Palladium(0)-Catalyzed Rearrangement of *N*-Allylenamines. Synthesis of δ,ε-Unsaturated Imines and γ,δ-Unsaturated Carbonyl Compounds

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Palladium-catalyzed rearrangement of *N*-allylenamines proceeds readily in the presence of a catalytic amount of trifluoroacetic acid to give δ,ε-unsaturated imines. Conveniently, δ,ε-unsaturated imines can be prepared directly by the reactions of allylamines with carbonyl compounds under the same conditions highly efficiently. The reaction involves oxidative addition of Pd(0) species to allylenammonium salts to give π-allylpalladium complexes, which undergo intramolecular nucleophilic reaction with enamines to give imines. The δ,ε-unsaturated imines are versatile synthetic precursors such as γ,δ-unsaturated carbonyl compounds. Synthetic applications are also described.

Cope and Claisen rearrangements are of importance in view of synthetic and mechanistic aspects and have been utilized for various synthetic strategies. Unfortunately, the rearrangements require high temperature (generally ~200 °C). To solve this problem, two approaches have been extensively studied. First, the rearrangements are accelerated by placing electron-donating or -withdrawing groups in the substrates,[1] or more remarkable by introducing a positive charge,[2] a negative charge,[3] or a zwitterion[4] in the system. The second approach is to find catalysts that will accelerate these reactions. Rearrangements catalyzed by metals have been found, and their synthetic utility was enhanced. Overman reported for the first time that the palladium(II)-promoted Cope rearrangement can be conducted in a catalytic fashion.[5] Catalytic Cope rearrangements have been extensively investigated, by using transition metal catalysts such as Hg(II),[6] Pd(II),[7] Pd(0),[8] Pt(0),[9] Rh(I),[7] and Ir(I)[7] complexes and various rearrangements such as allyl carboxylate (C–O → C–O) rearrangement,[10,11] *O*-allyl thiocarboxylate (C–O → C–S) rearrangement,[7b] allyl imidate (C–O → C–N) rearrangement,[7a,8c] allyl thioimidate (C–S → C–N) rearrangement,[12] *O*-allyl phosphorothionate (C–O → C–S) rearrangement,[8d] and allyl vinyl ether (C–O → C–C) rearrangement[8a,8b,13] are conducted under mild conditions.

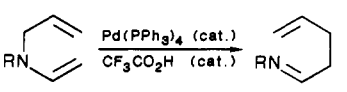
Table I. Effect of Acids on the $Pd(PPh_3)_4$-Catalyzed Rearrangement of 1 to 2[a]

acid	convn,[b] %	pK_a[c]
none	<5	
HCl[d]	<5	−7
CH_3SO_3H	100	−1.86
p-TsOH·H_2O	100	−1.34
CCl_3CO_2H	<5	0.51
CF_3CO_2H	100	0.52
Cl_2CHCO_2H	85	1.35
$ClCH_2CO_2H$	14	2.87
$PhCO_2H$	30	4.20
CH_3CO_2H	10	4.75

[a] A mixture of 1 (0.5 mmol), $Pd(PPh_3)_4$ (10 mol %), and acid (10 mol %) in benzene (3 mL) was stirred at 50 °C for 20 h under Ar. [b] Conversions were determined by ^1H NMR analysis (allylic methylene signals: convn, % = 2/(1 + 2) × 100). [c] In aqueous solution (ref 18). [d] HCl in benzene (0.33 M).

The 3-aza-Cope (C–N → C–C) rearrangement is highly useful because the substrate *N*-allylenamines are readily prepared from allylamines and carbonyl compounds[14] and the selective carbon–carbon bond formation gives various imines and related compounds. Since thermal 3-aza-Cope rearrangements require elevated temperature,[15] catalytic 3-aza-Cope rearrangement has been investigated by using titanium tetrachloride as a Lewis acid catalyst;[16] however, the titanium-promoted reaction is not satisfactory, because the converted yields are low and the reaction is applied to the *N*-allylenamines of aldehydes but not to those of ketones.

We have found that *N*-allylenamines undergo palladium(0)-catalyzed 3-aza-Cope rearrangement to give the corresponding δ,ε-unsaturated imines in the presence of a catalytic amount of a strong protic acid such as trifluoroacetic acid as depicted in eq 1. Further, we have



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found that δ,ε-unsaturated imines can be obtained con-

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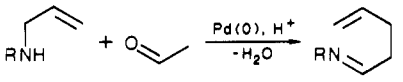
Table II. Palladium Catalysts for the Rearrangement of 1[a]

entry	catalyst	acid	convn,[b] %
1	$Pd(PPh_3)_4$	CF_3CO_2H	100
2	$Pd_2(dba)_3 \cdot CHCl_3$–PPh_3	CF_3CO_2H	83
3	$Pd(OAc)_2$–PPh_3	CF_3CO_2H	77
4	$Pd(OCOCF_3)_2$–PPh_3	none	100
5	$Pd(OAc)_2$–dppe[c]	CF_3CO_2H	0
6	$Pd(OAc)_2$–PPh_3	none	0
7	$Pd_2(dba)_3 \cdot CHCl_3$–PPh_3	none	0
8	$Pd(OAc)_2$	CF_3CO_2H[d]	0
9	$Pd(OCOCF_3)_2$	CF_3CO_2H	0
10	$Pd_2(dba)_3 \cdot CHCl_3$	CF_3CO_2H	0

[a] A mixture of 1 (0.5 mmol), palladium catalyst (10 mol %), PPh_3 (40 mol %), and acid (10 mol %) in benzene (3 mL) was stirred at 50 °C for 20 h under Ar. [b] Conversions were determined by ^1H NMR analysis. [c] 1,2-Bis(diphenylphosphino)ethane (dppe) (20 mol %). [d] 5 mol % of CF_3CO_2H was used.

veniently by one-pot palladium(0)/acid-catalyzed reactions of allylamines with carbonyl compounds as depicted in eq 2. Full details of palladium(0)/acid-catalyzed 3-aza-Cope



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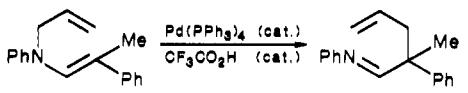
rearrangements are described with respects to scope, limitation, mechanism, and synthetic applications.[17]

