

Stereoselective Synthesis of 5-Substituted Pyrrolo[1,2-c]imidazol-3-ones: Access to Annulated Chiral Imidazol(in)ium Salts

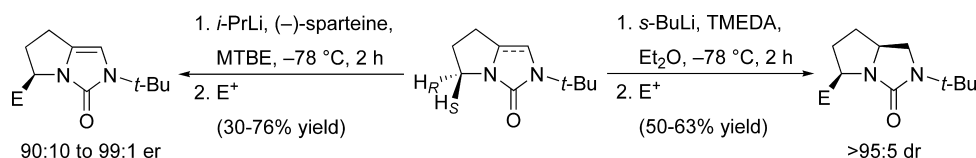
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ABSTRACT



A two-step synthesis of *N*-heterocyclic carbene (NHC) precatalysts by diastereoselective or enantioselective lithiation of pyrrolo[1,2-c]imidazol-3-ones followed by POCl₃-induced salt formation is described. The resulting 3-chloro-pyrroloimidazol(in)ium salts may be coordinated to palladium(II) upon NHC generation with *t*-BuLi at low temperature. The method may facilitate exploitation of these compounds as chiral organocatalysts or ligands in metal catalysis.

Pyrroloimidazoles (**1**, Figure 1) resemble plant-derived pyrrolizidine alkaloids¹ (e.g., **2**) and constitute a small but potent class of biologically active molecules. Compounds with a framework represented by **1** have anxiolytic properties² and exhibit nanomolar inhibitory activity against aldosterone synthase and aromatase.³ As such, they may be useful in the treatment of hypokalemia, hypertension, and congestive heart failure. Previous syntheses of α -arylated pyrroloimidazoles give racemic products that require resolution of the constituent enantiomers, which often differ in their levels of efficacy.³

Compounds with a pyrroloimidazol(in)e skeleton have also been used as guanidine organocatalysts⁴ (e.g., **3**), although these do not possess stereogenic centers in the same place as **1**. More appropriate structural comparisons can be made

to chiral *N*-heterocyclic carbene (NHC) precatalysts such as triazolium (**4**) and thiazolium (**5**) salts.⁵ However, the related imidazol(in)ium salts⁶ (**6**) are more challenging to prepare and to date have limited structural diversity because they originate from *syn*-1,2-aminoalcohols.⁷ Development of a stereoselective synthesis of pyrroloimidazol(in)es, which contain one or two stereogenic centers α to nitrogen in the pyrrolidine ring, would provide access to biologically active compounds and serve to increase the number of annulated C₁-symmetric imidazol(in)ium derived NHCs.⁸ The latter may be useful precursors to nucleophilic or transition metal catalysts.

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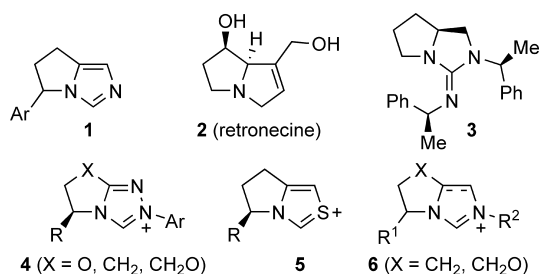


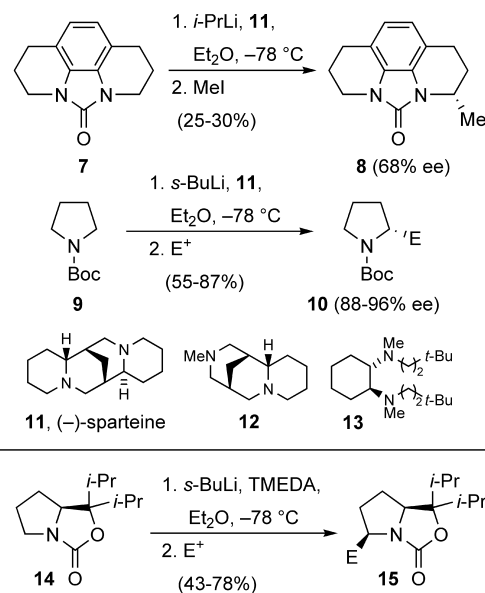
Figure 1. Examples of compounds with pyrroloimidazol(in)e (**1**, **3**, **6**), pyrrolizidine (**2**), triazoline (**4**), and thiazoline (**5**) frameworks.

