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FULL PAPER

Steric Course of Deprotonation/Substitution of Chelating/Dipole-Stabilizing Group-Substituted α-Amino- and α-Oxynitriles

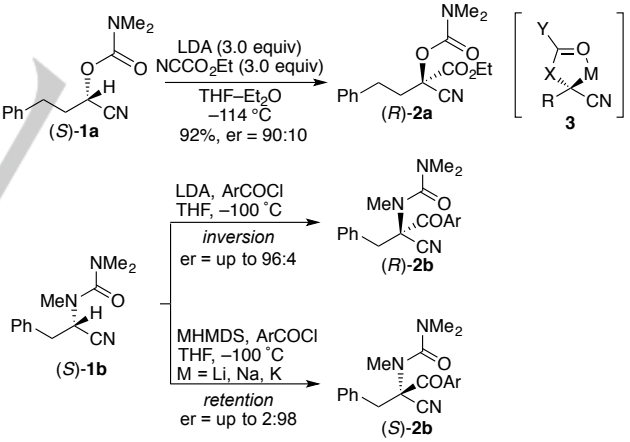
Michiko Sasaki,*[a],[‡] Rumiko Shimabara,[a] Tomo Takegawa,[a] Yuri Kotomori,[a] Yuko Otani,*[b] Tomohiko Ohwada,[b] Kei Takeda[a],[‡‡]

Abstract: The stereochemical course of electrophilic substitutions of α-nitrile metallocarbanions was investigated using deprotonation of enantioenriched α-amino- and α-oxynitriles bearing a carbamoyl or a methoxycarbonyl group in the presence of an electrophile. The results suggested that the dipole-stabilizing substituents can not only affect the configurational stability and chemical reactivity of α-nitrile metallocarbanions but also can change the steric course of the electrophilic substitution (retention vs inversion). While the reaction of α-aminonitrile bearing a dimethylaminocarbonyl group on the nitrogen atom with LiHMDS in the presence of PhCOCl resulted in the formation of a retention product (93:7), the case with that bearing a methoxycarbonyl group was reversed in favor of the inversion product (37:63). Thus, a methoxycarbonylamino group increases the degree of planarization of the anionic center with maintenance of the planar chirality more than does a ureido group, leading to preferable attack of an electrophile from the rear face.

Introduction

Electrophilic substitution reactions of α-heteroatom-substituted lithiocarbanions may proceed with retention or inversion of configuration depending on a variety of factors, including the nature of an electrophile and the presence or absence of a dipole-stabilizing group on the heteroatom.[1,2] Since the organolithiums used in these studies should be required to retain their configuration on the timescale of the reaction with an electrophile, benzyl-type, allyl-type, or benzyl-allyl type lithiocarbanions appear to be at the upper end of the range of applicability.[1a-d] More synthetically useful but much more configurationally labile lithiocarbanions next to a conjugative electron-withdrawing group have not been explored with a few exceptions.[3,4] If generation and enantioselective trapping of these kinds of lithiocarbanions become possible and the steric course of the electrophilic substitutions is understood, the foundations for a dramatic breakthrough in asymmetric synthesis would be provided.[5]

We recently reported that chiral acyclic α-nitrile metallocarbanions adjacent to a carbamoyloxy or ureido group have sufficient configurational stability to be trapped by a carbon electrophile with almost no loss of enantiopurity (Scheme 1).[6] Obviously, the success of this methodology relies on the capability of the chelating/dipole-stabilizing groups[7,8] to fix the configuration of chiral α-nitrile carbanions **3** and on *in situ* rapid trapping of the carbanion by an electrophile present in the system. Particularly noteworthy is base-dependent enantiodivergence observed in the ureido cases. Thus, LDA and MHMDS (M = Li, Na, K[9]) lead to the opposite enantioselectivity.[6c] For the stereochemical outcome, we have proposed a mechanistic rationale that involves participation of an electrophile through precomplexation to the counter cation of MHMDS during deprotonation.



Scheme 1. Generation and Trapping of Chiral α-Nitrile Carbanions by Carbon Electrophiles.

In this paper, we report the stereochemical results of deprotonation/benzoylation of α-amino- and α-oxynitriles **1a**-**1d** bearing a chelating/dipole-stabilizing group on the α-heteroatoms (Figure 1). Although it has been shown that carbamate-type dipole-stabilizing groups increase the configurational stability of α-heteroatom-substituted lithiocarbanions,[10] very little is known about the difference in the extents of stabilization among the groups. Furthermore, because of the unique structural feature of metalated nitriles, which can exist in several types involving *N*- and *C*-coordinated structures depending on the metal, the solvent,

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and the temperature,[11] a change in the counter cation from Li through Na to K[12] should influence both the configurational stability of the corresponding carbanions and the steric course. [13]

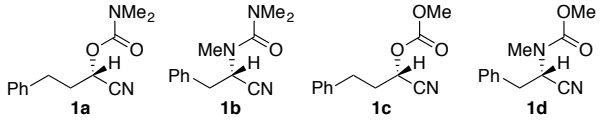
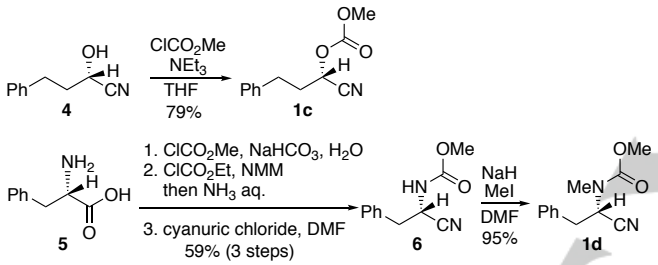


Figure 1. Chelating/Dipole-Stabilizing Group-Substituted α-Amino- and α-Oxynitriles.

Results and Discussion

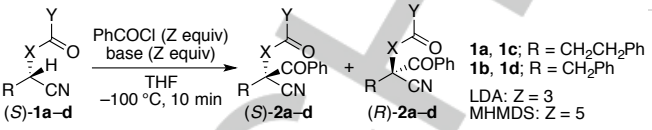
O-Methoxycarbonyl derivative (**1c**) and *N*-methoxycarbonyl derivative (**1d**) were prepared from (*S*)-2-hydroxy-4-phenylbutanenitrile **4** and L-phenylalanine **5**, respectively (Scheme 2).



Scheme 2. Preparation of **1c** and **1d**.

