Asymmetric Synthesis

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Remarkable Configurational Stability of Magnesiated Nitriles**

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The nitrile group is an important structural feature in many natural products and pharmaceutical molecules used for the treatment of a diverse range of conditions.[1] In addition, nitriles play a key role in synthesis due to their ready conversion to many other functional groups and due to the ease of their deprotonation and electrophilic quench adjacent to the nitrile group. Our interest in alkaloid synthesis using nitrile anion chemistry[2] led us to wonder if it were possible to control the stereochemistry of the deprotonation–quench procedure to give enantiomerically enriched α-substituted nitriles.[3,4]

Fleming and co-workers have studied the diastereoselectivity on alkylation of metalated nitriles, revealing differences depending on whether a lithium or magnesium cation is used.[5] This was ascribed to differences in the structures of the lithiated and magnesiated intermediates.[6] With a lithium cation, there is a preference for a planar intermediate with the lithium coordinating to the nitrogen atom (Figure 1 a). However, with a magnesium cation, a *C*-metalated species can be formed (Figure 1 b, or Figure 1 c for a separated ion pair). This opens the possibility of forming enantiomerically enriched *C*-metalated nitriles and hence the potential for a new method for asymmetric synthesis.

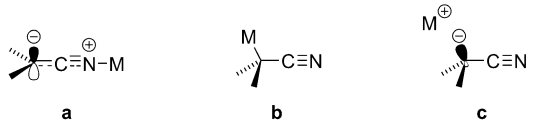
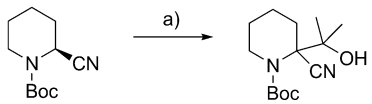


Figure 1. Some depictions of metalated nitriles.

At the outset of our work, the closest precedent was from Carlier and co-workers, who found that bromine–magnesium exchange provides a magnesiated cyclopropylnitrile that can maintain its configuration.[7] We decided to explore the proton abstraction of enantiomerically enriched nitriles with magnesium bases, followed by electrophilic quench to give enantiomerically enriched products. We report here the preliminary results of this study that have led to the formation of highly enantiomerically enriched substituted nitriles.

Initial studies focused on pipecolic acid-derived nitrile **1**, which was synthesized in two steps from *N*-Boc-pipecolic acid according to a literature procedure.[8] We were delighted to find (by chiral stationary phase GC on the crude reaction mixture) high values for the enantiomer ratio (e.r.) of the product **2** using magnesium bases (Table 1).[9]

Table 1: Metalation–acetone quench of nitrile **1**.



1 **2**

Entry	Base	Order of addition	*t* [s]	e.r.[a]
1	*i*PrMgCl	normal	5	82:18
2	*i*PrMgCl	inverse	5	96:4
3	TMPMgCl·LiCl	normal	5	74:26
4	TMPMgCl·LiCl	inverse	5	83:17
5	TMPMgCl	normal	5	92:8
6	TMPMgCl	inverse	5	93:7
7	TMPMgCl	normal	600	91:9

[a] Enantiomer ratio determined by CSP-GC. a) Base (1.2 equiv in THF), Et_2O, −107 °C, then, after time *t*, acetone, 30 min, then $NH_4Cl_{(aq)}$. TMP = 2,2,6,6-tetramethylpiperidine.

Two different methods of addition were tested: "normal" addition, where the base was added to a solution of the starting material in THF/Et_2O, and "inverse" addition where the starting material in a small amount of solvent was added to the base. Better enantiomer ratios of product **2** were achieved when using inverse addition, particularly in the absence of LiCl. Remarkably, high e.r. values were obtained even after leaving the reaction for 10 min before addition of acetone as the electrophile (Table 1, entry 7). However, only traces of product **2** were obtained in all cases. Due to the inability to isolate product **2** under these conditions, we were not able to determine its absolute stereochemistry. The low yield may be due to the reversibility of the reaction and the difficulty of quenching the organomagnesium species at low temperature (see Supporting Information). Other electrophiles gave similarly poor yields.

Therefore our attention turned to the nitrile **3a**, first reported by Takeda and co-workers to give very poor enantioselectivity (e.r. < 56:44) using LDA (lithium diisopropylamide; in THF, −78 °C) then BnBr as the electrophile,[10] although recently found to give improved results (e.r. 74:26) using LDA (Et_2O, −98 °C) and in situ EtOCOCN.[11] Addition of nitrile **3a** (e.r. 99:1) to a solution of TMPMgCl (Et_2O, −107 °C), followed after 2 min by addition of acetone gave the product **4a** with reasonable yield and e.r. (Scheme 1). Repetition using the brominated substrate **3b** (e.r. 97:3) gave

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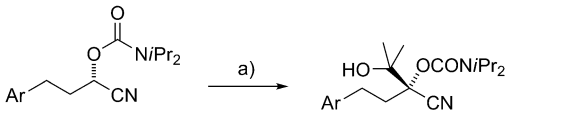
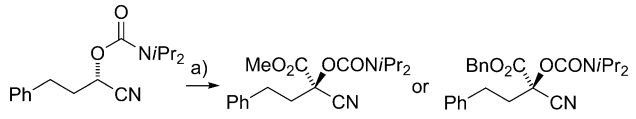


3a Ar = C_6H_5 50% **4a** e.r. 88:12
3b Ar = 4-BrC_6H_4 77% **4b** e.r. 80:20
(e.r. >99:1 after recryst.)

