pentadienyl cation **2**. This intermediate can undergo thermally allowed conrotatory ring closure to cyclic cation **3**. Loss of residue R^4 as a stable cation in an irreversible step leads to the observed product, cross-conjugated cyclopentenone **4**.



There are several points to be noted concerning this process. Cleavage of cation R^4 from intermediate **3** must take place rapidly, otherwise competing reaction pathways involving rearrangements or proton loss or both from **3** will erode the yield of **4**. We have had our best successes when R^4 has been an alkoxyalkyl group, so that the cation $^+R^4$ is stabilized by electron pair donation from the adjacent oxygen atom. The stereodetermining step is the cyclization of **2** to **3**. If protonation of **1** is reversible and if the cyclization is slow, erosion of the geometrical integrity of the trisubstituted alkene can take place. Loss of the stereochemical information of the alkene results in a nonstereoselective cyclization reaction. This suggests that the mildest possible conditions for the cyclization may not be optimal for maintaining the stereospecificity of the cyclization. For maximal stereospecificity it is useful to have a high concentration of strong acid, leading to a high concentration of **2**, and a fast cyclization.

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(1) For example, see: (a) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1984**, *25*, 1539. (b) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset, J.-B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438. (c) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1989**, *30*, 2333. (d) Tius, M. A.; Zhou, X.-M. *Tetrahedron Lett.* **1989**, *30*, 4629. (e) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871. (f) Tius, M. A.; Drake, D. J. *Tetrahedron* **1996**, *52*, 14651. (g) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219. (h) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1998**, *63*, 5971. (i) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419.

(2) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895.

(3) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447.

(4) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509.

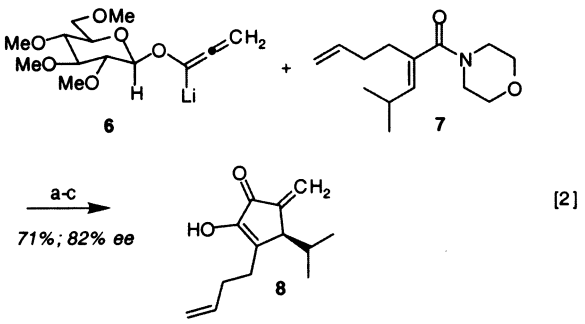
(5) Hashmi and co-workers have noted similar reactivity in a related system: Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Scharz, L. *Tetrahedron Lett.* **1998**, *39*, 7491.

(6) (a) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865. (b) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443. (c) Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543.

(7) For discussions of the Nazarov reaction, see: Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Shen, C. *Acc. Chem. Res.* **1996**, *29*, 471 and Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158.

In cases in which $R^1 \neq H$, the allene function is stereogenic. Consideration of the two modes of conrotation that are available to **2** suggests that the preferred mode, as indicated in eq 1, takes place so as to move R^1 *away* from the steric bulk of R^2, leading to the *Z* exocyclic double bond geometry in **3** and **4**. In preliminary work we have shown that this preference is amplified when R^1 is a large group, e.g., *tert*-butyl. By controlling the direction of conrotation, one can transfer the axial chirality of the allene function in **1** to the tetrahedral ring carbon atom in **4**.[2]

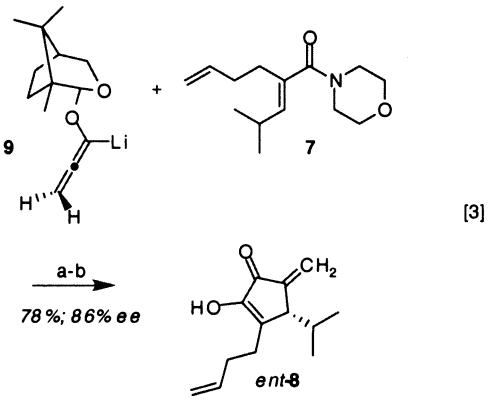
It is useful to consider two cases for performing the cyclopentannelation reaction of eq 1 enantioselectively. First, in the case in which $R^1 \neq H$, control of the axial chirality of the allene ether function in **1** results in control of absolute stereochemistry in **4**, as indicated in the preceding paragraph. There is as yet no convenient method for preparing nonracemic allene ethers.[8] Although Hoppe and co-workers have demonstrated an elegant synthesis of enantiomerically enriched axially chiral allenyl carbamates, it is not clear whether their method can be adapted to the synthesis of allene ethers.[9] The allenyl carbamates have been explored in the cyclopentannelation reaction, and it appears that they react largely through a different manifold.[10] Second is the case in which $R^1 = H$, in which the allene function in **1** is not stereogenic. Here there are two options for controlling the absolute stereochemistry of product **4**. One can either use a chiral auxiliary as a control element, or one can consider using a chiral Lewis acid catalyst in place of proton in the first step of eq 1. The ease with which the cyclopentannelation process always proceeds, even during workup with aqueous KH_2PO_4 in all cases, suggests that a better application of the chiral Lewis acid approach will be to cyclizations that are slower than the one in eq 1. This makes the chiral auxiliary approach the most attractive avenue for investigation.



[2]

(a) LiCl, THF, -78 °C; (b) add **7**; -78 °C, 1 h; warm to -40 °C; cool to -78 °C; (c) HCl, HFIP, 0 °C.

Our first investigations of chiral auxiliaries led us to consider pyranose derivatives, since they are cheap and readily available.[3] Furthermore, loss of the sugar residue as a stable oxo cation (cf. $^+R^4$, eq 1) can take place following cyclization. Although the reactions of allenes substituted with these auxiliaries led to cyclopentenones in good yield and in good enantiomeric excess (up to 82% ee, eq 2), in many cases, there were two shortcomings that limited their utility. First, the nucleophilicity of allenyllithium reagent **6** was limited. It was necessary to add several equivalents of LiCl to the reaction mixtures in order for the addition to morpholino enamides (e.g., **7**) to take place efficiently.[11] Second, whereas the ee of products was good on modest scale (up to 0.2 mmol), we discovered that marked erosion of the ee took place upon scaling up of the reaction to 4 mmol. The preparation of the sugar-derived auxiliaries was also tedious on large scale. For these reasons we developed a second-generation chiral auxiliary based on camphor which was not subject to the three limitations cited above. Camphor is an attractive starting point for the synthesis of chiral auxiliaries since both enantiomeric forms are available and are reasonably cheap. Equation 3 summarizes our first result with the camphor-derived auxiliary **9**.[4] Addition of **9** to morpholino enamide **7**, followed by treatment with HCl in a mixture of hexafluoroisopropanol (HFIP)[12] and trifluoroethanol (TFE) at −78 °C led to cyclopentenone *ent*-**8** in 78% yield in 86% ee on a 1 g scale. Cyclopentenone *ent*-**8** was the key intermediate in our synthesis of natural roseophilin. Following this early demonstration of the utility of **9** in total synthesis, we wanted to determine the scope and the limits of applicability of **9** to the enantioselective construction of cross-conjugated cyclopentenones. We also wanted to explore the effects on yield and enantioselectivity of introducing substituents at the distal carbon atom of the allene function in **9**. We describe our findings in what follows.



