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Metalated Nitriles: Internal 1,2-Asymmetric Induction

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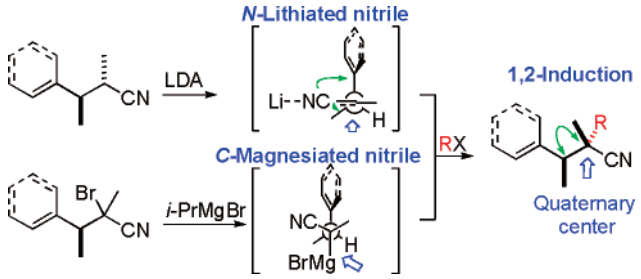

Alkylations of conformationally constrained *acyclic* nitriles containing vicinal dimethyl groups and an adjacent phenyl group or trisubstituted alkene are exceptionally diastereoselective. Probing the alkylation stereoselectivity with a series of *C*- and *N*-metalated nitriles implicates a reactive conformation in which an sp^2-hybridized substituent projects over the metalated nitrile to avoid allylic strain. Steric screening thereby directs the electrophilic attack to the face of the metalated nitrile opposite the projecting substituent. Excellent stereoselectively is maintained in a diverse range of alkylations that efficiently install quaternary centers, even with isopropyliodide in which a contiguous array of tertiary−quaternary−tertiary stereocenters is created! Screening the conformational requirements with a series of acyclic nitriles and esters reveals the key structural requirements for high selectivity while providing a robust, predictive model that accounts for comparable ester alkylations affording the opposite diastereomer! The intensive survey of metalated nitrile alkylations identifies the key structural features required for high 1,2-asymmetric induction, addresses the long-standing challenge of asymmetric alkylations with acylic metalated nitriles, and provides a versatile method for installing hindered quaternary centers with excellent stereocontrol.

Introduction

Internal asymmetric induction provides a powerful means of stereocontrol.[1] Historically, internal asymmetric induction emerged from Felkin-type additions to chiral electrophiles and from the use of chiral auxiliaries for relaying an inherent stereochemical bias during alkylations at prostereogenic centers.[2] As the requirements for molecular recognition became better understood several privileged chiral scaffolds emerged, particularly chiral oxazolidinones, that allow stereoselective alkylations with predictable stereochemistry.[3]

A renaissance in internal asymmetric induction issued from the persistent influence of relatively remote stereocenters in matched and mismatched alkylations linking together large chiral fragments.[4] Driven by an increased emphasis upon efficiency and atom economy, the inherent substrate chirality was subsequently harnessed in chiral alkylations with remarkable levels of asymmetric induction over relatively large distances.[5] Substrate-controlled aldol reactions, for example, provide excellent stereocontrol for 1,3- and even 1,5-asymmetric induction.[6]

Internal asymmetric induction with acyclic metalated nitriles is considerably more challenging than for analogous enolates.[7] The challenge stems partly from the inherent bonding of metalated nitriles, which precludes direct attachment of a chiral auxiliary to the CN group,[8] and partly from the structure of metalated nitriles. Lithiated nitriles[9] demonstrate an inherent

(1) Braun, M. Formation of C-C Bonds by Addition of Enolates to Carbonyl Groups. In *Methoden der Organishen Chemie Stuttgart; Thieme Methods of Organic Chemistry*, 4th ed.; Helmchen, G., Hoffman, W. R., Mulzo, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E 21b, p 1603.

(2) *Principles and Applications of Asymmetric Synthesis*; Lin, G.-Q., Li, Y.-M., Chan, A. S. C., Eds.; Wiley-Interscience; Chichester, 2001; Chapter 2.

(3) Frater, G. Alkylation of Ester Enolates. In *Houben-Weyl, Methods of Organic Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart 1995; Vol. E21b; p 726.

(4) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

(5) Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917.

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propensity[10] for planar, nitrogen-coordinated dimers in the solid state[11] and solution[12] (Figure 1). Strategies for asymmetric alkylations of lithiated nitriles through addition of chelating ligands therefore locate the source of chirality relatively remote from the site of alkylation, typically resulting in a modest preference for one enantiomer.[13]

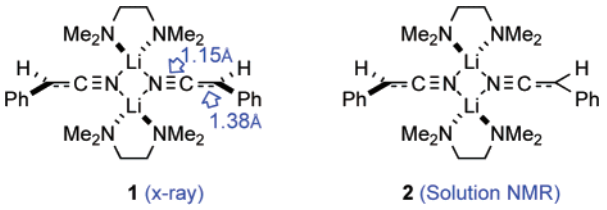


FIGURE 1. Prototypical X-ray and solution structures of lithiated nitriles.

A potentially more effective means of chiral induction with metalated nitriles is to selectively alkylate *C*-metalated nitriles in which the metal is directly bound to the stereogenic carbon (**4**, Figure 2). In contrast to lithium, several metals exhibit an inherent preference for coordination to the formally anionic carbon of metalated nitriles. Among the solid-state structures of transition metal-bound alkylnitriles there is a roughly equal preference for *N*-[14] and *C*-metalation.[15] The seminal heat-induced interconversions of the crystalline ruthenium *N*- and *C*-phenylsulfonylacetonitriles **3** and **4** (Figure 2) are illustrative, with the preference for *N*- or *C*-coordination depending on the phosphine ligand.[16]

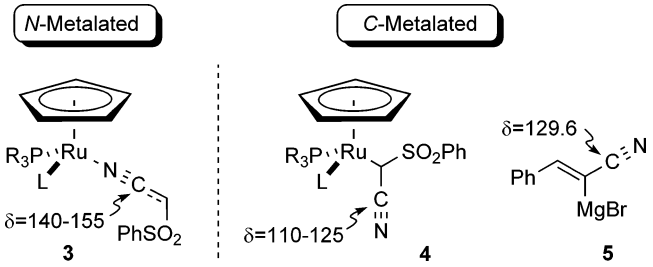


FIGURE 2. Diagnostic structures and ^{13}C chemical shifts of *N*- and *C*-metalated nitriles.

Magnesiated nitriles, such as **5**[17] (Figure 2), exhibit a distinctive preference for coordination to carbon as reflected in the diagnostic solution ^{13}C NMR shifts. Experimentally, magnesiated nitriles exhibit alkylation selectivities consistent with a preference for coordination to carbon.[18] As a standard point

(6) (a) Dias, L. C.; de Marchi, A. A.; Ferreira, M. A. B.; Aguilar, A. M. *Org. Lett.* **2007**, *9*, 4869. (b) Evans, A. D.; Cote, B.; Coleman, J. P.; Conell, T. B. *J. Am. Chem. Soc*. **2003**, *125*, 10893. (c) Paterson, I.; Collett, A. L. *Tetrahedron Lett.* **2001**, *42*, 1187. (d) Evans, A. D.; Dart, J. M.; Duffy, L. J.; Yang, G. M. *J. Am. Chem. Soc*. **1996**, *118*, 4322. (e) Paterson, I.; Gibson, R. K.; Oballa, M. R. *Tetrahedron Lett.* **1996**, *37*, 8585. (f) Evans, A. D.; Dart, J. M.; Duffy, L. J.; Reiger, L. D. *J. Am. Chem. Soc*. **1995**, *117*, 9073.

