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Cyclic Nitriles: Stereodivergent Addition−Alkylation−Cyclization to *cis*- and *trans*-Abietanes

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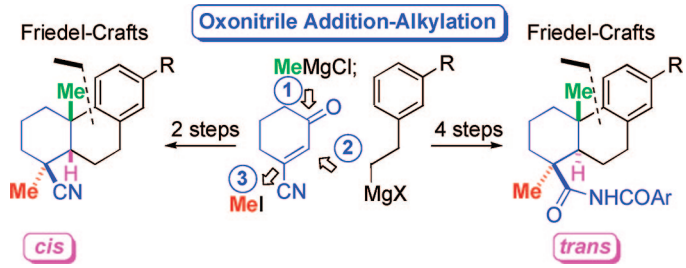

Diverse cyclic hydroxy nitriles are readily synthesized through sequential 1,2−1,4-Grignard addition−methylations to 3-oxo-1-cyclohexene-1-carbonitrile. Acid-catalyzed intramolecular cyclizations of the cyclic hydroxy nitriles reveal fundamental stereoselectivity trends in Friedel−Crafts cyclizations to *cis*- and *trans*-abietanes. In contrast to previous assumptions, comparative cationic cyclizations with electron-rich and electron-poor aromatic nucleophiles exhibit similar preferences for cyclization to *cis*-abietanes. Optimizing the cyclizations for *trans*-abietanes has identified $ZrCl_4$ as an exceptional Lewis acid which, for cyclizations of iminolactones, favors *trans*-abietanes as the only observable diastereomer. The sequential oxonitrile addition−Friedel−Crafts cyclization strategy provides a rapid, stereodivergent synthesis of *cis*- or *trans*-abietanes, demonstrates the dramatic influence of $ZrCl_4$ in promoting cationic cyclizations, and in contrast to previous assumptions suggests that the cyclization stereoselectivity is *not* correlated with the electronic nature of the aromatic nucleus.

Introduction

Abietane diterpenoids are widely distributed in coniferous plants.[1] Resinous secretions from pine trees are rich in abietanes where they serve a defensive role in healing plants by forming a solid, cross-linked protective coating over external lesions.[2] These solid secretions, or pine rosins, are integral constituents in a diverse range of commercial products[3] and are featured as valuable precursors[4] in several natural product syntheses.[5]

Abietane diterpenoids are partitioned into two main classes: dehydroabietanes **1** and the hydrogenated abietane counterparts

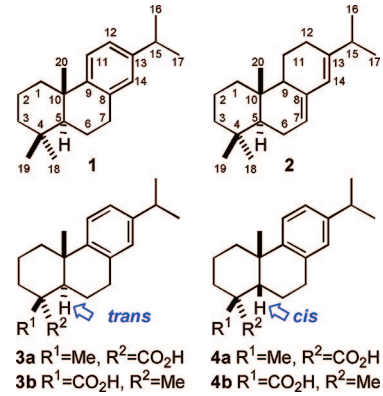

FIGURE 1. Abietane diterpenoids.

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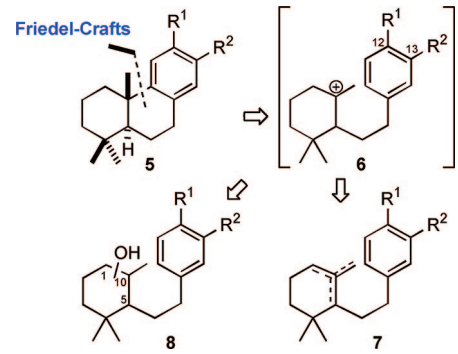
2 (Figure 1). Dehydroabietanes are somewhat more prevalent than their abietane counterparts, perhaps due to their formation from abietanes through acid-catalyzed disproportionation.[6] In both series, the *trans*-fused ring junction stereochemistry predominates,[7] often with varying levels of oxidation at carbon 12 and the methyl groups. The presence of a carboxylic acid or an acid derivative at C-18 and C-19 is particularly common (**3** and **4**, Figure 1).[8]

