Solvent-Free Synthesis of a Secondary *N*-Benzhydrylamine as a Chiral Reagent for Asymmetric Deprotonation of Bicyclic *N*-Benzylamino Ketones

Aneta Nodzewska,* Katarzyna Sidorowicz, Michal Sienkiewicz

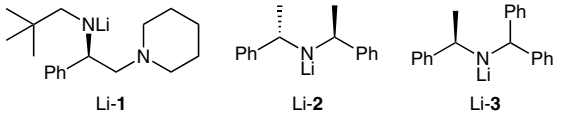
Institute of Chemistry, University of Bialystok, Hurtowa 1, 15-399 Bialystok, Poland
Fax +48(85)7470113; E-mail: annodz@uwb.edu.pl

Received: 20.12.2013; Accepted after revision: 17.02.2014

Abstract: Several chiral secondary *N*-benzhydrylamines were synthesized in good yields (68–92%) without racemization by the direct alkylation of amines with benzhydryl chloride under solvent-free conditions. Using the solvent-free conditions (*R*)-*N*-benzhydryl-1-phenylethylamine was obtained with the highest yield (92%), purified on ion-exchange resin, and converted to its hydrochloride salt. The resulting chiral amine hydrochloride was transformed into lithium amide/lithium chloride mixture used in asymmetric deprotonations of *N*-benzyl analogues of tropinone and granatanone followed by aldol reactions giving products in high diastereomeric purities (up to 96%) and enantiomeric excesses of 77 to 96%.

Key words: aldol reaction, N-alkylation, asymmetric synthesis, amines, enantioselectivity

The use of chiral lithium amides in asymmetric deprotonation[1] followed by aldol reaction is a successful method for C–C bond construction in enantioselective synthesis.[2] Koga's bidentate lithium amide Li-**1** (Figure 1)[3] and lithium bis(1-phenylethyl)amide (Li-**2**) (popularized by Simpkins)[4] are the most typical and effective chiral amide bases used in the deprotonation–aldol reaction of bicyclic bridged *N*-methyl β-amino ketones such as tropinone (**4**)[5] and granatanone (pseudopelletierine, **5**).[6]



Li-**1** Li-**2** Li-**3**

Figure 1 Chiral lithium amides used in the deprotonation of ketones

The enantiomerically pure enolates and aldols of tropinone obtained in this way have been used as key intermediates in stereoselective synthesis of tropane-based alkaloids.[7] Unfortunately, the substituted aldols of *N*-Bn, *N*-Cbz, and *N*-triazene analogues are generally formed with lower enantioselectivities (ee below 86%) by using Li-**1** and Li-**2**.[8] Efficient enantioselective synthesis of *N*-benzylnortropinone and *N*-benzylnorgranatanone aldols followed by hydrogenolysis of benzyl group may be vital for accessing nor-analogues of aldols and related synthetic intermediates for possible tropane or granatane based pharmaceutical agent.[9]

SYNTHESIS 2014, 46, 1475–1480
Advanced online publication: 24.03.2014
DOI: 10.1055/s-0033-1340955; Art ID: SS-2013-T0827-OP

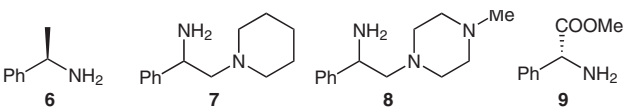
In search of selective deprotonating reagents, a decision was made to employ another known chiral lithium amide Li-**3**,[6] derivative from *N*-benzhydryl-1-phenylethylamine. Until now, the enantiomerically pure amine **3** has been prepared by a two-step low-yielding (up to 42%) procedure: (i) imine synthesis and (ii) reduction of imine to secondary amine ($LiAlH_4$,[10] H_2, Pd/C,[11] or catecholborane[12]) or in moderate yield (70–75%) by the reaction of α-methylbenzylamine (**6**) with *N*-benzhydryl bromide in DMPU.[13] Although N-alkylation of primary amines using benzhydryl halide is a well-known transformation, the typical reaction conditions involve the use of solvent such as DMF,[14] DCE,[15] $CHCl_3$,[16] MeCN,[17] or DMPU[13,18] and purification of products by column chromatography.

Herein, we wish to report a one-step, solvent-free, and chromatography-free synthesis of a chiral amine hydrochloride, the precursor of lithium amide Li-**3**, via direct N-benzhydrylation of 1-phenylethylamine (**6**). In this more environmentally benign process, other chiral primary amines can also be converted into corresponding *N*-benzhydryl derivatives.

Synthesis of Chiral *N*-Benzhydrylamines

Chiral secondary amines were obtained by the reaction of selected primary amines **6**–**8** (Figure 2, Table 1) with benzhydryl chloride in the absence of organic solvent at high temperature in good to excellent yields (68–92%). The product **3** was synthesized with the highest yield (92%) in 18 hours at 140 °C without racemization. The optical purity was checked by measuring the specific optical rotation of pure, free amine **3** ($[\alpha]_D^{20}$ +43.2, *c* 1.0, $CHCl_3$) and comparing it with the literature values ($[\alpha]_D^{25}$ +44.7, *c* 1.5, $CHCl_3$;[13] $[\alpha]_D^{20}$ +43.7, *c* 1.6, CH_2Cl_2[19]).