(7) (a) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2007**, *9*, 1461. (b) Ruano, J. L. G.; Martin-Castro, A. M.; Tato, F.; Pastor, C. J. *J. Org. Chem*. **2005**, *70*, 7346. (c) Viteva, L.; Gospodova, T. Z.; Stefanovsky, Y.; Angelova, S.; Gorrichon, L. *Tetrahedron* **2005**, *61*, 5855. (d) Chen, Y.-J.; Gao, L.-J.; Murad, I.; Verstuyf, A.; Verlinden, L.; Verboven, C.; Bouillon, R.; Viterbo, D.; Milanesio, M.; Haver, D. V.; Vanderwalle, M.; Clercq, P. J. D. *Org. Biomol. Chem.* **2003**, *1*, 257. (e) Halim-Partogyan, K.; Besson, L.; Aitken, D. J.; Husson, H.-P. *Eur. J. Org. Chem*. **2003**, 268. (f) Viteva, L.; Gospodova, T. Z.; Stefanovsky, Y.; Angelova, S.; Gorrichon, L. *Tetrahedron* **2002**, *58*, 3371. (g) Fujishima, T.; Zhaopeng, L.; Konno, K.; Nakagawa, K.; Okano, T.; Yamaguchi, K.; Takayama, H. *Bioorg. Med. Chem.* **2001**, *9*, 525. (h) Fall, Y.; Fernandez, C.; Gonzalez, V.; Mourino, A. *Synlett* **2001**, 1567. (i) Salomon, J. C.; Labadie, R. G. *Molecules* **2000**, *5*, 252. (j) Fall, Y.; Fernandez, C.; Vitale, C.; Mourino, A. *Tetrahedron Lett.* **2000**, *41*, 7323. (k) Chen, J.-Y.; Clercq, D. P.; Vandewalle, M. *Tetrahedron Lett.* **1996**, *37*, 9361. (l) Gmeiner, P.; Hummel, E.; Haubmann, C. *Liebigs Ann*. **1995**, 1987. (m) Reetz, T. M.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1994**, *35*, 8769. (n) Schlessinger, H. R.; Graves, D. D. *Tetrahedron Lett.* **1987**, *28*, 4385. (o) Fleming, I.; Hill, M. H. J.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318. (p) Maigrot, M.; Mazaleyrat, J.-P.; Welvart, Z. *J. Org. Chem*. **1985**, *50*, 3916. (q) Okawara, T.; Harada, K. *J. Org. Chem.* **1972**, *37*, 3286.

(8) For chiral auxiliaries bearing an adjacent nitrile group see: (a) Partogyan-Halim, K.; Besson, L.; Aitken, D. J.; Husson, H.-P. *Eur. J. Org. Chem*. **2003**, 268. (b) Cativiela, C.; Diaz-de-Villegas, D. M.; Galvez, A. J.; Lapena, Y. *Tetrahedron* **1995**, *51*, 5921. (c) Cativiela, C.; Diaz-de-Villegas, D. M.; Galvez, A. J. *J. Org. Chem*. **1994**, *59*, 2497. (d) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463. (e) Maigrot, N.; Mazaleyrat, J.-P.; Welvart, Z. *J. Org. Chem.* **1985**, *50*, 3916.

(9) (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React*. **1984**, *31*, 1.

(10) *C*-Lithiated nitriles, although rare, have been characterized by crystallography in a lithiated cyclopropane[a] and were identified as fluxional species in solution[b] for a lithioacetonitrile-chiral ligand complex. (a) Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc*. **1988**, *110*, 6925. (b) Scott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc*. **2004**, *126*, 6798.

(11) Boche, G. *Angew. Chem., Int. Ed*. **1989**, *28*, 277.

(12) (a) Carlier, P. R.; Lo, C.; W.-S. *J. Am. Chem. Soc*. **2000**, *122*, 12819. (b) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc*., **1994**, *116*, 11602.

(13) (a) Carlier, R. P.; Lam, -F. W.; Wan, C. N.; Williams, D. I. *Angew. Chem., Int. Ed*. **1998**, *37*, 2252. (b) Brunner, H.; Zintl, H. *Monatsh. Chem.* **1991**, *122*, 841. (c) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett*. **2003**, *5*, 3147. (d) Mi, Q. A.; Wang, Y. Z.; Jiang, Z. Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1957. (e) Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron: Asymmetry* **1992**, *3*, 677. (f) Soai, K.; Mukaiyama, T. *Bull. Chem. Soc. J.* **1979**, *52*, 3371.

(14) For *N*-metalated nitriles, see: (a) Tanabe, Y.; Seino, H.; Ishii, Y.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 1690. (b) Murahashi, S.-I.; Take, K.; Naota, T.; Takaya, H. *Synlett* **2000**, 1016. (c) Triki, S.; Pala, J. S.; Decoster, M.; Molinié, P.; Toupet, L. *Angew. Chem. Int. Ed.* **1999**, *38*, 113. (d) Hirano, M.; Takenaka, A.; Mizuho, Y.; Hiraoka, M.; Komiya, S. *J. Chem. Soc., Dalton Trans.* **1999**, 3209. (e) Yates, M. L.; Arif, A. M.; Manson, J. L.; Kalm, B. A.; Burkhart, B. M.; Miller, J. S. *Inorg. Chem.* **1998**, *37*, 840. (f) Jäger, L.; Tretner, C.; Hartung, H.; Biedermann, M. *Chem. Ber*. **1997**, *130*, 1007. (g) Zhao, H.; Heintz, R. A.; Dunbar, K. R. *J. Am. Chem. Soc.* **1996**, *118*, 12844. (h) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (i) Hirano, M.; Ito, Y.; Hirai, M.; Fukuoka, A.; Komiya, S. *Chem. Lett.* **1993**, 2057. (j) Mizuho, Y.; Kasuga, N.; Komiya, S. *Chem. Lett.* **1991**, 2127. (k) Schlodder, R.; Ibers, J. A. *Inorg. Chem. Soc.* **1974**, *13*, 2870. (l) Ricci, J. S.; Ibers, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 2391.

