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Synthetic Applications and Inversion Dynamics of Configurationally Stable 2-Lithio-2-arylpyrrolidines and -piperidines

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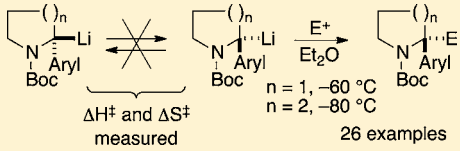
Supporting Information

ABSTRACT: In diethyl ether, *N*-Boc-2-lithio-2-arylpiperidines have been found to be configurationally stable at −80 °C, whereas *N*-Boc-2-lithio-2-arylpyrrolidines are configurationally stable at −60 °C. Several tertiary benzylic carbanions derived from enantioenriched 2-aryl heterocycles have been successfully alkylated or acylated with little to no loss of enantiopurity. The scope of the reactions has been explored. The enantiomerization dynamics of *N*-Boc-2-lithio-2-phenylpyrrolidine and *N*-Boc-2-lithio-2-phenylpiperidine have been studied in the presence of different solvents and achiral ligands.



INTRODUCTION

Enantioenriched 2-arylpyrrolidines and -piperidines have recently become available by a lithiation/transmetalation/arylation sequence. Specifically, Campos demonstrated that enantioenriched *N*-Boc-2-arylpyrrolidines are available by enantioselective deprotonation using *sec*-butyllithium/(−)-sparteine followed by transmetalation with $ZnCl_2$ and Pd-mediated arylation.[1] Coldham and co-workers reported the dynamic thermodynamic resolution (DTR) of *N*-Boc-2-lithiopiperidine (**1**), achieving enantiomer ratios as high as 85:15 using stoichiometric amounts of monolithiated diaminoalkoxide ligands.[2] Inspired by Coldham's work, we showed that **1** is amenable to a catalytic dynamic resolution (CDR) using 10 mol % of diastereomeric ligands (*S*,*S*)-**2** and (*S*,*R*)-**2** (Figure 1A) at −45 °C in Et_2O with 4 equiv of TMEDA.[3] Combination of the CDR with Campos' arylation procedure effected enantioselective arylation of *N*-Boc-piperidine, affording compounds such as **3**−**7** in the er's shown in Figure 1.[4]

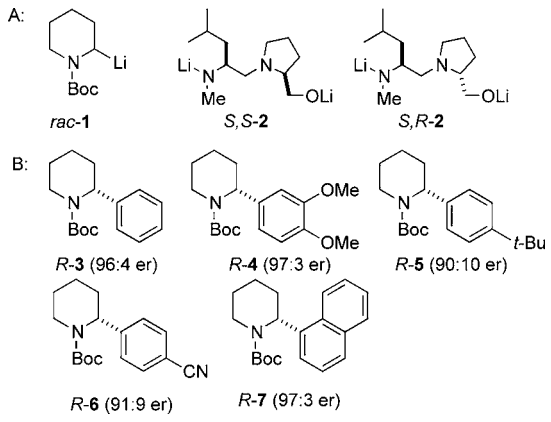


Figure 1. (A) *N*-Boc-2-lithiopiperidine and chiral ligands used to resolve it under CDR conditions and (B) enantioenriched 2-arylpiperidines.

If lithiation/alkylation occurred at the benzylic position without racemization of the intermediate carbanion, quaternary stereocenters could be obtained by electrophilic substitution. Benzylic organolithium compounds that exhibit significant configurational stability are relatively rare.[5] A recent review cites several examples of quantitative studies on the inversion dynamics of tertiary benzylic organolithiums where free energy barriers ranging from 9 to 14 kcal/mol at −80 °C were measured.[6] Such low barriers indicate a high degree of configurational instability of benzylic organolithiums (half-life for inversion ≤10 min), which provides a challenge to stereoselective synthesis.[7] Approaches to lithiation/alkylation sequences at benzylic sites often employ chiral auxiliaries[8] or chiral ligands such as (−)-sparteine[9] or a bisoxazoline[7e,10] to impose configurational stability in the ground state or diastereomeric bias in the transition state, thus leading to diastereomerically or enantiomerically enriched products. Many years ago, the necessity of diastereomeric bias in the alkylation of a benzylic dipole-stabilized α-aminoorganolithium compound was demonstrated by Meyers, who showed that an enantioenriched tertiary tetrahydroisoquinoline formamidine (97:3 er), in which the lithium was also intramolecularly chelated, produced racemic product after a lithiation/substitution sequence in THF at −100 °C.[11]

In their synthesis of a 2,2-disubstituted piperidine NK_1 antagonist, Xiao and co-workers reported that lithiation of *rac*-*N*-Boc-2-phenylpiperidine (**3**) at −78 °C using *n*-BuLi occurs exclusively at the benzylic position.[12] We therefore decided to explore stereoselective lithiation/substitutions of *N*-Boc-2-arylpiperidines and -pyrrolidines, in the absence of any chiral ligand or auxiliary. We find that enantioenriched 2,2-disubstituted pyrrolidines and piperidines are produced with little to no loss of enantiomeric purity. We then conducted a detailed study of the effects of ligands and solvents on the dynamics of enantiomerization of *N*-Boc-2-lithio-2-phenyl-

Received: January 5, 2012
Published: August 11, 2012

   dx.doi.org/10.1021/ja306276w | *J. Am. Chem. Soc.* 2012, 134, 14764−14771

pyrrolidine and *N*-Boc-2-lithio-2-phenylpiperidine and determined the enthalpies and entropies of activation for carbanion inversion under several different conditions. While an earlier version of this paper was in preparation, we became aware of a related mechanistic study that included important details of deprotonation relative to rotamer interconversion of these same compounds.[13]

RESULTS AND DISCUSSION

Previously, we and Coldham measured the dynamics of enantiomerization of *N*-Boc-2-lithiopiperidine (**1**) in Et_2O and found that its configurational stability depended on the amount of TMEDA present.[14] Given these results, we investigated the configurational stability of the benzylic lithiopiperidine **8** in the presence and absence of TMEDA.

