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Stereochemical Course of Deprotonation-Acylation of *N*-Boc- and *N*-Carbamoyl-2-cyano-6-methylpiperidines

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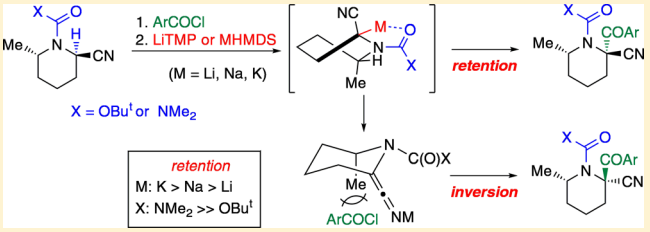
Supporting Information

ABSTRACT: The stereochemical course of electrophilic substitution of α-nitrile metallocarbanions generated by deprotonation from *N*-Boc- and *N*-carbamoyl-2-cyano-6-methylpiperidines was investigated. Deprotonation in the presence of an electrophile taking advantage of the high acidity of α-nitrile protons allowed examination of the effects of a chelating group on the nitrogen atom, a countercation, and the reactivity of an electrophile on the steric course. Analyses of reactions using aroyl chlorides and methyl iodide revealed the following: (1) the substitution reactions basically proceed with retention of configuration, (2) the extent of an inversion product increases with decreasing chelating ability of the *N*-substituent and with increasing leaving ability (ionic character) of a countercation (Li, Na, K) of the anionic species, and (3) the use of a more reactive electrophile results in an increase of the retention product.

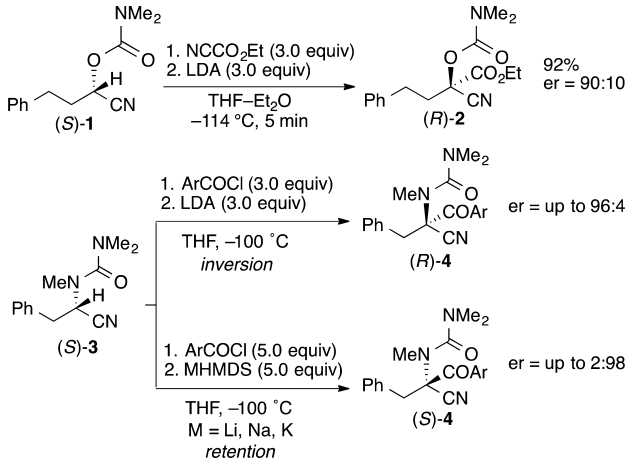


INTRODUCTION

Electrophilic substitution of organolithiums may proceed with either sense of retention ($S_E2$ret) or inversion ($S_E2$inv), depending on various factors including an electrophile, a countercation, and structures of the carbanions because both of the processes are allowed by orbital symmetry unlike the S_N2 counterpart.[1] We recently reported that chiral nonracemic acyclic α-nitrile carbanions adjacent to a carbamoyloxy or a ureido group, generated by deprotonation, have sufficient configurational stability to be trapped by a carbon electrophile virtually without loss of enantiopurity in the absence of any further chiral elements (Scheme 1).[2] It is particularly noteworthy that the process is highly enantiodivergent in the latter cases, as well as the fact that a chiral acyclic α-nitrile carbanion, which has been considered to be extremely configurationally labile,[3,4] is able to be trapped by a carbon electrophile virtually without racemization.[5] Thus, in contrast to LDA/benzoylation that proceeds in an invertive manner, reactions with $MN(SiMe_3)_2$ (M = Li, Na, K[6]) afford a retentive substitution product.

We became interested in the steric course of the corresponding reactions in cyclic variants that are generally more configurationally stable than their acyclic counterparts[7] and chose 2-cyanopiperidine derivatives as substrates. Although electrophilic substitutions of piperidine derivatives have been investigated in detail by Beak, Gawley, and others,[8−10] relatively little work has been performed on the stereochemical course of the substitution at the 2-position of 2-substituted piperidine derivatives. Recently, Gawley[11] and Coldham[12] demonstrated that *N*-Boc-2-lithio-2-arylpiperidines have configurational stability at lower temperatures and that their electrophilic substitutions occur with retention of configuration. Regarding 2-cyano derivatives, lithiation/methylation and magnesiation/acetone quenching of *N*-Boc-2-cyanopiperidines were reported by Rychnovsky and Wolckenhauer[13] and by Coldham and coworkers,[14] respectively, the latter showing that α-nitrile magnesiocarbanions have appreciable configurational stability at −107 °C, though the steric course of the reactions was not

Scheme 1. Deprotonation/Acylation of α-Oxy/α-Amino Nitriles



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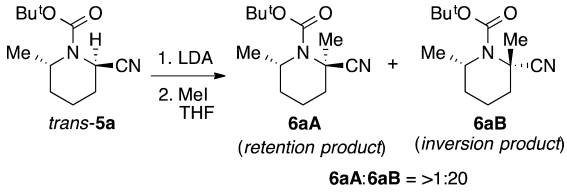
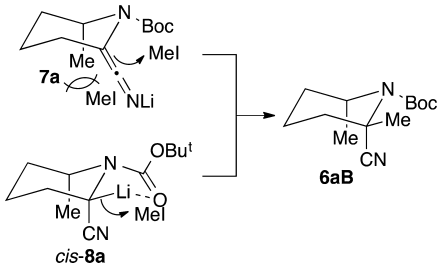
described. Rychnovsky and Wolckenhauer also reported that treatment of *trans*-*N*-Boc-2-cyano-6-methylpiperidine (*trans*-**5a**) with LDA followed by addition of MeI affords *trans*-dimethyl derivative **6aB**, an inverted methylation product, in a highly stereoselective manner (Scheme 2).[15]

Scheme 2. Methylation of *trans*-*N*-Boc-2-cyano-6-methylpiperidine



They rationalize the stereochemical outcome by an equatorial attack of an electrophile on *N*-lithiated keteniminate **7a** or a retentive electrophilic attack on an inverted *C*-lithiated nitrile *cis*-**8a** having been evoked (Scheme 3). The axial

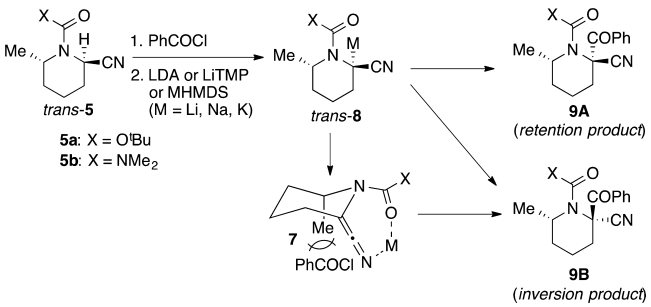
Scheme 3. Intermediates Leading to the Formation of 6aB



disposition of the 6-methyl group in **7a** and *cis*-**8a** and the inversion of the α-lithionitrile in *trans*-**8a** are due to the relief of severe $A^{1,3}$-strain[9e,f,h,16] with the *N*-Boc moiety and due to coordinative stabilization between the Boc group and the equatorial lithium, respectively.[9f] Their results indicate that *N*-Boc-2-cyano-2-lithiopiperidine is configurationally much less stable than the corresponding 2-aryl derivatives as might be expected and that the formation of inversion products **6aB** would correspond to the racemization in an enantioenriched acyclic system (*S*)-**3**.