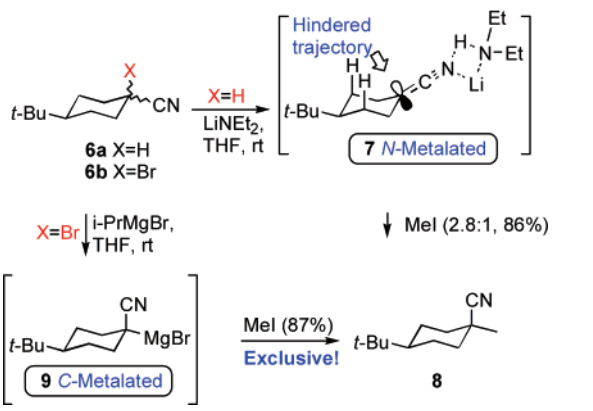
(15) For *C*-metalated nitriles, see: (a) Naota, T.; Tannna, A.; Kamuro, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2002**, *124*, 6842. (b) Naota, T.; Tannna, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2000**, *122*, 2960. (c) Alburquerque, P. R.; Pinhas, A. R.; Krause Bauer, J. A. *Inorg. Chim. Acta* **2000**, *298*, 239. (d) Ruiz, J.; Rodríguez, V.; López, G.; Casabó, J.; Molins, E.; Miravitlles, C. *Organometallics* **1999**, *18*, 1177. (e) Ragaini, F.; Porta, F.; Fumagalli, A.; Demartin, F. *Organometallics* **1991**, *10*, 3785. (f) Porta, F.; Ragaini, F.; Cenini, S.; Demartin, F. *Organometallics* **1990**, *9*, 929. (g) Ko, J. J.; Bockman, T. M.; Kochi, J. K. *Organometallics* **1990**, *9*, 1833. (h) Cowan, R. L.; Trogler, W. *J. Am. Chem. Soc.* **1989**, *111*, 4750. (i) Del Pra, A.; Forsellini, E.; Bombieri, G.; Michelin, R. A.; Ros, R. *J. Chem. Soc., Dalton Trans.* **1979**, 1862. (j) Lenarda, M.; Pahor, N. B.; Calligaris, M.; Graziani, M.; Randaccio, L. *J. Chem. Soc., Chem. Commun.* **1978**, 279. (k) Schlodder, R.; Ibers, J. A.; Lenarda, M.; Graziani, M. *J. Am. Chem. Soc.* **1974**, *96*, 6893. (l) Yarrow, D. J.; Ibers, J. A.; Lenarda, M.; Graziani, M. *J. Organomet. Chem.* **1974**, *70*, 133.

(16) (a) Naota, T.; Tannna, A.; Murahashi, S.-I. *Chem. Commun.* **2001**, 63. (b) Naota, T.; Tannna, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2000**, *122*, 2960. For an analogous interconversion of palladium complexes, see: Kujime, M.; Hikichi, S.; Akita, M. *Organometallics* **2001**, *20*, 4049.

(17) (a) Thibonnet, J.; Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787. (b) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319.

(18) (a) Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2006**, *71*, 1430. (b) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200. (c) Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *Org. Lett.* **2005**, *7*, 447. (d) Fleming, F. F.; Zhang, Z.; Knochel, P. *Org. Lett.* **2004**, *6*, 501.

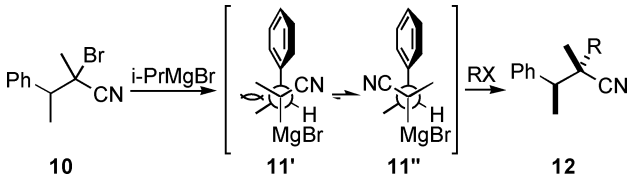
SCHEME 1. *N*- vs *C*-Metalated Nitrile Alkylation Selectivity



of comparison the planar, *N*-lithiated nitrile **7** modestly favors an electrophilic approach from the equatorial direction by a factor of 2.8:1.[19] In comparison, rapid bromine−magnesium exchange of the bromonitrile **6b** favors the putative *C*-magnesiated nitrile **9** in which the large solvated metal preferentially adopts an equatorial orientation.[18] Alkylation with methyl iodide occurs exclusively from the equatorial direction to afford **8** as the sole nitrile diastereomer (Scheme 1).

Rapid conversion of the diastereomeric bromonitriles **6b** to a single *C*-magnesiated nitrile **9** suggests the intriguing possibility of using equilibration to relay the inherent chirality of an adjacent chiral center to favor a single configuration at the stereogenic carbon of a *C*-metalated nitrile. Stereoselective alkylation of the resulting chiral metalated nitrile conceptually provides a method for asymmetric alkylation. *N*-Metalated nitriles[20] bearing an adjacent chiral center have on occasion induced modest to excellent stereoselectivity,[7] providing precedent for the internal asymmetric induction of metalated nitriles. The phenyl-substituted butyronitrile **10**[21] (Scheme 2)

SCHEME 2. Strategy for 1,2-asymmetric Induction with a *C*-Metalated Nitrile



was envisaged to provide an ideal chiral environment based on the exceptionally selective allylation of a closely related naphthyl-substituted butyronitrile.[22] Bromine−magnesium exchange of **10** and equilibration of the resulting *C*-magnesiated nitriles **11** should favor diastereomer **11″** from which retentive alkylation would afford **12**. An intensive survey of metalated nitrile alkylations identifies the key structural features required for high 1,2-asymmetric induction in this type of alkylation, addresses the long-standing challenge of diastereoselective alkylations with acylic metalated nitriles, and provides a versatile method for installing hindered quaternary centers with excellent stereoselectivity.

Results and Discussion

Diastereoselective Alkylations of *C*-Metalated Nitriles. The requisite phenethyl-containing nitrile **10** was readily synthesized by alkylating propionitrile (**13a**) with racemic phenethyl bromide and brominating[23] the resulting nitrile **14a** (Scheme 3). Conversion of **10** to the corresponding *C*-magnesiated nitrile **11** featured an in situ alkylation procedure[18b] in which a solution of *i*-PrMgCl was added to a −78 °C THF solution of the bromonitrile **10** and methyl cyanoformate. Alkylation of the intermediate metalated nitrile is remarkably selective, generating **12a** as a single nitrile diastereomer.[24] Confirmation of the mechanistically assigned stereochemistry was secured through chemoselective reduction of the ester functionality in **12a**, esterification with *p*-nitrobenzoyl chloride, and X-ray crystallographic analysis of the resulting ester **16**.[25] Retrospectively relaying the chirality of **16** to nitrile **12a** confirms the sense of asymmetric induction as being consistent with a retentive alkylation of the *C*-magnesiated nitrile **11″** (Scheme 3).[26]

Addition of *i*-PrMgBr to the bromonitrile **10** is presumed to generate the bromate **15**[27] (Scheme 3) which could fragment directly to the *C*-metalated nitriles **11′** or **11″** or to the corresponding *N*-magnesiated nitrile **11‴**. In either case, rapid[28] conducted tour equilibration[29] through the *N*-magnesiated nitrile **11‴** is anticipated to favor conformation[30] **11″** in which the largest substituents, the phenyl ring and the solvated magnesium bromide, are antiperiplanar and where the phenyl group projects toward the *C*-metalated nitrile to avoid allylic strain with the benzylic methyl group.[31] Propagation of the phenethyl chirality along the carbon chain favors conformer **11″** in which the steric compression between the gauche methyl groups in **11′** is relieved by positioning the small nitrile group[32] in the sterically more demanding environment.