[3]

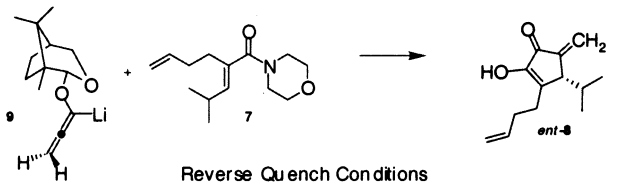
(a) add **7**; -78 °C to -30 °C, 1 h; (b) HCl, HFIP/TFE (1:1), -78 °C.

Results and Discussion

A limited series of experiments was performed first to optimize yield and optical purity for the reaction of eq 3. The results of this study are summarized in Table 1. It is easy to overinterpret these results, but it can be stated with confidence that use of the polar solvent HFIP led to the best enantiomeric excesses of product and that lower temperature was better than higher temperature. The yield of *ent*-**8** in Table 1, entry 5, is given as 60%. This is for a reaction that was conducted with 0.2 mmol of **7**. On 4 mmol scale, the yield of *ent*-**8** improved to 78%, whereas the ee was unaffected. Since HFIP has a high melting point, it was advantageous to use a mixture with TFE so that the cyclization reaction could be conducted at −78 °C. Only two experiments involved the use of Lewis acid catalysts

(8) However, see: Alexakis, A.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4197.
(9) Schultz-Fademrecht, C.; Wibbeling, B.; Frölich, R.; Hoppe, D. *Org. Lett.* **2001**, *3*, 1221 and references therein.
(10) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1532.
(11) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.
(12) Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927.

Table 1. Optimization of Yield and Ee of *Ent*-**8**[a]

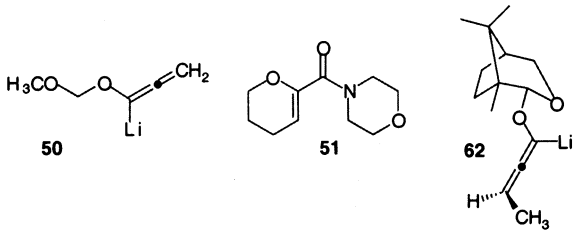


entry	solvent[b]	acid(equiv)/temp(°C)	% yield (ee) of *ent*-**8**
1	ethanol	HCl(11)/−78	56 (64)
2	HFIP	HCl(47)/0	59 (80)
3	HFIP	HCl(41)/−40	36 (84)
4	HFIP/TFE (1/1)	HCl(44)/−78	53 (85)
5[c]	**HFIP/TFE (1/1)**	**HCl(39)/−78**	**60 (86)**
6	$MeNO_2$	HCl(44)/−40	64 (64)
7	HFIP	TFA(39)/−40	67 (64)
8	THF	$ZnCl_2$(2)/−78	58 (66)
9	CH_2CI_2	$FeCl_3$(2)/−78	67 (69)

[a] All reactions were performed in THF with 1.8 equiv of **9**. [b] The volume of the quenching solvent was equal to the volume of the reaction solvent, except for entry 5. [c] The volume of HFIP/TFE was double the volume of the reaction solvent.

(entries 8 and 9). This is an area that we must examine in greater detail in the future.

The scope of the reaction of eq 3 was probed with the series of enamides shown in Table 2.[13] The yields of cyclic products varied from 33% (Table 2, entry 17) to 84% (entries 3 and 10), whereas the enantiomeric excess of products varied between 55% (entry 1) and 87% (entry 10). The absolute configuration of the products shown in Table 2 has been assigned by analogy with the result of eq 3. Since we converted *ent*-**8** to natural roseophilin[4] and since Boger prepared the enantiomer of roseophilin by an independent method, the assignment of absolute stereochemistry in the case of *ent*-**8** is secure.[14] The stereochemistry of **33** has also been determined rigorously, by correlating it to a compound whose absolute stereostructure we determined crystallographically.[2] The fact that the major enantiomer in all cases cited in Table 2, with the exception of entry 1, is also the *less mobile* of the two on the Chiralcel-OD HPLC column is reassuring but does not constitute proof of stereochemistry. It should therefore be stated clearly that the stereochemistry of the products shown in Table 2 must be considered tentative until confirmed through independent methods. This is especially true for cyclopentenone **11**. This compound is an outlier for two reasons. First, because of the reversal in chromatographic mobility of the major enantiomer, mentioned above, and second, because it had the lowest ee of all cases in Table 2. It is certainly conceivable that cyclization of the allene adduct of enamide **10** takes place according to a mechanistically distinct pathway. Compound **11** also illustrates another potential pitfall, as it is exceptionally crystalline. It is quite easy to inadvertently produce samples of **11** that are highly enriched (>96% ee) in the major enantiomer by allowing crystallization to take place during workup or purification.



The results that are summarized in Table 2 allow several generalizations to be made. Entries 1−4 indicate that aryl substitution at one or at both C-3 and C-4 of the cyclopentenone is tolerated. The difference in the optical purity of **13** and **15** follows the same trend that we described for the D-glucose-derived auxiliary and in all likelihood has the same origin.[3] Since the only difference in the two substrates **12** and **14** is the presence in **14** of the 4-methoxy group on the aromatic ring, one must attribute the erosion in the ee of **15** relative to that of **13** to its presence. The additional stabilization of the protonated ring-opened intermediate (i.e., compound **2** in eq 1) by electron pair donation by the oxygen atom through the phenyl ring renders the cyclization reaction reversible. This, in turn, can compromise the stereospecificity by allowing competing cyclization processes to take place, possibly involving the geometrical isomer of **2** (eq 1, R^2 and R^3 *anti*).

Entries 5, 6, and 13 of Table 2 show that halogen is also tolerated. The halogenated cyclopentenones **19** and **21** did not separate on the Chiralcel-OD or Chiralcel-OJ columns due to extensive tailing of the peaks; however, derivatizing the hydroxyl made it possible to separate the enantiomers. In the case of **19**, exposure to trimethyloxonium tetrafluoroborate and Hünig's base led to rapid (<5 min) conversion to the methyl ether derivative for which baseline separation of the enantiomers took place. In the case of **21**, the derived benzoate was used for the determination of optical purity by HPLC. Similar difficulties were encountered during the analysis of bromocyclopentenone **35** (entry 13). In this case, conversion of **35** to the acetate allowed the separation of enantiomers to take place.