Previously, we demonstrated that annulated chiral benzimidazolium salts could be obtained from **7** (Scheme 1), in which a fused urea served as a directing group for enantioselective lithiation of the piperidyl ring.⁹ It was envisioned that this method could be extended to pyrroloimidazol(in)-3-ones. This approach is based on the known ability of *N*-Boc pyrrolidine (**9**) to undergo enantioselective lithiation-substitution with (–)-sparteine to give products in good yields and enantiomeric purity.¹⁰ Recently, this method has become more versatile by the development of (+)-sparteine surrogates¹¹ (e.g., **12** and **13**) and the ability to install aromatic substituents α to nitrogen.¹² Moreover, cyclic carbamates (e.g., **14**) have been shown to undergo diastereoselective lithiation to give exclusively *syn*-configured products **15** in good yields.¹³

To begin our investigations, the required starting materials were prepared from *t*-Bu amide **16** (Scheme 2), which was obtained from Cbz-protected L-proline by standard methods.¹⁴ Removal of the Cbz group (cyclohexene, Pd/C) and reduction of the amide (LiAlH₄) gave a volatile diamine that, without purification, was converted to urea **17** with triphosgene. The unsaturated congener **19** was prepared by reduction of **16** with LiAlH₄, which gave **18** as an epimeric mixture of hemiaminals. Addition of dilute acid (0.1 M aqueous HCl) to this mixture induced elimination of water to afford urea **19** in good overall yield.

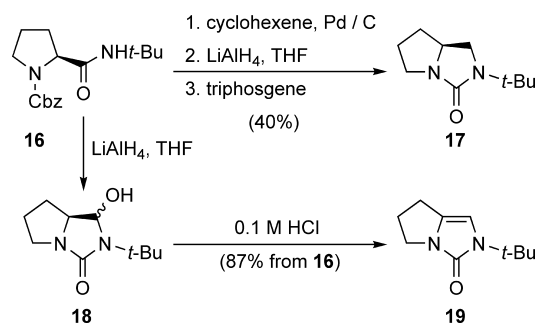
With respect to diastereoselective lithiation of **17**, computational minimization¹⁵ indicated that the distances between the urea oxygen and the pro-*S* or pro-*R* α -methylene

Scheme 1. Enantioselective Lithiation of **7** and **9**, and Diastereoselective Lithiation of **14**



hydrogens of the pyrrolidine ring were 2.51 and 3.69 Å, respectively. The difference between these distances (1.18 Å) is greater than what was calculated for cyclic carbamate **14**¹³ (0.92 Å based on O $\cdots$ H_S = 2.78 Å and O $\cdots$ H_R = 3.70 Å), suggesting that α -lithiation of **17** would be at least as selective as **14**.

Scheme 2. Synthesis of Chiral Urea **17** and Achiral Urea **19**



Accordingly, deprotonation of **17** (1.1 equiv *s*-BuLi, TMEDA, Et₂O, –78 °C) followed by addition of benzophenone gave **20a** as a single diastereomer in 60% yield (Scheme 3). Several other substituents were introduced into the 5-position with equal facility, including methyl (55%), allyl (50%), trimethylsilyl (63%) and trimethylstannyl (55%). All of the preceding products were obtained as single diastere-

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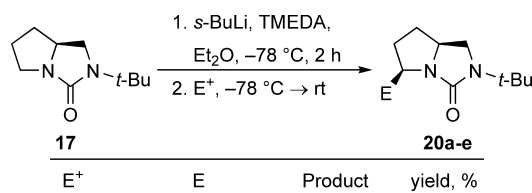
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(15) Compound **17** was minimized at the B3LYP/6-31G(d) level as implemented in Gaussian 03.

