Carbanions

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Enantiodivergent Deprotonation/Acylation of α-Amino Nitriles**

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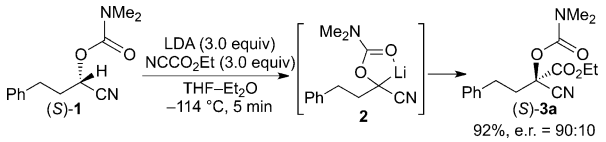
Although α-nitrile carbanions are outstanding nucleophiles for carbon–carbon bond formation because of their powerful nucleophilic character resulting from the small steric demand,[1] the difficulties that have been associated with their generation in an enantioselective manner have presented serious limitations to their usage in asymmetric synthesis. A recent publication[2] from our laboratory has shown that enantioselective in situ trapping of extremely stereolabile[3,4] chiral α-oxycarbanions of acyclic nitriles is possible at a practically promising level by taking advantage of the powerful chelating ability of an O-carbamoyl group[5] for configurational stabilization of a carbanion, where no chiral elements other than a preexisting stereogenic center are present (Scheme 1). Coldham and co-workers successfully extended this approach to magnesiated nitriles.[6] Herein, we report an enantiodivergent trapping of a chiral α-carbanion generated from α-amino nitrile derivatives, in which the stereogenecity of a single enantiomer can be used to produce both enantiomers.



Scheme 1. In situ deprotonation/acylation of (*S*)-**1**. LDA = lithium diisopropylamide, THF = tetrahydrofuran.

Our continuing studies in this area aim to further improve and generalize the methodology through the design of even more efficient fixation of a lithiocarbanion, and the use of more readily available enantioenriched substrates. We focused on enantioselective trapping of a chiral α-nitrile carbanion adjacent to an α-ureido group, which would have a more powerful fixing ability for a carbanion than an α-carbamoyloxy group,[7,8] particularly on the basis of analogy with *N*,*N*′-dimethylpropyleneurea.[9] Although a number of reports concerning enantioselective carbamate- or ureido-directed lithiation and substitution of carbanions adjacent to a nitrogen atom have appeared in the literature,[10,11] most of them have been limited to carbanions such as allylic and benzylic systems, which are much more configurationally stable than an α-nitrile carbanion, and to the processes using a chiral auxiliary or a chiral ligand such as (−)-sparteine.[12]

For an enantioselective trapping of α-amino carbanions adjacent to a conjugative electron-withdrawing group, it has been reported that azyridynyllithiums α to an ester carbonyl group are configurationally stable enough to undergo electrophilic quenching with no loss of enantiomeric purity,[13,14] and is explained in terms of enhanced angle strain in the transition state of the inversion. For α-amino acid esters or cyclic amides, Kawabata,[15] Carlier[16] and others have proposed the concept of memory of chirality or self-regeneration of stereocenters via stereolabile axially chiral intermediates,[17] which allow for the enantioselective introduction of an electrophile at an enolizable chiral center next to carbonyl functions. However, such ideas would not be applicable to α-nitrile carbanions, which probably cannot generate axially chiral intermediates because of the linear nature of a ketenimine.[18]

We chose the N-carbamoyl α-amino nitrile (*S*)-**4**, which is readily derived from L-phenylalanine (see the Supporting Information), and investigated its enantioselective deprotonation/substitution reaction.[19] The optimized reaction conditions[2] found for the carbamoyloxy derivative (*S*)-**1** were applied to (*S*)-**4** and resulted in the formation of the acylated product **6a** in poor yield and with moderate enantioselectivity (Table 1, entry 1) together with the recovery of a significant amount of the starting material and no loss of enantiomeric purity. This result was attributable to consumption of LDA through reaction with ethyl cyanoformate, probably because of lower reactivity of (*S*)-**4** relative to (*S*)-**1** toward deprotonation,[2] therefore less reactive electrophiles were examined. Whereas reaction with ethyl chloroformate gave **6a** in 83% yield and in racemic form, the use of benzoyl chloride improved both the yield and enantioselectivity to give **6b** (Table 1, entries 2 and 3). An X-ray analysis of a derivative of

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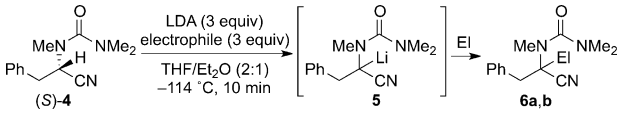
Table 1: In situ deprotonation/electrophilic trapping of (*S*)-**4** with LDA.



