Stereoselective Synthesis of Highly Functionalized Cyclopropanes. Application to the Asymmetric Synthesis of (1*S*,2*S*)-2,3-Methanoamino Acids

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One-pot palladium(0)-catalyzed alkylation and $S_{N'}$ cyclization of 1,4-dichlorobut-2-ene **1** by the anion of α-substituted carbonitriles **2a**−**d** can provide highly functionalized cyclopropanes (*E*)-**4a**−**d**, diastereoselectivity, (de 88−100%). Several attempts to achieve the asymmetric synthesis of the 1-amino-2-ethenylcyclopropanecarbonitrile (*E*)-**9**, by means of this new procedure, i.e., using chiral palladium ligands, chiral aminoacetonitriles (−)- and (+)-**12** (from 1-hydroxypinanone) or chiral allyl chlorides (4*S*)-**20b**−**d** and (4*R*)-**20e** (from (2*S*) ethyl lactate) have pointed up the reversibility of the palladium-catalyzed cyclization step, responsible for the low enantioselectivity observed (ee ≤ 32%) and for the formation of byproducts, i.e., azepine derivatives **8a,b** arising from subsequent aza Cope ring expansion. Molecular mechanics calculations using a modified MM2 type force field adapted to the π-allyl palladium complexes have explained these results. However, when performed under the Mitsunobu reaction conditions (DEAD, PMe_3), therefore, in the absence of palladium catalyst, the $S_{N'}$ cyclization occurred also diastereoselectively (de > 88%) and provided the enantiomerically enriched 1-amino-2-propenylcyclopropanecarbonitrile (*E*)-**22** (ee > 83%) suitable precursor of (1*S*,2*S*)-2,3-methanoamino acids.

The uniqueness of the cyclopropane ring resulting from its unusual bonding and inherent ring strain (27.5 kcal/mol) has been extensively demonstrated and is now well acknowledged.[1] In fact, the three-membered ring's utility grows when it is suitably substituted by functional groups; then it provides building blocks of unprecedented potential. Thus for instance, 1-alkenylcyclopropanol derivatives can undergo stereoselective $C_3 \rightarrow C_{4-20}$ ring expansions which have been incorporated into many effective synthetic schemes;[2,3] while on the other hand, vicinally donor−acceptor substituted cyclopropanes undergo ring-opening reactions leading to polyfunctional compounds or to carbocyclic and heterocyclic systems.[4]

Moreover, natural and synthetic cyclopropanes bearing simple functionalities are endowed with a large spectrum of biological properties ranging from enzyme inhibitions to antibiotic, antibacterial, antiviral, antitumoral, and neurochemical properties.[5] The mechanisms responsible for these various bioactivities have been recently explained.[6] Therefore development of chemo-, regio-, and stereoselective methods of cyclopropane formation, including the new atom economy requirement,[7] still currently presents a challenging area of research.[8] We are investigating novel strategies for the stereoselective synthesis of this attractive class of compounds.

Diastereoselective Synthesis of Highly Functionalized Cyclopropanes. A new approach toward the variously 1-substituted 2-ethenylcyclopropanecarbonitriles (*E*)-**4a**−**d** was based on the one-pot palladium(0)-catalyzed tandem alkylation and $S_{N'}$ cyclization of 1,4-dichlorobut-2-ene **1** by the anions of different α-substituted acetonitriles **2a**−**d**.[9] Thus, slow addition of 2 equiv of sodium hydride to an equimolar solution of (*N*-(diphenylmethylene)amino)acetonitrile **2a**[10] and of a commercially available 85:15 mixture of (*E* and *Z*)-**1** in THF containing 0.05 equiv of palladium(0) catalyst (prepared from $Pd(dba)_2$ and 2 PPh_3) gave within 15 min at room temperature the diastereochemically pure (*E*)-1-(*N*-(diphenylmethylene)amino)-2-ethenylcyclopropanecarbonitrile **4a**, isolated in 74% yield after usual chromatography. The reaction likely proceeded through the zwitterionic intermediate π-allyl palladium complex **3a** (Scheme 1).

On the other hand, addition of only 1 equiv of NaH to the same mixture of (*E*,*Z*)-**1** and **2a** containing Pd(0) provided a 62:38 mixture of 6-chloro-2-(*N*-(diphenylmethylene)amino)hex-4-enenitrile and of cyclopropanecarbonitrile (*E*)-**4a**. Therefore the cyclization step appeared faster than the alkylation of (*E*,*Z*)-**1**. Then basic treatment of this mixture in the absence of Pd(0) catalyst, by potassium carbonate in DMF at room temperature for instance,[11,12] led in 84% yield to a 78:22 mixture of (*E*)- and (*Z*)-**4a** (de 56%), proving that the catalyst

(1) For recent books, see: Carbocyclic Three- and Four-membered Ring Systems. In *Methods of Organic Chemistry, Houben-Weyl*; de Meijere, A., Ed.; Thieme: Stuttgart, New York, 1997; Vol. 17a−f.

(2) For reviews, see: Salaün, J. Rearrangements involving the cyclopropyl group. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley and Sons: New York, 1987; p 809; Salaün, J. *Top. Curr. Chem.* **1988**, *144*, 1.

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(8) Yamazaki, S.; Takada, T.; Imanishi, T.; Moriguchi, Y.; Yamabe, S. *J. Org. Chem.* **1998**, *63*, 5919 and references therein.

(9) (a) Gaucher, A.; Dorizon, Ph.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **1995**, *36*, 2979. (b) Franzone, G.; Carle, S.; Dorizon Ph.; Ollivier, J.; Salaün, J. *Synlett* **1996**, 1067.

(10) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

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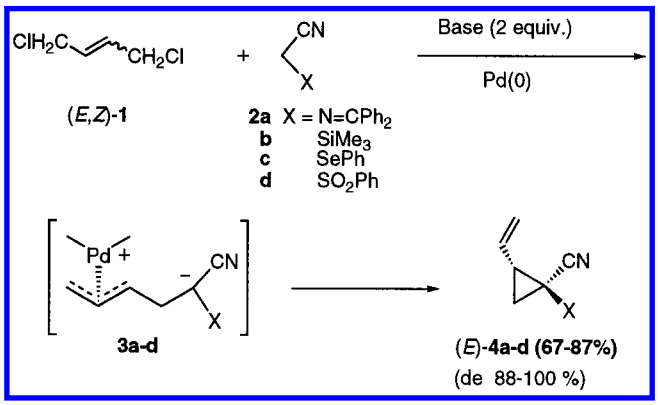
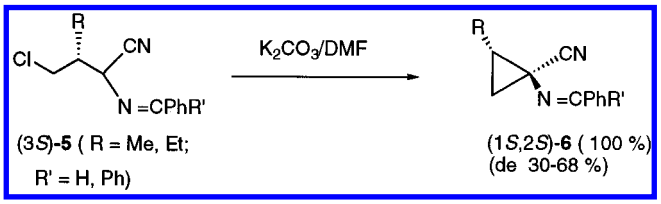
Scheme 1



Scheme 2



was essential to induce the diastereoselectivity of the cyclization.

Comparatively, we had previously reported that the base-induced cyclization of 2-(*N*-benzylideneamino)- and 2-(*N*-(diphenylmethylene)amino)-4-chlorobutyronitrile derivatives (3*S*)-**5** (R = Me or Et; R′ = H, Ph) provided in 80−100% yields the (1*S*,2*S*)-1-aminocyclopropanecarbonitriles **6** with 68% (R = Me, R′ = H), 60% (R = Et, R′ = H), and 30% (R = Et, R′ = Ph) diastereomeric excesses, respectively (Scheme 2).[12]

The total diastereoselectivity observed now in the cyclization of the zwitterionic intermediate **3a** resulted from the attack of the π-allyl palladium moiety by the carbanion with complete inversion of configuration; the difference of steric hindrance between the linear carbonitrile moiety and the bulkier (diphenylmethylene)amino group entailed the formation of the (*E*)-stereoisomer, therefore presenting the sterically favored syn relationship between the ethenyl and carbonitrile groups (Scheme 1).[13] Molecular mechanics calculations have been performed with the MAD (Molecular Advanced Design), version 2.3, using a modified MM2 type force field.[14] It appeared clear that the difference in total steric energies $\Delta E = -2.46$ kcal/mol (corresponding to de 96%) for the optimized geometries of the π-allyl palladium complexes **3aE** and **3aZ** leading to (*E*)- and to (*Z*)-**4a**, respectively, and that the difference of relative stabilities (*thermodynamic control*) of (*E*)- and (*Z*)-**4a** $\Delta E = -2.12$ kcal/mol (de 96%) were both in agreement with the exclusive formation of (*E*)-**4a**. The MM2-minimized geometries of **3aE** and **3aZ** determined by a grid search are reported in Figure 1.

This palladium(0)-catalyzed tandem reaction has been also sucessfully achieved with the anion of dimethyl malonate,[9,13] and diastereoselectively with the anions of 2-(trimethylsilyl)acetonitrile **2b** (X = $SiMe_3$),[15] of 2-(phenylseleno)acetonitrile **2c** (X = SePh),[16] and of commercially available 2-(phenylsulfonyl)acetonitrile **2d** (X = SO_2Ph), which provided in 67−87% yields the 1-substituted-2-vinylcyclopropanecarbonitrile (*E*)-**4b**−**d** (de 88−100%, Scheme 1).[9,17]

Asymmetric Syntheses of 2-(1-Alkenyl)-1-Aminocyclopropanecarbonitriles. Taking into account the excellent diastereoselectivity obtained from the tandem reaction (*E*,*Z*)-**1** → (*E*)-**4a**−**d**, which provided readily highly functionalized cyclopropanes, it appeared then worthwhile to adapt this strategy toward the asymmetric synthesis of such three-membered ring derivatives. Due to their noteworthy biological activities (enzymatic process control and inhibition, plant growth regulation, peptides activation and stabilization, pharmacological properties, etc.), considerable efforts are particularly and currently devoted toward the total synthesis of natural and nonnatural 1-aminocyclopropanecarboxylic acids (ACCs).[5,6,18] We have concentrated our study on the asymmetric synthesis of (*E*)-**4a**, a suitable precursor of these challenging amino acids.

First of all, the tandem reaction (*E*,*Z*)-**1** → (*E*)-**4a** was performed in the presence of chiral palladium complexes, prepared, for instance, from $Pd(dba)_2$ and (*S*)-(−)-2,2′-bis-(diphenylphosphino-1,1′-binaphthyl) [(*S*)-BINAP] as chiral ligand.[19] Contrary to the reaction reported in Scheme 1, the tandem reaction induced by 2 equiv of NaH must be now performed at −78 °C for 4 h, to avoid the formation of byproducts. Under these conditions, diastereochemically pure (*E*)-**4a** was obtained in 44% yield. Otherwise, an increase of the reaction mixture temperature to −30 °C for 3 h produced a 52/48 mixture of the cyclopropanecarbonitrile (*E*)-**4a** and of 1-aza-2-cyano-7,7-diphenylcyclohepta-2,4-diene **8a**. This seven-membered ring **8a** most probably arose from a $C_3 \rightarrow C_7$ aza-Cope ring expansion of (*Z*)-**4a** into **7a**, because the vicinal 1-diphenylmethyleneamino and 2-vinyl groups in the diastereomer (*Z*)-**4a**, if really formed, offered the cis relationship required to allow such a rearrangement.[20] Then under the reaction conditions, **7a** underwent a 1,3-hydrogen shift to provide finally **8a** (Scheme 3).

The determination of the enantiomeric excess of diastereomerically pure (*E*)-**4a** obtained from the tandem reaction driven at −78 °C was first carried out following the procedure previously reported for the asymmetric syntheses of 2,3-methanoamino acids.[21] Thus, acidic

(11) Salaün, J.; Marguerite, J.; Karkour, B. *J. Org. Chem.* **1990**, *55*, 4276.
(12) Gaucher, A.; Ollivier, J.; Marguerite, J.; Paugam, R.; Salaün, J. *Can. J. Chem.* **1994**, *72*, 1312.
(13) For an analogous but stepwise palladium(0)-catalyzed preparation of methyl 1-(methoxycarbonyl)-2-vinylcyclopropanecarboxylate from 2-acetoxy-5-chlorohex-3-enes and dimethyl malonate anion, see: Bäckvall, J. E.; Vägberg, J. O.; Zercher, C.; Genêt, J. P.; Denis, A. *J. Org. Chem.* **1987**, *52*, 5430.
(14) Norrby, P. O.; Akermark, B.; Hoeffner, F.; Hansson, S.; Blomberg, M. *J. Am. Chem. Soc.* **1993**, *115*, 4869.
(15) Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans 1* **1979**, 26.
(16) Curran, D. P.; Martin-Esker, A. A.; Ko, S.-B.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4691.
(17) Only the preparation of cyclopropyl sulfone (*E*)-**4d** was recently reported with de 66%; see: Lai, J. Y.; Yu, J.; Hawkins, R. D.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5691.
(18) For recent reviews, see: (a) Burgess, K.; Ho, H.-H.; Moye-Sherman, D. *Synlett* **1994**, 575. (b) Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5. (c) Stammer, C. A. *Tetrahedron* **1990**, *46*, 2231. (d) Salaün, J. *Zh. Org. Kh.* **1997**, *33*, 806.
(19) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
(20) (a) Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310. (b) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A. *Synlett* **1993**, 349. (c) Brown, J. M.; Golding, B. T.; Stofko, J. J. *J. Chem. Soc., Chem. Commun.* **1973**, 319. (d) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1.
(21) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796.

