Asymmetric Induction

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Metalated Nitriles: Internal 1,2-Asymmetric Induction**

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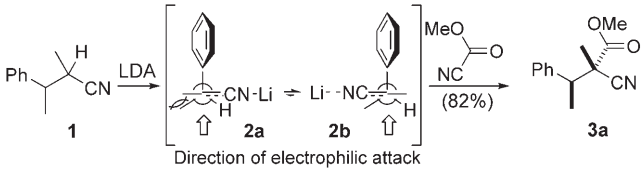
Installing quaternary asymmetric centers is a fundamental challenge in asymmetric synthesis.[1] Alkylation reactions creating quaternary centers from carbonyl derivatives typically combine controlled enolate formation within a sterically biased scaffold to direct electrophilic alkylations.[2] Chiral lactams and lactones[3] obviate selective (*E*)- or (*Z*)-enolate formation by employing small rings; they use strategically oriented substituents to impart topological differences to direct selective electrophilic attack on one face of the enolate. Asymmetric alkylations of acyclic α,α-disubstituted enolates are more challenging because of the difficulty in selectively generating one (*E*)- or (*Z*)-enolate and restricting conformational mobility for facial discrimination during alkylation.[4]

Stereoselective alkylations of acyclic nitriles are even more challenging.[5] The difficulty lies partly in the inherent bonding of metalated nitriles, which precludes direct attachment of a chiral auxiliary to the CN group, and partly in the site of metal coordination. Lithiated nitriles demonstrate an inherent propensity for coordination to the nitrile nitrogen atom,[6] which places lithium-bound chiral ligands relatively far away from the stereogenic "carbanion."[7] Despite these challenges, metalated nitriles remain ideal nucleophiles for installing quaternary centers because of their exceptional nucleophilicity and minimal steric demand.[8]

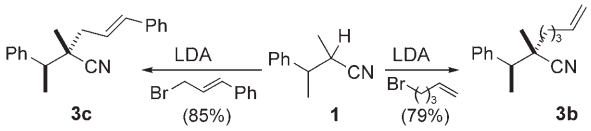
Intermittent alkylations of metalated nitriles bearing an adjacent chiral center induce modest to excellent stereoselectivity.[9] A highly selective allylation of a naphthyl-substituted butyronitrile[10] suggested the phenethyl-bearing nitrile **1**[11] as a viable candidate for diastereoselective alkylations. Deprotonating **1** with a lithium amide base is expected to generate an N-lithiated nitrile that is predisposed toward a conformation that minimizes the inherent allylic strain (Scheme 1).[12] Conformer **2a** incurs a Me–Me gauche-type interaction, whereas the analogous Me–CN interaction in **2b** is significantly smaller because of the extremely small steric demand of a nitrile group (the A value is a mere 0.2 kcal mol^{-1}).[13] Conformer **2b** minimizes the steric interactions with the benzylic methyl group by placing the small nitrile group in the more sterically demanding environment. This conformation projects the phenyl group over the planar,



Scheme 1. Diastereoselective alkylation of an N-metalated nitrile. LDA = lithium diisopropylamide; yield given in parentheses.

N-lithiated nitrile to favor electrophilic attack from the opposite face. Experimentally, deprotonation of the racemic nitrile **1** with subsequent addition of methyl cyanoformate affords **3a** as a single diastereomer.[14]

X-ray crystallography confirmed that the configuration of the newly installed quaternary center in **3a** was consistent with the alkylation model given in Scheme 1. Although the N metalation inherent in this predictive model is almost always favored with lithium counterions, unusual structural features[15] and ligand effects[16] sporadically lead to C-lithiated nitriles. C-metalated nitriles, particularly C-magnesiated nitriles, are capable of stereodivergent alkylations with alkyl halides (retention), methyl cyanoformate (inversion), and allylic halides (unselective), thus prompting alkylations of **2** with two additional test electrophiles.[17] Intercepting the lithiated nitrile **2** with 4-pentenyl bromide and cinnamyl bromide affords **3b** and **3c**, respectively, as single diastereomers[18] (Scheme 2) with asymmetric induction analogous to



Scheme 2. Investigation of alkylation selectivity with test electrophiles.

3a (Scheme 1). Installing the quaternary centers in **3a**–**c** with the same stereochemical sense is fully consistent with the sterically controlled alkylation of the N-lithiated nitrile via conformer **2b**.

The stereoselective alkylations of **1** stimulated analogous alkylations with **8** as a potentially attractive synthetic precursor for installing quaternary centers. Acylation of racemic alcohol **4**[19] provided the ester **5**; an Ireland–Claisen rearrangement then afforded acid **7** (Scheme 3).[20] Conversion to the corresponding amide with subsequent dehydration provided the requisite nitrile **8**. Sequential deprotonation and alkylation with methyl cyanoformate affords **9a** as a single nitrile diastereomer[14] with the same relative configuration as **3a** (Table 1, entry 1).