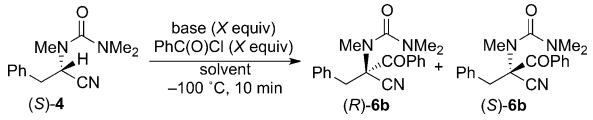
Entry	Electrophile	6	6a,b		4	
			Yield [%][a]	e.r.	Yield [%][a]	e.r.
1	$NCCO_2Et$	**6a**	25	79:21	72	100:0
2	$ClCO_2Et$	**6a**	83	51:49	0	–
3	PhC(O)Cl	**6b**	79	91:9	0	–

[a] Yield is that of isolated product.

6b indicated that the substitution occurs with inversion of configuration, which is the same as the case of (*S*)-**1**.

The different behaviors toward an electrophile led us to examine variables of the reaction including temperature, solvent, and additives by using benzoyl chloride as an electrophile. Although Et_2O could not be used because of the poor solubility of (*S*)-**4**, the use of THF at −100 °C gave better enantioselectivity and addition of HMPA did not significantly lower the enantioselectivity (Table 2, entries 1–5). Since it is well documented that a metal cation can control the geometry of metalated nitriles,[20] effects of the base and

Table 2: In situ deprotonation/benzoylation of (*S*)-**4** by amide bases.



Entry	Base	*X*	Solvent	Yield [%][a]	e.r.[b]
1	LDA	3	THF/Et_2O (2:1)	77	92:8
2	LDA	3	Et_2O	–	–
3	LDA	3	THF	81	96:4
4	LDA	3	THF[c]	85	95:5
5	LDA	3	THF[d]	39	92:8
6	LiTMP	5	THF	82	92:8
7	LiHMDS	5	THF	14[e]	13:87
8	LiHMDS	5	THF	29[f]	25:75
9	NaHMDS	5	THF	95	3:97
10	KHMDS	5	THF	88	3:97

[a] Yield is that of isolated product. [b] (*R*)-**6**/(*S*)-**6**. Determined by HPLC on a chiral stationary phase. [c] Added 4 equiv of HMPA. [d] Added 10 equiv of HMPA. [e] Recovered 73% of the starting material with no loss of enantiopurity. [f] Reaction was carried out at −90 °C for 10 min and 66% of the starting material was recovered with no loss of enantiopurity. HMDS = hexamethyldisilazide, TMP = tetramethylpiperidine.

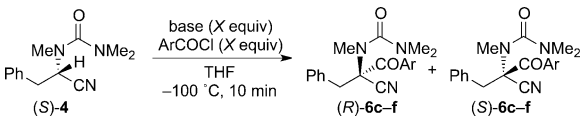
counter cation on the enantioselectivity were examined. The most striking feature is enantiodivergence: hexamethyldisilazide bases dramatically changed the stereochemical outcome of substitution from inversion to retention to give the enantiomeric product (*S*)-**6b** (Table 2, entries 7–10), for which the best chemical and enantiomeric yields were obtained with NaHMDS. The same trend was also observed for the carbamoyloxy derivative (*S*)-**1**, albeit in much lower enantioselectivity [LDA: 86% (60:40); NaHMDS: 92% (46:54)].