After treatment of *R*-**3** of 96:4 er (0.06 M in Et_2O or THF) with 1 equiv of *s*-BuLi at −80 °C in the presence or absence of TMEDA, **8** was generated and immediately trapped with MeOD. The extent of lithiation was monitored using GC-MS by comparing the integral ratio of the base beak for the singly deuterated product, **3**·$\mathbf{d_1}$, to that of the starting material **3**. After complete deuteration (as noted by the disappearance of *m*/*z* 206 and appearance of *m*/*z* 207; see Figure 2 and the Supporting Information), the enantiomer ratios of **3** and **3**·$\mathbf{d_1}$ were evaluated by CSP-SFC. In the presence of TMEDA (1 or 4 equiv) and with Et_2O as the solvent, quenching with MeOD showed complete deuteration after 30 min at −80 °C and **3**·$\mathbf{d_1}$ of 96:4 er (Table 1, entries 1 and 2) was obtained. When the reaction mixture was quickly transferred to a bath at −55 °C and stirred for 1 h, quenching at −80 °C with MeOD gave **3**·$\mathbf{d_1}$ of 85:15 er (entry 3). In the absence of a ligand, after 60 min of lithiation, **3**·$\mathbf{d_1}$ was obtained in 91:9 er (entry 4). In THF, slight loss of enantiopurity was observed (entries 5 and 6), which was most pronounced in the absence of TMEDA (entry 7).

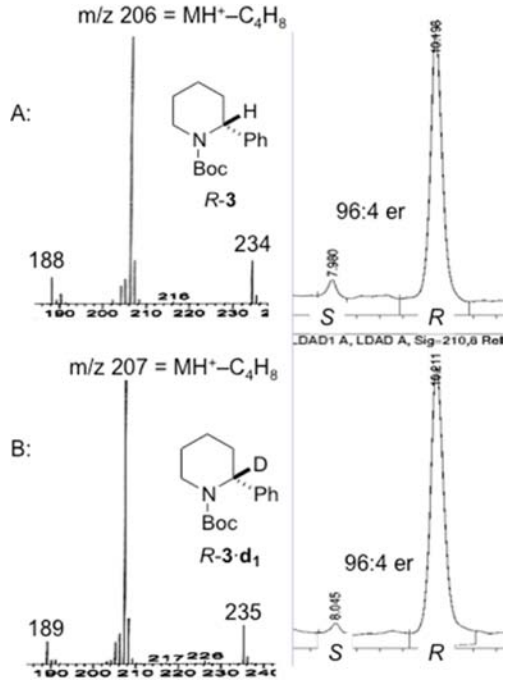
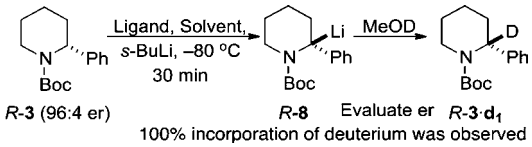


Figure 2. GC-MS and CSP-SFC traces for *R*-**3** and *R*-**3**·$\mathbf{d_1}$.

The following findings emerged from these experiments.

Table 1. Evaluating the Configurational Stability of *N*-Boc-2-lithio-2-phenylpiperidine (8)



entry	solvent	ligand (amt, equiv)	er of **3**·$\mathbf{d_1}$ (*R*:*S*)
1	Et_2O	TMEDA (1)	96:4
2	Et_2O	TMEDA (4)	96:4
3[a]	Et_2O	TMEDA (4)	85:15
4	Et_2O	none[b]	91:9
5	THF	TMEDA (1)	94:6
6	THF	TMEDA (4)	95:5
7	THF	none[b]	92:8

[a]Transferred to a bath at −55 °C and stirred for 1 h. [b]Lithiated for 1 h.

(i) The tertiary α-amino benzylic organolithium **8** racemizes slowly in both Et_2O and THF at −80 °C in the absence of TMEDA. TMEDA enhances the configurational stability of **8** in both solvents.

(ii) As expected, **8** is configurationally less stable at higher temperatures (Table 1, entry 2 vs 3).

(iii) Deuteration of **8** with MeOD is stereoretentive.

Several other electrophiles and arylpiperidines were investigated, and the results are summarized in Table 2. In all cases, good yields were obtained and retention of configuration was observed. Methylation of **8** with Me_2SO_4 gave *R*-**9** in 79% yield and 95:5 er (Table 2, entry 2). Removal of the Boc group using gaseous HCl gave unprotected **9**, with the same sign of specific rotation as that recently reported by Aggarwal for enantiopure deprotected *R*-**9**.[5f] On the basis of retentive deuteration and methylation, and the recently reported work of O'Brien and Coldham in which the steric course of several such substitutions were characterized,[13] we have assigned all the substitutions reported herein as retentive. Quenching with Me_3SiCl afforded *S*-**10** in 88% yield and 96:4 er (entry 3). Quenching with ethyl chloroformate afforded the ester *R*-**11** in 85% yield, with no loss of er (entry 4). A carbonyl electrophile was also evaluated. Quenching with $(CD_3)_2CO$[15] and warming to room temperature before adding methanol gave rise to the oxazolidinone **12** in 90% yield and 95:5 er.