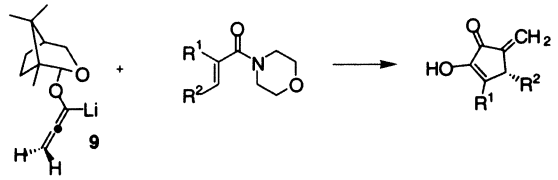
Entries 7−12 summarize the synthesis of alkyl substituted cyclopentenones. In this series there is an improvement in the ee of product with increasing branching at C-4, as a comparison of the optical purities of **23**, **25** and **27** reveals. It would appear that there is little to be gained in terms of optical purity in going from isopropyl (see **27**) or from cyclohexyl (see **31**) to a C-4 *tert*-butyl group (see **29**).

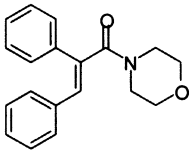
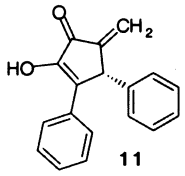
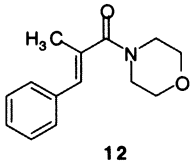
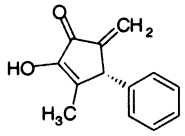
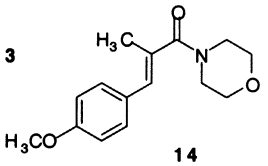
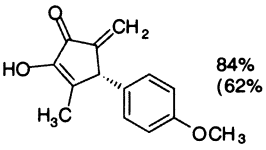
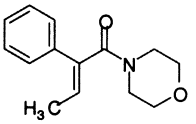
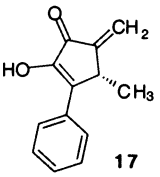
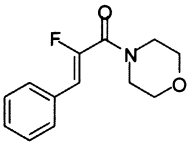
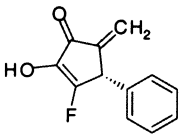
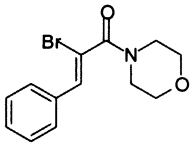
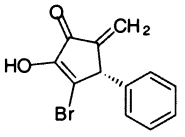
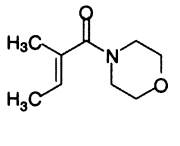
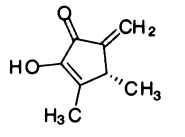
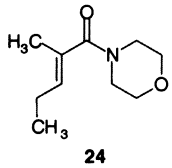
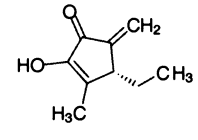
Entries 14−17 show that substitution by trialkylsilyl at C-3 is also tolerated. Although the enantiomeric excesses of the silylated products are in all cases good, the same is not true for the isolated yield of products. The low yield of **37** is due to protiodesilylation that takes place during exposure to concentrated strong acid. The difference in the yields of **41** and **43** (entries 16 and 17) is at first puzzling, since one would reasonably expect a higher yield for **43**, which is more robust in the presence of acid. We believe that the discrepancy is due to our failure to control contact times with acid during the execution of the early parts of this work. We have since modified our procedure such that the reactions are quenched at

(13) The addition−cyclization reaction sequence was repeated for each of the 20 enamides in Table 2 using allenyllithium species **50** to secure a sample of the racemic product. Since the determination of optical purity of the cyclopentenone product in each case was performed by chiral HPLC, it is essential that a sample of the racemate be available. In the absence of a chromatogram of the racemate as a reference, it is impossible to determine whether separation of the enantiomers from the enantioselective reaction has been accomplished. The measured peak areas for each of the enantiomers in the racemic samples never deviated from 50% by more than 1%. Therefore, one can conservatively estimate that the enantiomeric excesses that are reported in Table 1 are accurate to within ±2%.

(14) Boger's result is essential, as there had been no independent confirmation of the absolute stereochemical assignment of roseophilin prior to our total synthesis. Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.

Table 2. Cyclizations with Terminally Unsubstituted Allene[a]



Entry	Amide	Cyclopentenone	Yield (ee)
1	 **10**	 **11**	74% (55% ee)
2	 **12**	 **13**	71% (77% ee)
3	 **14**	 **15**	84% (62% ee)
4	 **16**	 **17**	70% (72% ee)
5	 **18**	 **19**	55% (58% ee)[b]
6	 **20**	 **21**	53% (78% ee)[c]
7	 **22**	 **23**	67% (65% ee)
8	 **24**	 **25**	69% (74% ee)

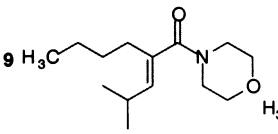
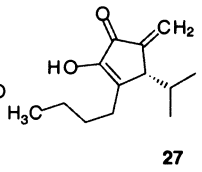
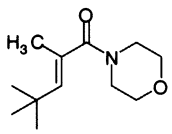
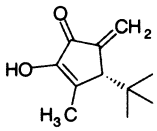
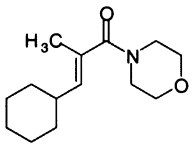
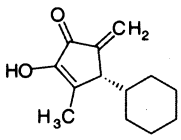
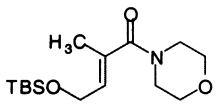
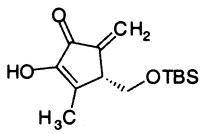
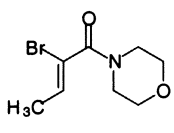
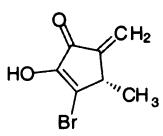
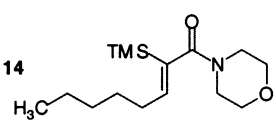
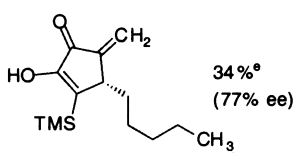
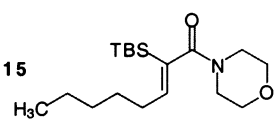
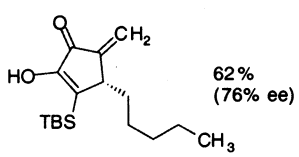
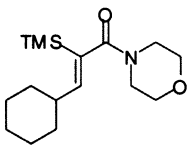
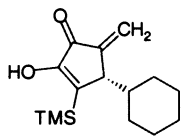
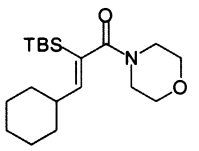
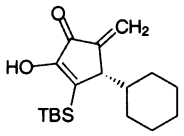
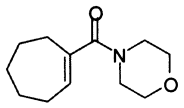
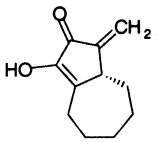
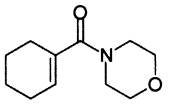
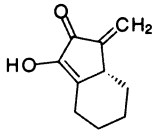
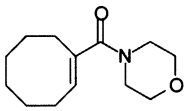
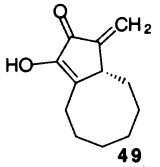
Entry	Amide	Cyclopentenone	Yield (ee)
9	 **26**	 **27**	62% (86% ee)
10	 **28**	 **29**	84% (87% ee)
11	 **30**	 **31**	65% (83% ee)
12	 **32**	 **33**	81% (65% ee)
13	 **34**	 **35**	74% (85% ee)[d]
14	 **36**	 **37**	34%[e] (77% ee)
15	 **38**	 **39**	62% (76% ee)
16	 **40**	 **41**	60% (85% ee)

