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Nitrile anion cyclizations

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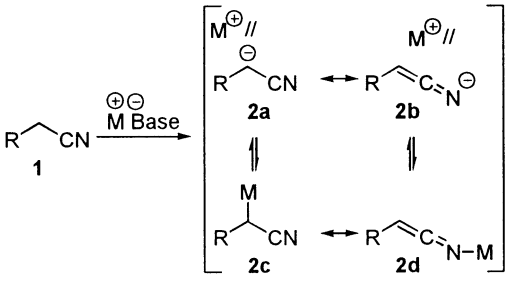
Contents

1. Introduction

Alkylation of stabilized carbanions is the most fundamental carbon–carbon bond-forming reaction in organic chemistry.[1] Recent NMR and X-ray analyses, stimulated by the central role of stabilized carbanions, identify most 'carbanions' as being complex aggregates,[2] although the common term carbanion succinctly encapsulates the observed reactivity and may actually exist in highly polar media.[3] Numerous stabilized carbanions provide reactive intermediates for C–C bond construction, among which nitrile-stabilized anions occupy a unique position as being particularly powerful nucleophiles, ideally suited for installing hindered quaternary centers.[4]

Nitrile-stabilized carbanions are extremely important synthetic intermediates.[4] Despite the long history of nitrile anion alkylations[4] the exact nature of the 'anion' remains elusive, reflecting a complex interplay between solvation, charge delocalization, and inductive stabilization. Conceptually, the powerful electron-withdrawing effect of the nitrile is most consistent with an sp^3 hybridized carbanion (**2a**), as either a contact or separated ion pair, whereas the greater electronegativity of nitrogen over carbon suggests an sp^2 hybridized 'keteniminate' (**2b**) as the preferred structure (Scheme 1). In the extreme these species might be envisaged as C- or N-metallated nitriles **2c** and **2d**, respectively.



Scheme 1.

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1.1. Recent structural studies of nitrile anions

'Nitrile anions' **2a**, **2c** and 'keteniminates' **2b**, **2d** are deceptively simplistic representations of the true constitution of deprotonated nitriles. X-Ray[5] crystallographic analyses reveal a remarkable structural characteristic; the deprotonated nitrile has almost no delocalization into the nitrile group with the C≡N bond length being only slightly longer than the mean distance found in neutral nitriles (compare **3**,[6] **4**,[7] and **5**,[8] with **1**,[9] Fig. 1).

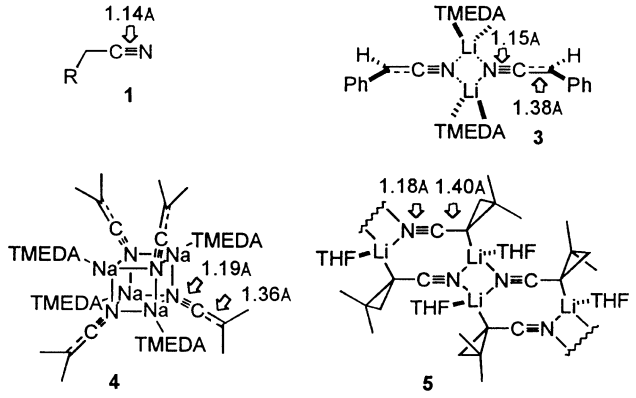


Figure 1. X-Ray structures of nitrile and nitrile anions.

X-Ray analyses consistently show deprotonated nitriles as having partial double bond character with the adjacent carbon and only slight weakening of the CN triple bond (Fig. 2)! A modest lengthening of the CN bond (1.15–1.20 Å) implies delocalization with the adjacent carbon (**2e**, Fig. 2),[10] while in other cases, such as **3**, the triple bond and an adjacent double bond character persists. The apparent preference for a carbon with a bond order greater than four bonds perhaps explains the reluctance against adopting **2f** as the general structure of nitrile anions (Fig. 2). Simplistically, the partial double bond character may reflect the extremely strong inductive stabilization of the CN group[11] resulting in a strong, polarized attraction, similar to ylide stabilization.

Figure 2. Representations of nitrile anion structures.

X-Ray analyses reveal an unusual pyramidalization of aliphatic nitrile anions consistent with the charge stabilization implied in **2f** (Fig. 2). Whereas the X-ray structures of numerous α-aromatic nitrile anions are planar,[12] typified by the partial structure **3a**[6] (Fig. 3), and in agreement with

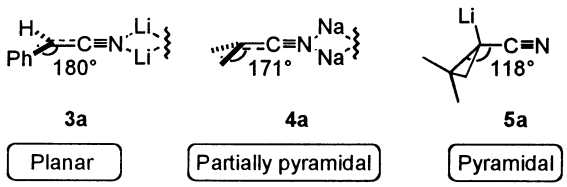


Figure 3. Partial X-ray structures of nitrile anions.

expectation, the alkanenitrile anion structure **4a** shows a modest, yet particularly significant pyramidalization. Pyramidalization is conveniently measured by comparing the deformation angles,[13] defined as the C_N–C–X angle where X is the midpoint between the two substituents at the anionic carbon (Fig. 3). The pyramidalization of alkylnitrile **4a** is reproduced in numerous molecular modeling calculations[13,14] and is consistent with the inductive stabilization implied in **2f** without requiring planarity. Collectively the structures of **3**–**5** represent a continuum of nitrile anions varying from being planar (**3**), partially pyramidalized (**4**), and pyramidal (**5**) that may be a key feature in stereoselective nitrile anion alkylations.

Extensive NMR analyses reveal similar surprises for the structure of deprotonated nitriles. ^{7}Li and ^{31}P NMR establish that HMPA generates solvent separated ion pairs[15] where the anion has only minimal delocalization into the carbon–nitrogen triple bond, the same solvent separated ion pairs being implied for solvation in DMSO.[11b] Comprehensive ^{13}C NMR analysis of **3** demonstrates that the anion is preferentially delocalized into the benzene ring rather than the nitrile group,[11b] at least in DMSO and HMPA. Changing from HMPA–THF to THF causes a solvation change from a solvent-separated ion pair to a contact ion pair.[15]

The unusual charge stabilization of nitriles correlates with the excellent nucleophilicity of nitrile anions. Minimal delocalization into the nitrile group localizes most of the charge density on the adjacent carbon, enhancing carbon's nucleophilicity. Consequently, nitrile anions alkylate almost exclusively on carbon with silyl[16] and acetyl[10] chlorides being virtually[17] the only electrophiles with a propensity for reaction on nitrogen.

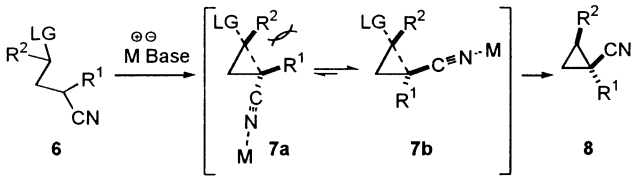
Deprotonation of nitriles, and alkylation of the resulting anions, feature as key steps in many syntheses. Numerous bases trigger nitrile anion cyclizations with strong bases, particularly hexamethyldisilazides (HMDS), being used to deprotonate aliphatic nitriles (pK_a~29–31),[11a,18] whereas weak bases, Et_3N, NaOH, KOH, K_2CO_3, and Cs_2CO_3, are used with the more acidic arylacetonitriles (pK_a~22).[19] Regardless of the base strength, many nitrile anion cyclizations tolerate a diverse array of functional groups without complicating either the deprotonation or cyclization.

The use of nitrile anions in synthesis, the increasing isolation of nitrile-containing natural products,[20] and novel transition metal reactions[21] have resulted in several advances in nitrile anion cyclizations. The central importance of nitrile anions is encapsulated in an older review of nitrile anion inter- and intramolecular alkylations[4] that comprises an entire volume of Organic Reactions. This review aims to highlight subsequent developments in nitrile anion cyclizations by focusing on literature published after 1986.

2. Cyclization by nucleophilic intramolecular displacements (S_Ni)[22]

Nitrile anions are robust nucleophiles that have been used

extensively in intramolecular alkylations. The high thermal stability of nitrile anions enables difficult alkylations at relatively high temperatures, providing a reliable alkylation route to strained and sterically hindered carbocycles. Cyclizations are facilitated by the inherently small size of the nitrile group, the *A* value is a miniscule 0.2 kcal mole^{-1},[23] that minimizes the steric interactions during the formation of strained carbocycles and quaternary stereocenters.



Scheme 2.

2.1. Cyclizations to cyclopropanes

Nitrile anion stability and the small steric demand make nitrile anions ideal for assembling substituted cyclopropanes (Table 1). Distinct stereoselectivity trends are apparent in the cyclizations of nitrile anions containing adjacent stereogenic centers (Table 1, entries 3 and 4) and for cyclizations with secondary leaving groups (Table 1, entries 8–11). Cyclopropanes are preferentially formed with the small nitrile group eclipsing the adjacent alkyl group (Table 1, entries 3, 4 and 8–11). The small steric demand of the nitrile group[23] directs cyclization through the less congested transition state **7b** (Scheme 2) where the nitrile preferentially eclipses the alkyl substituent to avoid the larger steric interaction of two eclipsed alkyl groups (**7a**). Usually stereoisomer **8** is the exclusive cyclopropanecarbonitrile, implying a late transition state for cyclopropane formation, in contrast to intermolecular alkylations.[24] The cyclization of **25** is an exception in providing the stereoisomer with the two alkyl groups eclipsed (Table 1, entry 9).

Nitrile anion cyclizations to cyclopropanes generally employ halonitriles as isolable intermediates or, less often, the corresponding mesylate or tosylate. Operationally, direct alkylation of substituted acetonitriles with *bis*-electrophiles is more efficient and is effective for a variety of halide and sulfonate *bis*-electrophiles (Table 1, entries 12–16).

