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Application of Catalytic Dynamic Resolution of *N*-Boc-2-lithiopiperidine to the Asymmetric Synthesis of 2-Aryl and 2-Vinyl Piperidines

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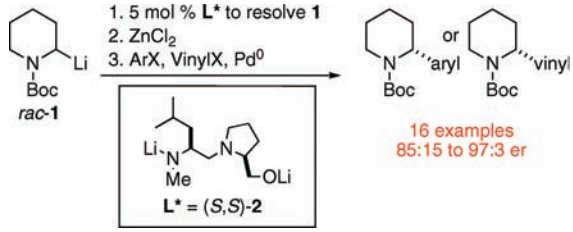
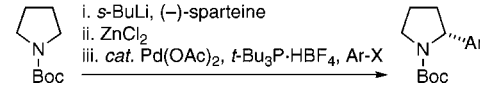
ABSTRACT



The highly enantioselective synthesis of 2-aryl- and 2-vinyl-piperidines has been accomplished through a catalytic dynamic resolution (CDR) of *N*-Boc-2-lithiopiperidine. The method has been applied to the synthesis of both enantiomers of the tobacco alkaloid anabasine.

Optically active 2-aryl- and 2-vinyl-piperidines are found in a variety of natural products, and some have useful pharmacological properties.[1−3] Previously, Dieter demonstrated that transmetalation of *N*-Boc-2-lithiopyrrolidine to its organocopper counterpart provides a convenient way to synthesize vinylated pyrrolidines.[4,5] Using an asymmetric deprotonation methodology with the chiral base *s*-BuLi/(−)-sparteine[6,7] to generate an enantioenriched organolithium, Dieter achieved enantioselective vinylations with er's up to 93:7. Later, Campos used the asymmetric deprotonation methodology and transmetalation to an organozinc species, followed by a palladium-mediated Negishi coupling with aryl bromides, to prepare *N*-Boc-2-arylpyrrolidines in good yields and ≥96:4 er's (Scheme 1).[8−11]

Scheme 1. Campos Conditions for Enantioselective Arylation of *N*-Boc-pyrrolidine[8]



The remarkable chemical and configurational stability of the intermediate organozinc compound, even at 60 °C, and

(1) Amat, M.; Canto, M.; Llor, N.; Bosch, J. *Chem. Commun.* **2002**, 526.
(2) Castro, A.; Ramirez, J.; Juarez, J.; Teran, J. L.; Orea, L.; Galindo, A.; Gnecco, D. *Heterocycles* **2007**, *71*, 2699.
(3) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(4) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726.
(5) Dieter, R. K.; Topping, C. M.; Chandupatla, K. R.; Lu, K. *J. Am. Chem. Soc.* **2001**, *123*, 5132.
(6) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
(7) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422.
(8) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538.
(9) O'Brien, P.; Bilke, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 2734.
(10) Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C.-Y. *J. Org. Chem.* **2008**, *73*, 4986.
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the high degree of tolerance for both electron-rich and electron-deficient aryl halides make this transformation very attractive.

Previous attempts to synthesize enantioenriched 2-aryl-piperidines via Negishi coupling conditions have been less successful. O'Brien recently reported an asymmetric deprotonation of *N*-Boc-piperidine using *s*-BuLi and O'Brien's diamine[12] (Figure 1), followed by trapping with

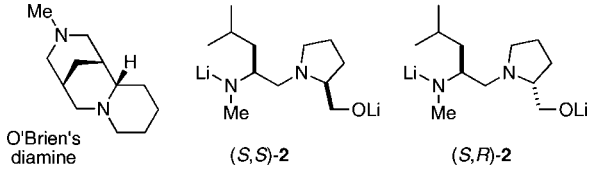
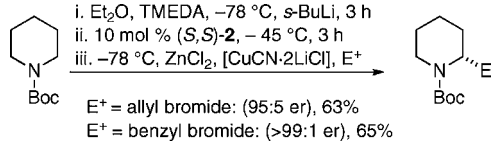


Figure 1. Chiral ligands.

4-bromoveratrole, affording the arylated product in 33% yield and 82:18 er (*S*:*R*).[11] Although the Coldham group successfully synthesized racemic members of this family via Negishi coupling,[13] attempts to effect enantioselectivity by dynamic thermodynamic resolution (DTR) using a stoichiometric amount of chiral ligand led to no arylation products.[14] They reported two examples of enantioenriched 2-aryl-piperidines (er 82:18 (*R*:*S*)) obtained by transmetalation of an enantioenriched stannane to the organolithium under conditions that ensured the configurational stability of the latter.

