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The First Enantioenriched Metalated Nitrile Possessing Macroscopic Configurational Stability

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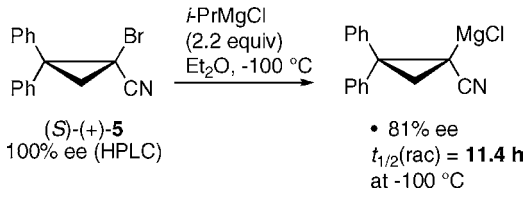
ABSTRACT



Magnesium–bromine exchange on enantiopure cyclopropyl bromonitrile 5 at −100 °C for 1 min followed by a D_2O quench gives the deuterionitrile in 81% ee (retention); additional trapping experiments establish $t_{1/2}$(rac) = 11.4 h at −100 °C. These experiments provide the first glimpse into the stereochemical aspects of Mg–Br exchange. The intermediate formed is the first metalated nitrile demonstrated to possess *macroscopic* configurational stability.

By virtue of their excellent nucleophilicity, metalated nitriles have found wide application in synthesis.[1] Metalated nitriles would prove even more useful if they could be generated as enantiopure reactive intermediates (e.g., **1**, **2**, Figure 1) that possess configurational stability on the *macroscopic*[2] time scale. Walborsky demonstrated that (*R*)-(−)-**3** was capable of highly retentive H/D exchange in 1.0 M NaOMe in CH_3OD at 50 °C,[3] indicating *microscopic* configurational stability of the sodium salt. This microscopic configurational stability is a consequence of carbanion pyramidalization, engendered by angle strain.[4] However, deprotonation of (*R*)-(−)-**3** by LDA in Et_2O gave an intermediate that racemized within 10 min at −78 °C.[5] This behavior clearly distinguishes lithiated **3** from metalated cyclopropanes lacking electron withdrawing groups, which are well-known to possess macroscopic configurational stability at temperatures as high as 35 °C.[6]

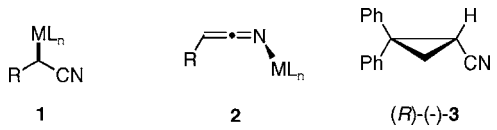


Figure 1. Chiral metalated nitriles **1** and **2**, and Walborsky's enantiopure cyclopropylnitrile **3**

In this Letter we confirm the microscopic configurational stability of the Na salt of **3**, and determine an upper bound for the racemization barrier of the rapidly inverting Li salt

(1) (a) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1−364. (b) Carlier, P. R.; Lo, K.-M.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511−7517. (c) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747−789.

(2) (a) Kapeller, D.; Barth, R.; Mereiter, K.; Hammerschmidt, F. *J. Am. Chem. Soc.* **2007**, *129*, 914−923. (b) Hoffmann, R. W.; Nell, P. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 338−340. (c) Schulze, V.; Hoffmann, R. W. *Chem. Eur. J.* **1999**, *5*, 337−344.

(3) Measured rate ratio k_{ex}/k_{rac} = 9.060: Walborsky, H. M.; Motes, J. M. *J. Am. Chem. Soc.* **1970**, *92*, 2445−2450.

(4) (a) X-ray crystallography of a related lithiated cyclopropylnitrile shows C-lithiation (e.g. **1**, Figure 1): Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925−6926. (b) Enantiopure acyclic nitriles undergo racemizing H−D exchange (ref 3).

(5) Walborsky, H. M.; Hornyak, F. M. *J. Am. Chem. Soc.* **1955**, *77*, 6026−6029.

(6) (a) Li Walborsky, H. M.; Impastato, F. J.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3283−3288. (b) Na Pierce, J. B.; Walborsky, H. M. *J. Org. Chem.* **1968**, *33*, 1962−1965. (c) Mg Walborsky, H. M.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3288−3296.

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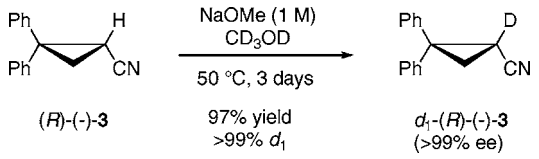
of **3**. Most importantly, we demonstrate macroscopic configurational stability of the Mg salt of **3** in diethyl ether at −100 °C (racemization $t_{1/2}$ = 11.4 h), indicating a racemization barrier of 14 kcal/mol.

