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Memory of chirality trapping of low inversion barrier 1,4-benzodiazepin-2-one enolates

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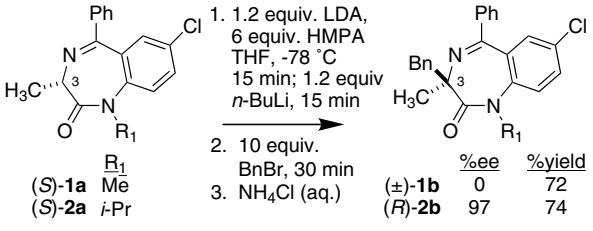
Abstract—We have previously demonstrated that chiral, enantiopure 3-substituted 1,4-benzodiazepin-2-ones undergo retentive deprotonation/trapping at −78 °C, if the N1-substituent is sufficiently large (e.g., *i*-Pr). Stereocontrol in this reaction is attributed to the formation of an enantiopure, conformationally chiral enolate; at −78 °C a large N1 substituent (e.g., *i*-Pr) is needed to impart a sufficient barrier to enolate racemization. Herein, we report strategies to achieve high enantiomeric excess in deprotonation/alkylation of low inversion barrier 1,4-benzodiazepin-2-ones featuring small N1 substituents.

1. Introduction

1,4-Benzodiazepin-2-ones, for example, **1a** and **2a**, are considered privileged scaffolds, because they have supported the development of drug candidates for a wide array of biomolecular targets.[1] To further expand the structural diversity within this scaffold, we developed an enantioselective route to analogs that feature a quaternary stereogenic center at C3 (e.g., **2b** in Scheme 1);[2] note that prior to our work these compounds were largely unknown.[3] Whereas deprotonation/alkylation of (*S*)-**1a** gives racemic **1b**, identical treatment of (*S*)-**2a** gives (*R*)-**2b** in 97% ee. Stereocontrol in the second case was attributed to 'memory of chirality',[4] whereby the original central chirality of **2a** is memorized in a chiral conformation of the derived enolate intermediate.[2]



(*S*)-**1a**
(*S*)-**2a**
(±)-**1b**
(*R*)-**2b**

Scheme 1. Enantioselective synthesis of quaternary 1,4-benzodiazepin-2-ones.

The racemic outcome realized with (*S*)-**1a** was proposed to be a consequence of the smaller N1 substituent and rapid racemization of the enolate at −78 °C. However, the possibility that **1a** forms an achiral enolate could not be ruled out. Herein, we report successful techniques for the enantioselective deprotonation/trapping of 1,4-benzodiazepin-2-ones that bear sterically small substituents at N1, such as **1a**. These results suggest the intermediacy of conformationally chiral enolate intermediates and open the way to the synthesis of enantiopure quaternary 1,4-benzodiazepin-2-ones bearing diverse N1 substitution.

2. Results and discussion

To test the hypothesis that the enolate derived from (*S*)-**1a** is conformationally chiral but rapidly racemizing, we sought to generate it under conditions where it could be instantaneously quenched. Thus, we performed an H–D exchange of *N*-methyl 1,4-benzodiazepin-2-ones (*S*)-**1a** and **3a**–**5a** (Scheme 2).

The required 'tertiary' 1,4-benzodiazepin-2-one starting materials (*S*)-**1a** and **3a**–**7a** were prepared in 100% ee from the corresponding (*S*)-*N*-Boc amino acids, according to our variation[2] of Shea and co-workers protocol.[5,6] H–D exchange of **1a** and **3a**–**5a** proved slow in basic CD_3OD, but after 6–13 days deuterium incorporation exceeded 94% (^{1}H NMR). As was hoped, analysis by chiral stationary phase HPLC indicated retention and

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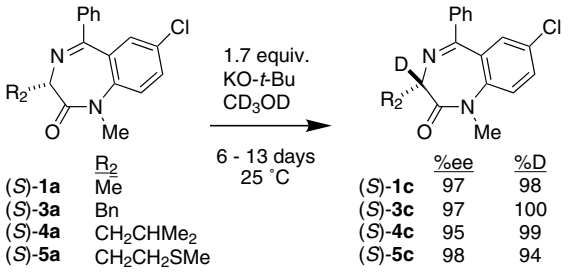


Scheme 2. Enantioselective H–D exchange of *N*-Me 1,4-benzodiazepin-2-ones **1a** and **3a**–**5a**.