Cyclizations generating quaternary centers proceed with remarkable efficiency (Table 1, entries 17–24). Strained carbocycles readily cyclize with the expected invertive displacement, allowing predictable formation of highly bridged ring systems as encapsulated in the simultaneous formation of three cyclopropane rings (Table 1, entry 24). Mechanistic experiments suggest that the remarkable cyclization proceeds through a trianion complex that favors an axial conformation for cyclization.[47]

2.2. Cyclizations to cyclobutanes

Nitrile anion cyclizations to cyclobutanes fall into two distinct categories, S_Ni displacements (Table 2, entries 1–4) and additions to benzynes (Table 2, entries 5–9, respectively). The small number of intramolecular displacements to cyclobutanes belies a high reaction efficiency, particularly with relatively strained carbocycles as

Table 1. Nitrile anion cyclizations to cyclopropanes

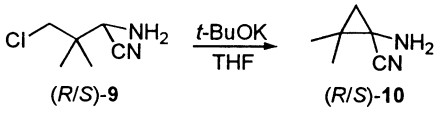
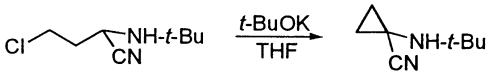
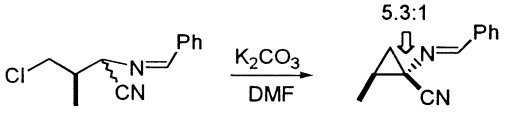
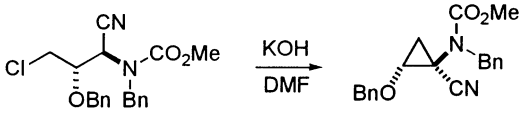
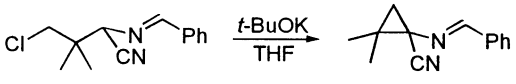
Entry	Reaction	Yield (%)
1	 (*R*/*S*)-**9** → (*R*/*S*)-**10**	41[25]
2	 (*R*/*S*)-**11** → **12**	79[26]
3	 (3*R*)-**13** → (1*S*, 2*S*)-**14**	80[27]
4	 (2*R*,3*S*)-**15** → (2*S*,3*R*)-**16**	82[28]
5	 (*R*/*S*)-**17** → (*R*/*S*)-**18**	100[29]

Table 1. (*continued*)

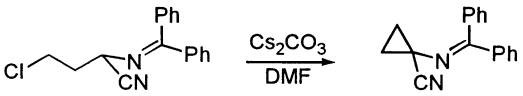
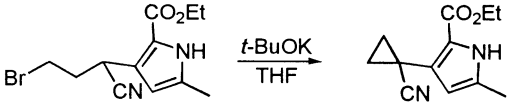
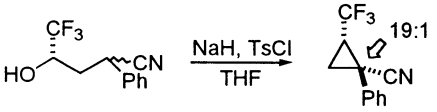
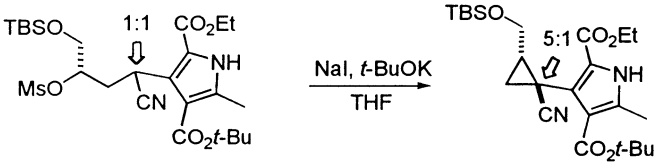
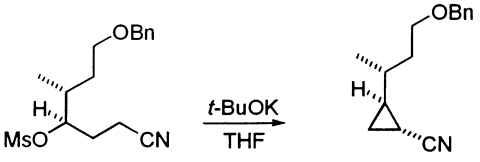
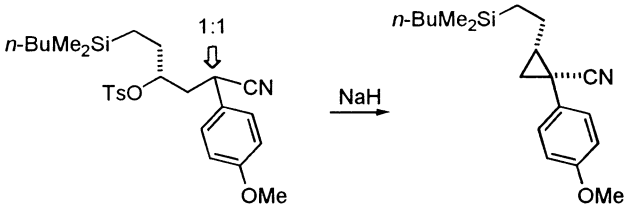
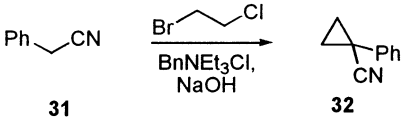
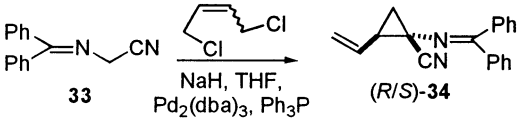
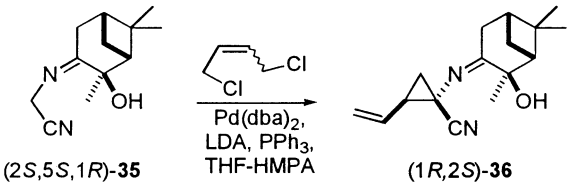
Entry	Reaction	Yield (%)
6	 (*R*/*S*)-**19** **20**	100[30]
7	 (*R*/*S*)-**21** **22**	90[31]
8	 (4*S*)-**23** (1*S*, 2*S*)-**24**	75[32]
9	 (*R*/*S*)-**25** (*R*/*S*)-**26**	–[33]
10	 (3*R*, 4*R*)-**27** (1*R*, 2*R*)-**28**	86[34]
11	 (4*R*)-**29** (1*S*, 2*S*)-**30**	67[35]
12	 **31** **32**	62[36]
13	 **33** (*R*/*S*)-**34**	74[37]
14	 (2*S*,5*S*,1*R*)-**35** (1*R*,2*S*)-**36**	69[38]

Table 1. (*continued*)

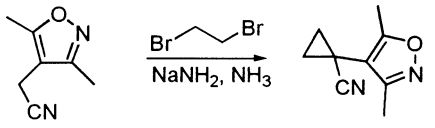
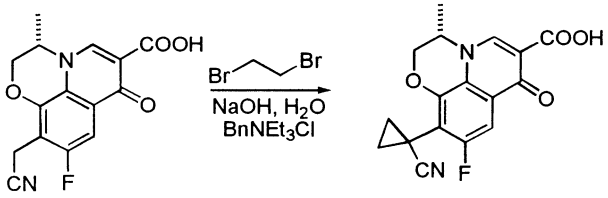
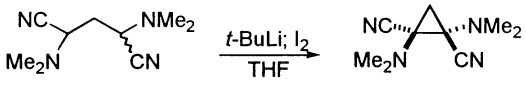
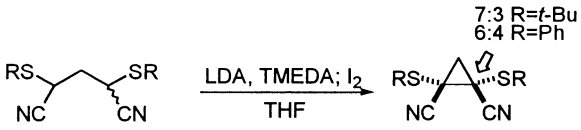
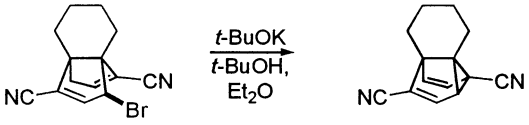
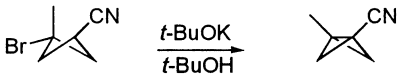
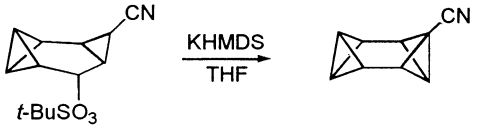
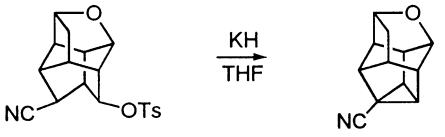
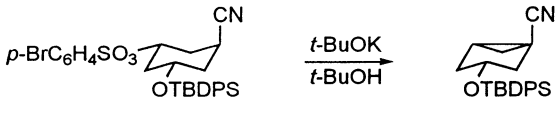
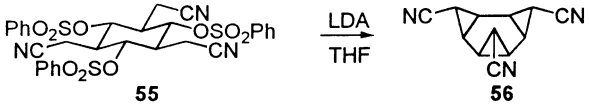
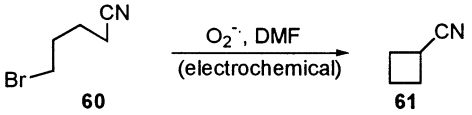
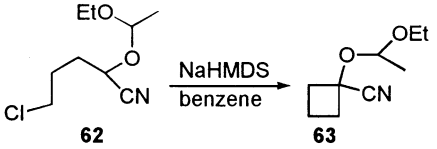
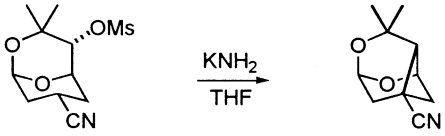
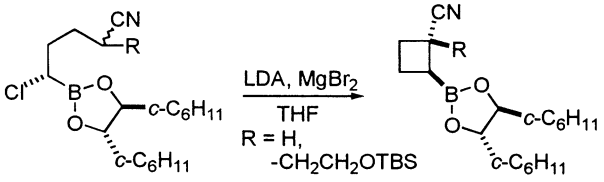
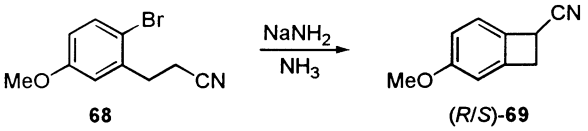
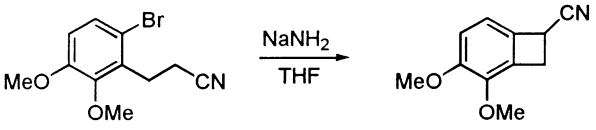
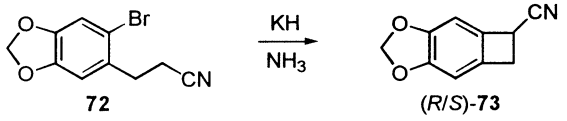
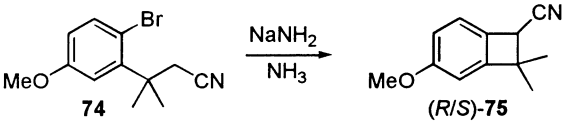
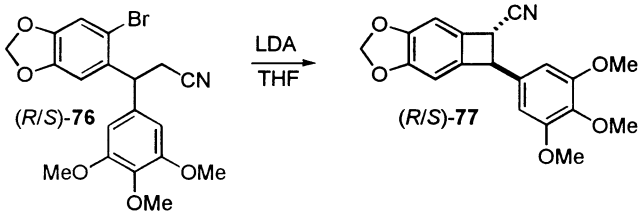
Entry	Reaction	Yield (%)
15	 **37** **38**	21[39]
16	 (*S*)-**39** (*S*)-**40**	86[40]
17	 (*R*/*S*)-**41** (*R*/*S*)-**42**	55[41]
18	 (*R*/*S*)-**43** **44**	60–65[41]
19	 (*R*/*S*)-**45** (*R*/*S*)-**46**	38[42]
20	 **47** **48**	91[43]
21	 (*R*/*S*)-**49** **50**	50[44]
22	 (*R*/*S*)-**51** (*R*/*S*)-**52**	61[45]
23	 (1*S*,3*R*,5*R*)-**53** (1*R*,3*S*,5*R*)-**54**	99[46]
24	 **55** **56**	35[47]