The prevalence of acid-containing abietanes in commercial products combined with their therapeutic activity[8] as promising antimicrobial[9] and antitumor agents[10] continues to spur the isolation and modification of these metabolites.[9,11] By far the most biologically active are the dehydroabietic acids bearing a carboxylic acid group at C-18 (**3** and **4**, Figure 1). The parent metabolite, dehydroabietic acid (**3a**), exhibits antitumor activity,[12] whereas the diastereomer callistrisic acid (**3b**) elicits antimicrobial activity.[13] Although less common, the corresponding *cis* diastereomers **4a** and **4b** have been isolated, the former in wastewater eluant from hardboard production[14] while the latter, **4b**, is a constituent of kauri gum, a rosin from an indigenous New Zealand hardwood.[15]

For over 50 years, abietane diterpenoids have been synthesized by Friedel−Crafts cyclizations[16] of arylethyl-substituted cyclohexanes (Scheme 1>).[17] Protonating a diverse range of alkenes **7** or alcohols **8** (hydroxylation at C-5, C-10, or C-1) triggers cyclizations with the same stereoselectivity implying that a fully dissociated carbocation **6** is the key intermediate.[18] Enantioselective syntheses employing Friedel−Crafts cyclizations therefore require installation of the correct stereocenter at C-5 because the stereochemistry of the methine carbon affects the facial attack on the intermediate carbocation **6** (Scheme 1).[19]

An intriguing substituent effect in the aromatic nucleus influences the cyclization selectivity (Scheme 1, **6**→**5**). An empirical trend, gleaned from Friedel−Crafts cyclizations over the last four decades,[20] is that unsubstituted or C-12 oxygenated aromatic nucleophiles (**6**, R^1 = OR, R^2 = H) generally favor *trans*-fused abietanes whereas cyclizations with alkyl or alkoxy substituents at C-13 (**6**, R^1 = H, R^2 = OR) afford *cis*- and *trans*-fused abietanes with minimal stereocontrol. Surveying these trends has fostered the proposal that there is a correlation between the electronic properties of the aromatic nucleophile and the cyclization selectitivity.[20,21] A key test of this proposal is to monitor the stereoselectivity in Friedel−Crafts cyclizations with a series of arenes having electron-withdrawing and electron-donating substituents. Electron-withdrawing substituents

SCHEME 1. Friedel−Crafts Approach to Abietane Diterpenoids



deactivate the aromatic nucleophile toward Friedel−Crafts cyclization,[22] perhaps explaining why a systematic investigation has not been performed.

Grignard addition−alkylations with oxonitriles rapidly assemble hydroxy nitriles[23] ideally suited for testing the proposed correlation between the stereoselectivity of Friedel−Crafts cyclizations and the electronic nature of the arene. For example, sequential addition of MeMgCl, the phenethyl Grignard **10**, and MeI to oxonitrile **9**[24] installs the entire abietane skeleton as a prelude to Friedel−Crafts cyclization (Scheme 2). Exposing **11** to methanesulfonic acid affords **12**, which is efficiently hydrolyzed to complete a short synthesis of *epi*-dehydroabietic acid (**13**).[25] Using this strategy, an extensive series of Friedel−Crafts cyclizations establishes the versatility of oxonitriles for synthesizing *cis*- and *trans*-abietanes, expands the repertoire of cationic cyclizations with oxidized abietane precursors,[26] demonstrates the dramatic influence of $ZrCl_4$ in promoting cationic

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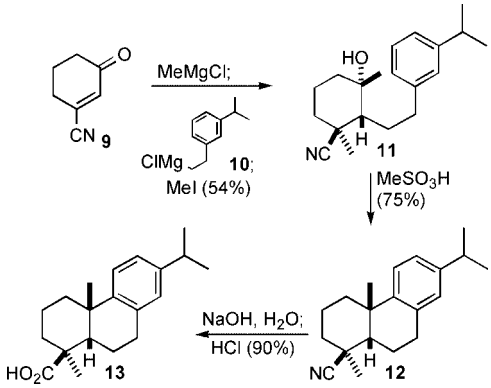
SCHEME 2. Oxonitrile-Based *epi*-Dehydroabietic Acid Synthesis