95–98% ee in each case. This successful outcome can be rationalized in terms of a thermodynamically unfavorable deprotonation to a conformationally chiral enolate and instantaneous deuteration of this otherwise rapidly racemizing intermediate.

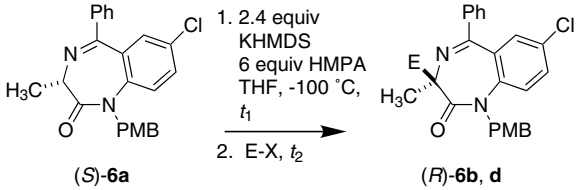
Encouraged by this success, we then attempted the enantioselective deprotonation/alkylation of *N*-PMB analog (*S*)-**6a**; realization of this goal would greatly expand the scope of our protocol, since facile removal of the PMB group would allow subsequent diverse functionalization at N1 (Table 1).

As we anticipated a low inversion barrier for the enolate derived from **6a**, we began our synthetic investigations at −100 °C (Et_2O/CO_2). Concurrent with these investigations, we examined a range of deprotonation protocols. Whereas, LiHMDS was ineffective for the deprotonation of **6a**, KHMDS proved an excellent base and offered a much simplified alternative to our published LDA/*n*-BuLi protocol.[2] After a 5 min deprotonation time (t_1) at −100 °C, the addition of BnBr essentially gave racemic **6b** (Table 1, entry 1). This unsatisfactory outcome led us to develop an in situ protocol ($t_1 = 0$) that involves deprotonation in the presence of the electrophile. The use of KHMDS proved essential here, since LDA apparently undergoes a competitive reaction with the electrophile. An immediate improvement in ee was observed which depended on the amount of electrophile added (Table 1, entries 2 and 3). Although 80% ee could be attained in the presence of 100 equiv of BnBr (Table 1, entry 3) it was clear that further improvement would require an acceleration of the alkylation rate constant. Benzyl iodide proved to be incompatible with the in situ protocol, most likely due to the rapid reaction with KHMDS. However, following a 10 s deprotonation time, the desired product (*R*)-**6b** was obtained in 88 ee (Table 1, entry 4).

The data in Table 1 indicate that the enolate derived from (*S*)-**6a** racemizes within minutes, even at −100 °C. To determine the approximate racemization half-life of this species, we performed deprotonation/quenching experiments. After considerable experimentation, we found superior results with the *N*-Bn analog (*S*)-**7a**: Following deprotonation for a time t, a protic quench was applied. Following the approach of Kawabata et al.[4b] the recovered starting material was analyzed by a chiral stationary phase HPLC, and $\ln(\%ee_t)$ was plotted versus time t (Fig. 1).

Note that the 61% benzylation yield obtained after a 10 s deprotonation of (*S*)-**6a** (Table 1, entry 4) suggests that the deprotonation of **7a** should be substantially complete at the first time point (30 s) in Figure 1. Similarly, the low ee (8%) obtained after 480 s indicates >90% deprotonation within 8 min. Therefore the recovered starting material **7** at all time points can be assumed to arise predominantly from protonation of an enolate intermediate. The plot of ln(%ee/100) versus t appeared roughly linear over three half-lives; the slope corresponds to $-k_{rac}$ and indicates an estimated racemization $t_{1/2}$ of 2.3 min at −100 °C. This value is consistent with the dependence of alkylation %ee on the deprotonation time (Table 1, entries 1 and 2). The dependence of alkylation %ee on the electrophile concentration (Table 1, entries 2 and 3) and reactivity (Table 1, entries 2 and 4) also shows competition between the racemization and alkylation. Application of the Eyring equation[7] to the estimated k_{rac} for the enolate derived from **7a** indicates a barrier to inversion ($\Delta G^{\ddagger}_{rac}$) of 12.0 kcal/mol at