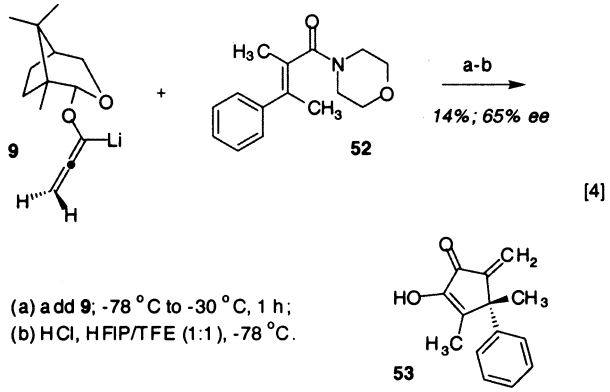
Table 2 (*Continued*)

Entry	Amide	Cyclopentenone	Yield (ee)	Entry	Amide	Cyclopentenone	Yield (ee)
17	 **42**	 **43**	33%[e] (75% ee)	19	 **46**	 **47**	45% (65% ee)
18	 **44**	 **45**	62% (69% ee)	20	 **48**	 **49**	48% (67% ee)

[a] All reactions were performed according to the optimal conditions shown in entry 5 of Table 1. [b] Determined by chiral HPLC of the derived methyl ether. [c] Determined by chiral HPLC of the derived benzoate. [d] Determined by chiral HPLC of the derived acetate. [e] Low yield due to protiodesilylation.

low temperature with bicarbonate. With these modified procedures it should be possible to preserve the trialkylsilyl group in the product.

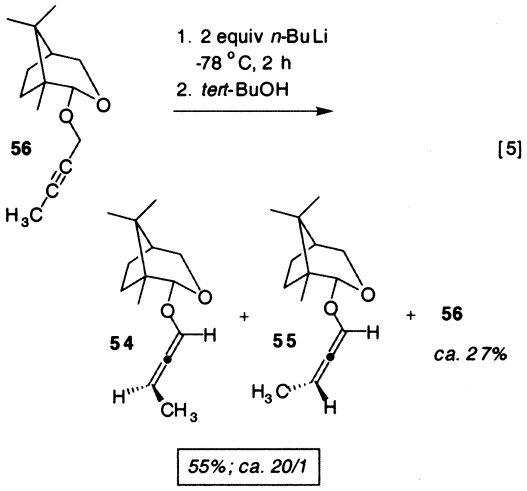
Entries 18−20 show that the method can be used to prepare fused carbocyclic rings, which adds to the versatility of the process. The only fused heterocyclic ring that we examined, dihydropyran **51**, provided cyclic product of undetermined ee in only 29% yield. It may be that the tetrahydropyranyl function in **51** provides additional pathways for acid-catalyzed decomposition of the adduct with **9**.



[4]

We examined a single example of a β,β-disubstituted morpholino enamide (eq 4). The addition reaction of **52** with **9**, followed by exposure of the adduct to acid under the conventional reaction conditions, produced cyclopentenone **53** in 14% yield, along with a large amount of recovered amide **52**. The low yield in this case is apparently a consequence of proton transfer from the β-methyl group to **9**. Although the ee of **53** is not particularly high, this example is significant in that it demonstrates that the asymmetric cyclopentannelation reaction is suitable for the synthesis of cyclopentenones bearing quaternary carbon atoms. The cyclization reactions of tetrasubstituted enamides and esters will be interesting to study, since they potentially offer a solution to a difficult problem in synthesis.[15]

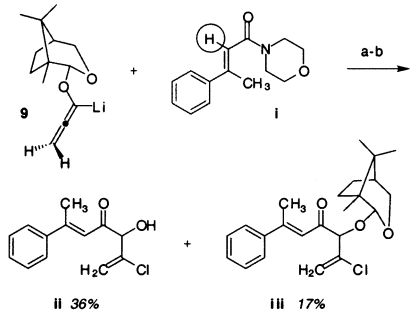
The limitations that have been cited above notwithstanding, the asymmetric cyclopentannelations of **9** are preparatively useful. Our next goal was to determine whether useful yields of enantiomerically enriched cyclic products could be obtained



[5]

from substituted allenyllithiums related to **9**. Our first target was methylallene **54** (eq 5). When the allene is stereogenic, as it is in **54**, one must consider matched and mismatched cases

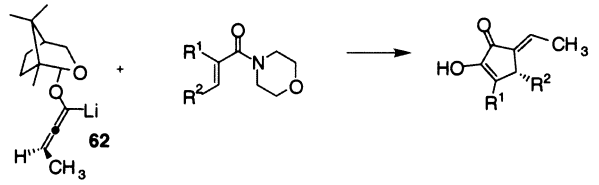
(15) A limitation of all versions of the cyclopentannelation reaction is the requirement of a non-hydrogen substituent at the α-carbon atom of the acyclic intermediate ($R^3 \neq H$ in **1**, eq 1). The reason for this is not completely obvious. We have postulated that when $R^3 \neq H$ the reactive U-shaped conformer of the pentadienyl cation **2** is favored for steric reasons.[1e] We were therefore not surprised that the attempted cyclopentannelation reaction of morpholino enamide **i** failed to produce the desired product. The major products that were isolated from the reaction were chloroenones **ii** and **iii**. It is likely that **ii** is derived from **iii**. Both these products suggest that the high concentration of chloride during the cyclization reaction may provide a competing reaction pathway that may erode the yield of cyclic product in some cases.