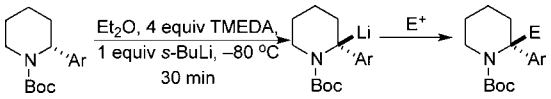
After transmetalation of the benzylic organolithium *R*-**8** to its organozinc counterpart, copper-mediated allylation and benzylation[3] afforded *S*-**13** (entry 6) and *S*-**14** (entry 7), respectively, in good yields and er's.

Lithiation/substitution of highly electron-rich *R*-**4** of 97:3 er also proceeded easily, and the products *R*-**4**·$\mathbf{d_1}$ and *R*-**15** were formed after quenching with MeOD and $(CD_3)_2CO$, respectively (entries 8 and 9). The presence of a bulky electron-rich substituent on the aryl moiety did not affect the configurational stability of the benzylic organolithium, as *R*-**5** of 90:10 er also gave *R*-**5**·$\mathbf{d_1}$ with no loss of er after deuteration with MeOD (entry 10). When electron-deficient *R*-**6** of 91:9 er was employed, lithiation and deuteration or reaction with Me_2SO_4 provided *R*-**6**·$\mathbf{d_1}$ and *R*-**16**, respectively, with no loss of enantiopurity (entries 11 and 12). Sterically crowded *R*-**7** of 97:3 er gave *R*-**7**·$\mathbf{d_1}$ and *R*-**17** after deuteration and methylation, respectively (entries 13 and 14).

The configurational stability of the homologous *N*-Boc-2-arylpyrrolidines was also evaluated. Initially, *R*-**18** of 96:4 er was

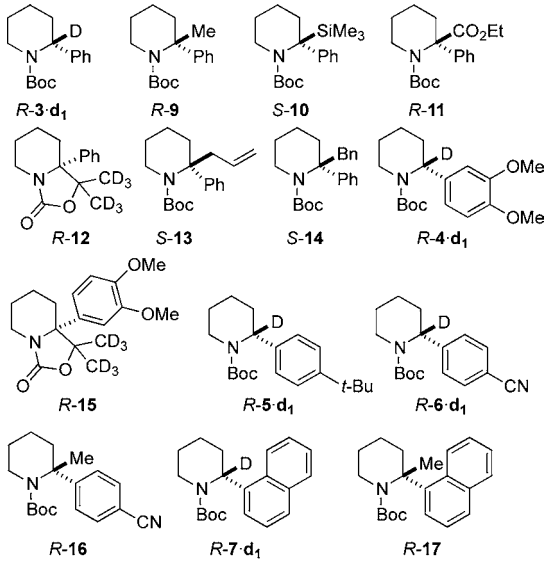
dx.doi.org/10.1021/ja306276w | J. Am. Chem. Soc. 2012, 134, 14764−14771

Table 2. Lithiation/Substitution of Enantioenriched *N*-Boc-2-arylpiperidines[a]



entry	Ar	er (*R*:*S*)	E^+	product	yield, %	er of product
1	Ph	96:4	MeOD	*R*-**3**·$\mathbf{d_1}$	100[b]	96:4
2	Ph	96:4	Me_2SO_4	*R*-**9**	79	95:5
3	Ph	96:4	Me_3SiCl	*S*-**10**	88	96:4
4	Ph	96:4	EtOCOCl	*R*-**11**	85	96:4
5	Ph	96:4	$(CD_3)_2CO$	*R*-**12**	90	95:5
6	Ph	96:4	allyl-Br[c]	*S*-**13**	66	92:8
7	Ph	96:4	BnBr[c]	*S*-**14**	71	94:6
8	3,4-$(MeO)_2$-C_5H_3	97:3	MeOD	*R*-**4**·$\mathbf{d_1}$	100[b]	97:3
9	3,4-$(MeO)_2$-C_6H_3	97:3	$(CD_3)_2CO$	*R*-**15**	93	97:3
10	4-(^{t}Bu)-C_6H_4	90:10	MeOD	*R*-**5**·$\mathbf{d_1}$	100[b]	90:10
11	4-(NC)-C_6H_4	90:10	MeOD	*R*-**6**·$\mathbf{d_1}$	100[b]	90:10
12	4-(NC)-C_6H_4	90:10	Me_2SO_4	*R*-**16**	71	90:10
13	1-Np	97:3	MeOD	*R*-**7**·$\mathbf{d_1}$	100[b]	97:3
14	1-Np	97:3	Me_2SO_4	*R*-**17**	74	93:7

[a]See also Figure 1B. [b]Percent conversion by GC. [c]Via zinc and copper-mediated coupling.



synthesized using the Campos procedure, which employs a stoichiometric amount of (−)-sparteine.[1a] However, following a recent report by O'Brien and Campos on the use of catalytic amounts of the chiral ligand to effect a catalytic enantioselective arylation of *N*-Boc-pyrrolidine, subsequent (*R*)-*N*-Boc-2-arylpyrrolidines (*R*-**18**–*R*-**21**, Figure 3) were synthesized using this method.[1b,16] The enantiomeric (*S*)-*N*-Boc-2-arylpyrrolidines (*S*-**18** and *S*-**22**) were synthesized using Beak's lithiation/cyclization method.[17]

Xiao et al. reported that lithiation/alkylation of *rac*-**18** occurred at C2 at −78 °C using *n*-BuLi/TMEDA in THF.[12] We found that lithiation of *R*-**18**, using *s*-BuLi/TMEDA in Et_2O, was somewhat slower than that of **3** under the conditions used for the piperidines. Although we were able to obtain 100% lithiation of **18** at −80 °C using *s*-BuLi/TMEDA, Coldham and O'Brien have shown that interconversion of rotamers at −80 °C is slow, and lithiation at C-5 is competitive at this temperature.[13]