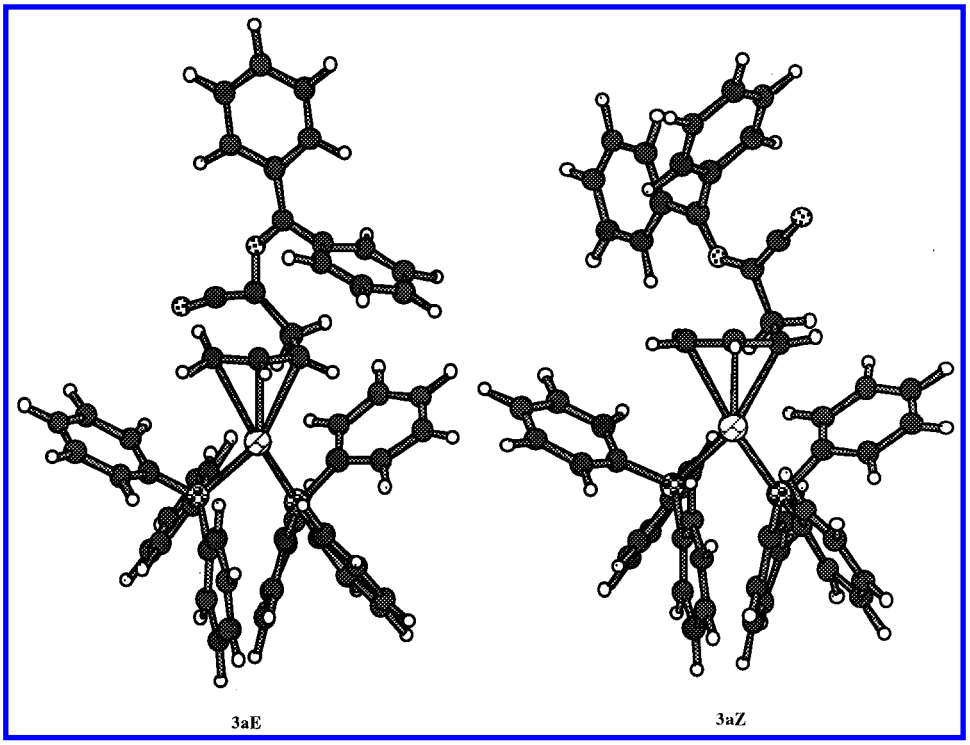
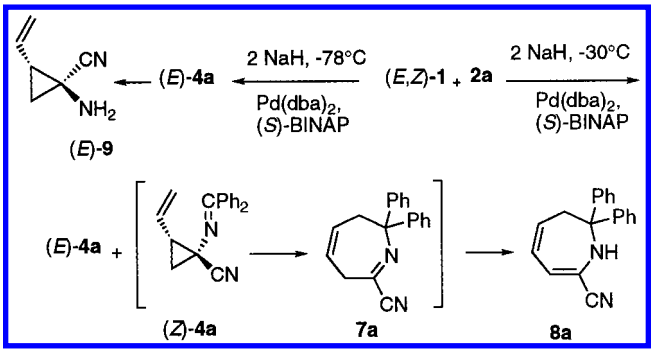


Figure 1. MM2-minimized geometries of π-allyl palladium complexes **3aE** and **3aZ**.

Scheme 3



hydrolysis (2 N HCl) of (*E*)-**4a** gave quantitatively the corresponding cyclopropylamine hydrochloride, which was reacted with 1 equiv of (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetic acid chloride (MTPA-Cl),[22] in the presence of 4 equiv of propylene oxide in THF at reflux for 30 min. For comparison, this amide was also prepared in strictly the like manner from racemic (*E*)-**4a**. ^{19}F NMR spectra of the crude products displayed two well-separated signals at δ −69.93 and −69.80 (relative to CF_3CH_2OH used as internal reference), corresponding to the two diastereomeric MTPA amides derived from (*E*)-**4a**. However, a kinetic resolution evidenced by obtaining different ratios of the diastereomeric MTPA amides depending on their reaction times of formation, i.e., 79% and 47% on heating at reflux for 30 min or 2 days, respectively, was apparent and caused erroneous determination of the enantiomeric purity. To overcome this problem, we have then examined by chiral capillary gas chromatography (CYBEX B column, 55 °C, 0.9 He atm) the free cyclopropylamine (*E*)-**9**, obtained from acidic cleavage (2 N HCl) of (*E*)-**4a** in THF at room temperature and treatment of the corresponding hydrochloride with propylene oxide, comparatively to the free amine prepared from racemic (*E*)-**4a**. This accurate determination of the enantiomeric composition of (*E*)-**9**, prepared either from (*S*)- or (*R*)-BINAP as chiral palladium(0) ligands, revealed only 2% and 4% of enantiomeric excesses, respectively (Table 1, entries 1, 2).

After these disappointing results, we have prepared the asymmetric ketimine (−)-**12** from the enantiomerically pure (−)-(1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone **11**, which is readily available from (+) α-pinene permanganate oxidation.[23] Thus condensation of aminoacetonitrile **10** with the chiral ketone (−)-**11** in benzene containing 10% of boron trifluoride etherate gave, on heating at reflux for 18 h, the ketimine (−)-**12**[24] in 93% yield. Formation of only one diastereomer, likely (*E*)-**12**, stabilized by the occurrence of intramolecular nitrogen−hydrogen bond,[25] was clearly deduced from its ^{1}H and ^{13}C NMR spectra. As a matter of fact, use of hydroxypinanone ketimines as chiral templates has been reported for the successful asymmetric synthesis of amino acids (ee 83−98%) with recovery of the chiral auxiliary in high yields.[26,27] Accordingly it appeared worthwhile to investigate the tandem palladium(0)-catalyzed alkylation and $S_{N'}$ cyclization of the dichloride (*E*,*Z*)-**1** with the chiral ketimine (−)-**12** in order to achieve the asymmetric synthesis of the cyclopropanecarbonitrile (*E*)-**13** (Scheme 4).

(22) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

(23) Schmidt, H. *Chem. Ber.* **1960**, *93*, 2485; Carlson, R. G.; Pierce, J. K. *J. Org. Chem.* **1971**, *36*, 2319; the enantiomeric purities of (−)-(1*S*,2*S*,5*S*)- and of (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanones (ee 100%) were determined by gas chromatography using a chiral capillary column (Lypodex E, 0.75 bar He, 70 °C).

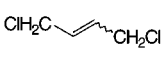
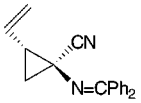
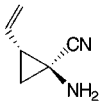
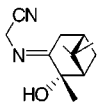
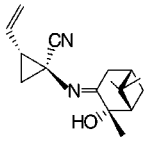
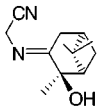
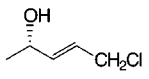
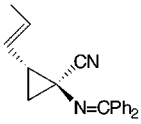
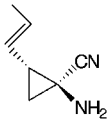
(24) Minowa, N.; Hirayama, M.; Fukatsu, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1761.

(25) Bujgrowicz, J. A.; Cossec, B.; Pigière, Ch.; Jacquier, R.; Viallefont, Ph. *Tetrahedron Lett.* **1984**, *25*, 1789.

(26) For the first use of (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one as chiral auxiliary, see: Yamada, S. I.; Oguri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1976**, 136.

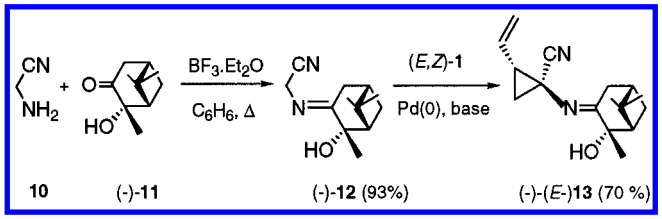
(27) Oguri, T.; Kawai, N.; Shioiri, T.; Yamada, S. I. *Chem. Pharm. Bull.* **1978**, *26*, 803. Jacob, M.; Roumestant, M. L.; Viallefont, Ph.; Martinez, J. *Synlett* **1997**, 691. Solladié-Cavallo, A.; Nsenda, T. *Tetrahedron Lett.* **1998**, *39*, 2191 and references therein.

Table 1. Enantioselectivity of the Diastereoselective Alkylation and $S_{N'}$ Cyclization

Entry	Allylic chloride	Ketimine[a]	Ligand,	Y %,		Ee %[b]
1			(*S*)-BINAP	 44		2
	(*E*,*Z*)-**1**	**2a**		(*E*)-**4a**	(*E*)-**9**	
2	(*E*, *Z*)-**1**	**2a**	(*R*)-BINAP	(*E*)-**4a**	44 (*E*)-**9**	4
3	(*E*,*Z*)-**1**		PPh_3	 70	(*E*)-**9**	2.4
		(-)-**12**		(-)-(*E*)-**13**		
4	(*E*,*Z*)-**1**		PPh_3	(+)-(*E*)-**13**	70 (*E*)-**9**	13.5
		(+)-**12**				
5	(*E*,*Z*)-**1**	(-)-**12**	(*S*)-BINAP	(-)-(*E*)-**13**	77 (*E*)-**9**	3
6	(*E*,*Z*)-**1**	(-)-**12**	(*R*)-BINAP	(-)-(*E*)-**13**	45 (*E*)-**9**	32
7	(*E*,*Z*)-**1**	(-)-**12**	(+)-DIOP	(-)-(*E*)-**13**	63 (*E*)-**9**	5
8	(*E*,*Z*)-**1**	(+)-**12**	(*S*)-BINAP	(+)-(*E*)-**13**	38 (*E*)-**9**	19
9	(*E*,*Z*)-**1**	(-)-**12**	(*R*)-BINAP	(+)-(*E*)-**13**	51 (*E*)-**9**	15
10		**2a**	PPh_3	 77		> 83
	(4*S*)-**21a** (94% ee)[c]			(1*S*,2*R*)-**22**[d]	(1*S*,2*R*)-**26**	
11				(1*S*,2*R*)-**22**[d]	(1*S*,2*R*)-**9**[e]	>69

[a] The ketimine anions were obtained from **2a** with NaH, or from (−) and (+)-**12** by successive addition of 2.3 and 1.3 equiv of LDA in the presence of 5 equiv of HMPA. [b] Ee was determined from chiral capillary gas chromatography with a CYDEX B column (25 m) at 55 °C and 0.9 bar helium pressure. [c] From ethyl lactate (2*S*)-**19** (94% ee). [d] (1*S*,2*R*)-**22** was obtained from the PMe_3/DEAD-induced cyclization of (6*S*)-**21a**. [e] From (1*S*,2*R*)-**22** after ozonolysis and Wittig reaction.

Scheme 4



Addition of NaH (3.3 equiv),[28] which was efficient to induce the tandem reaction (E,Z)-**1** → (*E*)-**4a** (Scheme 1), to an equimolecular solution of (*E*,*Z*)-**1** and ketimine (−)-**12** in THF containing palladium (0), led after stirring for 4 days only to traces of (*E*)-**13**. However addition of LDA at −78 °C to the same solution containing HMPA as cosolvent,[29] provided the expected three-membered ring (*E*)-**13** (de 100%). To avoid byproduct formation, for instance azepine derivative analogous to **8a** (Scheme 3), it appeared necessary to add the required amount of base in two parts. Indeed, addition of the ketimine (−)-**12** to a solution of 2.3 equiv of LDA in THF at −78 °C followed, after stirring for 30 min, by 5 equiv of HMPA at −78 °C, produced, after stirring for 90 min at −78 °C, a dianion which was then added to a solution of 1.2 equiv of dichloride (*E*,*Z*)-**1** in THF at −78 °C containing 0.05 equiv of palladium(0) ($Pd(dba)_2$, 2 PPh_3). After stirring this mixture for 8 h, 1.1 equiv of LDA was again added at −78 °C. As monitored by TLC, the tandem alkylation and $S_{N'}$ cylization were achieved within 21 h at −78 °C to provide, after usual workup, in 70% yield, the diastereochemically pure (2′*S*,3′*S*,5′*S*)-1-(*N*-(2′-hydroxypinylidene)-amino)-2-ethenylcyclopropanecarbonitrile (*E*)-(−)-**13** (Scheme 4). Otherwise, use of *N*-methyl-2-pyrrolidinone (NMP), a cheaper and less toxic cosolvent, under the same conditions, furnished (*E*)-(−)-**13** in lower yield

(28) The one-pot Pd(0)-catalyzed tandem alkylation + $S_{N'}$ cyclization of (*E*,*Z*)-**1** by the racemic imine **2a** required 2 equiv of NaH but with the imines (−)- and (+)-**12** derived from (−)- and (+)-hydroxypinanones, respectively, at least 3 equiv of base were obviously required.

(29) HMPA as cosolvent is well-known for its ability to accelerate nucleophilic reactions. See for instance, Pfiffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1970**, *35*, 262.

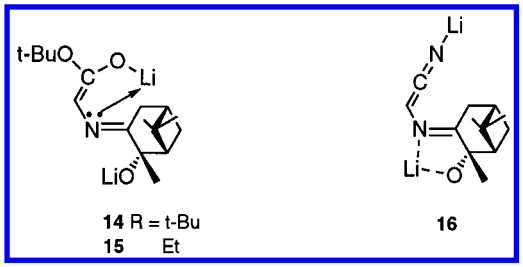


Figure 2. Dilithium dianions **14**−**16**.

(42%), besides a mixture of simple alkylation product (2.5%) and a byproduct arising from NMP allylation by dichloride (*E*,*Z*)-**1**. Finally acidic hydrolysis (2 N HCl) of (*E*)-(−)-**13**, followed by treatment with propylene oxide led again to the diastereomerically pure free 1-amino-2-vinylcyclopropanecarbonitrile (*E*)-**9** (Table 1, entry 3).

