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Enantioselective, Palladium-Catalyzed α-Arylation of *N*-Boc-pyrrolidine

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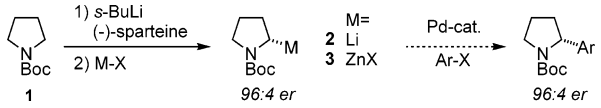
2-Arylpyrrolidines constitute an important structural motif in biologically active compounds and effective chiral controllers in asymmetric synthesis.[1] Few methods exist for the synthesis of these privileged structures, and all suffer from either long synthetic sequences, low yields, lack of generality, or modest enantioselectivity.[2] We reasoned that the most direct method to access enantioenriched 2-arylpyrrolidines would be the arylation of (*R*)-2-lithio-*N*-Boc-pyrrolidine (**2**) obtained from (−)-sparteine-mediated, enantioselective deprotonation of *N*-Boc-pyrrolidine (**1**).[3] However, whereas the stereoselective capture of **2** with a variety of electrophiles is well established,[4] the enantioselective arylation of **2** is unprecedented. Herein we report a general, enantioselective, palladium-catalyzed arylation of **1** that proceeds via in situ generated 2-pyrrolidinozinc reagent **3**. This convergent, one-pot synthesis of 2-aryl-*N*-Boc-pyrrolidines provides each adduct in a 96:4 enantiomeric ratio (er), regardless of the coupling partner. This remarkable feature clearly signals the high stereochemical fidelity of configurationally stable 2-pyrrolidinometal (Li, ZnX, Pd) reagents during each stage of the process.

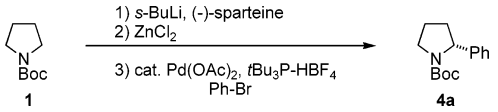


Although **2** would serve as the most logical intermediate to introduce both the enantioselectivity and functionalization required for an asymmetric arylation of **1**, the stereochemical lability of **2** at temperatures above −60 °C[5] and the lack of a general method for the arylation of alkyllithium reagents have prohibited the development of this transformation.[6] Attempts to circumvent the configurational instability of **2** via transmetalation with CuCN·2LiCl were moderately successful; however, the enantioselectivities were variable and rarely more than 90%, which suggested that epimerization of some intermediate was still occurring.[7]

Despite the documented configurational integrity of secondary alkylzinc reagents,[8] there have been no reports of the direct metalation of **1** with organozinc reagents to produce **3**.[9] Alternatively, **3** should be readily accessed by treatment of **2** with $ZnCl_2$. Moreover, **3** should be configurationally stable in a broad range of temperatures and should undergo facile transmetalation with organopalladium species.[10] If a suitable catalyst could be identified that preserved the configurational identity through the coupling, this process would constitute a direct, enantioselective arylation of **1**.

To test this hypothesis, the enantioselective deprotonation of **1** was performed according to literature precedent,[3] and the resulting anion was treated with 1 equiv of $ZnCl_2$. The presumed organozinc reagent **3** was warmed to room temperature to provide a homogeneous solution, which was readily subdivided for screening with a variety of palladium catalysts in the arylation with bromobenzene (Table 1). Despite the failure of $PdCl_2$(dppf), historically the catalyst of choice for Negishi couplings,[11] Pd catalysts derived from Buchwald's Ru-phos,[12] Hartwig's Q-phos,[13] and Fu's *t*-Bu_3P−HBF_4 [14] delivered arylated product **4a** in good yield and a 96:4 er,

Table 1. Enantioselective Arylation of *N*-Boc-pyrrolidine[a]



entry	ligand	Pd source	$ZnCl_2$ equiv	% yield (er)
1	−	$PdCl_2$dppf	1.0	<5 (nd)
2	1,1′-di-(*t*Bu_2P)ferrocene	$Pd(OAc)_2$	1.0	<5 (nd)
3	Cy_3P−HBF_4	$Pd(OAc)_2$	1.0	12 (96:4)
4	*t*Bu_2PMe-HBF_4	$Pd(OAc)_2$	1.0	<5 (nd)
5	*t*Bu_3P−HBF_4	$Pd(OAc)_2$	1.0	83 (96:4)
6	Ru-phos	$Pd(OAc)_2$	1.0	80 (96:4)
7	Q-phos	$Pd(OAc)_2$	1.0	80 (96:4)
8	*t*Bu_3P−HBF_4	Pd_2dba_3	1.0	82 (96:4)
9	*t*Bu_3P−HBF_4	$PdCl_2$	1.0	70 (96:4)
10	−	Pd(*t*$Bu_3P)_2$	1.0	70 (96:4)
11	−	[PdBr(*t*Bu_3P)]$_2$	1.0	78 (96:4)
12	*t*Bu_3P−HBF_4	$Pd(OAc)_2$	0.1	<5 (nd)
13	*t*Bu_3P−HBF_4	$Pd(OAc)_2$	0.3	79 (96:4)
14	*t*Bu_3P−HBF_4	$Pd(OAc)_2$	0.6	80 (96:4)