The amine **3** was isolated and purified on ion-exchange resin (Dowex 50WX2) by scavenging and subsequent releasing of the amine product. Thus, instead of using harmful organic solvents and time-consuming, hard-to-scale-up column chromatography on silica gel, we used more environmentally friendly solvents, that is, water, methanol, and aqueous ammonia in faster ion-exchange extraction, in order to remove the unreacted benzhydryl chloride

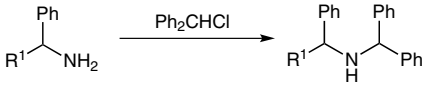


6 **7** **8** **9**

Figure 2 Substrates subjected to N-benzhydrylation under neat conditions

and side products (benzhydryl alcohol) from the amine. In this case, the use of an acid–base extraction during the workup was inadvisable due to poor dissolution and formation of emulsions. The resulting final amine product (methanol solution) was converted into hydrochloride salt by addition of aqueous hydrochloric acid and crystallized from a mixture of ethanol and ethyl acetate. The dried hydrochloride salt was a convenient form to use in the deprotonation reaction. Use of hydrochloride salt of *N*-benzhydryl-1-phenylethylamine contrary to free amine (sticky oil) offers many advantages. The solid salt is easy to dry, can be weighed accurately, and is easy to manipulate without a protective gas atmosphere. Unlike the free amine, the hydrochloride salt does not absorb carbon dioxide and water from the air during storage. Besides that, the reaction of amine hydrochloride salt with two equivalents of *n*-butyllithium generates a 1:1 mixture of lithium amide and lithium chloride, which often gives superior enantioselectivity in deprotonations of ketones.[5c] There is no need for addition of inorganic salts to improve selectivity, for example, lithium chloride, which may be hard to dry and dissolve in tetrahydrofuran, simplifies the reaction procedures significantly.

Table 1 Benzhydrylation of Primary Amines under Solvent-Free Conditions



Primary amine	*N*-Benzhydrylamine	Yield (%)
(*R*)-**6**	(*R*)-**3**	92
(*R*)-**7**	(*R*)-**10**	80
(*S*)-**7**	(*S*)-**10**	68
(*R*)-**8**	(*R*)-**11**	81
(*S*)-**8**	(*S*)-**11**	72
(*R*)-**9**	*rac*-**12**	52

Unfortunately, the solvent-free method of direct benzhydrylation has limitations: under neat N-alkylation conditions neither amino acid ester **9** nor amino alcohol (2-phenylglycinol obtained by the reduction of **9**) reacted selectively. In the reaction of **9** with *N*-benzhydryl chloride at 140 °C racemization of product occurred, whereas the corresponding amino alcohol did not react chemoselectively. The reaction gave a mixture of *N*-benzhydryl and *O*-benzhydryl products in a ratio of 1:4.

Application of Chiral *N*-Benzhydrylamines 3, 10, and 11 in Aldol Reactions

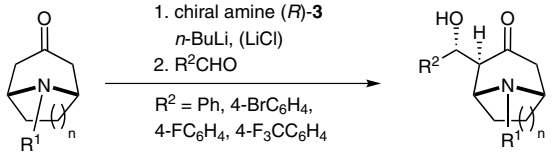
Tropinone and pseudopelletierine (granatanone) are stereoselectively deprotonated with chiral amide bases (under optimized condition) in the presence of lithium chloride, which is known to increase the enantioselectivity.[6,7b,20] In all cases the products are formed with excellent *exo*,*anti*-diastereoselectivity, up to 96%. Below, the optimization of conditions for the efficient, highly enantioselective, and easy to carry out deprotonation of *N*-benzyl analogues of tropinone **13** and granatanone **14** are described. During our earlier[8] and current research we have noticed that lithium *N*-benzhydryl-1-phenylethylamide (Li-**3**, 92% ee, Table 2, entry 3) was the most effective chiral deprotonating reagent of the three lithium amides (Li-**1**, Li-**2**, Li-**3**) tested in the aldol reactions of *N*-benzylnortropinone (**13**) with benzaldehyde.

Herein, we present the applications of this chiral lithium amide Li-**3** and other *N*-benzhydryl base amides for enantioselective aldol reactions of *N*-benzyl bicyclic amino ketones **13** and **14**, and the comparison of two typical procedures of asymmetric deprotonation. In the first procedure, free amine **3**, *n*-butyllithium (1.1 equiv), and lithium chloride additive were employed in an optimal[5c] amount range of 0.5–1 equivalent (per amide). In the second procedure, 1 equivalent of amine hydrochloride salt **3**·HCl and 2 equivalents of *n*-butyllithium were used. In all reactions, the lithium amide[21] was generated at 0 °C in THF solution, and cooled to –78 °C before the slow addition of a dissolved ketone. For the aldol reaction of *N*-benzylnortropinone with a representative aldehyde – benzaldehyde – the best results were obtained with the addition of a half equivalent of lithium chloride (92% ee, Table 2, entry 3). However, we observed that differences in achieved enantioselectivities with an amount of lithium chloride ranging from 0.5 to 1 equivalent were practically insignificant (within experimental error, Table 2, entries 2–6). Therefore, in the rest aldol reaction with *N*-benzylamino ketones, the easier and simpler procedure using amine hydrochloride salt was applied. In the asymmetric aldol reactions of *N*-benzylnortropinone and norgranatanone four aldehydes were employed: benzaldehyde, 4-bromobenzaldehyde, 4-fluorobenzaldehyde, and 4-trifluoromethylbenzaldehyde. The *exo*,*anti*-aldols were the only detectable products and were obtained in good yields (up to 88%) and with high enantiomeric excesses 77–96% (Table 2). Preparation of the lithium amide/lithium chloride mixture from amine hydrochloride gave good results by adding lithium chloride to lithium amide before deprotonation (Table 2, entries 5, 6, 9, 10, 14, 15).