Although it may be considered that the structural difference between lithio- and sodiocarbanions plays a crucial role in determining the enantioselectivity,[21] the fact that LDA and LiHMDS lead to the opposite enantioselectivity suggests the possibility that the deprotonation step as well as the electrophilic quenching step is associated with determining the enantioselectivity.[22]

For the enantiodivergence observed, depending on the base used, we propose the following stereochemical hypothesis, taking into account the fact that the deprotonation is carried out in the presence of benzoyl chloride. In the LDA-induced reactions, the preferred attack of benzoyl chloride can occur from the less-hindered and uncoordinated rear face of a ureido-chelated lithiocarbanion intermediate as suggested by Hoppe and co-workers for the corresponding O-benzyl carbamates,[23] in which electron density significantly increases because of the much more conjugated nature of an α-nitrile carbanion relative to that of a benzyl carbanion, to give an inversion product. For hexamethyldisilazide-induced reactions, deprotonative metalation is conducted by a base in which a metal cation is precomplexed[24] with two carbonyl groups of a ureido group and benzoyl chloride, and a cyano group, probably because of the less basic nature of a hexamethyldisilazide than that of diisopropylamide.[25] Precomplexation with benzoyl chloride in the transition state of deprotonation would enhance the basicity and bring the electrophilic center near the metalocarbanion, thus resulting in retention of stereochemistry.

In fact, treatment of (*S*)-**4** with LiHMDS in THF at −100° and −90 °C for 10 minutes in the absence of benzoyl chloride resulted in recovery of **4** with e.r. = 99:1 and e.r. = 90:10, respectively, thus indicating that, correspondingly, only 2% and 20% of the substrate were deprotonated under the reaction conditions (see Table 2, entries 7 and 8).[26] Consequently, the rate of deprotonation can be enhanced by the presence of benzoyl chloride. This result prompted us to test this hypothesis by conducting reactions using other aroyl chlorides whose carbonyl group may have potentially different abilities to complex a metal cation and different reactivity toward a metalocarbanion, and may thus cause changes in the e.r. values. The results are shown in Table 3.

Table 3: In situ deprotonation/quenching by aroyl chlorides.