omers, which entails a diastereomeric ratio (dr) of >95:5 for the α -lithio intermediate before electrophile quench. The *syn* relative stereochemistry of products **20a**, **20b**, **20c**, and **20e** were verified by NOESY or 1-D NOE spectroscopy, which is consistent with the stereochemistry of products **15**. That the α -carbanion of **17** had configurational stability at -78°C was demonstrated by transmetalation of stannane **20e** (*n*-BuLi, Et₂O, 4.5 h), which upon Me₂SO₄ quench gave *syn*-**20b** exclusively.

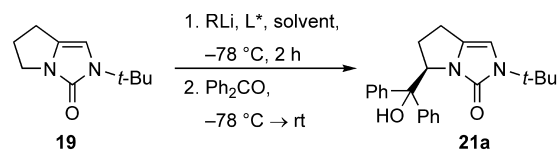
Scheme 3. Diastereoselective Lithiation of **17**



^a via CuCN·2LiCl transmetalation.

For enantioselective lithiation of **19**, several alkyllithium-ligand-solvent combinations were evaluated by examining the product of benzophenone quench of the putative α -carbanion (**21a**, Scheme 4). The best result was obtained using *i*-PrLi/(–)-sparteine in MTBE solvent, which provided **21a** in 67% yield and 90.5:9.5 enantiomeric ratio (81% ee). The combination of *i*-PrLi and (+)-sparteine surrogate **13** in Et₂O afforded the antipode of **21a** in 60% yield and 14.5:85.5 er (71% ee).

Scheme 4. Optimization Experiments for Enantioselective Lithiation of **19**



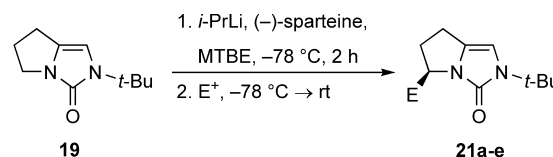
L*	RLi	solvent	yield, %	er (% ee), 21a
(–)-sparteine	<i>s</i> -BuLi	Et ₂ O	73	68.5:31.5 (37)
(–)-sparteine	<i>i</i> -PrLi	Et ₂ O	64	82:18 (64)
(–)-sparteine	<i>i</i> -PrLi	MTBE	67	90.5:9.5 (81)
(–)-sparteine	<i>i</i> -PrLi	PhMe	8	82.5:17.5 (65)
13	<i>i</i> -PrLi	Et ₂ O	60	14.5:85.5 (71)
13	<i>i</i> -PrLi	MTBE	62	15.5: 84.5 (69)
13	<i>i</i> -PrLi	PhMe	44	14.5:85.5 (71)

Applied to other electrophiles (Scheme 5), the optimum *i*-PrLi/(–)-sparteine/MTBE conditions gave Me, allyl, and

stannyl derivatives **21b–d** in higher enantiomeric purity (94:6 to 99:1 er; 88–98% ee) and yields ranging from 63–76%. Phenylation according to the procedure described for *N*-Boc pyrrolidine¹² afforded **21e** in lower yield (30%) but similar enantiomeric purity (93.5:6.5 er; 87% ee).

The absolute stereochemistry of **21b** was determined by reduction of the enamine (NaBH₃CN, MeOH/AcOH, reflux), which gave a mixture of *anti*- and *syn*-**20b**. *Syn*-**20b** had the same specific rotation ([α]_D²⁰ –4) as **20b** derived from **17** ([α]_D²⁰ –4.4). The relative stereochemistry of *anti*-**20b** was verified by 1-D NOE experiments.¹⁶ In addition, transmetalation of stannane **21d** (*n*-BuLi, THF, -100°C) and quench with Me₂SO₄ gave **21b** with the same optical rotation as **21b** made directly from **19**. Based on these results and the expectation that the enantioselectivity during (–)-sparteine-mediated lithiation of **19** arises from an asymmetric deprotonation step,¹⁰ the same relative stereochemistry may be tentatively assigned to all products **21a–e**.