These results demonstrate that amide Li-**3** was an effective enantiodifferentiating reagent, especially in asymmetric deprotonation of *N*-benzylnortropinone followed by reaction with 4-fluorobenzaldehyde (96% ee, entries 9, 10). Our earlier work[8] showed that reactions of N-substituted bicyclic amino ketones (**13**, **14**, and *N*-Cbz, *N*-triazene analogues of tropinone) using lithium amide bases (Li-**1** and Li-**2**) gave the aldols **16**, **18** with low to moderate enantiomeric excesses (8–86%). Using the reagent (*R*)-**3** for deprotonation–aldol reaction of *N*-benzylnortropinone and *N*-benzylnorgranatanone gave notably better results (72–96% ee).

The amide bases (*R*)-Li-**10** and (*R*)-Li-**11** were also tested in the deprotonation–aldol reactions of tropinone and *N*-benzylnortropinone with benzaldehyde. However, these reactions gave unsatisfactory conversions and yields. Un-

Table 2 Application of Amine (*R*)-**3** in Deprotonations of Bicyclic Amino Ketones



4 n = 1, R^1 = Me
13 n = 1, R^1 = Bn
5 n = 2, R^1 = Me
14 n = 2, R^1 = Bn

15 n = 1, R^1 = Me
16 n = 1, R^1 = Bn
17 n = 2, R^1 = Me
18 n = 2, R^1 = Bn

Entry	Ketone	Aldol[a] (R^2)	LiCl (equiv)[b]	Yield (%)	ee (%)[c]
1	**4**	**15a**[a] (Ph)	0.7	78	77
2	**13**	**16a**[a] (Ph)	0	88	85
3	**13**	**16a** (Ph)	0.5	87	92
4	**13**	**16a** (Ph)	0.7	85	90
5	**13**	**16a** (Ph)	1	87	91
6	**13**	**16a** (Ph)	1[d]	81	90
7	**13**	**16b**[a] (4-BrC_6H_4)	0.5	76	75
8	**13**	**16b**[a] (4-BrC_6H_4)	1[d]	80	75
9	**13**	**16c** (4-FC_6H_4)	1	89	96
10	**13**	**16c** (4-FC_6H_4)	1[d]	88	96
11	**13**	**16d** (4-$F_3CC_6H_4$)	1[d]	90	80
12	**5**	**17a**[a] (Ph)	0.5	78	83
13	**5**	**17a**[a] (Ph)	1	82	82
14	**14**	**18a**[a] (Ph)	1	70	76
15	**14**	**18a**[a] (Ph)	1[d]	72	77
16	**14**	**18b** (4-BrC_6H_4)	1[d]	75	72
17	**14**	**18c** (4-FC_6H_4)	1[d]	65	85
18	**14**	**18d** (4-$F_3CC_6H_4$)	1[d]	70	78

[a] Syntheses and characterizations of compounds **15a**,[7c] **16a**,[22a] **16b**,[25] **17a**,[6] and **18a**[22b] are described in the literature.
[b] The amount of LiCl used in the reaction (per amide).
[c] The enantiomeric excesses of the crude products were measured by ^{1}H NMR in the presence of (*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol [(*R*)-TFAE].
[d] One equivalent of amine hydrochloride and two equivalents of *n*-BuLi were used.

der optimized conditions, the corresponding aldols **15a** and **16a** were formed with 23% and 10% conversion and enantiomeric excess of 70% and 49%, respectively, clearly indicating that sterically hindered reagents were unsuitable. Therefore, we abandoned further testing of these amide bases in asymmetric deprotonation of ketones **4**, **5**, **13**, and **14**.

In our earlier work, the relative configurations of *exo*,*anti*-aldols[22] **16b**, **18a** and *exo*,*syn*-**16b** were positively determined by X-ray crystal structure analysis. Based on previous experience with this type of aldols[23] the relative configurations of the new products **16c**,**d** and **18b–d** were defined as *exo*,*anti* by analogy to the known *exo*,*anti*-**16b** using relevant coupling constants of the characteristic doublets of the carbinol hydrogen C*H*(OH)–R (for all the *exo*,*anti*-isomers, *J* ranged from 2.5 to 3.6 Hz).[24]

The enantiomeric excesses of all the prepared *exo*,*anti*-aldols were measured by ^{1}H NMR spectroscopy in the presence of (*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol [(*R*)-TFAE]. Under these conditions, the doublet of carbinol hydrogen C*H*(OH)–R was separated into two doublets allowing for quick calculation of enantiomeric excesses. The characteristic doublet of the predominantly formed, known 1*R*,2*S*,5*S*,9*R*-enantiomer **16b**[25] was easily distinguishable because the signal for this enantiomer was downfield (4.96 ppm) relative to the doublet of the minor enantiomer (4.93 ppm). The absolute configuration of the major 1*R*,2*S*,5*S*,9*R*-enantiomer **16b**[25] formed in the deprotonation–aldol reaction with chiral amide (*R*)-Li-**3** was determined from crystal structure. The absolute configuration of all major enantiomers of aldols formed in the tested reactions were determined from the relative position of signals corresponding to the carbinol hydrogen C*H*(OH)–R in ^{1}H NMR spectra recorded in the presence of (*R*)-TFAE (as shown in Table 2).