Scheme 1. Metalation–acetone quench of nitriles **3**. a) TMPMgCl (4 equiv) in Et_2O, −107 °C, then, after 2 min, acetone, 30 min, then $NH_4Cl_{(aq)}$ (e.r. determined by CSP-HPLC).

the product **4b**, in which single-crystal X-ray analysis revealed that reaction had occurred with retention of configuration (see Supporting Information).

These results are remarkable in that reasonable e.r. values can be obtained without the need for an in situ electrophilic quench. Therefore the organomagnesium intermediate must have appreciable configurational stability, at least at −107 °C. Attempts to conduct the reaction at −78 °C gave the product **4a** as a racemic mixture. As expected, however, using an in situ electrophile gave even higher enantioselectivities (Scheme 2). Thus, adding a mixture of the nitrile **3a** and



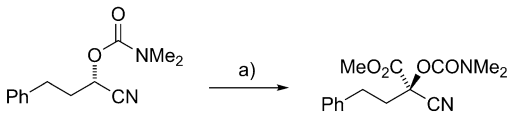
3a 40% **5** e.r. 91:9 52% **6** e.r. 91:9

Scheme 2. In situ metalation quench of nitrile **3a**. a) Nitrile **3a** and MeOCOCN or BnOCOCN added to TMPMgCl (3 equiv) in Et_2O, −107 °C, then, after 30 min, $NH_4Cl_{(aq)}$ (e.r. determined by CSP-HPLC).

methyl cyanoformate or benzyl cyanoformate to TMPMgCl at −107 °C resulted in the formation of the products **5** or **6** with good e.r. These reactions are assumed to proceed with inversion of configuration based on the results below.

While conducting this work, Takeda and co-workers reported that the less hindered nitrile **7** gave e.r. up to 90:10 using the base LDA with in situ EtOCOCN at −114 °C.[11] We therefore screened this substrate using magnesium bases. The base *i*PrMgCl gave none of the desired product, however TMPMgCl gave good results (Table 2). In situ IR spectroscopy[12] (Figure 2) revealed that three equivalents of TMPMgCl gave complete deprotonation in less than 2 min at −107 °C (the C=O stretch at 1724 cm^{-1} for **7** is replaced completely by a C=O stretch at 1660 cm^{-1} for the metalated compound). Best conditions were found using a mixture of the nitrile **7** with in situ electrophile added dropwise over 4 min to TMPMgCl at −107 °C. Using these conditions resulted in the product **8** with good yield and e.r. 97:3 (Table 2, entry 1). By adding MeOCOCN after 10 s (rather than in situ), a slightly lower e.r. was obtained (entry 2). Using a higher temperature of −78 °C, high e.r. was still obtained using the in situ method (entry 3), however racemization is fast under these conditions and poor selectivity is obtained

Table 2: Comparison of in situ and non-in situ quenches.



7 **8**

Entry	*T* [°C]	Method	Yield **8** [%]	e.r.[a]
1	−107	in situ	66	97:3
2	−107	10 s	71	92:8
3	−78	in situ	69	95:5
4	−78	10 s	69	59:41

[a] Enantiomer ratio determined by CSP-HPLC. a) For in situ: nitrile **7** (e.r. 99:1) and MeOCOCN added to TMPMgCl (3 equiv) in Et_2O/THF (1:1), −107 °C over 4 min, then, after 10 min, $NH_4Cl_{(aq)}$; for non-in situ: nitrile **7** (e.r. 99:1) added to TMPMgCl (3 equiv) in Et_2O/THF (1:1), −107 °C over 4 min, then, after 10 s, MeOCOCN added, then, after 10 min, $NH_4Cl_{(aq)}$.