Deprotonation/benzoylation was carried out by adding an amide base to a cooled (–100 °C) THF solution of **1a**–**d** and benzoyl chloride. Although we reported the reactions of **1a** with LDA in the presence of $NCCO_2Et$ in THF-Et_2O (2:1) at –114 °C, in which 90:10 er was obtained (Scheme 1),[6a] the reactions were performed to secure comparability to results for **1b**–**d**. The results are shown in Table 1. The enantioselectivities observed varied from 50:50 to 1:99. Carbamoyl derivatives provided better enantioselectivity than did methoxycarbonyl derivatives (**1a** *vs* **1c** and **1b** *vs* **1d**). This observation is consistent with that by Pearson for α-aminocarbanions lacking an α-cyano group.[10] The results obtained with the reactions of **1b** and **1d** bring up an interesting point regarding the relation between enantioselectivity and a dipole-stabilizing group. Thus, while the use of **1d** in reactions with LDA resulted in high inversion selectivity (entry 13) like in the case with **1b**, reactions with MHMDS (M = Li, Na, and K) (entries 14-16) showed countercation-dependency of the ratio of retention products. Especially noteworthy is the fact that in the case of LiHMDS, the enantioselectivity (37:63) was reversed in favor of the (*R*)-isomer, an inversion product (entries 14 and 6). To obtain information about the effect of inorganic salts, which accumulate progressively in the reaction medium, we conducted the experiment on **1d** using 1.0 equiv of NaHMDS and 5.0 equiv of PhCOCl, providing (*S*)-**2d** and (*R*)-**2d** in 51% yield and 81:19 er, together with recovery of the starting material (23%). The er was almost the same as the case using 5.0 equiv each of the reagents.

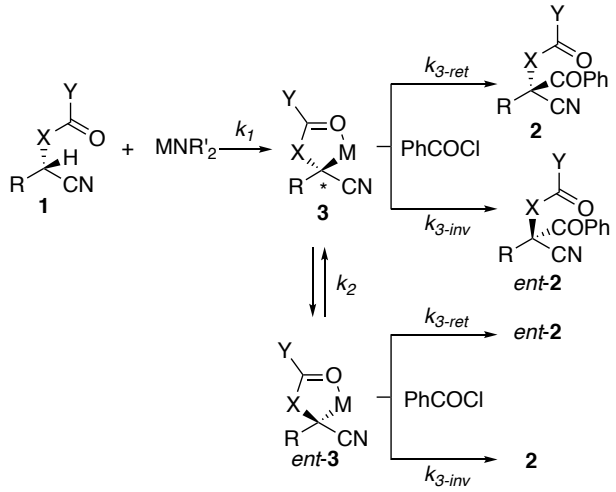
Table 1. In situ Deprotonation/Benzoylation of **1a-d** by Amide Bases.



entry	1	X	Y	base	yield (%)	*S*:*R*
1	**1a**	O	NMe_2	LDA	86	40:60
2	**1a**	O	NMe_2	LiHMDS	0	–
3	**1a**	O	NMe_2	NaHMDS	92	54:46
4	**1a**	O	NMe_2	KHMDS	92	53:47
5[a]	**1b**	NMe	NMe_2	LDA	88	1:99
6[a]	**1b**	NMe	NMe_2	LiHMDS	10	93:7
7[a]	**1b**	NMe	NMe_2	NaHMDS	97	99:1
8[a]	**1b**	NMe	NMe_2	KHMDS	81	99:1
9	**1c**	O	OMe	LDA	92	50:50
10	**1c**	O	OMe	LiHMDS	29	50:50
11	**1c**	O	OMe	NaHMDS	99	50:50
12	**1c**	O	OMe	KHMDS	95	50:50
13	**1d**	NMe	OMe	LDA	70	4:96
14	**1d**	NMe	OMe	LiHMDS	49	37:63
15	**1d**	NMe	OMe	NaHMDS	92	80:20
16	**1d**	NMe	OMe	KHMDS	92	91:9

[a] updated data from previously reported[6c]

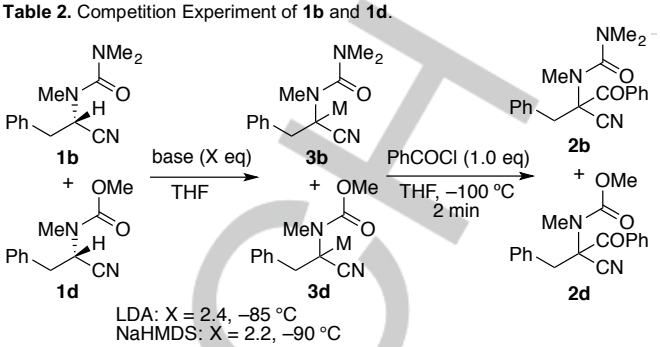
The major factors that determine the stereochemical outcome in the reaction of **1** should be (1) the configurational stability of a chiral metallocarbanion **3** (k_2) (Scheme 3), (2) the relative rates between reactions of **3** with an electrophile and racemization ($k_{3\text{-ret}}$, and $k_{3\text{-inv}}$ vs k_2), and (3) the steric course (retention or inversion) of the electrophilic substitution ($k_{3\text{-ret}}$ vs $k_{3\text{-inv}}$). Thus, the apparent enantioselectivity becomes lower when benzoyl chloride can react by competing retention and inversion pathways even if metallocarbanions **3** are configurationally stable on the time scale of the electrophilic quenching.



Scheme 3. Stereochemical Pathway of In Situ Deprotonation/Benzoylation of **1**.

Because in this reaction deprotonation is conducted in the presence of benzoyl chloride, regarding the above second item, a difference in the reactivity of the metallocarbanions toward benzoyl chloride, reflected by the rate constants k_3, should be considered. If metallocarbanions **3b** and **3d** are quenched by benzoyl chloride at different rates due to the different steric environments and electronic nature, the stereochemical outcome should be different even if **3b** and **3d** have the same configurational stability. Therefore, we decided to conduct competition experiments using **3b** and **3d**. When a mixture of **1b** (1.0 equiv) and **1d** (1.0 equiv) was treated with LDA (2.4 equiv) at –85 °C for 3 min followed by addition of 1.0 equivalent of PhCOCl, benzoylated products **2b** and **2d** were obtained in 34% and 65% yields together with recovery of the starting materials in 57% and 27% yields, respectively, indicating that **3d**–**Li** is more reactive than **3b**–**Li** (Table 2). Reaching completion of deprotonation before addition of PhCOCl was confirmed by the fact that the products and the starting materials recovered were completely racemic. A competition experiment using NaHMDS resulted in the formation of **2b** and **2d** in 12% and 79% yields along with 74% and 0% recoveries of the starting materials, respectively, indicating higher reactivity of **3d**–**Na** relative to **3b**–**Na**. Consequently, the decreased enantioselectivity in the reaction of **1d** cannot be attributed to an increased racemization originating from the lower reactivity of the carbanions **3d**.