For comparison the corresponding ketimine (+)-**12**[24] was prepared under the same conditions, from the acid-induced (BF_3-Et_2O) condensation of acetonitrile **10** with the (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone (available from (−)-α-pinene).[23] Palladium(0)-catalyzed reaction of (+)-**12** with (*E*,*Z*)-**1**, following strictly the same procedure (2.3 equiv of LDA + 5 equiv of HMPA, and 8 h later 1.1 equiv of LDA, in THF at −78 °C) provided diastereomerically pure (*E*)-(+)-**13**. Acidic hydrolysis (2 N HCl) followed by treatment with propylene oxide provided in the same way, diastereomerically pure (*E*)-**9**. As reported in Table 1, the enantiomeric excesses measured by chiral capillary gas chromatography of the free cyclopropylamine (*E*)-**9** (de 100%) obtained from either asymmetric ketimines (−)-**12** or (+)-**12**, were 2.4% and 13.5%, respectively (Table 1, entries 3, 4).

Ketimines were also prepared from (−)-pinanone **11** and either *tert*-butyl or ethyl glycinate, as previously reported,[26,30,31] instead of aminoacetonitrile **10**. A higher chelated-enforced chirality transfer from the lithium enolates **14** and **15** was then expected, comparatively to the acetonitrile dianion **16** (Figure 2). However, under these conditions, **14** and **15** reacted sluggishly with allylic dichloride (*E*,*Z*)-**1**, providing the corresponding 1-amino-2-vinylcyclopropanecarboxylate derivatives in less than 11% yield (from (−)-**14**) or as traces (from (−)-**15**). Use of palladium(0) catalysis has been shown to improve the rate and diastereoselectivity of the tandem reaction (*E*,*Z*)-**1** → (*E*)-**4a**−**d** (Scheme 1), but it appeared to hamper the reaction from glycinates (−)-**14** and **15**, most probably by steric hindrance, if dimeric aggregates from the dilithium dianion **15** were, as recently suggested, also involved in such reactions.[31]

Double chiral induction by using both asymmetric ketimines (−)- or (+)-**12** and (*S*)- or (*R*)-BINAP as chiral palladium(0) ligands were attempted systematically, to determine the well-matched pair of chiral ketimine and metal ligand which could entail an enantioselective tandem alkylation and $S_{N'}$ cyclization process. First of all, it must be underlined that, whatever the reactants the tandem reaction was still totally diastereoselective, (−)- and (+)-(*E*)-**13** being often obtained in good yields and always as a single diastereomer under the conditions reported in Table 1 (entries 5−9). When only 2.5 equiv of LDA and 3.5 equiv of HMPA were used, therefore less than the required amount of base for the tandem reaction,[28] the exclusive formation of (*E*)-**13** was observed, indicating again that the cyclization step was faster than the alkylation one. The enantiomeric purities of the different samples of the free cyclopropylamine (*E*)-**9**, obtained after acidic hydrolysis (2 N HCl) and treatment with propylene oxide, were determined as previously, by chiral capillary gas chromatography. Disappointingly again, the enantioselectivity of the tandem reaction remained rather weak, the higher enantiomeric purity (ee 32%) being obtained from ketimine (−)-**12** and (*R*)-BINAP (entry 6). Use of other ligands, (+)-DIOP for instance, led also to poor asymmetric induction (ee ∼ 5%, entry 7). The free cyclopropylamine (*E*)-**9** obtained with 32% enantiomeric purity (entry 6) was retransformed into the corresponding *N*-protected 1-amino-2-vinylcyclopropane carbonitrile (−)-(*E*)-**13** upon treatment with (−)-pinanone **11** in the presence of BF_3-Et_2O. It was then observed that when treated under the reaction conditions, i.e., in the presence of the (*R*)-BINAP−Pd(0) complex for 22 h at −78 °C, (−)-(*E*)-**13** underwent epimerization. Effectively, after acidic hydrolysis (2 N HCl) and treatment with propylene oxide, (*E*)-**9** was obtained again, but with the opposite enantiomeric excess (ee 9% from chiral capillary GC).[32]

Palladium(0) complexes were reported to induce the nucleophilic ring cleavage of activated vinylcyclopropane,[33] and a novel route to a variety of heterocycles and carbocycles was based on the palladium-catalyzed annulation of vinylcyclopropanes by aryl halides (Heck reaction).[34] In fact, the results reported in Table 1 evidence the reversibility of this reaction. Most likely the Pd(0)-catalyzed alkylation of the allylic dichloride (*E*,*Z*)-**1** by the ketimine (−)-**12**, for instance, involved the formation of a zwitterionic species such as **17** with a configuration laid down by the chiral pinanone ketimine template, which then underwent the diastereoselective $S_{N'}$ cyclization into (−)-(1*S*,2*R*)-**13** (de 100%). However, as Pd(0) complexes are also able to induce the ring cleavage of vinylcyclopropanes,[33,34] this reverse reaction occurred readily even at −78 °C from (1*S*,2*R*)-**13** by palladium coordination of the vinylic cyclopropane bond, but now without regard of the chiral auxiliary, which has a trans relationship with this double bond. Thus a zwitterionic Pd(0) complex such as **18** could be also formed, which led to the enantiomeric (1*R*,2*S*)-cyclopropanecarbonitrile **13**, and therefore the diastereoselective tandem alkylation and $S_{N'}$ cyclization was obtained with low enantioselectivity (Scheme 5). An analogous palladium-induced racemization of asymmetric 5-vinyloxazolidinones involving successive ring opening and $S_{N'}$ cyclization has been recently observed.[35]

On the other hand, it had recently been reported that Pd(0)-catalyzed nucleophilic substitution of asymmetric

(30) Hoarau, S.; Fauchere, J. L.; Pappalardo, L.; Roumestant, M. L.; Viallefont, Ph. *Tetrahedron: Asymmetry* **1996**, *7*, 2585.

(31) Solladié-Cavallo, A.; Simon-Wermeister, M.-C.; Schwartz, J. *Organometallics* **1993**, *12*, 3743. Solladié-Cavallo, A.; Koessler, J.-L.; Isarno, T.; Roche, D.; Andrimiadanarivo, R. *Synlett* **1997**, 217.

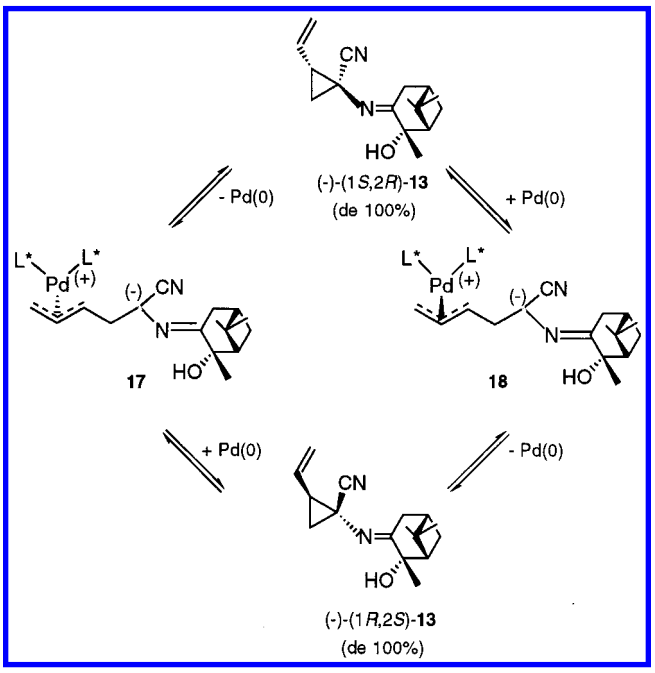
(32) (*E*)-**9** (ee 32%) displayed on the capillary GC chromatogram (Cydex B, 0.9 bar He, 55 °C) two peaks at 52.75 (34%) and 55.83 min (66%). After re-treatment in the presence of (*R*)-BINAP−Pd(0) of (*E*)-**13** (ee 32%), the corresponding free amine (*E*)-**9** obtained after *N*-deprotection (2 N HCl, propylene oxide) displayed two peaks at 52.74 (55%) and 56 min (45%), indicating ee 9%.

(33) Yamamoto, K.; Ishida, T.; Tsuji, J. *Chem. Lett.* **1987**, 1157. Burgess, K. *Tetrahedron Lett.* **1985**, *26*, 3049.

(34) Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529; Larock, R. C.; Varaprath, S. *J. Org. Chem.* **1984**, *49*, 3432.

(35) Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998,** *39*, 3405. Cook, G. R.; Shanker, P. S., Pararajasingham, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 110.

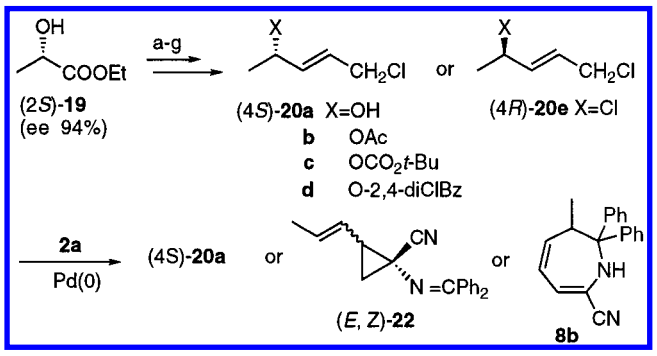
Scheme 5



1-alkenylcyclopropyl esters, involving π-1,1-dimethyleneallyl palladium complexes,[36] occurred with total retention of the configuration and enantiomeric purity of the stereogenic center.[37] Thus, enantiomerically pure (1*R*,2*S*)-2,3-methanoamino acids have been obtained from the diastereoselective azidation of such palladium complexes.[38]

The third possibility to achieve the asymmetric synthesis of 1-amino-2-vinylcyclopropanecarbonitriles such as (*E*)-**9** was to use the asymmetric allyl chloride (4*S*)-**20a** as chiral precursor.[39] For this purpose, the cheap commercially available ethyl lactate (2*S*)-**19** was chosen as source of the stereogenic center. Thus O-protection of (2*S*)-**19** (DHP, PPTS, CH_2Cl_2)[40] and partial reduction by 0.9 equiv of diisobutylaluminum hydride (DIBALH) in dichloromethane at −78 °C gave the corresponding lactaldehyde,[40] which underwent Wadsworth−Emmons reaction with triethyl phosphonoacetate (LiCl, DBU)[41] in acetonitrile at 20 °C,[42] to provide after reduction (2.5 equiv of DIBALH), a diastereomerically pure allyl alcohol.[43] On the other hand Wittig reaction with methyl (triphenylphosphino)acetate and DIBALH reduction gave a 90:10 mixture of allyl alcohol. Finally, chlorination (methanesulfonyl chloride in diethyl ether at 0 °C, lithium chloride in NMP at room temperature) led, after O-deprotection (EtOH, PPTS, 55 °C) of the secondary allyl alcohol, to the (4*S*)-1-chloropent-2-en-4-ol **20a** (X = OH) with 55% overall yield from (2*S*)-**19**. Its enantiomeric purity (ee 94%) was determined by ^{19}F NMR of the ester obtained from the reaction of (4*S*)-**20a** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid in dichloromethane at 0 °C in the presence of 2,4-(dimethylamino)-pyridine (DMAP) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (Scheme 6).[44] Esterification of (4*S*)-**20a** by acetic anhydride (DMAP, 0 °C), di-*tert*-butyl dicarbonate (DMAP, Et_3N, THF) and 2,4-dichlorobenzoyl chloride (pyridine, DMAP, CH_2Cl_2, rt) gave the allylic derivatives (4*S*)-**20b** (X = OAc), (4*S*)-**20c** (X = OCO_2t-Bu) and (4*S*)-**20d** (X = O-2,4-diClBz) in 81−100% yields (Scheme 6). Unfortunately, palladium(0)-catalyzed reaction of these allyl chlorides with the anion of the Schiff base **2a** did not provide cyclopropanecarbonitrile derivatives as reported with (*E*,*Z*)-**1** (Scheme 1). Under various basic conditions (2 equiv of NaH, DBU, *n*-BuLi, etc.) the products of the reactions were either the allyl alcohol (4*S*)-**20a** from acetate cleavage or the 1-aza-2-cyano-7,7-diphenyl-6-methylcyclohepta-2,4-diene **8b**, likely arising as the seven-membered ring **8a** from a subsequent $C_3 \rightarrow C_7$ aza-Cope ring expansion. It must be underlined that in the absence of Pd(0) catalyst, no reaction occurred within 5 days. Otherwise, palladium(0)-catalyzed reaction of (4*R*)-1,4-dichloropent-2-ene **20e** (X = Cl)[45] (prepared from chlorination with total inversion of configuration of the allyl alcohol (4*S*)-**20a** by *N*-chlorosuccinimide and triphenylphosphine) with **2a** in the presence of 2 equiv of NaH gave in 49% yield a 35:14 mixture of (*E*)- and (*Z*)-**22** (de 42%), besides **8b** as byproduct (24%) (Scheme 6). While in the absence of Pd(0) catalyst, treatment of an equimolecular mixture of (4*R*)-**20e** and **2a** by 2 equiv of NaH for 1 h in THF at room temperature, provided in 49% yield a 77:23 mixture of (*E*)- and (*Z*)-**22** (de 54%), exclusively. At least in this case, it can be concluded that the formation of the azacycloheptadiene **8b** was Pd(0) catalyzed (Scheme 6).

Scheme 6



On the other hand, palladium(0)-catalyzed [Pd(dppe)$_2$] simple alkylation of (4*S*)-**20a** by the Schiff base **2a**, in the presence of 1 equiv of NaH, led in 97% yield to the (*E*)-2-(*N*-(diphenylmethylene)amino)-6-hydroxyhept-4-enenitrile (6*S*)-**21a** (X = OH). Esterification by acetic anhydride, 2,4-dichlorobenzoyl chloride (pyridine, CH_2Cl_2), and benzoic anhydride (DMAP, Et_2O) gave in 98−100% yields the corresponding heptenenitriles (6*S*)-**21b** (X = OAc), (6*S*)-**21d** (X = *O*-2,4-diClBz), (6*S*)-**21f** (X = OCOPh), while esterification with 2,6-dichlorobenzoyl chloride (DMAP, NEt_3) gave (6*S*)-**21g** (X = O-2,6-diClBz) in only 32% yield.