In summary, an efficient (92% yield), solvent-free synthesis of chiral *N*-benzhydryl-1-phenylethylamine (**3**) via direct N-alkylation reaction of α-methylbenzylamine (**6**) was developed. Product isolation using ion-exchange resin and crystallization provided chiral amine hydrochloride salt, which was an effective and convenient reagent to use for the asymmetric deprotonations of *N*-benzylnortropinone and *N*-benzylnorgranatanone. The reagent provided the highest, so far observed, enantioselectivity in deprotonation the *N*-benzyl analogues of tropinone and granatanone. Use of Li-**3**/LiCl mixture, generated from **3**·HCl, allowed to reach enantioselectivity up to 96% in the reaction of *N*-benzylnortropinone with 4-fluorobenzaldehyde. The aldol reactions of the bicyclic ketones mediated by the synthesized reagent provided products in good yields (65–89%) and with good enantiomeric excesses (77–96%).

Granatanone (**5**, pseudopelletierine), *N*-benzylnortropinone (**13**), and *N*-benzylnorgranatanone (**14**) were synthesized by an adapted literature procedure.[26] All air sensitive reactions were carried out under argon. THF was distilled under argon from sodium/benzophenone. TLC was performed on precoated plates (silica gel 60, F254). The spots were detected using UV light (254 nm), and phosphomolybdic acid. ^{1}H and ^{13}C NMR spectra were recorded at r.t. in $CDCl_3$ at 200 or 400 MHz and 50 or 100 MHz, respectively. The chemical shifts are reported relative to TMS. IR spectra were recorded on a FTIR spectrophotometer in $CHCl_3$. High-resolution mass spectra were recorded on a TOF spectrometer in ESI mode. The enantiomeric purities of aldols were determined by ^{1}H NMR in the presence of (*R*)-(–)-1-(9-anthryl)-2,2,2-trifluoroethanol [(*R*)-TFAE].

N-Alkylation of Secondary Amines: (*R*)-*N*-Benzhydryl-1-phenylethylamine Hydrochloride [(*R*)-3·HCl);[27] Typical Procedure

Anhydrous K_2CO_3 (3.04 g, 22.0 mmol) was added to a mixture of (*R*)-(+)-α-methylbenzylamine (**6**; 6.45 mL, 6.06 g, 50.0 mmol) and benzhydryl chloride (11.6 mL, 13.2 g, 65.0 mmol). The suspension was heated at 140 °C for 18 h, and then poured into EtOH (1 L) and H_2O (150 mL). The mixture was loaded on activated Dowex-50WX2 (ion-exchange resin), washed with MeOH (300 mL) and EtOAc (100 mL), and then eluted with MeOH–NH_3·H_2O (9:1) until no product was observable by TLC (eluent: MeOH–CH_2Cl_2 sat. with NH_3, 5.95). Collected ammonia solutions were concentrated. Then 10% aq HCl (4.5 mL) was added to the crude product, and H_2O was evaporated in vacuo. The product was crystallized from a mixture of EtOH and EtOAc to give (*R*)-**3**·HCl as a white solid; yield: 12.6 g (78%); mp 203–204 °C; $[\alpha]_D^{20}$ –99.0 (*c* 1.10, $CHCl_3$).

IR (KBr): 3375, 2937, 2784, 1577, 1457 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.66 (t, *J* = 11.0 Hz, 1 H, NH·HCl), 10.43 (t, *J* = 11.0 Hz, 1 H, NH·HCl), 7.72–7.05 (m, 15 H, ArH), 4.73 [d, *J* = 9.4 Hz, 1 H, C*H*(Ph)$_2$], 4.07–3.96 (m, 1 H, C*H*Me), 1.36 (d, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2, 134.6, 133.8, 133.0, 129.2, 129.1, 129.0, 128.7, 128.64, 128.59, 128.5, 128.4, 64.6, 58.6, 20.0.

(*R*)-*N*-Benzhydryl-1-phenyl-2-(piperidin-1-yl)ethanamine [(*R*)-10]

Isolated from **10**·HCl solution by extraction; yield: 1.48 g (80%, 5 mmol scale); yellow oil; $[\alpha]_D^{20}$ –76.6 (*c* 0.70, $CHCl_3$); R_f = 0.7 (MeOH–CH_2Cl_2, 1:9).

