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

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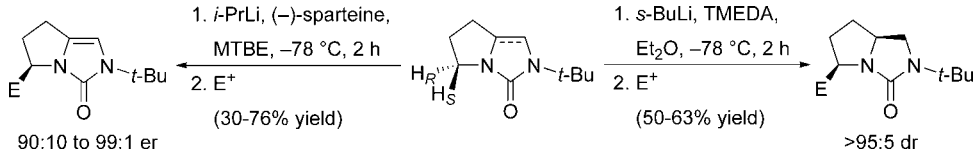
ABSTRACT



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 $POCl_3$-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 alkaloids[1] (e.g., **2**) and constitute a small but potent class of biologically active molecules. Compounds with a framework represented by **1** have anxiolytic properties[2] and exhibit nanomolar inhibitory activity against aldostereone synthase and aromatase.[3] As such, they may be useful in the treatment of hypoalkemia, 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 organocatalysts[4] (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 salts[6] (**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 C_1-symmetric imidazol(in)ium derived NHCs.[8] The latter may be useful precursors to nucleophilic or transition metal catalysts.

(1) Huang, J.-M.; Hong, S.-C.; Wu, K.-L.; Tsai, T.-M. *Tetrahedron Lett.* **2004**, *45*, 3047, and references therein.

(2) (a) Fontanella, L.; Corsico, N.; Diena, A.; Occelli, E. *Farmaco, Ed. Sci.* **1984**, *39*, 133. (b) Fontanella, L.; Occelli, E.; Perazzi, A. *Farmaco, Ed. Sci.* **1973**, *28*, 463. (c) Fontanella, L.; Occelli, E. *Farmaco, Ed. Sci.* **1971**, *26*, 685.

(3) (a) Ksander, G. M.; Meredith, E.; Monovich, L. H.; Papillon, J.; Firooznia, F.; Hu, Q. WO 024945 (2007). (b) Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E. *J. Med. Chem.* **1991**, *34*, 725.

(4) Isobe, T.; Fukuda, K.; Ishikawa, T. *J. Org. Chem.* **2000**, *65*, 7770.

(5) (a) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872. (b) Rovis, T. *Chem. Lett.* **2008**, *37*, 2. (c) de Alaniz, J. R.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (e) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632. (f) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951. (g) He, L.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Synthesis* **2008**, 2825.

(6) (a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (b) Nair, V.; Babu, B. P; Vellalath, S.; Varghese, V.; Raveendran, A. E.; Suresh, E. *Org. Lett.* **2009**, *11*, 2507. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (d) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130.

(7) (a) Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957. (b) Struble, J. R.; Bode, J. W. *Tetrahedron* **2008**, *64*, 6961. Review: (c) Arduengo, A. J.; Iconaru, L. I. *Dalton Trans.* **2009**, 6903.

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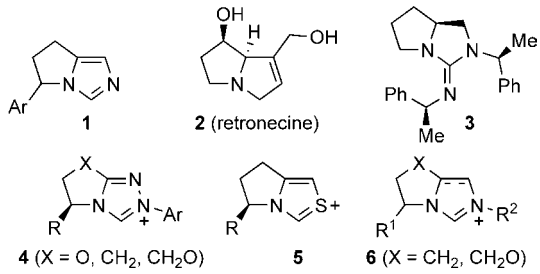