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(38) Atlan, V.; Racouchot, S.; Rubin, M.; Bremer, C.; Ollivier, J.; de Meijere, A.; Salaün, *Tetrahedron: Asymmetry* **1998**, *9*, 1131.
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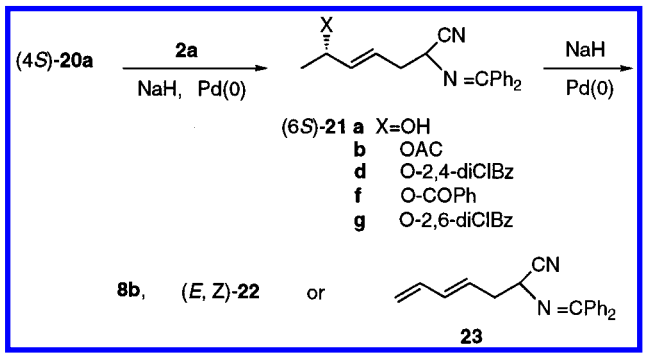
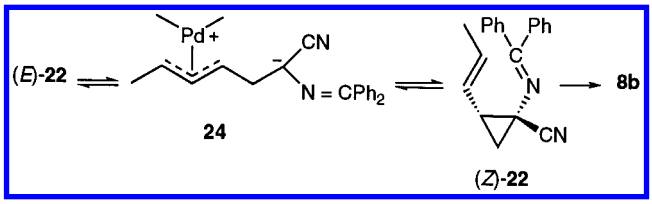
(42) Mulzer, J.; Salimi, N.; Harti, H. *Tetrahedron: Asymmetry* **1993**, *4*, 457.
(43) Okay, G. *Synth. Commun.* **1989**, *19*, 2125.
(44) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(45) Lasne, M. C.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1974**, 1142.

Scheme 7



Scheme 8



Attempted Pd(0)-catalyzed $S_{N'}$ cyclization of (6*S*)-**21b** provided either exclusively **8b** with NaH (80%), or a 29:8 mixture of (*E*)- and (*Z*)-**22** (de 57%) with DBU as base (55%), besides **8b** (27%) and the (*E*)-2-(*N*-(diphenylmethylene)amino)hepta-4,6-dienenitrile **23** (36%) arising from acetic acid elimination.[46] Treated under the same conditions the benzoates (6*S*)-**21d** and (6*S*)-**21f** led unavoidably to mixtures of the seven-membrered ring **8b** and of the elimination product **23** in 25−85% yields (Scheme 7). These results can be interpreted, as previously for the Pd(0)-catalyzed reaction of (*E*,*Z*)-**1** with the chiral ketimines (−) or (+)-**12** (double induction), by the occurrence of a reversible reaction.

Molecular mechanics calculations (MAD)[14] were again in favor of the formation of (*E*)-**22**, comparatively to its stereoisomer (*Z*)-**22**; effectively the difference of total steric energies for the optimized geometries of the π-allyl palladium complexes was $\Delta E = -11.67$ kcal/mol, and the difference of relative stabilities (*thermodynamic control*) of (*E*)- and (*Z*)-**22** was $\Delta E = -1.46$ kcal/mol. Consequently, the direct formation of (*Z*)-**22** precursor of **8b** (aza-Cope $C_3 \rightarrow C_7$ ring expansion) appeared unlikely. On the other hand, formation of a zwitterionic palladium complex **24** in equilibrium with (*E*)- or (*Z*)-**22**, as a result of the facile Pd(0)-catalyzed vinylcyclopropane ring opening,[33] could explain the formation of the seven-membered ring **8b** (Scheme 8). It has been effectively checked that upon standing under the conditions of the $S_{N'}$ cyclization, i.e., in the presence of 1.1 equiv of NaH and 5% of Pd(0) in THF at room temperature for 15 h, a 92/8 mixture of (*E*)- and (*Z*)-**22** (de 85%) underwent complete transformation into **8b**. Upon standing in the presence of palladium catalyst alone, the (*E*) → (*Z*) isomerization and the $C_3 \rightarrow C_7$ ring expansion were achieved more slowly, 77% of **8b** being formed within 4 days. Therefore, it appeared clearly that use of palladium catalyst in the $S_{N'}$ cyclization step must be precluded in order to avoid such rearrangements.

The Solution: $S_{N'}$ Cyclization under the Mitsunobu Reaction Conditions. Alternatively, the dehydrative alkylation of alcohols by carbon nucleophiles induced by azodicarboxylates and phosphines (Mitsunobu reaction) provides also a mild procedure for carbon−carbon bond formation.[47−49] Thus, for instance, under these conditions γ-nitroalkanols were converted in excellent yields into α-nitrocyclopropanes with *inversion* of configuration,[50] and condensation of alcohols with bis-sulfone methylene afforded alkylation and annulation products.[51] The intramolecular annulation of allylic alcohols has been reported to afford carbocycles with *inversion* of configuration when the attack occurred at the α-carbon and *retention* of configuration when the attack occurred at the γ-olefinic carbon.[52] For instance, reaction of but-2-ene-1,4-diol with (phenylsulfonyl)acetonitrile **2d** under the Mitsunobu conditions (ADDP/Me_3P) was recently reported to provide also (*E*)-**4d** (Scheme 1), with comparable yield (88%) but with a lower diastereoselectivity (de 67%).[17] Therefore to overcome the problem resulting from the reversibility of the palladium-catalyzed cyclization of (6*S*)-**21b**,**d**−**f** into (*E*)-**22**, it then appeared worthwhile to apply this new strategy to (6*S*)-**21a**, previously obtained in high yield (Scheme 7). Thus, simple addition of 2 equiv of diethyl azodicarboxylate (DEAD) to a mixture of (6*S*)-**21a** and trimethylphosphine (Me_3P, 2 equiv) in THF at room temperature provided instantaneously in 77% yield a 73:7 mixture of (*E*)- and (*Z*)-**22** (de 82%), besides 15% of **8b**. The diastereoselectivity was improved to 88% when this reaction was performed at −25 °C, but use of less volatile and less toxic tributylphosphine (Bu_3P) gave a lower yield (56%) and a weaker diastereoselectivity (de 78%), while DEAD/PPh_3 was ineffective, even after 8 days at room temperature. When treated under these conditions, i.e., by DEAD/PMe_3 at room temperature for 5 days, a sample of (*E*)-**22** (de 88%) was recovered unaltered, proving that the (*E*) → (*Z*) isomerization did not occur.

Whatever it may be, the cyclization of the readily available allyl alcohol (6*S*)-**21a** by DEAD/PMe_3 at −25 °C offered in good yield (64%) the expected 1-aminocyclopropanecarbonitrile (1*S*,2*R*)-**22**, with high diastereoselectivity (de 88%) and enantiomeric purity (ee > 83%, entry 10), as shown by its further transformation into a known ACC derivative (vide infra).

Applications to the Diastereoselective Synthesis of 2,3-Methanoamino Acids. The one-pot palladium(0)-catalyzed tandem alkylation and $S_{N'}$ cyclization (*E*,*Z*)-**1** by the anion of **2a**, which gave the diastereomerically pure 1-amino-2-ethenylcyclopropanecarbonitrile (*E*)-**4a** (Scheme 1) provides without doubt the shortest and cheapest entry to ACCs. Thus, reduction of (*E*)-**4a** by 3 equivalents of diimide (dipotassium azodicarboxylate, acetic acid, pyridine, methanol)[53] led to the 1-(*N*-(diphenylmethylene)amino)-2-ethylcyclopropanecarbonitrile (*E*)-**24**.[12] Diimide reduction of the 94/6 mixture of (1*S*,2*R*)- and (1*R*,2*R*)-**22** (de 88%), arising from ethyl lactate (2*S*)-**19** (ee 94%), via the cyclization of (6*S*)-**21a** under the

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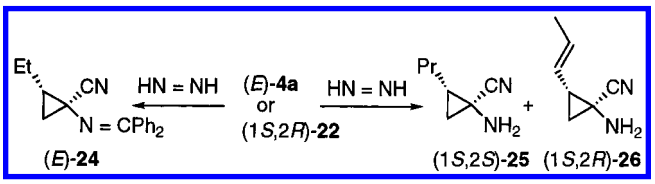
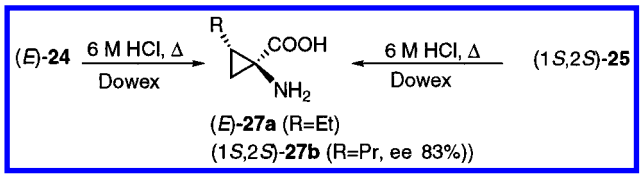
(53) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91.

Scheme 9



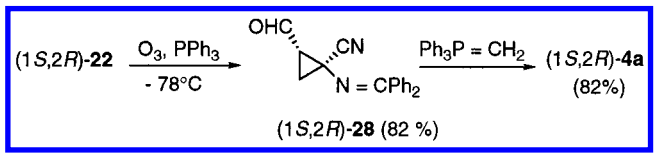
Scheme 10



conditions of the Mitsunobu reaction, appeared comparatively more difficult. It required a larger excess of reactants; thus, reduction by 5.2 equiv of diimide in methanol at room temperature for 7 days gave in 68% yield a 3:2 mixture of (1*S*,2*S*)-1-amino-2-propylcyclopropanecarbonitrile **25** and (1*S*,2*R*)-**26**, resulting from partial double bond reduction and *N*-protective group cleavage, while complete double bond reduction required the portionwise addition of 74 equiv of diimide within 7 days. The formation of the seven-membered ring **8b** (6%) from (*Z*)-**22** as byproduct (6%), made the purification of (1*S*,2*S*)-**25** easier, which was then obtained diastereomerically pure in 39% yield after liquid chromatography. Otherwise, upon heating in methanol at reflux for 36 h in the presence of 13.6 equiv of diimide, a 9:1 mixture of (1*S*,2*S*)-**25** and (1*S*,2*R*)-**26** was obtained in 51% yield (Scheme 9).

Acidic hydrolysis (6 N HCl, at reflux) of (*E*)-**24** furnished, after treatment with propylene oxide or ion exchange liquid chromatography (Dowex resin), the racemic coronamic acid (*E*)-**27a** (R = Et),[12] in 72% overall yield from (*E*)-**4a** (Scheme 10). It is known that 2-alkyl-1-aminocyclopropanecarboxylic acids can undergo enzymatic or chemical resolution to provide enantiomerically pure ACCs.[54] Otherwise, the free 1-amino-2-ethenylcyclopropanecarbonitrile (*E*)-**9**, resulting from acidic hydrolysis of (*E*)-**4a** (2 N HCl) and treatment with an ion-exchange resin, constitutes a suitable precursor of dehydrocoronamic acids.[55] Acidic hydrolysis of (1*S*,2*S*)-**25** (6 N HCl, at reflux) gave in 97.5% yield the corresponding amino acid hydrochloride,[21] which after ion exchange chromatography provided in 95% yield the (1*S*,2*S*)-1-amino-2-propylcyclopropanecarboxylic acid **27b** (homocoronamic acid) (de 100%, Scheme 10).[21] It is noteworthy that competitive formation of any byproducts arising from three-membered ring opening under these acidic conditions has not been observed. Reaction of (1*S*,2*S*)-**27b** hydrochloride with Mosher's acid chloride[22] in the presence of propylene oxide (4 equiv), following a reported procedure,[21] gave the corresponding MTPA amide; racemic (*E*)-**27b** and its MTPA amide were prepared from racemic ethyl lactate for comparison. In these cases, and contrary to the cyclopropanecarbonitrile (*E*)-**4a**, no kinetic resolution was observed during the preparation of these amides. Then ^{19}F NMR, which displayed two signals at δ −69.95 and −69.85, indicated that (1*S*,2*S*)-**27b** was obtained from ethyl lactate (2*S*)-**19** (ee 94%) with >83% of enantiomeric purity.

Scheme 11



Oxidative cleavage of (1*S*,2*R*)-**22** by ozone in dichloromethane at −78 °C gave, after addition of PPh_3, the cyclopropanecarboxaldehyde (1*S*,2*R*)-**28** in 82% yield, with total preservation of the carbonitrile and imine moieties. Reaction of (1*S*,2*R*)-**28** with methylenetriphenylphosphorane (prepared in situ from methyltriphenylphosphonium bromide and 1 equiv of *n*-BuLi) provided (1*S*,2*R*)-**4a** in 82% yield. In fact use of a 94:6 mixture of (1*S*,2*R*)- and (1*R*,2*R*)-**28** gave a 94:6 mixture of diastereomeric aldehydes **28**, which upon Wittig reaction gave diastereomerically pure (1*S*,2*R*)-**4a**, besides 6% of **8b** readily removed by liquid chromatography (Scheme 11). (1*S*,2*R*)-**4a** was then *N*-deprotected (2 N HCl, propylene oxide) to give the corresponding free cyclopropylamine (1*S*,2*R*)-**9**; its enantiomeric purity > 69% revealed a partial racemization, likely of aldehyde (1*S*,2*R*)-**28** induced by the basic phosphorane during the Wittig reaction (entry 11).