IR ($CHCl_3$): 3291, 2938, 1493, 1453, 909 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.11 (m, 15 H, ArH), 4.62 [s, 1 H, C*H*(Ph)$_2$], 3.66 (dd, *J* = 11.2, 3.2 Hz, 1 H, NHC*H*CH_2), 2.52 [t, *J* = 11.7 Hz, 1 H, PhCHC*H*(H)N], 2.35–2.22 (m, 2 H, CH of piperidine ring), 2.22–2.18 [m, 3 H, PhCHC*H*(H)N, CH of piperidine ring], 1.64–1.48 (m, 4 H, piperidine CH_2), 1.48–1.32 (m, 2 H, piperidine CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 143.9, 143.1, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5, 127.1, 126.8, 126.4, 66.4, 62.7, 56.5, 54.5, 26.1, 24.4.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{31}N_2$: 371.2487; found: 371.2473.

(*R*)-*N*-Benzhydryl-2-(4-methylpiperazin-1-yl)-1-phenylethanamine [(*R*)-11]

Isolated from **11**·HCl solution by extraction; yield: 1.56 g (81%, 5 mmol scale); yellow oil; $[\alpha]_D^{20}$ –80.2 (*c* 0.85, $CHCl_3$); R_f = 0.5 (MeOH–CH_2Cl_2, 1:9).

IR ($CHCl_3$): 3294, 2943, 2804, 1455, 1165, 909 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.42 (m, 2 H, ArH), 7.41–7.17 (m, 13 H, ArH), 4.62 [s, 1 H, C*H*(Ph)$_2$], 3.65 (dd, *J* = 11.2, 3.2 Hz, 1 H, NHC*H*CH_2), 3.28 (br s, 1 H, NH), 2.52 [t, *J* = 11.9 Hz, 1 H, PhCHC*H*(H)N], 2.65–2.15 (m, 8 H, CH of piperazine ring), 2.33 (s, 3 H, CH_3), 2.65 [dd, *J* = 12.3 Hz, 3.3 Hz, 1 H, PhCHC*H*(H)N].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 143.9, 142.6, 128.33, 128.25, 128.0, 127.9, 127.6, 127.4, 127.1, 126.9, 126.4.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{32}N_3$: 386.2596; found: 386.2589.

Methyl *rac*-2-(Benzhydrylamino)-2-phenylacetate (12)[28]

Isolated from **12**·HCl solution by extraction; yield: 0.862 g (52%, 5 mmol scale); yellow oil; R_f = 0.43 (hexanes–EtOAc, 85:15).

IR ($CHCl_3$): 3339, 3065, 1735, 1494, 1454, 1173 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.46–7.18 (m, 15 H, ArH), 4.75 [s, 1 H, C*H*(Ph)$_2$], 4.36 (s, 1 H, C*H*CO_2Me), 3.68 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4, 143.03, 143.02, 138.0, 128.6, 128.5, 128.4, 128.0, 127.44, 127.37, 127.31, 127.2, 127.1, 64.2, 62.7, 52.0.

Enantioselective Deprotonation Using Amine Hydrochloride Followed by Aldol Reaction; (–)-(1*R*,2*S*,5*S*)-8-Benzyl-2-[(*R*)-(4-fluorophenyl)(hydroxy)methyl]-8-azabicyclo[3.2.1]octan-3-one [(–)-*exo*,*anti*-16c]; Typical Procedure

To a cooled (0 °C) solution of chiral (*R*)-**3**·HCl (0.517 g, 1.60 mmol, 1.05 equiv) in THF (4 mL) was added a solution of *n*-BuLi in hexane (1.28 mL, 2.50 M, 3.19 mmol, 2.1 equiv) in THF (2 mL). The mixture was stirred for 50 min, cooled to –78 °C and a solution of *N*-benzylnortropinone (**13**; 0.327 g, 1.52 mmol, 1 equiv) in THF (2 mL) was added dropwise. After stirring for 1 h, 4-fluorobenzaldehyde (0.208 g, 1.67 mmol, 1.1 equiv) was added. The mixture was stirred for another 10 min, and then the reaction was quenched with aq NH_4Cl (10 mL), and extracted with CH_2Cl_2 (3 × 12 mL). The combined extracts were dried (Na_2SO_4) and concentrated under vacuum. Precipitation from a mixture of CH_2Cl_2–hexane gave *exo*,*anti*-**16c**; yield: 0.454 g (88%); 96% ee [^1H NMR in the presence of (*R*)-TFAE]; white solid; mp 110–111 °C; 99% ee after recrystallization; $[\alpha]_D^{20}$ –33.8 (*c* 0.65, MeOH); R_f = 0.5 (hexanes–EtOAc–Et_3N, 72:18:10).

IR ($CHCl_3$): 3011, 2962, 1712, 1607, 1511, 1069 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.32 (m, 5 H, ArH), 7.20–7.11 (m, 2 H, ArH), 6.90–6.70 (m, 2 H, ArH), 5.07 [d, *J* = 2.9 Hz, 1 H, C*H*(OH)Ph], 3.75–3.66 (m, 3 H, NC*H*$_2$Ph, NCH, C1), 3.63–3.55 (m, 1 H, NCH, C5), 2.79 [ddd, *J* = 15.9, 4.7, 1.8 Hz, 1 H, *ax*-C*H*(H)CO], 2.40 [d, *J* = 2.2 Hz, 1 H, C*H*CH(OH)Ar], 2.38–2.15 [m, 3 H, *eq*-C*H*(H)CO, C*H*(H) (C6, C7)], 1.75–1.52 [m, 2 H, C*H*(H) (C6, C7)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.2, 161.9 (d, $^1J_{C,F}$ = 243 Hz), 137.5, 137.4 (d, $^4J_{C,F}$ = 3 Hz), 129.0, 128.8, 127.8, 127.1 (d, $^3J_{C,F}$ = 8 Hz), 114.8 (d, $^2J_{C,F}$ = 21 Hz), 75.9, 65.0, 64.4, 58.9, 57.0, 51.6, 26.8, 26.4.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{23}FNO_2$: 340.1713; found: 340.1708.