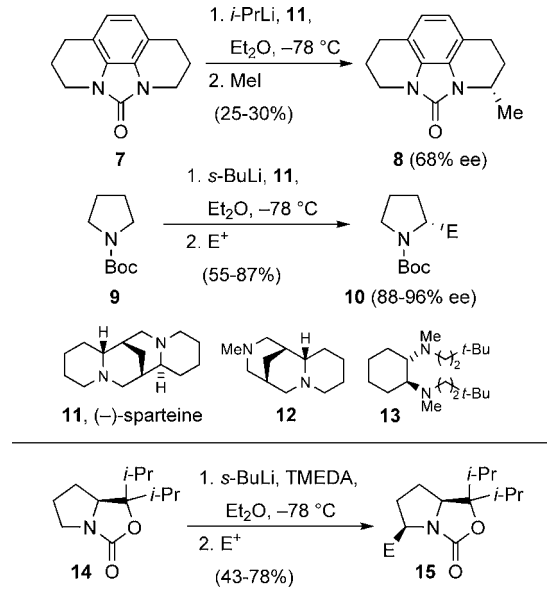
Figure 1. Examples of compounds with pyrroloimidazol(in)e (**1**, **3**, **6**), pyrrolizidine (**2**), triazoline (**4**), and thiazoline (**5**) frameworks.

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 surrogates[11] (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 ($LiAlH_4$) 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 $LiAlH_4$, 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.

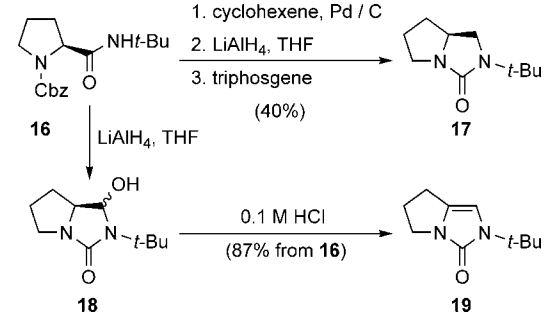
With respect to diastereoselective lithiation of **17**, computational minimization[15] indicated that the distances between the urea oxygen and the pro-*S* or pro-*R* α-methylene

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, Et_2O, −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-

(8) For α-chiral annulated NHCs in transition metal catalysis, see: (a) Metallinos, C.; Du, X. *Organometallics* **2009**, *28*, 1233. (b) Metallinos, C.; Barrett, F. B.; Wang, Y.; Xu, S.; Taylor, N. J. *Tetrahedron* **2006**, *62*, 11145. (c) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344. (d) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704. (e) Baskakov, D.; Herrmann, W. A.; Herdtweck, E.; Hoffmann, S. D. *Organometallics* **2007**, *26*, 626.

(9) Metallinos, C.; Dudding, T; Zaifman, J.; Chaytor, J. L.; Taylor, N. J. *J. Org. Chem.* **2007**, *72*, 957.

(10) (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (b) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (c) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282.

(11) (a) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409. (b) Mealey, M. J.; Luderer, M. R.; Bailey, W. F.; Sommer, M. B. *J. Org. Chem.* **2004**, *69*, 6042. (c) O'Brien, P. *Chem. Commun.* **2008**, 655.

(12) (a) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (b) O'Brien, P.; Bilke, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 2734.

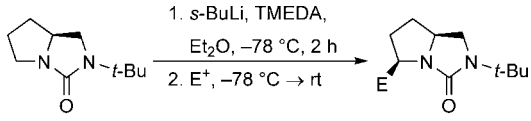
(13) Bertini Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.

(14) (a) Corma, A.; Iglesias, M.; del Pino, C.; Sánchez, F. *J. Organomet. Chem.* **1992**, *431*, 233. (b) Corey, E. J.; Saizo, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.

(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, Et_2O, 4.5 h), which upon Me_2SO_4 quench gave *syn*-**20b** exclusively.

Scheme 3. Diastereoselective Lithiation of **17**



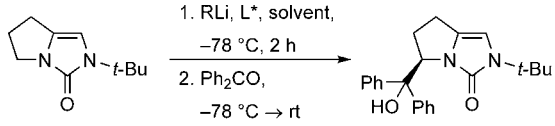
17 **20a-e**

E^+	E	Product	yield, %
Ph_2CO	Ph_2COH	**20a**	60
Me_2SO_4	Me	**20b**	55
allyl bromide[a]	allyl	**20c**	50
$SiMe_3Cl$	$SiMe_3$	**20d**	63
$SnMe_3Cl$	$SnMe_3$	**20e**	55