We were intrigued by the steric course in electrophilic substitutions of *trans*-**5a** in which deprotonation by the amide bases is conducted in the presence of PhCOCl. *N*-Carbamoyl derivative *trans*-**5b** was also selected to examine the influence on the steric course of the difference in the conformational rigidity of the metallocarbanions depending on the chelating group[17] on the nitrogen atom in addition to comparing the stereochemical outcome with (*S*)-**3** (Scheme 4). If **9A**, a retention product, is formed, electrophilic trapping should occur before *trans*-**8** loses its stereochemical integrity by conversion to keteniminate **7** (*trans*-**8** → **7**). Although the possibility of intermediacy of *cis*-**8** inverted at C-2 and stabilized by Boc−Li coordination cannot be ruled out, it seems to be more reasonable to assume keteniminate **7** because twist-boat conformation of *trans*-**5a**,**b** (vide infra) places the hydrogen atom on C2 in an equatorial disposition, leading to more facile stabilization of the resulting lithio derivative through chelation by the carbonyl oxygen without inversion of the configuration at C2. Conversely, the formation of **9B**, an inversion product, indicates at least two possibilities, the intermediacy of **7** and the

Scheme 4. Conceivable Process of in Situ Deprotonation/Benzoylation of *trans*-5

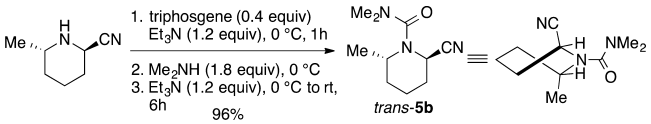


intervention of an S_E2inv process from *trans*-**8** to **9B**, though the latter process appears to be less favorable because of more energetic requirements for a structural reorganization that is needed to reach an sp^2-hybridized transition structure in comparison with the corresponding acyclic cases.[1a]

RESULTS AND DISCUSSION

N-Carbamoyl derivative *trans*-**5b** (X = C(O)NMe$_2$) was prepared by treatment of 2-cyano-6-methylpiperidine[15,18] with triphosgene/NEt$_3$ followed by dimethylamine (Scheme 5). In

Scheme 5. Preparation of *trans*-5b



the ^{1}H NMR spectra of *trans*-**5a** and *trans*-**5b** in THF-d_8, signals for the C-2 protons appear at 4.80 and 4.30 ppm as a doublet of doublets (apparent triplet) with coupling constants of 4.1 and 4.6 Hz, respectively, suggesting a twist-boat conformation in which both the cyano and methyl groups are in pseudoaxial positions.[9c,19] The preference of a twist-boat conformation can be understood in terms of avoidance of the above-mentioned $A^{1,3}$-strain between the methyl group and the *N*-substituent, and in terms of an anomeric-type effect,[20] although the latter may be attenuated by the carbonyl group.

The conditions used by Rychnovsky and Wolckenhauer for methylation of *trans*-**5a** involve treatment with LDA and DMPU in THF at −78 °C for 1.5 h followed by reaction with MeI at the same temperature for 1.5 h. For determination of the stereochemical course of benzoylation of preformed keteniminates, *trans*-**5a** was treated with amide bases (LDA, LiTMP, LiHMDS, NaHMDS, and KHMDS) in THF for 10 min at −100 °C and then quenched by PhCOCl (Table 1). Although the reactions with bases other than LiTMP **5a** were partially recovered and the reaction with LiHMDS required an elevated reaction temperature (−60 °C), **9aB** was exclusively obtained with no detectable amount of **9aA**. The structures of **9aB** and **9aA** were determined on the basis of X-ray analysis of **9aA** (vide infra), showing a twist-boat conformation with the cyano and methyl groups both in pseudoaxial positions. Because the reaction of *trans*-**5a** proceeded more cleanly with LiTMP than with LDA, LiTMP was used for a subsequent study, the former base showing almost the same behavior toward (*S*)-**3** as that of LDA.

Because deprotonation of *N*-carbamoyl derivative *trans*-**5b** at −100 °C was not fast enough to be completed, the temperature

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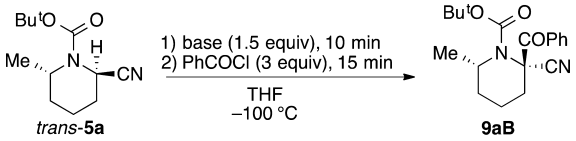
Table 1. Benzoylation of Preformed α-Nitrile Carbanion from *trans*-5a

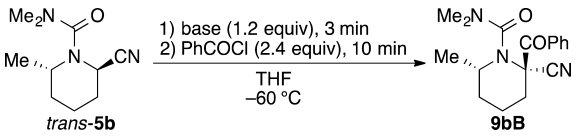


entry	base	yield (%) 9aB	5a
1	LDA	75	16
2	LiTMP	88	
3[a]	LiHMDS	61	23
4	NaHMDS	50	28
5	KHMDS	68	6

[a]Reaction was conducted at −60 °C.

was raised to −60 °C and the reaction time for deprotonation was shortened to 3 min to prevent decomposition at the expense of yields, except for the case of LiHMDS, for which the reaction time was prolonged to 15 min due to slow deprotonation (Table 2). The stereochemistry of **9bB** was determined by X-ray crystallography, which showed a chairlike conformation with the cyano and methyl groups both in an axial position.

Table 2. Benzoylation of Preformed α-Nitrile Carbanion from *trans*-5b



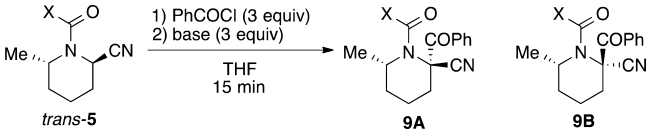
entry	base	yield (%) 9b (9bB:9bA)	5b
1	LiTMP	36 (96:4)	18
2[a]	LiHMDS	36 (93:7)	40
3	NaHMDS	48 (98:2)	29
4	KHMDS	35 (98:2)	39

[a]Reaction time for deprotonation is 15 min.