Table 1. Sequential versus in situ enantioselective deprotonation/trapping of *N*-PMB 1,4-benzodiazepin-2-one (*S*)-**6a** at −100 °C



Entry	E–X (equiv)	t_1	t_2 (min)	Product	ee[a]	Yield (%)
1	BnBr (10)	5 min	120	**6b**	3	100
2	BnBr (20)	0 min	5	**6b**	75	78
3	BnBr (100)	0 min	1	**6b**	80	46
4	BnI (20)	10 s	1	**6b**	88	61
5	C_3H_5Br (100)	0	1	**6d**	65	38

[a] All reactions run at [**6a**] = 1.2 mM; enantiomeric excess determined by HPLC. Retention is assumed based on H–D exchange results in Scheme 2 and benzylation of the enolate derived from (*S*)-**2a**.

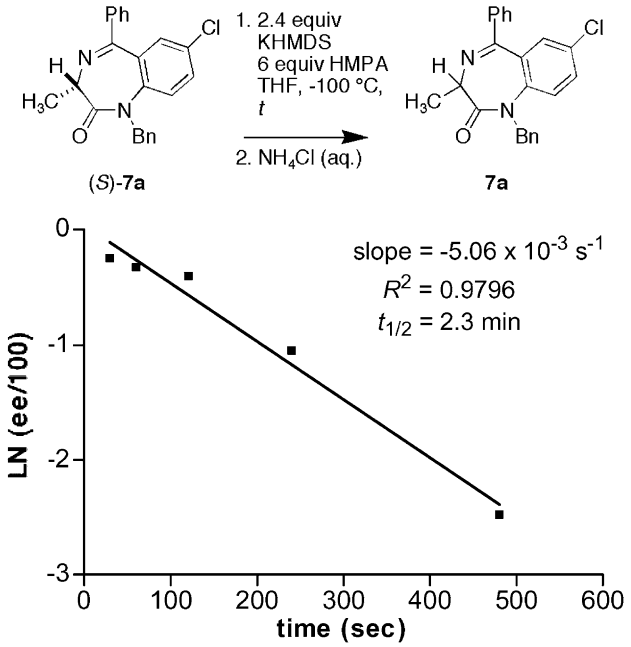


Figure 1. Estimation of the racemization half-life of the enolate derived from **7a**.

173 K, similar to the 11.5 kcal/mol previously calculated for the *N*-Me analog.[2] In contrast the enolate derived from *N*-*i*-Pr analog **2a** was calculated to have an inversion barrier of 17.5 kcal/mol (195 K).[2]

In the hope that slightly lowering the reaction temperature would result in a significantly improved enantioselection, we investigated deprotonation/alkylation reactions at −109 °C (THF/N_2 cooling bath). Indeed, at this temperature we found that excellent enantioselection could be obtained using a sequential protocol (20 min deprotonation time) and allylic and benzylic iodides (Table 2). Whereas, the highest %ee attained for benzylation at −100 °C was 88%, at −109 °C, product **6b** was obtained in 97 ee (Table 2, entry 1).[8] Reaction with allyl iodide occurs in 89% ee at −109 °C, which is a significant improvement from the 65% ee attained with allyl bromide at −100 °C (Table 2, entry 2). Substituted benzyl iodides also react in excellent enantiomeric excess (Table 2, entries 3 and 4). Finally, ethyl iodide reacts very slowly with the enolate at −109 °C. After 60 min, reaction time, only 8% of the desired product **6g** was obtained, while the 46% ee observed evidences substantial enolate racemization during the slow alkylation reaction.