(19) Fleming, F. F.; Gudipati, S.; Zhang, Z.; Liu, W.; Steward, O. W. *J. Org. Chem.* **2005**, *70*, 3845.

(20) For a preliminary communication focusing on 1,2-asymmetric induction in alkylations of *N*-lithiated nitriles, see: Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 7098.

(21) Although the alkylations were performed on a racemate, chiral, *β*-substituted nitriles are readily available in high enantiomeric purity by conjugate reduction: Lee, D.; Kim, D.; Yun, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2785.

(22) Gay, R.; Maugras, M. *C. R. Chim.* **1962**, *255*, 2123.

(23) Stevens, C. L.; Holland, W. *J. Org. Chem.* **1953**, *18*, 1112.

(24) ^{1}H NMR analysis of the crude reaction mixture failed to reveal any trace of a diastereomer.

(25) The authors have deposited the crystallographic data with the Cambridge Crystallographic Data Centre. The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(26) Differentiating between *C*- and *N*-metalated transition structures is experimentally challenging. The identity of the *C*-magnesiated nitrile **11″** is based on the known preference for generating *C*-magnesiated nitriles by halogen-magnesium exchange.[18b,d] Evolution of the ground state *C*-magnesiated nitrile to an *N*-magnesiated transition structure is virtually impossible to detect without recourse to computational modeling but seems highly unlikely given the divergent reactivity preferences of *C*- and *N*-metalated nitriles **7** and **9** (Scheme 1). Despite these nitriles bearing different metals the stark selectivity differences are difficult to explain through a common *N*-metalated transition structure.

(27) (a) Hoffmann, R. W.; Brönstrup, M.; Muller, M. *Org. Lett.* **2003**, *5*, 313. (b) Schulze, V.; Brönstrup, M.; Böhm, V. P. W.; Schwerdtfeger, P.; Schimeczek, M.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 824. (c) Reich, H. J.; Green, D. P.; Phillips, N. H.; Borst, J. P.; Reich, I. L. *Phosphorus, Sulfur, Silicon* **1992**, *67*, 83.

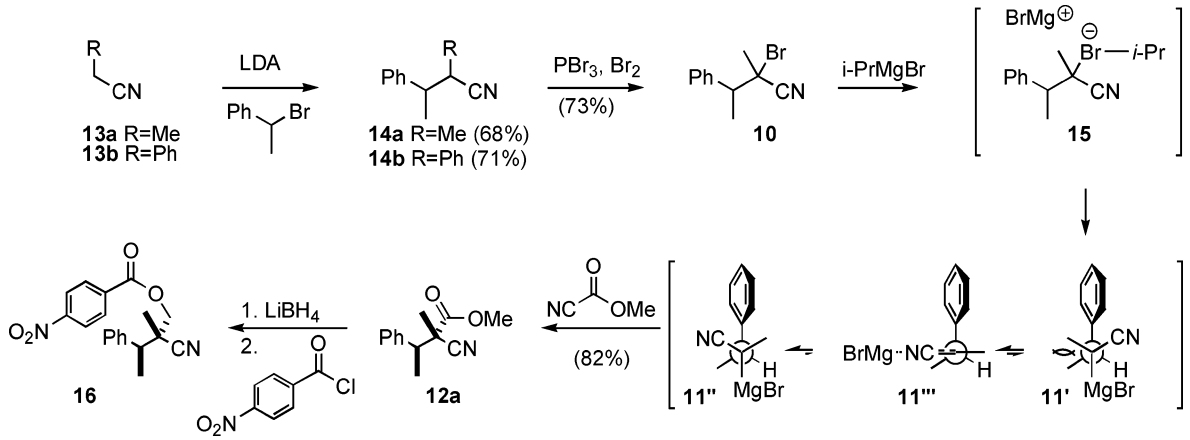
(28) For a related equilibration, see: Reich, H. J.; Medina, M. A.; Bowe, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 11003.

(29) (a) Carlier, P. R. *Chirality* **2003**, *15*, 340. (b) Koch, R.; Wiedel, B.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523.

(30) For a similar conformational analysis, see: (a) Fleming, I.; Lewis, J. *J. Chem. Soc. Chem., Commun.* **1985**, 149. (b) Crump, C. N. A. R.; Fleming, I.; Hill, M. H. J.; Parker, D.; Reddy, L. N. *J. Chem. Soc., Perkin. Trans. 1* **1992**, 3277.

(31) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

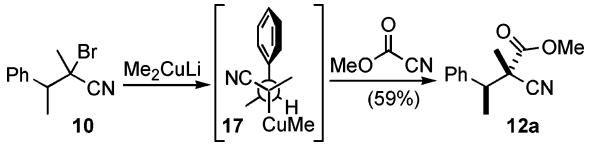
SCHEME 3. Diastereoselective Acylation of a *C*-Magnesiated Nitrile



Intercepting the *C*-magnesiated nitrile **11″** with a diverse range of electrophiles generates substituted nitriles with contiguous tertiary−quaternary centers (Table 1, column a). Exceptional diastereoselectivity is maintained with a range of electrophiles varying from relatively reactive carbonyl and silylchloride electrophiles (Table 1, entries 1−4) through cinnamyl bromide to the less reactive 4-pentenyl bromide (Table 1, entries 5 and 6, respectively). In each case, the alkylations were performed by adding *i*-PrMgBr to a −78 °C, THF solution containing bromonitrile **10** and the electrophile. Only a single diastereomer at the nitrile bearing carbon is obtained,[24] except in one instance where cyclohexanone was added and the reaction allowed to warm to room-temperature prior to protonation. Repeating the alkylation but protonating at −78 °C afforded only nitrile **12b** (Table 1, entry 2), implying that the stereochemical leakage was due to a retro-aldol−aldol type equilibration.[13a,33] The equilibration proved fortuitous because while **12b** was not crystalline the diastereomer afforded crystals suitable for X-ray crystallography, allowing assignment of the configuration of both diastereomers.[25]