We sought reaction conditions that would maximize the efficient generation of the C2-lithiated pyrrolidine **24** without compromising its configurational stability. After lithiation of a

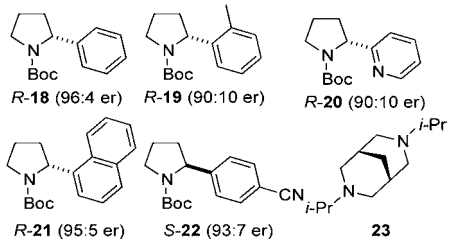
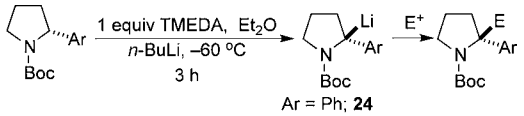


Figure 3. Enantioenriched 2-arylpyrrolidines and diisopropylbispidine (**23**).

solution of *R*-**18** of 96:4 er in Et_2O using *n*-BuLi at −60 °C in the absence of a ligand, quenching of **24** with MeOD revealed complete lithiation after 3 h. CSP-SFC analysis also revealed stereoretentive deuteration, and *R*-**18**·$\mathbf{d_1}$ was obtained in 96:4 er. Similar configurational stability was observed in the presence of stoichiometric or excess amounts of TMEDA. For example, when *S*-**18** of 96:4 er, in Et_2O containing 1 equiv of TMEDA at −60 °C, was treated with *n*-BuLi for 3 h and then quenched with MeOD, *S*-**18**·$\mathbf{d_1}$ having 96:4 er was obtained. In the

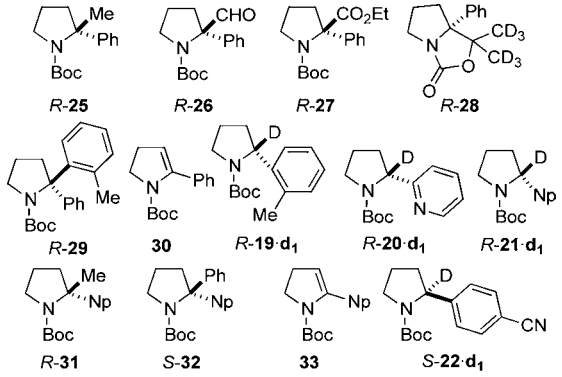
dx.doi.org/10.1021/ja306276w | J. Am. Chem. Soc. 2012, 134, 14764–14771

Table 3. Lithiation/Substitution of Enantioenriched *N*-Boc-2-aryl pyrrolidines Using Indicated Conditions, Except As Noted



entry	Ar	er (*R*:*S*)	E^+	product	yield, %	er
1	Ph	96:4	Me_2SO_4	*R*-**25**	86[a]	94:6
2	Ph	96:4	DMF	*R*-**26**	83[b] (88[c])	>99:1
3	Ph	96:4	EtOCOCl	*R*-**27**	70[b] (79[c])	94:6
4	Ph	96:4	$(CD_3)_2CO$	*R*-**28**	85[b] (92[c])	94:6
5	Ph	96:4	2-bromotoluene	*R*-**29**	8[b,d]	92:8
6	Ph	50:50	2-bromotoluene	*rac*-**29**	12[a,d,e]	50:50
7	2-tolyl	90:10	MeOD	*R*-**19**·$\mathbf{d_1}$	100[c]	90:10
8	2-pyridyl	90:10	MeOD	*R*-**20**·$\mathbf{d_1}$	100[c]	90:10
9	1-Np	95:5	MeOD	*R*-**21**·$\mathbf{d_1}$	100[c]	95:5
10	1-Np	95:5	Me_2SO_4	*R*-**31**	91[a]	95:5
11	1-Np	95:5	PhBr	*S*-**32**	<5[c,d,e]	95:5
12	4-(NC)-C_6H_4	7:93	MeOD	*S*-**22**·$\mathbf{d_1}$	100[c]	93:7

[a]Isolated yield. [b]Isolated yield of C2 and C5 substitution products after deprotonation by *s*-BuLi/TMEDA. [c]Percent conversion by GC after deprotonation using *n*-BuLi/TMEDA. [d]Via Pd-catalyzed coupling for 48 h at 40 °C. [e]Lithiated in the absence of TMEDA.



presence of hindered diisopropylbispidine **23**,[18] *R*-**18**·$\mathbf{d_1}$ of 95:5 er was obtained. O'Brien and Coldham have shown that, at this temperature, rotation of the Boc group is fast enough for interconversion, and C-5 deprotonation is not competitive when *n*-BuLi is used as the base.[13]

Knowing that configurationally stable *R*-**24** can be efficiently generated after 3 h at −60 °C in the presence or absence of TMEDA in Et_2O, other electrophiles and arylpyrrolidines were evaluated, and the results are summarized in Table 3. Lithiation of *R*-**18** of 96:4 er with *n*-BuLi/TMEDA followed by alkylation with Me_2SO_4 gave *R*-**25** of 94:6 er in 86% yield (Table 3, entry 1). Lithiation with *sec*-BuLi/TMEDA and quenching with dimethyl formamide afforded crude aldehyde *R*-**26** in 96:4 er. After column chromatography on silica, a slight improvement in the er was observed and enantiopure *R*-**26** was obtained in 83% yield (entry 2), possibly due to self-disproportionation of enantiomers on the achiral stationary phase.[19] Ethyl chloroformate gave ester *R*-**27** in 70% yield and 95:5 er (entry 3). With $(CD_3)_2CO$, oxazolidinone *R*-**28** was obtained in 85% yield and 96:4 er (entry 4). When *R*-**24** was transmetalated to its organozinc counterpart followed by Pd-catalyzed coupling to 2-bromotoluene, *R*-**29** was obtained in very low yield (entry 5). Entries 2−5 of Table 3 were initially conducted by deprotonationation using *sec*-BuLi/TMEDA at −80 °C and probably produced a mixture of C2 and C5 lithiation/substitution products.[13] The products of C2 substitution were characterized after chromatographic purification. Later, entries 2−5 of Table 3 were repeated using *n*-BuLi/TMEDA, which gives only C2 lithiation, but only analyzed for percent conversion by GC.