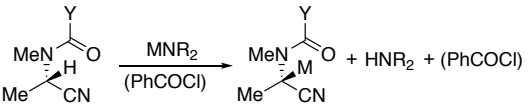
Table 2. Competition Experiment of **1b** and **1d**.



base	**2b** (**1b**)	**2d** (**1d**)
	yield (%)	yield (%)
LDA	34 (57)	65 (27)
NaHMDS	12 (74)	79 (0)

It is difficult to experimentally determine whether the lower enantioselectivity observed in **1d** than in **1b** is due to the lesser configurational stability of **3d** or the lowering of the stereoselectivity ($k_{3\text{-}ret}$ vs $k_{3\text{-}inv}$). In a previous paper,[6c] we proposed that the preference of a retention product observed in **1b** with MHMDS results from participation of PhCOCl through precomplexation to the counter cation (M^+) of less basic MHMDS[14] during deprotonation.[15,16] Thus, in the case of MHMDS, the transition state structures for electrophile-assisted deprotonation, which were obtained by DFT calculations for the model compound **7b** (Table 3), are more favorable than non-assisted ones. In sharp contrast to the results, both processes with LDA have almost the same energy barriers, which are very low. In order to gain insights into the difference in enantioselectivity between **1b** and **1d**, energetics for deprotonation with and without benzoyl chloride were examined using **7d** as model compounds and LDA, LiHMDS, and NaHMDS as a base (Table 3, results[6c] with **7b** are also shown for comparison). Contrary to expectations based on the observed reversal of enantioselectivity, in the case of **7d** with LiHMDS, the benzoyl chloride-assisted transition structures were more favorable than non-assisted ones (entries 3 and 4). The results obtained by using two different DFT hybrid functionals (B3PW91 and B3LYP) showed the same tendency. This discrepancy led us to focus on the structural differences between the metallo anionic species **8b** and **8d** that were obtained as products of deprotonation of **7b** and **7d** from the calculations (Table 3).

Table 3. Free energies of activation for PhCOCl-Assisted Deprotonation and Non-Assisted Deprotonation of **7b** and **7d**.



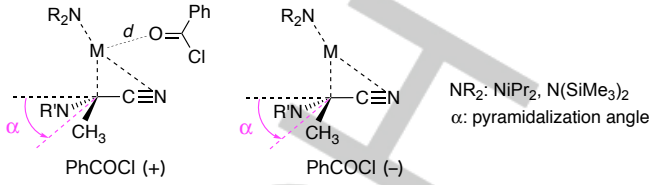
7b: Y = NMe_2 **8b**: Y = NMe_2
7d: Y = OMe **8d**: Y = OMe

entry	base	PhCOCl	**7d** (kcal/mol) [a]	**7b** (kcal/mol) [a]
1	LDA	+	2.5 (4.4)	–0.4 (0.5)
2	LDA	–	0.6 (2.2)	1.8 (3.6)
3	LiHMDS	+	9.0 (11.1)	10.6 (12.9)
4	LiHMDS	–	12.0 (11.4)	14.3 (16.6)
5	NaHMDS	+	8.8 (10.6)	10.0 (12.2)
6	NaHMDS	–	9.7 (12.0)	11.5 (14.0)

[a] $\Delta G^{\ddagger}_{(-100\,^{\circ}C)}$ at the level of IEFPCM (THF)-B3PW91/6-311++G(d,p)//B3LYP/6-31G(d). $\Delta G^{\ddagger}_{(-100\,^{\circ}C)}$ at the level of IEFPCM (THF)-B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) are shown in parentheses.

There are several intriguing structural aspects of a comparison of the intermediates with and without benzoyl chloride. Noteworthy is the deviation of the structure of the stereogenic carbon atom from a pyramidal geometry and the variations in the distances between the metal cation and the carbonyl oxygen atom of benzoyl chloride. Most striking is the case of **8d**-LiHMDS (without PhCOCl), where the pyramidalization angle (deformation angle)[17, 11c] is –9.0 °, which is in sharp contrast to the corresponding case of **8b**-LiHMDS (21.2 °) (Table 4, entries 10 and 4, Figure 2). This means that in the former, the anionic species has a slightly puckered geometry towards the lithium cation side and a considerable electron density at the rear face. Although the same trend was also found in the case of **8d**-NaHMDS **(**without PhCOCl) (–6.5 °) (entry 12), a remarkable difference in the distance between the metallo cation and the carbonyl oxygen (5.190 Å vs 2.425 Å) was observed in the corresponding PhCOCl-complexed intermediates **8d**-LiHMDS-PhCOCl and **8d**-NaHMDS-PhCOCl (entries 9 and 11, Figure 2). Consequently, an inversion product may be formed via planarization of the complexed intermediate (**8d**-LiHMDS-PhCOCl → **8d**-LiHMDS) followed by electrophilic quenching, probably because of the longer distance between the metallo cation and the carbonyl oxygen atom of the complexed benzoyl chloride and because of the lower reactivity of lithioanion than that of the corresponding sodio counterpart.

Table 4. DFT-Optimized Structures of the Metallo Anionic Species (B3LYP/6-31G(d)).