Excellent stereoselectivity is maintained in alkylations of nitrile **8** with a diverse array of electrophiles (Table 1). In each

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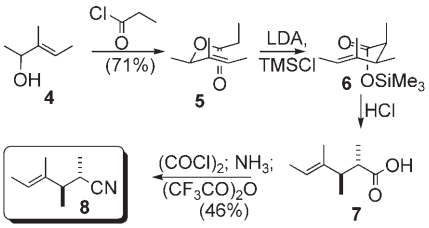
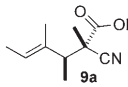
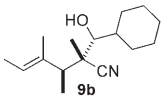
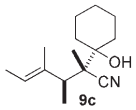
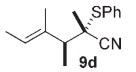
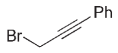
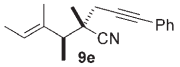
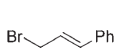
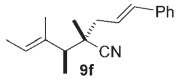
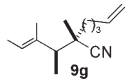
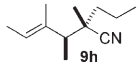
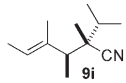


Scheme 3. Claisen rearrangement route to nitrile **8**. TMS = Me_3Si.

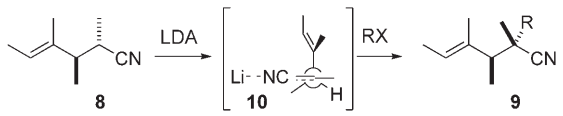
Table 1: Diastereoselective alkyations of nitrile **8**.

Entry	Electrophile	Quaternary nitrile[a]	Yield [%]
1		 **9a**	58
2		 **9b**	84[b]
3		 **9c**	80
4	$PhSO_2SPh$	 **9d**	72
5		 **9e**	79
6		 **9f**	78
7		 **9g**	82
8		 **9h**	72
9		 **9i**	52

[a] The configuration of **9a** was determined by derivatization followed by X-ray crystallography with the remaining stereochemical assignments made by analogy. [b] Oxidation affords a single ketone diastereomer.

instance, only one diastereomer is detectable in the crude reaction mixture, except with cyclohexanecarboxaldehyde, for which the stereoselectivity is maintained at the nitrile-bearing carbon atom with a 1:1 ratio of carbinol diastereomers (Table 1, entry 2). The alkylation is equally effective with reactive carbonyl electrophiles (Table 1, entries 1–3) as with less reactive alkyl halides (Table 1, entries 7–9). Intercepting the metalated nitrile with the secondary alkyliodide *i*PrI (Table 1, entry 9) is less efficient and probably reflects the increased steric demand accompanying the installation of a contiguous array of tertiary–quaternary–tertiary centers.

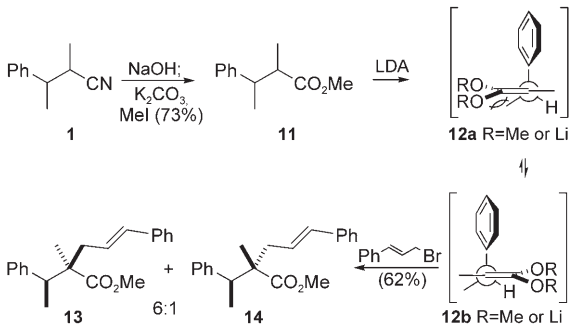
Mechanistically, the stereoselective alkylations of **8** are consistent with an electrophilic approach to rotamer **10** from the face opposite the alkene (Scheme 4). The trisubstituted alkene in **8** effectively acts as a truncated benzene ring (relative to **1**, which has a full phenyl ring), affording the



Scheme 4. Diastereoselective alkylations of lithiated nitrile **10**.

alkylated nitriles **9** with the same stereochemical sense as the alkylation of **1** to give **3** (Scheme 1).

In contrast to the exceptionally selective alkylations of nitriles **1** and **8**, alkylation of the analogous ester **11** affords **13** and **14** in a 6:1 ratio (Scheme 5).[21] Presumably, the modest



Scheme 5. Diastereoselective alkylations of ester **11**.

selectivity reflects a preferential electrophilic attack on the sterically less congested rotamer **12b**. Rotamer **12b** incurs a Me–Me gauche-type interaction, whereas the analogous Me–OR interaction in **12a** is significantly greater, because the enolate geometry forces the alkoxy substituent to project toward the benzylic methyl group.

Exceptional diastereoselectivity is observed in alkylations of appropriately substituted metalated nitriles. Embedding vicinal methyl groups in an alkyl chain containing a trisubstituted alkene, or a benzene ring, creates a strong bias for the stereoselective installation of quaternary stereocenters. Excellent stereoselectivity is maintained with a diverse range of electrophiles, providing the first general strategy for diastereoselective alkylations of acyclic nitriles.