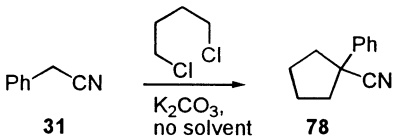
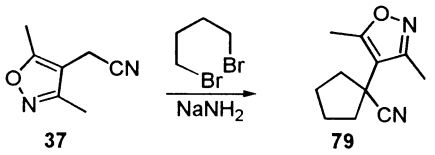
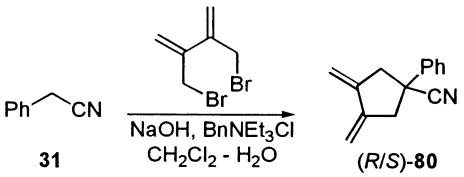
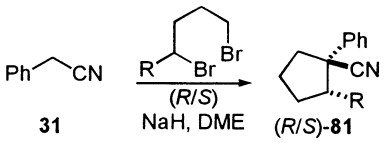
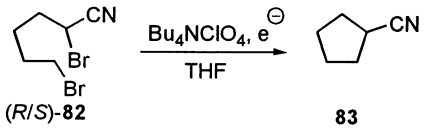
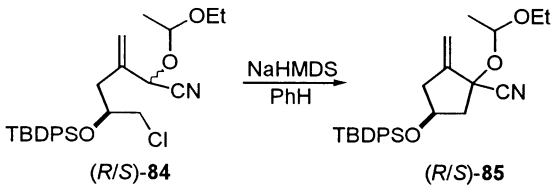
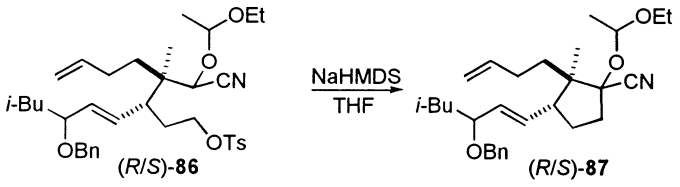
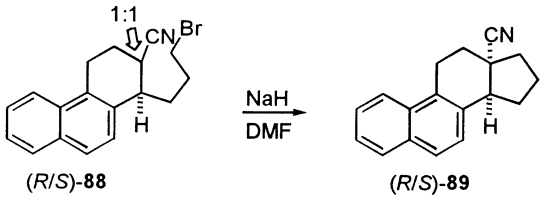
Table 2. Nitrile anion cyclizations to cyclobutanes

Entry	Reaction	Yield (%)
1	 **60** **61**	85[48]
2	 **62** **63**	76[19]
3	 (7*S*)-**64** (7*S*)-**65**	69[49]
4	 (5*R*)-**66** (5*R*)-**67**	89[50]
5	 **68** (*R*/*S*)-**69**	64[51]
6	 **70** (*R*/*S*)-**71**	62[52]
7	 **72** (*R*/*S*)-**73**	80[53]
8	 **74** (*R*/*S*)-**75**	63[54]
9	 (*R*/*S*)-**76** (*R*/*S*)-**77**	48[55]

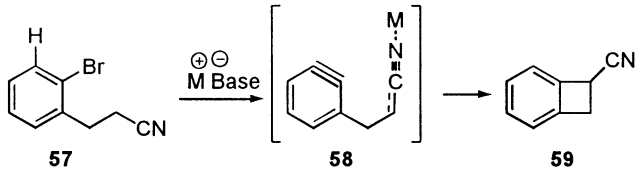
illustrated in the key cyclization of **64** performed during the synthesis of lineatin (Table 2, entry 3).[49] Although formation of cyclobutylboronic ester **67** formally involves an S_Ni displacement (Table 2, entry 4), the cyclization most likely proceeds via the intermediacy of a 5-membered borate[50] that subsequently suffers a migratory displacement to give the cyclobutane.

Intramolecular cyclizations of nitrile anions with benzynes provide a rapid route to benzocyclobutanes for subsequent

Table 3. Nitrile anion cyclizations to cyclopentanes

Entry	Reaction	Yield (%)
1		75[57]
2		35[39]
3		80[58]
4		60–91[59]
5		66[60]
6		52>[61]
7		90[62]
8		80[63]

Diels–Alder cycloadditions (Table 2, entries 5–9). Typically *o*-bromophenylpropionitriles **57** (Scheme 3) are deprotonated with excess $NaNH_2$, generating a nitrile anion and an adjacent benzyne, **58**, that cyclizes to the corresponding benzocyclobutane **59**. The close proximity of the reactive nitrile anion and the highly electrophilic benzyne provides a particularly efficient route to sterically congested cyclobutanes that are otherwise difficult to access[54] (Table 2, entries 8 and 9).



Scheme 3.

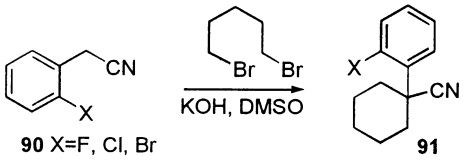
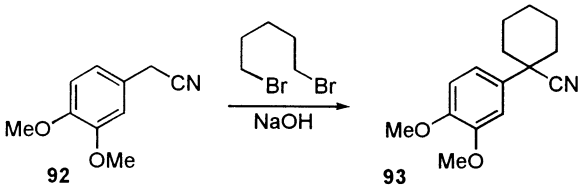
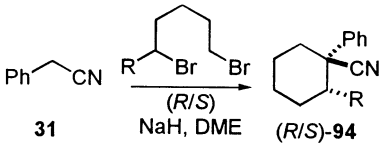
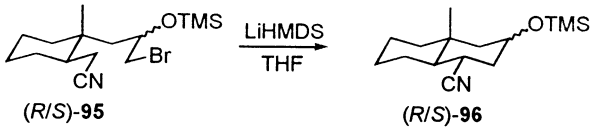
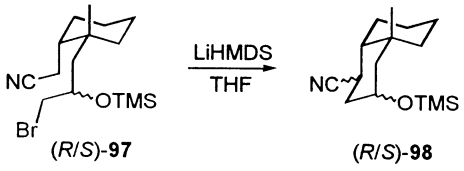
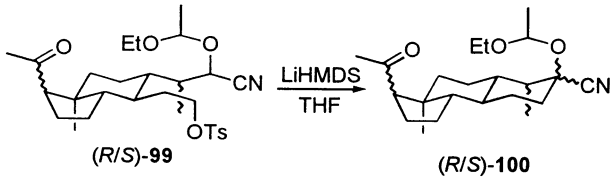
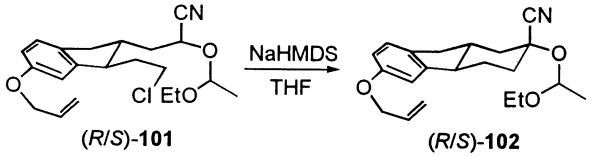
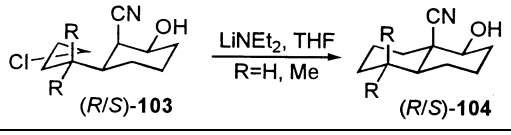
2.3. Cyclizations to cyclopentanes

Several *bis*-alkylations with arylacetonitriles effectively generate cyclopentanecarbonitriles in a single synthetic operation (Table 3, entries 1–4). Conventional cyclizations of nitrile-containing halides and tosylates are equally successful with electrochemically generated anions (Table 3, entry 5), cyanohydrin anions (Table 3, entries 6, 7), and for cyclic nitrile anions (Table 3, entry 8). The stereoselectivity has been examined in detail for cyclizations generating cyclopentanecarbonitriles (see Section 3) and for cyclizations to *cis*-hydrindanes[56] (Table 3, entry 8).

2.4. Cyclizations to cyclohexanes

Considering the central importance of 6-membered rings in natural products there are surprisingly few cyclohexanecarbonitrile cyclizations. Stereoselective cyclizations generating cyclohexane rings preferentially eclipse the two largest substituents (Table 4, entry 3), analogous to cyclopentanecarbonitrile cyclizations (Table 3, entry 4).