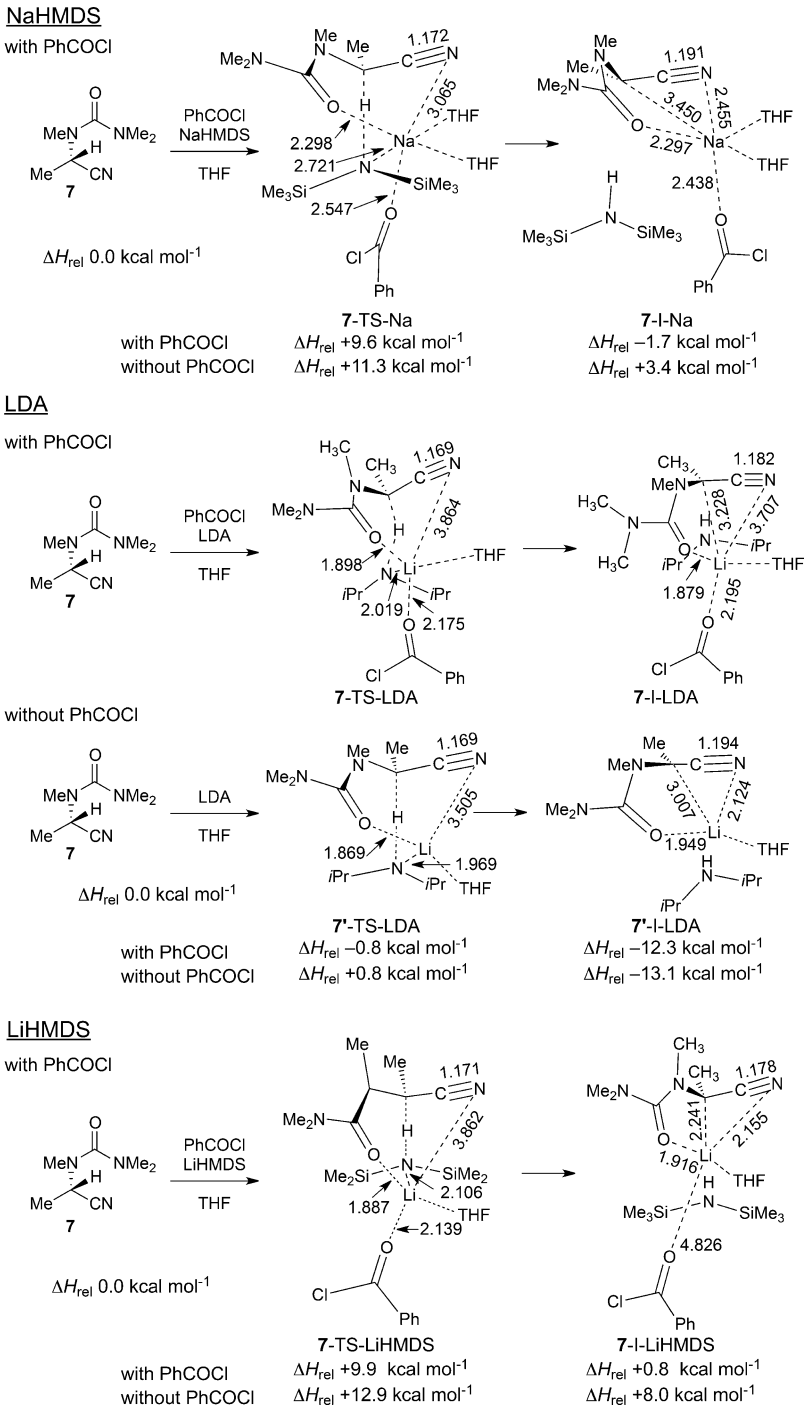


Entry	Base	*X*	Ar	6	Yield [%][a]	e.r.[b]
1	LDA	3	4-$MeOC_6H_4$	**6c**	83	81:19
2	LDA	3	4-$NO_2C_6H_4$	**6d**	–	–
3	LDA	3	2-FC_6H_4	**6e**	84	94:6
4	LDA	3	2-ClC_6H_4	**6f**	69	93:7
5	NaHMDS	5	4-$MeOC_6H_4$	**6c**	90	5:95
6	NaHMDS	5	4-$NO_2C_6H_4$	**6d**	–	–
7	NaHMDS	5	2-FC_6H_4	**6e**	91	3:97
8	NaHMDS	5	2-ClC_6H_4	**6f**	90	2:98

[a] Yield is that of isolated product. [b] (*R*)-**6**/(*S*)-**6**. Determined by HPLC on a chiral stationary phase.

In the case of LDA, the use of 4-methoxybenzoyl chloride, which forms a strong complex but has low electrophilicity, resulted in decreased enantioselectivity (Table 3, entry 1). However, for NaHMDS, which requires complexation for deprotonation, the reaction led to almost the same enantioselectivity as that with benzoyl chloride (Table 3, entry 5). In the case of 4-nitrobenzoyl chloride, unfortunately the reactions with both the bases resulted in recovery of the starting material (Table 3, entries 2 and 6), presumably as a consequence of consumption of 4-nitrobenzoyl chloride by reaction with the base. Anticipating an increase in an inversion product with NaHMDS because of its reduced ability to form a complex, we attempted reactions with 2-fluoro- and 2-chloro derivatives and they afforded almost the same enantioselectivity (Table 3, entries 3, 4, 7, and 8), probably because the enhanced reactivity of the 2-halognated derivatives toward an anionic species compensates for the reduced ability to complex a sodium cation. The results, however, show the generality of the enantiodivergent process that is dependent upon a base.