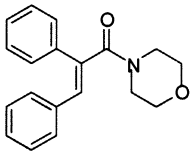
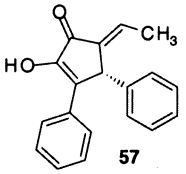
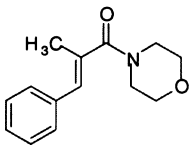
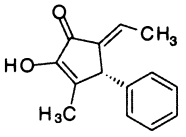
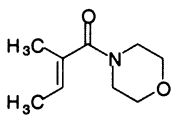
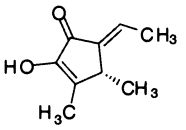
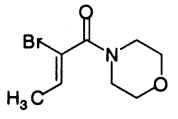
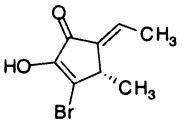
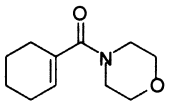
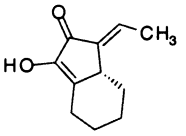


separately. When we initiated this phase of the work, we had no indication of whether the auxiliary or whether the stereogenic allene would exert the dominant influence on the absolute stereochemical course of the cyclization. Certainly the alkyl substituent on the allene significantly affects the stereochemical course of the cyclization. For example, we had shown in earlier work that in the absence of auxiliary, a *n*-butyl group on the γ-carbon of an enantiomerically enriched allene leads to 84% transfer of asymmetry during the cyclization.[2] Butynyl ether **56** (eq 5) was prepared in high yield by trapping the corresponding lithium acetylide with iodomethane. Exposure of **56** to *n*-butyllithium in THF at −78 °C, followed by quenching the reaction mixture at −78 °C with a solution of *tert*-butyl alcohol in THF led to a ca. 20/1 mixture of diastereomers **54** and **55**. We were able to tentatively assign the stereochemistry of the major diastereomer through two experiments. In the first experiment, the 20/1 mixture of **54** and **55** was deprotonated with *n*-butyllithium to produce lithioallene **62** and its diastereomer. These were allowed to react with morpholino enamide **12** (entry 2, Table 3), and cyclization was effected in the usual way, with HCl in HFIP/TFE at −78 °C. This led to cyclic product **58** in 67% yield and in 79% ee.

Diastereomers **54** and **55** were not completely separable by flash column chromatography, however, a ca. 3/4 mixture of the two could be obtained by combining chromatography fractions. The addition−cyclization sequence with enamide **12** was repeated with the mixture of allenes that was enriched with the minor diastereomer. The yield of **58** from this experiment was 67% (virtually unchanged), but the ee fell from 79 to 71%. Since the reproducibility of the measurement of ee by chiral HPLC is ±2%,[13] this is a significant difference, and the erosion in the ee of **58** must be the result of a *mismatched* reaction proceeding through **55**. The axial chiralities of allenes **54** and **55** favor conrotation in opposite directions. Although we had not predicted that the matched diastereomer **54** would predominate in the isomerization step (eq 5), this observation can be understood as the result of two diastereoselective proton transfers. Exposure of **56** to *n*-butyllithium results in the selective abstraction of the pro-*S* propargylic proton, leading to internally chelated structure **63** (eq 6). Removal of the pro-*R* proton would have placed the 1-propynyl group in close proximity to the bulk of the auxiliary and is apparently disfavored for this reason. The protonation of **63** by *tert*-butyl alcohol must also take place stereoselectively, as shown in eq 6. The *anti* stereoselectivity that has been postulated for this process is plausible. The hypothesis that is summarized in eq 6 also postulates a role for the auxiliary that is consistent with its effect on the stereochemical course of the cyclization. This is shown for the matched case in eq 7. The adduct of lithioallene **62** and enamide **12**, following acid-catalyzed collapse of the tetrahedral intermediate, leads to **64**. Electron pair donation by the pyranyl oxygen atom of the auxiliary stabilizes the pentadienyl cation and restricts it to the conformation indicated in the structure. Conrotation in **64** is biased to take place through a counterclockwise motion, as shown, for two reasons. First, counterclockwise rotation moves the phenyl ring in **64** away from the steric bulk of the auxiliary. Second, conrotation in this direction moves the methyl group on the allene away from the phenyl. Under the reaction conditions cyclic cation **65** is probably formed irreversibly. Loss of the chiral auxiliary as a stable cation

Table 3. Cyclizations of Allene Terminally Substituted with a Methyl Group[a]



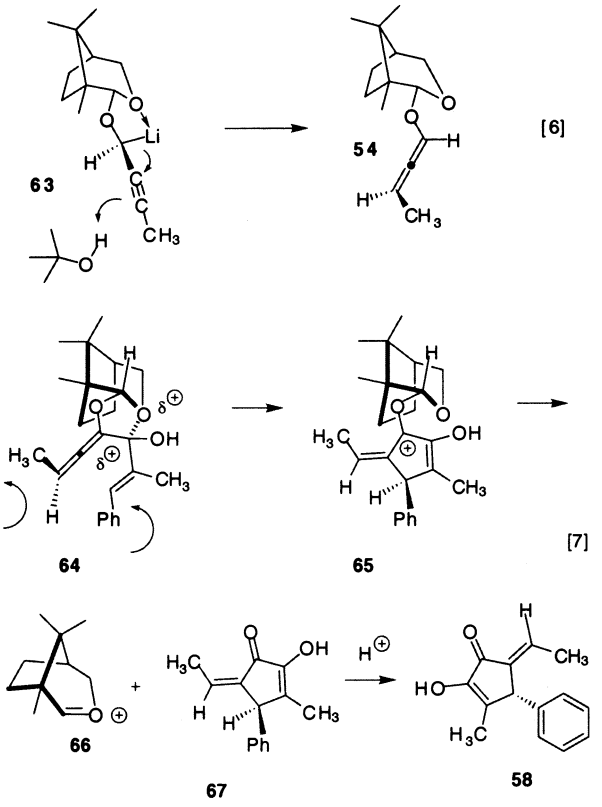
Entry	Amide	Cyclopentenone	Yield (ee)
1	 10	 57	64% (73% ee)
2	 12	 58	67% (79% ee)
3	 22	 59	62% (85% ee)
4	 34	 60	56% (81% ee)[b]
5	 44	 61	68% (70% ee)

[a] All reactions were performed according to the optimal conditions shown in entry 5 of Table 1 starting with the ca. 20/1 mixture of **54** and **55**. [b] Determined by chiral HPLC of the derived benzoate.