Although a trace amount of the retention product **9bA** was formed in the case of *trans*-**5b**, both *trans*-**5a** and **5b** exhibited the same trend as that shown in the reaction of *trans*-**5a** with MeI in which electrophilic substitution of preformed anionic species from *trans*-**5a** proceeds with inversion of configuration due to steric hindrance by the axial methyl group in **7**.

Having established the stereochemical course of benzoylation of preformed anionic species from *trans*-**5a,b**, we applied the conditions employed for acyclic α-aminonitriles (*S*)-**3** to benzoylation of 6-methyl-2-cyanopiperidine derivatives *trans*-**5a** and *trans*-**5b**. Treatment of *trans*-**5a** with amide bases (3 equiv) in the presence of benzoyl chloride (3 equiv) in THF at −100 °C for 15 min afforded benzoylated products in good to excellent yields (Table 3, entries 1, 3, and 4), except for the case of LiHMDS (entry 2) where *trans*-**5a** was recovered, suggesting that no deprotonation occurred. In contrast to the results for reactions of preformed anions (Table 1), retention product **9aA** was formed in addition to the inversion product **9aB**, and the ratios of the retention product increased from LiTMP through NaHMDS to KHMDS and became the major product in the latter two cases. Raising the reaction temperature to −60 °C

Table 3. In Situ Deprotonation/Benzoylation of *trans*-5



entry	trans-5	base	temp (°C)	yield (%)	*ret*:*inv* (9A:9B)
1	**5a**	LiTMP	−100	76	10:90
2	**5a**	LiHMDS	−100	trace	
3	**5a**	NaHMDS	−100	85	60:40
4	**5a**	KHMDS	−100	95	80:20
5	**5a**	LiTMP	−60	96	2:98
6	**5a**	LiHMDS	−60	92	2:98
7	**5a**	NaHMDS	−60	95	47:53
8	**5a**	KHMDS	−60	93	50:50
9	**5b**	LiTMP	−60	83	74:26
10[a]	**5b**	LiTMP	−60	93	76:24
11	**5b**	LiHMDS	−60	86	77:23
12	**5b**	NaHMDS	−60	75	76:24
13	**5b**	KHMDS	−60	78	94:6
14[b]	**5b**	KHMDS	−60	55	89:11
15[c]	**5b**	KHMDS	−40	69	87:13

[a]LiCl (1 equiv) was added. [b]HMPA (5 equiv) was added. [c]Two equiv of KHMDS was used.

enabled deprotonation by LiHMDS (entry 6) and resulted in an increase in the ratios of the inversion product in all cases. In the reactions of *trans*-**5b** at −60 °C, the retention product **9bA** predominated over the invertive **9bB** (entries 9−13). To obtain information about the effect of lithium chloride,[21] which accumulates progressively in the reaction medium, we conducted the reaction in the presense of LiCl (entry 10) and resulted in no significant change in the *ret*:*inv* selectivity. KHMDS showed the highest ratio of **9bA**, which remained almost unchanged when HMPA[22] was added or the reaction temperature was raised to −40 °C (entries 14 and 15).

The fact that retention products **9aA** and **9bA** are obtained in all cases suggests that the metalated species *trans*-**8a,b** have sufficiently long lifetimes to permit trapping by an electrophile present in the system before the complete loss of stereochemical integrity. It should be noted that reactions of *N*-carbamoyl derivative *trans*-**5b** resulted in predominant formation of the retention product with all bases, including LiTMP, which afforded almost exclusively the inversion product in the case of (*S*)-**3**.[2b] This seems to suggest that the intervention of an S_E2inv process from *trans*-**8** to **9B** is unlikely and that **9B** may be formed via keteniminate **7**. This is consistent with results reported by Hoppe and co-workers showing that the difference in the stereochemical outcomes in 1-lithiocarbamate derivatives of 1-indanol and 1-phenylethyl alcohol can be attributed to the different barriers to planarization.[7] In the reactions of *N*-Boc derivative *trans*-**5a** at −60 °C, the ratios of inversion product increase, probably because of poorer chelating ability[17a,b] of the *N*-Boc group than that of the *N*-carbamoyl group, which should be associated with the rate of conversion to keteniminate **7**. It seems that the trend of increasing ratios of the retention product at −100 °C reflects the decreased rate of conversion to keteniminate **7**. Furthermore, the results obtained from the reactions of *cis*-**5a,b** are supportive of this proposal. Thus, even the addition of a base in the presence of benzoyl chloride did not produce an

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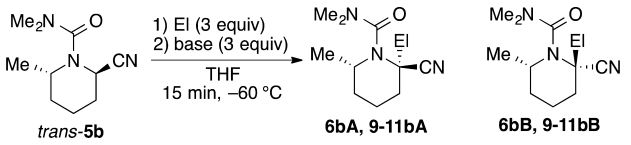
inversion product **9A** in any of the cases but resulted in the exclusive formation of retention product **9B**.

For the retention preference observed with the benzoylation of (*S*)-**3** with MHMDS (M = Li, Na, and K), we previously proposed a hypothesis that deprotonation by a base precomplexed with an aroyl chloride, which would enhance the basicity of bases weaker than LDA and LiTMP, bring the electrophile near the metalocarbanion, thus resulting in retention of the configuration. To obtain information on participation of a base precomplexed with an electrophile in the deprotonation and on the relationship between the steric course and reactivity of an electrophile, we examined reactions of *trans*-**5b** with 4-methoxybenzoyl chloride, 2-chlorobenzoyl chloride, and methyl iodide. In comparison with benzoyl chloride, the former two can be more strongly cation-complexing but less electrophilic and less strongly cation-complexing but more electrophilic, respectively. In the case of methyl iodide, it is not possible to proceed with retention of the configuration while keeping complexation of an iodine atom with a countercation due to the symmetry forbidden nature.[1c] The results are shown in Table 4.