We assigned the temperature of this protocol as −109 °C based on individual temperature measurements and the known freezing point of THF. However, localized supercooling in the THF/N_2 cooling slush may be partly responsible for these high enantioselectivities.

3. Conclusion

In conclusion, we have demonstrated enantioselective deprotonation/trapping sequences for 3-substituted 1,4-benzodiazepin-2-ones **1a**–**7a**. The observed dependencies of reaction %ee on temperature and the size of the N1 substituent add further support to our proposal that these transformations rely upon memory of chirality. Even when the barrier to inversion of the enolate is in the order of 12 kcal/mol (e.g., **1a** and **6a**), high enantioselectivities can be attained by room temperature base-catalyzed H–D exchange, or by sequential deprotonation/trapping at −109 °C. Finally, since the PMB protecting group of **6b**,**d**–**f** can be easily removed under mildly acidic conditions, this methodology could be used to prepare enantiopure quaternary benzodiazepines with diverse N1-functionalization.

Acknowledgments

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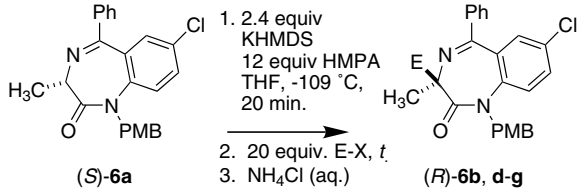
Table 2. Sequential enantioselective deprotonation/trapping of (*S*)-**6a** at −109 °C (THF/N_2)



Entry	E–X (equiv)	*t* (min)	Product	ee[a] (%)	Yield (%)
1	BnI	10	**6b**	97	93
2	C_3H_5I	5	**6d**	89	88
3	2-$PhC_6H_5CH_2I$	30	**6e**	97	81
4	4-$MeC_6H_5CH_2I$	10	**6f**	93	92
5	EtI	60	**6g**	46	8

[a] All reactions run at [**6a**] = 1.2 mM; % enantiomeric excess determined by HPLC. Retention is assumed based on H–D exchange results in Scheme 2 and benzylation of the enolate derived from (*S*)-**2a**.