8b, **8d**

entry	**8**	base	PhCOCl	α (°)	d (Å)
1	**8b**	LDA	+	38.4	2.195
2	**8b**	LDA	–	18.1	–
3	**8b**	LiHMDS	+	43.9	4.826
4	**8b**	LiHMDS	–	21.2	–
5	**8b**	NaHMDS	+	28.0	2.438
6	**8b**	NaHMDS	–	29.2	–
7	**8d**	LDA	+	5.7	5.176
8	**8d**	LDA	–	6.1	–
9	**8d**	LiHMDS	+	43.4	5.190
10	**8d**	LiHMDS	–	–9.0	–
11	**8d**	NaHMDS	+	12.5	2.425
12	**8d**	NaHMDS	–	–6.5	–

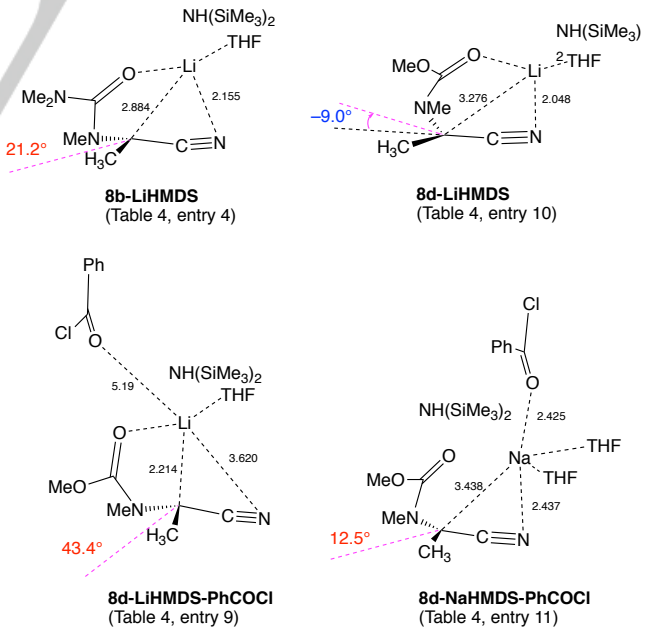
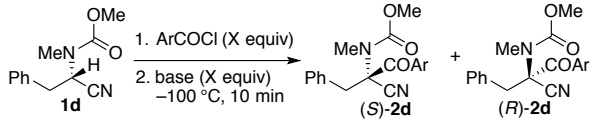


Figure 2. DFT-Optimized Structures of the metallo anionic species.

Since the above results suggested that the degree of participation of complexation of the electrophile with the metal can change depending on a base used, we performed reactions of **1d** with *p*-methoxybenzoyl chloride and *o*-chlorobenzoyl chloride, which have a stronger complexing but less electrophilic character and a weaker complexing but more electrophilic character, respectively.[18] The enantiomeric ratios with LDA and LiHMDS were hardly influenced by the electronic nature of the electrophiles (Table 5, entries 1-6). On the other hand, in reactions with NaHMDS, an obvious electrophile-dependent enantioselectivity was observed (entries 7-9). Thus, the ratio of retention versus inversion increases as the complexation ability of an electrophile increases from *o*-chlorobenzoyl chloride through benzoyl chloride to *p*-methoxybenzoyl chloride. The independency of the steric course on the complexation ability of an electrophile and the reversal of enantioselectivity observed with LiHMDS suggest that the precomplexation plays no important role in determining the selectivity.

Table 5. In Situ Deprotonation/Acylation of **1d** with Aroyl Chlorides.



entry	base	Ar-	**2d**	yield (%)	*S*:*R*
1	LDA	*p*-MeOC$_6$H$_4$-	**2d'**	82	6:94
2	LDA	C$_6$H$_5$-	**2d**	70	4:96
3	LDA	*o*-ClC$_6$H$_4$-	**2d"**	58	5:95
4	LiHMDS	*p*-MeOC$_6$H$_4$-	**2d'**	50	54:46
5	LiHMDS	C$_6$H$_5$-	**2d**	49	37:63
6	LiHMDS	*o*-ClC$_6$H$_4$-	**2d"**	49	44:56
7	NaHMDS	*p*-MeOC$_6$H$_4$-	**2d'**	97	90:10
8	NaHMDS	C$_6$H$_5$-	**2d**	92	80:20
9	NaHMDS	*o*-ClC$_6$H$_4$-	**2d"**	86	71:29

Conclusions

We have investigated the steric course of deprotonation/benzoylation of acyclic α-amino- and α-oxynitriles bearing a carbamoyl or a methoxycarbonyl group on the α-heteroatoms. The most relevant finding is that the steric course of deprotonation/substitution of (*S*)-**1**, retention or inversion, is variable depending on a subtle change in the carbonyl substituent on the α-nitrogen atom as well as the strength of the base used for deprotonation. These results indicate the importance of the stereochemical course, S$_E$2ret and S$_E$2inv, as a factor determining the stereochemical outcome in the deporotonation/substitution of α-nitrile carbanions as well as racemization associated with the configurational stability of the anionic center. The findings not only offer a potential for manipulating chiral α-nitrile carbanions in an enantioselective carbon-carbon bond formation but also open up new perspectives in asymmetric synthesis.

Experimental Section

General: All moisture-sensitive reactions were performed under a positive pressure of nitrogen. Anhydrous $MgSO_4$ was used for drying all organic solvent extracts in workup unless otherwise indicated, and removal of the solvents was performed with a rotary evaporator. Dry solvents and reagents were obtained by using standard procedures. Thin-layer chromatography was performed on precoated glass-backed silica gel 60 F-254 plates. For routine chromatography, the following adsorbents were used: silica gel 60N of particle size 63-210 μm or 40-50 μm. Liquid chromatography under medium pressures (MPLC) was carried out using prepacked columns (22 mm x 100 mm (5 μm silica gel) or 22 mm x 300 mm (10 μm silica gel)). ^{1}H NMR spectra (500 MHz) were taken in $CDCl_3$ with internal standards as follows: $CDCl_3$ (δ 7.26). ^{13}C NMR spectra (125 MHz) were taken in $CDCl_3$ with internal standards as follows: $CDCl_3$ (δ 77.2). The assignment of ^{1}H and ^{13}C NMR spectra was based on H-H decoupling and HMQC experiments.