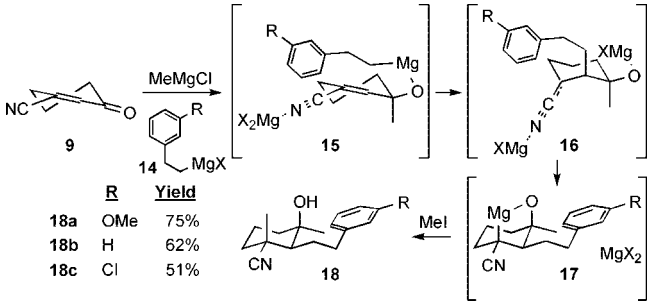


cyclizations, and suggests that the cyclization stereochemistry is *not* correlated with the electronic nature of the aromatic nucleus.

Results and Discussion

Cyclic oxonitrile **9**[24] contains three juxtaposed electrophilic sites ideally tuned for a multiple alkylation cascade.[27] Harnessing the synergistic reactivity of the oxonitrile functionality through sequential addition-alkylations installs all of the carbons required in the abietane skeleton from four readily varied precursors; oxonitrile **9**, MeMgCl, a phenethyl Grignard reagent **14**, and methyl iodide (Scheme 3). Experimentally, addition of methylmagnesium chloride to 3-oxo-1-cyclohexene-1-carbonitrile (**9**)[24] generates a halomagnesium alkoxide[28] that suffers a halogen−alkyl exchange[29] on addition of Grignard **14**. Positioning the resulting alkylmagnesium alkoxide **15** proximal to the alkenenitrile triggers a stereoelectronically controlled axial conjugate addition[30] that effectively unites rings A and C of the abietane skeleton. Conducted tour equilibration[31] of the *N*-magnesiated nitrile **16** generated from the addition event, favors the internally coordinated, *C*-magnesiated nitrile **17** in which the two alkyl groups are relaxed into the sterically less demanding equatorial orientation. Retentive methylation[32] of the *C*-magnesiated nitrile **17** effectively installs the last stereocenter with excellent stereochemical fidelity. Incorporating varying aryl -substituents into the Grignards **14** provides an efficient synthesis of electron-rich, neutral, and electron-deficient arene precursors **18** for Friedel−Crafts cyclization. Key to this multiple bond-forming strategy is the synthesis of the functionalized Grignard reagents **14a** and **14c** without internal deprotonation and ejection of chloride or methoxide. Formation of Grignard **14c** is particularly unusual because of the added requirement for selective insertion of magnesium into the terminal C−Br bond without rupturing the sp^2 C−Cl bond.

SCHEME 3. Four-Component Synthesis of Hydroxy Nitrile Abietane Precursors



	R	Yield
18a	OMe	75%
18b	H	62%
18c	Cl	51%

Friedel−Crafts cyclization of the hydroxy nitrile **18** provides a mixture of the *cis*- and *trans*-abietanes **21** and **23** (Scheme 4). Screening a series of acid-solvent combinations, using hydroxy nitrile **18b** as a prototype, identified an excess of methanesulfonic acid in nitromethane as the optimal reagent. Remarkably, the cyclizations are all relatively efficient, even for the nitrile **18c** in which the arene nucleus is deactivated by chlorine substitution.[22] In each case, almost identical ratios of *cis*/*trans* diastereomers were obtained regardless of the electronic nature of the substituents in the aromatic nucleus. The efficient cyclization of the chlorine-substituted aromatic is particularly significant in providing a convenient handle for introducing alkyl substituents[33] present in a number of naturally occurring abietanes.[1]

Predominant cyclization of the hydroxy nitriles **18** to the *cis*-decalins **21** implies ionization of the tertiary alcohol to a discrete carbocation because the newly formed C−C bond retains the same configuration as in the original alcohol.[34] Presumably protonation of **18** first affords the carbocation **19′** in which nucleophilic attack from the axial direction is geometrically precluded by the severe nonbonding interactions between the axial methyl group and the peri-hydrogen. The steric impediment would favor a conformational inversion to the twist conformer **19″** or the chair **19‴** which avoid the allylic strain[35] inherent in the planar carbocation **19′**.[34] Cyclization through **19″** is analogous to Friedel−Crafts cyclizations of conformationally locked cyclohexanols that proceed through twist conformations.[36] Cyclization via conformer **19‴** similarly avoids allylic strain at the expense of positioning the arylethyl side chain in an axial orientation but with the advantage of achieving an ideal alignment for cyclization (Scheme 4). Proton loss from the resulting carbocation **20** and rearomatization leads to the *cis*-fused abietane **21**.