We reasoned that the low yield in entry 5 could be due to steric crowding or the presence of TMEDA, known to be problematic in the Pd-catalyzed arylation of racemic *N*-Boc-2-lithiopyrrolidine, obtained from deprotonation of *N*-Boc-pyrrolidine using *sec*-BuLi/TMEDA.[1b] To test this possibility, we generated *rac*-**24** by deprotonation using *n*-BuLi and subjected it to the same arylation conditions, affording *rac*-**29** in just 12% yield (entry 6). GC-MS analysis of the crude product mixture showed complete consumption of *rac*-**18**, but a significant byproduct was found, dehydropyrrolidine **30**, probably produced by *β*-hydride elimination of the organopalladium intermediate.

Other arylpyrrolidines with varying stereoelectronic properties were also evaluated after deprotonation using *n*-BuLi/TMEDA in Et_2O. Lithiation/deuteration of electron-rich *R*-**19** and heteroaromatic *R*-**20** proceeded with high levels of configurational stability (entries 7 and 8, respectively). The naphthyl substituent was found to be compatible, as *R*-**21** of 95:5 er gave *R*-**21**·$\mathbf{d_1}$ and *R*-**31** after deuteration and methylation, respectively (entries 9 and 10). When *R*-**21** was lithiated in the absence of TMEDA, transmetalation to the organozinc and palladium-catalyzed coupling to bromobenzene afforded only trace amounts of *S*-**32** (entry 11). Enamide **33** was also detected, consistent with undesirable *β*-hydride elimination during the arylation. We therefore concluded that the low yield in the arylation at C-2 of the 2-arylpyrrolidines

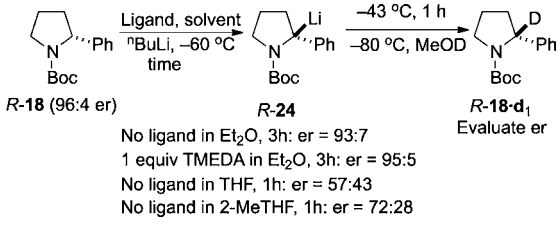
dx.doi.org/10.1021/ja306276w | J. Am. Chem. Soc. 2012, 134, 14764−14771

was largely due to steric hindrance. Complete and efficient lithiation of *S*-**22** of 93:7 er followed by quenching with MeOD gave *S*-**22**·$\mathbf{d}_1$ (entry 12).

Enantiomerization Dynamics of α-Amino Tertiary Benzylic Organolithiums 24 and 8. The dynamics of enantiomerization of benzylic organolithiums through a solvent-separated ion pair has been reported by Peoples and Grutzner using a benzylic lithiohydrocarbon[20] and by Ahlbrecht et al. using α-thio and α-seleno compounds.[21] Cram and coworkers reported the enantiomerization of a chelated α-silylbenzylic organolithium[22] via the conducted tour mechanism.[23] In all of these examples, negative entropies of activation were observed, consistent with additional solvation in the transition state. In collaboration with the Coldham group, we have studied the dynamics of carbanion inversion of α-amino organolithium compounds. The activation parameters for enantiomerization of *N*-substituted 2-lithiopyrrolidines[24] and for dynamic thermodynamic resolution (DTR) and racemization of *N*-Boc-2-lithiopiperidine[3,14] have been measured. It became clear to us that the role of an additive such as TMEDA in the racemization of α-amino organolithium compounds can change dramatically, depending on conditions. For example, whereas TMEDA catalyzes the racemization of *N*-Boc-2-lithiopyrrolidine,[24c] the effect of TMEDA on the racemization of *N*-Boc-2-lithiopiperidine is dependent on the stoichiometry. TMEDA catalyzes the racemization of *N*-Boc-2-lithiopiperidine up to 1 equiv,[14] but 2 equiv of TMEDA retards racemization.[3] In another striking difference, when generated by tin−lithium exchange, enantioenriched *N*-Boc-2-lithiopiperidine racemizes in a matter of minutes at −80 °C in the presence of 1 equiv of diisopropylbispidine (DIB) in Et_2O, whereas *N*-Boc-2-lithiopyrrolidine exhibits configurational stability under identical conditions.[24c] We therefore undertook an investigation of the activation parameters for enantiomerization of pyrrolidine **24** and piperidine **8** in the presence of varying solvents and ligands.

Dynamics of Inversion of ***24****.* Detailed kinetic measurements on the effects of solvents and ligands on the rate of enantiomerization of *R*-**24** were performed using previously reported methods.[14,24c,d] Thus stock solutions of *R*-**18** of 96:4 er (0.06 M in Et_2O, THF, or 2-methyltetrahydrofuran (2-MeTHF)) were prepared and placed in six oven-dried, septum-capped test tubes, each equipped with a stir bar. Prior to embarking on the time-dependent studies, we performed exploratory runs using different solvents and ligands at −43 °C. The results are summarized in Scheme 1. These data clearly indicate configurational stability in Et_2O, even at −43 °C, and significantly faster racemization at the same temperature in either THF or 2-MeTHF. As a result of these experiments, we realized that the dynamics of inversion in Et_2O would have to be studied at temperatures higher than −43 °C.

