J|A|C|S COMMUNICATIONS

Published on Web 08/12/2010

# Highly Enantioselective Catalytic Dynamic Resolution of *N*-Boc-2-lithiopiperidine: Synthesis of (*R*)-(+)-*N*-Boc-Pipecolic Acid, (*S*)-(−)-Coniine, (*S*)-(+)-Pelletierine, (+)-*β*-Conhydrine, and (*S*)-(−)-Ropivacaine and Formal Synthesis of (−)-Lasubine II and (+)-Cermizine C

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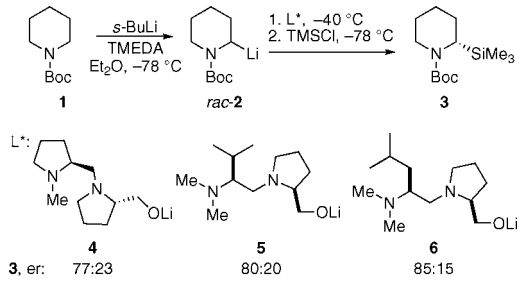
***Abstract:*** The catalytic dynamic resolution (CDR) of *rac*-2-lithio-*N*-Boc-piperidine using chiral ligand **8** or its diastereomer **9** in the presence of TMEDA has led to the highly enantioselective syntheses of both enantiomers of 2-substituted piperidines using a wide range of electrophiles. The CDR has been applied to the synthesis of (*R*)- and (*S*)-pipecolic acid derivatives, (+)-*β*-conhydrine, (*S*)-(+)-pelletierine, and (*S*)-(−)-ropivacaine and the formal synthesis of (−)-lasubine II and (+)-cermizine C.

2-Substituted piperidines are found in many alkaloids and medicinal compounds that are derived from pipecolic acid. In 1989, Beak showed that racemic members of this class of compounds can be conveniently prepared by deprotonation and electrophilic quenching of *N*-Boc-piperidine (**1**) using *s*-BuLi and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA).[1] Although the chiral base *s*-BuLi/(−)-sparteine efficiently and enantioselectively deprotonates *N*-Boc-pyrrolidine,[2] the same base complex is less effective with *N*-Boc-piperidine.[3] Partial success has recently been reported using O'Brien's (+)-sparteine surrogate, which affords up to 88:12 er (*R*:*S*) in variable yield (depending on the electrophile), but this method is limited to one enantiomer.[4]

An alternative approach is the use of dynamic resolutions, and the most successful results to date for resolution of 2-lithiopiperidines have been reported by the Coldham group.[5] In dynamic thermodynamic resolutions (DTRs), chiral ligands coordinate to the metal of a chiral organolithium, causing it to undergo carbanion inversion at a selected temperature and populate one stereoisomer through equilibration. After the mixture is cooled to freeze the equilibrium, reaction with an electrophile gives enantioenriched products.[6] Coldham recently reported that *N*-Boc-2-lithiopiperidine (**2**) can be resolved by DTR using several monolithiated diaminoalkoxide ligands (Scheme 1).[5]

***Scheme 1.*** DTR of *N*-Boc-2-lithiopiperidine (**2**)[5]




A catalytic dynamic resolution (CDR) of 2-lithio-*N*-trimethylallylpyrrolidine was recently reported.[7] We now report the discovery of a CDR of *rac*-**2** using new ligands that afford excellent enantioselectivity *for either enantiomer of 2-substituted piperidines.*

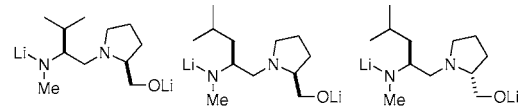



***Figure 1.*** Dilithio ligands for dynamic resolution.

In their report on the stoichiometric DTR of *rac*-**2**, Coldham et al.[5] indicated that the resolution is facilitated by the addition of lithium isopropoxide. With this in mind, we investigated the enantioselectivity of dilithiodiaminoalkoxides **7**−**9** in a stoichiometric DTR using the Coldham conditions. We were gratified to find the high er's shown in Figure 1. Notably, diastereomeric ligands **8** and **9** afford very high er and *opposite* configurations of **3**.