(+)-(1*R*,2*S*,5*S*)-8-Benzyl-2-{(*R*)-hydroxy[4-(trifluoromethyl)phenyl]methyl}-8-azabicyclo[3.2.1]octan-3-one [(+)-*exo*,*anti*-16d]

Yield: 0.526 g (90%); white solid; mp 120–122 °C; 80% ee; $[\alpha]_D^{20}$ +1.8 (*c* 1.15, $CHCl_3$); R_f = 0.5 (hexanes–EtOAc–Et_3N, 72:18:10).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.3 Hz, 2 H, ArH), 7.48–7.32 (m, 5 H, ArH), 7.31 (d, *J* = 8.4 Hz, 2 H, ArH), 5.13 [d, *J* = 2.5 Hz, 1 H, C*H*(OH)Ph], 3.77–3.66 (m, 3 H, NC*H*$_2$Ph, NCH, C1), 3.63–3.57 (m, 1 H, NCH, C5), 2.79 [ddd, *J* = 16.0, 4.7, 1.9 Hz, 1 H, *ax*-C*H*(H)CO], 2.45 [d, *J* = 2.0 Hz, 1 H, C*H*CH(OH)Ar], 2.40–2.18 [m, 3 H, *eq*-C*H*(H)CO, C*H*(H) (C6, C7)], 1.76–1.59 [m, 2 H, C*H*(H) (C6, C7)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8, 145.6, 137.4, 129.3 (q, $^2J_{C,F}$ = 32 Hz), 129.1, 128.9, 127.9, 125.9, 125.0 (q, $^3J_{C,F}$ = 4 Hz), 124.2 (q, $^1J_{C,F}$ = 272 Hz), 76.0, 65.1, 63.9, 59.0, 57.0, 51.6, 26.9, 26.5.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{23}F_3NO_2$: 390.1681; found: 390.1684.

(+)-(1*R*,2*S*,5*S*)-9-Benzyl-2-[(*R*)-(4-bromophenyl)(hydroxy)methyl]-9-azabicyclo[3.3.1]nonan-3-one [(+)-*exo*,*anti*-18b]

Yield: 0.466 g (75%); white solid; mp 124–125 °C; 72% ee; $[\alpha]_D^{20}$ +7.1 (*c* 0.60, $CHCl_3$); R_f = 0.37 (hexanes–EtOAc–Et_3N, 72:18:10).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.48 (m, 7 H, ArH), 7.07 (d, *J* = 8.4 Hz, 2 H, ArH), 6.98 (br s, 1 H, OH), 5.10 [d, *J* = 3.6 Hz, 1 H, C*H*(OH)Ph], 4.08 (d, *J* = 12.8 Hz, 1 H, NC*H*$_2$Ph), 4.04 (d, *J* = 12.8 Hz, 1 H, NC*H*$_2$Ph), 3.43 (d, *J* = 3.5 Hz, 1 H, NCH, C1), 3.37 (br s, 1 H, NCH, C5), 2.87 [dd, *J* = 16.4 Hz, *J* = 7.0 Hz, 1 H,

ax-C*H*(H)CO], 2.51 [d, *J* = 3.5 Hz, 1 H, C*H*CH(OH)Ar], 2.43 [d, *J* = 16.4 Hz, 1 H, *eq*-C*H*(H)CO], 2.21–2.09 [m, 2 H, C*H*(H) (C6, C8)], 1.68–1.59 [m, 2 H, C*H*(H) (C6, C8)], 1.42–1.30 [m, 2 H, CH_2 (C7)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 140.5, 137.2, 131.1, 129.1, 128.9, 127.9, 127.3, 121.1, 77.03, 61.1, 58.6, 56.0, 51.2, 48.5, 23.3, 22.8, 16.5.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}BrNO_2$: 414.1069; found: 414.1065.

(–)-(1*R*,2*S*,5*S*)-9-Benzyl-2-[(*R*)-(4-fluorophenyl)(hydroxy)methyl]-9-azabicyclo[3.3.1]nonan-3-one [(+)-*exo*,*anti*-18c]