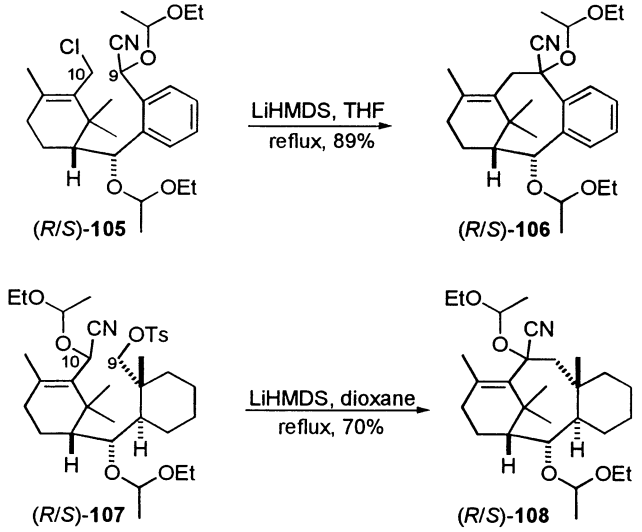
Table 4. Nitrile anion cyclizations to cyclohexanes

Entry	Reaction	Yield (%)
1	 **90** X=F, Cl, Br **91**	15–36[64]
2	 **92** **93**	–[65]
3	 **31** (*R*/*S*)-**94**	70–88[66]
4	 (*R*/*S*)-**95** (*R*/*S*)-**96**	63–100[67]
5	 (*R*/*S*)-**97** (*R*/*S*)-**98**	60–100[67]
6	 (*R*/*S*)-**99** (*R*/*S*)-**100**	98[68]
7	 (*R*/*S*)-**101** (*R*/*S*)-**102**	90[69]
8	 (*R*/*S*)-**103** (*R*/*S*)-**104**	78–84[70]

Alkylnitriles and cyanohydrins appended to rings cyclize to *cis*- and *trans*-decalins as dictated by the orientation of the substituents on the pre-existing ring (Table 4, entries 4–7) whereas stereoelectronic constraints direct cyclic nitrile anions to form exclusively *trans*-decalins (Table 4, entry 8, see Section 3). Cyclization of the β-hydroxy nitrile **103** proceeds through a dianion that avoids dehydration of the cyano-aldol.

2.5. Cyclizations to medium-sized rings

Historically the cyclizations of dinitriles provided one of the first efficient methods of generating medium-sized rings.[71] Despite this precedent, the intramolecular displacements were not investigated until relatively recently through the cyclization of a series of protected cyanohydrins. Cyanohydrin ethers cyclize efficiently generating 10–16-membered rings[72] through S_Ni displacements of alkyl iodides, allylic halides, and tosylates. Most impressive are the recent constructions of the highly strained 8-membered B ring of taxoids (Scheme 4).[73] The strategy is successful in cyclizing the nitrile anion from C-9 to C-10 (**105→106**) or from C-10 to C-9 (**107→108**). The cyclization of **107** spectacularly generates the strained 8-membered ring through the displacement of a neopentyl tosylate!

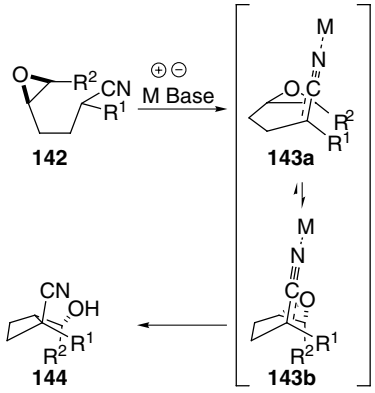


Scheme 4.

2.6. Cyclizations with epoxides[74]

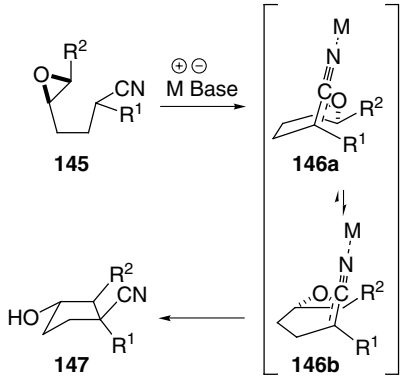
Nitrile anions are selectively generated from epoxynitriles, triggering facile cyclizations to small and medium-sized rings. Sharpless epoxidation of nitrile-containing allylic alcohols provide enantiomerically enriched epoxide precursors in an efficient, highly selective, route to cyclic nitriles containing up to three stereocenters (Table 5, entries 2–4 and 12–15). Alternatively, alkylating nitrile anions with chiral epoxides containing an additional leaving group generates cyclic, chiral nitriles with the same stereoselectivity (Table 5, entries 3 and 4). Close scrutiny of the *bis*-alkylation with **113** (Table 5, entry 3) establishes the initial alkylation as occurring by displacement of the halide, or the corresponding triflate, mesylate, or tosylate, followed by invertive ring-opening of the epoxide.[77] From this precedent the cyclization of **117** (Table 5, entry 4) presumably occurs first at the benzenesulfonate (OBs) followed by epoxide ring opening.[78]

Pioneering ring opening of epoxides[88] with nitrile anions demonstrates a high regioselectivity during the cyclization of 3–6-membered rings. Cyclizations to cyclopropanes are always favored over cyclobutane formation (Table 5, entries 1–8) whereas the regioselective cyclizations to 4-, 5-, and 6-membered rings depends on the epoxide and nitrile substituents.[89] δ-Epoxides with *cis*-substituents generate cyclobutanes through an exocyclic ring closure with the alkyl substituents R^1 and R^2 staggered (Scheme 5, **143b**) to reduce the steric interactions in the transition state—leading to the more crowded *cis*-cyclobutane (Table 5, entry 9).[89] The alternative endocyclic ring opening, **143a**, is destabilized by an optimal ring-opening alignment that eclipses the two alkyl groups. Complete regioselectivity is maintained[89] even when R^1=H suggesting a particularly close proximity between R^1 and R^2 in the endocyclic arrangement **143a**. An exception to this regioselectivity is the cyclization of the arylnitrile **129** (Table 5, entry 10), that presumably cyclizes through **143a** to minimize the steric compression between the aromatic and *gem*-dimethyl groups.[84]



Scheme 5.

δ-Epoxides without terminal *cis*-substituents afford predominantly cyclopentanes (Scheme 6).[89] Endocyclic ring opening is favored through a more easily attained confor-



Scheme 6.

Table 5. Nitrile anion cyclizations with epoxides

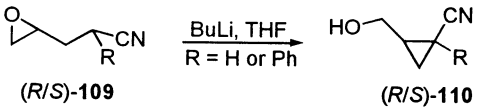
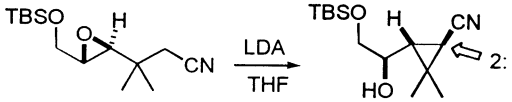
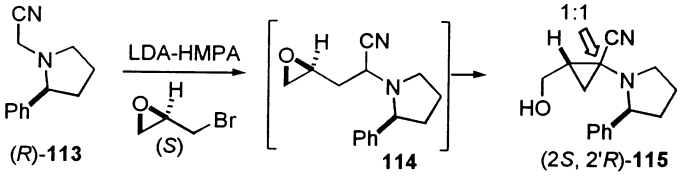
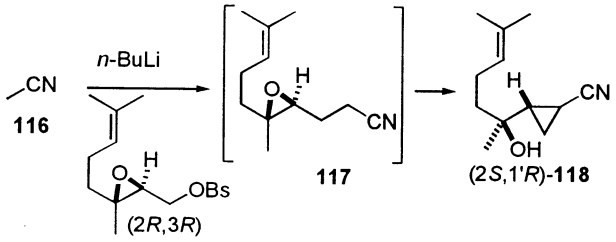
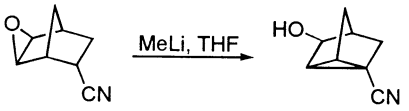
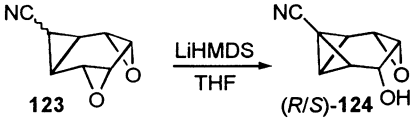
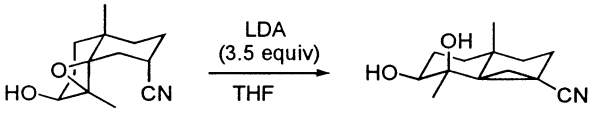
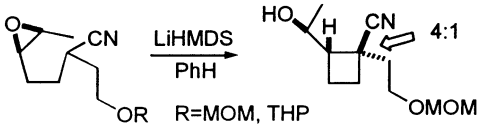
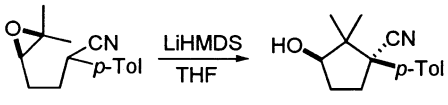
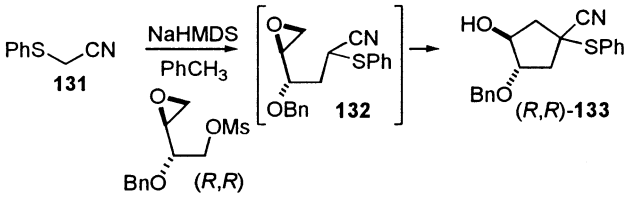
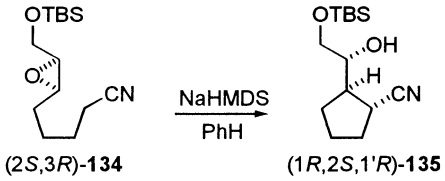
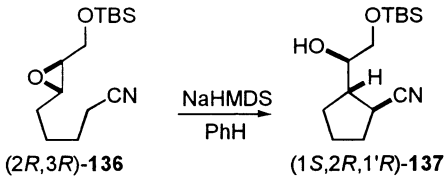
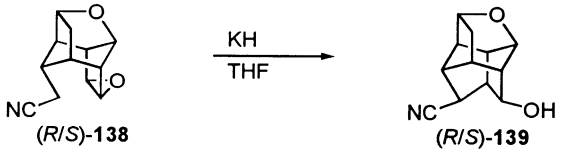
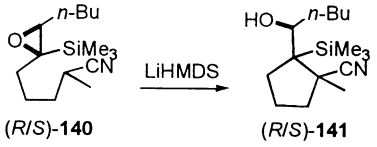
Entry	Reaction	Yield (%)
1	 (*R*/*S*)-**109** (*R*/*S*)-**110**	40–72[75]
2	 (4*S*, 5*R*)-**111** (1′*S*, 1*R*,3*R*)-**112**	86[76]
3	 (*R*)-**113** (*S*) **114** (2*S*, 2′*R*)-**115**	80[77]
4	 **116** **117** (2*S*,1′*R*)-**118** (2*R*,3*R*)	87[78]
5	 (*R*/*S*)-**119** (*R*/*S*)-**120**	100[79]
6	 (*R*/*S*)-**121** (*R*/*S*)-**122**	94[80]
7	 **123** (*R*/*S*)-**124**	50[81]
8	 (*R*/*S*)-**125** (*R*/*S*)-**126**	100[82]
9	 (*R*/*S*)-**127** (*R*/*S*)-**128**	60–61[83]
10	 (*R*/*S*)-**129** (*R*/*S*)-**130**	60[84]