Preparation of (*S*)-1-cyano-3-phenylpropyl methyl carbonate (1c): To a solution (25 °C) of (*S*)-2-hydroxy-4-phenylbutanenitrile **4**[6a] (600 mg, 3.72 mmol) and triethylamine (623 μL, 4.47 mmol) in THF (15 mL) was added methyl chloroformate (343 μL, 4.47 mmol). After being stirred at the same temperature for 1.5 h, the mixture was diluted with H_2O (20 mL) and AcOEt (20 mL). The aqueous phase was extracted with AcOEt (20 mL x 2). The combined organic phases were dried, filtered, and concentrated. The residual oil was subjected to column chromatography (silica gel (40–50 μm) 35 g, elution with *n*-hexane/AcOEt = 4:1) to give **1c** (645 mg, 79%, (98:2 er)) as a colorless oil. R_f = 0.34 (*n*-hexane:AcOEt = 4:1); $[\alpha]^{24}_D$ –40.8 (*c* 1.05, $CHCl_3$) (98:2 er); CHIRALPAK® AD-H (4.8 x 250 mm), *n*-hexane/EtOH = 100:3, flow rate 1.0 mL/min, detection at 220 nm, *tr* = 12.9 min (minor) and 16.5 min (major); IR (NaCl) 3029, 2960, 1762, 1445 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.20–2.36 (m, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 3.87 (s, 3H), 5.14 (t, *J* = 6.9 Hz, 1H), 7.19 (d, *J* = 7.1 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.30-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 30.6, 34.0, 56.0, 64.3, 116.5, 126.9, 128.5, 129.0, 138.9, 154.3; HRMS-ESI-LTQ Orbitrap (*m*/*z*): [M + Na]$^+$ calcd for $C_{12}H_{13}NO_3Na$ 242.0788, found 242.0786.

Preparation of (*S*)-1-cyano-3-phenylpropyl methyl carbonate (1d): To a solution (25 °C) of L-phenylalanine (2.0 g, 12.1 mmol) and $NaHCO_3$ (4.5 g, 53.3 mmol) in H_2O (16 mL) was added methyl chloroformate (1.4 mL, 18.2 mmol). After being stirred at the same temperature for 22.7 h, the mixture was diluted with CH_2Cl_2 (40 mL) and H_2O (10 mL), and the aqueous phase was extracted with

CH_2Cl_2 (20 mL x 2). The aqueous phase was acidified to pH 1 with 2 N HCl and extracted with AcOEt (20 mL x 3). The combined organic phases were washed with brine (10 mL), dried, filtered, and concentrated. The product was used in the following step without further purification. To a cooled (in an ice-salt bath) solution of the above crude product in THF (54 mL) was added *N*-methylmorpholine (1.30 mL, 11.8 mmol) and ethyl chloroformate (1.13 mL, 11.8 mmol). After being stirred at the same temperature for 30 min, aqueous NH_3 solution (4.7 mL) was added over a period of 7 min. After being stirred stirred for 1 h, CH_2Cl_2 (40 mL) was added and the phases were separated. The organic phase was successively washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated. *n*-hexane was added to the product and the heterogeneous solution was filtered and concentrated. The product was used in the following step without further purification. To a cooled (–30 °C) solution of the above crude product (2.1 g) in DMF (47 mL) was added cyanuric chloride (3.3 g, 17.7 mmol). After being stirred at the same temperature for 3 h, the mixture was diluted with cooled 0.5 M NaOH aqueous solution (60 mL) and extracted with AcOEt (30 mL x 3). The combined organic phases were successively washed with water (50 mL x 2) and brine (40 mL), dried over Na_2SO_4, and concentrated. The residual oil was subjected to column chromatography (silica gel (63–210 μm) 70 g, elution with *n*-hexane/AcOEt = 2:1) to give nitrile **6** (1.46 g, 59%, 3 steps) as a white solid. Recrystallization (*n*-hexane/AcOEt) gave colorless needles. R_f = 0.28 (*n*-hexane:AcOEt = 2:1); mp 104–105 °C; $[\alpha]^{27}_D$ –42.9 (*c* 0.52, $CHCl_3$); IR (KBr) 3317, 3062, 3035, 2971, 2936, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 50 °C) δ = 3.08 (dd, *J* = 13.9, 6.9 Hz, 1H), 3.13 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.72 (brs, 3H), 4.86 (brs, 1H), 4.90 (brs, 1H), 7.28 (d, *J* = 6.9 Hz, 2H), 7.30–7.40 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 39.2, 43.9, 53.2, 118.2, 128.2, 129.3, 129.7, 133.8, 155.7; HRMS-ESI-LTQ Orbitrap (*m*/*z*): [M + Na]$^+$ calcd for $C_{11}H_{12}N_2O_2Na$ 227.0791, found 227.0788.

To a cooled (0 °C) solution of **6** (1.00 g) and methyl iodide (2.45 mL, 39.2 mmol) in DMF (9.8 mL) was added NaH (60% dispersion in mineral oil, 196 mg, 4.90 mmol). The mixture was stirred at 0 °C for 30 min and then saturated NH_4Cl (30 mL) and AcOEt (30 mL) were added. The aqueous phase was extracted with AcOEt (30 mL x 3). The combined organic phases were successively washed with water (30 mL x 3) and brine (20 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel (40-50 μm) 60 g, elution with *n*-hexane/AcOEt = 2:1) to give **1d** (1.02 g, 95%, >99:1 er) as a colorless oil. R_f = 0.23 (*n*-hexane:CH_2Cl_2:Et_2O = 10:10:1); $[\alpha]^{25}_D$ –47.3 (*c* 1.06, $CHCl_3$) (>1:99 er); CHIRALPAK® AD-H (4.8 x 250 mm), *n*-hexane/EtOH = 20:1, flow rate 1.0 mL/min, detection at 220 nm, *tr* = 14.8 min (minor) and 17.2 min (major); IR (NaCl) 3031, 2956, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 2.96 (s, 3H), 3.05 (dd, *J* = 13.8, 7.6 Hz, 1H), 3.14 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.68 (brs, 3H), 5.32 (brs, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.8 and 31.1, 37.7 and 38.1, 49.9, 53.6, 117.2, 127.9, 129.0, 129.3, 134.3, 155.3 and 156.4; HRMS-ESI-LTQ Orbitrap (*m*/*z*): [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_2Na$ 241.0948, found 241.0948.

General Procedure for Acylation: Reaction of (*S*)-1d with NaHMDS and benzoyl chloride (Table 1, entry 15): To a cooled (–100 °C) solution of (*S*)-**1d** (13:87 er, 32.1 mg, 0.147 mmol) and benzoyl chloride (85 μL, 0.735 mmol) in THF (2.10 mL) was added dropwise a solution of NaHMDS (0.99 M in THF, 747 μL, 0.735 mmol) over a period of 6 min. The mixture was stirred at the same temperature for 10 min before addition of CH_3COOH (1.0 M in THF, 735 μL, 0.735 mmol). The mixture was diluted with Et_2O (10 mL) and saturated aq $NaHCO_3$ (10 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (10 mL x 2). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried, filtered, and concentrated. The residual oil was subjected to column chromatography (silica gel (40–50 μm) 13 g, elution with *n*-hexane/CH_2Cl_2/Et_2O = 10:10:1) to give **2d** (43.5 mg, 92%, 28:72 er) as a white solid.