Results and Discussion

3-Aza-Cope Rearrangement of *N*-Allylenamines. Palladium-catalyzed 3-aza-Cope rearrangement of *N*-allyl-*N*-phenyl-2-phenyl-1-propenylamine (1) was investigated precisely. By using palladium(II) catalysts, the rearrangement did not take place; however, by using palladium(0) catalysts such as $Pd(PPh_3)_4$, $Pd(OAc)_2$–PPh_3, and $Pd_2(dba)_3 \cdot CHCl_3$–PPh_3, a small amount of *N*-(2-methyl-2-phenyl-4-pentenylidene)aniline (2) was obtained. Surprisingly, the addition of a catalytic amount of a strong protic acid enhanced the rate of the rearrangement drastically (eq 3). The effect of the addition of 10 mol % of



1 2 (3)

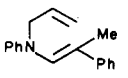
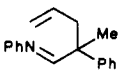
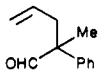
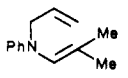
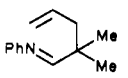
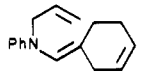
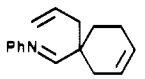
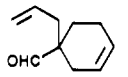
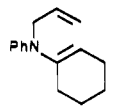
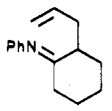
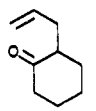
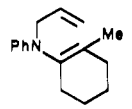
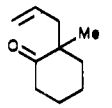
various acids for the reaction of 1 in the presence of 10 mol % of $Pd(PPh_3)_4$ catalyst in benzene at 50 °C is summarized in Table I. Strong organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, and trifluoroacetic acid enhance the reaction of 1 enormously. The conversion of 1 is dependent on the pK_a values of organic acids.[18] In the presence of Lewis acids such as $AlCl_3$ and $BF_3 \cdot OEt_2$ and weak acids such as acetic acid, the reaction does not take place. Trichloroacetic acid, hydrochloric acid, and alkyl halides such as methyl iodide are not effective probably because these compounds react with $Pd(PPh_3)_4$ to give the corresponding Pd(II) complexes.[19] The addition of excess of an acid catalysts in comparison with the palladium(0) catalyst decreases the yield of 2. The rearrangement of 1 in the presence of an equivalent of trifluoroacetic acid gives 2 in only 20% yield. Pd(II) complexes are not effective even in the presence of trifluoroacetic acid.

Table III. The Solvent Effect on the Palladium-Catalyzed Reaction of 1[a]

solvent	convn,[b] %	solvent	convn,[b] %
C_6H_6	100	CH_3CN	<5
$CH_3C_6H_5$	100	CH_2Cl_2	0
THF	24		

[a] A solution of 1 (0.5 mmol), $Pd(PPh_3)_4$ (10 mol %), and CF_3CO_2H (10 mol %) in a solvent (3 mL) was stirred at 50 °C for 20 h under Ar. [b] Conversion was determined by ^1H NMR analysis.

Table IV. Palladium(0)-Catalyzed 3-Aza-Cope Rearrangement of *N*-Allylenamines[a]

substrate	temp, °C	product	yield,[b] %
 1	50	 2	82
1	50	 3	78[c]
 4	100	 5	99[d]
 6	100	 7	98
6	50	 8	85[c]
 9	50	 10	72
9	50	 11	77[c]
 12	100	 13	69[c]

[a] The reactions are similar to the general procedure described in the experimental section. [b] Isolated yields by Kugelrohr distillation. [c] Hydrolysis with a 0.5 N HCl solution. [d] Isolated yields by column chromatography on Al_2O_3.

Next, the effect of palladium catalysts on the rearrangement of 1 in the presence of trifluoroacetic acid was examined precisely. The representative results are summarized in Table II. Pd(0)–phosphine catalysts show excellent catalytic activity (entries 1–3). Pd(II) complexes (entries 8, 9) and other complexes such as Ru(II), Rh(I), and Mo(0) complexes show no catalytic activity even in the presence of appropriate acids. $Pd(OCOCF_3)_2$–PPh_3 shows catalytic activity because of liberation of a small amount of trifluoroacetic acid (entry 4). It is noteworthy that diphosphine ligands are not effective (entry 5).

The solvent effect was also examined on the same reaction of 1. As shown in Table III, nonpolar solvents such as benzene and toluene gave excellent conversion. THF

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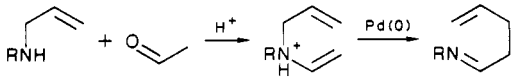
gave a poor result, and acetonitrile and dichloromethane gave no rearranged product.

The representative results of the palladium(0)-catalyzed 3-aza-Cope rearrangement of various *N*-allylenamines are shown in Table IV. δ,ε-Unsaturated imines were obtained in 72–99% isolated yields. Enamines that have weak nucleophilicity require higher reaction temperature. The reaction of isobutyraldehyde enamine requires higher reaction temperatures in comparison with 2-phenylpropanal enamine. The treatment of δ,ε-unsaturated imines with an aqueous acidic solution gives γ,δ-unsaturated carbonyl compounds readily in 62–85% isolated yields.

Direct Synthesis of δ,ε-Unsaturated Imines. Since acid-catalyzed condensation of secondary allylamines with carbonyl compounds gives *N*-allylenamines, direct synthesis of δ,ε-unsaturated imines was attempted by the palladium-catalyzed reaction of allylamines with carbonyl compounds. Indeed, δ,ε-unsaturated imines were obtained efficiently with removal of water by azeotropic distillation (eq 4). Without removal of water, γ,δ-unsaturated car-