In summary, we have shown that the 1-amino-2-ethenylcyclopropanecarbonitrile (*E*)-**9**, efficient precursor of natural and non natural ACCs as well as of various cyclopropanes of biological importance, can be obtained diastereoselectively in a simple one-pot palladium(0)-catalyzed tandem alkylation and $S_{N'}$ cyclization of allylic dichloride (*E*,*Z*)-**1** by ketimines derived from aminoacetonitrile. But due to the reversibility of the palladium-induced vinylcyclopropane ring opening, the reaction performed from asymmetric substrates and/or in the presence of chiral catalyst ligands was obtained with a weak enantioselectivity (≤32% ee). However, this epimerization problem can be overcome by achieving the cylization step, under the Mitsunobu reaction conditions, i.e., in the absence of Pd(0); then, asymmetric 2-(1-alkenyl)-1-aminocyclopropanecarbonitrile derivatives such as (1*S*,2*R*)-**22** can be obtained with high enantiomeric purity (ee > 83%).

Experimental Section

(*E*)-1-((Diphenylmethylene)amino)-2-ethenylcyclopropanecarbonitrile 4a. A solution of 28 mg (0.05 mmol) of Pd(dba)$_2$ and 26.3 mg (0.1 mmol) of PPh_3 in 4 mL of THF was stirred under argon for 10 min. Then was added a solution of 125 mg (1 mmol) of a 85:15 mixture of (*E*,*Z*)-1,4-dichlorobut-2-ene **1** in 2 mL of THF, and the mixture was stirred at room temperature until its color turned from deep red to orange-yellow. Then were successively added a solution of 252 mg (1.2 mmol) of (*N*-(diphenylmethylene)amino)acetonitrile **2a**[10] in 2 mL of THF and 107 mg (2 mmol) of a 45% sodium hydride dispersion in mineral oil, and the mixture was stirred for 15 min. After filtration through Celite, the organic phase was washed with 3 mL of water and with 3 mL of saturated sodium chloride aqueous solution (thrice), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with petroleum ether/diethyl ether (4:1) to give (*E*)-**4a** (202 mg, 74%) (R_f 0.56) as a pale yellow oil; IR (neat) 2130, 1665, 1600 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.69 (dd, J = 8.2, 5.6 Hz, 1H), 1.94 (dd, J =

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8.2, 5.6 Hz, 1H, H_3), 2.37 (ddd, J = 8.2, 8.2, 7.1 Hz, 1H), 5.24−5.36 (m, 2H), 5.55 (ddd, J = 15.3, 8.4, 7.1 Hz, 1H), 7.12−7.65 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 23.72, 26.43, 34.83, 115.08, 118.61, 128.55, 128.80, 129.86, 130.92, 133.44, 174.13; MS (EI) *m/z* (relative intensity) 272 (M^+, 71), 271 (62), 195 (100), 77 (58). Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92. Found: C, 83.81; H, 5.84.

(*E*)-2-Ethenyl-1-(trimethylsilyl)cyclopropanecarbonitrile 4b. Addition of 2 equiv of LDA at −78 °C to an equimolar solution of (*E*,*Z*)-**1** and 2-(trimethylsilyl)acetonitrile **2b**[15] in THF containing 0.05 equivalent of Pd(0) and stirring the mixture for 6 h at 0 °C gave after usual workup (as described above) (*E*)-**4b** containing 2% of (*Z*)-**4b** (139 mg, 86%) as a colorless oil; IR (neat) 2205, 1640 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.15 (s, 9H), 1.21 (dd, J = 7.60, 4.80 Hz, 2H), 1.29 (dd, J = 6.0, 4.8 Hz, 1H), 1.78 (dq, J = 6.0, 1.7 Hz, 1H), 5.21 (dd, J = 10.1, 1.1 Hz, 1H), 5.31 (dd, J = 17, 1.1 Hz, 1H), 5.64 (ddd, J = 17, 10.1, 1.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) −3.66, 4.21, 17.91, 25.51, 117.28, 121.88, 135.55; MS (EI) *m/z* (relative intensity) 165 (M^+, 0.6), 150 (4), 73 (100), 43 (11); exact mass M^+ 165.0963 (calcd for $C_9H_{15}NSi$ 165.0973).

(*E*)-2-Ethenyl-1-(phenylseleno)cyclopropanecarbonitrile 4c. Addition of 2 equiv of LDA at room temperature to an equimolar solution of (*E*,*Z*)-**1** and (phenylseleno)acetonitrile **2c**[16] in THF containing 0.05 equiv of Pd(0) gave after stirring the mixture for 10 min and usual workup (see above) (*E*)-**4c** (167 mg, 67%); IR ($CDCl_3$) 2260, 1645 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.65−1.75 (m, 2H), 2.33 (q, J = 8.3 and 7.8 Hz, 1H), 5.20−5.40 (m, 2H), 5.61 (ddd, J = 16.9, 10.0, 8.3 Hz, 1H), 7.55 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 14.12, 24.09, 33. 44, 117.67, 119.32, 128.52, 129.16, 133.09, 133.45, 134. 66; MS (EI) *m/z* (relative intensity) 249 (M^+, 13), 92 (100), 77 (74); exact mass M^+ 249.0051 (calcd for $C_{12}H_{11}NSe$ 249.0056).

(*E*)-2-Ethenyl-1-(phenylsulfonyl)cyclopropanecarbonitrile 4d.[17] Addition of 2 equiv of DBU at room temperature to an equimolar solution of (*E*,*Z*)-**1** and commercially available (phenylsulfonyl)acetonitrile **2d** in THF containing 0.05 equiv of Pd(0) gave, after stirring the mixture for 18 h and usual workup (see above), a 94:6 mixture of (*E*)- and (*Z*)-**4d** (203 mg, 87%); IR (neat) 2230, 1630 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.71 (dd, J = 7.70, 6.20 Hz, 1H), 2.16 (ddd, J = 8.02, 6.15, 1.38 Hz, 1H), 2.92 (dd, J = 7.98, 7.44 Hz, 1H),5.34−5.72 (m, 3H), 7.36−8.09 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 20.92, 30.34, 39.15, 114.25, 121.82, 128.30, 128.72, 129.68, 134.92, 137.09; MS (EI) *m/z* (relative intensity) 233 (M^+, 4), 168 (100), 92 (32), 39 (50); exact mass M^+ 233.0517 (calcd for $C_{12}H_{11}NO_2S$ 233.0511).

1-Aza-2-cyano-7,7-diphenylcyclohepta-2,4-diene 8a. Addition of 2 equiv of NaH to an equimolar solution of (*E*,*Z*)-**1** and **2a** in THF at −78 °C containing 0.05 equiv of Pd(0) prepared from $Pd(dba)_2$ and (*S*)-BINAP[19] produced on stirring the reaction mixture at −30 °C for 3 h and after usual workup (see above) a 52/48 mixture of (*E*)-**4a** and **9a**, purified by column chromatography over silica gel eluting with pentane/diethyl ether (4:1) to give **9a** as a orange-yellow oil; IR (CCl_4) 2230, 1660 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 3.19 (d, J = 6.0 Hz, 2H), 4.72 (d, J = 1.4 Hz, 1H), 5.43 (dd, J = 6.8, 1.4 Hz, 1H), 5.74 (dd, J = 10.7, 6.8 Hz, 1H), 5.90 (dt, J = 10.7, 6.0 Hz, 1H), 7.12−7.38 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 44.32, 67.76, 110.79, 117.74, 125.30, 126.76, 127.46, 128.57, 131.66, 145.79; MS (EI) *m/z* (relative intensity) 272 (M^+, 71), 271 (67), 195 (100), 77 (59). Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92. Found: C, 83.81; H, 5.84.

(*E*)-1-Amino-2-ethenylcyclopropanecarbonitrile 9. To a solution of 76 mg (0.28 mmol) of **4a** in 20 mL of diethyl ether was added 10 mL of a 2 N aqueous solution of hydrochloric acid at room temperature. The reaction mixture was stirred for 16 h. The aqueous phase was concentrated in vacuo to give 41 mg (100%) of 1-amino-2-ethenylcyclopropanecarbonitrile as a brown solid; ^{1}H NMR (250 MHz, D_2O) δ (ppm) 1.54 (d, 7.4 Hz, 2H), 2.23 (ddd, J = 7.4, 7.4, 7.4 Hz, 1H), 5.08 (m, 2H), 5.40 (ddd, J = 17.1, 10.3, 7.4 Hz, 1H); ^{13}C NMR (63 MHz, D_2O) δ (ppm) 18.53, 27.72, 43.85, 120.99, 127.71, 130.76.

To a solution of 44 mg (0.3 mmol) of 1-amino-2-ethenylcyclopropanecarbonitrile in 10 mL of THF under argon stream was added dropwise 82 μL (1.2 mmol) of propylene oxide. The mixture was stirred at room temperature for 4 h and evaporated in vacuo. The residue was added to 10 mL of diethyl ether, filtered through Celite, and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with dichloromethane/methanol (99:1) to give (*E*)-**9** (26 mg, 80%) as a pale yellow oil; IR (CCl_4) 2220, 1645 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.28 (dd, J = 8.1, 5.5 Hz, 1H), 1.4 (dd, J = 8.1, 5.5 Hz, 1H), 1.98 (ddd, J = 8.3, 8.1, 8.1 Hz, 1H), 2.16 (s, 2H), 5.3 (m, 2H), 5.59 (ddd, J = 17.0, 10.2, 8.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 22.93, 29.34, 31.99, 118.06, 121.44, 133.92; MS (EI) *m/z* (relative intensity) 108 (M^+, 58), 81 (94), 80 (100), 41 (69); exact mass M^+ 108.0679 (calcd for $C_6H_8N_2$ 108.0687).

(−)-(2*S*,3*S*,5*S*)-[(2-Hydroxypinylidene)amino]acetonitrile 12.[24] A solution of 1.35 g (24 mmol) of aminoacetonitrile **10** and of 2 g (12 mmol) of (1*S*,2*S*,5*S*)-2-hydroxy-3-pinanone (−)-**11**[23] in 30 mL of benzene containing 100 μL of boron trifluoride etherate was refluxed for 18 h in a flask fitted with a Dean−Stark condenser. The mixture was evaporated in vacuo, and the black residue was purified by column chromatography over silica gel eluting with diethyl ether/hexane (75:25) to give (−)-**12** (2.3 g, 93%) as white crystals. $[\alpha]^{20}_D$ −2.7, *c* 0.56, $CHCl_3$; IR (CCl_4) 3580, 2250, 1650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.81 (s, 3H), 1.31 (s, 3H), 1.48 (s, 3H), 1.58 (m, 1H), 2.07 (d, J = 5.6 Hz, 2H), 2.37 (m, 1H), 2.50 (m, 2H), 3.06 (s, 1H), 4.21 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 22.63, 26.95, 27.82, 33.72, 37.85, 38.10, 38.41, 50.15, 76.37, 117.04, 183.03; MS (EI) *m/z* (relative intensity) 206 (M^+, 1.5), 71 (100), 43 (78), 39 (26). Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80. Found: C, 69.83; H, 9.03.

(+)-(2*R*,3*R*,5*R*)-[(2-Hydroxypinylidene)amino]acetonitrile 12.[24] Following the same procedure, (+)-**12** was obtained in 93% yield from acetonitrile **10** and (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone (+)-**11**.[23] $[\alpha]^{20}_D$ +2.9, *c* 0.56, $CHCl_3$. Exact mass M^+ 206.1419 (calcd for $C_{12}H_{18}N_2O$ 206.1410).

(−)-(2′*S*,3′*S*,5′*S*)-1-((2′-Hydroxypinylidene)amino)-2-ethenylcyclopropanecarbonitrile 13 (General Procedure). To a solution of 967 μL (6.9 mmol) of diisopropylamine (freshly distilled on calcium hydride) in 4 mL of THF were added dropwise under argon stream at −78 °C a 1.4 N solution of *n*-butyllithium in hexane. The mixture was stirred for 30 min, and then was added at −78 °C a solution of 618 mg (3 mmol) of (−)-**12** in 3 mL of THF. After stirring the mixture for 30 min, 2.65 mL (15.1 mmol) of HMPA was added, and the mixture was stirred for 1 h at −78 °C. To a separate flask, under an argon stream, were added 104 mg (0.18 mmol) of $Pd(dba)_2$ and 105 mg (0.4 mmol) of triphenylphosphine in 4 mL of THF, and then after stirring for 10 min 381 μL (3.6 mmol) of a 85/15 mixture of (*E*,*Z*)-**1** was added. To this π-allyl palladium complex, cooled to −78 °C, was added the reactant previously prepared from (−)-**12** and LDA, and the mixture was stirred at −78 °C for 8 h. Then 3.9 mmol of LDA was added again. The mixture was stirred at −78 °C for 21 h, until completion of the reaction as monitored by TLC. After addition of diethyl ether and of a saturated aqueous solution of ammonium chloride, the organic phase was filtered through Celite and washed with water and with saturated sodium chloride aqueous solution (thrice). The aqueous phase was extracted with diethyl ether (thrice). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo to leave a yellow oil. The residue was purified by column chromatography over silica gel eluting with dichloromethane/diethyl ether (9:1) to give (−)-**13** (530 mg, 69%) as a pale yellow oil; $[\alpha]^{20}_D$ −24.1, *c* 0.98, $CHCl_3$; IR (CCl_4) 3580, 2230, 1640 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.86 (s, 3H), 1.34 (s, 3H), 1.44 (s, 3H), 1.5−1.74 (m, 3H), 2.06−2.44 (m, 6H), 2.8−3.1 (m, 2H), 5.28−5.40 (m, 2H), 5.66−5.84 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 22.78, 23.55, 27.99, 32.15, 35.60, 35.84, 38.25, 38.55, 76.50, 117.92, 118.53, 133.4, 186.2; MS (EI) *m/z* (relative intensity) 258 (M^+, 6), 92 (49), 71 (100), 39 (34). Anal. Calcd for $C_{16}H_{22}NO$: C, 58.68; H, 8.37. Found: C, 59.37; H, 8.62.

