Amination of Optically Active Azaallylic Anions[†][‡]

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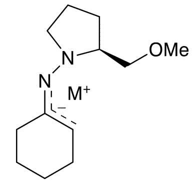
The reaction of azaallylic anions with ethyl *N*-[4-nitrobenzenesulfonyl)oxy]carbamate in the presence of a base gives a mixture of an α-amino ketone derivative with a slight preference for the (*S*) enantiomer and of an α-hydrazino ketone derivative as by-product; the same azaenolates react with bis(*tert*-butoxycarbonyl)diazene giving the analogous α-hydrazino ketone derivative, with a slight preference for the (*R*) enantiomer.

Chiral enamines, imines and hydrazones allow good enantio- and diastereo-selectivity in carbon–carbon bond-forming reactions.[1] We have recently been exploring the formation of carbon–nitrogen bonds starting from enamines.[2] Our attention was then directed towards the amination reaction of azaallylic anions derived from imines.

In this paper we describe results concerning the reactions of two aminating agents, namely ethyl *N*-[(4-nitrobenzenesulfonyl)oxy]carbamate ($NsONHCO_2Et$) and bis(*tert*-butoxycarbonyl)diazene [$N_2(CO_2Bu^t)_2$, TBD] with azaallylic anions. The reaction of $NsONHCO_2Et$ in the presence of LiOH was first carried out with the *N*-cyclohexylidenebenzylamine lithium salt **1** in order to optimise the yields of 2-[(ethoxycarbonyl)amino]cyclohexanone **2** (Scheme 1). The best results were obtained using a mixture of THF or DME and CH_2Cl_2. As a base we first chose LiOH in order to have a common cation in the reaction mixture. The best conditions are those of entry 5 (Table 1).

We note that this is the first successful amination by $NsONHCO_2Et$ at low temperatures, although electrophilic amination by TBD of ester enolates[3] and chiral amide cuprates[4] has been reported.



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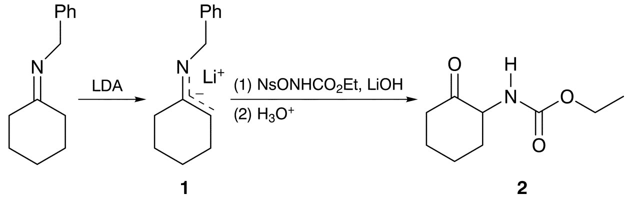
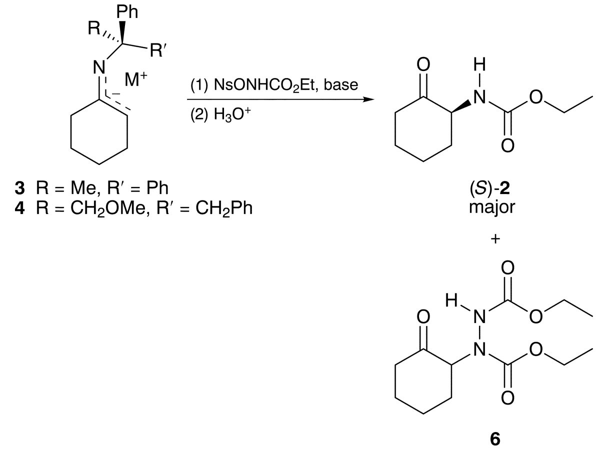
The reaction was then extended to chiral substrates **3** and **4** (Scheme 2). The chiral metallated hydrazone **5**, usually employed in alkylation reactions,[5] was unreactive. In Table 2 the results of reactions run using $NsONHCO_2Et$ are collected. Entries 1, 7 and 9 refer to the best conditions of Table 1.



Scheme 1

The major enantiomer of **2** showed an *S* configuration[6] as expected on the basis of an attack from the less hindered side and as previously noted in the amination of (*S*)-(−)-1-(1-cyclohexenyl)-2-(methoxymethyl)pyrrolidine in the presence of calcium oxide.[2b] When the anion was generated by the use of KH (entries 4, 6 and 8) the e.e. rose slightly, according to data reported for the alkylation of *N,N*-disubstituted amides.[7] The large excess of LiOH required for the $NsONHCO_2Et$ deprotonation, might be responsible for the low e.e. observed in the aminations of **4**, probably interfering with the formation of a rigid five membered chelate.[8]



Scheme 2

Table 1 Amination of compound **1** with $NsONHCO_2Et$ and LiOH

Entry	Solvent	*T* (°C)	Molar ratio **1**: $NsONHCO_2Et$: LiOH	Reaction time (h)	Yield of **2** (%)
1	THF	0	1:3:10	20	2
2	THF	–50	1:3:10	24	5
3	DME	–70	1:3:10	3	16
4	THF/CH_2Cl_2	–70	1:3:10	2	10
5	DME/CH_2Cl_2	–70	1:3:10	3	32
6	DME/CH_2Cl_2	–70	1:5:10	3	31

TBD gives a slow amination reaction only in the presence of HMPA, showing a lower reactivity towards this kind of azaenolates than that observed towards enolates.[9] The reaction conditions and the yield of 2-[*N,N*′-bis(*tert*-butoxycarbonyl)hydrazino]cyclohexanone **7** (Scheme 3) are reported in Table 3. The *R* configuration of the major enan-

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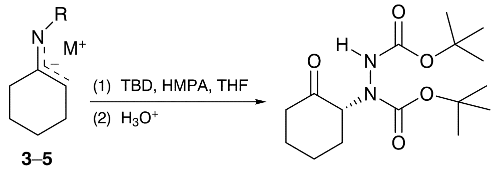
Table 2 Amination of compounds **3**, **4** and **5** with $NsONHCO_2Et$