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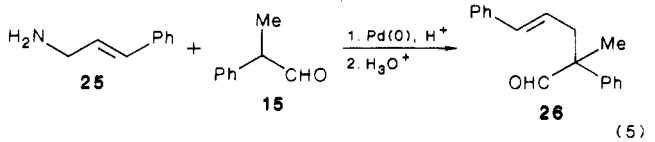
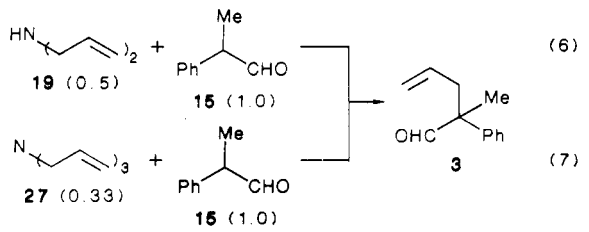
bonyl compounds were obtained in good to excellent yields. The representative results of the synthesis of δ,ε-unsaturated imines and γ,δ-unsaturated carbonyl compounds are summarized in Table V. The present reaction can also be applied to ketones in contrast to the titanium-promoted reaction of secondary allylamines, which gives poor yields of γ,δ-unsaturated aldehydes and does not work at all to form ketones.[16] The present reaction can be applied to primary allylamines. Thus, the palladium(0)/CF_3CO_2H-catalyzed reaction of 3-phenylallylamine (**25**) with 2-phenylpropanal (**15**) at 80 °C gave 2-methyl-2,5-diphenyl-4-pentenal (**26**) in 65% yield (eq 5). The intermediate



(5)

aldimine was hydrolyzed under the reaction conditions. It is noteworthy that both diallylamines and triallylamines can be utilized as the source of the allyl moiety. Thus, the reaction of aldehyde **15** with 0.5 equiv of diallylamine (**19**) gave **3** in 84% yield (eq 6), while the similar reaction with 0.33 equiv of triallylamine (**27**) gave **3** in 76% yield (eq 7).



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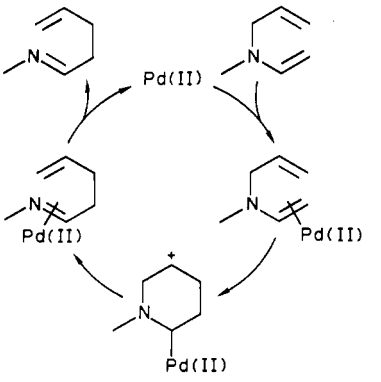
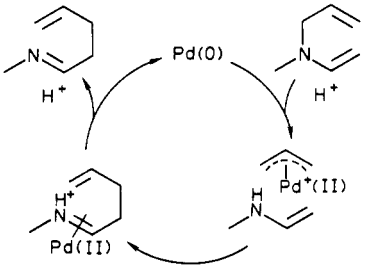
(7)

Mechanism. The palladium-catalyzed 3-aza-Cope rearrangement of *N*-allylenamines can be rationalized by assuming two pathways. The first is the palladium(II)-promoted reaction as shown in Scheme I. Coordination of the Pd(II) species to the carbon–carbon double bond of enamines and subsequent nucleophilic reaction of the γ-carbon of allylamines gives a six-membered palladated intermediate **28**, which undergoes elimination of Pd(II) species to give [3, 3] rearranged imines. An alternative Pd(II)-promoted mechanism that involes the coordination of Pd(II) species to the carbon–carbon double bond of the

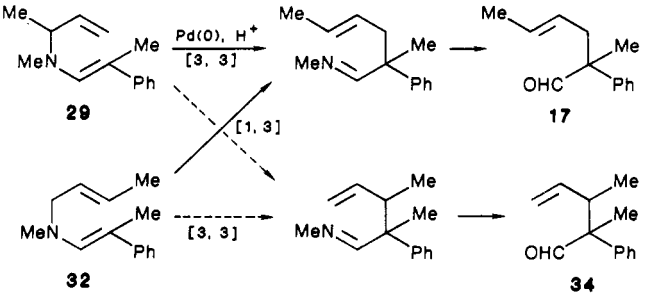
Scheme I



Scheme II



Scheme III



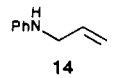
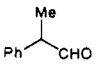
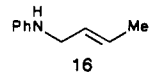
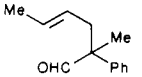
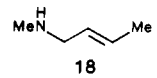
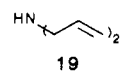
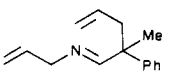
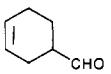
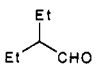
allylamine followed by nucleophilic attack of the enamine seems unlikely, because the carbon–carbon double bond of enamines has a stronger coordinating ability to Pd(II) species, although the β-carbon of enamines is more nucleophilic than the γ-carbon of allylamines. It is noteworthy that the Pd(II)-promoted rearrangement of allyl vinyl ethers does not proceed because Pd(II) species coordinate to the vinylic carbon–carbon double bond rather than the allylic carbon–carbon double bond.[5c,13]

The second mechanism is the Pd(0)-promoted pathway shown in Scheme II. Oxidative addition of a Pd(0) species to the carbon–nitrogen bond of allylenammonium ion gives the π-allylpalladium complex and enamines. Nucleophilic reaction of enamines gives rearranged imines. The role of the acid catalyst is the formation of the reactive substrate *N*-allylenammonium ions. Oxidative addition of Pd(0) species to quarternary salts of allylamines proceeds faster than that to allylamines.[20]

This Pd(0)-catalyzed mechanism is supported by the regioselectivity of the reactions of methyl-substituted *N*-allylenamines as shown in Table VI. The palladium-catalyzed reactions of *N*-(1-methylallyl)enamine **29** and *N*-(2-methylallyl)enamine **30** followed by hydrolysis gave [3, 3] rearranged **17** and **31**, respectively. However, the

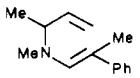
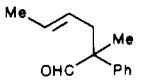
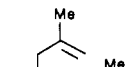
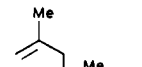
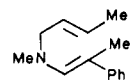
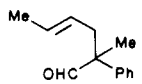
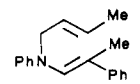
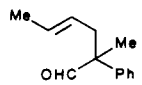
(20) Hirao, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *J. Organomet. Chem.* **1982**, *236*, 409.

Table V. Reaction of Secondary Allylamines with Carbonyl Compounds[a]

allylamine	carbonyl compound	product	yield,[b] %
 14	 15	2	86
 16	15	 17	84[c]
 18	15	17	63[c]
 19	15	 20	81
14	 21	7	99
14	21	8	77[c]
14	 22	 23	64[c]
14	 24	11	61[c]

[a] The reactions are similar to the general procedure described in the Experimental Section. [b] Isolated yields by column chromatography on Al_2O_3. [c] Hydrolysis with a 2 N HCl solution.