A successful CDR depends on several factors, including a lower barrier for DTR than for racemization at a given temperature.[8] A plot of $\Delta G^{\ddagger}$ versus temperature for racemization of **2** in the presence of TMEDA and DTR of **2**·**8** in the presence of TMEDA revealed that the barrier for DTR is lower than that for racemization below −27 °C [see the Supporting Information (SI)]. Thus, a CDR was attempted by generation of *rac*-**2** by deprotonation in $Et_2O$ at −78 °C with *s*-BuLi/TMEDA followed by addition of 10 mol % **8**, warming to −45 °C for 3 h, cooling to −78 °C, and quenching with $Me_3SiCl$. We were gratified to obtain **3** in 74% yield and 96:4 er (Table 1, entry 1). Several other electrophiles were evaluated under the same CDR conditions, and the results are summarized in Table 1, entries 2−14. Excellent enantiomer ratios and good yields were obtained in all cases. Procedures for recovery of the chiral ligand are included in the SI.

CDR using ligand **8** followed by quenching with $Bu_3SnCl$ afforded (*S*)-**10** in 66% yield and 96:4 er. With ligand **9**, (*R*)-**10** was obtained in 62% yield and 97:3 er. When $CO_2$ was used as the electrophile, *N*-Boc-(*R*)-(+)-pipecolic acid [(*R*)-**11**] was obtained in 78% yield and 98:2 er using **8**. Quenching with $ClCO_2Me$ afforded enantiopure methyl pipecolate ester (*R*)-**12** using ligand **8** and (*S*)-**12** using ligand **9**. Reaction with PhNCO afforded enantiopure anilide (*R*)-**13** using ligand **8**.

The electrophilic bimolecular substitutions discussed above (entries 1−7) proceed via a polar pathway, presumably with retentive substitution at the metal-bearing carbon ($S_E2ret$).[9] However, when (*S*)-**2** was trapped directly with either allyl chloride or benzyl bromide, nearly racemic products were obtained. These nonselective reactions probably proceed through a single electron transfer (SET) pathway.[10] The enantioselectivity of the allylations was therefore evaluated under Negishi conditions, which have been successfully applied in this system,[4] whereby **2** is transmetalated with $ZnCl_2$ and coupled using CuCN·2LiCl. Under these conditions, allyl bromide afforded (*R*)-**14** with ligand **8** in 63% yield and 95:5



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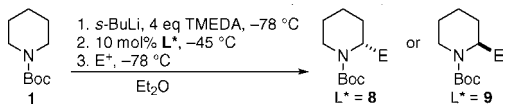
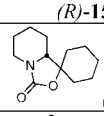
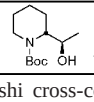
***Table 1.*** CDR of **2** at −45 °C for 3 h Using Ligand **8** (or **9** Where Noted)




| Entry | $E^+$ | Product(s) | % Yield | er |
|---|---|---|---|---|
| 1 | $Me_3SiCl$ | *(S)*-**3** | 74 | 96:4 |
| 2 | $Bu_3SnCl$ | *(S)*-**10** | 66 | 96:4 |
| 3 | $Bu_3SnCl$ | *(R)*-**10** | 62 | 97:3[a] |
| 4 | $CO_2$ | *(R)*-**11** | 78 | 98:2 |
| 5 | MeOCOCl | *(R)*-**12** | 88 | >99:1 |
| 6 | MeOCOCl | *(S)*-**12** | 85 | >99:1[a] |
| 7 | PhNCO | *(R)*-**13** | 68 | >99:1 |
| 8 | Allyl bromide | *(R)*-**14** | 63 | 95:5[b] |
| 9 | Allyl bromide | *(S)*-**14** | 59 | 96:4[a,b] |
| 10 | BnBr | *(R)*-**15** | 65 | >99:1[b] |
| 11 | Cyclohexanone |  *(R)*-**16** | 60 | 94:6 |
| 12 | PhCHO[c] |  **17** | 74 (62:38 dr) | >99:1 & 98:2 |
| 13 | 1-NpCHO[c] |  **18** | 66 (82:18 dr) | 94:6 & 93:7 |
| 14 | $CH_3CHO$[c] |  **19** | 78 (85:15 dr) | >99:1 for both |

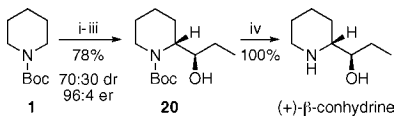
[a] Using ligand **9**. [b] Via Negishi cross-coupling. [c] Major diastereomer illustrated.

er (entry 8). When CDR using ligand **9** was employed, (*S*)-**14** was obtained in 59% yield and 96:4 er (entry 9). A similar protocol using ligand **8** and Negishi coupling with benzyl bromide gave enantiopure (*R*)-**15** in 65% yield (entry 10).