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6. Synthesis of (*S*)-(+)-**6a** from L-Boc-Ala-OH. *Coupling reaction*: 2-amino-5-chlorobenzophenone (1.35 g, 5.81 mmol, 1.0 equiv) and L-Boc-Ala-OH (1.00 g, 5.82 mmol, 1.0 equiv) were combined in CH_2Cl_2 (20 mL) and DCC (1.20 g, 5.81 mmol, 1.0 equiv) was added at 0 °C. After stirring overnight, the urea by-product was filtered off and the filtrate was concentrated in vacuo. Flash chromatography yielded a white solid (1.57 g, 3.89 mmol, 75% yield), mp 152.5–153.9 °C; $[\alpha]_D^{25} = -49.5$ (*c* 1.00, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.48 (d, $^3J_{HH} = 7.3$ Hz, 3H), 4.33 (br s, 1H), 5.09 (br s, 1H), 7.49–7.54 (m, 4H), 7.62 (tt, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 1.2$ Hz, 1H), 7.69 (dd, $^3J_{HH} = 7.1$ Hz, $^4J_{HH} = 1.4$ Hz, 2H), 8.63 (d, $^3J_{HH} = 9.4$ Hz, 1H), 11.16 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 18.62, 28.34, 51.72, 80.46, 123.04, 125.04, 127.62, 128.59, 130.00, 132.69, 133.00, 133.94, 137.89, 138.62, 172.15, 198.03 (17C, found: 16); HRMS (FAB) calcd for $C_{21}H_{24}N_2O_4Cl$ $[M+H]^+$: 403.1425. Found: 403.1410 (−3.6 ppm, −1.5 mmu). HPLC $t_R(R)$: 16.6 min; $t_R(S)$: 20.0 min [Chiralpak AD (0.46 cm × 25 cm, Daicel Chemical Ind., Ltd.), hexane/*i*-PrOH, 90/10, 1.0 mL/min] 100% ee.
   Cyclization reaction: the above material (1.45 g, 6.25 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and trifluoroacetic acid (6 mL) added with stirring at 0 °C. After 1 h, the reaction mixture was concentrated in vacuo and dissolved in methanol (20 mL). This solution was stirred with 10% $NaHCO_3$/10% Na_2CO_3 (20 mL, both w/v) overnight, diluted with water (20 mL) and extracted with CH_2Cl_2 (6 × 50 mL). Flash chromatography yielded a white solid (1.10 g, 3.88 mmol, 62% yield), mp 204.9–205.5 °C; $[\alpha]_D^{25} = +124$ ($c = 0.925$, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.76 (d, $^3J_{HH} = 6.7$ Hz, 3H), 3.75 (q, $^3J_{HH} = 6.4$ Hz, 1H), 7.16 (dd, $^3J_{HH} = 8.7$ Hz, $^4J_{HH} = 2.7$ Hz, 1H), 7.29 (d, $^4J_{HH} = 2.1$ Hz, 1H), 7.37 (t, $^3J_{HH} = 7.7$ Hz, 2H), 7.42–7.47 (m, 2H), 7.51 (d, $^3J_{HH} = 8.1$ Hz, 2H), 9.50 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 17.07, 58.86, 122.72, 128.45, 128.74, 129.03, 129.77, 130.50, 130.57, 131.82, 137.17, 138.74, 167.91, 172.86; HRMS (FAB) calcd for $C_{16}H_{14}N_2OCl$ $[M+H]^+$: 285.0795. Found: 285.0779 (−5.5 ppm, −1.6 mmu). HPLC $t_R(R)$: 11.1 min; $t_R(S)$: 14.1 min [Chiralpak AD (0.46 cm × 25 cm, Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] 100% ee.
   N1-Alkylation reaction: the above material (200 mg, 0.70 mmol, 1.0 equiv) was dissolved in dry THF (10 mL), cooled to 0 °C and added to NaH (29 mg, 0.73 mmol, 1.05 equiv, 60% in mineral oil). After stirring for 20 min at 0 °C for 20 min, PMB–Br (2.11 mmol, 3.0 equiv) was added dropwise. After 10 min at 0 °C, TLC indicated complete reaction. The reaction was quenched at 0 °C with 10 mL of saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (5 × 20 mL). The combined extracts were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to afford (*S*)-**6a** as a white solid (217 mg, 0.535 mmol, 76% yield), mp 160.9–161.5 °C; $[\alpha]_D^{25} = +129$ (*c* 0.985, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.77 (d, $^3J_{HH} = 6.5$ Hz, 3H), 3.70 (s, 3H), 3.8 (q, $^3J_{HH} = 6.4$ Hz, 1H), 4.58 (d, $^2J_{HH} = 15.1$ Hz, 1H), 5.68 (d, $^2J_{HH} = 15.2$ Hz, 1H), 6.62 (d, $^3J_{HH} = 8.7$ Hz, 2H), 6.90 (d, $^3J_{HH} = 8.7$ Hz, 2H), 7.13 (d, $^4J_{HH} = 2.3$ Hz, 1H), 7.29–7.36 (m, 5H), 7.40 (dd, $^3J_{HH} = 8.8$ Hz, $^4J_{HH} = 2.4$ Hz, 1H), 7.44 (t, $^3J_{HH} = 7.