Table 4. In Situ Deprotonation/Quenching by Electrophiles of *trans*-5b



entry	base	electrophile	product	yield (%)	*ret*:*inv* (**A**:**B**)
1	LiTMP	4-MeOC$_6$H$_4$COCl	**10b**	93	48:52
2	LiTMP	C$_6$H$_5$COCl	**9b**	83	74:26
3	LiTMP	2-ClC$_6$H$_4$COCl	**11b**	91	89:11
4	LiTMP	MeI	**6b**	75	1:99
5	LiHMDS	4-MeOC$_6$H$_4$COCl	**10b**	87	27:73
6	LiHMDS	C$_6$H$_5$COCl	**9b**	86	77:23
7	LiHMDS	2-ClC$_6$H$_4$COCl	**11b**	83	97:3
8	LiHMDS	MeI	**6b**	71	3:97
9	NaHMDS	4-MeOC$_6$H$_4$COCl	**10b**	96	82:18
10	NaHMDS	C$_6$H$_5$COCl	**9b**	75	76:24
11	NaHMDS	2-ClC$_6$H$_4$COCl	**11b**	22[a]	80:20
12	NaHMDS	MeI	**6b**	88	57:43
13	KHMDS	4-MeOC$_6$H$_4$COCl	**10b**	86	93:7
14	KHMDS	C$_6$H$_5$COCl	**9b**	78	94:6
15	KHMDS	2-ClC$_6$H$_4$COCl	**11b**	27[b]	94:6
16	KHMDS	MeI	**6b**	83	75:25

[a]Recovered 64% of the starting material. [b]Recovered 54% of the starting material.

It should be noted that, in the reactions of methyl iodide, retention products were obtained as the major products for NaHMDS and KHMDS (entries 12 and 16). The two bases gave rise to almost the same selectivity among all of the aroyl chlorides, which seems to be attributed to enhanced reactivities of the corresponding anionic species, a somewhat narrow reactivity range of the aroyl chlorides, or both. However, the low conversion observed with 2-chlorobenzoyl chloride, probably due to competing reactions of the electrophile with a base that may be faster than deprotonation of *trans*-**5b**, makes a simple comparison difficult (entries 11 and 15). In the cases of LiTMP and LiHMDS, the ratios of retention products increased from 4-methoxybenzoyl chloride through benzoyl chloride to 2-chlorobenzoyl chloride. These results suggest that the reactivity of an electrophile plays a more important role in the formation of the retention products than does their cation-complexing ability. This led us to verify the reactivity of the aroyl chlorides toward anionic species derived from *trans*-**5b** with LiTMP and LiHMDS by three independent sets of competition experiments between benzoyl chloride and the other three electrophiles (Scheme 6). Thus, *trans*-**5b** (1 equiv) was treated with a base (3.0 equiv) in the presence of benzoyl chloride (1.5 equiv) and 4-methoxybenzoyl chloride (1.5 equiv) at −60 °C for 15 min. The same experiments were performed with 2-chlorobenzoyl chloride and methyl iodide, respectively. These experiments established that the reactivity order is as follows: 2-chlorobenzoyl chloride > benzoyl chloride > 4-methoxybenzoyl chloride > methyl iodide. As a consequence, the ratios of retention products increase in proportion to the reactivity of an electrophile.

A key to understanding the steric course should be configurational stability and chemical reactivity of *trans*-**8**, which can be controlled by several factors (Scheme 7). Thus, the enhanced chelating ability of an *N*-substituent would suppress the isomerization to **7**[23] and, as a result, provide a greater opportunity to be trapped by an electrophile leading to retention product **9A**. The fact that higher ratios of a retention product were observed with *N*-carbamoyl derivative *trans*-**5b** than with *N*-Boc derivative *trans*-**5a** can be ascribed to the stronger coordinating ability of the urea-type oxygen than that of the carbamate-type oxygen and is consistent with those reported previously by us[2] and others.[17a,b,23] The difference in reactivity of the metallocarbanions depending on the *N*-substituent can also potentially affect the ratio.[24] Thus, the more reactive the metallocarbanion is, the more the retention product would be produced. In metallocarbanion *trans*-**8**, the negative charge on carbon can be stabilized by the α-nitrogen atom, which is the positive end of a dipole[9j,17c] and, as a result, becomes less reactive. The development of a more positive charge on the ring nitrogen atom of *trans*-**8a** (X = *tert*-BuO) than that of *trans*-**8b** is suggested from the results of X-ray analyses of **9aA** and **10bA**, although those are benzoylated products (Figure 1). Thus, the sum of bond angles[7] and a pyramidalization angle[25] at the ring nitrogen atom of **10bA** are calculated to be 339.9° and 43.1°, respectively, and those for **9aA** are 357.0° and 17.5°, respectively. These results indicate that *N*-Boc derivative **9aA** is more planarized, being attributable to more electron donation from the ring nitrogen to the carbonyl carbon originating from the much poorer electron-donating ability of a *tert*-BuO group than that of a dimethylamino group. This can force it to adopt a twist-boat conformation to alleviate the A^{1,3}-type allylic strain.

Also, the increase in leaving ability[26] of a metal cation in *trans*-**8** (K > Na > Li) and use of a more reactive electrophile would result in an increase of **9A**. It is interesting that the enhanced reactivity of an anionic species by the change from Li through Na to K surpasses an inevitable increase of its configurational instability.[27]

On the basis of these arguments and previously reported results for (*S*)-**3**,[2b] we offer the following rationalization for the stereochemical outcome observed in the electrophilic substitution of α-nitrile metallocarbanions having nitrogen on the metal-bearing carbon, which are configurationally stabilized by a chelating group on the nitrogen atom. Retentive electrophilic substitution may be the default pathway in α-nitrile metal-