To begin our investigations we resynthesized (*R*)-(−)-**3** and treated it with NaOMe in CD_3OD (Scheme 1).

Scheme 1. Enantiospecific H/D Exchange of **3**



After 3 days the reaction was quenched to reveal >99% deuteration and >99% ee, thus confirming the microscopic configurational stability of the sodium salt of **3**.[7] We then carried out numerous deprotonation/trapping experiments at temperatures as low as −135 °C. Regardless of the identity of base (LDA, LiHMDS, KHMDS), solvent (THF, Et_2O, Me_2O, toluene), and electrophile (MeI, BnI, D_2O), racemic products were obtained, even under in situ trapping conditions. An illustrative example: deprotonation of (*R*)-(−)-**3** by LDA in THF at −100 °C for 1 min, followed by D_2O quench gave a 91:9 mixture of d_1-**3** and **3**, in a combined <2% ee. Given that total racemization would require at least 5 half-lives, the upper bound for the racemization $t_{1/2}$ ($t_{1/2}$(rac)) is 12 s, indicating an inversion barrier of ≤11.1 kcal/mol at −100 °C.[8]

Recent work by Fleming and Knochel has established that halogen−metal exchange on α-halonitriles provides an excellent non-deprotonative route to lithiated and magnesiated nitriles.[9] Magnesiated nitriles in particular appeared attractive, as they might be expected to possess improved configurational stability.[10] We thus first prepared racemic bromoacid (±)-**4** from 1,1-diphenylethene, according to the literature procedure.[11] Resolution with (−)-brucine[12] and salt break gave (+)-**4**. Conversion to the primary amide and dehydration gave the desired bromonitrile (+)-**5**; X-ray crystallography established (*S*)-configuration, thus providing independent confirmation of the (*S*)-configuration of (+)-**4** (Scheme 2).[12]

Application of Fleming and Knochel's exchange/in situ trapping protocol was then carried out at −100 °C in Et_2O with 1.05 equiv of *n*-BuLi and 6 equiv of CH_3I (Table 1, entry 1). Unexpectedly, little of the desired methylation product **6a** was observed (32 mol %), and considerable amounts of protionitrile **3** (36 mol %) and bromonitrile **5** (32 mol %) were seen. Furthermore, not only were the products **6a** and **3** racemic, but the recovered starting material **5** also had significantly reduced enantiopurity. Interestingly, performance of the same reaction with CD_3I and a D_2O quench gave no deuteriontrile d_1-**3**, suggesting that the protionitrile **3** results from E2 elimination of the *n*-butyl bromide formed in the lithium−bromine exchange reaction

Scheme 2. Synthesis and Thermal Ellipsoid Plot (50% Probability) of Enantiopure Bromonitrile (*S*)-(+)-**5**

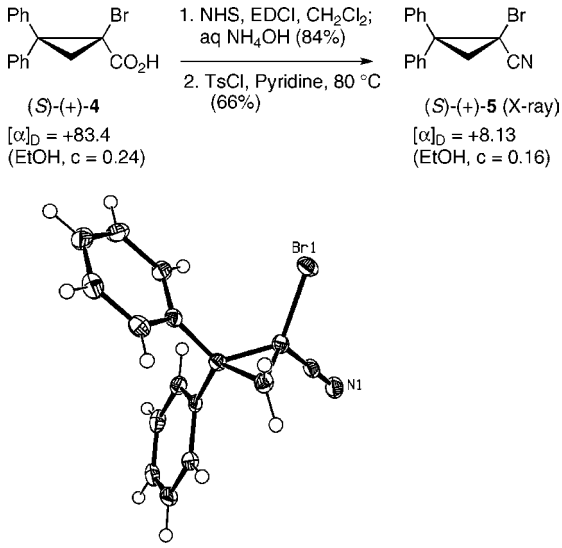
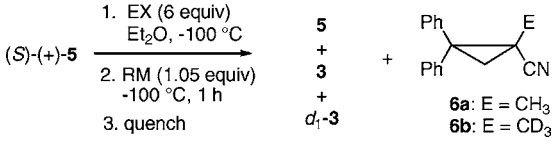