(+)-(2′*R*,3′*R*,5′*R*)-1-((2′-Hydroxypinylidene)amino)-2-ethenylcyclopropanecarbonitrile 13. Following the same procedure (+)-**13** was obtained in 70% yield from (+)-**12**. $[\alpha]^{20}_D$ +24.1, *c* 0.965, $CHCl_3$.

(4*S*)-1-Chloropent-2-en-4-ol 20a. To a solution of 10 g (84.8 mmol) of freshly distilled (2*S*) ethyl lactate **23** (bp 65−67 °C, 27 mmHg) and of 11.6 mL (127 mmol) of freshly distilled 3,4-dihydro-2*H*-pyran (bp 85−86 °C, 760 mmHg) in 100 mL of anhydrous dichloromethane was added dropwise a solution of 2.3 g (8.5 mmol) of pyridinium *p*-toluenesulfonate (PPTS) in 10 mL of dichloromethane. The mixture was stirred for 2 h at room temperature and evaporated in vacuo. The residue was dissolved in diethyl ether; the organic phase was washed by 20 mL of half-saturated sodium chloride aqueous solution, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography eluting with pentane/diethyl ether (6:4) or distilled (bp 118−122 °C, 15 mmHg) to give a 1:1 diastereomeric mixture of (2*S*) ethyl 2-(2-tetrahydroxypyranyloxy)propanoate (15.7 g, 92%) as a colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.29 (d, J = 6.6 Hz and d, J = 6.3 Hz, 6H), 1.40 (d, J = 6.3 Hz, 3H), 1.47 (d, J = 6.6 Hz, 3H), 1.97−1.51 (m, 12H), 3.41−3.58 (m, 2H), 3.81−4.01 (m, 2H), 4.12−4.28 (m, 5H), 4.45 (q, J = 6.6 Hz, 1H), 4.67−4.75 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 13.89, 17.87, 18.89, 25.07, 30.20, 62.12, 69.68, 72.29, 97.26, 98.04, 173.01, 173.08.

To a solution of 4.8 g (20.7 mmol) of this ethyl propanoate in 50 mL of dichloromethane was added dropwise at −78 °C 19 mL (19 mmol) of a 1 M solution of diisobutylaluminum hydride (DIBALH) in hexane. After stirring for 1 h at −78 °C was added 2 mL of methanol. The colorless mixture was poured into 100 mL of an aqueous saturated solution of sodium and potassium tartrate (Rochelle salt) cooled to 0 °C. The milky-white mixture was stirred at room temperature for 4 h, and the aqueous phase was extracted by dichloromethane (four times). The combined organic phases were washed by water, dried (Na_2SO_4), filtered through silica gel, and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane/diethyl ether (2:1) to give the (−)-(2*S*)-2-(2-tetrahydropyranyloxy)propanal[40] (2.6 g, 79.5%) as a 1:1 diastereomeric mixture, besides (2*S*)-**19** (538 mg, 13%); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.28 (d, J = 6.9 Hz, 3H), 1.36 (d, J = 7.1 Hz, 3H), 1.55−1.90 (m, 12H), 3.51 (m, 2H), 3.89 (m, 2H), 3.97 (dq, J = 2.3, 6.9 Hz, 1H), 4.25 (dq, J = 7.1, 1.3 Hz, 1H), 4.72 (m, 1H), 9.66 (2s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 15.04−15.56, 19.20, 19.84, 25.03, 25.12, 30.40, 30.52, 62.56−63.39, 76.35−78.43, 98.14−99.24, 202.99−203.29; IR ($CDCl_3$) 1740 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 158 (M^+, 1.3), 85 (100), 57 (42), 56 (55), 41 (31); MS (CI, NH_3) *m*/*z* (relative intensity) 176 (M +18).

A mixture of 2.125 g (50 mmol) of lithium chloride, of 9.9 mL (50 mmol) of triethyl phosphonoacetate, and 6.22 mL (42 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 120 mL of dry acetonitrile was stirred for 30 min at room temperature under argon stream. Then a solution of 6.57 g (41.6 mmol) of (2*S*)-2-(2-tetrahydropyranyloxy)propanal in 25 mL of acetonitrile was added dropwise; the mixture turned to milky-white within 1 h. The solution was evaporated in vacuo, and the residue was purified by column chromatography over silica gel eluting with pentane/diethyl ether (75:25) to give 8.8 g (93%) of (*E*)-(4*S*) ethyl 4-(2-tetrahydropyranyloxy)pent-2-enoate[42] as a 1:1 diastereomeric mixture, as a colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.21−1.35 (m, 12H), 1.55−1.88 (m, 12H), 3.49 (m, 2H), 3.89 (m, 2H), 4.21 (q, J = 7.1 Hz, 4H), 4.46 (p, J = 6.5 Hz, 2H), 4.58 (t, J = 2.9 Hz, 1H), 4.79 (t, J = 3.2 Hz, 1H), 5.95 (dd, J = 15.7, 1.1 Hz, 1H), 6.07 (dd, J = 15.7, 1.7 Hz, 1H), 6.83 (dd, J = 15.7, 6.1 Hz), 6.98 (dd, J = 15.7 Hz, 1H).

To a solution of 10 g (43.9 mmol) of this ethyl pentenoate in 150 mL of dichloromethane was added dropwise at −78 °C under argon stream, 110 mL (110 mmol) of a 1 M solution of DIBALH in hexane. The reaction was complete after stirring for 1 h at −78 °C, as monitored by TLC, 14 mL of methanol was added at −78 °C, and the mixture was poured into a saturated solution of Rochelle salt at 0 °C. The resulting milky-white mixture was stirred overnight. The aqueous phase was extracted by dichloromethane (four times), and the combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane/diethyl ether (5:5) to give the (4*S*)-4-(2-tetrahydropyranyloxy)pent-2-enol (7.95 g, 97%) as a 1:1 diastereomeric mixture; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.22 (d, J = 6.3 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.48−1.91 (m, 14H), 3.48 (m, 2H), 3.91 (m, 2H), 4.16 (t, J = 6.4 Hz, 4H), 4.33 (m, 2H), 4.64 (t, J = 3 Hz, 1H), 4.73 (t, J = 3.2 Hz, 1H), 5.58 (dd, J = 16.4, 7.2 Hz, 2H), 5.82 (dt, J = 16.4, 6.4 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 19.27, 19.36, 19.58, 25.18, 25.25, 30.49, 30.71, 62.14, 62.31, 62.50, 71.31, 71.50, 95.32, 96.07, 129.03, 131.27, 131.87, 133.36; MS (EI) *m*/*z* (relative intensity) 101 (14), 85 (100), 55 (45); MS (CI, NH_3) *m*/*z* (relative intensity) 204 (M + 18).

To a solution of 435 mg (2.34 mmol) of this allylic alcohol in 12 mL of diethyl ether containing 981 μL (7 mmol) of triethylamine was added at 0 °C dropwise 272 μL (3.52 mmol) of freshly distilled (bp 50−52 °C/20 mmHg) methanesulfonyl chloride, while the mixture turned from colorless to milky-white. When the reaction was over as monitored by TLC, the mixture was allowed to reach room temperature and diethyl ether was added, followed by water. The organic phase was washed with 0.5 N hydrochloride solution (twice) until acidity and then with saturated sodium bicarbonate and saturated sodium chloride. The organic phase was dried (Na_2SO_4) and evaporated to give 593 mg (96%) of (4*S*)-4-(2-tetrahydropyranyloxy)pent-2-enyl methanesulfonate as a yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.25 (d, J = 5.3 Hz, 3H), 1.30 (d, J = 5.3 Hz, 3H), 1.50−1.90 (m, 12H), 3.03 (s, 6H), 3.50 (m, 2H), 3.85 (m, 2H), 4.35 (p, J = 5.3, 5.3 Hz, 2H), 4.75 (d, J = 5.8 Hz, 4H), 4.55−4.80 (m, 2H), 5.70−5.90 (m, 2H), 6.0 (dd, J = 15.8, 5.3 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 19.36, 21.38, 25.20, 30.49, 30.69, 37.79, 37.89, 62.34, 62.63, 69.45, 69.86, 69.88, 70.51, 95.89, 96.29, 121.19, 123.21, 138.64, 139.92; IR ($CDCl_3$) 3140, 1790, 1720 cm^{-1}. This mesylate was too unstable to give MS spectra or elemental analysis).

To a suspension of 555.4 mg (13.07 mmol) of lithium chloride in 10 mL of *N*-methylpyrrolidinone (NMP) was added dropwise at room temperature a solution of 2.3 g (8.7 mmol) of the mesylate in 8 mL of NMP. The reaction was complete after stirring for 1 h as monitored by TLC, and then 20 mL of water was added. The aqueous phase was extracted by 20 mL of diethyl ether (thrice), and the combined organic phases were washed with water (twice), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel to give 1.55 g (87%) of (4*S*)-1-chloro-4-(2-tetrahydropyranyloxy)pent-2-ene as a 1:1 diastereomeric mixture; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.20 (d, J = 6.6 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.50−1.90 (m, 12H), 3.50 (m, 2H), 3.85 (m, 2H), 4.05 (d, J = 5.9 Hz, 4H), 4.35 (p, J = 6.6, 6.6 Hz, 2H), 4.55−4.80 (m, 2H), 5.65 (dd, J = 13.8, 6.6 Hz, 2H), 5.75 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 19.70, 21.50, 25.27, 30.74, 44.14, 44.56, 62.62, 70.64, 70.75, 95.68, 96.15, 125.25, 127.42, 135.92, 137.07; IR ($CDCl_3$) 3050, 1650 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 103 (68), 85 (100), 41 (53); MS (CI, NH_3) *m*/*z* (relative intensity) 222 (M + 18, 5), 205 (M + 1). Anal. Calcd for $C_{10}H_{17}O_2Cl$: C, 58.68; H, 8.37; Cl, 17.32. Found: C, 59.37; H, 8.62; Cl, 17.07.

A solution of 294 mg (1 mmol) of the tetrahydropyranyl ether in 8 mL of ethanol containing 25 mg of PPTs was heated at 50−55 °C under argon stream for 3 h. After evaporation in vacuo, the residue was dissolved in 20 mL of diethyl ether. The organic phase was washed with half-saturated aqueous NaCl solution, dried (Na_2SO_4), and evaporated in vacuo to give (4*S*)-**20a** (110 mg, 91%), as colorless oil; $[\alpha]^{20}_D$ 15.1, *c* 1.325, Cl_2CH_2; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.30 (d, J = 7.2 Hz, 3H), 1.65 (s, 1H), 4.05 (d, J = 7.2 Hz, 2H), 4.35 (p, J = 6.6, 6.6 Hz, 1H), 5.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 23.08, 44.37, 67.73, 125.47, 138.56; IR ($CDCl_3$) 3700, 3610, 1610 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 105 (15), 85 (27), 69 (29), 58 (16), 43 (100); MS (CI, NH_3) *m*/*z* (relative intensity) 138 (M + 18, 100). Anal. Calcd for C_5H_9OCl: C, 49.81; H, 7.52. Found: C, 49.61; H, 7.22.

Mosher Ester of (4*S*)-20a. To a solution of 92 mg (0.39 mmol) of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid in 1 mL of dry dichloromethane was added dropwise at 0 °C a solution of 142 mg (1.18 mmol) of (4*S*)-**20a** in 1 mL of dichloromethane containing 5 mg of 2,4-(dimethylamino)-pyridine (DMAP). Then, under an argon stream, 97 mg (1.42 mmol) of *N*,*N*-dicyclohexylcarbodiimide (DCC) was added. When the reaction was complete as monitored by TLC, the mixture was allowed to warm to room temperature and was filtered through Celite. The organic phase was washed by 0.5 N HCl (thrice) until acidity and then by a saturated solution of sodium bicarbonate and a saturated solution of NaCl. The organic phase was dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by column chromatography over silica gel, eluting with pentane/diethyl ether (9:1) to give the corresponding Mosher ester (338 mg, 85%) as a diastereomeric mixture; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.44 (d, J = 6.8 Hz, 6H), 3.57 (s, 3H), 3.62 (s, 3H), 3.97 (d, J = 6 Hz, 1H), 4.05 (d, J = 7.2 Hz, 2H), 5.61 (p, J = 6.8, 6.8 Hz, 2H), 5.82 (m, 4H), 7.32−7.58 (m, 10H); ^{19}F NMR (235 MHz, $CF_3CH_2OH/CDCl_3$) δ (ppm) −72.49 (s, 3F), −72.44 (s, 3F); MS (EI) *m*/*z* (relative intensity) 189 (100), 103 (19), 67 (18); MS (CI, NH_3) *m*/*z* (relative intensity) 356 (M + 18, 31), 354 (M + 18, 100).

(4*S*)-4-Acetoxy-1-chloropent-2-ene 20b. To a solution of 200 mg (1.7 mmol) of (4*S*)-**20a** in 50 mL of anhydrous diethyl ether containing 223 mg (1.9 mmol) of DMAP was added dropwise, at 0 °C under an argon stream, 240 μL (2.5 mmol) of acetic anhydride. The reaction was complete within 1 h as monitored by TLC; the mixture was evaporated in vacuo, and the residue was dissolved in petroleum ether, filtered through Celite, and evaporated in vacuo. The residue was purified by column chromatography over silica gel deactivated by a 1% solution of NEt_3 in petroleum ether, eluting with pentane/diethyl ether (98:2) to give **20b** (219 mg, 81%) as a pale yellow oil. $[\alpha]^{20}_D$ −53.8, *c* 1.11, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.32 (d, J = 6.4 Hz, 3H), 2.06 (s, 3H), 4.05 (d, J = 5.2 Hz, 2H), 5.37 (p, J = 6.4, 6.4 Hz, 1H), 5.72−5.85 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 19.95, 21.24, 44.05, 59.61, 127.34, 133.78, 170.14.

