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Enantioselective trapping of an α-chiral carbanion of acyclic nitrile by a carbon electrophile†

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An α-chiral nitrile carbanion generated by deprotonation of enantioenriched *O*-carbamoyl cyanohydrin was trapped *in situ* with ethyl cyanoformate to give the corresponding ester derivative in 92% yield and 90 : 10 er, providing the first example of trapping of an α-chiral acyclic nitrile carbanion that has been considered to be very configurationally labile.

Although α-nitrile carbanions have been extensively used for carbon–carbon bond formation because of their powerful nucleophilic character due to the small steric demand,[1] extension to an enantioselective version using enantiopure chiral carbanions next to a nitrile group has been considered to be challenging because the chirality is immediately lost by the formation of an sp^2-hybridized keteniminate. Carlier reported that the calculated inversion barrier for lithioacetonitrile was extremely low (0.45 kcal mol^{-1}),[2] and X-ray analysis of lithiophenylacetonitrile indicated the geometry to be planar.[3] For carbonyl counterparts, Kawabata *et al.*,[4] Carlier *et al.*,[5] and others have proposed the concept of "memory of chirality" or "self-regeneration of stereocenters *via* stereolabile axially chiral intermediates"[6] that allows for the enantioselective introduction of an electrophile at an enolizable chiral center next to carbonyl functions. However, since the method is based on transfer of the central chirality at a chiral center to a transient axial chirality in the enolate intermediate, it would not be applicable to α-nitrile carbanions that probably cannot generate axially chiral intermediates. Although we have also reported that an α-nitrile carbanion formally generated *via* an S_E2' process in allylsilicates can be trapped by benzyl bromide[7] and protic solvents[8] in modest and good enantioselectivities, respectively, the possibility of intervention of a concerted process not involving a discrete α-nitrile carbanion cannot be ruled out and the methods lack substrate generality.

The only exception is a chiral cyclopropyl nitrile carbanion in which enantiospecific deuteration can be achieved in basic CH_3OD, which is explained in terms of enhanced angle strain in the inversion transition state.[9] It was also found in those studies that the corresponding chiral aliphatic nitrile derivative suffered extensive racemization under the same conditions. We report the first enantioselective *in situ* trapping of a chiral carbanion generated by deprotonation of an enantioenriched acyclic α-chiral nitrile at a practically promising level.

Successful embodiment of the formidable task would rely heavily on how to retain the configurational integrity of the extremely labile α-nitrile carbanions during the trapping process. The key elements in our approach are the use of *N*,*N*-dialkylcarbamoyloxy groups as a fixing agent for the lithium to the carbon atom in chiral carbanions generated by deprotonation of an enantioenriched precursor and the use of a highly reactive electrophile. Although *N*,*N*-dialkylcarbamoyloxy groups have become a powerful tool for generation of a chiral carbanion in combination with (−)-sparteine[10] since being introduced by Hoppe as dipole-stabilizing and directing groups in electrophilic substitution of allyllithium derivatives,[11] they have also been used as a fixing agent for a chiral carbanion in the absence of an external chiral ligand.[12] Thus, Hoppe and coworkers reported the generation of chiral α-lithio derivatives of 2-alkenyl, 2-alkynyl, and benzyl carbamates,[13] which are much more configurationally stable in comparison with the corresponding α-nitrile carbanions.

First, we chose enantioenriched *O*-carbamoyl cyanohydrin derivative **1a**, readily obtained from the corresponding *O*-acetyl derivative, as a substrate on the basis of our previous observation,[7] and we searched for a carbon electrophile that allows a rapid *in situ* trapping of a carbanion generated by deprotonation of **1a**. When LDA (1.1 equiv.) was added to a solution of **1a** and BnBr (5.0 equiv.) in Et_2O and the reaction was allowed to proceed at the same temperature for 5 min, benzylated product **3** was obtained in 45% yield and 52 : 48 enantiomeric ratio (er), along with the starting material in 42% yield and 62 : 38 er (Table 1, entry 1). The low enantiomeric purities of the benzylated product and of the starting material recovered indicate that the reactivity of BnBr is not high enough to trap the carbanion before racemization. Therefore we turned our attention to ethyl chloroformate and ethyl cyanoformate[14] as more reactive electrophiles, which were previously shown to be highly reactive towards α-nitrile anions.[15] The reaction with ethyl chloroformate was completed within 5 min to give ester derivative **4a** in 85% yield, but the enantiomeric ratio

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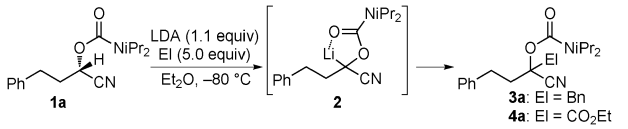
Table 1 Reaction of **1a** with LDA in the presence of an electrophile