Table 1. Metal−Bromine Exchange/Trapping Reactions of **5**[a]



entry	RM	EX	quench	mol % **5** (% ee)	mol % **6** (% ee)	mol % **3**:d_1-**3** (% ee)
1	*n*-BuLi	CH_3I	NH_4Cl aq	32 (30 *S*)	32 (0)	36:0 (0)
2	*n*-BuLi	CD_3I	D_2O	23 (9 *S*)	52 (0)	25:0 (0)
3	*i*-PrMgBr	CD_3I	NH_4Cl aq	48 (>95 *S*)	6 (0)	46:0 (69 *R*)
4	*i*-PrMgBr	CD_3I	D_2O	37 (>95 *S*)	7 (0)	25:31 (72 *R*)

[a] Product ratios measured by ^1H NMR; % ee measured by chiral stationary phase HPLC (**5**, **6**: OD; **3**/d_1-**3**: AD). Note that the % ee of **3** and d_1-**3** cannot be deconvoluted by HPLC.

(Table 1, entry 2). It should be noted that these reactions are very clean and the product ratios are easily obtained from the ^1H NMR spectra of the crude products, due to the excellent spectral dispersion of the cyclopropyl ring protons in **3**, d_1-**3**, **5**, and **6**.[13]

(7) To the best of our knowledge this is the first preparation of enantiopure d_1-**3** using Walborsky's protocol; percent ee measured by chiral stationary phase HPLC.

(8) Eyring equation: Eyring, H. *Chem. Rev.* **1935**, *17*, 65−77.

(9) (a) Fleming, F. F.; Zhang, Z.; Knochel, P. *Org. Lett.* **2004**, *6*, 501−503. (b) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200−2205.

(10) For studies of the configurational stabilities of unstabilized primary alkyl organolithiums and organomagnesiums see: Witanowski, M.; Roberts, J. D *J. Am. Chem. Soc.* **1966**, *88*, 737−741.

(11) Baird, M. S.; Nizovtsev, A. V.; Bolesov, I. G. *Tetrahedron* **2002**, *58*, 1581−1593.

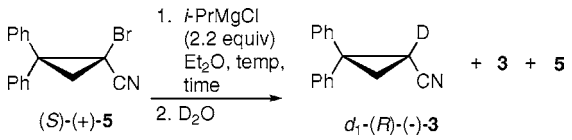
(12) Walborsky, H. M.; Barash, L.; Young, A. E.; Impastato, F. J. *J. Am. Chem. Soc.* **1961**, *83*, 2517−2525. Correlation performed by the quasi-racemate method; the absolute (*S*)-configuration of (+)-**4** is correctly noted in ref 6a.

Use of *i*-PrMgBr for Mg−Br exchange and CD_3I as electrophile gave dramatically different results (Table 1, entries 3 and 4). First of all, little alkylation product **6b** was recovered in either case. Thus the magnesionitrile derived from **5** is much less reactive than its lithium counterpart, magnesiated cyclopropanes lacking directly attached electron-withdrawing groups,[14] and other magnesiated nitriles.[9]

Second, use of D_2O as quench resulted in significant but not exclusive formation of the deuterionitrile d_1-**3** (Table 1, entry 4). Thus in the magnesium−bromine exchange reactions some metalated nitrile remains before addition of the quench. Third, the recovered bromonitrile **5** was found to retain enantiopurity. Last, and most importantly, the protio- and deuterionitriles **3** and d_1-**3** possess significant retention of configuration, suggesting increased configurational stabilility of the magnesiated cyclopropylnitrile relative to its lithium analogue.

Our inability to deconvolute the enantiopurities of protionitrile **3** and deuterionitrile d_1-**3**[15] prompted us to carry out magnesium−bromine exchange with 2.2 equiv of the Grignard reagent, so as to minimize participation of the magnesiated nitrile in elimination and thus improve the ratio of d_1-**3** to **3**. We found improved enantiopurities with *i*-PrMgCl and carried out a series of sequential exchange/deuteration experiments at −100 and −78 °C (Table 2).[16]

Table 2. Mg−Br Exchange/Deuteration Reactions of **5**[a] with USe of 2.2 equiv of *i*-PrMgCl



entry	temp (°C)	time (min)	mol % d_1-**3**:**3** (% ee, *R*)	mol % **5**
1	−100	1	90:6 (81)	4
2	−100	5	88:7 (79)	5
3	−100	30	89:7 (79)	4
4	−100	180	85:14 (67)	1
5	−78	1	90:7 (76)	3
6	−78	5	90:7 (75)	3
7	−78	30	88:8 (66)	4

[a] Product ratios measured by ^{1}H NMR; % ee measured by chiral stationary phase HPLC (**3**: AD; **5** OD).