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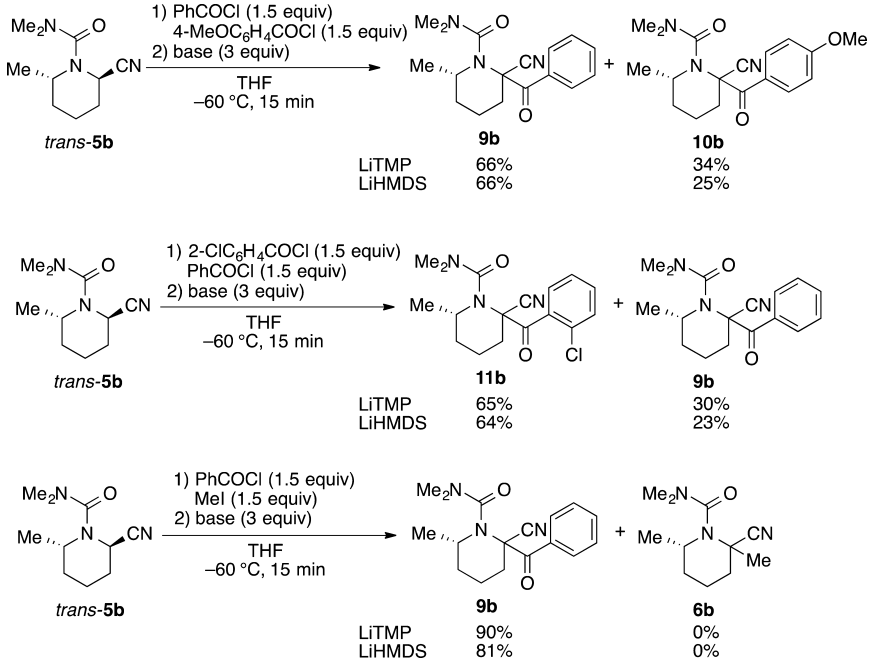
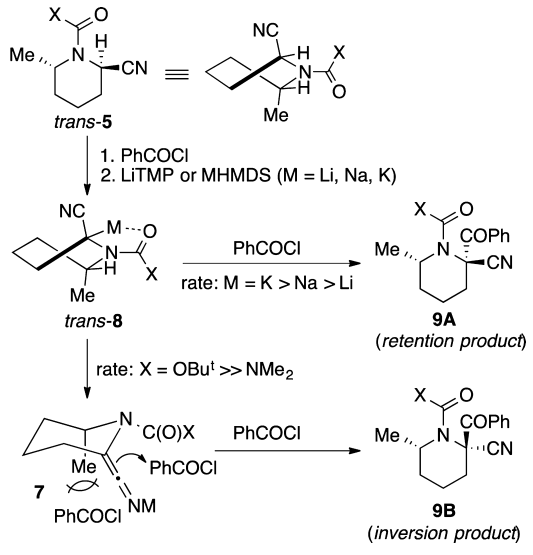
Scheme 6. Competition Experiments Between Benzoyl Chloride and the Other Electrophiles[a]



[a]The stereochemistry of the products are not shown for the sake of simplicity.

Scheme 7. Possible Explanation for the Stereochemical Outcomes



locarbanions regardless of whether they go through or do not go through deprotonation by a base precomplexed with an aroyl chloride and regardless of being cyclic or acyclic. Inverted electrophilic substitution can occur in cases in which planarization without cleavage of a carbon–metal bond can occur faster than electrophilic trapping due to relatively low reactivity of the anionic species. Because the central chirality of the starting material is retained as a planar chirality, an electrophile can potentially attack from the less-hindered and uncoordinated backside of the molecule having increased electron density to provide products with inversion of configuration. This is the case with LiTMP (LDA) in the reaction of (*S*)-**3**, because the planarization in cyclic cases would be a much slower process.[7] In the reaction of (*S*)-**3** with

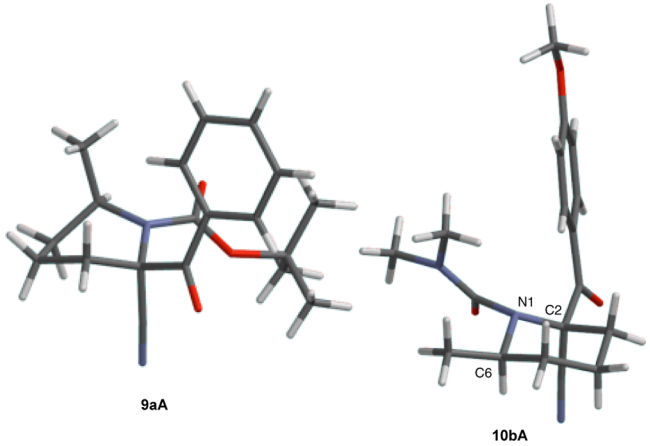


Figure 1. X-ray crystal structures of **9aA** and **10bA**.

LiHMDS, a much weaker base than LiTMP, NaHMDS, and KHMDS, the deprotonation is carried out with the aid of precomplexation by an electrophile, leading to retention products.

CONCLUSIONS

We demonstrated that electrophilic substitution of α-nitrile metallocarbanions generated by deprotonation from *N*-Boc-2-cyano-6-methylpiperidine proceeds with retention of configuration and that the extent of an inversion product increases with decreasing chelating ability of the *N*-substituent and leaving ability (ionic character) of a countercation of the anionic species. Until very recently, α-nitrile carbanions had not been a major subject of stereochemical studies on electrophilic substitution because of their extreme configurational lability, except for special cases such as cyanocyclopropanes.[4a,b] Therefore, if the construction of a stereogenic center adjacent to a cyano group through deprotonation/electrophilic quench-

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ing is possible, and its stereochemical process is well understood, it would make a dramatic breakthrough in asymmetric synthesis. In our works,[2] we focused on the much higher acidity of α-nitrile protons in comparison with the related benzyl protons as well as on the unusual higher nucleophilicity of α-nitrile carbanions.[28] Although the properties can cause a rapid loss of stereochemical integrity, they make possible the use of a much weaker base such as LiHMDS than *sec*-BuLi/TMEDA, change in a counterion from Li to Na and K, and deprotonation in the presence of an electrophile. The latter not only allows for trapping before the complete loss of stereochemical integrity but also enables information about the microscopic configurational stability that is associated with the rate of metallocarbanions with an electrophile to be obtained. We are currently exploring the stereochemistry in lithiation/electrophilic quenching using acyclic α-oxy- and α-aminonitrile derivatives with several different kinds of chelating groups on the hetero atoms corresponding to (*S*)-**3**, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Methods. 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 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 pressure (MPLC) was carried out using prepacked columns (22 mm × 100 mm (5 μm silica gel) or 22 mm × 300 mm (10 μm silica gel)). ^{1}H NMR spectra (500 MHz) were taken in $CDCl_3$ and THF-d_8 with internal standards as follows: $CDCl_3$ (δ 7.26) and THF-d_8 (δ 1.73). ^{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 trans-2-Cyano-N,N,6-trimethylpiperidine-1-carboxamide (trans-**5b**).* To a cooled (ice−water) solution of triphosgene (793 mg, 2.94 mmol) in Et_2O (24.2 mL) was added triethylamine (1.23 mL, 8.82 mmol). After being stirred for 10 min, a solution of *trans*-6-methylpiperidine-2-carbonitrile[13] (913 mg, 7.35 mmol) in Et_2O (6.85 mL) was added. After being stirred for 1 h, dimethylamine (2.0 M in THF, 6.62 mL, 13.23 mmol) and triethylamine (1.23 mL, 8.82 mmol) were added successively. After stirring for 6 h at room temperature, the mixture was filtered through a pad of Celite using AcOEt and concentrated. The residual oil was subjected to column chromatography (silica gel (40−50 μm) 70 g, elution with hexane/AcOEt = 1:1) to give *trans*-**5b** (1.37 g, 96%) as a colorless oil. R_f = 0.29 (hexane:AcOEt = 1:1); IR (NaCl) 2941, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, *J* = 6.2 Hz, 3H), 1.31−1.43 (m, 1H), 1.65−1.77 (m, 3H), 1.83−1.94 (m, 2H), 2.92 (s, 6H), 3.35−3.43 (m, 1H), 4.08 (app t, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 19.5, 29.3, 31.7, 37.2, 47.3, 50.4, 118.3, 163.4; HRMS-ESI-LTQ Orbitrap (*m*/*z*) [M + Na]$^+$ calcd for $C_{10}H_{17}N_3ONa$ 218.1264, found 218.1260.