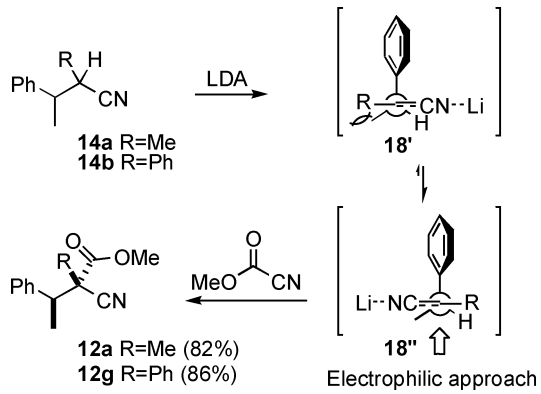
Exclusive formation of one diastereomer from the magnesiated nitrile alkylations stimulated an analogous alkylation of the *C*-cuprated nitrile **17** (Scheme 4).[34] Me_2CuLi directly engages bromonitriles in a bromine-copper exchange to afford *C*-cuprated nitriles with a reactivity profile similar to that of alkylcuprates.[18b] Sequential addition of Me_2CuLi and methyl cyanoformate to bromonitrile **10** afforded ester nitrile **12a** with complete stereochemical fidelity, consistent with a retentive alkylation of the *C*-cuprated nitrile **17** (Scheme 4).

SCHEME 4. Diastereoselective Acylation of a *C*-Cuprated Nitrile



Diastereoselective Alkylations of *N*-Metalated Nitriles. The exceptionally selective alkylations of the *C*-magnesiated nitrile **11″** and the *C*-cuprated nitrile **17** inspired a series of alkylations with the corresponding *N*-lithiated nitrile **18** (Scheme 5). Although *N*-lithiated nitriles are planar,[11,12] the phenethyl chirality was anticipated to favor rotamer **18″** over **18′**, with alkylation from **18″** occurring opposite the projecting phenyl group. Experimentally, intercepting the *N*-lithiated nitrile **18** with methyl cyanoformate generates a single diastereomer both for the methyl- and phenyl-substituted nitriles **14a** and **14b**[35] (Scheme 5). Alkylations of the *N*-lithiated nitrile **18** (R = Me) with the same series of electrophiles as those employed with the *C*-magnesiated nitrile **11**, afford a single diastereomer with exactly the same sense of 1,2-asymmetric induction (Table 1, column b). Increasing the steric demand by deprotonating and alkylating the α-phenyl-substituted nitrile **14b** similarly generates a single diastereomer with the same stereochemical preference as for **14a**. The 1,2-asymmetric induction is consistent with alkylation via a favored conformation similar to that observed with *C*-metalated nitriles (Scheme 5). Of the two possible

SCHEME 5. Diastereoselective Alkylations of *N*-Lithiated Nitriles



rotamers **18′** and **18″**, in which the phenyl group projects over the planar *N*-lithiated nitrile, the latter experiences the least steric compression since the small nitrile group occupies the more demanding gauche-like orientation. Electrophilic attack is thereby directed to conformer **18″** opposite the phenyl group.

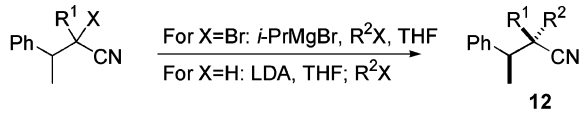
(32) Eliel, Ernest L.; Wilen, Samuel H.; Mander, Lewis N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−697.

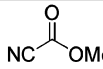
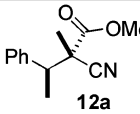
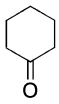
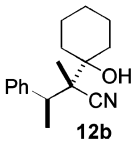
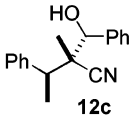
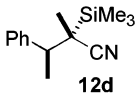
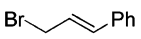
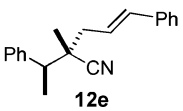
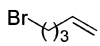
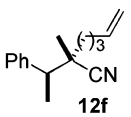
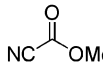
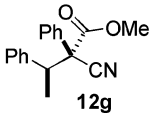
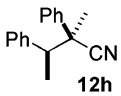
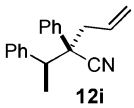
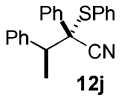
(33) (a) Carlier, P. R.; Lo, C. W.-S.; Lo, M. M.-C.; Wan, N. C.; Williams, I. D. *Org. Lett.* **2000**, *2*, 2443. (b) Liu, G.; Smith, T. C.; Pfander, H. *Tetrahedron Lett.* **1995**, *36*, 4979.

(34) For additional examples of *C*-cuprated nitriles, see: (a) ref 18b. (b) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc.* **1989**, *111*, 6474−6476. (c) Tsuda, T.; Nakatsuka, T.; Hirama, T.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1974**, 557. (d) Corey, E. J.; Kuwajima, I. *Tetrahedron Lett.* **1972**, 487.

(35) Nitrile **14b** was prepared by alkylating phenylacetonitrile with phenethyl bromide (Scheme 3, **13b→14b**).

TABLE 1. Diastereoselective Metalated Nitrile Alkylations

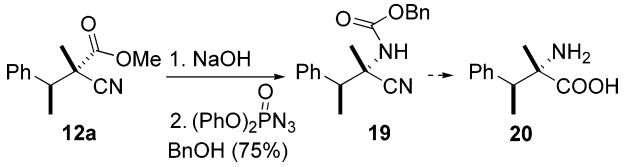


entry	R^1	electrophile	quaternary nitrile	yield (%) a[a]	yield (%) b[b]
1	Me		 **12a**	75[c]	88[c]
2	Me		 **12b**	66[c]	72[c]
3	Me	PhCHO	 **12c**	52[e]	78[e]
4	Me	Me_3SiCl	 **12d**	58[d]	79[d]
5	Me		 **12e**	79[e]	88[e]
6	Me		 **12f**	79[e]	79[e]
7	Ph		 **12g**	-	86[d]
8	Ph	MeI	 **12h**	-	80[d]
9	Ph		 **12i**	-	81[d]
10	Ph	$PhSSO_2Ph$	 **12j**	-	82[c]

[a] *i*-PrMgBr, R^2X, −78 °C. [b] LDA, R^2X, −78 °C. [c] The configuration was determined by X-ray crystallography of a derivative or diastereomer. [d] The stereochemical assignment is made by analogy. [e] The configuration is based on a chemical correlation with **16** as outlined in the Supporting Information.