As hoped, at −100 °C the use of 2.2 equiv of *i*-PrMgCl gave excellent conversion (95−99 mol %) and a predominance of deuterionitrile d_1-**3** relative to protionitrile **3**. These results are consistent with the idea that the excess Grignard reagent preferentially induced elimination of the *i*-PrX coproduct. As the delay (*t*) between the addition of the Grignard and when the deuterium quench increased, the enantiomeric excess of the combined protio- and deuterionitriles at −100 °C decreased from 81% (1 min, Table 2, entry 1) to 67% (180 min, Table 2, entry 4) suggesting slow racemization of the magnesionitrile.

By plotting ln(% ee(d_1-**3**/**3**)/100) vs time it is possible to estimate the rate of racemization[17] and similar studies were then carried out at −78 °C (Figure 2). In this way $t_{1/2}$(rac)

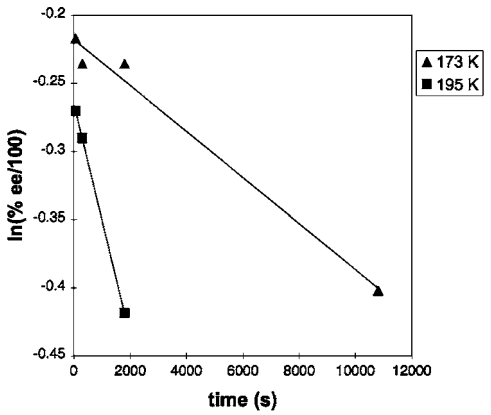


Figure 2. Plot of ln(% ee/100) of d_1-**3** and **3** vs delay time in Mg−Br exchange/deuteration experiments on (*S*)-(+)-**5** (Table 2).

of 11.4 ± 1 and 2.3 ± 0.1 h were determined at −100 and −78 °C, respectively. Application of the Eyring equation indicates a barrier to inversion of 14 kcal/mol at −100 °C. Extrapolation of the data in Figure 2 to the Y-intercept (time = 0 s) indicates (81 ± 1)% ee and (77 ± 1)% ee at −100 and −78 °C, respectively.[18] Thus Mg−Br exchange of **5** is **not** stereospecific, and enantioselectivity appears to deteriorate at higher temperature. Competition between stereospecific and racemizing exchange mechanisms may account for these results; the latter process could involve an electron-transfer chain mechanism.[19]

Attempts to alkylate the magnesiated nitrile at −100 and −78 °C with a variety of carbon electrophiles were unsuccessful. However, at −42 °C, a small amount (8 mol %) of racemic methylated nitrile **6a** was obtained by treatment of the magnesiated nitriles with MeOTf (6 equiv, 30 min, following a 2 min magnesium/bromine exchange) and a D_2O quench. Since d_1-**3** (72 mol %) and **3** (18 mol %) were recovered from this reaction in a combined 41% ee, it appears that methylation of the magnesiated cyclopropylnitrile is not only slow, but *racemizing*. Thus it is possible that methyl-

(13) See Figure S2 in the Supporting Information for an overlay of the ^{1}H NMR spectra of these compounds. No other products were observed in the ^{1}H NMR spectra of the crude products; mass balance following chromatography in these reactions ranged from 60% to 75%.

(14) (a) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351−352. (b) Kopp, F.; Sklute, G.; Polborn, K.; Marek, I.; Knochel, P. *Org. Lett.* **2005**, *7*, 3789−3791.

(15) The isotopomers co-elute on HPLC; attempts to determine the enantiopurity of protionitrile **3** apart from d_1-**3** by ^{1}H NMR (chiral lanthanide shift reagents, observation of the α-proton) were unsuccessful.