*^{1}H NMR Data of trans-**5a** in THF-d_8.* ^{1}H NMR (THF-d_8) δ 1.20 (d, *J* = 6.7 Hz, 3H), 1.42 (s, 9H), 1.50−1.58 (m, 1H), 1.67−1.77 (m, 2H), 1.89−2.06 (m, 3H), 3.87−3.95 (m, 1H), 4.80 (app t, *J* = 4.1 Hz, 1H).

*^{1}H NMR Data of trans-**5b** in THF-d_8.* ^{1}H NMR (THF-d_8) δ 1.11 (d, *J* = 6.2 Hz, 3H), 1.32−1.44 (m, 1H), 1.65−1.79 (m, 3H), 1.87−1.93 (m, 2H), 2.94 (s, 6H), 3.30−3.38 (m, 1H), 4.30 (app t, *J* = 4.6 Hz, 1H).

*Preparation of cis-2-Cyano-6-methylpiperidine-1-carboxylc Acid tert-Butyl Ester (cis-**5a**).* To a cooled (−100 °C) solution of *trans*-**5a** (200.6 mg, 0.894 mmol) in THF (16.8 mL) was added dropwise a solution of NaHMDS (0.98 M in THF, 1.1 mL, 1.07 mmol) over a period of 7 min. The mixture was stirred at the same temperature for 10 min before addition of CH_3COOH (1.0 M in THF, 1.1 mL, 1.07 mmol). The mixture was diluted with Et_2O (20 mL) and saturated aq $NaHCO_3$ (20 mL). The aqueous phase was extracted with Et_2O (20 mL × 2). The combined organic phases were washed with saturated brine (20 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel (40−50 μm) 15 g, elution with hexane/AcOEt = 7:1) to give *cis*-**5a**[15] (182 mg, 91%) as a colorless oil.

*Preparation of cis-2-Cyano-N,N,6-trimethylpiperidine-1-carboxamide (cis-**5b**).* To a cooled (ice−water) solution of triphosgene (252 mg, 0.934 mmol) in Et_2O (7.7 mL) was added triethylamine (391 μL, 2.80 mmol). After being stirred for 10 min, a solution of *cis*-6-methylpiperidine-2-carbonitrile[15] (290 mg, 2.34 mmol) in Et_2O (2.2 mL) was added. After being stirred for 1 h, dimethylamine (2.0 M in THF, 2.1 mL, 4.20 mmol) and triethylamine (391 μL, 2.80 mmol) were added successively. After stirring for 18.5 h at room temperature, the mixture was filtered through a pad of Celite using AcOEt and concentrated. The residual oil was subjected to column chromatography (silica gel (40−50 μm) 35 g, elution with hexane/AcOEt = 1:1) to give *cis*-**5b** (357 mg, 78%) as a pale yellow solid. Recrystallization (hexane/AcOEt) gave colorless prisms. R_f = 0.19 (hexane:AcOEt = 1:1); mp 78−79 °C; IR (KBr) 2959, 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (d, *J* = 7.1 Hz, 3H), 1.55−1.63 (brd, *J* = 13.1 Hz, 1H), 1.63−1.84 (m, 3H), 1.94−2.07 (m, 2H), 2.86 (s, 6H), 3.81−3.90 (m, 1H), 4.56 (dd, *J* = 2.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2, 17.8, 29.0, 29.7, 38.7, 43.1, 51.0, 121.2, 164.6; HRMS-ESI-LTQ Orbitrap (*m*/*z*) [M + Na]$^+$ calcd for $C_{10}H_{17}N_3ONa$ 218.1264, found 218.1258.

*General Procedure for Acylation of trans-**5a**: Reaction of trans-**5a** with (1) LiTMP and (2) Benzoyl Chloride (Table 1, entry 2).* To a cooled (−100 °C) solution of *trans*-**5a** (22.5 mg, 0.10 mmol) in THF (1.72 mL) was added dropwise a solution of LiTMP (0.8 M in THF, 188 μL, 0.15 mmol) over a period of 4 min. The mixture was stirred at the same temperature for 10 min before addition of a solution of benzoyl chloride (3.0 M in THF, 100 μL, 0.30 mmol). After being stirred at the same temperature for 15 min, CH_3COOH (1.0 M in THF, 150 μL, 0.15 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 saturated brine (10 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel (40−50 μm) 10 g, elution with hexane/AcOEt = 5:1) to give **9aB** (29 mg, 88%) as a colorless oil.

*General Procedure for Acylation of trans-**5a**: Reaction of trans-**5a** with LiTMP and benzoyl chloride (Table 3, entry 1).* To a cooled (−100 °C) solution of *trans*-**5a** (22.7 mg, 0.10 mmol) and benzoyl chloride (35 μL, 0.304 mmol) in THF (1.61 mL) was added dropwise a solution of LiTMP (0.8 M in THF, 380 μL, 0.304 mmol) over a period of 5 min. The mixture was stirred at the same temperature for 15 min before the addition of CH_3COOH (1.0 M in THF, 304 μL, 0.304 mmol). 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 × 2). The combined organic phases were washed with water (10 mL) and saturated brine (10 mL), dried, and concentrated. The residual yellow solid was subjected to column chromatography (silica gel (40−50 μm) 10 g, elution with hexane/AcOEt = 5:1) to give **9a** (25.2 mg, 76% **9aA**:**9aB** = 10:90) as a white solid.