The potential of this alkylation strategy is illustrated with the synthesis of the protected α-aminonitrile **19** (Scheme 6). Hydrolysis of ester-nitrile **12a** provides the corresponding acid that was subjected to a Curtius rearrangement by sequential

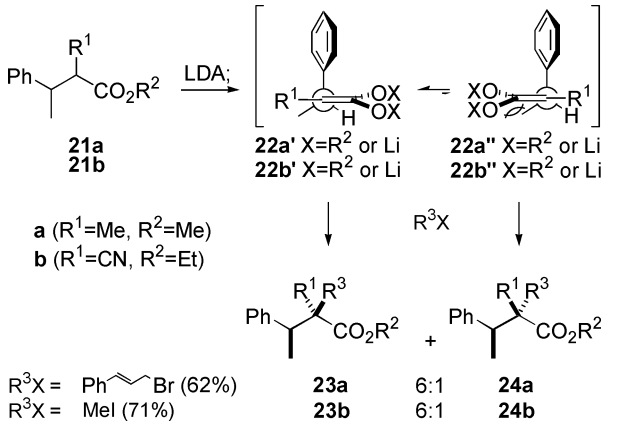
SCHEME 6. Potential Route to a Constrained α-Amino Acid



exposure to diphenyl phosphoryl azide, thermolysis, and addition of benzyl alcohol.[36] The resulting nitrile **19** is ideally suited for hydrolysis[37] to **20**, an amino acid targeted for conformationally constraining peptides.[38]

Consistent with the pictorial alkylation model for the *C*- and *N*-metalated nitriles, the alkylations of the corresponding esters **21a** and **21b** (Scheme 7) preferentially afford the opposite diastereomer! Deprotonating ester **21a**[39] and alkylating with cinnamyl bromide, generates the diastereomeric esters **23a** and **24a** in a 6:1 ratio.[40] Enolate **22a**, derived by deprotonating **21a**, differs significantly from the metalated nitriles **18** (Scheme 5) in projecting an alkoxy substituent toward the phenethyl group. Of the two resulting rotamers, **22a″** experiences drastic steric compression between the distal alkoxy substituent and the benzylic methyl group. Rotamer **22a′** relieves the Me-OX interaction at the expense of an additional Me-R^1 gauche-type interaction. Presumably, electrophilic attack on the sterically less-congested rotamer **22a′** predominates with competitive, but diminished, attack on rotamer **22a″**.

SCHEME 7. Diastereoselective Enolate Alkylations



The dominance of the ester enolate in controlling the alkylation selectivity is apparent from the analogous alkylation of the ester-nitrile **21b**[41] (Scheme 7). Intercepting the intermedi-

(36) Deprotonating nitrile **14a** and alkylating with DEAD installs an α-nitrogen substituent directly but attempts to reduce the N−N bond were uniformly unsuccessful.

(37) (a) Cativiela, C.; Dias-de-Villegas, M.; Galvez, J. A. *Tetrahedron Asymm.* **1994**, *5*, 261. (b) Cativiela, C.; Dias-de-Villegas, M.; Galvez, J. A.; Lapea, Y. *Tetrahedron* **1995**, *51*, 5921. (c) Cativiela, C.; Dias-de-Villegas, M.; Galvez, A. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1445.

(38) (a) Cromez Catalan, J.; Perez, J. J.; Jimenez, A. I.; Cativiela, C. *J. Pep. Sci.* **1999**, *5*, 251. (b) Davis, F. A.; Liang, C. H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. (c) Soloshonok, V A.; Tang, X.; Hruby, V. J.; Meervelt, L. V. *Org. Lett.* **2001**, *3*, 341. (d) Kazmierski, W. M.; Urbanczyk-Lipowska, Z.; Hruby, V. J. *J. Org. Chem.* **1994**, *59*, 1789.

(39) Prepared by sequential hydrolysis of nitrile **14a** with NaOH and alkylative esterification (K_2CO_3, MeI, 73% for two steps).

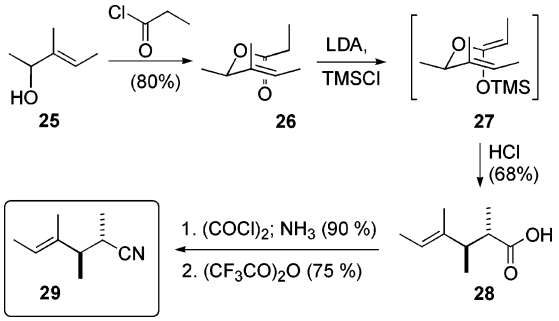
(40) The configuration of **24a** was chemically correlated with that of **12e** (Supporting Information).

(41) Prepared by alkylating ethyl cyanoacetate with phenethyl bromide in the presence of K_2CO_3 (72%).

ate enolate **22b** with methyl iodide installs the quaternary center with exactly the same 6:1 selectivity as observed for the alkylation of ester **21a**. The enolates derived from **21a** and **21b** share a common structural preference for **22′** since the steric demand of the enolate overrides the much smaller steric demand of either the methyl group, for **21a**, or the nitrile, for **21b**.

The exceptionally selective alkylations of the metalated phenethyl nitriles stimulated extending the same design features to nitrile **29**, a potentially attractive synthetic precursor for stereoselectively installing hindered quaternary centers (Scheme 8). Although nitrile **29** was synthesized as a racemate,[42] the strategy was guided by the potential for synthesizing either enantiomer of **25**[43] and relaying the hydroxyl configuration to the carbon stereocenters in **29**. Acylation of **25** provides ester **26** that was subjected to an Ireland−Claisen rearrangement[44] to efficiently install the two stereocenters in the intermediate acid **28**.[45] Conversion of the acid **28** to the amide[46] and dehydration with trifluoroacetic anhydride[47] provided nitrile **29** in an operationally simple sequence of reactions (Scheme 8).

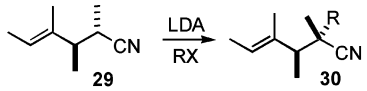
SCHEME 8. Synthesis of Nitrile 29: A Versatile Synthetic Precursor

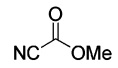
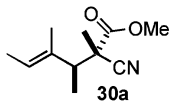
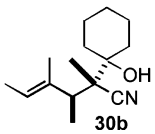
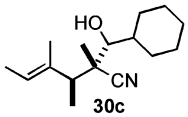
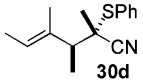
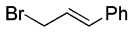
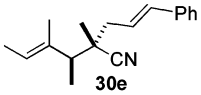
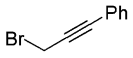
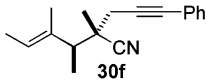
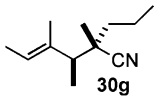
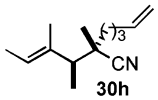
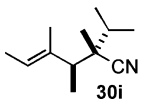


Alkylations of the lithiated nitrile derived from **29** are remarkably stereoselective (Table 2). Intercepting the lithiated nitrile with diverse electrophiles affords a single diastereomer at the nitrile bearing carbon in all cases. Trapping the intermediate lithiated nitrile with cyclohexenecarboxaldehyde affords the alkylated nitrile **30c** as a 1:1 mixture at the carbinol stereocenter but with complete stereochemical fidelity at the nitrile bearing carbon (Table 2, entry 3). Alkylations with allylic and propargylic bromides afford only S_N2 displacement products with no trace of S_N2' substitution (Table 2, entries 5 and 6). Exclusive stereocontrol is maintained in the alkylation with *i*-PrI, a carbon−carbon bond construction which stereoselectively installs a contiguous tertiary-quaternary-tertiary array (Table 2, entry 9).