2-Cyano-1-oxo-1,4-diphenylbutan-2-yl methyl carbonate (2c): 2c was obtained from **1c** (33.1 mg) using NaHMDS and benzoyl chloride in 99% yield (48.3 mg, 50:50 er) as a colorless oil. R_f = 0.31 (*n*-hexane:AcOEt = 4:1); CHIRALPAK® AD-H (4.8 x 250 mm), *n*-hexane/EtOH = 20:1, flow rate 1.0 mL/min, detection at 254 nm, *tr* = 13.1 min and 17.7 min; IR (NaCl) 3029, 2961, 1768, 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.48–2.66 (m, 2H), 2.97–3.10 (m, 2H), 3.82 (s, 3H), 7.18–7.25 (m, 3H), 7.27-7.32 (m, 2H), 7.49-7.53 (m, 2H), 7.62-7.67 (m, 1H), 8.08-8.12 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.3, 39.1, 56.3, 80.8, 115.9, 126.9, 128.5, 128.9, 129.2, 129.3, 131.9, 134.6, 139.0, 153.5, 188.8; HRMS-ESI-LTQ Orbitrap (*m*/*z*): [M + Na]$^+$ calcd for $C_{19}H_{17}NO_4Na$ 346.1050, found 346.1053.

Methyl (*S*)-(2-cyano-1-oxo-1,3-diphenylpropan-2-yl)(methyl)carbamate (2d): 2d was obtained from (*S*)-**1d** (13:87 er, 32.1 mg) using NaHMDS and benzoyl chloride in 92% yield (43.5 mg, 28:72 er). Recrystallization (*n*-hexane/AcOEt) gave colorless prisms. R_f = 0.35 (*n*-hexane:CH_2Cl_2:Et_2O = 1:1:0.1); mp 151 °C; $[\alpha]^{27}_D$ 86.2 (*c* 0.36, $CHCl_3$) (28:72 er); CHIRALPAK® AD-H (4.8 x 250 mm), *n*-hexane/EtOH = 20:1, flow rate 1.0 mL/min, detection at 254 nm, *tr* = 10.9 min (minor) and 14.5 min (major); IR (KBr) 3060, 3031, 3002, 2957, 1710, 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.71 (s, 3H), 3.51 (brs, 3H), 3.58 (d, *J* = 14.0 Hz, 1H), 3.78 (brd, *J* = 14.0 Hz, 1H), 7.25–7.40 (m, 5H), 7.42-7.48 (m, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.8, 40.6, 53.5, 67.6, 116.1, 128.1, 128.5, 128.7, 129.0, 130.7, 133.5, 133.8, 155.0, 189.1; HRMS-ESI-LTQ Orbitrap (*m*/*z*): [M + Na]$^+$ calcd for $C_{19}H_{18}N_2O_3Na$ 345.1210, found 345.1211.

General Procedure for Competition Experiment: To a cooled (–85 °C) solution of **1b** (23.4 mg, 0.10 mmol) and **1d** (22.1 mg, 0.10 mmol) in THF (1.70 mL) was added dropwise a solution of LDA (1.2 M in THF, 200 μL, 0.24 mmol) over a period of 5 min. The mixture was stirred at the same temperature for 3 min. The mixture was cooled to –100 °C before addition of a solution of benzoyl chloride (1.0 M in THF, 100 μL, 0.10 mmol). After being stirred at the same temperature for 2 min, CH_3COOH (1.0 M in

THF, 240 μL, 0.24 mmol) was added. The mixture was diluted with Et_2O (10 mL) and saturated aq $NaHCO_3$ (10 mL). The aqueous phase was extracted with Et_2O (10 mL x 2). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried, and concentrated. The residual mixture of yellow solid and oil was subjected to column chromatography (silica gel (40–50 μm) 13 g, elution with *n*-hexane/CH_2Cl_2/Et_2O = 10:10:1) to give **2b** (11.5 mg, 34%) as a white solid and **2d** (21.1 mg, 65%) as a white solid. **1b** (13.3 mg, 57%) and **1d** (5.9 mg, 27%) were recovered.

Methyl (*S*)-(2-cyano-1-(4-methoxyphenyl)-1-oxo-3-phenylpropan-2-yl)(methyl)carbamate (2d'): 2d' was obtained from **1d** (33.7 mg) using NaHMDS and *p*-methoxybenzoyl chloride in 97% yield (52.9 mg, 10:90 er). Purification by MPLC (elution with *n*-hexane/CH_2Cl_2/Et_2O = 1:1:0.1) gave **2d'** (Ar = 4-$MeOC_6H_4$) as a white solid. R_f = 0.23 (*n*-hexane:CH_2Cl_2:Et_2O = 1:1:0.1); mp 113–114 °C; $[\alpha]^{28}_D$ 118.3 (*c* 1.00, $CHCl_3$) (10:90 er); CHIRALPAK® AD-H (4.8 x 250 mm), *n*-hexane/EtOH = 10:1, flow rate 1.0 mL/min, detection at 254 nm, *tr* = 14.8 min (minor) and 28.3 min (major); IR (KBr) 2998, 2966, 1704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.71 (s, 3H), 3.49-5.57 (m, 4H), 3.77 (brd, *J* = 14.0 Hz, 1H), 3.86 (s, 3H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.25–7.39 (m, 5H), 7.89 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.7, 40.5, 53.4, 55.6, 67.5, 114.0, 116.3, 126.1, 128.0, 128.9, 130.7, 130.9, 133.9, 155.0, 163.8, 187.3; HRMS-ESI-LTQ Orbitrap (*m*/*z*): [M + Na]$^+$ calcd for $C_{20}H_{20}N_2O_4Na$ 375.1315, found 375.1318.