We recently reported the highly enantioselective synthesis of 2-substituted piperidines by catalytic dynamic resolution (CDR) of *N*-Boc-2-lithiopiperidine **1** using diastereomeric ligands (*S*,*S*)-**2** and (*S*,*R*)-**2** (Figure 1).[15] In our report, we utilized copper-mediated coupling to synthesize enantioenriched 2-allyl- and 2-benzyl-piperidines (Scheme 2) via an

Scheme 2. CDR of *N*-Boc-2-lithiopiperidine Followed by Copper-Mediated Allylation and Benzylation



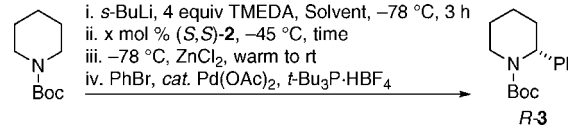
organozinc reagent formed by transmetalation of the resolved *N*-Boc-2-lithiopiperidine.

We know (Scheme 2) that during transmetalation of lithium to zinc, then to copper, the configurational stability is maintained. Based on Campos' results (Scheme 1), we hoped that, during transmetalation from zinc to palladium, the configurational integrity would be retained.

Considering that we are able to resolve *N*-Boc-2-lithiopiperidine catalytically, we investigated a CDR in the Negishi arylations and vinylations. We herein expand the synthetic potential of our methodology to the direct enantioselective synthesis of 2-aryl and 2-vinyl-piperidines. Good yields and er's are obtained with a 5% catalyst loading. Our method obviates the need for an enantioselective deprotonation or the asymmetric synthesis of a precursor stannane.

The conditions for the CDR of *rac*-**1** were optimized as illustrated in Table 1, beginning with the previously opti-

Table 1. Optimization of the Enantioselective Arylation of *N*-Boc-2-lithiopiperidine by CDR



entry	(*S*,*S*)-**2** (mol %)	time (h)	solvent	yield (%) of **3**	er of **3** (*R*:*S*)
1	10	3	Et_2O	74	90:10
2	10	3	MTBE	65	86:14
3	5	3	Et_2O	70	93:7
4	5	5	Et_2O	68	96:4
5	5	5	MTBE	60	89:11
6	100	3	Et_2O	71	53:47

mized conditions.[15] In oven-dried septum-capped flasks, *rac*-**1** was generated by deprotonation of *N*-Boc-piperidine in either Et_2O or MTBE at −78 °C with *s*-BuLi/TMEDA, followed by addition of (*S*,*S*)-**2**, warming to −45 °C for 3 to 5 h, and then cooling to −78 °C. A solution of $ZnCl_2$ in THF was added prior to warming to room temperature and introduction of $Pd(OAc)_2$, *t*-Bu_3P•HBF_4, and phenyl bromide sequentially (details are in the Supporting Information). After the mixture stirred for 3 h with 10 mol % of (*S*,*S*)-**2** in the presence of Et_2O, we were pleased to obtain *R*-**3** in 74% yield and 90:10 er (entry 1). With MTBE, *R*-**3** was obtained in 65% yield and 86:14 er (entry 2). After lowering the catalyst loading to 5 mol %, stirring at −45 °C for 3 h in Et_2O improved the er to 93:7 (entry 3). Performing the CDR for an additional 2 h at −45 °C led to a further enhancement in the er of *R*-**3** to 96:4 (entry 4). However, with MTBE, the same conditions afforded *R*-**3** in 60% yield and 89:11 er (entry 5).

Two important findings emerged from our optimization: (i) the yields and er's are lower in MTBE than in Et_2O, (ii) the er's are higher with a lower loading of (*S*,*S*)-**2**. Intriguingly, when a DTR using a stoichiometric amount of (*S*,*S*)-**2** was carried out, nearly racemic **3** was obtained (entry 6). The reason for the loss of enantioselectivity is not fully understood at this point.