Since, to the best of our knowledge, there is no literature precedent for intermolecular electrophile-assisted deprotonation,[24] energetics for deprotonation were examined using α-(trimethylureido)propiononitrile (**7**; Scheme 2) as a model compound (DFT at the B3PW91/6-311++G(d,p) level) to estimate the possibilities of the participation of benzoyl chlorides in the transition-state structures of the deprotonation step by forming a precomplex with the metal cation of hexamethyldisilazide. It was found that in the case of NaHMDS, the benzoyl-chloride-assisted transition-structure **7**-TS-Na is 1.7 kcal mol^{-1} more favorable than a nonassisted one, thus leading to the intermediate **7**-I-Na ($\Delta H_{rel} = -1.7$ kcal mol^{-1}), which is 5.1 kcal mol^{-1} more favorable than an intermediate not involving benzoyl chloride ($\Delta H_{rel} = +3.4$ kcal mol^{-1}). In contrast, in the case of LDA, both a PhCOCl-assisted deprotonation leading to the transition-structure **7**-TS-LDA and a non-assisted deprotonation leading to the transition structure **7′**-TS-LDA were found to be much less endothermic than those of the sodium counterpart. These deprotonation processes generated thermodynamically stable intermediates, **7**-I-LDA and **7′**-I-LDA (−12.3 and −13.1 kcal mol^{-1}), which have about the same relative energy. It should also be noted that the carbanion species in **7′**-I-LDA is almost planarized and the pyramidalization angle is 20°. Consequently, it is reasonable to assume that in LDA-induced deprotonation/acylation, a precomplexed base with benzoyl chloride does not play an important role in determining the enantioselectivity. The results with LDA are consistent with the general trend that attack on carbon electrophiles by a relatively stable lithiocarbanion can occur from the less-hindered and uncoordinated backside of the molecule in which the electron density increases because of the partially flattened nature of the carbanion.[23] This behavior is not the case with LiHMDS, which despite having the same counter cation shows an energetic profile similar to



Scheme 2. DFT optimized structures for PhCOCl-assisted deprotonation of **7** and for formation of metalated anions by NaHMDS, LDA, and LiHMDS and their relative energies in simulated THF. Selected bond lengths [Å].

that obtained with NaHMDS. Thus, a PhCOCl-assisted deprotonation to generate the transition structure **7**-TS-LiHMDS is 3.0 kcal mol^{-1} more favorable than a nonassisted one, and the relative energy of the lithio anion intermediate **7**-I-LiHMDS is much higher than that of the corresponding intermediate generated by LDA (**7**-I-LDA), and even higher than that obtained by NaHMDS. This data is consistent with the experimental observation that the LiHMDS procedure is a rather low-yielding process. Although further detailed theoretical and structural investigations are required before definitive conclusions can be drawn, the present computational studies along with our experimental work provide support for the proposed hypothesis.

In conclusion, we have demonstrated that the deprotonation/benzoylation of α-ureidonitriles proceeds in a highly enantiodivergent manner, depending on the base used, to give both enantiomers of a benzoylated product in the absence of any further chiral elements. Based on the reactions using benzoyl halides which bear electronically different substituents and based on DFT calculations, a stereochemical rationale, which involves participation of an electrophile through precomplexation to the countercation of the base used in deprotonation, for the enantiodivergence was proposed.

Experimental Section

General procedure for acylation of (*S*)-**4**: Reaction of (*S*)-**4** with LDA and benzoylchloride: A solution of LDA (1.2 M in THF, 433 μL, 0.51 mmol) was added dropwise over a period of 2 min to a cooled (−100 °C) solution of (*S*)-**4** (40 mg, 0.17 mmol) and benzoyl chloride (60 μL, 0.51 mmol) in THF (2.97 mL). The mixture was stirred at the same temperature for 10 min before addition of CH_3COOH (1.0 M in THF, 0.51 mL, 0.51 mmol). The mixture was diluted with H_2O (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic phases were washed with saturated brine (10 mL), dried, and concentrated. The white solid was subjected to column chromatography (silica gel 10 g, elution with Et_2O) to give (*S*)-**6b** (51 mg, 87 %, e.r. = 94:6) as a white solid.

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