The Friedel−Crafts cyclization of **18** to the *trans*-abietane **23** requires a reaction trajectory in which the aromatic ring approaches the planar carbocation from the equatorial direction. Cyclization through **19⁗** competes remarkably effectively given the inherent allylic strain and the conformational demands required in processing to a *trans*-fused ring system. Presumably the energy required for cyclization via **19⁗** is only slightly greater than for **19″** or **19‴** because the *cis*-abietanes **21** are only modestly favored by 3−4.5:1.[37]

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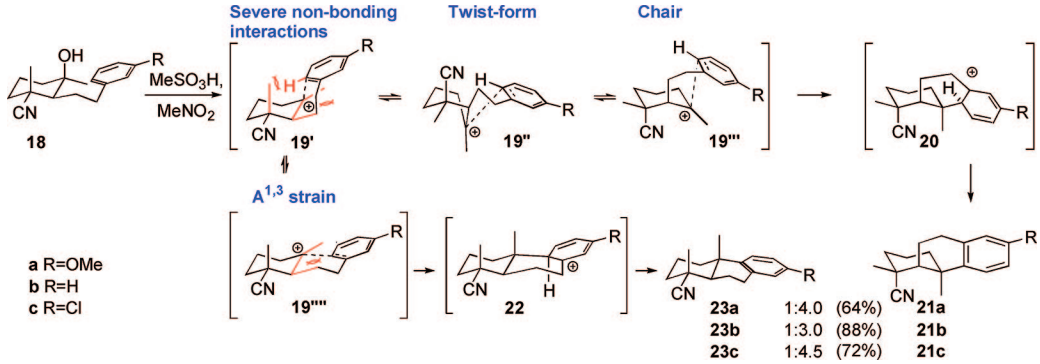
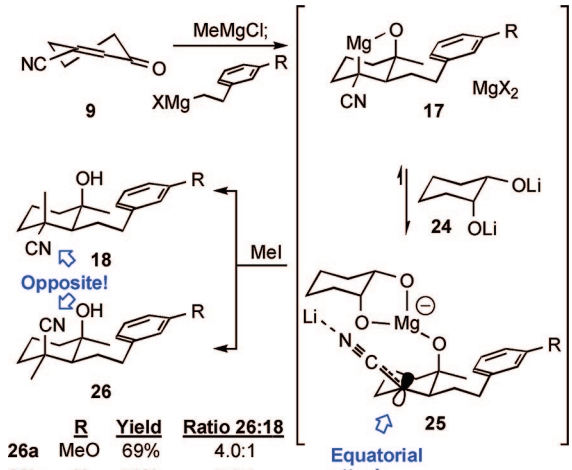
(37) Virtually identical ratios are obtained in related arylethyl cyclizations onto tertiary alcohols embedded within decalin scaffolds.[34]

SCHEME 4. Friedel−Crafts Cyclizations with Electronically Tuned Aromatic Nucleophiles



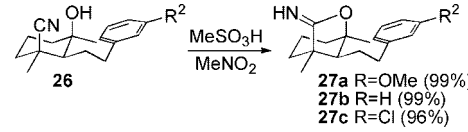
The consistent preference for *cis*-abietanes in Friedel−Crafts cyclizations with electronically disparate arenes stimulated a series of cyclizations with hydroxy nitriles having the opposite stereochemistry at the nitrile-bearing carbon (Scheme 5, compare **26** with **18**). A particularly attractive feature of Grignard addition-alkylations to oxonitrile **9** lies in reversing the alkylation stereoselectivity by tuning the nature of the metalated nitrile prior to alkylation.[38] Addition of dilithium cyclohexane-1,2-diolate (**24**) to the *C*-magnesiated nitrile **17** is thought to interact with the electrophilic magnesium to form the ate complex **25** with concomitant formation of a planar *N*-lithiated nitrile. Localizing the sterically demanding magnesiate in the axial orientation favors an equatorial electrophilic trajectory to the planar lithiated nitrile. Methylation affords predominantly the axial nitrile **26** accompanied by the equatorial nitrile **18** that presumably arises through methylation with uncomplexed *C*-magnesiated nitrile **17**.