Yield: 0.345 g (65%); white solid; mp 68–69 °C; 85% ee; $[\alpha]_D^{20}$ –11.8 (*c* 0.75, $CHCl_3$); R_f = 0.5 (hexanes–EtOAc–Et_3N, 72:18:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.27 (m, 5 H, ArH), 7.21–7.13 (m, 2 H, ArH), 6.98 (t, *J* = 8.7 Hz, 2 H, ArH), 5.12 [d, *J* = 3.6 Hz, 1 H, C*H*(OH)Ph], 4.09 (d, *J* = 12.8 Hz, 1 H, NCH_2Ph), 4.04 (d, *J* = 12.8 Hz, 1 H, NCH_2Ph), 3.43 (d, *J* = 3.2 Hz, 1 H, NCH, C1), 3.37 (br s, 1 H, NCH, C5), 2.89 [dd, *J* = 16.3, 7.0 Hz, 1 H, *ax*-C*H*(H)-CO], 2.51 [d, *J* = 3.2 Hz, 1 H, C*H*CH(OH)Ar], 2.43 [d, *J* = 16.3 Hz, 1 H, *eq*-C*H*(H)CO], 2.25–2.08 [m, 2 H, C*H*(H) (C6, C8)], 1.70–1.52 [m, 2 H, C*H*(H) (C6, C8)], 1.43–1.30 [m, 2 H, CH_2 (C7)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.4, 162.0 (d, $^1J_{C,F}$ = 243 Hz), 137.4, 137.2 (d, $^4J_{C,F}$ = 3 Hz), 129.1, 128.9, 127.9, 127.2 (d, $^3J_{C,F}$ = 8 Hz), 114.9 (d, $^2J_{C,F}$ = 21 Hz), 77.1, 61.5, 58.6, 56.1, 51.4, 48.6, 23.3, 22.8, 16.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}FNO_2$: 354.1869; found: 354.1875.

(–)-(1*R*,2*S*,5*S*)-9-Benzyl-2-{(*R*)-hydroxy[4-(trifluoromethyl)phenyl]methyl}-9-azabicyclo[3.3.1]nonan-3-one [(+)-*exo*,*anti*-18d]

Yield: 0.424 g (70%); white solid; mp 132–134 °C; 90% ee after recrystallization; $[\alpha]_D^{20}$ –3.7 (*c* 0.90, $CHCl_3$); R_f = 0.5 (hexanes–EtOAc–Et_3N, 72:18:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.2 Hz, 2 H, ArH), 7.48–7.30 (m, 5 H, ArH), 7.33 (d, *J* = 8.2 Hz, 2 H, ArH), 7.17 (br s, 1 H), 5.18 [d, *J* = 3.3 Hz, 1 H, C*H*(OH)Ph], 4.10 (d, *J* = 12.8 Hz, 1 H, NCH_2Ph), 4.06 (d, *J* = 12.8 Hz, 1 H, NCH_2Ph), 3.49 (d, *J* = 3.9 Hz, 1 H, NCH, C1), 3.39 (br s, 1 H, NCH, C5), 2.88 [dd, *J* = 16.4, 7.0 Hz, 1 H, *ax*-C*H*(H)CO], 2.59–2.55 [m, 1 H, C*H*CH(OH)Ar], 2.44 [d, *J* = 16.4 Hz, 1 H, *eq*-C*H*(H)CO], 2.27–2.12 [m, 2 H, CH_2 (C6, C8)], 1.70–1.50 [m, 2 H, C*H*(H) (C6, C8)], 1.48–1.32 [m, 2 H, C*H*(H) (C7)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.9, 145.4, 137.2, 129.4 (q, $^2J_{C,F}$ = 32 Hz), 129.1, 128.9, 128.0, 125.9, 125.0 (q, $^3J_{C,F}$ = 4 Hz), 124.2 (q, $^1J_{C,F}$ = 272 Hz), 77.2, 60.9, 58.8, 56.1, 51.3, 48.4, 23.3, 22.8, 16.5.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{25}F_3NO_2$: 404.1837 found: 404.1841.