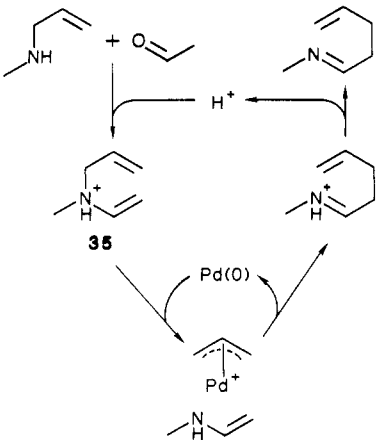
Table VI. Rearrangement of Methyl-Substituted *N*-Allylenamines[a]

substrate	product	yield,[b] %
 29	 17	79[c]
 30	 31	78
 32	 17	62
 33	 17	58

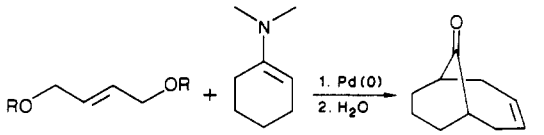
[a] The reactions are similar to the general procedure described in the Experimental Section. The products were hydrolyzed with a 0.5 N HCl solution. [b] Isolated yields by Kugelrohr distillation. [c] Isolated yield by column chromatography on Al_2O_3.

similar reaction of *N*-2-butenylenamine **32** afforded the [1, 3] rearranged product of 4-hexenal **17**. That is, *N*-(1-methylallyl)enamine **29** was converted into the [3, 3] rearranged product, while *N*-2-butenylenamine **32** was converted into [1, 3] rearranged product (Scheme III). These results exclude the mechanism that involves a Pd(II)-promoted [3, 3] rearrangement.

Scheme IV



In 1973 we reported that the palladium(0)-catalyzed reaction of 1,4-dialkoxy-2-butene with cycloalkanone enamines gives bicyclic ketones highly efficiently (eq 8).[21]

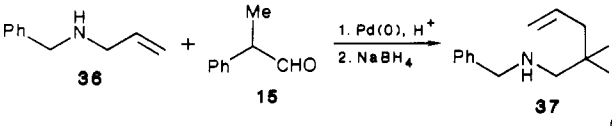


(8)

The key step of the reaction is the insertion of Pd(0) species into the C–OR bond of allyl ethers to give π-allylpalladium complexes, which undergo electrophilic reaction with enamines. Enamines are excellent nucleophiles toward π-allylpalladium complexes to form carbon–carbon bonds. The present reaction seems to involve a similar pathway, which involes nucleophilic reactions of enamines.

The reaction mechanism for the direct formation of δ,ϵ-unsaturated imines can be rationalized by assuming Scheme IV. Acid-catalyzed condensation of allylamines with carbonyl compounds gives enammonium ion **35**. Oxidative addition of **35** into a Pd(0) species gives the π-allylpalladium complex and enamine. Nucleophilic addition of the enamine followed by removal of the Pd(0) species and a proton gives the product imine to complete the catalytic cycle.

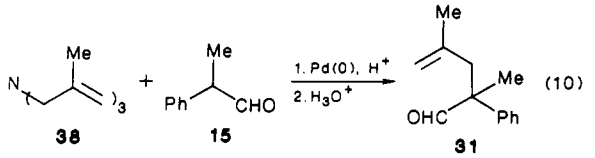
Synthetic Application. The δ,ϵ-unsaturated imines, which are readily derived from the present 3-aza-Cope rearrangement, are important synthetic key intermediates. For example, simple reduction of imines with $NaBH_4$ gives the corresponding δ,ϵ-unsaturated amines. 4-Pentenylamine **37** can be prepared by the reaction of *N*-allylbenzylamine (**36**) and 2-phenylpropanal (**15**), followed by reduction with $NaBH_4$ in 66% yield (eq 9). The γ,δ-unsaturated aldehydes are also valuable intermediates. 2,4-Dimethyl-2-phenyl-4-pentenal (**31**), which is the flavor fragrance of rose geranium,[22] can be readily prepared by the palladium-catalyzed reaction of 2-phenylpropanal (**15**) with tris(2-methylallyl)amine (**38**) in 93% yield (eq 10). Further, 2,4-dimethyl-4-phenyltetrahydrofuran (**40**), which is a flavor of citrus,[23] is prepared simply. Thus, the re-



(9)

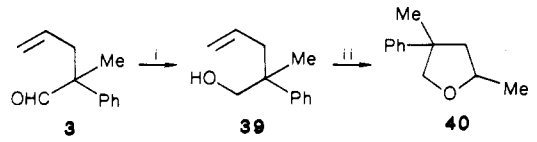
(21) Onoue, H.; Moritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973**, 121.

(22) Terraes, R. F. U.S. Pat. 3 996 290, 1976; *Chem. Abstr.* **1977**, *86*, P89394c.



38 15 31

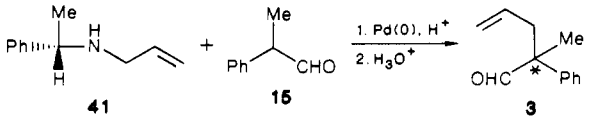
duction of pentenal **3**, which was prepared from **14** and **15** in 82% yield, gave alcohol **39** in 90% yield. Oxymercuration of **39** with $Hg(OAc)_2$ and subsequent $NaBH_4$ reduction gave **40** in 88% yield.



3 39 40

(i) $LiAlH_4$; (ii) $Hg(OAc)_2$, $NaBH_4$.

Since asymmetric induction at the quarternary carbon is of interest,[24] possibility of the application of the present rearrangement was examined. Only one example of asymmetric 3-aza-Cope rearrangement has been reported concerning the titanium-promoted reaction of (+)-*N*-(1-methylallyl)-*N*-phenyl-2-phenyl-1-propenylamine, which gave (+)-2-methyl-2-phenyl-4-hexenal in 15% ee.[16] The reaction of optically active *N*-allyl-(*S*)-1-phenylethylamine (**41**) with 2-phenylpropanal (**15**) in the presence of $Pd(PPh_3)_4$ (5 mol %) and CF_3CO_2H (2.5 mol %) in benzene at 80 °C followed by hydrolysis gave **3** in 84% yield. The



41 15 3

optical yield of **3** ($[\alpha]^{21}_D$ +9.78° (*c* 3.82, $CHCl_3$)) was determined to be 12% ee by the NMR analysis of MTPA ester (1-methoxy-1-(trifluoromethyl)phenylacetate) of alcohol **39**,[25] which was derived from the reduction of **3** with $LiAlH_4$. Satisfactory asymmetric induction to quarternary carbon could not be obtained at even lower temperature (50 °C, $[\alpha]^{22}_D$ +9.29° (*c* 3.3, $CHCl_3$)) at the present stage.