CDR of *rac*-**2** followed by addition to aldehydes and ketones was also investigated, and the results are summarized in Table 1, entries 11−14. Not surprisingly,[11] the adducts from addition to cyclohexanone, benzaldehyde, and 1-naphthaldehyde cyclized to oxazolidinones in situ, the latter two as mixtures of diastereomers. Nevertheless, the configuration at the lithium-bearing carbon of **2** was maintained, with all adducts exhibiting high er's. Quenching with acetaldehyde provides a convenient way to prepare the enantiopure alcohol **19** in 78% yield as a mixture of diastereomers (85:15 dr; entry 14).

When (*S*)-**2** was quenched with propionaldehyde, alcohol **20** was obtained as a 70:30 mixture of diastereomers, both of which had 96:4 er. Separation of the diastereomers by column chromatography and hydrolysis of the carbamate from the major diastereomer afforded the alkaloid (+)-*β*-conhydrine (Scheme 2).

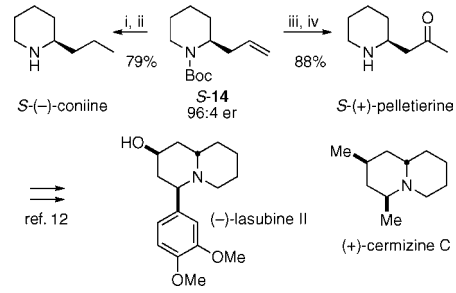
***Scheme 2.*** Synthesis of (+)-*β*-Conhydrine[a]




[a] (i) *s*-BuLi (1.2 eq), $Et_2O$, TMEDA (4.0 eq), −78 °C, 3 h; (ii) **8**, (10 mol %), −45 °C, 3 h; (iii) EtCHO, −78 °C, 2 h; (iv) $CF_3CO_2H$, $CH_2Cl_2$.

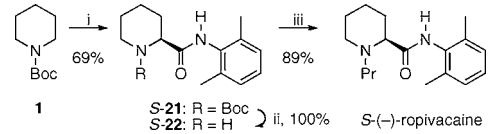
Hydrogenation of (*S*)-**14** and deprotection afforded (*S*)-(−)-coniine; Wacker oxidation and deprotection afforded (*S*)-(+)-pelletierine (Scheme 3). Cheng and co-workers[12] recently prepared (*S*)-**14** from glutaraldehyde in six steps and showed that (*S*)-**14** can be readily converted to (−)-lasubine II and (+)-cermizine C via (*S*)-(+)-pelletierine.

***Scheme 3.*** Synthesis of (*S*)-(+)-Pelletierine and (*S*)-(−)-Coniine and Formal Synthesis of (−)-Lasubine II and (+)-Cermizine C[a12]




[a] (i) $Pd(OH)_2$ (1.0 equiv), $H_2$ (1 atm), MeOH, rt, 48 h; (ii) $CF_3CO_2H$, $CH_2Cl_2$, 0 °C, 2 h, then NaOH; (iii) $PdCl_2$ (1.0 equiv), CuCl (10 mol %), $O_2$, 10:1 DMF/$H_2O$, rt, 10 h; (iv) $CF_3CO_2H$, $CH_2Cl_2$, 0 °C, 2 h, then NaOH.

***Scheme 4.*** Synthesis of (*S*)-(−)-Ropivacaine[a]




[a] (i) *s*-BuLi (1.2 equiv), $Et_2O$, TMEDA (4.0 equiv), −78 °C, 3 h, then **9** (10 mol %), −45 °C, 3 h, −78 °C, 2,6-dimethylphenyl isocyanate, 2 h, >99:1 er; (ii) $CF_3COOH$, $CH_2Cl_2$, rt, 10 h, then NaOH; (iii) isopropyl alcohol, 1-bromopropane (3.0 equiv), $K_2CO_3$ (3.0 equiv), $H_2O$, 100 °C, 6 h.

CDR of **2** with ligand **9** and electrophilic quenching with 2,6-dimethylphenyl isocyanate afforded enantiopure (>99:1 er) (*S*)-**21** in 69% yield (Scheme 4). After deprotection, alkylation with 1-bromopropane in the presence of $K_2CO_3$ yielded (*S*)-(−)-ropivacaine in 61% overall yield for three steps.

In summary, the discoveries of ligands **8** and **9** coupled with their ability to resolve *N*-Boc-2-lithiopiperidine catalytically have provided an efficient route for the highly enantioselective syntheses of 2-substituted piperidines having either absolute configuration.

**Acknowledgment.** This work was supported by the Arkansas Biosciences Institute and the National Science Foundation (CHE 0616352 and 1011788). Core facilities were funded by the National Institutes of Health (R15569) and the Arkansas Biosciences Institute. The authors are grateful to Professors Dieter Seebach and Iain Coldham for helpful discussions.

**Supporting Information Available:** Full experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA105772Z