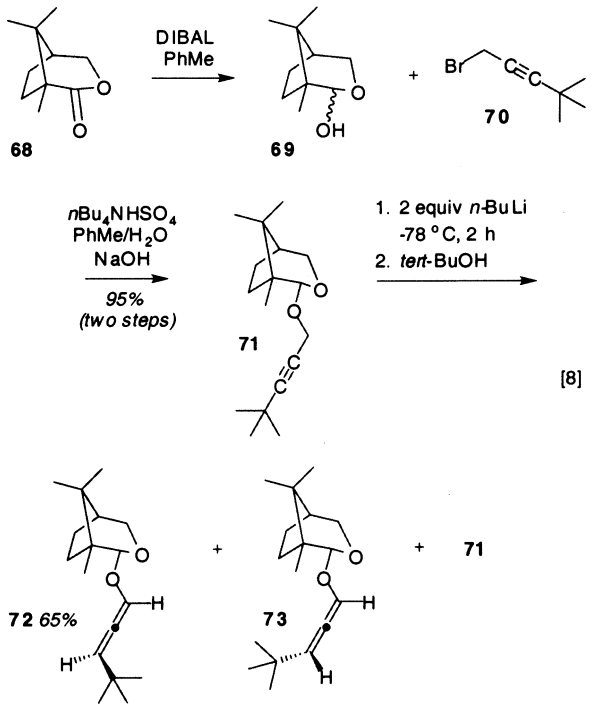
66 leads to cyclopentenone **67** as the kinetic product, which undergoes acid-catalyzed isomerization in situ to give *E* isomer **58** as the final product.[16]

The results of Table 3 show that the yield and ee of all cyclic products were good. For the sake of convenience, isomerization to the thermodynamically favored *E* isomers was allowed to take place, and data have been recorded for the *E* isomers only. With the exception of the result of entry 4, the ee values of all products are as good or better than the corresponding reactions of the same enamides with allenyllithium **9**. This is what one would predict for the products of the reaction in which auxiliary and allene chirality are matched. These results also suggest that, if one were to replace the methyl group in allene **54** by a larger

(16) Note that "clockwise" conrotation in **64** will produce a diastereomer of **67** in which the exocyclic double bond is *E*. Therefore, *Z*-to-*E* isomerization of the product in situ may erode the observed ee.



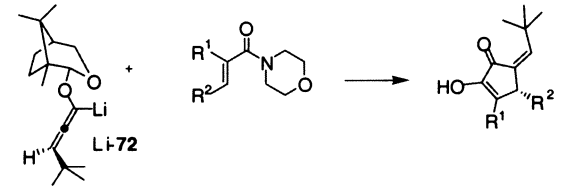
alkyl group, much higher enantioselectivities would be expected for the cyclic products. This is exactly what we have observed.

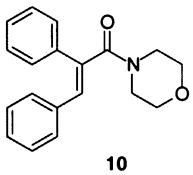
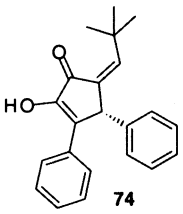
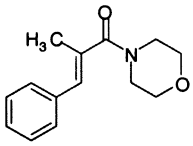
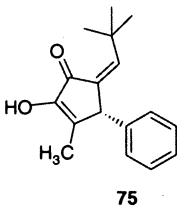
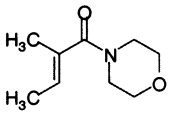
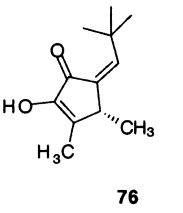
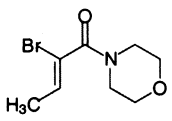
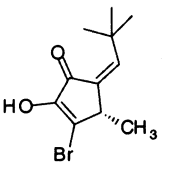
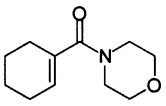
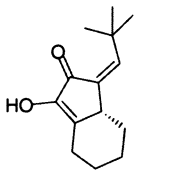


The γ-*tert*-butyl allene **72** was prepared according to the procedure that is summarized in eq 8. Lactone **68** was reduced to lactol **69**. Alkylation of **69** with 2 equiv of propargylic bromide **70**[17] under phase-transfer conditions produced α-isomer

(17) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed; Elsevier: New York, 1988; pp 248−249.

Table 4. Cyclizations of Allene Terminally Substituted with a *tert*-Butyl Group[a]



Entry	Amide	Cyclopentenone	Yield (ee)
1	 10	 74	74% (96% ee)
2	 12	 75	80% (96% ee)
3	 22	 76	61% (92% ee)
4	 34	 77	42% (93% ee)[b]
5	 44	 78	60% (92% ee)

[a] All reactions were performed according to the optimal conditions shown in entry 5 of Table 1. [b] Determined by chiral HPLC of the derived benzoate.

71 as the exclusive product. Because the signals in the ^{1}H NMR spectra at 300 MHz for the propargylic methylene and the camphor-derived portions of **71** and **56** deviated by less than 0.1 ppm in all cases, the stereochemistry of **71** was assumed to be as shown in eq 8. Isomerization of propargyl ether **71** to allenyl ethers **72** and **73** took place under the same conditions that were used for **56**. The major allene diastereomer **72** was isolated in 65% yield, along with 27% of a mixture of allene **73** and propargyl ether **71**. The approximate ratio of **72** to **73** was 3/1. In contrast to **54** and **55**, diastereomers **72** and **73** were easily separable by flash column chromatography. That major

isomer **72** has the stereochemistry indicated in the structure shown in eq 8 can be shown by the following two experiments (eqs 9 and 10).

Major allene diastereomer **72** was deprotonated, and the lithio allene was allowed to react with morpholino enamide **22** (eq 9). Acid-catalyzed cyclization, as before, provided (*Z*)-cyclopentenone **76** along with a small amount of *E* isomer **79**. Products **76** and **79** were isolated in 94 and 92% ee, respectively, suggesting that the reaction of eq 9 corresponds to the matched case. The experiment was repeated with a 9/1 mixture of allenes enriched in minor diastereomer **73** (eq 10). Cyclopentenones **80** and **81** were isolated from this experiment in lower yield and lower ee, 72 and 61% ee for **80** and **81**, respectively. The absolute stereochemistry at C-4 in products **80** and **81** is the *opposite* of that of products **76** and **79**. This proves that the reaction of eq 10 corresponds to the mismatched case, that the reaction of eq 9 corresponds to the matched case, and that the effect of the allene stereochemistry in the case of **73** completely overwhelms that of the auxiliary. By isomerizing **76** to **79** and comparing the chiral HPLC chromatograms it was shown that **76** and **79** have the same stereochemistry at C-4. The same experiment was done for **80** and **81**. The minor peak in the chromatogram of **79** was the major peak in the chromatogram of **81**.