Methyl (*S*)-(1-(2-chlorophenyl)-2-cyano-1-oxo-3-phenylpropan-2-yl)(methyl)carbamate (2d"): 2d" (Ar = 2-ClC_6H_4) was obtained from **1d** (33.6 mg, 0.154 mmol) using LDA and *o*-chlorobenzoyl chloride in 58% yield (31.6 mg, 95:5 er). Purification by MPLC (elution with *n*-hexane/CH_2Cl_2/Et_2O = 1:1:0.05) gave **2d"** (Ar = 2-ClC_6H_4) as a white solid. R_f = 0.38 (*n*-hexane:CH_2Cl_2:Et_2O = 1:1:0.1); mp 124–125 °C; $[\alpha]^{27}_D$ –202.6 (*c* 0.90, $CHCl_3$) (92:8 er); CHIRALCEL® OD-H (4.8 x 250 mm), *n*-hexane/*i*PrOH = 20:1, flow rate 1.0 mL/min, detection at 254 nm, *tr* = 8.9 min (major) and 15.0 min (minor); IR (KBr) 3033, 2963, 1723, 1691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.66 (s, 3H), 3.61 (s, 3H), 3.61–3.70 (brs, 1H), 3.80 (brs, 1H), 7.25–7.44 (m, 7H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.70 (dd, *J* = 7.8, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.3, 40.2 and 41.5, 54.0, 68.5, 116.1, 126.0, 128.2, 128.6, 129.0, 130.6, 131.8, 132.5, 133.6, 155.8, 190.1; HRMS-ESI-LTQ Orbitrap (*m*/z): [M + Na]$^+$ calcd for $C_{19}H_{17}ClN_2O_3Na$ 379.0820, found 379.0825.

Computational Methods: We carried out computational studies by using the Gaussian 09 suites of programs.[19] The geometries of the reactants, reactant complexes, intermediates, transition states, and products for deprotonation reaction and S_E2 reaction were fully optimized using the B3LYP/6-31G(d) level. Two coordination structures of a base and a reactant were considered: (i) coordination of the base metal (Li^+ in the case of LDA and LHMDS or Na^+ in the case of NaHMDS) to the urea carbonyl oxygen atom of the reactant (Coordination of the metal to the nitrile nitrogen atom sometimes simultaneously occurs.) and (ii) coordination of the base metal to the urea carbonyl oxygen atom of the reactant and simultaneously to the carbonyl oxygen atom of a model electrophile, i.e., benzoyl chloride PhCOCl. All of the stationary points in the paper were located at the level of B3LYP/6-31G(d), and frequency calculations were then performed at those geometries to confirm one or zero imaginary frequency and to determine the free energy correction to electronic energy at -100 °C. The zero-point vibrational energy corrections were done without scaling. Intrinsic reaction coordinate (IRC) computations of the transition structures verified the reactants, intermediates, and products on the potential energy surface (PES). Then single point energies were calculated at the levels of B3PW91/6-311++G(d,p) and B3LYP/6-311++G(d,p) on the basis of the B3LYP/6-31G(d) optimized structures. Bulk solvation effects (self-consistent reaction field, SCRF) in THF were simulated implicitly during single point energy calculations through the integral equation formalism polarizable continuum model (IEFPCM). [20] Here we present the activation free energies obtained by single point calculations at the levels of IEFPCM (THF) - B3PW91/6-311++G(d,p) and IEFPCM (THF) - B3LYP/6-311++G(d,p) on the basis of B3LYP/6-31G(d) optimized structures.

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[1] a) R. E. Gawley in *Stereochemical Aspects of Organolithium Compounds, Topics in Stereochemistry*, *Vol. 26* (Eds.: R. E. Gawley, J. Siegel), Wiley, **2010**, ch. 3; b) J. Clayden, *Organolithiums*; *Selectivity for Synthesis*; Pergamon; Oxford; **2002**; c) A. Basu, S. Thayumanavan, *Angew. Chem. Int. Ed.* **2002**, *41*, 716-738; d) H. Ikemoto, M. Sasaki, M. Kawahata, K. Yamaguchi, K. Takeda, *Eur. J. Org. Chem.* **2011**, 6553-6557; e) R. E. Gawley, E. Low, Q. Zhang, R. Harris, *J. Am. Chem. Soc.* **2000**, *122,* 3344-3350; f) R. E. Gawley, *Tetrahedron Lett.* **1999**, *40*, 4297-4300; g) A. Carstens, D. Hoppe, *Tetrahedron* **1994**, *50*, 6097-6108.

[2] a) N. C. Faibish, Y. S. Park, S. Lee, P. Beak, *J. Am. Chem. Soc*. **1997**, *119*, 11561-11570; b) D. Hoppe, D. F. Marr, M. Brüggemann In *Organolithiums in Enantioselective Synthesis* (Eds.: D. M. Hodgson) Springer, New York; **2003**; pp. 61–137.

[3] For α-amino acid esters or cyclic amides, Kawabata, Carlier and others have proposed the concept of memory of chirality or self-regeneration of stereocenters. a) T. Kawabata, K. Yahiro, K. Fuji, *J. Am. Chem. Soc*. **1991**, *113*, 9694-9696; b) D. Seebach, D. Wasmuth, *Angew. Chem. Int. Ed.* **1981**, *20*, 971; c) P. R. Carlier, H. Zhao, J. DeGuzman, P. C.-H. Lam, *J. Am. Chem. Soc*. **2003**, *125*, 11482-11483; d) M. Branca, D. Gori, R. Guillot, V. Alezra, C. Kouklovsky, *J. Am. Chem. Soc.* **2008**, *130*, 5864-

5865; e) M. Branca, S. Pena, R. Guillot, D. Gori, V. Alezra, C. Kouklovsky, *J. Am. Chem. Soc.* **2009**, *131*, 10711-10718.

[4] For enantioselective trapping of a cyclopropanenitirile carbanion, see: a) H. M. Walborsky, A. A. Youssef, J. M. Motes, *J. Am. Chem. Soc*. **1962**, *84*, 2465-2466; b) H. M. Walborsky, J. M. Motes, *J. Am. Chem. Soc*. **1970**, *92*, 2445-2450; c) F. F. Fleming, Z. Zhang, *Tetrahedron* **2005**, *61*, 747-789; d) P. R. Carlier, Y. Zhang, *Org. Lett*. **2007**, *9*, 1319-1322; e) N. N. Patwardhan, M. Gao, P. R. Carlier *Chem. Eur. J*. **2011**, *17*, 12250-12253.

[5] C. Wolf, *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, Royal Society of Chemistry, Cambridge, UK, **2008**.

[6] a) M. Sasaki, T. Takegawa, H, Ikemoto, M. Kawahata, K. Yamaguchi, K. Takeda, *Chem. Commun.* **2012**, *48*, 2897-2899; b) M. Sasaki, K. Takeda, *Synlett*, **2012**, *23*, 2153-2164; c) M. Sasaki, T. Takegawa, K. Sakamoto, Y. Kotomori, Y. Otani, T. Ohwada, M. Kawahata, K. Yamaguchi, K. Takeda, *Angew. Chem. Int. Ed.* **2013**, *52*, 12956-12960; d) Y, Kotomori, M. Sasaki, M. Kawahata, K. Yamaguchi, K. Takeda, *J. Org. Chem*. **2015**, *80*, 11013-11020.