Scheme 1. Enantiomer Ratios for the Racemization of 24 under Different Reaction Conditions at −43 °C



In order to determine the rate constants for enantiomerization at specified temperatures, the organolithium *R*-**24** was generated using *n*-BuLi at −60 °C for 3 h followed by transferring to a bath set at the desired temperature to monitor inversion. At various time intervals, duplicate tubes were transferred to a bath at −80 °C and quenched with MeOD. GC-MS analysis of the crude mixture of each tube was carried out to ensure 100% deuterium incorporation, prior to evaluation of the enantiomer ratio by CSP-SFC. The GC traces showed evidence of some decomposition at higher temperatures, but we were still able to obtain good kinetic data. Due to the slow racemization in Et_2O at −43 °C, the dynamics were subsequently studied at temperatures ranging from −20 to 18 °C. After generating **24** using *n*-BuLi at −60 °C for 1 h, we followed the evolution of er as a function of time in the absence of any ligand in THF at −57, −43, and −31 °C. With 2-MeTHF, the kinetics were studied at −31 °C. The zero-order plots for the enantiomerization are in the Supporting Information. Eyring analysis of the rate constants at their respective temperatures provided the activation parameters given in Table 4 (see the Supporting Information for details on the analysis of the kinetic data). Examination of the enthalpic and entropic contributions to the free energies for the enantiomerization revealed significant differences. In the absence of any ligand in Et_2O, carbanion inversion is mostly enthalpy controlled (Table 4, entry 1). Addition of TMEDA leads to little or no change in the enthalpy of activation but the entropic barrier changes by a factor of 2 (entry 2). With the hindered and weakly coordinating **23**, the racemization is enthalpy controlled (entry 3). On comparison of Et_2O and THF, the enthalpy of activation in THF drops from 18.0 to 8.6 kcal/mol and the entropy of activation changes from −8.6 to −37.5 cal/(mol K) (entries 1 vs 4). The activation parameters for enantiomerization of **24** in the absence of any ligand in 2-MeTHF were not determined, but we found that at −31 °C the rate of enantiomerization of **24** is 9 times faster in THF ($t_{1/2}$ = 11.7 min) than in 2-MeTHF ($t_{1/2}$ = 1.8 h).

Table 4. Thermodynamic Parameters for Inversion of 24

entry	description	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (cal/(mol K))
1	no ligand in Et_2O	18.0 ± 1.7	−8.6 ± 0.3
2	1 equiv of TMEDA in Et_2O	16.0 ± 1.3	−18.7 ± 1.6
3	1 equiv of **23** in Et_2O	21.3 ± 0.2	−1.0 ± 0.4
4	no ligand in THF	8.6 ± 1.6	−37.5 ± 2.5

A plot of $\Delta G^{\ddagger}$ vs temperature for the different systems studied is illustrated in Figure 4. Although the observed rate constants increase with an increase in temperature, the negative entropies of activation reveal that the free energy barriers increase with temperature. Interestingly, O'Brien and Coldham have recently reported deprotonation of *N*-Boc-2-phenylpyrrolidine using *n*-BuLi in THF at −50 °C for 5 min, followed by electrophilic quench.[13] The half-life for enantiomerization at this temperature is 50 min.

Dynamics of Inversion of ***8****.* Using the method described above for the dynamics of inversion of **24**, the barriers to enantiomerization of piperidine **8** in the absence of any ligands in Et_2O or THF, and in the presence of TMEDA in Et_2O, were measured. With Et_2O as the solvent, the dynamics of inversion of **8** were studied at temperatures ranging from −40 to −20 °C with and without TMEDA. In THF, colder temperatures (−60

dx.doi.org/10.1021/ja306276w | J. Am. Chem. Soc. 2012, 134, 14764−14771

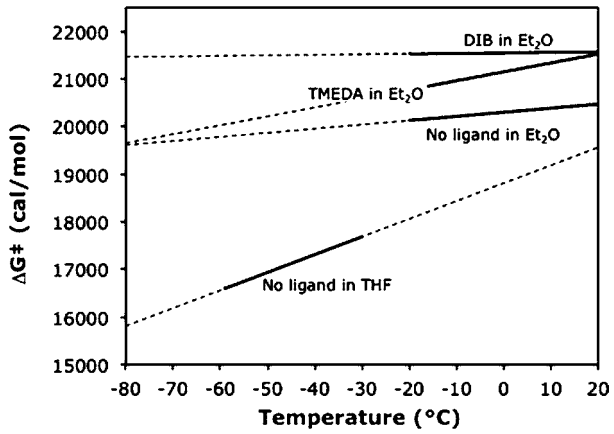


Figure 4. Relationship between free energy of activation and temperature for inversion of **24**. The solid lines indicate free energy barriers in the temperature region where the kinetics were measured; dashed lines are extrapolations.

to −40 °C) were required due to faster racemization. The activation parameters are given in Table 5 (details are in the Supporting Information), and a plot of $\Delta G^{\ddagger}$ vs temperature for the three systems studied is shown in Figure 5. The significantly higher barriers in Et_2O reveal significantly higher configurational stability than in THF. Our results in THF, from Tables 1 and 5 and Figure 5, are somewhat at odds with the results of O'Brien and Coldham.[13] Their conditions for deprotonation and alkylation of **3** in THF are −50 °C for 30 min, and they report 94:6 to 99:1 er's after alkylation. In our hands, we begin to see racemization of **8** even at −80 °C (Table 1, entry 7). One of our kinetic runs was conducted at −50 °C in THF; after 30 min, we observe 66:34 er. From the parameters of entry 3 of Table 5, we calculate a half-life for enantiomerization of 22 min. Slight differences in temperature produce small differences in free energy barriers, but these can result in significant differences in half-life due to the exponential relationship between $\Delta G^{\ddagger}$ and $t_{1/2}$.