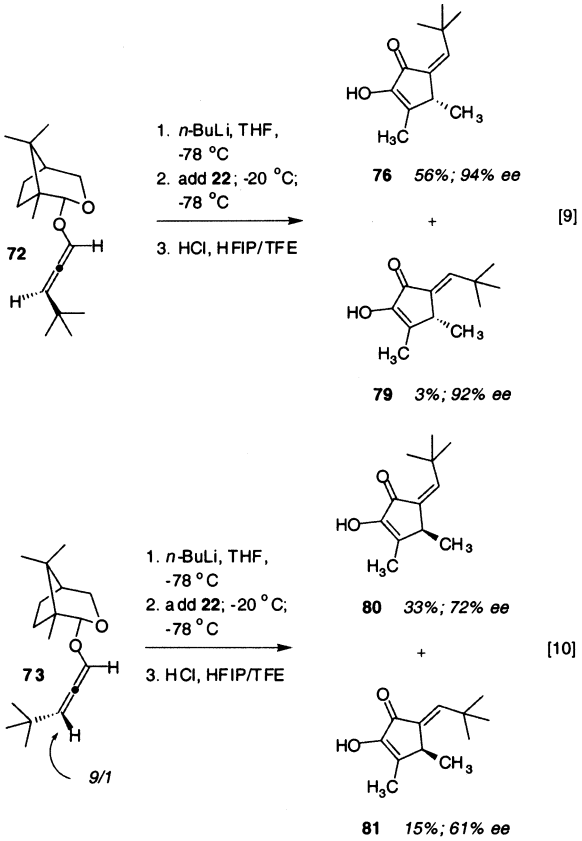
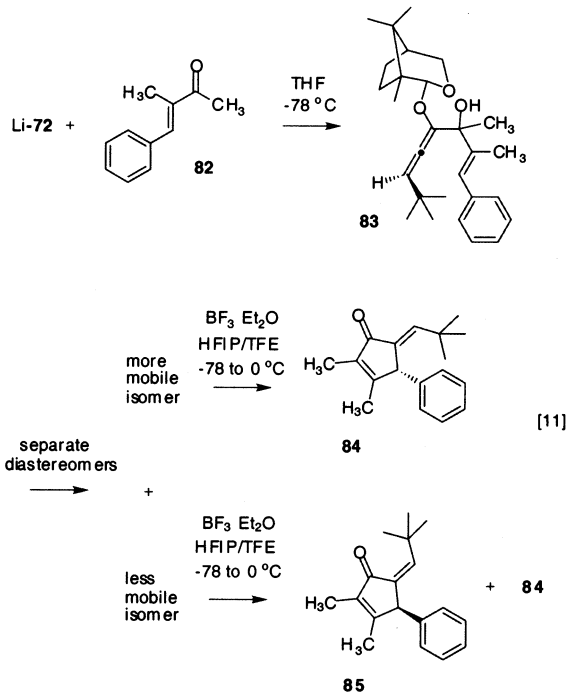


Table 4 summarizes the results of the cyclizations of **72** with representative morpholino enamides. In this work, the acid was neutralized at low temperature by the addition of saturated aqueous sodium bicarbonate. This modification of our normal procedure allows the kinetic product bearing the *Z* geometry of the exocyclic double bond to be isolated. Table 4 reflects this modified procedure. The enantiomeric excesses of the products are all excellent, and range from 92 to 96% ee.

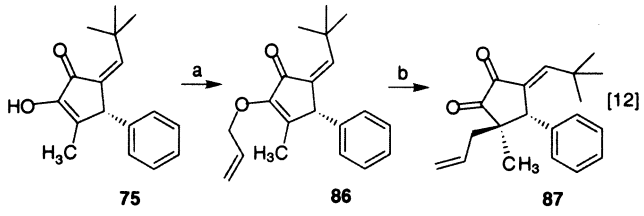
To probe the scope of this process a little further, the experiments that are summarized in eq 11 were carried out. Enamide **12** was allowed to react with methyllithium to give ketone **82**. Addition of the lithio allene derived from **72** led to a mixture of diastereomeric tertiary alcohols **83** that were separable by flash column chromatography. Pure samples of the two diastereomers were cyclized independently. Cyclization of the chromatographically less mobile diastereomer led to a 1:1 mixture of **84** and **85**, whereas cyclization of the more mobile diastereomer led almost exclusively to **84** along with a small amount (<5%) of a *Z* diastereomer of unknown absolute configuration.[18] These results suggest that in the case of tertiary alcohols such as **83**, the direction of conrotation is strongly influenced by the stereochemistry of the tertiary alcohol. This is somewhat surprising, since it clearly shows that formation of the carbon−carbon bond takes place at least in part before the ionization of the tertiary, bis-allylic alcohol has occurred.[10] For the cyclization of tertiary alcohols such as **83**, boron trifluoride etherate is usually the optimal catalyst;[19] however, we have not performed a completely comprehensive correlation of catalysts, yields, and enantiomeric excesses for the variants of the allene cyclopentannelation. At the present stage of development of the methodology, the enantioselective cyclization of tertiary alcohols is not preparatively useful.[20,21]



As a final illustration of some of the applications to synthesis that may follow, we performed the reactions that are summarized in eq 12. Cyclopentenone **75** was converted to allyl ether **86** in 90% yield, and then heated to 190 °C in *o*-dichlorobenzene for 30 min. This led to α-diketone **87** in 70% isolated yield,[22] isomerization of the exocyclic double bond having taken place during the Claisen reaction. Attempts to catalyze the Claisen process either with $PdCl_2(PhCN)_2$[23] or with $Ho(fod)_3$[24] failed.

(18) The overall yield of **84** (95% ee) for the two steps from **82** was 67%. *Z* diastereomer **85** was isomerized to *ent*-**84** (93% ee) in 22% overall yield from **82** by exposure to sunlight in benzene containing catalytic PhSSPh.
(19) See ref 13 in: Harrington, P. E.; Li. L.; Tius, M. A. *J. Org. Chem.* **1999**, *64*, 4025.

Product **87** was isolated as a single diastereomer. The assignment of stereochemistry of the quaternary carbon atom was made on the basis of the positive nOe between the benzylic methine proton and the allylic methylene protons. The positive nOe between the *tert*-butyl group and the benzylic methine and phenyl protons shows that the geometry of the exocyclic double bond is *E*.



75 **86** **87**

(a) *i*Pr$_2$NEt, allyl bromide, MeNO$_2$, 50 °C, 17 h, 90%; (b) *o*-DCB, 190 °C, 30 min, 70%.