[7] a) P. Beak, D. B. Reitz, *Chem. Rev*. **1978**, 275-316; b) P. Beak, G. R. Brubaker, R. F. Farney, *J. Am. Chem. Soc.* **1976**, *98*, 3621-3627; c) P. Beak, R. Farney, *J. Am. Chem. Soc.* **1973**, *95*, 4771-4772.

[8] For use as a fixing agent for configurationally labile α-oxycarbanions in the absence of an external chiral ligand, see: a) D. Hoppe, T. Krämer, *Angew. Chem. Int. Ed.* **1986**, *25*, 160-162; b) S. Dreller, M. Drybusch, D. Hoppe, *Synlett* **1991**, 397-400; c) D. Hoppe, A. Carstens, T. Krämer, *Angew. Chem. Int. Ed.* **1990**, *29*, 1424-1425; d) A. Carstens, D. Hoppe, *Tetrahedron* **1994**, *50*, 6097-6108; e) D. Hoppe, D. F. Marr, M. Brüggemann, In *Organolithiums in Enantioselective Synthesis* (Eds.; D. M. Hodgson) Springer, New York, **2003**, pp. 61.

[9] a) G. Stork, R. K. Boeckman, Jr. *J. Am. Chem. Soc.* **1973**, *95*, 2016-2017; b) H. D. Zook, W. L. Gumby, *J. Am. Chem. Soc.* **1960**, *82*, 1386-1389; c) F. J. Kronzer, V. R. Sandel, *J. Am. Chem. Soc.* **1972**, *94*, 5750-5759.

[10] a) W. H. Pearson, A. C. Lindbeck, *J. Org. Chem*. **1989**, *54*, 5651-5654; b) W. H. Pearson, A. C. Lindbeck, J. W. Kampf, *J. Am. Chem. Soc*. **1993**, *115*, 2622-2636; c) J. M. Chong, S. B. Park, *J. Org. Chem.* **1992**, *57*, 2220-2222.

[11] a) M. Purzycki, W. Liu, G. Hilmersson, F. F. Fleming, *Chem. Commun.* **2013**, *49*, 4700-4702; b) F. F. Fleming, S. Gudipati, *Eur. J. Org. Chem.* **2008**, 5365-5374; c) F. F. Fleming, Z. Zhang, *Tetrahedron*, **2005**, *61*, 747-789; d) F. F. Fleming, B. C. Shook, *Tetrahedron*, **2002**, *58*, 1-23; e) S. Arseniyadis, K. S. Kyler, D. S. Watt, *Org. React.* **1984**, *31*, 1-71; f) X. Yang, F. F. Fleming, *Acc. Chem. Res.* **2017**, *50*, 2556-2568.

[12] For comparison of the reactivity of metallo-enolates in alkylation reactions, see: a) A. L. Kurts, A. Macias, I. P. Beletskaya, O. A. Reutov, *Tetrahedron* **1971**, *27*, 4759-4767; b) A. L. Kurts, P. I. Dem'yanov, A. Macias, I. P. Beletskaya, *Tetrahedron* **1971**, *27*, 4769-4776.

[13] For studies of the stereochemistry of chiral magnesiated nitriles., see a) M. Gao, N. N. Patwardhan, P. R. Carlier, *J. Am. Chem. Soc*. **2013**, *135*, 14390-14400; b) A. Sadhukhan, M. C. Hobbs, A. J. H. M. Meijer, I. Coldham, *Chem. Sci.* **2017**, *8*, 1436-1441; c) M. R. Alshawish, G. Barker, N. D. Measom, I. Coldham, *C. R. Chemie* **2017**, *20*, 601-608.

[14] The reported pK_a values for diisopropylamine and hexamethyldisilazane in THF are 34.4 and 23.1, respectively. a) H. Ahlbrecht, G. Schneider, *Tetrahedron* **1986**, *42*, 4729-2741; b) A. Streitwieser, A. Facchetti, L. Xie, X. Zhang, E. C. Wu, *J. Org. Chem*. **2012**, *77*, 985-990.

[15] For theoretical studies of deprotonation of nitriles, see: R. Koch, B. Wiedel, E. Anders, *J. Org. Chem*. **1996**, *61*, 2523-2529.

[16] For deprotonative lithiation via the formation of a prelithiation complex, see: a) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak *Angew. Chem. Int. Ed*. **2004**, *43*, 2206-2225; b) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan S. *Acc. Chem. Res*. **1996**, *29*, 552-560; c) D. B. Collum, A. J. Mcneil, A. Ramirez, *Angew. Chem. Int. Ed.* **2007**, *46*, 3002-3017.

[17] K. B. Wiberg, H. Castejon, *J. Org. Chem.* **1995**, *60*, 6327-6334.

[18] The relative reactivity of the aroyl chlorides toward α-nitrile lithiocarbanions was established by competition experiments on *trans*-*N*-carbamoyl-2-cyano-6-methylpiperidine. See ref 6d.

[19] Gaussian 09, Revision **C.01**, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers,; K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W.Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[20] G. Scalmani, M. J. Frisch, *J. Chem. Phys.* **2010**, 132, 114110.

10.1002/ejoc.201800484

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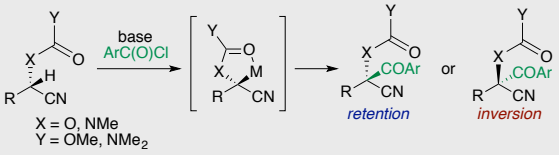

The stereochemistry of electrophilic substitutions of α-nitrile metallocarbanions was investigated using deprotonation of enantioenriched α-amino- and α-oxynitriles bearing a carbamoyl or a methoxycarbonyl group in the presence of an electrophile. The most relevant finding is that the dipole-stabilizing substituents can not only affect the configurational stability and reactivity of α-nitrile metallocarbanions but also can change the steric course (retention vs inversion).

Chiral α-Nitrile Carbanion *

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Steric Course of Deprotonation/Substitution of Chelating/Dipole-Stabilizing Group-Substituted α-Amino- and α-Oxynitriles