Structural Requirements for Diastereoselective Alkylations of Acyclic Metalated Nitriles. Stereoselective alkylations of the substituted nitriles stems directly from the steric influence of the phenethyl group or the truncated trisubstituted alkene equivalent. The source of the stereoselectivity was probed by examining alkylations of structurally related nitriles with a relaxed molecular architecture. Nitrile **31** (Scheme 9) was prepared from 3-penten-2-ol via the same acylation-Claisen-dehydration sequence as for **25** (Scheme 8) to evaluate the steric demand required of the substituent projecting over the plane of the metalated nitrile; nitrile **31** is the *des*-methyl analogue of **29** in which a proton at carbon 4 substitutes for the methyl group. Deprotonating **31** and alkylating with propyl iodide

TABLE 2. Diastereoselective Alkylations of Nitrile 29



entry	electrophile	product[a]	yield (%)
1		 **30a**	58[b]
2		 **30b**	80
3		 **30c**	84 (1:1)
4	$PhSO_2SPh$	 **30d**	72
5		 **30e**	78
6		 **30f**	78
7		 **30g**	72
8		 **30h**	82
9		 **30i**	52

[a] The relative stereochemistry was assigned by analogy to stereochemical assignment determined for **30a**, entry 1. [b] The stereochemical assignment is based on the stereochemistry of a derivative of **30a** whose structure was determined by X-ray crystallography.

(42) Hull, C.; Mortlock, S. V.; Thomas, E. J. *Tetrahedron* **1989**, *45*, 1007.

(43) Chiral *β*-amino alcohols permit exceptionally stereoselective addition of Me_2Zn to aldehydes giving this type of allylic alcohol: Hayashi, M.; Kaneko, T.; Oguni, N. *Chem. Soc. Perkin Trans. 1* **1991**, 25.

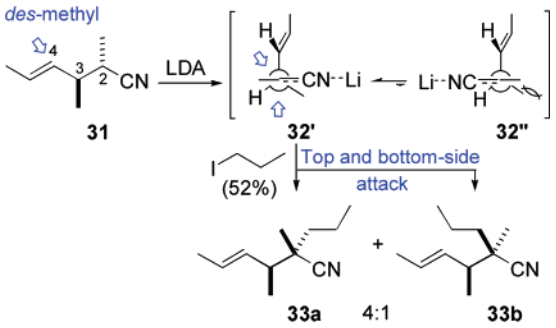
(44) (a) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Ireland, R. E.; Wipf, P.; Armstrong, D. J., III. *J. Org. Chem.* **1991**, *56*, 650.

(45) Dounay, A. B.; Gordon, J. F.; Akira, S.; Craig, J. F. *Tetrahedron* **2002**, *58*, 1865.

(46) (a) Hayashi, Y.; Shoji, M.; Yamaguchi, S.; Mukaiyama, T.; Yamaguchi, J.; Kakeya, H.; Osada, H. *Org. Lett.* **2003**, *5*, 2287. (b) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635. (c) Balsamo, A.; Barili, P. L.; Crotti, P.; Macchia, B.; Macchia, F.; Pecchia, A.; Cuttica, A.; Passerini, N. *J. Med. Chem.* **1975**, *18*, 842.

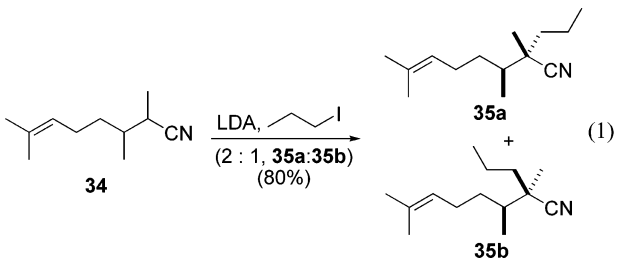
(47) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, *21*, 1813.

SCHEME 9. Probing the Structural Requirements for Selective Alkylation



affords two diastereomeric nitriles in a 4:1 ratio. The decreased selectivity, relative to **29**, is consistent with a less efficient steric screening of a proton on the top face of lithiated nitrile conformer **32′** compared to the methyl group in **29**. The diminished selectivity correlates with a preference for alkylation from conformer **32′** in which the small proton allows an electrophilic attack from both faces of the metalated nitrile.

The critical influence of an allylic chiral controller was further probed by relocating the olefin 2-carbons removed from the vicinal methyl groups. Alkylating **34**[48] with propyl iodide under identical conditions to those of **29** (Table 2) and **31** (Scheme 9) affords a 2:1 ratio of diastereomers **35a** and **35b** (eq 1). The low diastereoselectivity in the alkylation of **34** underscores the importance of allylic strain in relaying the chirality of the vicinal methyl groups into a sterically biased environment around the metalated nitrile.



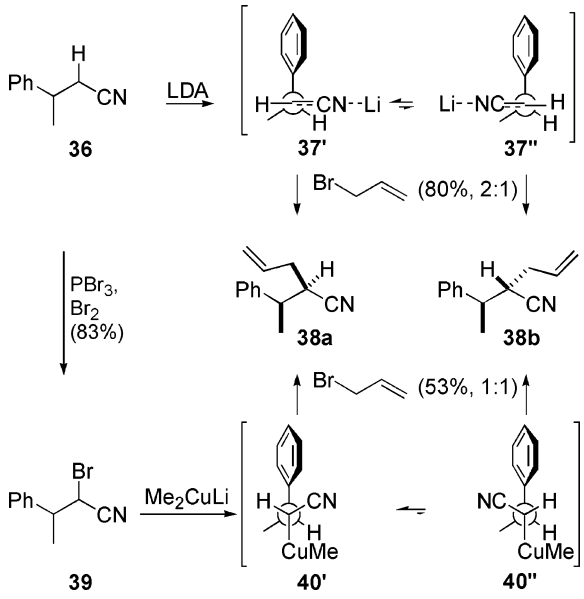
Substitution on the nitrile-bearing carbon is a second prerequisite for high diastereoselectivity in alkylations of these acyclic nitriles. Deprotonating the *des*-methyl 3-phenylbutenenitrile **36** (Scheme 10) with LDA and intercepting the intermediate lithiated nitrile **37** with allylbromide results in a 2:1 mixture of diastereomers **38a** and **38b**. Presumably the extremely small steric demand of the nitrile, a mere 0.2 kcal mol^{-1},[32] results in minimal steric discrimination between the rotamers **37′** and **37″**. Electrophilic attack on both conformers **37′** and **37″** opposite the phenyl group accounts for the slight preference for alkylation from **37′**.