Several other aryl and vinyl halides were evaluated under the optimized CDR conditions, with the results summarized in Table 2. In all cases, we obtained good yields and high

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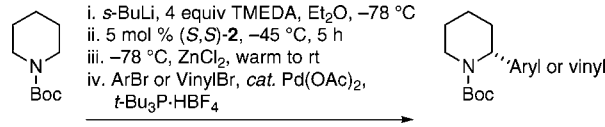
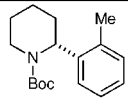
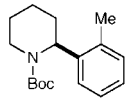
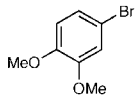
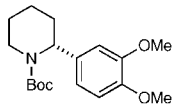
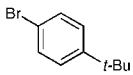
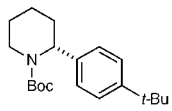
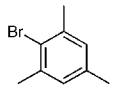
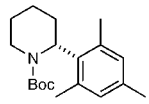
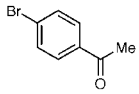
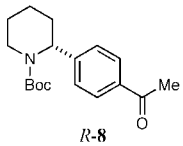
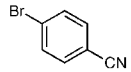
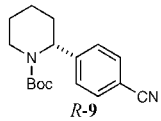
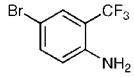
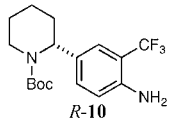
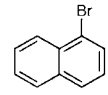
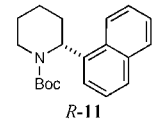
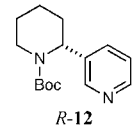
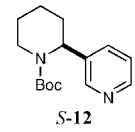
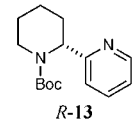
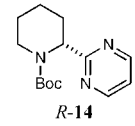
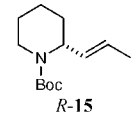
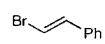
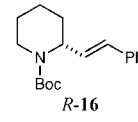
(14) Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem.—Eur. J.* **2010**, *16*, 4082.
(15) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216.

Table 2. CDR of *rac*-**1** and Negishi Arylation or Vinylation



entry	electrophile	product	yield (%)	er (*R*:*S*)
1[a]		 *R*-**4**	63	92:8
2[a,b]		 *S*-**4**	59	6:94
3[a]		 *R*-**5**	75	97:3
4[a]		 *R*-**6**	69	95:5
5[a]		 *R*-**7**	64	92:8
6[a]		 *R*-**8**	60	91:9
7[a,c]		 *R*-**9**	66	90:10
8[a]		 *R*-**10**	60	93:7

entry	electrophile	product	yield (%)	er (*R*:*S*)
9[c]		 *R*-**11**	67	97:3
10[d]		 *R*-**12**	46	88:12
11[b,d]		 *S*-**12**	51	10:90
12[d]		 *R*-**13**	50	93:7
13[d]		 *R*-**14**	53	85:15
14[a]		 *R*-**15**	63	92:8
15[a,e]		 *R*-**16**	66	93:7

[a] Stirred at rt for 18 h during step (iv). [b] CDR using (*S*,*R*)-**2**. [c] The aryl bromide contained a small amount of 2-bromobenzonitrile leading to formation of the *ortho* cyano constitutional isomer in 90:10 er. [d] Stirred at 60 °C for 22 h during step (iv), [e] A small amount of the *Z*-alkene was obtained as a minor isomer in 92:8 er.

er's. Quenching with *o*-bromotoluene afforded *R*-**4** in 63% yield and 92:8 er (entry 1) and *S*-**4** in 6:94 er using (*S*,*R*)-**2** (entry 2). Electrophilic quenching with 4-bromoveratrole gave *R*-**5** in 75% yield and 97:3 er (entry 3). Quenching with *p*-*tert*-butylbromobenzene afforded *R*-**6** in 69% yield and 95:5 er (entry 4) while 2-bromomesitylene gave *R*-**7** in 64% yield and 92:8 er (entry 5).

Some electron-deficient aryl bromides were evaluated in order to highlight the high degree of tolerance of aryl coupling. With *p*-bromoacetophenone, *R*-**8** was obtained in 66% yield and 91:9 er (entry 6). Electrophilic quenching with 4-bromobenzonitrile gave *R*-**9** in 66% yield and 90:10 er (entry 7).

Quenching with 4-bromo-2-trifluoromethyl aniline afforded *R*-**10** in 60% yield and 93:7 er (entry 8), thus illustrating that this Negishi arylation works even in the presence of an unprotected amine. Electrophilic quenching with 1-bromonaphthalene gave *R*-**11** in 67% yield and 97:3 er (entry 9).