Experimental Section

General deprotonation–alkylation procedure: The nitrile (1.0 equiv) in THF (0.3 M) was added to a solution of LDA, generated from butyllithium (1.05 equiv) and diisopropylamine (1.15 equiv), in THF (0.1 M) at −78 °C. 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.

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[1] *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.

[2] a) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105; b) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037.

[3] "Formation of C–C Bonds by Addition of Enolates to Carbonyl Groups": M. Braun in *Methoden der Organischen Chemie (Houben/Weyl) 4th ed. 1952–*, *Vol. E21a*, **1995**, pp. 1603–1666.

[4] For a recent approach, see: A. Arpin, J. M. Manthorpe, J. L. Gleason, *Org. Lett.* **2006**, *8*, 1359.

[5] Diastereoselective alkylations of acyclic nitriles typically incorporate heteroatoms for additional complexation: a) P. Gmeiner, E. Hummel, C. Haubmann, *Liebigs Ann.* **1995**, 1987; b) M. T. Reetz, F. Kayser, K. Harms, *Tetrahedron Lett.* **1994**, *35*, 8769.

[6] a) F. F. Fleming, B. C. Shook, *Tetrahedron* **2002**, *58*, 1; b) G. Boche, *Angew. Chem.* **1989**, *101*, 286; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277; .

[7] For leading references on the use of chiral ligands in metalated nitrile alkylations, see: a) Y. Suto, N. Kumagai, S. Matsunaga, M. Kanai, M. Shibasaki, *Org. Lett.* **2003**, *5*, 3147; b) R. P. Carlier, W.-F. Lam, C. N. Wan, D. I. Williams, *Angew. Chem.* **1989**, *101*, 2374; *Angew. Chem. Int. Ed.* **1998**, *37*, 2252; c) Q. A. Mi, Y. Z. Wang, Z. Y. Jiang, *Tetrahedron: Asymmetry* **1993**, *4*, 1957; d) K. Soai, Y. Hirose, S. Sakata, *Tetrahedron: Asymmetry* **1992**, *3*, 677.

[8] F. F. Fleming, Z. Zhang, *Tetrahedron* **2005**, *61*, 747.

[9] a) G. N. Varseev, M. E. Maier, *Org. Lett.* **2007**, *9*, 1461; b) Y.-J. Chen, L.-J. Gao, I. Murad, A. Verstuyf, L. Verlinden, C. Verboven, R. Bouillon, D. Viterbo, M. Milanesio, D. Van Haver, M. Vandewalle, P. J. De Clerq, *Org. Biomol. Chem.* **2003**, *1*, 257; c) T. Fujishima, L. Zhaopeng, K. Konno, K. Nakagawa, T. Okano, K. Yamaguchi, H. Takayama, *Bioorg. Med. Chem.* **2001**, *9*, 525; d) Y. Fall, C. Fernandez, V. González, A. Mouriño, *Synlett* **2001**, 1567; e) R. A. N. C. Crump, I. Fleming, J. H. M. Hill, D. Parker, N. L. Reddy, D. Waterson, *J. Chem. Soc. Perkin Trans. 1* **1992**, 3277.

[10] R. Gay, M. Maugras, *C. R. Hebd. Seances Acad. Sci.* **1962**, *255*, 2123.

[11] Although the alkylations were performed on a racemate, conjugate reduction yields chiral, β-substituted nitriles in high enantiomeric purity: D. Lee, D. Kim, J. Yun, *Angew. Chem.* **2006**, *118*, 2851; *Angew. Chem. Int. Ed.* **2006**, *45*, 2785.

[12] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.

[13] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 696–697.

[14] a) ^{1}H NMR spectroscopic analysis of the crude reaction mixture failed to identify any diastereomer; b) stereochemical assignment is based on X-ray crystallography of a derivative (see the Supporting Information).

[15] G. Boche, K. Harms, M. Marsch, *J. Am. Chem. Soc.* **1988**, *110*, 6925.

[16] R. Sott, J. Granander, G. Hilmersson, *J. Am. Chem. Soc.* **2004**, *126*, 6798.

[17] F. F. Fleming, Z. Zhang, G. Wei, O. W. Steward, *J. Org. Chem.* **2006**, *71*, 1430.

[18] The configurations of **3b** and **3c** were secured by chemical correlation with that of the ester nitrile **3a** as outlined in the Supporting Information.

[19] Employed as a racemate, although potentially available in either enantiomeric series: M. Hayashi, T. Kaneko, N. Oguni, *J. Chem. Soc. Perkin Trans. 1* **1991**, 25.

[20] R. E. Ireland, P. Wipf, D. J. Armstrong III, *J. Org. Chem.* **1991**, *56*, 650.

[21] The configuration of **14** was chemically correlated with that of **3c** (Scheme 2).