Conclusion

3-Aza-Cope rearrangement of *N*-allylenamines proceeds efficiently in the presence of both palladium(0) catalyst and acid catalyst. γ,δ-Unsaturated imines can be prepared simply from the reaction of allylamines with carbonyl compounds.

Experimental Section

General Procedures. NMR spectra were recorded on a 60-MHz Model PMX-60-SI (JEOL) and a 100-MHz JNM-FX-100 (JEOL) spectrometer. IR spectra were recorded on a Hitachi 215 spectrometer. GLC analyses was carried out on Shimadzu GC-8A flame ionization gas chromatograph by using a 1-m × 3-mm analytical column packed with 10% SE 30 on 80–120 mesh Uniport HP. Mass spectra were obtained on a Shimadzu GCMS-QP1000 by using analytical columns packed with silicon OV-17 on Chromosorb W or with SE 30 on Uniport HP. *N*-Allylaniline, diallylamine, and triallylamine were distilled over calcium hydride prior to use. *N*-Methyl-2-methylallylamine,[26] *N*-methyl-1-methylallylamine,[26] *N*-methyl-2-butenylamine,[26] *N*-(2-butenyl)aniline,[26] *N*-allylbenzylamine,[26] tris(2-methylallyl)amine,[26] *N*-allyl-(*S*)-1-phenylethylamine,[26] and 3-phenylallylamine[27] were prepared by the literature procedures. Dry benzene was distilled over benzophenone ketyl under argon. $Pd(PPh_3)_4$,[28] $Pd_2(dba)_3{\cdot}CHCl_3$,[29] $Pd(OAc)_2$,[30] and $Pd(CF_3CO_2)_2$[30] were prepared by the literature procedures. Trifluoroacetic acid was distilled over $KMnO_4$.

Preparation of *N*-Allylenamines. Into a 50-mL round-bottomed flask attached to a water separator filled with hexane were placed secondary allylamines (20–40 mmol), carbonyl compounds (20–40 mmol), benzene or xylene (30–40 mL), and *p*-toluenesulfonic acid monohydrate (10 mg). After the solution was heated at reflux for 20–40 h, the reaction mixture was distilled under reduced pressure to remove the solvent and unreacted starting materials. Distillation of the residue afforded *N*-allylenamines (36–88%).

***N*-Allyl-*N*-phenyl-2-phenyl-1-propenylamine (1)**: 88% yield; bp 104–120 °C (0.3 mmHg); ^1H NMR ($CDCl_3$) δ 1.95 (d, *J* = 1.5 Hz, 2.5 H), 2.09 (d, *J* = 1.5 Hz, 0.5 H), 4.11 (dt, *J* = 4.5, 1.5 Hz, 2 H), 4.96–5.43 (m, 2 H), 5.96 (ddt, *J* = 18, 10, 4.5 Hz, 1 H), 6.33 (d, *J* = 1.5 Hz, 1 H), 6.57–7.63 (m, 10 H).

***N*-Allyl-*N*-(2-methyl-1-propenyl)aniline (4)**: 85% yield; bp 109–115 °C (9 mmHg); mass spectrum (70 eV), *m/e* 187 (M^+); ^1H NMR ($CDCl_3$) δ 1.58 (s, 3 H), 2.15 (s, 3 H), 3.95 (dt, *J* = 5, 2 Hz, 2 H), 4.90–5.43 (m, 2 H), 5.53–6.26 (m, 2 H), 5.72 (m, 1 H), 6.30–7.37 (m, 5 H).

***N*-Allyl-*N*-phenyl-3-cyclohexenylidenemethylamine (6)**: 51% yield; bp 108–109 °C (0.23 mmHg); ^1H NMR ($CDCl_3$) δ 1.84–2.97 (m, 6 H), 3.90–4.14 (m, 2 H), 4.88–5.44 (m, 2 H), 5.44–6.30 (m, 4 H), 6.30–7.40 (m, 5 H).

***N*-Allyl-*N*-phenyl-1-cyclohexenylamine (9)**: 36% yield; bp 101–106 °C (0.5 mmHg); ^1H NMR ($CDCl_3$) δ 1.14–2.64 (m, 8 H), 3.73 (dt, *J* = 5, 1.5 Hz, 0.4 H), 4.00 (dt, *J* = 5, 1.5 Hz, 1.6 H), 4.91–5.37 (m, 2 H), 5.37–6.24 (m, 1 H), 6.4–7.4 (m, 5 H).

***N*-Allyl-*N*-phenyl-2-methyl-1-cyclohexenylamine (12)**: 42% yield; bp 80 °C (0.06 mmHg); ^1H NMR ($CDCl_3$) δ 1.4–2.5 (m, 8 H), 1.55 (s, 3 H), 3.88 (ddd, *J* = 4.9, 1.4, 1.4 Hz, 2 H), 5.04 (ddt, *J* = 9.5, 2, 1.4 Hz, 1 H), 5.12 (ddt, *J* = 17, 2, 1.4 Hz, 1 H), 5.89 (ddt, *J* = 17, 9.5, 4.9 Hz, 1 H), 6.41–7.13 (m, 5 H).

***N*-Methyl-*N*-(1-methylallyl)-2-phenyl-1-propenylamine (29)**: 70% yield; bp 115 °C (6 mmHg); ^1H NMR (CCl_4) δ 1.19 (d, *J* = 6.5 Hz, 3 H), 1.92 (d, *J* = 1 Hz, 0.6 H), 2.03 (d, *J* = 1 Hz, 2.4 H), 2.21 (s, 0.2 H), 2.52 (s, 0.8 H), 3.40 (dq, *J* = 6.8, 6.5 Hz, 1 H), 4.76–5.30 (m, 2 H), 5.50–6.16 (m, 1 H), 7.10 (br s, 5 H).