Table 5. (*continued*)

Entry	Reaction	Yield (%)
11		70[85]
12		74[86]
13		56[86]
14		78[45]
15		>60[87]

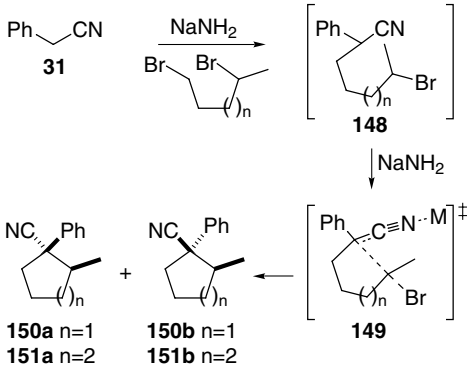
mation **146b** (Scheme 6) where steric interactions are minimized through a staggered orientation (Table 5, entries 10 and 11). The *cis–trans* epoxide stereochemistry appears to control the regioselectivity only with δ-epoxynitriles since the homologous ϵ-epoxynitriles undergo exocyclic ring-opening (Table 5, entries 12–15).

3. Stereoselective cyclizations

Almost 30 years ago two groups independently probed stereoselective cyclizations to cyclopentanecarbonitriles and cyclohexanecarbonitriles. Nitrile anion cyclizations are often highly stereoselective during installation of adjacent quaternary–tertiary centers. Despite these intensive investigations, a unified model accounting for the subtle solvent and cation stereoselectivity dependences has been elusive. Recent advances into the structure of nitrile anions allow for a reinterpretation of these cyclizations, providing a potentially useful model for predicting the stereoselectivity of nitrile anion cyclizations.

3.1. Monocyclic carbonitriles

Cyclopentane and cyclohexane carbonitriles are rapidly and selectively cyclized through *bis*-alkylation of phenylacetonitrile with dibromoalkanes (Scheme 7).[90] Control experiments[90a] demonstrate that alkylation occurs initially at the less-substituted carbon, followed by a stereochemistry-determining displacement of the secondary



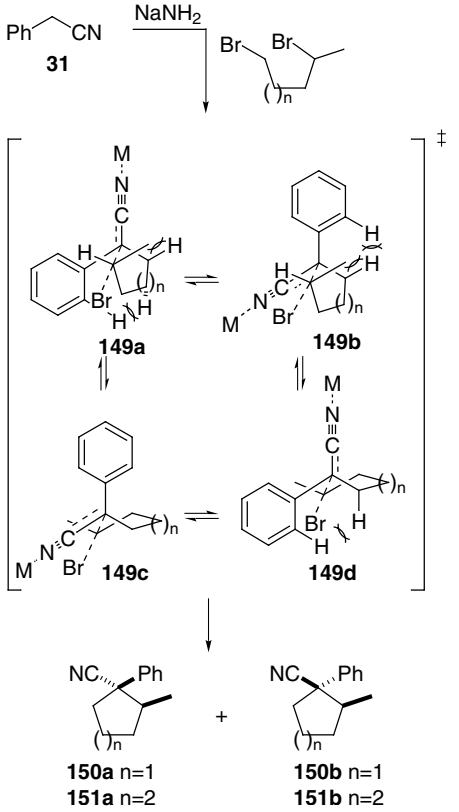
150a:150b

PhH	9.0:1
THF	4.0:1
DME	3.5:1
DMF	1.0:1
DMSO	1.0:1
HMPA	1.0:1.1

Scheme 7.

halide. Extensive screening of the reaction conditions demonstrate minimal temperature and base dependence but a significant stereoselectivity correlation with solvent polarity. Non-polar solvents lead predominantly to the sterically crowded cyclopentanecarbonitrile **150a** with *cis*-oriented phenyl and methyl groups, whereas cyclizations in polar solvents are non-selective. The extremely unusual preference for the more hindered isomer stimulated a reinvestigation that confirmed the original stereoselectivities.[66]

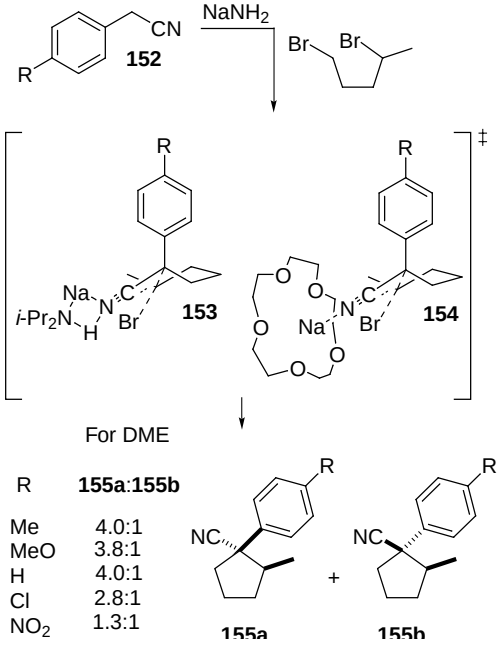
The cyclization stereoselectivity appears intimately related to the nature of the nitrile anion. Numerous structural studies of arylacetonitrile anions demonstrate an extensive charge delocalization into the aromatic ring,[11b] favoring a planar geometry of the nitrile anion. Assuming the intermediacy of an analogous planar nitrile anion in the cyclizations of **149**, four transition states emerge that differ in the conformation of the developing ring and the pseudoaxial–pseudoequatorial orientation of the nitrile and phenyl groups (Scheme 8). Conformers **149a** and **149b** incline the methyl group inside the forming ring, resulting in a serious eclipsing interaction with the ring methylene proton, whereas conformers **149c** and **149d** have minimal steric interactions since the methyl group is staggered between the phenyl and nitrile groups. Cyclization occurs preferentially through **149c** to minimize the allylic strain that is more pronounced in **149d**.



Scheme 8.

Surprisingly, cyclization to **150** occurs preferentially through conformation **149c** where the large phenyl group adopts a pseudoaxial orientation. The preference for conformation **149c** is unusual since the nitrile group has a very small steric demand[23] and is expected to adopt an axial orientation. Although the allylic strain appears better accommodated in **149c** than **149d**, originally the nitrile anion was proposed to complex with the metal ion,[90a] increasing the nitrile's steric demand over that of the phenyl group. The complexation model was subsequently challenged[66] when the addition of 18-crown-6 failed to alter the preference for the *syn*-isomer. However, recent X-ray analyses,[5–8] NMR,[15] and reactivity studies[91] demonstrate that deprotonated nitriles retain a close metal association even in the presence of crown ethers.

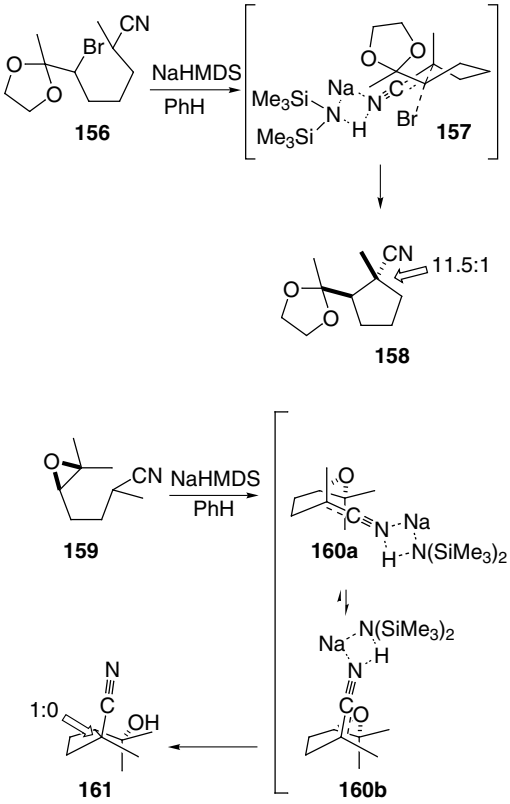
Cyclization through nitrile anion–amine[92] and nitrile anion–crown complexes[93] provides a potential solution to this previous stereochemical enigma. Cyclization through either an amine complex **153** or a crown ether complex **154** (Scheme 9) most likely impose greater steric demands than the phenyl substituent, directing cyclization through conformations with an axially oriented phenyl group to the more hindered nitrile **155a**. The analysis explains a series of cyclizations with *para*-substituted phenyl acetonitriles where electron donating substituents cyclize to **155a**, whereas electron withdrawing substituents cyclize with minimal selectivity. Electron withdrawing substituents[90b] facilitate delocalization into the benzene ring, decreasing the electron density on the nitrile nitrogen thereby preventing complexation. Cyclization of the resulting carbanion could be indiscriminate because the anion is more reactive and does not discriminate between **149c**, that has minimal allylic strain but a small, uncomplexed, equatorially oriented nitrile, and **149d** where the larger phenyl substituent is equatorial, but incurs several steric interactions (Scheme 8).