SCHEME 5. Stereodivergent Four-Component Oxonitrile Alkylations



	R	Yield	Ratio 26:18
26a	MeO	69%	4.0:1
26b	H	76%	7.8:1
26c	Cl	59%	7.2:1

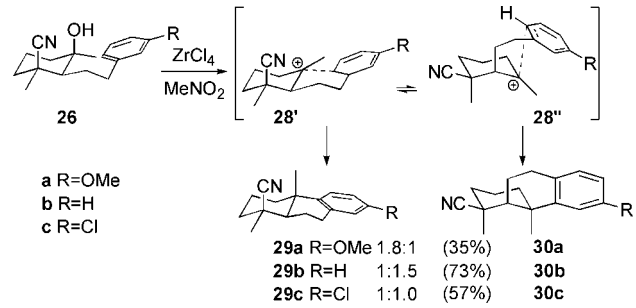
Exposing the axial nitriles **26** to $MeSO_3H-MeNO_2$ triggers a very facile cyclization. However, the cyclization is to the iminolactone **27** with installation of a new oxygen−carbon bond (eq 1) rather than a carbon−carbon bond! Presumably the proximity of the nitrile and alcohol groups favors protonation of the nitrile nitrogen and intramolecular attack by the axial alcohol.[39]



(1)

Guided by the high oxophilicity of metal halides, several Lewis acids were screened with the aim of selectively activating the axial alcohol rather than the nitrile functionality. The inability of several conventional Lewis acids[40] to cleanly cyclize **26** focused attention on $ZrCl_4$[41] because of the exceptional oxophilicity of zirconium.[42] Exposing the hydroxy nitriles **26** to $ZrCl_4$ in nitromethane opens a new reaction manifold leading to carbocyclic abietanes (Scheme 6). The cyclization selectivity is essentially the same for the three substituted arenes, affording roughly equal amounts of the *trans*- and *cis*-abietanes **29** and **30**. Compared with the $MeSO_3H-MeNO_2$ cyclizations of the diastereomeric nitrile **18** which favor the *cis*-abietane **21**

SCHEME 6. $ZrCl_4$-Promoted Friedel−Crafts Cyclizations



(Scheme 4), interchanging the small nitrile group[43] with a distinctly larger equatorial methyl group[43] in **26** is expected to favor conformer **28′** over **28″** (Scheme 6). Cyclization to the *trans*-abietane **29** must proceed through conformer **28′**, potentially explaining the increased preference for the *trans*-abietane from **26** relative to the $MeSO_3H$ cyclizations of **18**. As a direct point of comparison, the cyclization of **18b** with $ZrCl_4$ in $MeNO_2$ affords **21b** and **23b** in a 3:1 ratio (96% yield)—*exactly the same ratio as with $MeSO_3H$ but with a distinctly higher yield!*

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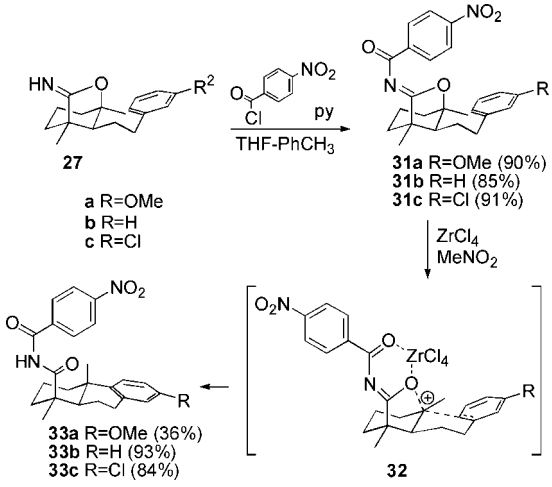
(40) $TiCl_4$, $SnCl_4$, and $BF_3 \cdot OEt_2$ gave complex reaction mixtures, whereas $AlCl_3$ triggered the cyclization of **26** to **29** and **30** but less effectively than with $ZrCl_4$.