***N*-Methyl-*N*-(2-methylallyl)-2-phenyl-1-propenylamine (30)**: 60% yield; bp 95–99 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 1.75 (br s, 3 H), 1.97 (d, *J* = 1 Hz, 0.6 H), 2.08 (d, *J* = 1 Hz, 2.4 H), 2.66 (s, 3 H), 3.37 (br s, 2 H), 4.71–5.01 (m, 2 H), 5.86 (q, *J* = 1 Hz, 0.2 H), 6.15 (q, *J* = 1 Hz, 0.8 H), 7.21 (br s, 5 H).

***N*-2-Butenyl-*N*-methyl-2-phenyl-1-propenylamine (32)**: **(32)**: 88% yield; bp 106–110 °C (3 mmHg); ^1H NMR (CCl_4) δ 1.55–1.83 (m, 3 H), 1.89 (d, *J* = 1 Hz, 0.6 H), 2.01 (d, *J* = 1 Hz, 2.4 H), 2.27 (s, 0.6 H), 2.56 (s, 2.4 H), 3.08–3.47 (m, 2 H), 5.10–5.67 (m, 2 H), 5.73 (q, *J* = 1 Hz, 0.2 H), 5.97 (q, *J* = 1 Hz, 0.8 H), 6.87–7.5 (m, 5 H).

***N*-2-Butenyl-*N*-phenyl-2-phenyl-1-propenylamine (33)**: 59% yield; ^1H NMR (CCl_4) δ 1.69 (m, 3 H), 1.91 (d, *J* = 1 Hz, 2.4 H), 2.05 (d, *J* = 1 Hz, 0.6 H), 4.00 (m, 2 H), 5.15–5.67 (m, 2 H), 5.98 (q, *J* = 1 Hz, 0.2 H), 6.20 (q, *J* = 1 Hz, 0.8 H), 6.40–7.60 (m, 10 H).

The Pd(0)/CF_3CO_2H-Catalyzed Rearrangement of *N*-Allylenamines: General Procedure. A 25-mL flask with side inlet was flushed with argon. In the flask were placed *N*-allylenamines (1.00 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), dry benzene (3 mL), and CF_3CO_2H (1.9 μL, 0.025 mmol). The reaction mixture was stirred at 50–100 °C for 20 h. After the solvent was removed under reduced pressure, the residue was subjected to short column

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chromatography on Al_2O_3 with ether–hexane as an eluent followed by Kugelrohr distillation to give δ,ε-unsaturated imines.

For the preparation of the corresponding γ,δ-unsaturated carbonyl compounds, a solution of δ,ε-unsaturated imines (1.0 mmol) in benzene (3 mL) was stirred with a 2 N hydrochloric acid solution (3 mL) at room temperature for 1 h. It was extracted with ether (5 mL × 3). The combined extracts were washed with a $NaHCO_3$ solution and brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, Kugelrohr distillation or column chromatography on SiO_2 gave γ,δ-unsaturated carbonyl compounds.

***N*-(2-Methyl-2-phenyl-4-pentenylidene)aniline (2)**: bp 150–152 °C (2 mmHg) (Kugelrohr); IR (neat) 1650 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (s, 3 H), 2.79 (d, J = 7 Hz, 2 H), 4.75–5.23 (m, 2 H), 5.69 (ddt, J = 17, 9, 7 Hz, 1 H), 6.85–7.50 (m, 5 H), 7.26 (s, 5 H), 7.76 (s, 1 H).

2-Methyl-2-phenyl-4-pentenal (3): bp 136–140 °C (31 mmHg) (Kugelrohr); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 2.65 (d, J = 7 Hz, 2 H), 4.79–5.22 (m, 2 H), 5.60 (ddt, J = 17, 9, 7 Hz, 1 H), 7.23 (s, 5 H), 9.43 (s, 1 H). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.38; H, 8.15.

***N*-(2,2-Dimethyl-4-pentenylidene)aniline (5)**: bp 100–118 °C (6 mmHg) (Kugelrohr); IR (neat) 1645 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 6 H), 2.27 (d, J = 7 Hz, 2 H), 4.76–5.33 (m, 2 H), 5.89 (ddt, J = 17, 9, 7 Hz, 1 H), 6.46–7.53 (m, 5 H, Ar H), 7.63 (s, 1 H, CH=N). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 82.83; H, 9.14; N, 7.31.

***N*-[(1-Allyl-3-cyclohexenyl)methylene]aniline (7)**: bp 115–120 °C (2.0 mmHg) (Kugelrohr); IR (neat) 1650 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33–2.47 (m, 8 H), 4.78–5.25 (m, 2 H), 5.41–6.32 (m, 3 H), 6.71–7.48 (m, 5 H), 7.57 (s, 1 H). Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.21; H, 8.54; N, 6.09.

1-Allyl-3-cyclohexene-1-carboxaldehyde (8): bp 110–112 °C (48 mmHg) (Kugelrohr); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–2.64 (m, 8 H), 4.83–6.06 (m, 5 H), 9.46 (s, 1 H). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.95; H, 9.26.

***N*-(2-Allylcyclohexylidene)aniline (10)**: bp 125 °C (1 mmHg) (Kugelrohr); IR (neat) 1655 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–2.9 (m, 11 H), 4.76–5.52 (m, 2 H), 5.52–6.46 (m, 1 H), 6.5–7.6 (m, 5 H).

2-Allylcyclohexanone (11): bp 95 °C (6 mmHg) (Kugelrohr); IR (neat) 1710 (C=O) cm^{-1}; ^1H NMR (CCl_4) δ 0.9–2.9 (m, 11 H), 4.72–5.28 (m, 2 H), 5.28–6.12 (m, 1 H). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.31; H, 10.13.

2-Allyl-2-methylcyclohexanone (13): bp 129 °C (23 mmHg) (Kugelrohr); IR (neat) 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.39–2.85 (m, 10 H), 4.77–5.23 (m, 2 H), 5.37–6.04 (m, 1 H). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.63; H, 10.67.

2-Methyl-2-phenyl-4-hexenal (17): bp 104–108 °C (6 mmHg) (Kugelrohr); IR (neat) 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.58 (dm, J = 5.5 Hz, 3 H), 2.58 (dm, J = 6 Hz, 2 H), 5.11 (dtm, J = 15, 6 Hz, 1 H), 5.47 (dqm, J = 15, 5.5 Hz, 1 H), 7.21 (s, 5 H), 9.41 (s, 1 H). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.65; H, 8.54.