Entry	Substrate	M	Added base	Molar ratio substrate:$NsONHCO_2Et$ base	Yield of **2** (e.e., %)	Yield of **6** (e.e., %)
1	**3**	Li	LiOH	1:3:10	23% (28)	–
2	**3**	Li	Et_3N	1:3:3.5	–	22% (–)
3	**3**	Li	–	2:1:–	–	13% (–)
4	**3**	K	LiOH	1:3:10	25% (34)	10% (8)
5	**3**	K	K_2CO_3	1:3:10	–	–
6	**3**	K	CaO	1:3:10	13% (30)	10% (8)
7	**4**	Li	LiOH	1:3:10	12% (24)	–
8	**4**	K	LiOH	1:3:10	10% (36)	5% (9)
9	**5**	Li	LiOH	1:3:10	–	–
10	**5**	K	LiOH	1:3:10	–	–

tiomer and the e.e. values were established on the basis of the $[\alpha]_D$ values (see Experimental section). In this case the observed reversal of facial selectivity might be rationalised if one assumes a role of HMPA, as suggested in alkylation of hydrazone lithio anions.[10]



3–5

(*R*)-**7**
major

Scheme 3

Free bases of the salts **1**, **3** and **5**, were treated directly with TBD in toluene at reflux, under conditions reported for Michael additions to the same substrates.[11] After 2–5 h of heating and subsequent hydrolytic work-up, the first two bases gave the same product **7** in 45 and 30% yield, respectively. In the last case only 5% e.e. was found.

Experimental

General Procedure for the Reactions of **1** *with* $NsONHCO_2Et$.—A solution of Bu^nLi in hexane (Fluka, 25 mmol, 1.6 M) was added dropwise to a solution of diisopropylamine (25 mmol) in 20 ml of THF or DME, under nitrogen at 0 °C, and stirred for 30 min to obtain LDA. Then *N*-cyclohexylidenebenzylamine (20 mmol) in 150 ml of anhydrous THF or DME or CH_2Cl_2 (Table 1, entries 4–6) was added slowly and the mixture stirred for 1.5 h. Anhydrous LiOH (Carlo Erba) was added batchwise and $NsONHCO_2Et$ added portionwise in 30 min. The mixture was allowed to warm to room temperature, poured into water–THF, acidified to pH ≈3 with 1 M oxalic acid and extracted with diethyl ether. Compound **2**[12] was collected by flash chromatography on silica gel (hexane–diethyl ether, 1:1) in the yields reported in Table 1.

Reaction of **3**, **4** *and* **5** *with* $NsONHCO_2Et$.—The general procedure was followed, changing the cation (entries 4–6, 8 and 10 of Table 2), the bases (entries 2, 3, 5 and 6) and the molar ratios (entries 2 and 3). After work-up, the products **2** and/or **6**[13] were separated by flash chromatography on silica gel. The e.e. was evaluated upon conversion into diastereomeric ketals with (2*R*,3*R*)-2,3-butanediol.[6] **6**: δ_C 14.20, 24.14 (CH_3) 26.56, 29.52, 30.58, 41.18 (CH_2), 61.84 (NCH), 62.19, 62.75 (OCH_2), 156.65 (CO_2) and 207.67 (CO).

Reaction of **3**, **4** *and* **5** *with* TBD.—A solution of Bu^nLi in hexane (50 mmol, 1.6 M) was added dropwise to a solution of diisopropylamine (50 mmol) in 200 ml of THF, under nitrogen at 0 °C, and stirred to obtain LDA. After 30 min HMPA (50 ml) and **3**, **4** or **5** (20 mmol) in 100 ml of anhydrous THF were added slowly and the mixture was stirred for 1.5 h. TBD (Fluka) in 100 ml of THF was added in the molar ratios reported in Table 3. After 1 h, the mixture was allowed to warm to room temperature and stirred (3–8 d) in the dark. After work-up with water–THF and 1 M oxalic acid, the mixture was extracted with diethyl ether and the organic layer washed with a saturated solution of NaCl. Compound **7**[2b] was collected by flash chromatography on silica gel (hexane–ethyl acetate, 8 : 2) in the yields and e.e. reported in Table 3. The e.e. was obtained by comparison between the $[\alpha]_D$ values (25 °C, *c* 0.12 in CH_2Cl_2) for **7** and that previously measured for a different enantiomeric mixture of the same α-hydrazino ketone derivative (–12, CH_2Cl_2).[2b]

Table 3 Amination of compounds **3**, **4** and **5** with TBD

Substrate	Molar ratio HMPA: substrate:TBD	Time (d)	Yield of **7** (e.e., %)	$[\alpha]_D$ of **7**
3	7:1:2.5	3	23% (–)	–
4	6:1:1.25	4	19% (29)	+9.0
5	6:1:1.25	8	28% (33)	+11.2

Reaction of free bases of **1**, **3** *and* **5** *with* TBD.—A solution of substrate (10 mmol) and TBD (12 mmol) and 50 ml of toluene was refluxed for 2–9 h. The mixture was poured into water–EtOH, acidified with 1 M oxalic acid and extracted with diethyl ether. After work-up, starting from the first two bases the product **7** was obtained by flash chromatography on silica gel (hexane–ethyl acetate, 8 : 2). Starting from the free base of **5**, only the substrate was recovered by flash chomatography.

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