Rapid proton transfer between lithiated nitriles and the alkylated product is a common complication in alkylations of metalated nitriles.[9b,49] Although no over-alkylation indicative of proton transfer was observed, deprotonation of **38** represents a viable mechanism for eroding the stereoselectivity. Proton transfer is suppressed in alkylations of the less-basic *C*-cuprated nitriles,[18b] and therefore, the *C*-cuprated nitrile **40** was prepared

(48) Obtained by alkylating 3,7-oct-6-enenitrile (a) with methyl iodide. (a) Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127.

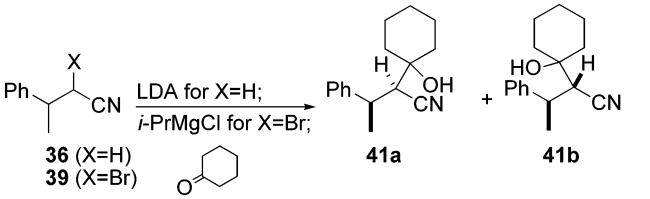
(49) For an expedient solution to rapid proton transfer with lithioacetonitrile, see: Taber, D. F.; Kong, S. *J. Org. Chem.* **1997**, *62*, 8575.

SCHEME 10. Alkylations of 3-Phenylbutyronitrile



by subjecting bromonitrile **39** to a bromine-copper exchange (Scheme 10). Unfortunately, intercepting the intermediate cuprated nitrile **40** with allyl bromide is completely unselective, suggesting the intervention of single electron-transfer processes that can lead to stereo-random alkylations with *C*-cuprated nitriles.[18b]

A complementary strategy to prevent proton transfers in alkylations of *N*- or *C*-metalated nitriles is to employ aldehyde or ketone electrophiles because the intermediate alkoxides do not equilibrate at −78 °C.[13a,33] Deprotonating **36** and intercepting the intermediate lithiated nitrile with cyclohexanone at −78 °C affords two diastereomeric nitriles **41a** and **41b** in a slightly improved 3.4:1 ratio (eq 2) compared to the corresponding allylations (Scheme 10). The modest selectivity increase may reflect the absence of proton transfers combined with a greater steric demand for cyclohexanone. Virtually identical stereoselectivity occurs by intercepting the corresponding magnesiated nitrile with cyclohexanone. The sense of asymmetric induction for the *C*-magnesiated nitrile derived from **39** is consistent with a preference for retentive alkylation from the more favored conformer (**40′** CuMe = MgX, Scheme 10).



Conclusion

Exceptional levels of diastereoselectivity are observed in alkylations of conformationally constrained *acyclic* nitriles containing vicinal dimethyl groups and an adjacent trisubstituted alkene or phenyl ring. Stereochemical control is derived from a preference for a reactive conformation in which allylic strain is avoided by positioning a methyl or phenyl group over the plane of the metalated nitrile. Extensive alkylations with a series

of *C*- and *N*-metalated nitriles are consistent with alkylation occurring opposite the projecting substituent which effectively screens the approach of an incoming electrophile.

The small size of the nitrile group is particularly important in controlling the sense of 1,2-asymmetric induction. Comparative alkylations of alkenenitriles and their esters analogues reveals the key structural requirements for high selectivity while providing a robust predictive model that accounts for the changeover in stereoselectivity observed in ester alkylations.

Alkylations of several structurally diverse metalated nitriles identify the precise molecular architecture required for highly selective alkylations of acyclic nitriles. The key requirement is a trisubstituted alkene or phenyl group bearing vicinal methyl groups within the nitrile chain. Collectively, the alkylations establish the molecular architecture required for high 1,2-asymmetric induction, address the long-standing challenge of diastereoselective alkylations with acylic metalated nitriles, and provide a versatile method for installing hindered quaternary centers with excellent stereoselectivity.

Experimental Section

General Nitrile Bromination Procedure. Neat bromine (1.1 equiv) and nitrile (1 equiv) were sequentially added to ice-cooled PBr_3 (1.1 equiv). The ice bath was removed and the reaction was then heated to 60 °C. After 5 h the mixture was poured onto ice, extracted with ether (3×), and then the crude extracts were washed with saturated, aqueous $NaHCO_3$ (3×), and water, and then dried ($MgSO_4$). Concentration and purification of the crude product by radial chromatography afforded analytically pure material.

Standard In Situ Exchange−Alkylation Procedure A. A THF solution of *i*-PrMgBr (1.05 equiv) was added to a −78 °C, THF solution of the bromonitrile (1.0 equiv) and the electrophile (1.05 equiv). After 3 h at −78 °C saturated, aqueous NH_4Cl was added, the crude product was extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford analytically pure material.

Standard Deprotonation−Alkylation Procedure. A THF solution of the nitrile (1.0 equiv) was added to a −78 °C, THF solution of LDA, generated from butyllithium (1.05 equiv) and diisopropylamine (1.15 equiv). After 50 min at −78 °C, neat electrophile (1.2 equiv) was added. After 3 h at −78 °C, saturated, aqueous NH_4Cl was added, the crude product was extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford analytically pure material.

General Bromine−Copper Exchange Procedure. A THF solution of the bromonitrile (1.0 equiv) was added to a 0 °C, ether solution of Me_2CuLi [generated by adding methyllithium (2.2 equiv) to copper iodide (1.2 equiv)]. After 1 h, the electrophile (1.3 equiv) was added neat and, after a further 2 h at 0 °C, saturated, aqueous NH_4Cl solution was then added. The mixture was stirred vigorously with exposure to air for 30 min, the crude product was extracted with ether and was then dried ($MgSO_4$). Concentration of the crude product and purification by radial chromatography afforded analytically pure material.

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Note Added after ASAP Publication. In the version published March 13, 2008, there was an error in the abstract and table of contents graphic; the corrected version was published March 14, 2008.

Supporting Information Available: Experimental procedures, ^1H NMR, and ^{13}C NMR spectra for all new compounds, and ORTEPs for all of the crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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