[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 Et_2O 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**



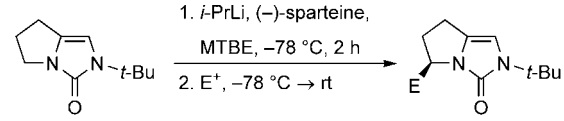
19 **21a**

L*	RLi	solvent	yield, %	er (% ee), **21a**
(−)-sparteine	*s*-BuLi	Et_2O	73	68.5:31.5 (37)
(−)-sparteine	*i*-PrLi	Et_2O	64	82:18 (64)
(−)-sparteine	*i*-PrLi	MTBE	67	90.5:9.5 (81)
(−)-sparteine	*i*-PrLi	PhMe	8	82.5:17.5 (65)
13	*i*-PrLi	Et_2O	60	14.5:85.5 (71)
13	*i*-PrLi	MTBE	62	15.5: 84.5 (69)
13	*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 pyrrolidine[12] 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 ($NaBH_3CN$, MeOH/AcOH, reflux), which gave a mixture of *anti*- and *syn*-**20b**. *Syn*-**20b** had the same specific rotation ($[\alpha]_D^{20}$ −4) as **20b** derived from **17** ($[\alpha]_D^{20}$ −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 Me_2SO_4 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**



19 **21a-e**

E^+	E	Product	yield, %	er (% ee)
Ph_2CO	Ph_2COH	**21a**	67	90.5:9.5 (81)
Me_2SO_4	Me	**21b**	63	97:3 (94)
allyl bromide[a]	allyl	**21c**	76	94:6 (88)
$SnMe_3Cl$	$SnMe_3$	**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 Me_2SO_4 quench. [c] via $ZnCl_2$ transmetalation and $Pd(OAc)_2/HBF_4 \cdot P(t\text{-}Bu)_3$ 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 $POCl_3$ produced chiral imidazolinium **22**, isolated as the tetraphenylborate salt. Likewise, sequential treatment of **19** or **21b** with $POCl_3$ and $NaBPh_4$ 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]

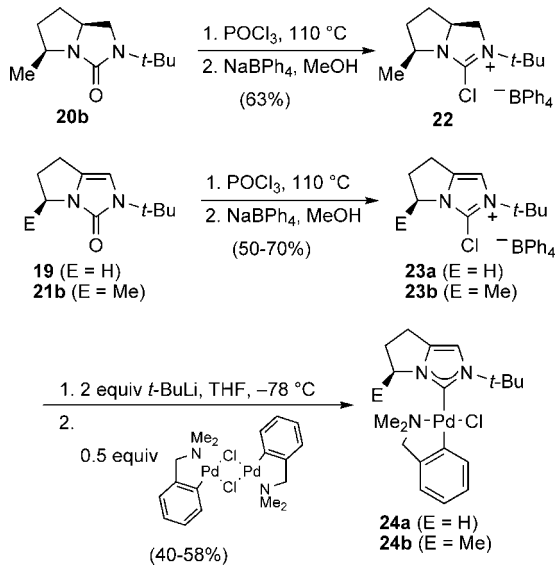
In conclusion, it has been shown that 5-substituted pyrroloimidazol(in)ium precatalysts can be prepared in two

(16) The pyrrolidine methyl group in *syn*-**20b** has a ^{13}C 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* streochemistry 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.

(17) Review: Crouch, D. R. *Tetrahedron* **2009**, *65*, 2387.

(18) Snead, D. R.; Ghiviriga, I.; Abboud, K. A.; Hong, S. *Org. Lett.* **2009**, *11*, 3274.

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 compounds 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 group[20] 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, ^{1}H 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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(19) (a) Chase, P. A.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7433. (b) Holschumacher, D.; Bannenberg, T.; Hrib, C. G.; Jones, P. G.; Tamm, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7428.

(20) Wen, Y.; Zhao, B.; Shi, Y. *Org. Lett.* **2009**, *11*, 2365.