Table 5. Thermodynamic Parameters for Inversion of 8

entry	description	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (cal/(mol K))
1	no ligand in Et_2O	17.5 ± 0.8	−2.0 ± 0.06
2	1 equiv of TMEDA in Et_2O	16.0 ± 1.3	−9.6 ± 0.5
3	no ligand in THF	10.1 ± 0.9	−29.1 ± 4.2

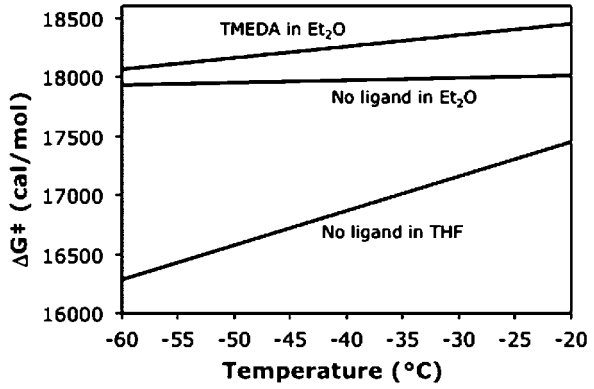


Figure 5. Relationship between the free energy of activation and temperature for inversion of **8**.

In Et_2O at similar temperatures, we find that the rate of inversion of piperidine **8** is significantly faster than that of pyrrolidine **24**. Interestingly, the observed trend is similar to that reported for the racemization of the secondary, non-benzylic organolithiums *N*-Boc-2-lithiopiperidine[14] and *N*-Boc-2-lithiopyrrolidine[24c] in Et_2O.

Mechanistic Hypothesis. A possible mechanism for the enantiomerization of **8** or **24** which is consistent with the observed negative entropies is via the conducted tour, known to be operative in the inversion of *N*-substituted 2-lithiopyrrolidines and -piperidines.[24a,b] Infrared studies have shown that the carbonyl oxygen chelates the lithium in both **8** and **24**.[13,25] In the conducted tour, the lithium−oxygen distance is shortened and the lithium−carbon distance is lengthened as the transition state is approached. This necessitates a reorganization of the coordination sphere around the lithium, but the lithium remains coordinated to the carbonyl oxygen as it moves from one face of the carbanion to the other. This is consistent with the observation that a strongly coordinating ligand (TMEDA) and a more coordinating solvent (THF) result in more negative entropies for the enantiomerization of **24** or **8** than in Et_2O alone. Since the coordinating ability of 2-MeTHF is intermediate between Et_2O and THF,[26] it is perhaps not surprising that the rate of enantiomerization of **24** is faster than with Et_2O but slower than with THF.

Summary and Conclusions. In summary, the configurational stability of several α-amino tertiary benzylic organolithiums has been demonstrated at low temperatures on two different heterocycles, in the absence of any chiral ligand or auxiliary. TMEDA enhances the configurational stability of both **8** and **24**. A variety of 2,2-disubstituted piperidines and pyrrolidines have been synthesized bearing α-amino quaternary stereocenters. The thermodynamic parameters for racemization of **8** and **24** in the absence of any ligand in Et_2O and THF are significantly different. In THF, the racemization is faster than in Et_2O and is mostly entropy-controlled.

■ EXPERIMENTAL SECTION

For general experimental conditions, see the Supporting Information.

Lithiation of (*R*)-*N*-Boc-2-arylpiperidine Followed by Direct Trapping with the Electrophile: General Procedure. In an oven-dried, septum-capped round-bottom flask equipped with a stir bar, freshly distilled TMEDA (4.0 equiv) and Et_2O under argon were added. The solution was cooled to −80 °C, and a solution of *s*-BuLi in cyclohexane (1.0 equiv) was added. A precooled solution of the *N*-Boc-2-arylpiperidine (1.0 equiv) in Et_2O was added to the flask containing the TMEDA/*s*-BuLi solution. After 30 min at this temperature, the reaction was quenched with the electrophile (~1.1−1.5 equiv). After 2−16 h, MeOH was added and the mixture was stirred for 5 min. After the mixture was warmed to room temperature, 2 M HCl was added. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product. The er was determined before and after purification by column chromatography. See the Supporting Information for details.

Lithiation of (*R*)-*N*-Boc-2-arylpiperidine Followed by Zinc and Copper-Mediated Allylation or Benzylation: General Procedure. In an oven-dried, septum-capped round-bottom flask equipped with a stir bar freshly distilled TMEDA (4.0 equiv) and Et_2O under argon were added. The solution was cooled to −80 °C, and a solution of *s*-BuLi in cyclohexane (1.0 equiv) was added. A precooled solution of the *N*-Boc-2-arylpiperidine (1.0 equiv) in Et_2O was added to the flask containing the TMEDA/*s*-BuLi mixture. After 30 min, a solution of $ZnCl_2$ (1.3 equiv, 1.0 M in Et_2O) was added slowly. After

dx.doi.org/10.1021/ja306276w | J. Am. Chem. Soc. 2012, 134, 14764−14771

30 min, a solution of CuCN·2LiCl (prepared from CuCN (1.2 equiv) and LiCl (2.5 equiv)) in THF was added. After 30 min, allyl bromide or benzyl bromide (1.1 equiv) was added. The mixture was stirred for 10 h at this temperature prior to addition of MeOH and warming to room temperature. A solution of NH_4Cl was added, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude product. The er was determined before and after purification by column chromatography. See the Supporting Information for details.