Scheme 9.

The cyclizations of **31** and **152** (Schemes 8 and 9) imply that similar complexation controls the stereoselective cyclization of *alkyl-substituted* nitrile anions. Nitrile anion

cyclizations with secondary halides[56a] and epoxides[88a] generate the more sterically congested carbocycles with the two alkyl substituents on the same side of the 5-membered ring. The stereoselectivity is consistent with cyclization through nitrile anion-amine complexes where the large, complexed nitrile unit preferentially adopts the pseudoequatorial orientation (Scheme 10). Not only are the stereoselectivities quite remarkable but the reactions efficiently install adjacent quaternary–tertiary centers!

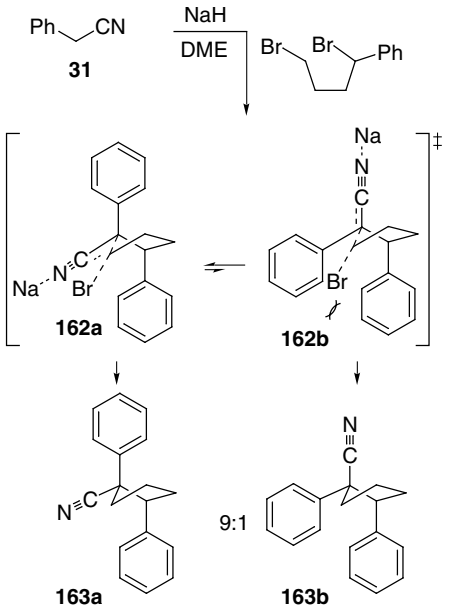


Scheme 10.

The cyclization of phenylacetonitrile with 1-phenyl-4-bromobutane is the only cyclization that preferentially generates the less sterically congested cyclopentanecarbonitrile (Scheme 11).[66] The most reasonable explanation is that a change in mechanism occurs, with the more reactive benzylic halide alkylating prior to cyclization of the primary alkylbromide. Assuming benzylic alkylation to occur first, the cyclization would then occur through conformation **162a** where the vicinal phenyl groups are disposed on opposite sides of the developing cyclopentane ring, leading to the observed stereoisomer **163a**.

3.2. Bicyclic carbonitriles

Nitrile anions are unique in their kinetic cyclization to *trans*-decalins. More than 30 years ago nitriles were reported[56b] to cyclize to *trans*-decalins—a key observation given the prominence of *trans*-decalins in biologically active molecules.[94] Despite numerous potential applications in synthesis, the fundamental stereoelectronic cyclization principles of nitrile anions were only recently elucidated.[70]

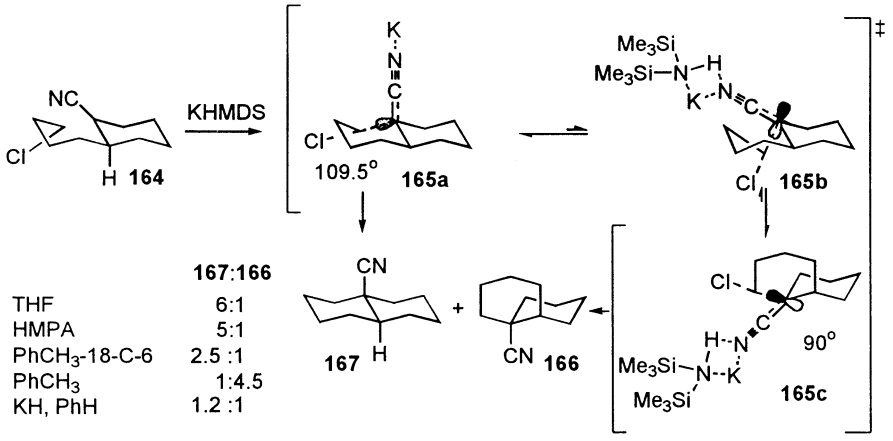


Scheme 11.

Extensive cyclizations of the nitrile **164** reveal a profound stereoselectivity dependence on solvent, base, and to a lesser extent cation. Formation of the *trans*-decalin **167** is favored in refluxing THF, in neat HMPA, or in toluene with crown ethers (Scheme 12). The stereoselectivity correlates with cyclization through a pyramidal transition state **165a** where the anion is directly oriented toward the electrophilic chloromethylene carbon for a stereoelectronically favored alkylation to a *trans*-decalin. The stereoselectivity differences correlate with varying pyramidalization of the nitrile anion in the transition state, reflecting differences in the metal-nitrile anion association.

Cyclization in toluene reverses the selectivity in favor of the *cis*-decalin **166**. A key observation made during cyclizations in toluene is the selectivity reversal on addition of 18-crown-6 that strongly supports the intermediacy of the nitrile anion–amine complex **165c** (Scheme 12). Amines generated by deprotonation remain complexed with the nitrile, resulting in preferential cyclization from transition state **165c** since the planar carbanion enforces considerable twisting for cyclization from the equatorially oriented conformer **165b**. Disrupting the complexation, by adding crown ethers, or through the use of KH as a non-amide base, restores the preference for the *trans*-decalin **167** through transition state **165a**.

The emerging picture is a continuum of nitrile anion transition states that vary from pyramidal, partially pyramidal, through to planar for the nitrile anion–amine complex (Fig. 4). Deprotonation with amide bases in hydrocarbon solvents appears to favor the planar complex **165c** while the presence of superior ligands, THF, HMPA, and 18-C-6, disrupt amine complexation in favor of pyramidalized transition states **165a** and **165d**. Selectively accessing one transition state allows tuning of the cyclization stereochemistry simply through judicious choice of solvents, base, and cation.



Scheme 12.

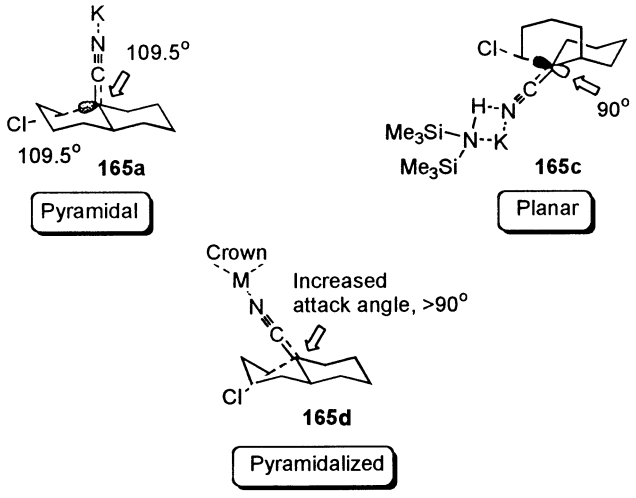
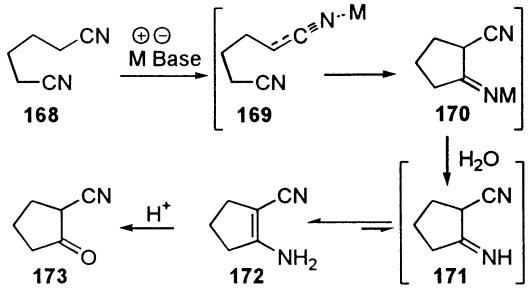


Figure 4. Variation in nitrile anion transition states.

4. Thorpe–Ziegler cyclizations

Thorpe–Ziegler dinitrile cyclizations provide a powerful method of assembling 5- to 33-membered rings.[95] Dinitrile cyclizations of 5- and 6-membered rings are particularly facile, often occurring during formation of the dinitrile precursors, with analogous 7- and 8-membered rings being similarly efficient and usually superior to analogous Dieckmann diester cyclizations. Mechanistically, exposure of a dinitrile to base generates an intermediate nitrile anion that attacks the neutral nitrile to generate an intermediate imine **170**. Tautomerization of the intermediate imine to the corresponding conjugated enaminonitrile **172** is usually followed by acidic hydrolysis to unmask the β-keto nitrile functionality (Scheme 13).



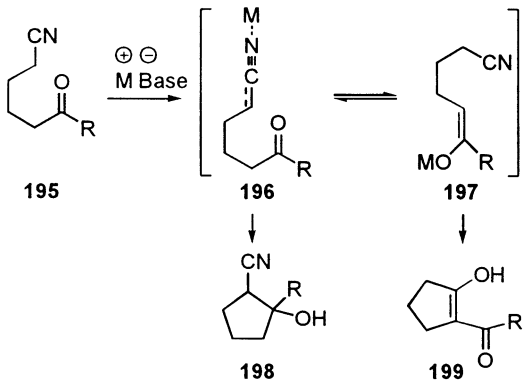
Scheme 13.

Traditionally dinitriles were cyclized with alkoxide or amide bases, although in some instances the cyclization is so favorable that very weak bases are effective.[95a] Several recent cyclizations illustrate the efficacy of mild bases (Table 6, entries 1, 2) with a new series of iridium complexes being particularly efficacious (Table 6, entry 5).

The Thorpe–Ziegler reaction exhibits a remarkable degree of regioselectivity. Cyclization of the fenestrane precursor **186** (Table 6, entry 7) generates a mixture of regioisomeric nitriles[102] with one of the 8-membered enaminonitriles predominating. Complete regioselectivity is observed in the pioneering cyclization of **191** that installs a bridged ring en route to several stemodane diterpenoids.[104] A recent repetition of the strategy triggers not only cyclization but prior equilibration, efficiently assembling the D-ring of maritimol[105] (Table 6, entry 10).