(16) Reactions with other Grignard reagents at −100 °C in Et_2O were also explored; EtMgBr and MeMgBr gave lower yields and enantioselectivities, whereas *t*-BuMgCl failed to promote exchange.

(17) Carlier, P. R.; Lam, P. C.-H.; DeGuzman, J.; Zhao, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2998−3002.

(18) Standard error; at the 95% confidence limit, the % ee values are 81 ± 3 (−100 °C) and 77 ± 4 (−78 °C), respectively (time = 0 s).

(19) Hoffmann, R. W.; Brönstrup, M.; Müller, M. *Org. Lett.* **2003**, *5*, 313−316.

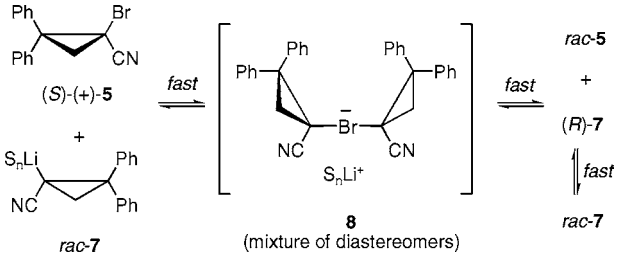
ation is occurring via an SET pathway,[20] rather than the S_E2-ret pathway that appears likely for protonation and deuteration. The extremely low nucleophilicity of the magnesiated cyclopropylnitrile relative to other magnesiated nitriles[9] is puzzling; we attribute the lack of reactivity to the steric bulk posed by the β,β-diphenyl substitution.

In contrast to the behavior seen with *i*-PrMgCl/Br, when lithium−bromine exchange of (*S*)-(+)-**5** was carried out with 2.2 equiv of *n*-BuLi for 1 min at −100 °C, followed by a D_2O quench, d_1-**3** (68 mol %) and **3** (31 mol %) were obtained as racemates. Use of *sec*-BuLi under these conditions again gave high conversion and a racemic outcome, affording d_1-**3** (94 mol %) and **3** (3 mol %). On the basis of our deprotonation/trapping experiments on (*R*)-(−)-**3**, we attribute the unfavorable outcome to rapid racemization of lithiated nitrile, rather than racemizing Li/Br exchange. If this is true we can again set an upper bound of 12 s for $t_{1/2}$(rac) of lithiated **3**, indicating a racemization barrier of less than 11.1 kcal/mol at −100 °C.

Finally, to account for the significant racemization of starting bromonitrile **5** seen in reactions employing only 1.05 equiv of *n*-BuLi (Table 1, entries 1 and 2), we considered the reaction of bromonitrile **5** and lithiated nitrile *rac*-**7** to transiently form ate complex **8** as a mixture of diastereomers (Scheme 3). Collapse of the ate complex would lead to **5** in racemic form or as the starting (*S*)-enantiomer; several cycles through the ate complex (coupled with rapid racemization of **7**) would lead to complete racemization of **5**.

To test this proposed mechanism we prepared *rac*-**7** by deprotonation of *rac*-**3** with LDA (1.1 equiv), and added it to 1 equiv of (*S*)-(+)-**5** at −100 °C in THF. After 30 min the reaction was subjected to protic quench, and bromonitrile **5** was recovered in 77% yield and 4% ee; the protionitrile **3** was recovered in 75% yield. Thus the lithiated nitrile induces

Scheme 3. Proposed Racemization Mechanism for (*S*)-(+)-**5**



racemization of bromonitrile **5**. At this point we cannot determine whether racemization of **5** is due to ate complex formation (Scheme 3) or an SET pathway. However, to date we have not detected any radical coupling products.

In conclusion, we have demonstrated that Mg−Br exchange on (*S*)-(+)-**5** produces a magnesiated nitrile that racemizes slowly at −100 °C ($t_{1/2}$(rac) = 11.4 h). Although this species has highly attenuated reactivity toward electrophiles, it represents the first example of a metalated nitrile possessing configurational stability on the macroscopic time scale. Finally, these experiments allow the stereoselectivity of Mg−Br exchange to be observed for the first time; further studies are in progress.

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Supporting Information Available: Synthetic procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225−230.