(2R,6S*)-2-Benzoyl-2-cyano-6-methylpiperidine-1-carboxylc Acid tert-Butyl Ester (**9aA**).* Compound **9a** was obtained from *trans*-**5a** (22.7 mg) using NaHMDS and benzoyl chloride in 85% yield (28.4 mg, **9aA**:**9aB** = 60:40) (Table 3, entry 3). Separation of isomers by MPLC (elution with hexane/AcOEt = 5:1) gave **9aA** as a white solid. Recrystallization (hexane/CH_2Cl_2) gave colorless prisms. R_f = 0.20 (hexane:AcOEt = 5:1); mp 139−140 °C; IR (KBr) 2969, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H), 1.49 (d, *J* = 6.9 Hz, 3H), 1.73−1.80 (m 1H), 1.88−2.07 (m, 2H), 2.24−2.44 (m, 3H), 4.27−4.36 (m, 1H), 7.44 (dd, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 7.8, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.1, 26.4, 28.0, 30.5, 48.4, 65.1, 83.4, 119.3, 128.6, 129.1, 133.4, 154.4, 191.7; HRMS-ESI-LTQ Orbitrap (*m*/*z*) [M + Na]$^+$ calcd for $C_{19}H_{24}N_2O_3Na$ 351.1679, found 351.1680.

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(2S,6S*)-2-Benzoyl-2-cyano-6-methylpiperidine-1-carboxylc Acid tert-Butyl Ester (**9aB**).* Compound **9aB** was obtained from *trans*-**5a** (22.5 mg) using LiHMDS and benzoyl chloride in 61% yield (20.2 mg) as a colorless oil (Table 1, entry 3). R_f = 0.17 (hexane:AcOEt = 5:1); IR (NaCl) 2979, 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.21 (brs, 9H), 1.41 (d, J = 6.9 Hz, 3H), 1.79−2.01 (m, 3H), 2.04−2.20 (m, 2H), 2.20−2.29 (brd, J = 12.2 Hz, 1H), 4.56 (brs, 1H), 7.41 (brdd, J = 7.5 Hz, 2H), 7.53 (brt, J = 7.5 Hz, 1H), 8.09 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 15.5, 16.7 and 17.7, 27.5 and 28.0, 29.3, 33.9, 48.2 and 48.7, 63.9 and 64.9, 82.6 and 84.5, 119.4, 128.3, 128.6, 128.8, 129.2, 132.1, 132.8, 133.6, 153.8 and 155.7, 189.8, and 190.7; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{19}H_{24}N_2O_3Na$ 351.1679, found 351.1679.

(2R,6S*)-2-Benzoyl-2-cyano-N,N,6-trimethylpiperidine-1-carboxamide (**9bA**).* Compound **9b** was obtained from *trans*-**5b** (19.7 mg) using LiTMP and benzoyl chloride in 83% yield (25.2 mg, **9bA**:**9bB** = 74:26) (Table 3, entry 9). Separation of isomers by column chromatography (silica gel (40−50 μm), elution with CH_2Cl_2/acetone = 30:1) gave **9bA** as a white solid. Recrystallization (hexane/AcOEt) gave colorless needles. R_f = 0.29 (CH_2Cl_2:acetone = 30:1); mp 101−102 °C; IR (KBr) 2940, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, J = 5.8 Hz, 3H), 1.40−1.52 (m, 1H), 1.76−1.82 (brd, J = 12.9 Hz, 1H), 1.86−2.10 (m, 3H), 2.30−2.34 (dt, J = 12.1, 1.9 Hz, 1H), 3.00 (s, 6H), 3.40 (dqd, J = 12.0, 5.8, 2.1 Hz, 1H), 7.45 (dd, J = 8.5, 8.2 Hz, 2H), 7.56 (tt, J = 8.2, 1.2 Hz, 1H), 8.08 (dd, J = 8.5, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3, 21.3, 33.4, 35.6, 37.9, 54.2, 68.0, 118.2, 128.5, 129.4, 133.4, 134.6, 164.2, 193.5; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{17}H_{21}N_3O_2Na$ 322.1526, found 322.1528.

(2S,6S*)-2-Benzoyl-2-cyano-N,N,6-trimethylpiperidine-1-carboxamide (**9bB**).* Compound **9b** was obtained from *trans*-**5b** (19.7 mg) using LiTMP and benzoyl chloride in 83% yield (25.2 mg, **9bA**:**9bB** = 74:26) (Table 3, entry 9). Separation of isomers by column chromatography (silica gel (40−50 μm), elution with CH_2Cl_2/acetone = 30:1) gave **9bB** as a white solid. Recrystallization (hexane/AcOEt) gave colorless needles. R_f = 0.22 (CH_2Cl_2:acetone = 30:1); mp 146−147 °C; IR (KBr) 2964, 1689, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 6.9 Hz, 3H), 1.74−1,18 (brd, J = 13.3 Hz, 1H), 1.82−1.90 (m, 1H), 1.92−2.01 (m, 1H), 2.01−2.10 (m, 1H), 2.12−2.24 (m, 1H), 2.33−2.39 (m, 1H), 2.76 (s, 6H), 4.04−4.10 (m, 1H), 7.39 (t, J = 7.8 Hz, 2H), 7.50 (tt, J = 7.8, 1.3 Hz, 1H), 7.95 (dd, J = 7.8, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.2, 17.2, 29.3, 35.0, 38.2, 51.5, 63.2, 121.1, 128.1, 129.2, 132.6, 134.7 164.0, 193.6; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{17}H_{21}N_3O_2Na$ 322.1526, found 322.1527.

(2R,6S*)-2-Cyano-2-(4-methoxybenzoyl)-N,N,6-trimethylpiperidine-1-carboxamide (**10bA**).* Compound **10b** was obtained from *trans*-**5b** (20.6 mg) using NaHMDS and *p*-methoxybenzoyl chloride in 96% yield (33.2 mg, **10bA**:**10bB** = 82:18) (Table 4, entry 9). Separation of isomers by column chromatography (silica gel (40−50 μm), elution with hexane/AcOEt = 1:1) gave **10bA** as a white solid. Recrystallization (hexane/CH_2Cl_2) gave colorless needles. R_f = 0.29 (hexane:AcOEt = 1:1); mp 158−159 °C; IR (KBr) 2929, 1676, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6.4 Hz, 3H), 1.39−1.49 (m, 1H), 1.75−1.84 (m, 1H), 1.84−1.98 (m, 2H), 1.98−2.11 (m, 1H), 2.31−2.38 (brd, J = 13.3 Hz, 1H), 3.03 (s, 6H), 3.40 (ddq, J = 11.9, 2.2, 6.4 Hz, 1H), 3.87 (s, 3H), 6.92 (d, J = 9.1 Hz, 2H), 8.17 (d, J = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 19.3, 21.4, 33.5, 35.8, 37.9, 54.0, 55.7, 67.3, 113.8, 118.7, 126.7, 132.2, 163.9, 164.3, 190.9; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{18}H_{23}N_3O_3Na$ 352.1632, found 352.1633.