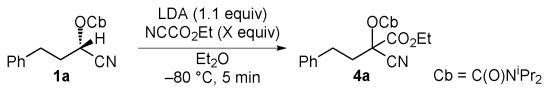
		3a, 4a		1a	
Entry	Electrophile	Yield (%)	er	Yield (%)	er
1	BnBr	45	52 : 48	42	62 : 38
2	$ClCO_2Et$	85	52 : 48	—	—
3	$CNCO_2Et$	39	74 : 26	57	100 : 0

remained low (52 : 48 er) (entry 2), suggesting the reactivity of chloroformate to be still too low. On the other hand, the use of ethyl cyanoformate greatly enhanced the enantiomeric ratio to 74 : 26, although the chemical yield sharply decreased to 39% and the starting material was recovered in 57% yield without racemization (entry 3). The results could be understood by assuming that LDA serves not only as a base but also as a nucleophile for cyanoformate because of its higher electrophilicity to give some byproducts and then a substantial amount of the starting material remained intact.

This analysis led us to use a reduced amount of cyanoformate, which would give a better chemical yield by suppressing its reaction with LDA. On changing its amount from five equivalents to one equivalent, a dramatic improvement of chemical yield from 39% to 76% was achieved as predicted, but the enantiomeric ratio was considerably lowered from 74 : 26 er to 63 : 37 er (Table 2, entries 1–5) probably because of the decreased concentration of cyanoformate. These results reveal that the rates of reaction of lithiocarbanion **2** with ethyl cyanoformate are similar in magnitude to that of racemization of α-nitrile carbanion **2**, which led us to conceive the idea that careful manipulation of experimental parameters would provide opportunities for successful enantioselective trapping of chiral α-nitrile-stabilized carbanions generated by deprotonation.

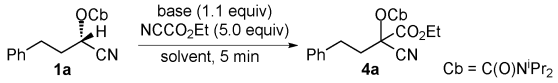
Change in solvent to toluene or THF decreased both the chemical yield and enantiomeric ratio (Table 3, entries 1–3). However, it should be noted that the use of THF provided **4** in moderate enantiomeric ratio (68 : 32), in sharp contrast to the result of chirality transfer in [2,3]-Wittig rearrangement employing a chiral allyl benzyl carbanion in which almost complete racemization was observed in THF against Et_2O.[16] Lowering of the reaction temperature improved the chemical yield and enantiomeric ratio (entries 1, 4 and 5) probably resulting from suppression of both the

Table 2 Effect of the amount of ethyl cyanoformate



		4a		1a	
Entry	X (equiv.)	Yield (%)	er	Yield (%)	er
1	5.0	39	74 : 26	57	100 : 0
2	4.0	41	73 : 27	53	100 : 0
3	3.0	51	67 : 33	47	100 : 0
4	2.0	69	67 : 33	26	100 : 0
5	1.0	76	63 : 37	—	—

Table 3 Effects of solvent and temperature



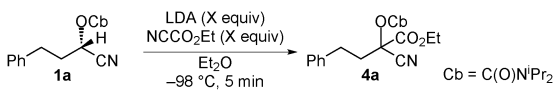
				4a		1a	
Entry	Solvent	T/°C	Base	Yield (%)	er	Yield (%)	er
1	Et_2O	−80	LDA	39	74 : 26	57	100 : 0
2	Toluene	−80	LDA	26	58 : 42	69	100 : 0
3	THF	−80	LDA	19	68 : 32	77	100 : 0
4	Et_2O	−50	LDA	32	66 : 34	66	100 : 0
5	Et_2O	−98	LDA	46	75 : 25	44	100 : 0
6	Et_2O	−98	LTMP	28	75 : 25	64	100 : 0
7	Et_2O	−98	$LiNEt_2$	10	—	85	100 : 0
8	Et_2O	−98	*t*-BuLi	—	—	93	100 : 0

racemization of **2** and the reaction of LDA with cyanoformate at lower temperatures. We next examined the effect of bulkiness and basicity of a base, which possibly affect the rates of deprotonation and of the reaction with cyanoformate. With less and more hindered bases, $LiNEt_2$ and LTMP, respectively, a decrease in chemical yield was observed in both cases (entries 6 and 7). The use of *t*-BuLi resulted in complete recovery of the starting material, probably due to the steric hindrance in deprotonation (entry 8).

Since the relatively low chemical yield in the reaction with cyanoformate is probably attributable to the competitive consumption of LDA by cyanoformate that was used in large excess to accelerate the reaction with carbanion **2**, we decided to use equal amounts of LDA and cyanoformate. The use of five equivalents resulted in a remarkable improvement in chemical yield (Table 4, entry 1). A decrease to three equivalents afforded almost the same result (entry 2), although a further decrease (1.1 equiv.) of the reagents led to a lowering of chemical yield (entry 3).