(4*S*)-4-(*tert*-Butyloxycarboxy)-1-chloropent-2-ene 20c. To a solution of 248 mg (1.2 mmol) of di *tert*-butyl carbonate in 2 mL of THF containing 0.15 mL (1.1 mmol) of freshly distillated triethylamine and 22 mg (0.18 mmol) of DMAP was added dropwise, under an argon stream at room temperature, 60 mg (0.5 mmol) of (4*S*)-**20a**. The reaction was complete within 15 min as monitored by TLC; the mixture was evaporated in vacuo and the residue dissolved in 2 mL of diethyl ether containing 100 μL of 1 N HCl. The organic phase was washed with 0.1 N HCl until acidity and then with 1 mL of saturated NaCl aqueous solution until neutrality. The organic phase dried over Na_2SO_4 was evaporated in vacuo, and the residue was purified by column chromatography over desactivated (grade IV) neutral alumina, eluting with pentane/diethyl ether (85:15) to give **20c** (93 mg, 84%) as a pale yellow oil. $[\alpha]^{20}_D$ −31.9, *c* 0.87, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.39 (d, J = 5.8 Hz, 3H), 1.51 (s, 9H), 4.05 (d, J = 5.3 Hz, 2H), 5.67 (p, J = 5.8, 5.8 Hz, 1H), 5.85 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 20.04, 27.76, 43.97, 72.59, 82.13, 127.70, 133?62, 152.69; IR (CCl_4) 3020, 1750 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 200 (M^+, 25), 205 (100), 57 (29), 41 (14); MS (CI, NH_3) *m*/*z* (relative intensity) 240 (M + 18, 33), 338 (M + 18, 100), 184 (30).

(4*S*)-1-Chloro-4-(2,4-dichlorobenzoyloxy)pent-2-ene 20d. To a solution of 102.5 mg (1 mmol) of (4*S*)-**26** in 5 mL of dichloromethane were added dropwise, under argon stream at room temperature, 162 μL (2 mmol) of freshly distilled pyridine and 168 μL (1.2 mmol) of 2,4-dichlorobenzoyl chloride. The reaction was complete after stirring for 18 h as monitored by TLC, and then dichloromethane was added to the mixture, followed by 2 mL of 0.5 N HCl. The organic phase was washed by 2 mL of 0.5 N HCl until acidity and then by water until neutrality. The aqueous phase was extracted by dichloromethane (thrice), and the combined organic phases were dried (Na_2SO_4) and evaporated in vacuo to give **20d** (278 mg, 95%) as a pale yellow oil. $[\alpha]^{20}_D$ +18, c 1.37, $CHCl_3$; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.47 (d, J = 6.4 Hz, 3H), 4.07 (d, J = 5.6 Hz, 2H), 5.64 (p, J = 6.4, 6.4 Hz, 1H), 5.91−5.97 (m, 2H), 7.29−7.58 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 19.78, 43.78, 71.15, 126.76, 127.27, 127.89, 130.68, 131.37, 132.23, 133, 133.40, 163.53; IR ($CHCl_3$) 3020, 1600 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 257 (44), 173 (100), 67 (51); MS (CI, NH_3) *m*/*z* (relative intensity) 311 (M + 18, 100), 309 (M + 18, 88). Anal. Calcd for $C_{12}H_{11}O_2Cl_3$: C, 49.10; H, 3.78; Cl, 36.23. Found: C, 48.89; H, 3.81; Cl, 36.18.

(4*R*)-1,4-Dichloropent-2-ene 20e.[45] To a solution of 315 mg (1.2 mmol) of triphenylphosphine in 20 mL of THF containing 187 mg (1.4 mmol) of *N*-chlorosuccinimide (freshly recrystallized from benzene) was added dropwise at room temperature, under an argon stream, a solution of 120.5 mg (1 mmol) of (4*S*)-**20a** in THF. When the reaction was complete as monitored by TLC, the mixture was added to 70 mL of diethyl ether and to 40 mL of water. The aqueous phase was extracted by diethyl ether (twice), and the combined organic phases were washed with saturated NaCl aqueous solution (twice), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel, eluting with dichloromethane to give (4*R*)-**20e** (129 mg, 93%) as a pale yellow oil; $[\alpha]^{20}_D$ +18, *c* 1.37, $CHCl_3$; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.61 (d, J = 6.3 Hz, 3H), 4.07 (d, J = 6.1 Hz, 2H), 4.58 (p, J = 6.3, 6.3 Hz, 1H), 5.83−5.95 (m, 2H); MS (EI) *m*/*z* (relative intensity) 138 (M, 8), 89 (100), 39 (74); MS (CI, NH_3) *m*/*z* (relative intensity) 140 (28), 139 (21), 138 (72), 137 (30), 120 (100).

(*E*)- and (*Z*)-1-(*N*-(diphenylmethylene)amino)-2-(1-propenyl)cyclopropanecarbonitrile 22. To a stirred solution of 29 mg (0.05 mmol) of $Pd(dba)_2$ and 29 mg (0.11 mmol) of PPh_3 in 4 mL of THF, under an argon stream, was added a solution of 139 mg (1 mmol) of **20e** in 2 mL of THF and the mixture was stirred at room temperature until its color turned from deep red to pale yellow. Then a solution of 242 mg (1.1 mmol) of **2a** in 2 mL of THF and 96 mg (2 mmol) of a 50% sodium hydride dispersion in mineral oil were successively added, and the mixture was stirred for 5 h. After filtration through Celite, the organic phase was washed with water and with saturated sodium chloride aqueous solution (thrice), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with dichloromethane to give in 49% yield a 77:23 mixture of (*E*)- and (*Z*)-**22** (de 54%) and **8b** (24%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.63 (dd, J = 7.9, 5.4 Hz, 6H), 1.76 (dd, J = 6.5, 1.6 Hz, 3H), 1.90 (dd, J = 8.8 Hz, 1H), 2.35 (ddd, J = 8.8, 8.3, 7.9 Hz, 1H), 5.25 (ddq, J = 15.5, 8.3, 1.6 Hz, 2H), 5.77 (dq, J = 15.5, 6.5 Hz, 2H), 7.10−7.70 (m, 20H) [(*Z*)-**22** was characterized by ^{1}H NMR signals at 1.84 (dd, J = 7.1, 1.9 Hz, 3H), 2.02 (dd, J = 9.1, 5.1 Hz, 1H), 2.62 (ddd, J = 9.1, 8.9, 8.3 Hz, 1H)]; ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 15.24, 18.02, 26.52, 34.26, 38.61, 65.82, 117.88, 125.98, 128.12, 129.44, 128.75, 129.77, 130.04, 130.79, 132.39, 135.87, 139.30, 172.46; IR ($CDCl_3$) 2225, 1665, 1595 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 286 (M, 35), 209 (100), 77 (48); exact mass M^+ 286.1465 (calcd for $C_{20}H_{18}N_2$ 286.1470).

(*E*)-(6*S*)-2-(*N*-(Diphenylmethylene)amino)-6-hydroxyhept-4,6-enenitrile 21a. To a solution of 93 mg (0.415 mmol) of $Pd(OAc)_2$ and 199 mg (0.498 mmol) of 1,2-bis(diphenylphosphino)ethane (dppe) in 1.5 mL of THF was added a solution of 1 g (8.3 mmol) of (4*S*)-**20a** in 2 mL of THF, and the resulting π-allyl palladium complex was stirred for 10 min at room temperature, under an argon stream. Then a solution of 2.01 g (9.13 mmol) of (diphenylmethyleneamino)acetonitrile **2a** in 2 mL of THF was transferred under an argon stream, previously treated by 438 mg (9.13 mmol) of a 50% oil suspension of sodium hydride. The mixture's color turned from orange-brown to black after stirring for 15 min, a saturated aqueous solution of ammonium chloride and diethyl ether were added, and the mixture was filtered through Celite. The organic phase was washed with saturated aqueous solution of NaCl, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel, eluting with dichloromethane/diethyl ether (90:10) to give (6*S*)-**21a** as orange oil (2.44 g, 97%); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.24 (d, J =

6.4 Hz, 3H), 1.87 (m, 1H), 4.27 (p, J = 6.4, 6.4, 6.4 Hz, 2H), 5.60−5.69 (m, 2H), 7.19−7.65 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 23.23, 37.55, 53.27, 68.22, 119.13, 123.22, 127.37, 128.21, 128.99, 135.09, 139.31, 173.19; IR (CCl_4) 3680, 3500, 3420, 2240, 1640, 1600, 1580 cm^{-1}; MS (EI) *m/z* (relative intensity) 304 (1), 116 (100), 89 (17), 77 (26); MS (CI, NH_3) *m/z* (relative intensity) 305 (M + 1, 100); exact mass M^+ 304.1558 (calcd for $C_{20}H_{20}N_2O$ 304.1576).

(*E*)-(6*S*)-6-Acetoxy-2-(*N*-(diphenylmethylene)amino)-hept-4-enenitrile 21b. Following the procedure to obtain (4*S*)-**20b** from (4*S*)-**20a** (vide supra), the acetate (6*S*)-**21b** was obtained from (6*S*)-**21a** (100%) as a 48:52 diastereomeric mixture; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.25 (d, J = 6.3 Hz, 6H), 1.90 (s, 3H), 2.65 (m, 4H), 4.25 (td, J = 6.8, 2.1 Hz, 2H), 5.30 (p, J = 6.3, 6.3 Hz, 2H), 5.65 (m, 4H), 7.11−7.75 (m, 20H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 20.13, 21.27, 37.71, 52.85, 70.36, 119.04, 125.80, 127.44, 128.20, 129.02, 135.17, 138.38, 170.17, 173.27; IR (hexane) 3050, 2250, 1750, 1645 cm^{-1}; MS (EI) *m/z* (relative intensity) 346 (M, 2.45), 116 (100), 43 (23); MS (CI, NH_3) *m/z* (relative intensity) 347 (M + 1, 80); exact mass M^+ 346.1672 (calcd for $C_{22}H_{22}N_2O_2$ 346.1681).

(*E*)-(6*S*)-6-(2,4-Dichlorobenzoyloxy)-2-((diphenylmethylene)amino)hept-4-enenitrile 21d. To a solution of 152 mg (0.5 mmol) of (6*S*)-**21a** in 5 mL of dichloromethane containing 81 μL (1 mmol) of freshly distilled pyridine was added dropwise at room temperature 84 μL (0.6 mmol) of 2,4-dichlorobenzoyl chloride, under an argon stream. The reaction was complete within 18 h, as monitored by TLC, and then dichloromethane was added, followed by 0.5 N HCl. The organic phase was washed by 0.5 N HCl until acidity and by water until neutrality. The aqueous phase was extracted by dichloromethane (thrice), and the combined organic phases were dried (Na_2SO_4) and evaporated in vacuo to give (6*S*)-**21d** (240 mg, 100%) as an unseparable diastereomeric mixture; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.46 (d, J = 5.9 Hz, 6H), 2.72 (t, J = 6.9 Hz, 4H), 4.30 (dt, J = 6.9, 1.6 Hz, 2H), 5.59 (p, J = 5.9, 5.9 Hz, 2H), 5.66−5.88 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 20.12, 20.19, 37.52, 37.60, 52.65, 52.83, 71.93, 72.05, 118.88, 118.93, 126.46, 126.82, 126.83, 126.89, 127.32, 128.40, 128.57, 129.32, 130.80, 133.94, 134.07, 134.79, 135.02, 135.08, 138.16, 138.22, 163.78, 163.84, 173.28; IR (CCl_4) 2240, 1745, 1625 cm^{-1}; MS (EI) *m/z* (relative intensity) 476 (M, 12), 116 (100); exact mass M^+ 476.1061 (calcd for $C_{27}H_{22}O_2Cl_2$ 476.1058).

(*E*)-(6*S*)-6-(Benzyloxy)-2-((diphenylmethylene)amino)-hept-4-enenitrile 21f. Following the procedure to obtain (4*S*)-**20d** from (4*S*)-**20a**, (6*S*)-**21f** was prepared by benzoylation of (6*S*)-**21a**. Thus, treatment of 100 mg (0.33 mmol) of (6*S*)-**21a** with 148 mg (0.66 mmol) of benzoic anhydride in the presence of 12 mg (0.1 mmol) of DMAP in 88 μL (0.63 mmol) of triethylamine in THF gave after usual workup (see above) 115 mg (85%) of (6*S*)-**21f** as a 1:1 diastereomeric mixture; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.43 (d, J = 6.4 Hz, 3H), 1.48 (d, J = 6.5 Hz, 3H), 2.71 (t, J = 6.8, 6.8 Hz, 4H), 4.29 (dt, J = 6.8, 1.6 Hz, 2H), 5.62 (p, J = 6.5, 6.5 Hz, 2H), 5.77 (m, 4H), 7.22−7.63 (m, 30H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 20.22, 20.26, 37.52, 37.58, 52.72, 52.83, 70.75, 70.87, 118.94, 118.99, 125.66, 127.35, 128.18, 128.23, 128.92, 129.97, 130.05, 132.36, 133.53, 171.76, 173.41; IR (CCl_4) 2240, 1745, 1625 cm^{-1}; MS (EI) *m/z* (relative intensity) 408 (M, 3), 116 (100), 105 (56), 77 (50); MS (CI, NH_3) *m/z* (relative intensity) 409 (M + 1, 100), 408 (M, 73); exact mass M^+ 408.1844 (calcd for $C_{27}H_{24}N_2O_2$ 408.1838).