(2S,6S*)-2-Cyano-2-(4-methoxybenzoyl)-N,N,6-trimethylpiperidine-1-carboxamide (**10bB**).* Compound **10b** was obtained from *trans*-**5b** (20.1 mg) using LiTMP and *p*-methoxybenzoyl chloride in 93% yield (31.7 mg, **10bA**:**10bB** = 48:52) (Table 4, entry 1). Separation of isomers by column chromatography (silica gel (40−50 μm), elution with hexane/AcOEt = 1:1) gave **10bB** as a white solid. Recrystallization (hexane/CH_2Cl_2) gave white powder. R_f = 0.13 (hexane:AcOEt = 1:1); mp 199−200 °C; IR (KBr) 2952, 1680, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 6.2 Hz, 3H), 1.77 (brd, J = 13.4 Hz, 1H), 1.81−1.88 (m, 1H), 1.90−2.10 (m, 2H), 2.13−2.25 (m, 1H), 2.35 (brd, J = 12.5 Hz, 1H), 2.81 (s, 6H), 3.84 (s, 3H), 4.07 (app quin, J = 6.2 Hz, 1H), 6.88 (d, J = 8.9 Hz, 2H), 8.05 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 16.2, 17.2, 29.3, 35.1, 38.2, 51.5, 55.6, 63.1, 113.4, 121.4, 126.6, 131.9, 163.3, 164.0, 191.2; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{18}H_{23}N_3O_3Na$ 352.1632, found 352.1629.

(2R,6S*)-2-Cyano-2-(2-chlorobenzoyl)-N,N,6-trimethylpiperidine-1-carboxamide (**11bA**).* Compound **11b** was obtained from *trans*-**5b** (19.6 mg) using LiTMP and 2-chlorobenzoyl chloride in 91% yield (30.6 mg, **11bA**:**11bB** = 89:11) (Table 4, entry 3). Separation of isomers by column chromatography (silica gel (40−50 μm), elution with hexane/AcOEt = 1.5:1) gave **11bA** as a white solid. R_f = 0.50 (hexane:AcOEt = 1:1); mp 150−151 °C; IR (KBr) 2936, 1718, 1661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.4 Hz, 3H), 1.40−1.52 (m, 1H), 1.78 (brd, J = 13.1, 1H), 1.81−1.92 (m, 2H), 1.92−2.00 (m, 1H), 2.21 (brd, J = 12.6 Hz, 1H), 3.07 (s, 6H), 3.28−3.37 (dqd, J = 11.9, 6.4, 2.1 Hz, 1H), 7.34−7.44 (m, 3H), 8.00 (dd J = 6.5 Hz, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3, 21.0, 33.3, 34.6, 38.1, 54.4, 70.2, 117.5, 126.4, 130.1, 130.2, 130.6, 132.1, 135.9, 164.4, 195.0; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{17}H_{20}ClN_3O_2Na$ 356.1136, found 356.1139.

(2S,6S*)-2-Cyano-2-(2-chlorobenzoyl)-N,N,6-trimethylpiperidine-1-carboxamide (**11bB**).* Compound **11b** was obtained from *trans*-**5b** (19.6 mg) using LiTMP and 2-chlorobenzoyl chloride in 91% yield (30.6 mg, **11bA**:**11bB** = 89:11) (Table 4, entry 3). Separation of isomers by column chromatography (silica gel (40−50 μm), elution with hexane/AcOEt = 1.5:1) gave **11bB** as a white solid. R_f = 0.44 (hexane:AcOEt = 1:1); mp 147−148 °C; IR (KBr) 2953, 1723, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, J = 6.9 Hz, 3H), 1.70 (brd, J = 12.8 Hz, 1H), 1.77−1.93 (m, 3H), 1.97−2.08 (m, 1H), 2.32 (brd, J = 12.8 Hz, 1H), 2.94 (s, 6H), 4.00−4.07 (m, 1H), 7.33−7.42 (m, 3H), 8.22−8.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.9, 17.2, 29.0, 35.0, 38.3, 51.4, 63.2, 120.9, 126.2, 129.9, 130.6, 131.0, 131.9, 135.6, 164.8, 194.5; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{17}H_{20}ClN_3O_2Na$ 356.1136, found 356.1139.

*trans-2-Cyano-N,N,2,6-tetramethylpiperidine-1-carboxamide (**6bA**).* Compound **6b** was obtained from *trans*-**5b** (19.7 mg) using KHMDS and methyl iodide in 83% yield (17.8 mg, **6bA**:**6bB** = 75:25) (Table 4, entry 16). Separation of isomers by MPLC (elution with hexane/Et_2O = 1:4) gave **6bA** as a white solid. R_f = 0.18 (hexane:AcOEt = 1:1); mp 74−75 °C; IR (KBr) 2937, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.2 Hz, 3H), 1.19−1.32 (m, 1H), 1.39 (s, 3H), 1.53−1.61 (m, 1H), 1.67−1.88 (m, 3H), 1.91 (brd, J = 13.2 Hz, 1H), 3.04 (brs, 6H), 3.08−3.16 (ddq, J = 11.9, 2.4, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 21.6, 25.4, 33.3, 37.3, 38.2, 53.3, 55.6, 120.7, 163.3; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{11}H_{19}N_3ONa$ 232.1420, found 232.1419.

*cis-2-Cyano-N,N,2,6-tetramethylpiperidine-1-carboxamide (**6bB**).* Compound **6bB** was obtained from *trans*-**5b** (19.6 mg) using LiTMP and methyl iodide in 75% yield (19.9 mg, **6bA**:**6bB** = 1:99) (Table 4, entry 4). Recrystallization (hexane/CH_2Cl_2) gave colorless prisms (hexane/CH_2Cl_2). R_f = 0.18 (hexane:AcOEt = 1:1); mp 95 °C; IR (KBr) 2942, 1658 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.32 (d, J = 7.1 Hz, 3H), 1.54 (s, 3H), 1.55−1.68 (m, 3H), 1.70−1.78 (m, 1H), 1.94−2.10 (m, 2H), 2.93 (s, 6H), 3.56−3.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.1, 16.5, 28.2, 30.1, 37.3, 39.6, 49.1, 51.8, 124.1, 163.4; HRMS-ESI-LTQ Orbitrap (m/z) [M + Na]$^+$ calcd for $C_{11}H_{19}N_3ONa$ 232.1420, found 232.1419.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02178.

Crystallographic data of **9aA** (CIF)
Crystallographic data of **9bB** (CIF)
Crystallographic data of **10bA** (CIF)
Copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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