Zirconium tetrachloride exerts a distinct advantage over $MeSO_3H$ in Friedel−Crafts cyclizations of hydroxy nitriles; $ZrCl_4$ is highly chemoselective and higher yielding. One limitation is the decreased efficiency with the methoxy-substituted nitrile **26a**. Although speculative, the oxophilic $ZrCl_4$ may bind competitively to the methoxy group causing decomposition of the abietanes **29a** and **30a** or the precursor nitrile **26a**.

Attempts to derivatize the iminolactone **27b** for crystallography prompted an intriguing strategy for selectively accessing the *trans*-abietane stereochemistry common to most naturally occurring abietanes[1] (Scheme 7). Acylation of the imino lactones **27** generates the acyl imines **31** that are ionized to the *trans*-abietanes **33** upon addition of $ZrCl_4$.[44] Exclusive[45] installation of the trans stereochemistry is consistent with cyclization through a cationic intermediate **32** in which the departing acyl imine maintains an association with the carbocation.[46] Previous Friedel−Crafts cyclizations with bridged lactones parallel this type of assisted displacement.[26a,c] The $ZrCl_4$-assisted cyclizations of activated iminolactones are remarkably efficient in the absence of additional oxygenation, and are not

SCHEME 7. Promoted Friedel−Crafts Cyclization to *trans*-Abietanes



accompanied by competitive lactone formation that complicates the cyclizations of related hydroxy esters.[26c,47]

(41) Although $ZrCl_4$ appears not to have been previously employed in Friedel−Crafts cyclizations, the use of chrial zirconium alkoxides promotes highly enantioselective cyclizations. Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601.

(42) The bond energy of ZrO is 7.94 eV: (a) Loock, H.-P.; Simard, B.; Wallin, S.; Linton, C. *J. Chem. Phys.* **1998**, *109*, 8980. For the use of $ZrCl_4$ in ionizing tertiary alcohols, see: (b) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2006**, *47*, 93.

(43) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−7.

(44) The stereochemistry of **33b** was secured through a NOESY experiment showing a cross-peak for the axial methyl group and the imide NH proton. The stereochemistry of **33a** and **33c** was assigned by analogy to **33b** based on the distinctive ^1H and ^{13}C chemical shifts: (a) Del Corral, J. M. M.; Gordaliza, M.; Salinero, M. A.; San Feliciano, A. *Magn. Reson. Chem.* **1994**, *32*, 774. (b) Qing, N.; Colebrook, L. D.; Commodari, F. *Magn. Reson. Chem.* **1991**, *29*, 459. (c) Wenkert, E.; Afonso, A.; Beak, P.; Carney, R. W. J.; Jeffs, P. W.; McChesney, J. D. *J. Org. Chem.* **1965**, *30*, 713.

(45) ^1H NMR analysis of the very clean, crude reaction mixtures for **33b** and **33c** provided no evidence for the presence of a *cis*-abietane.

(46) Ghatak, U. R.; Chatterjee, N. R.; Sanyal, B. *J. Org. Chem.* **1979**, *44*, 1992.

(47) (a) Fuji, K.; Zheng, S.-Z.; Node, M.; Hao, X.-J. *Chem. Pharm. Bull.* **1991**, *39*, 202. (b) Banerjee, A. K.; Nasipuri, D.; Pakrashi, S. C. *J. Org. Chem.* **1990**, *55*, 3952. (c) Mancini, V.; Fringuelli, F.; Taticchi, A. *Gazz. Chim. Ital.* **1969**, *99*, 953. (d) Barnes, R. A.; Hirschler, H. P.; Bluestein, B. R. *J. Am. Chem. Soc.* **1952**, *74*, 32.