Scheme 5. (–)-Sparteine-Mediated Lithiation of **19**



E ⁺	E	Product	yield, %	er (% ee)
Ph ₂ CO	Ph ₂ COH	21a	67	90.5:9.5 (81)
Me ₂ SO ₄	Me	21b	63	97:3 (94)
allyl bromide ^a	allyl	21c	76	94:6 (88)
SnMe ₃ Cl	SnMe ₃	21d	68	99:1 (98) ^b
PhBr ^c	Ph	21e	30	93.5:6.5 (87)

^a via CuCN·2LiCl transmetalation. ^b After transmetalation (*n*-BuLi, THF, -100°C , 1 h) and Me₂SO₄ quench. ^c via ZnCl₂ transmetalation and Pd(OAc)₂/HBF₄·P(*t*-Bu)₃ coupling.

Preliminary experiments indicate that ureas **20b**, **19**, and **21b** may be converted to imidazol(in)ium salts with phosphorus oxychloride (Scheme 6).¹⁷ For example, a heated solution of **20b** in POCl₃ produced chiral imidazolium **22**, isolated as the tetraphenylborate salt. Likewise, sequential treatment of **19** or **21b** with POCl₃ and NaBPh₄ gave the 3-chloroimidazolium salts **23a,b**, which were immediate precursors to Pd(II) complexes **24a,b** by chlorine–lithium exchange with *t*-BuLi at low temperature.¹⁸

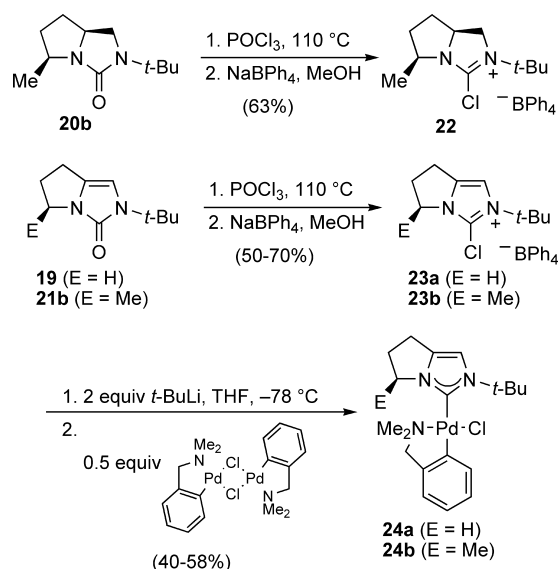
In conclusion, it has been shown that 5-substituted pyrroloimidazol(in)ium precatalysts can be prepared in two

(16) The pyrrolidine methyl group in *syn*-**20b** has a ¹³C NMR chemical shift of 18.2 ppm compared to 22.5 ppm in *anti*-**20b**. The difference in resonance frequency can be attributed to a γ -effect and may be used to assign *syn* and *anti* stereochemistry in these ureas and related chiral bicyclic ketones with a high degree of confidence. See: (a) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (b) Hudlicky, T.; Koszyk, F. J.; Dochwat, D. M.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 2911.

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Scheme 6. Conversion of Pyrroloimidazol(in)ones to NHC Precursors **22**, **23a**, and **23b**



steps by stereoselective lithiation-electrophile quench of pyrrolo[1,2-c]imidazol(in)-3-ones **17** or **19**, followed by POCl_3 -induced salt formation. These results establish a new method to access enantiomerically enriched α -chiral com-

pounds of general structure **6**, which are relatively uncommon and challenging to make by conventional routes.⁷ Additional work is underway to explore the utility of these materials as precursors to chiral “frustrated” Lewis pairs,¹⁹ nucleophiles and ligands in asymmetric catalysis. Procedures to remove and/or replace the *N*-*t*-Bu group²⁰ with other substituents are also being studied. The outcomes of these investigations will be reported as results permit.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra, NOESY/NOE spectra, plus the minimized structure of **17**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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