Conclusions

The scope of an asymmetric cyclopentannelation reaction that we recently developed for a synthesis of natural roseophilin has been defined. Yields and enantiomeric excesses of cyclic products are generally good in the case of the terminally unsubstituted allene (Table 2). Moreover, a wide variety of carbon and heteroatomic substituents are tolerated, suggesting broad synthetic utility. In the cases in which the allene bears a terminal substituent one must consider matched and mismatched cases, since allene chirality as well as chiral auxiliary affect the stereochemical outcome of the cyclization. We were fortunate that the isomerization of propargyl ether to allenyl ether was controlled by the auxiliary so as to produce a preponderance of matched products **54** and **72** (eqs 5 and 8). The higher enantiomeric excesses of the products of Tables 3 and 4 versus those of Table 2 reflect the chiral auxiliary and axial chirality of the allene working in concert. The effect of the large *tert*-butyl substituent in allene ether **72** leads to the highest enantiomeric excesses we have been able to achieve to date (Table 4). A challenge for the future will be to replace the *tert*-butyl group with an easily cleavable sterically demanding group.

The selective isomerization of propargyl ethers to allene ethers of defined axial stereochemistry has not been examined in detail. It may be possible through manipulation of reaction conditions to improve the diastereomeric ratio of products. This would be significant, as there is currently no general method for the preparation of axially chiral allenyl ethers.[8]

A question that we had early in our investigation was whether the cyclization would prove to be suitable for the asymmetric construction of quaternary carbon atoms β to the enolic hydroxyl group. Our preliminary results (eq 4) suggest that this is the case, however, improvement of the reactivity of the morpholino enamide, the electrophilic partner in the addition step, will be necessary in order to fully exploit the potential of this process. One can use the method for the asymmetric construction of quaternary carbon atoms through the Claisen reaction shown in eq 12. Trost has demonstrated excellent transfer of asymmetry in a related system.[24]

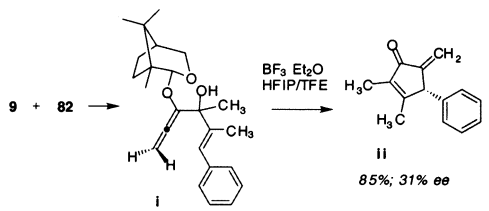
There appear to be (at least) two mechanistic pathways for the cationic cyclization. In the case of the morpholino enamides, the stereochemical outcome of the reactions is consistent with a thermally allowed conrotation (eq 7). By contrast, enones apparently belong to a different manifold of reactions in which the stereochemistry of the tertiary alcohol adduct influences the stereochemical course of the cyclization (eq 11). Since we now appear to have an understanding of the mechanism of the asymmetric cyclopentannelations, improvements in auxiliary design can be contemplated.[25]

Experimental Section

Representative Procedure. Preparation of 29. To a solution of allene **H-9** (115 mg, 0.544 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (225 μL, 2.46 M in hexanes, 0.554 mmol). After 30 min, a solution of amide **28** (84 mg, 0.40 mmol) in THF (3 mL) at −78 °C was added via cannula. The reaction mixture was warmed from −78 to −35 °C over 1 h, cooled to −78 °C, and quenched by rapid addition, through a large bore cannula, to HCl in HFIP/TFE (generated by the addition of 750 μL of acetyl chloride to a mixture of 3 mL of HFIP and 3 mL of TFE) at −78 °C. The flask was removed from the cooling bath, warmed to room temperature, and diluted with saturated $NaHCO_3$, pH 7 buffer, brine, and EtOAc. The aqueous phase was extracted with EtOAc (3×), and the combined organic extracts were washed with brine (1×) and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (5−10% EtOAc in hexanes) gave cyclopentenone **29** (60 mg, 84% yield, 87% ee) as a white solid: mp 97−98 °C; R_f = 0.39 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.99 (s br, 1H), 5.31 (s, 1H), 2.95 (s br, 1H), 2.09 (d, J = 1.0 Hz, 3H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 152.3, 143.5, 142.3, 116.3, 54.6, 35.1, 28.9, 15.7; IR (neat) 3310 (br), 2960, 1685, 1620, 1405, 1360, 1195, 1105 cm^{-1}; EIMS *m*/*z* 125 (9), 124 (100), 95 (7); HREIMS calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1280; chiral HPLC (5% 2-propanol in hexanes, Chiralcel OD, 250 mm × 10 mm, 254 nm, 1 mL/min) t_R = 22.1 min (major), t_R = 24.7 min (minor).

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support, and Dr. Oliver Weichold for the synthesis of the carboxylic acids that were used for the

(20) For example, cyclization of **i**, the adduct of **9** with enone **82**, led to cyclopentenone **ii** in good yield, however the ee was only 31%.



i **ii**

85%; 31% ee

(21) The results of eq 11 apparently contradict earlier observations made in our group.[2] It may be possible to reconcile the two sets of results if ionization of the tertiary benzylic alcohol derived from (−)-**16** (Scheme 3 in ref 2) is complete prior to the development of the C3−C4 bond in (−)-**17**.

(22) Ponaras, A. A. *Tetrahedron Lett.* **1980**, *21*, 4803.
(23) Hiersemann, M. *Synlett* **1999**, 1823.
(24) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **2000**, *122*, 3785.

(25) A reviewer raised the question of potential racemization of the final products. Circumstantial evidence strongly suggests that if any racemization takes place, this is a very slow process under the reaction conditions. First, our measurement of the enantiomeric excess of each of the reaction products has been invariant, within the confidence limits of our measurement, over two or more runs. As mentioned in ref 13 above, our uncertainty in the HPLC measurements is no more than ±2%. Second, since we did not take great pains to reproduce the times of exposure of the intermediate products to the strongly acidic conditions for the cyclization process, if acid-catalyzed racemization were taking place at an appreciable rate, it is very likely that we would have detected this in at least one of the examples. For example, the reaction of eq 9 was warmed to room temperature in the presence of HCl/HFIP/TFE, and product **76** was isolated with 94% ee. The *same* product is reported in Table 4, entry 3, from a reaction that was quenched at −78 °C in which the ee of **76** was 92%. There is no difference in the enantiomeric excess of the product from the two reactions, within the uncertainty of the measurement.

preparation of enamides **46** and **48**. We thank Callery Chemical Co. for a generous gift of potassium *tert*-butoxide.

Supporting Information Available: Experimental procedures and spectroscopic data for **54**, **71**, **72**, **84**, **86**, **87**, and **ii**. Spectroscopic data for **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25**, **27**, **31**, **33**, **35**, **37**, **39**, **41**, **43**, **45**, **47**, **49**, **53**, **56**−**61**, and **74**−**78**, (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA020591O