5. Cyclizations with esters, ketones and lactones

Conceptually, two regioisomeric cyclizations can occur between nitriles and carbonyl compounds (Scheme 14). Deprotonation generates either a nitrile anion (**196**) or an



Scheme 14.

Table 6. Thorpe–Ziegler dinitrile cyclizations

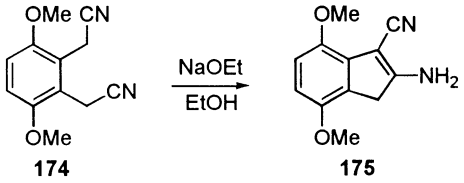
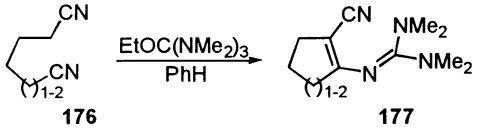
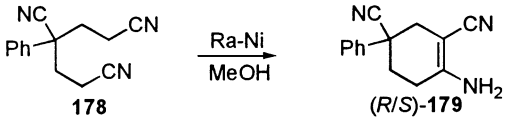
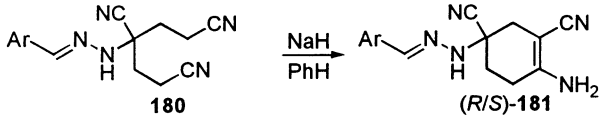
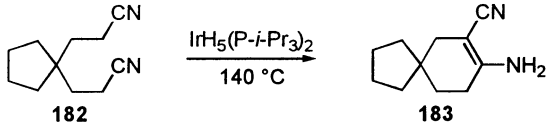
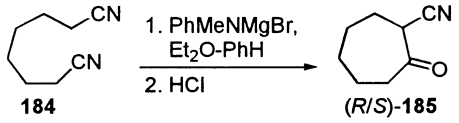
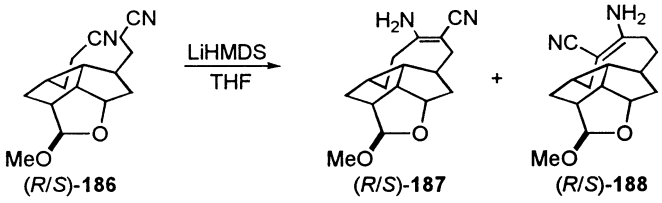
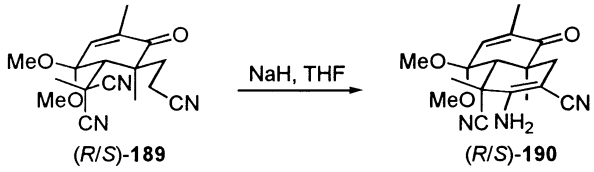
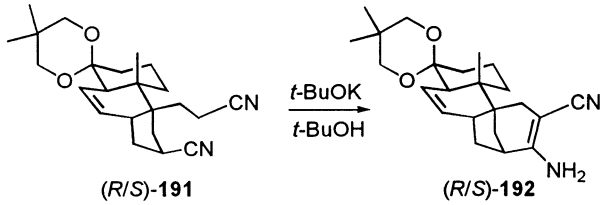
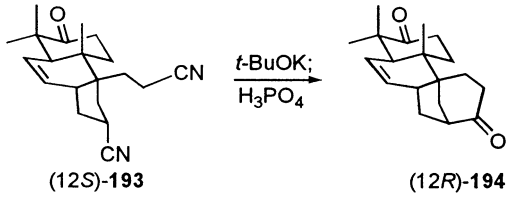
Entry	Reaction	Yield (%)
1		97[96]
2		66–87[97]
3		60[98]
4		40–58[99]
5		76[100]
6		40[101]
7		63[102]
8		67[103]
9		90[104]
10		68[105]

Table 7. Nitrile anion cyclizations with carbonyl compounds

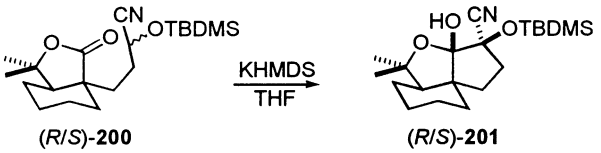
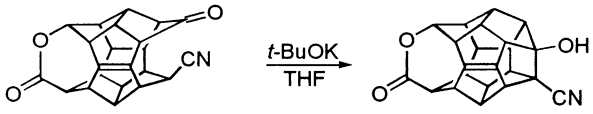
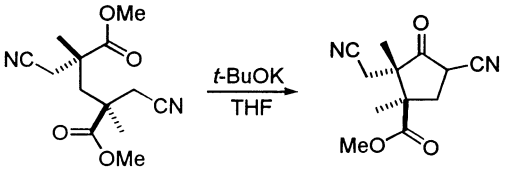
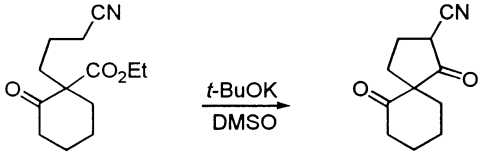
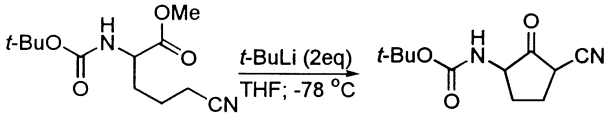
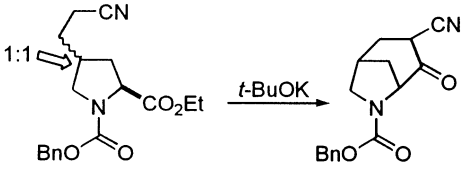
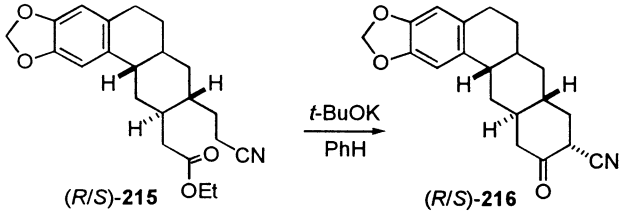
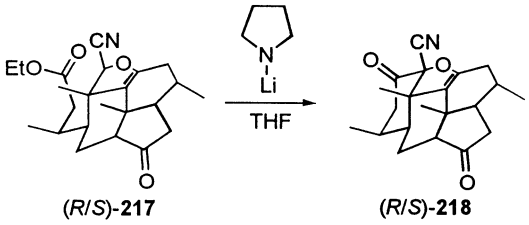
Entry	Reaction	Yield (%)
1	 (*R*/*S*)-**200** (*R*/*S*)-**201**	62[107]
2	 (*R*/*S*)-**202** (*R*/*S*)-**203** (*R*/*S*)-**204**	73[108]
3	 (*R*/*S*)-**205** (*R*/*S*)-**206**	95[109]
4	 **207** (*R*/*S*)-**208**	54[110]
5	 (*R*/*S*)-**209** (*R*/*S*)-**210**	52[111]
6	 (*R*/*S*)-**211** (*R*/*S*)-**212**	50[112a]
7	 (2*S*)-**213** (*R*/*S*)-**214**	65[112b,c]
8	 (*R*/*S*)-**215** (*R*/*S*)-**216**	87[113]

Table 7. (*continued*)

Entry	Reaction	Yield (%)
9	 (*R*/*S*)-**217** (*R*/*S*)-**218**	79[114]

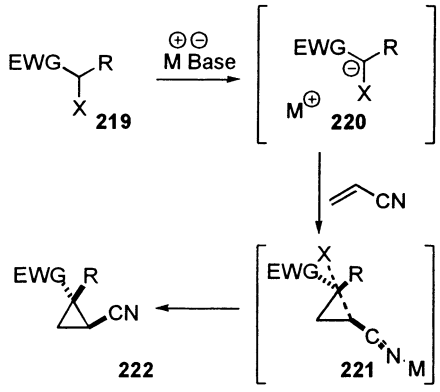
enolate (**197**) that can potentially equilibrate through either inter- or intramolecular proton transfer. Several examples avoid the regioisomeric ambiguity by employing non-enolizable carbonyl electrophiles (Table 7, entries 1–4), a strategy that is completely stereoselective in two cyanohydrin cyclizations (Table 7, entries 1 and 2).

The regioselective cyclization of nitrile anions with esters is remarkable (Table 7, entries 4–9). Collectively, the racemization of **214** (Table 7, entry 7) and the chemoselective cyclization of **215** suggest an inherent propensity for nitrile anions to add to esters rather than ester enolate addition to nitriles, a regioselectivity consistent with a poorer electrophilicity of nitriles compared to esters.[106] Cyclizations of α-methylenenitriles generate enolizable ketonitriles that are deprotonated, effectively promoting the reaction (Table 7, entries 4–7).

Several cyclizations are remarkably tolerant of additional functionality (Table 7, entries 2–9). The cyclizations tolerate ketone, ester, and urethane groups, efficiently assembling functionalized ketonitriles. Cyclization of the functionalized nitrile **217** is particularly revealing in closing a highly strained system having ring strain and severe steric interactions.

6. Domino reactions

Domino reactions install high levels of molecular complexity in a single synthetic operation.[115] Domino sequences featuring nitrile anions most often proceed by conjugate addition to acrylonitrile with a stabilized anion bearing a leaving group (Table 8, entries 1–9), followed by cyclization of the intermediate nitrile anion (Scheme 15). Access to the same intermediate anion is achieved through cleavage of TMS acetals in a sequential ring opening-ring closing domino reaction (Table 8, entries 12 and 13).