Lithiation of (*R*)-*N*-Boc-2-arylpyrrolidine Followed by Direct Trapping with the Electrophile: General Procedure. In an oven-dried, septum-capped round-bottom flask equipped with a stir bar, freshly distilled TMEDA (1.0 equiv) and Et_2O under argon were added. The mixture was cooled to −60 °C, and a solution of *n*-BuLi in hexanes (1.0 equiv) was added. A precooled solution of the *N*-Boc-2-arylpyrrolidine (1.0 equiv) in Et_2O was added to the flask containing the TMEDA/*n*-BuLi mixture. After 3 h at this temperature, the mixture was quenched with the electrophile (∼1.1−1.5 equiv). After 2−16 h, MeOH was added and the mixture was stirred for 5 min. After the mixture was warmed to room temperature, 2 M HCl was added. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated to obtain the crude product. The er was determined before and after column chromatography.

Lithiation of (*R*)-*N*-Boc-2-arylpyrrolidine Followed by Zinc- and Palladium-Catalyzed Arylation: Attempted Synthesis of 32. In an oven-dried, septum-capped round-bottom flask equipped with a stir bar, *R*-**21** of 95:5 er (75 mg, 0.25 mmol, 1.0 equiv) in Et_2O (2 mL) under argon was added. The mixture was cooled to −60 °C, and a solution of *n*-BuLi in hexanes (0.1 mL, 0.25 mmol, 2.5 M, 1.0 equiv) was added slowly. After 3 h at this temperature, a solution of $ZnCl_2$ (0.15 mL, 1.0 M solution in Et_2O, 0.6 equiv) was added slowly over a 2 min period and the mixture was stirred for 30 min followed by warming to room temperature. After 30 min, $Pd(OAc)_2$ (2.5 mg, 4 mol %), *t*-$Bu_3P{\cdot}HBF_4$ (6 mg, 8 mol %), and phenyl bromide (0.033 mL, 0.28 mmol, 1.1 equiv) were added sequentially. After it was stirred for 48 h at 40 °C, the heterogeneous mixture was warmed to room temperature. NH_4OH (2 mL, 10% aqueous solution) was added dropwise, and the mixture was stirred for 30 min. The resulting slurry was filtered through Celite and rinsed with 5 mL of Et_2O. The filtrate was washed with 1 M HCl(aq) (10 mL) and then with water (2 × 5 mL), dried over Na_2SO_4, and evaporated under reduced pressure to obtain the crude product. Analysis of the crude product by CG-MS showed complete conversion of **21** but less than a 5% yield of **32** was present.

Activation Parameters for Racemization of 24 with 1.0 equiv of TMEDA in Et_2O: Typical Kinetic Run. In oven-dried, septum-capped tubes equipped with a stir bar, *R*-**18** (0.06 M in ether, 0.5 mL) and 0.06 M TMEDA (1.00 equiv) were treated with *n*-BuLi (1.0 equiv) at −60 °C for 3 h under nitrogen. The total volume of each tube was maintained at 1.0 mL. The tubes were quickly transferred to a second bath thermostated at the desired temperature. At various time intervals, a tube was transferred to the bath at −80 °C and the mixture rapidly quenched with MeOD. Each tube was analyzed by GC-MS to ensure 100% deuterium incorporation (indicative of complete lithiation). The enantiomer ratio (er) of **18**·$\mathbf{d_1}$ was determined by CSP-SFC monitoring at 210 nm under the following column conditions: column, Pirkle Whelk-O-1; flow rate, 2.0 mL/min; polarity modifier, 2.0% EtOH. *S*-**18**·$\mathbf{d_1}$ elutes after ∼4.2 min, and *R*-**18**·$\mathbf{d_1}$ elutes after ∼5.7 min. The rate constants were determined by nonlinear fitting of the zero-order plots using reversible first-order kinetics. See the Supporting Information for details.

Activation Parameters for Racemization of 8 without a Ligand in Et_2O: Typical Kinetic Run. In oven-dried, septum-capped tubes equipped with a stir bar, *R*-**3** (0.06 M in Et_2O, 1.0 mL) was treated with *n*-BuLi (1.0 equiv) at −80 °C for 1 h under nitrogen. The tubes were quickly transferred to a second bath thermostated at the desired temperature. At various time intervals over a 4 h period, a tube was transferred to the bath at −80 °C and the mixture rapidly quenched with MeOD. Each tube was analyzed by GC-MS to ensure 100% deuterium incorporation (indicative of complete lithiation). The enantiomer ratio (er) of **3**·$\mathbf{d_1}$ was determined by CSP-SFC monitoring at 210 nm under the following column conditions: column, Pirkle Whelk-O-1; flow rate, 0.5 mL/min; polarity modifier, 10.0% IPA. *S*-**3**·$\mathbf{d_1}$ elutes after ∼17.2 min, and *R*-**3**·$\mathbf{d_1}$ elutes after ∼21 min. In some cases, the enantiomer ratio (er) of **3**·$\mathbf{d_1}$ was determined by CSP-HPLC monitoring at 254 nm. The rate constants were determined by nonlinear fitting of the zero-order plots using reversible first-order kinetics. See the Supporting Information for details.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving full experimental details and spectroscopic and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Arkansas Biosciences Institute and the National Science Foundation (CHE 1011788) for direct support of this work. Core facilities were funded by the Arkansas Biosciences Institute and the National Institutes of Health (P30 RR031154 and GM103450). J.S.W. thanks the NSF-REU for a summer fellowship (CHE 0851505). We are grateful to Professors Peter O'Brien and Iain Coldham for sharing their related manuscript[13] prior to publication.

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