2,4-Dimethyl-2-phenyl-4-pentenal (31): bp 124 °C (30 mmHg) (Kugelrohr); IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (dd, J = 2, 1 Hz, 3 H), 1.44 (s, 3 H), 2.66 (s, 2 H), 4.50–4.92 (m, 2 H), 7.26 (s, 5 H), 9.49 (s, 1 H). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.87; H, 8.66.

Direct Synthesis of δ,ε-Unsaturated Imines and γ,δ-Unsaturated Carbonyl Compounds from Allylamines and Carbonyl Compounds. A solution of allylamines (4.80 mmol), carbonyl compounds (4.80 mmol), $Pd(PPh_3)_4$ (166 mg, 0.14 mmol), and CF_3CO_2H (5.5 μL, 0.07 mmol) in dry benzene (15 mL) was heated at 80 °C for 20 h under argon. Water generated was removed by azeotropic distillation with benzene. After removal of the solvent, the reaction mixture was subjected to column chromatography on Al_2O_3. Rapid elution with hexane gave δ,ε-unsaturated imines.

The preparation of γ,δ-unsaturated carbonyl compounds was carried out as follows: A solution of δ,ε-unsaturated imines in ether was treated with a 2 N HCl solution for 1 h with vigorous stirring. The ether extract was washed with a $NaHCO_3$ solution and brine and dried over $MgSO_4$. The evaporation of the solvent gave γ,δ-unsaturated carbonyl compounds.

***N*-(2-Methyl-2-phenyl-4-pentenylidene)allylamine (20)**: ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 2.80 (dm, J = 7 Hz, 2 H), 4.09 (dt, J = 5.4, 1.2 Hz, 2 H), 4.78–6.45 (m, 6 H), 7.31 (s, 5 H), 7.69 (t, J = 1.2 Hz, 1 H).

2,2-Diethyl-4-pentenal (23): IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (tm, J = 6.4 Hz, 6 H), 1.47 (qm, J = 6.4 Hz, 4 H), 2.18 (dm, J = 6.2 Hz, 2 H), 4.58–5.21 (m, 2 H), 5.60 (ddt, J = 18, 8.2, 6.2 Hz, 1 H), 9.33 (s, 1 H).

2-Methyl-2,5-diphenyl-4-pentenal (26): IR (neat) 1725 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3 H), 2.77 (d, J = 6.8 Hz, 2 H), 5.90 (dt, J = 16, 6.8 Hz, 1 H), 6.41 (d, J = 16 Hz, 1 H), 7.21 (s, 5 H), 7.28 (s, 5 H), 9.51 (s, 1 H).

Preparation of *N*-Benzyl-2-methyl-2-phenyl-4-pentenylamine (37). A solution of *N*-allylbenzylamine (**36**) (704 mg, 4.79 mmol), 2-phenylpropanal (**15**) (642 mg, 4.79 mmol), $Pd(PPh_3)_4$ (166 mg, 0.144 mmol), and CF_3CO_2H (5.4 μL, 0.072 mmol) in dry benzene (15 mL) was heated at 80 °C for 20 h under argon. Water generated was removed by azeotropic distillation with benzene. After removal of the solvent, the reaction mixture was subjected to column chromatography on Al_2O_3. Rapid elution with hexane gave the δ,ε-unsaturated imine (1.09 g, 86%). A solution of the imine in dry MeOH (10 mL) was treated with $NaBH_4$ (157 mg, 4.14 mmol) for 1 h in an ice bath. After the usual workup, column chromatography on SiO_2 (hexane–ethyl acetate) gave **37** as a colorless liquid: 845 mg (66%); R_f 0.50 (ethyl acetate–hexane, 2:8); IR (neat) 3320 (N—H), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (br s, 1 H), 1.34 (s, 3 H), 2.28 (dd, J = 14, 6.4 Hz, 1 H, CH_2 (allyl)), 2.56 (dd, J = 14, 6.8 Hz, 1 H), 2.63 (d, J = 15.2 Hz, 1 H), 2.82 (d, J = 15.2 Hz, 1 H), 3.66 (s, 2 H), 4.73–5.18 (m, 2 H), 5.57 (dddd, J = 15.7, 8.8, 6.8, 6.4 Hz, 1 H), 7.19 (s, 5 H), 7.24 (s, 5 H).

Preparation of 2,4-Dimethyl-4-phenyltetrahydrofuran (40). Aldehyde **3** (429 mg, 2.47 mmol) in dry ether (2 mL) was added dropwise to the solution of $LiAlH_4$ (27 mg, 0.70 mmol) in dry ether (3 mL) over 10 min under argon. The reaction mixture was quenched with water. The ether extract was washed with a 10% H_2SO_4 solution (2 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a pale yellow liquid of 2-methyl-2-phenyl-4-pentenol (**39**): 390 mg (90%); bp 110 °C (6 mmHg); IR (neat) 3350 (O–H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H), 1.56 (br s, 1 H), 2.19 (ddm, J = 13.2, 6.8 Hz, 1 H), 2.60 (ddm, J = 13.2, 5.6 Hz, 1 H), 3.47 (d, J = 12.4 Hz, 1 H) 3.76 (d, J = 12.4 Hz, 1 H), 4.75–5.20 (m, 2 H), 5.55 (dddd, J = 16.8, 7.6, 6.8, 5.6 Hz, 1 H), 7.23 (s, 5 H).

To the solution of mercuric acetate (500 mg, 1.57 mmol) in water (1.5 mL) and THF (1.2 mL) was added a solution of alcohol **39** (85 mg, 0.48 mmol) in dry THF (1.0 mL) with stirring. After the solution was stirred for 15 h, a solution of 0.5 M $NaBH_4$ in aqueous 3.0 M NaOH solution (1.6 mL, 0.8 mmol) was added. The mixture was extracted with ether (5 mL × 3), and the combined extracts were dried over Na_2SO_4. Column chromatography on SiO_2 (3 g, 3.0 × 1.2 cm) with ether–hexane as an eluent gave **40** as a colorless liquid: 75 mg (88%); R_f 0.58–0.74 (ethyl acetate–hexane, 3:7); ^1H NMR ($CDCl_3$) δ 1.27 and 1.32 (d, J = 5.8 Hz, 3 H), 1.40 and 1.42 (s, 3 H), 1.57–2.57 (m, 2 H), 3.74–4.47 (m, 1 H), 3.90 (br s, 2 H), 7.17 and 7.20 (s, 5 H).