Acknowledgment

We are grateful for the support from the University of Bialystok (BST-125, BMN-172) and the National Science Centre of Poland (Grant No. N N204 546939). We also thank Prof. R. Lazny for helpful discussion.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (b) Simpkins, N. S.; Weller, M. D. *Asymmetric Deprotonations using Chiral Lithium Amide Bases*, In *Topics in Current Stereochemistry*; Vol. 26; Gawley, R. E., Ed.; Wiley-VCH: Weinheim, **2010**.
(2) (a) Majewski, M.; Nowak, P. *J. Org. Chem.* **2000**, *65*, 5152. (b) Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y. *J. Org. Chem.* **2007**, *72*, 3065.
(3) Shirai, R.; Aoki, K.; Sato, D.; Kim, H.-D.; Murakata, M.; Yasukata, T.; Koga, K. *Chem. Pharm. Bull.* **1994**, *42*, 690.
(4) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.
(5) (a) Pollini, G. P.; Benetti, S.; De Risi, C.; Zanirato, V. *Chem. Rev.* **2006**, *106*, 2434. (b) Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3113. (c) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465. (d) Newcombe, N. J.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1995**, 831.
(6) Lazny, R.; Wolosewicz, K.; Zielinska, P.; Urbanczyk-Lipkowska, Z.; Kalicki, P. *Tetrahedron* **2011**, *67*, 9433.
(7) (a) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825. (b) Sienkiewicz, M.; Wilkaniec, U.; Lazny, R. *Tetrahedron Lett.* **2009**, *50*, 7196. (c) Lazny, R.; Sienkiewicz, M.; Olenski, T.; Urbanczyk-Lipkowska, Z.; Kalicki, P. *Tetrahedron* **2012**, *68*, 8236. (d) Majewski, M.; Lazny, R.; Ulaczyk, A. *Can. J. Chem.* **1997**, *75*, 754. (e) Majewski, M.; Lazny, R. *Tetrahedron Lett.* **1994**, *35*, 3653. (f) Lazny, R.; Nodzewska, A.; Sienkiewicz, M. *Pol. J. Chem.* **2006**, *80*, 659; *Chem. Abstr.* **2007**, *146*, 338050.
(8) Lazny, R.; Nodzewska, A.; Sienkiewicz, M. *Lett. Org. Chem.* **2010**, *7*, 21.
(9) Kusano, G.; Orihara, S.; Tsukamoto, D.; Shibano, M.; Coskun, M.; Guvenc, A.; Erdurak, C. S. *Chem. Pharm. Bull.* **2002**, *50*, 185.
(10) Duhamel, L.; Ravard, A.; Plaquevent, J. C.; Ple, G.; Davoust, D. *Bull. Soc. Chim. Fr.* **1990**, 787.
(11) Nowak, P. *Ph.D. Disssertation*; University of Saskatchewan: Canada, **1998**, http://library.usask.ca/theses/available/etd-10212004-001009/unrestricted/NQ32795.pdf (30.08.2012).
(12) Enders, D.; Rembiak, A.; Seppelt, M. *Tetrahedron Lett.* **2013**, *54*, 470.
(13) Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243.
(14) Lovick, H. M.; An, D. K.; Livinghouse, T. S. *Dalton Trans.* **2011**, *40*, 7697.
(15) Kirincich, S. J.; Xiang, J.; Green, N.; Tam, S.; Yang, H. Y.; Shim, J.; Shen, M. W. H.; Clark, J. D.; McKew, J. C. *Bioorg. Med. Chem.* **2009**, *17*, 4383.
(16) Page, P. C. B.; Allin, S. M.; Dilly, S. J.; Buckley, B. R. *Synth. Commun.* **2007**, *37*, 2019.
(17) Miyake, A.; Itoh, K.; Tada, N.; Tanabe, M.; Hirata, M.; Oka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2329.
(18) Selim, K. B.; Matsumoto, Y.; Yamada, K.-I.; Tomioka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8733.
(19) Sciebura, J.; Gawronski, J. *Tetrahedron: Asymmetry* **2013**, *24*, 683.
(20) Majewski, M.; Wang, F. *Tetrahedron* **2002**, *58*, 4567.
(21) In the reaction of *N*-benzhydrylamine with *n*-BuLi, the secondary amine hydrogen is removed, not the benzhydryl proton. Although the pK_a of diphenylmethane ($PhCH_2Ph$) is lower than that of the secondary amine, the rate of abstraction of the CH proton by *n*-BuLi is much slower than the rate of abstraction of proton from the heteroatom, that is, the kinetic acidity, not the thermodynamic acidity determines the deprotonation selectivity. The faster rate of proton abstraction can be observed experimentally. In the

presence of deuterated solvent, for example, MeOD, only the NH hydrogen is substituted by deuterium and is invisible in the NMR spectrum in contrast to Ph_2CH {^{1}H NMR (400 MHz, MeOD): δ = 7.45–7.08 (m, 15 H, ArH), 4.56 [s, 1 H, C*H*$(Ph)_2$], 3.64 (q, *J* = 6.7 Hz, 1 H, C*H*Me), 1.36 (d, *J* = 6.7 Hz, 3 H, CH_3)}. Signal from Ph_2CH is observed in the NMR spectrum of Li-**3**, obtained in the reaction of amine **3** with *n*-BuLi in THF-d_8 under typical reaction condition (0 °C, 30 min) in NMR tube {^{1}H NMR (400 MHz, THF-d_8): δ = 7.38–6.92 (m, 15 H, ArH), 4.81 [s, 1 H, C*H*$(Ph)_2$], 3.74 (q, *J* = 6.4 Hz, 1 H, C*H*Me), 0.95 (d, *J* = 6.6 Hz, 3 H, CH_3)}.

(22) (a) Brzezinski, K.; Lazny, R.; Sienkiewicz, M.; Wojtulewski, S.; Dauter, Z. *Acta Crystallogr., Sect. E* **2012**, *68*, o149. (b) Lazny, R.; Wolosewicz, K.; Dauter, Z.; Brzezinski, K. *Acta Crystallogr., Sect. E* **2012**, *68*, o1367.

(23) (a) Lazny, R.; Nodzewska, A.; Sidorowicz, K.; Kalicki, P. *Beilstein J. Org. Chem.* **2012**, *8*, 1877. (b) Lazny, R.; Wolosewicz, K. *Tetrahedron Lett.* **2013**, *54*, 1103.

(24) In many cases, heating during crystallization caused the *anti-syn* isomerization and the formation of *exo,syn*-products. The characteristic doublet of the carbinol hydrogen in the *exo,syn*-isomer was shifted upfield (about 0.1–0.2 ppm) and had a lower coupling constant (up to 2.2 Hz).

(25) Brzezinski, K.; Lazny, R.; Nodzewska, A.; Sidorowicz, K. *Acta Crystallogr., Sect. C* **2013**, *69*, 303.

(26) Momose, T.; Toshima, M.; Toyooka, N.; Hirai, Y.; Hans Eugster, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1307.

(27) Collino, F. *Boll. Chim. Farm.* **1969**, *108*, 355; *Chem. Abstr.* **1969**, *71*, 101431.

(28) Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2005**, *46*, 2025.