[a] Deprotonation was performed with 1.2 equiv of **1**, 1.2 equiv of *s*-BuLi, 1.2 equiv of (−)-sparteine, in MTBE (0.4 M) at −70 °C. Coupling was performed at RT overnight using 4 mol % Pd and 5 mol % ligand. Enantiomeric excess was determined by CSP HPLC (Chiralcel AD-H).

which was established in the deprotonation step! The absolute configuration of **4a** was assigned by deprotection to 2-phenylpyrrolidine and comparison of the optical rotation to that reported in the literature,[15] confirming that the transmetalation/Negishi coupling occurred with retention of configuration. In contrast to the dogma that secondary alkyl ligands on Pd rapidly undergo *β*-hydride elimination,[16] products resulting from this pathway amounted to <8%. For reasons of cost, availability, and practicality, we selected *t*-Bu_3P−HBF_4 for further development.

The nature of the palladium source was found to have a profound effect on the rate of the coupling reaction. In particular, $Pd(OAc)_2$ provided a significantly faster reaction than all other palladium sources.[17] It is interesting to note that either a 1:1 or 2:1 ratio of ligand-to-Pd provided competent in situ generated catalysts; however, the preformed catalyst Pd[(P*t*-$Bu_3)_2$][18] afforded only ∼80% conversion, whereas with [PdBr(P*t*-Bu_3)]$_2$[19] the reaction went to completion.

Because of the potential to form different organozinc species (RZnCl, R_2Zn, or R_3ZnLi), an examination of the dependence of yield and selectivity on the stoichiometry of $ZnCl_2$ was undertaken. We were delighted to find that the amount of $ZnCl_2$ could be reduced to as low as 0.33 equiv (with respect to **2**) without significant change in yield or enantioselectivity!

The enantioselective deprotonation/transmetalation/Negishi coupling was found to be quite general, affording a diverse array of 2-arylpyrrolidines in good yield and 96:4 er (Table 2). Not only were a variety of aryl bromides tolerated, but preliminary results suggested that aryl chlorides were also suitable coupling partners (entry 2, unoptimized). Phenyl triflate and phenyl tosylate were unreactive under the standard conditions.

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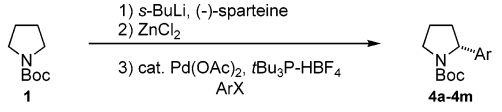
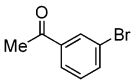
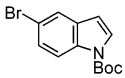
Table 2. General Enantioselective Arylation of *N*-Boc-pyrrolidine[a]



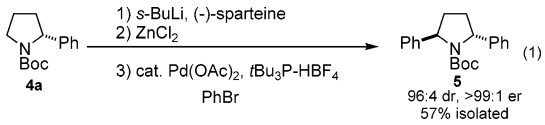
Entry	Ar-X	Product	% Yield (er)[b,c]
1	X = Br	**4a**	82 (96:4)
2	Cl	**4a**	48 (96:4)
3	OTf	**4a**	<5%
4	OTs	**4a**	<5%
5	R= F	**4b**	75 (96:4)
6	NMe_2	**4c**	78 (96:4)
7	CO_2Me	**4d**	81 (96:4)
8	SO_2Me	**4e**	87 (97:3)
9	CN	**4f**	80 (96:4)
10	NH_2	**4g**	70 (96:4)
11	R = Me	**4h**	71 (96:4)
12	OMe	**4i**	72 (96:4)
13		**4j**	78 (96:4)
14		**4k**	81 (96:4)
15		**4l**	77 (96:4)
16		**4m**	60 (96:4)[d]

[a] Deprotonation was performed with 1.2 equiv of **1**, 1.2 equiv of *s*-BuLi, 1.2 equiv of (−)-sparteine, in MTBE (0.4 M) at −70 °C. Transmetalation was performed with 0.6 equiv of $ZnCl_2$. Coupling was performed at RT overnight using 4 mol % Pd and 5 mol % tBu$_3$P−HBF$_4$. [b] Absolute stereochemistry was assigned by analogy to **4a**. [c] ee values were determined using CSP HPLC (Chiralcel AD-H). [d] Coupling was performed at 60 °C.