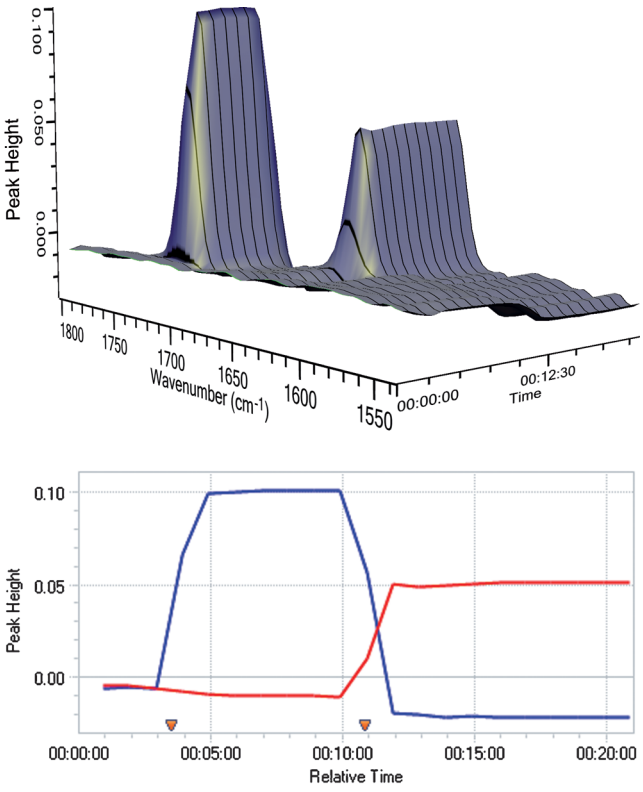
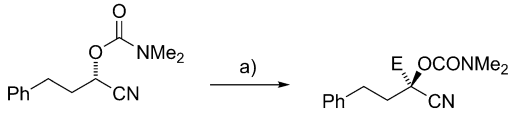


Figure 2. The in situ IR 3-D (top) and 2-D plots (bottom) of the metalation of **7** with 3 equiv TMPMgCl (added after ca. 10 min) at −107 °C. Lines represent the intensity of the C=O stretching frequency of **7** (peak at 1724 cm^{-1}; blue line) and of metalated **7** (peak at 1660 cm^{-1}; red line) over time.

without an in situ quench at −78 °C (entry 4). In each case the reaction proceeds with inversion of configuration, as judged by comparison of the specific rotation with that reported using EtOCOCN as the electrophile.[11]

The optimized conditions were then applied to a range of different electrophilic quenches (Table 3). The best electrophiles were the cyanoformates (entries 1–3), which gave good yields and excellent enantioselectivities under the in situ conditions. Benzoyl chloride gave a good yield but only

Table 3: Using the optimized conditions with different electrophiles.



7 **8–14**

Entry	Electrophile	E	Product	Yield [%]	e.r.[a]
1	MeOCOCN	CO_2Me	**8**	66	97:3
2	EtOCOCN	CO_2Et	**9**	75	92:8
3	BnOCOCN	CO_2Bn	**10**	65	97:3
4	PhCOCl	COPh	**11**	73	82:18
5	*t*BuCOCl	CO*t*Bu	**12**	73	50:50
6	$PhSSO_2Ph$	SPh	**13**	84	89:11[b]
7	MeI	Me	**14**	0	–

[a] Enantiomeric ratio determined by CSP-HPLC. [b] Reaction conducted at −78 °C, configuration of major enantiomer not determined. a) Nitrile **7** (e.r. 99:1) and electrophile added to TMPMgCl (3 equiv) in Et_2O/THF (1:1), −107 °C over 4 min, then, after 10 min, $NH_4Cl_{(aq)}$.

a moderate e.r. (entry 4), whereas pivaloyl chloride gave racemic product (entry 5). These acid chloride electrophiles are presumably slower reacting and give time for the intermediate to racemize. Remarkably, the electrophile $PhSSO_2Ph$ gave good yield and e.r., even at −78 °C (entry 6), although alkyl halides such as iodomethane were unsuccessful (entry 7). Attempts to form product **14** by transmetalation from magnesium to copper using CuI, CuCN or CuCN·2 LiCl followed by addition of iodomethane were also unsuccessful. The absolute configuration of the major enantiomer of products **9** and **11** was determined by comparison with the literature.[11] It is highly likely that products **8** and **10** are likewise formed by inversion of configuration. The absolute configuration of the sulfide **13** was not determined.

Kinetic experiments were conducted to determine the rate of enantiomerization of the organomagnesium species. By measuring the e.r. of the product **8** over time, it was possible to determine from a first-order plot (see Supporting Information) the value for the rate constant $k \approx 3 \times 10^{-4}\ s^{-1}$, equating to a half-life for enantiomerization, $t_{1/2} \approx 38$ min at −107 °C. Racemization was fast at −78 °C and the half-life for enantiomerization can be estimated as $t_{1/2} \approx 8$ s at −78 °C, which fits with the data in Table 2. The organomagnesium species has considerable configurational stability at lower temperatures. This stability may be aided by chelation of the magnesium to the carbonyl oxygen atom of the carbamate group.

In summary, we have developed a method for deprotonating an enantioenriched nitrile with a stereocenter α to the nitrile group using a magnesium base, which upon quenching with a variety of electrophiles gives high enantiomer ratios of the products in good yields. The reaction is best conducted using the electrophile in situ, although good e.r. values can remarkably even be obtained by forming the organomagnesium species first, followed by subsequent electrophilic quench.

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