Scheme 15.

Conjugate reduction and cyanide additions to unsaturated nitriles similarly generate intermediate nitrile anions for cyclizations with esters and ketones (Table 8, entries 14 and 15). The cyanide-induced cyclization (Table 8, entry 15) demonstrates an inherent propensity for proton transfer followed by nitrile anion cyclization rather than a Dieckmann cyclization of the first-formed ester enolate. The observed regiochemistry is consistent with related cyclizations of nitrile anions onto carbonyl compounds (Section 5).

Two ring-enlargement strategies feature nitrile anions in domino syntheses of medium-sized rings (Table 8, entries 16 and 17). Attack of the nitrile anion onto the ketone generates an intermediate alkoxide (**254**) that cleaves to generate medium-sized β-keto nitriles (Table 8, entry 16). A particularly clever route to medium-sized ketonitriles relies on a sequential 'retro-aldol'-intramolecular conjugate addition (Table 8, entry 17). The surprisingly facile reaction provides excellent yields of medium-sized ketones that are often otherwise difficult to efficiently assemble. A conceptually related conjugate addition generates the cyclization precursor **260** (Table 8, entry 18) through alkylation, effectively triggering a domino displacement-conjugate addition.

7. Synopsis

Nitrile anions are outstanding nucleophiles, ideally suited for cyclizations by virtue of a high nucleophilicity and a minimal steric demand. Collectively these features allow facile syntheses of strained, sterically hindered, and medium-sized rings through alkylations with a variety of electrophiles. Excellent, predictable regioselectivity is observed in S_Ni displacements with halide, sulfonate, and epoxide electrophiles and in chemoselective condensations with carbonyl electrophiles.

Nitrile anion cyclizations assemble carbocycles with excellent control of up to three stereogenic centers. The stereoselectivity directly hinges on the nitrile anion pyramidalization in the transition state, allowing selective access to diastereomeric nitriles simply by solvent selection. The stereochemical control, combined with the high functional group tolerance, conspires to make nitrile anion cyclizations extremely attractive. These advantages have

Table 8. Domino nitrile anion cyclizations

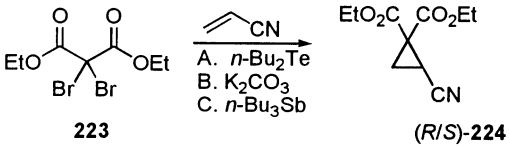
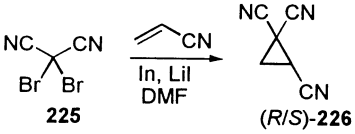
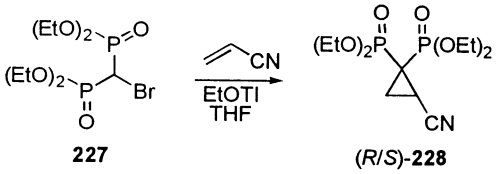
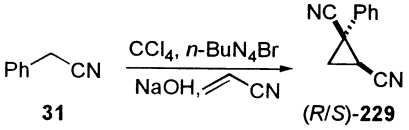
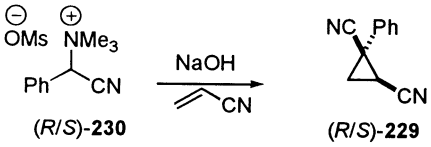
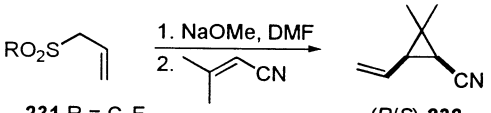
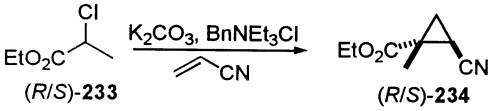
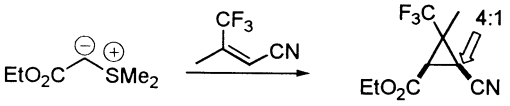
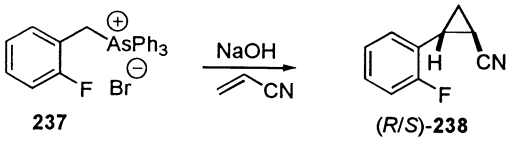
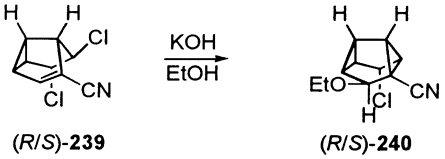
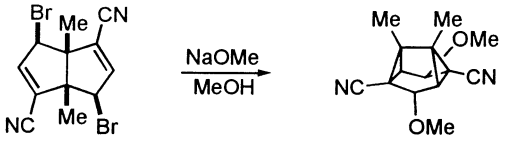
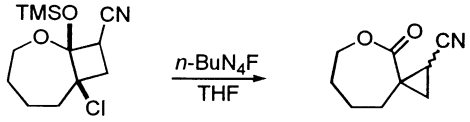
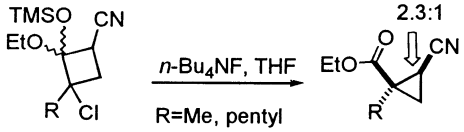
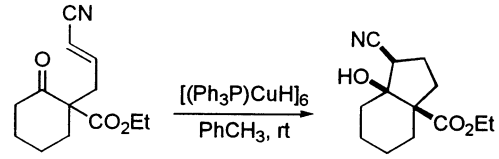
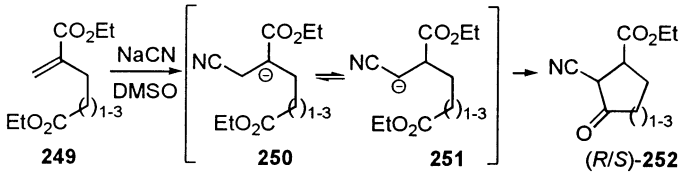
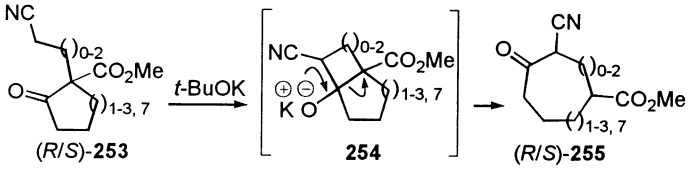
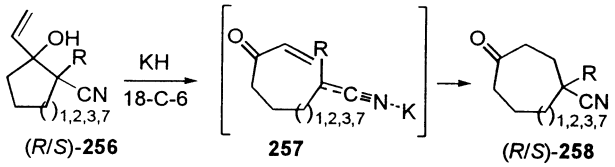
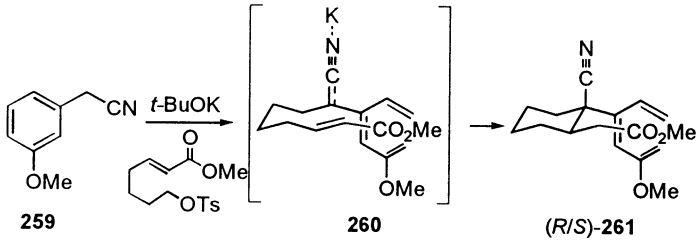
Entry	Substrate	Yield (%)
1	 **223** → (*R*/*S*)-**224**	A 57,[116] B 95,[117] C 88[118]
2	 **225** → (*R*/*S*)-**226**	53[119]
3	 **227** → (*R*/*S*)-**228**	46–59[120]
4	 **31** → (*R*/*S*)-**229**	52[121]
5	 (*R*/*S*)-**230** → (*R*/*S*)-**229**	96[122]
6	 **231** R = C_4F_9, Ph → (*R*/*S*)-**232**	27 (C_4F_9),[123] 73 (Ph)[124]
7	 (*R*/*S*)-**233** → (*R*/*S*)-**234**	50[125]
8	 **235** → (*R*/*S*)-**236**	40[126]
9	 **237** → (*R*/*S*)-**238**	89[127]
10	 (*R*/*S*)-**239** → (*R*/*S*)-**240**	80>[128]

Table 8. (*continued*)

Entry	Substrate	Yield (%)
11	 (*R*/*S*)-**241** (*R*/*S*)-**242**	97[129]
12	 (*R*/*S*)-**243** (*R*/*S*)-**244**	47[130]
13	 (*R*/*S*)-**245** (*R*/*S*)-**246**	80–83[130]
14	 (*R*/*S*)-**247** (*R*/*S*)-**248**	66[131]
15	 **249** **250** **251** (*R*/*S*)-**252**	73–84[132]
16	 (*R*/*S*)-**253** **254** (*R*/*S*)-**255**	39–63[111,133]
17	 (*R*/*S*)-**256** **257** (*R*/*S*)-**258**	51–86[134]
18	 **259** **260** (*R*/*S*)-**261**	>29[135]

been exploited in several domino reactions that point towards the continued influence of nitrile anion cyclizations in the future.

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Biographical sketch

Fraser Fleming earned his B.Sc. (Hons.) at Massey University, New Zealand, in 1986 and then pursued a PhD under the direction of Edward Piers at the University of British Columbia, Canada. After graduating in 1990 he moved to Oregon State University for postdoctoral research with James D. White and in 1992 joined the faculty at Duquesne University where he is currently an associate professor. His research interests lie in developing new reactions of unsaturated nitriles and stereoselective nitrile anion alkylations.

Brian Shook completed his undergraduate studies at the University of Pittsburgh, Johnstown, graduating with a B.S. degree in 1996. He then pursued a PhD with Fraser Fleming focusing on stereoselective nitrile anion cyclizations. After completing his degree in 2001 he accepted a postdoctoral position with Robert Boeckman where his research focus is on stereoselective natural product synthesis.