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.46, 49.58, 55.26, 59.02, 114.11, 124.25, 128.33, 128.67, 129.00, 129.44, 129.55, 129.87, 130.55, 131.21, 132.74, 138.15, 140.37, 158.97, 167.27, 170.42; HRMS (FAB) calcd for $C_{24}H_{22}N_2O_2Cl$ $[M+H]^+$: 405.1370. Found: 405.1364 (−1.4 ppm, −0.6 mmu). HPLC $t_R(R)$: 12.9 min; $t_R(S)$: 18.5 min [Chiralpak AD (0.46 cm × 25 cm, Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] 100% ee.
7. Activation free energy is calculated as $\Delta G^{\ddagger} = -RT[\ln(k_{rac}) + \ln(h/2kT)]$: Eyring, H. *Chem. Rev.* **1935**, *17*, 65–77.
8. Synthesis of (*R*)-(+)-**6b**: to a stirred solution of (*S*)-**6a** (20.0 mg, 0.0494 mmol, 1.0 equiv) and HMPA (103 μL, 0.593 mmol, 12.0 equiv) in anhydrous THF (4.0 mL) at −109 °C (THF/N_2 slush) was added KHMDS (237 μL, 0.119 mmol, 2.4 equiv, 0.5 M in toluene). The resulting solution was stirred for a further 20 min before the benzyl iodide (216 mg, 0.99 mmol, 20 equiv) was added dropwise via syringe. The reaction was stirred at −109 °C until the starting benzodiazepine was consumed (TLC). The reaction was quenched at −109 °C with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to afford (*R*)-**6b** as a colorless oil (22.8 mg, 0.0461 mmol, 93% yield), $[\alpha]_D^{25} = +11.5$ (*c* 1.17, $CHCl_3$), ^{1}H NMR ($CDCl_3$) indicated a 60:40 mixture of axial-Me and equatorial-Me conformers δ 0.89 (s, 3H × 0.6 ax-Me), 1.85 (s, 3H × 0.4 eq-Me), 2.62 (d, $^2J_{HH} = 13.6$ Hz, 1H × 0.4 eq-Me), 2.68 (d, $^2J_{HH} = 13.6$ Hz, 1H × 0.4 eq-Me), 3.36 (d, $^2J_{HH} = 14.0$ Hz, 1H × 0.6 ax-Me), 3.79 (s, 3H), 3.84 (d, $^2J_{HH} = 14.0$ Hz, 1H × 0.6 ax-Me), 4.89 (d, $^2J_{HH} = 16.4$ Hz, 1H × 0.6 ax-Me), 4.93 (d, $^2J_{HH} = 17.2$ Hz, 1H × 0.4 eq-Me, overlapping with peak at 4.89), 5.56 (d, $^2J_{HH} = 15.2$ Hz, 1H × 0.4 eq-Me), 5.59 (d, $^2J_{HH} = 15.6$ Hz, 1H × 0.6 ax-Me, overlapping with peak at 5.56), 6.77 (d, $^3J_{HH} = 8.4$ Hz, 2H), 6.94–7.64 (m, 15H); ^{13}C NMR ($CDCl_3$) was consistent with an approximate 60:40 mixture of axial-Me and equatorial-Me conformers (46 resonances found for a possible 2 × 25 unique carbons): δ 17.61, 28.52, 37.81, 47.70, 51.62, 52.03, 55.31 (2 overlapping peaks), 66.07, 68.16, 114.15, 114.19, 123.37, 123.89, 126.31, 126.76, 127.57, 128.27, 128.42, 128.58, 128.93, 128.96, 129.09, 129.16, 129.36, 129.54, 129.66, 129.94, 130.36, 130.42, 131.33, 131.61, 132.25, 133.56, 133.64, 136.73, 138.46,

139.87, 139.96, 140.91, 140.93, 158.92, 158.96, 165.32, 165.86, 172.12, 172.80; HRMS (FAB) calcd for $C_{31}H_{28}N_2O_2Cl[M+H]^+$: 495.1839. Found: 495.1852 (+2.6 ppm, +1.3 mmu). HPLC $t_R(S)$: 11.1 min; $t_R(R)$: 16.5 min [Chiralpak AD (0.46 cm × 25 cm, Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] 97% ee.