Although 0.33 equiv of $ZnCl_2$ could be used in the coupling with bromobenzene, substrates containing acidic functionalities were incompatible with these reaction conditions, presumably due to proton transfer. Surprisingly, this could be circumvented simply by changing the amount of $ZnCl_2$. For example, the coupling of 4-bromoaniline with 0.33 equiv of $ZnCl_2$ provided only 18% of the desired product; however, employing 0.6 equiv of $ZnCl_2$ under the same reaction conditions delivered arylated product **4g** in 70% yield (entry 10). Even unprotected indoles were tolerated with this protocol, providing adducts such as **4l** in good yield (entry 15).

The consistent observation of the arylated products with 96:4 er confirms that the enantioselectivity of the asymmetric deprotonation was preserved during the transmetalation with $ZnCl_2$ and was retained during the Pd-catalyzed coupling. In fact, the Negishi coupling with 3-bromopyridine (entry 16) was performed at 60 °C and still provided **4m** with a 96:4 er, which constitutes a formal total synthesis of (*R*)-nicotine.[20]

Having demonstrated a practical and reliable method to access 2-arylpyrrolidines in high enantioselectivity, we felt that a noteworthy extension of this methodology would lie in its application to monoarylated products **4**, providing a rapid and efficient approach to enantiopure C_2-symmetric 2,5-diarylpyrrolidines, which have been identified as valuable chiral auxiliaries and chiral ligands.[21] Toward this end, substrate **4a** was subjected to the standard arylation conditions, which produced 2,5-diphenyl-*N*-Boc-pyrrolidine (**5**) as a 96:4 diastereomeric ratio, and was isolated in 57% yield (eq 1).[22]



In conclusion, we have developed an unprecedented asymmetric arylation of *N*-Boc-pyrrolidine that relies on a (−)-sparteine mediated asymmetric deprotonation, followed by transmetalation with as little as 0.33 equiv of $ZnCl_2$ and subsequent Pd-catalyzed Negishi coupling with aryl bromides. The method was applicable to a host of aryl halides to provide a diverse array of 2-arylpyrrolidines in good yield and a 96:4 er, regardless of the nature of the aryl bromide component. This sequence offers a number of advantages over existing methods and represents the most convenient and practical synthesis of enantiomerically enriched 2-arylpyrrolidines and 2,5-diarylpyrrolidines. The use of **3** in other reactions and the application of the asymmetric deprotonation/transmetalation/Negishi coupling to other substrates will be reported shortly.

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Supporting Information Available: Experimental details and full characterization of key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Lewis, J. R. *Nat. Prod. Rep.* **2001**, 95−128. (b) Elliot, R. L.; Kopeka, H.; Lin, N.-H.; He, Y.; Garvey, D. S. *Synthesis* **1995**, 772−774. (c) Lin, N.-H.; Carrera, G. M., Jr.; Anderson, D. J. *J. Med. Chem.* **1994**, *37*, 3542−3553. (d) Higashiyama, K.; Inonue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083−1092 and references cited therein.
(2) (a) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2109−2113. (b) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715−721 and references cited therein.
(3) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239.
(4) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan S. *Acc. Chem. Res.* **1996**, *29*, 552−560.
(5) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716−738.
(6) The racemic Pd-catalyzed coupling of **2** with aryl iodides using CuCN has been reported. Dieter, R. K.; Li, S.-J. *J. Org. Chem.* **1997**, *62*, 7726−7735.
(7) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076−3086.
(8) (a) Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415−2432. (b) Guijarro, A.; Rieke, R. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1475−1479.
(9) Transmetalation with $ZnCl_2$ was reported on a chiral lithiated alkyl carbamate prepared following Hoppe's method; however, the intermediate was further transmetalated with CuCN. See: Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2002**, *4*, 119−122.
(10) Negishi, E.-I. In *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999; Chapter 11.
(11) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.
(12) Milne, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028−13032.
(13) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176−11177.
(14) Netherton, M.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.
(15) $[\alpha]_D$ +19.6 (*c* 0.3, MeOH); see ref 2.
(16) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146−151.
(17) It is possible that acetate stabilizes either the catalyst or its resting state. Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824−15832.
(18) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.
(19) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746−4748.
(20) Girard, S.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Tetrahedron Lett.* **2000**, *41*, 9245−9249.
(21) (a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 71655−71656. (b) He, S.; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 190−191. (c) Choi, Y. H.; Choi, J. Y.; Yang, H. Y.; Yong, H. *Tetrahedron: Asymmetry* **2002**, *11*, 801−804.
(22) *s*-BuLi/TMEDA produced **5** in lower d.r. (66:34) and yield (42%).

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