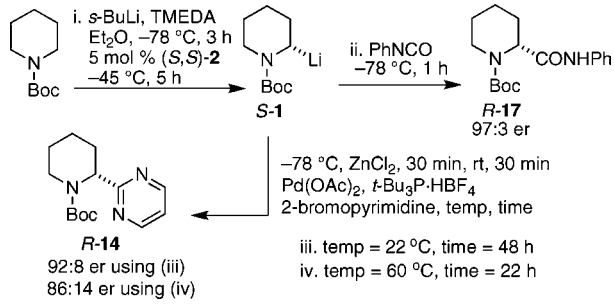
When heteroaryl halides were employed, the arylations occurred rather slowly and required mild heating to 60 °C. Quenching with 3-bromopyridine gave *R*-**12** in 46% yield and 88:12 er (entry 10). When the CDR was carried out using (*S*,*R*)-**2**, *S*-**12** was obtained in 51% yield and 90:10 er (entry 11). With 2-bromopyridine, *R*-**13** in 50% yield and 93:7 er

was obtained (entry 12). Electrophilic quenching with 2-bromopyrimidine gave *R*-**14** in 53% yield and 85:15 er (entry 13).

Vinylation was also investigated using the same reaction conditions. Thus, quenching with 1-bromo-1-propene afforded *R*-**15** in 63% yield and 92:8 er (entry 14). With β-bromostyrene, *R*-**16** was obtained in 66% yield and 93:7 er (entry 15).

We wondered whether the comparatively low er's in the heterocycle arylations (entries 10−13) were due to a slight loss of configurational stability at 60 °C or some unidentified process. Scheme 3 shows a control experiment in which the

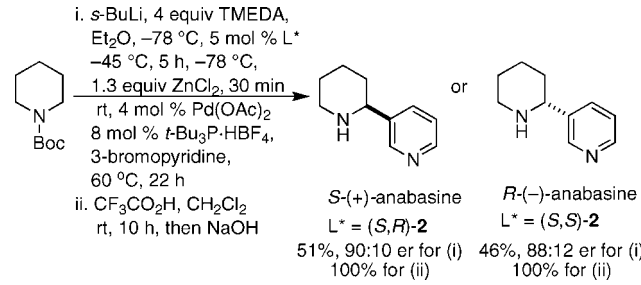
Scheme 3. Monitoring of the er during Enantioselective Arylation



er was monitored at some key stages of the reaction. After a CDR was performed at −45 °C for 5 h and then cooling to −78 °C, we quenched an aliquot with phenyl isocyanate[15] and found the product, *R*-**17**, to have 97:3 er. After addition of $ZnCl_2$ to the remaining mixture, warming to room temperature, and introduction of the $Pd(OAc)_2$, *t*-$Bu_3P{\cdot}HBF_4$, and 2-bromopyrimidine, a second aliquot was allowed to stir for two days at room temperature. This aliquot showed that *R*-**14** had 92:8 er. The remaining heterogeneous mixture was heated to 60 °C for 22 h and then cooled. The er from this sample was 86:14. Although the slight loss of er from 97:3 to 92:8 was anticipated, the significant loss of er to 86:14 reveals that the configurational stability with the piperidine system is compromised at 60 °C, in contrast with the pyrrolidines.[8]

Synthesis of Anabasine Enantiomers: The synthesis of either enantiomer of the tobacco alkaloid anabasine was

Scheme 4. Preparation of (*R*) and (*S*)-Anabasine[16]



accomplished as illustrated in Scheme 4. CDR of *rac*-**1** using either (*S*,*S*)-**2** or (*S*,*R*)-**2**, transmetalation, and Negishi coupling with 3-bromopyridine afforded *R*-**12** or *S*-**12** respectively. Hydrolysis of the enantiomeric carbamates with trifluoroacetic acid afforded (*R*)-anabasine in 46% and 88:12 er ($[\alpha]_D^{22}$ 70.9 (*c* = 1.0, MeOH)) or (*S*)-anabasine in 50% and 90:10 er ($[\alpha]_D^{22}$ −73.4 (*c* = 1.0, MeOH), lit.[16] $[\alpha]_D^{20}$ −80 (92% ee; *c* = 0.91, MeOH)) in just two steps.

In summary, the asymmetric arylation and vinylation of *N*-Boc-piperidine has been accomplished through catalytic dynamic resolution of *N*-Boc-2-lithiopiperidine followed by transmetalation and Negishi coupling. Most aryl and vinyl halides produce coupling products of the chiral organozinc intermediate with high enantioselectivity at room temperature. When somewhat elevated temperatures are required, such as with π-deficient heterocycles, some racemization occurs.

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

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