Pd(0)-Catalyzed Asymmetric Reaction of *N*-Allyl-(*S*)-1-phenylethylamine (41) with 2-Phenylpropanal (15). A solution of *N*-allyl-(*S*)-1-phenylethylamine (**41**) (161 mg, 1.00 mmol), 2-phenylpropanal (**15**) (134 mg, 1.00 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), and CF_3CO_2H (1.9 μL, 0.025 mmol) in dry benzene (3 mL) was heated at 80 °C for 20 h under argon. Water generated was removed by azeotropic distillation with benzene. The reaction mixture was treated with a 2 N HCl solution for 1 h. After extraction with ether and washing with a 10% $NaHCO_3$ solution and brine, a short column chromatography on Florisil with hexane afforded a colorless liquid of (+)-2-methyl-2-phenyl-4-pentenal (**3**): 146 mg (84%). Optical rotation of **3** was determined after Kugelrohr distillation (83 °C, 2 mmHg): $[\alpha]^{21}_D$ +9.78° (*c*, 3.82, $CHCl_3$). The optical yield of **3** was determined as follows. A solution of the aldehyde **3** (102 mg, 0.59 mmol) in ether was reduced upon treatment with a solution of $LiAlH_4$ (7.4 mg, 0.20 mg) in ether. After the usual workup, thin-layer chromatography on SiO_2 (AcOEt–hexane, 2:8) gave a colorless liquid of (+)-2-

methyl-2-phenyl-4-pentenol (39): 40 mg (39%): $[\alpha]^{21}_D$ +2.99° (c 1.64, MeOH). A mixture of 41 (20 mg, 0.11 mmol), (–)-MTPA-Cl (1-methoxy-1-(trifluoromethyl)phenylacetyl chloride) (37 mg, 0.15 mmol), CCl_4 (50 μL), and pyridine (20 μL) was stirred at room temperature overnight under argon. The reaction mixture was quenched with water and extracted with ether. Thin-layer chromatography on SiO_2 ($CHCl_3$) gave 2-methyl-2-phenyl-4-pentenyl 1-methoxy-1-(trifluoromethyl)phenylacetate (42): 44 mg (94%); ^1H NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 1.68 H), 1.36 (s, 1.32 H), 2.16–2.18 (m, 2 H), 3.20–3.40 (m, 3 H), 4.29 and 4.30 (d, J = 12 Hz, 1 H), 4.46 and 4.48 (d, J = 12 Hz, 1 H), 4.70–5.06 (m, 2 H), 5.22–5.72 (m, 1 H), 7.26 (s, 5 H), 7.29 (s, 5 H).

Acyclic Control of Stereochemistry via a Reiterative (*E* or *Z*)-1-Propenyllithium-Derived Cuprate Opening of a Chiral Epoxide/Reepoxidation Sequence

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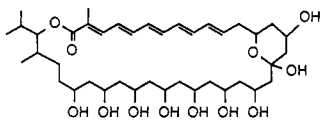
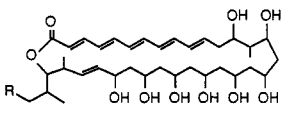
The 1,3-relationship between syn hydroxyl and syn or anti methyl groups can be established in a homochiral fashion by using a regioselective (*Z*)- or (*E*)-propenyllithium-based cuprate opening of a chiral epoxide, followed by stereoselective reepoxidation. The two-step sequence is reiterative.

As part of our program in polyene macrolide synthesis with emphasis on the 36-membered pentaene roflamycoin,[2] we developed a two-pot reiterative protocol[3] for arriving at the key polyol sections in homochiral form.[4] The



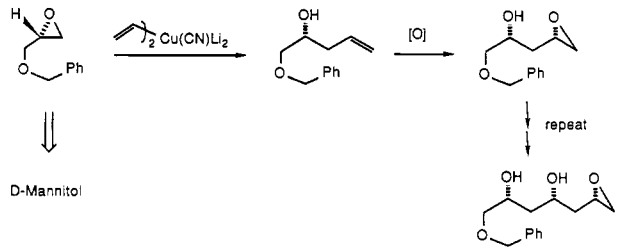
Roflamycoin



Mycoticin A (R = H)
Mycoticin B (R = CH_3)

method relies on a higher order (HO) vinyl cuprate opening of a chiral epoxide to afford a homoallylic alcohol, followed by stereoselective reepoxidation (Scheme I).[3] Although this approach permits construction of polyacetate-derived systems, many macrolides of this type contain one or more propionate portions, the Mycoticins being two such representative examples.[5] Since even the relative stereochemistry of all but two of the polyene macrolides is as yet unknown,[6] a synthetic strategy aimed at establishing vicinal hydroxy–methyl arrays must be sufficiently flexible to respond to either a syn or anti disposition between the two groups. We now report that the conceptually straightforward use of an (*E*)- or (*Z*)-propenyllithium-based HO cuprate, in place of the simple vinyllithium-derived reagent used previously (Scheme I),[3] allows rapid construction of these desired stereochemical relationships.

Scheme I



Results and Discussion

Treatment of readily available,[7] optically pure (*S*)-epoxide 1 with the HO cuprate derived from (*Z*)- or (*E*)-propenyllithium[8] regiospecifically affords homoallylic alcohols 2[9] and 3,[9] respectively (Scheme II). Epoxidation of 2 to 4 (R = H), and 3 to 5 (R = H), using the modified Cardillo route[10] developed earlier[3] (procedure A in Scheme II), proceeds in a one-pot, four-step sequence to give the required syn disposition of the two newly generated chiral centers. More efficient oxirane formation could be achieved by using the Mihelich procedure,[11] which is also easier to carry out and leads to identical products 4 (94%) and 5 (84%). Interestingly, both routes were essentially stereospecific, as judged by capillary GLC analyses[12] of the crude reaction mixtures.

With epoxides 4 and 5 in hand, it was anticipated that their electrophilic cuprate couplings would follow the traditional pathway[13] of reaction at the least hindered, desired position (i.e., next to the methyl group) so as to

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