(*E*)-(6*S*)-6-(2,6-Dichlorobenzyloxy)-2-((diphenylmethylene)amino)hept-4-enenitrile 21g. Following the procedure used for the preparation of (6*S*)-**20d**, reaction of 405 mg (1.33 mmol) of (6*S*)-**20a** with 424 μL (2.93 mmol) of 2,6-dichlorobenzoyl chloride gave, after stirring for 72 h at room temperature and usual workup (see above), 203 mg (32%) of (6*S*)-**21g**, besides 280 mg (68%) of (6*S*)-**20a**; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.45 (d, J = 6.1 Hz, 6H), 2.61−2.82 (m, 4H), 4.28 (t, J = 6.8 Hz, 2H), 5.68 (p, J = 6.1, 6.1 Hz, 2H), 5.78 (m, 4H), 7.15−7.73 (m, 26H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 19.92, 37.55, 52.84, 72.55, 118.94, 126.56, 127.09, 127.26, 127.73, 128.92, 130.71, 131.93, 133.47, 134.99, 138.22, 163.74, 173.24; IR (CCl_4) 2240, 1745, 1625 cm^{-1}; MS (EI) *m/z* (relative intensity) 477 (M, 8), 476 (M, 8), 116 (100), 77 (51); MS (CI, NH_3) *m/z* (relative intensity) 480 (28), 479 (68), 478 (41), 477 (100).

1-Aza-2-cyano-7,7-diphenyl-6-methylcyclohepta-2,4-diene 8b. The seven-membered ring **8b** was obtained in 80% yield as single product from the Pd-catalyzed cyclization of (6*S*)-**21b**. $[\alpha]^{20}_D$ −80.9, *c* 1.58, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.02 (d, J = 6.8 Hz, 3H), 3.70 (dq, J = 7.6, 6.8 Hz, 1H), 5.08 (s, 1H), 5.43 (dd, J = 8.0, 2.0 Hz, 1H), 5.62 (dd, J = 10.9, 7.6 Hz, 1H), 6.20 (dd, J = 10.9, 8.0 Hz, 1H), 7.15−7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 16.76, 29.68, 44.56, 111.91, 123.08, 126.39, 126.75, 127.13, 128.55, 138.39, 146.47; IR ($CDCl_3$) 3435, 2250, 1635, 1600 cm^{-1}; MS (EI) *m/z* (relative intensity) 286 (M, 82), 271 165 (100), 104 (82); exact mass M^+ 286.1470 (calcd for $C_{20}H_{18}N_2$ 286.1452).

(1*S*,2*R*)-1-(*N*-(Diphenylmethylene)amino)-2-(1-propenyl)cyclopropanecarbonitrile 22. To a solution of 3.65 g (12 mmol) of (6*S*)-**21a** in 24 mL of THF at −25 °C under argon stream was added 24 mL of a 1 M solution (24 mmol) of trimethylphosphine in THF. Then 3.75 mL (24 mmol) of diethyl azodicarboxylate (DEAD) were added dropwise at −25 °C. The reaction was complete within 10 min as monitored by TLC, and the mixture was added to diethyl ether containing saturated ammonium chloride aqueous solution and was allowed to warm to room temperature. The organic phase was washed with 5 mL of saturated NaCl aqueous solution and with 5 mL of water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by chromatography over silica gel eluting with dichloromethane/pentane (8:2) to give 2.19 g (63%) of a 94:6 diastereomeric mixture of (1*S*,2*R*)-**22** and (1*R*,2*R*)-**22**, with spectroscopic and analytical data identical to those reported for (*E*)- and (*Z*)-**22** (vide supra).

(*E*)-2-((*N*-Diphenylmethylene)amino)hepta-4,6-dienenitrile 23. This diene **23** was obtained as single product, in 76% yield, from the Pd-catalyzed attempted cyclization of the anions of (6*S*)-**21f** (vide supra); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.71 (m, 4H), 4.28 (t, J = 6.6 Hz, 2H), 5.15 (m, 4H), 5.63 (dt, J = 14.5, 6.6 Hz, 2H), 6.25 (m, 4H), 7.07−7.88 (m, 20H); ^{13}C NMR (50.4 MHz, $CDCl_3$) δ (ppm) 37.99, 53.26, 117.33, 127.16, 127.40, 128.22, 129, 129.38, 131.20, 135.32, 136.23, 173.04; IR ($CDCl_3$) 3080, 3060, 3020, 2240, 1660, 1620, 1600 cm^{-1}; MS (EI) *m/z* (relative intensity) 286 (M, 4), 233 (17), 219 (30), 166 (4), 165 (14), 117 (10), 116 (100), 89 (16), 77 (25).

(*E*)-1-(*N*-(Diphenylmethylene)amino)-2-ethylcyclopropanecarbonitrile 24. To a solution of 300 mg (1.1 mmol) of (*E*)-**4a** in 3 mL of methanol containing 810 μL (10 mmol) of pyridine was added, at room temperature under an argon stream, 650 mg (3.32 mmol) of potassium azodicarboxylate (freshly prepared from potassium hydroxide and azodicarbonamide[49]), followed by 420 μL (7 mmol) of acetic acid. The mixture was stirred for 18 h, and then water and diethyl ether were added. The aqueous phase was extracted by of diethyl ether (twice), and the combined organic phases were washed with a saturated NaCl aqueous solution, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with dichloromethane/pentane (9:1) to give (*E*)-**24** (231 mg, 77%) as a yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.06 (t, J = 6.6 Hz, 3H), 1.22−1.78 (m, 5H), 7.11−7.62 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 12.76, 23.60, 27.11, 33.36, 37.37, 118.21, 128.08, 128.44, 128.56, 129.66, 130, 130.64, 136.06, 139.32, 171.56; MS (EI) *m/z* (relative intensity) 274 (M, 29), 165 (100), 77 (32). Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18.10; H, 6.61; Cl, 36.23. Found: C, 83.45; H, 6.39.

(±)-(*E*)-1-Amino-2-ethylcyclopropanecarboxylic Acid [(±)-coronamic acid] 27a.[12,21] To a solution of 69 mg (0.25 mmol) of (*E*)-**24** in diethyl ether was added dropwise 1.6 mL of a 2 N HCl solution, and the mixture was stirred at room-temperature overnight. The aqueous phase was extracted by diethyl ether (twice) and evaporated in vacuo to give 40 mg (100%) of 1-amino-2-ethylcyclopropanecarbonitrile hydrochloride.[12] A solution of 37 mg (0.25 mmol) of this hydrochloride in a 6 N solution of HCl was heated at reflux for 15 h. After filtration through Celite, the solution was evaporated in vacuo. The residue was dissolved in distilled water and purified by

chromatography through an ion-exchange resin (Dowex 50 × 8−100) to give 31.2 mg (97%) of (±)-coronamic acid (*E*)-**27a**, with spectral and analytical data in total agreement with reported data.[12,21]

(1*S*,2*S*)-1-Amino-2-propylcyclopropanecarbonitrile 25. Following the procedure of the diimide reduction of (*E*)-**4a** (see above), 450 mg (1.54 mmol) of (1*S*,2*R*)-**22** in 10 mL of methanol containing 2.1 mL (26 mmol) of pyridine were treated with 23 g (116 mmol) of potassium azodicarboxylate and 15 mL (230 mmol) of acetic acid. After usual workup, 76 mg (39%) of (1*S*,2*S*)-**25** were obtained as a pale yellow oil, while use of only 5.2 equiv of diimide gave in 68% yield a 3:2 mixture of (1*S*,2*S*)-**25** and (1*S*,2*R*)-**26**).

(1*S*,2*S*)-1-Amino-2-propylcyclopropanecarbonitrile 25: $[\alpha]^{20}_D$ +36, *c* 0.02, $CHCl_3$ ^{1}H NMR (250 MHz, C_6H_6) δ (ppm) 0.41 (dd, J = 7.9, 4.9 Hz, 1H), 0.61 (dd, J = 7.9, 4.9 Hz, 1H), 0.73−0.87 (m, 4H), 1.06−1.38 (m, 6H); ^{13}C NMR (63 MHz, C_6H_6) δ (ppm) 13.78, 22.13, 22.98, 27.89, 28.53, 32.57, 122.06; IR (CCl_4) 3400, 3330, 2220 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 124 (M, 0.5), 95 (16), 81 (100); MS (CI, NH_3) *m*/*z* (relative intensity) 142 (M + 18, 100), 125 (M + 1, 16).

(1*S*,2*R*)-1-Amino-2-(1-propenyl)cyclopropanecarbonitrile 26: ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.18−1.35 (m, 2H), 1.72 (d, J = 6.4 Hz, 3H), 1.91 (ddd, J = 8.4, 8.2, 8.0 Hz, 1H), 2.24 (s, 2H), 5.23 (dd, J = 14.9, 8.2 Hz), 5.72 (dq, J = 14.9, 6.4 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 17.89, 22.95, 29.04, 31.23, 121.81, 126.55, 129.43; IR (CCl_4) 3420, 3352, 2240 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 122 (M, 08), 121 (92), 94 (100), 39 (41); MS (CI, NH_3) *m*/*z* (relative intensity) 140 (M + 18, 100), 123 (M + 1, 79).

(1*S*,2*S*)-1-Amino-2-propylcyclopropanecarboxylic Acid (or homocoronamic acid) 27b. A mixture of 30 mg (0.24 mmol) of (1*S*,2*S*)-**27b** in 5 mL of a 6 M HCl solution was heated at reflux for 15 h. Evaporation in vacuo left 42 mg (97.5%) of (1*S*,2*S*)-1-Amino-2-propylcyclopropanecarboxylic acid hydrochloride; [21] ^{1}H NMR (200 MHz, D_2O) δ (ppm) 0.64 (t, J = 7.0 Hz, 3H), 0.95−1.58 (m, 7H); ^{13}C NMR (63 MHz, D_2O) δ (ppm) 13.23, 19.28, 22.03, 28.37, 28.40, 40.46, 172.48.

A chromatography column filled with ion-exchange resin (Dowex 50 × 8−100) was washed with distilled water until neutrality, and 17 mg (0.05 mmol) of this hydrochloride was added. Eluting with a 2 M ammonium hydroxide solution gave 13 mg (95%) of (1*S*,2*S*)-**27b** with spectral and analytical data in total agreement with reported data.[21] Its enantiomeric excess (ee 83%) was determined by ^{19}F NMR of the corresponding MTPA amide[22] following a reported procedure,[21] comparatively to racemic (*E*)-**27b**, prepared in the same way from racemic ethyl lactate.

(1*S*,2*R*)-1-(*N*-(Diphenylmethylene)amino)-2-formylcyclopropanecarbonitrile 28. Into a solution of 572 mg (2 mmol) of (1*S*,2*R*)-**22** in dichloromethane was bubbled ozone at −78 °C, until the appearance of a persistent blue color. The solution was stirred for 30 min at −78 °C; the ozone excess was removed by an argon stream, and 525 mg (2 mmol) of triphenylphosphine was added. The mixture was allowed to warm to room temperature and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with pentane/diethyl ether (65:35) to give (1*S*,2*S*)-**28** (450 mg, 82%) as a orange-yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.09 (dd, J = 9.9, 8.6 Hz, 1H), 2.28 (dd, J = 9.9, 7.9 Hz, 1H), 2.68 (ddd, J = 8.6, 7.9, 6.9 Hz, 1H), 7.26−7.68 (m, 10H), 9.32 (d, J = 6.9 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 24.14, 38.82, 39.21, 115.75, 128.21, 128.24, 128.79, 128.99, 129.99, 130.21, 131.58, 135.19, 175.89, 194.97; IR ($CDCl_3$) 2220, 1740 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 274 (M, 63), 245 (100), 115 (53), 77 (31); exact mass M^+ 274.1115 (calcd for $C_{18}H_{14}N_2O$ 274.1106).

(1*S*,2*R*)-1-(*N*-(Diphenylmethylene)amino)-2-ethenylcyclopropanecarbonitrile 4a. To a suspension of 429 mg (1.2 mmol) of methyltriphenylphosphium bromide in 5 mL of dry THF was added 687 μL (1.1 mmol) of a 1.6 M *n*-BuLi solution in hexane, and the mixture was stirred at room temperature for 2 h. Then a solution of 274 mg (1 mmol) of a 94:6 diastereomeric mixture of (1*S*,2*R*)-**28** and (1*R*,2*R*)-**28** in 1 mL of THF was added dropwise under an argon stream, and the resulting mixture was stirred for 18 h at room temperature. The solution was diluted with 10 mL of diethyl ether, washed with 2 mL of saturated NaCl solution (twice), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with petroleum ether/diethyl ether (8:2) to give, besides **8b** (16.3 mg, 6%), (1*S*,2*R*)-**4a** (223 mg, 82%), with spectral and analytical data identical to those reported above for racemic (*E*)-**4a**. It was then transformed into (1*S*,2*R*)-**9**, following the procedure used for the transformation (*E*)-**4a** → (*E*)-**9** (vide supra); its enantiomeric excess (ee > 69%) was also determined by chiral capillary gas chromatography (CYBEX B column, 55 °C, 0.9 He atm), comparatively to racemic (*E*)-**9**.

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Supporting Information Available: Copies of ^{13}C NMR spectra for compounds **4b**, **4c**, **4d**, (*E*)-**9**, (+)-**12**, (+)-**13**, mesylate and tetrahydropyranyloxy-precursors of (4*S*)-**20a**, Mosher ester of (4*S*)-**20a**, (4*S*)-**20c**, **8b**, (*E*)-**22**, (6*S*)-**21a**, (6*S*)-**21b**, (6*S*)-**21c**, (6*S*)-**21d**, (6*S*)-**21f**, (6*S*)-**21g**, **23**, (1*S*,2*S*)-**25**, (1*S*,2*R*)-**26**, (1*S*,2*S*)-**27b** hydrochloride, (1*S*,2*R*)-**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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