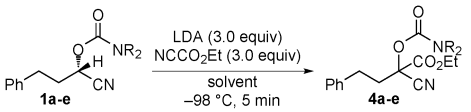
Having established that the use of equal amounts of LDA and cyanoformate gave an excellent chemical yield and a moderate enantiomeric ratio, we next focused our attention on improvement in enantioselectivity. We ascribed the origin of the moderate enantioselectivity observed under the above conditions to deceleration of the reaction of the carbanion with cyanoformate by the steric hindrance around the carbon atom next to the CN group. The steric congestion also retards the deprotonation process and, as a consequence, gives rise to the reaction of LDA with cyanoformate that may lead to more chance for racemization by lowering of the concentration of cyanoformate. From this point of view, we examined reactions using substrates bearing a carbamoyl group with different steric bulkiness. As expected, dimethylcarbamoyl derivative **1b**, the least sterically hindered, showed the highest enantioselectivity (85 : 15 er) (Table 5, entry 2),

Table 4 Effects of the amount of LDA and cyanoformate



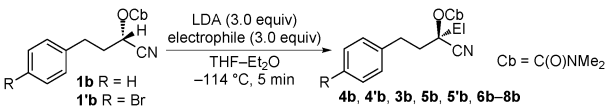
		4a		1a	
Entry	X	Yield (%)	er	Yield (%)	er
1	5.0	89	74 : 26	—	—
2	3.0	92	74 : 26	—	—
3	1.1	77	73 : 27	16	100 : 0

Table 5 Effect of the alkyl group in carbamate



				4a–e		1a–e	
Entry	1	NR_2	Solvent	Yield (%)	er	Yield (%)	er
1	**1a**	N^iPr_2	Et_2O	92	74 : 26	—	—
2	**1b**	NMe_2	THF : Et_2O (2 : 1)	88	85 : 15	—	—
3	**1c**	NEt_2	Et_2O	89	80 : 20	—	—
4	**1d**	$N(CH_2)_4$	Et_2O	72	76 : 24	23	100 : 0
5	**1e**	$N(CH_2)_5$	Et_2O	85	80 : 20	—	—

Table 6 Reactions of **1b** and **1′b** with an electrophile



Entry	R	Electrophile	El	Product	Yield (%)	er
1	H	$NCCO_2Et$	CO_2Et	**4b**	92	90 : 10
2	Br	$NCCO_2Et$	CO_2Et	**4′b**	81	88 : 12
3	H	BnBr	Bn	**3b**	89	50 : 50
4	H	$ClCO_2Et$	CO_2Et	**4b**	89	53 : 47
5	H	PhCOCl	COPh	**5b**	90	84 : 16
6	Br	PhCOCl	COPh	**5′b**	93	89 : 11
7	H	$CH_3CH_2CH_2$-COCl[a]	$COCH_2CH_2CH_3$	**6b**	84	81 : 19
8	H	$(CH_3)_2CHCOCl$	$COCH(CH_3)_2$	**7b**	85	74 : 26
9	H	$(CH_3)_3CCOCl$	$COC(CH_3)_3$	**8b**	87	61 : 39

[a] Five equivalents of LDA and butyryl chloride were used, respectively.

in which a mixed solvent system (THF–Et_2O = 2 : 1) was used because of the low solubility of **1b** in Et_2O.

Finally, we were pleased to find that lowering the reaction temperature to −114 °C provided further improvement in chemical yield and enantioselectivity, affording **4b** in 92% yield and 90 : 10 er (Table 6, entry 1). The absolute configuration of the major enantiomer was determined on the basis of X-ray crystallographic analysis with anomalous dispersion of a compound derived from the corresponding *p*-bromophenyl derivative **1′b** (entry 2, see ESI†), indicating that the substitution reaction occurs with inversion of the configuration, which is consistent with expectations from previous findings.[17]

The optimized conditions for ethyl cyanoformate were applied to the reactions with BnBr, ethyl chloroformate, and some acid chlorides. Whereas the former two reagents led to the formation of racemic or almost racemic products (entries 3 and 4), reactions with an acid chloride provided acylated derivatives in enantiomeric ratios depending on the reactivity of acid chlorides (entries 5–9).[18] The fact that the enantiomeric ratios increase as an acid chloride is more reactive or less bulky suggests again that the rate of racemization of the lithiocarbanion is similar in magnitude to that of reaction with the electrophiles.

In conclusion, we have demonstrated that a chiral α-nitrile carbanion generated by deprotonation of enantioenriched *O*-carbamoylcyanohydrin is able to be trapped by a carbon electrophile in up to 90 : 10 er by taking advantage of a combination of the fixing ability of a carbamoyl group and the high reactivity of an acylating agent. As a result, the scope of the fixation effect of carbamates was greatly expanded to include lithiocarbanions next to a nitrile group. The upper limit has so far been carbanions between allyl and benzyl groups.[17a] To our knowledge, this represents the first example of successful enantioselective trapping of an α-chiral acyclic nitrile carbanion.

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18 The absolute configurations of the major enantiomers of acylated products **5b–8b** were assigned by analogy to **5′b** whose absolute configuration was confirmed by X-ray crystallographic analysis with anomalous dispersion.