Conclusion

An extensive series of intramolecular Friedel−Crafts cyclizations with cyclic hydroxy nitriles provides rapid, selective access to *cis*- and *trans*-abietanes. Diastereomeric hydroxy nitriles with complementary configurations at the nitrile-bearing carbon are readily assembled through sequential 1,2−1,4-addition−alkylations to oxonitriles by simply tuning the structure of the metalated nitrile prior to the final alkylation event. Acid-catalyzed cyclizations of diastereomeric hydroxy nitriles intimately depend on the relative stereochemistry of the nitrile and alcohol groups. Diastereomers with remote nitrile and hydroxyl groups cyclize in acid to abietanes whereas the proximal diastereomers cyclize to iminolactones. Methanesulfonic acid-initiated abietane cyclizations exhibit essentially the same stereoselectivity preferences for methoxyphenyl, phenyl, and chlorophenyl arenes suggesting that the stereoselectivity is not correlated with the electronic nature of the aromatic nucleus.

Zirconium tetrachloride promotes a highly efficient, potentially general, Friedel−Crafts cyclization for hydroxy nitriles regardless of the relative configuration of the nitrile and hydroxyl groups. In comparable cyclizations, zirconium tetrachloride is significantly more efficient than methanesulfonic acid with the added advantage of increased functional group tolerance. Collectively, the nitrile-based cyclizations provide rapid access to diastereomeric *cis*- and *trans*-abeitanes, demonstrate the dramatic influence of zirconium tetrachloride in Friedel−Crafts cyclizations and provide insight into the factors controlling the cyclization stereoselectivity.

Experimental Section

General Grignard Addition−Alkylation Procedure with Oxonitrile 9. A THF solution of MeMgCl (1.05−1.10 equiv) was added to a −15 °C THF solution (0.1 M) of the oxonitrile **9**. After 2 h, a second Grignard reagent (1.2−1.5 equiv) was added, and the solution was then allowed to warm to room temperature. After 2 h, neat methyl iodide (3.0−10 equiv) was added, and after 16 h, saturated aqueous NH_4Cl was added. The phases were separated, and the aqueous phase was extracted with EtOAc. The extracts were combined, washed with brine, and dried (Na_2SO_4). Concentration and purification of the crude product by radial chromatography afforded the pure nitrile.

General Cyclization Procedure with $MeSO_3H$. $MeSO_3H$ (70 equiv) was added neat to a −15 or 0 °C $MeNO_2$ solution (0.05 M) of the nitrile **18**. After 2 h, saturated aqueous $NaHCO_3$ was added, the phases were separated, and the aqueous phase was extracted with EtOAc three times. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated to afford a crude product that was purified by radial chromatography to afford the *cis*- and *trans*-cyclic nitriles.

General Addition−Alkylation Procedure for Synthesizing Nitriles 26. A THF solution of MeMgCl (1.05−1.10 equiv) was added to a −15 °C THF solution (0.1 M) of the oxonitrile **9**. After 2 h, a second Grignard reagent (1.2−1.5 equiv) was added, and the solution was then allowed to warm to room temperature. After 2 h, the solution was transferred by syringe to a 0 °C THF solution (0.3 M) of *cis*-cyclohexane-1,2-diol (3 equiv) to which BuLi (3.3 equiv) had been added. The resulting solution was cooled to −78 °C, and after 0.5 h, the electrophile (3.0−10 equiv) was added neat. After 1 h, the solution was allowed to warm to room temperature, and after 16 h, saturated aqueous NH_4Cl was added. The phases were separated, and the aqueous phase was extracted with EtOAc. The extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated to afford a crude product that was purified by radial chromatography to afford the pure nitrile.

General Procedure for Cyclization with $ZrCl_4$. A $MeNO_2$ solution (0.25 M) of nitrile **26** was added to a 0 °C $MeNO_2$ solution (0.25 M) of $ZrCl_4$ (12 equiv). After 16 h, aqueous 2 M HCl was added, the phases were separated, and the aqueous phase was then extracted with EtOAc three times. The combined extracts were washed with saturated aqueous $NaHCO_3$ and water and then dried (Na_2SO_4). After removal of the solvent, the crude material was purified by radial chromatography to afford the pure cyclic nitriles.

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Supporting Information Available: Experimental procedures, ^1H NMR and ^{13}C NMR spectra for all new compounds, and an ORTEP for **30b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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