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α-Pyridylation of Chiral Amines via Urea Coupling, Lithiation and Rearrangement

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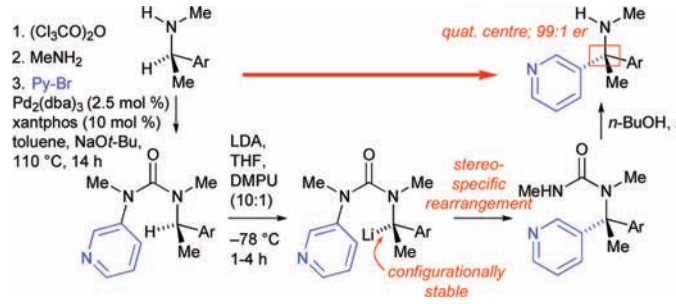
ABSTRACT



2-, 3- and 4-Bromopyridine, along with other brominated electron-deficient arenes, undergo palladium-catalyzed coupling with ureas of structure RNMeCONHMe. Where R is a chiral, α-substituted benzyl group, treatment with LDA leads to a benzylic organolithium which undergoes rearrangement with stereospecific and regiospecific transfer of the pyridyl group, generating a quaternary stereogenic center with high enantioselectivity. Alcoholysis of the urea under neutral conditions reveals the pyridyl amine.

Pyridines such as **1** bearing chiral substituents at various positions of the ring form an important class of biologically active compounds[1] (including nicotine and its analogues[1a]) and chiral ligands.[2] Methods for the construction of a stereogenic center adjacent to a pyridine ring[3] typically employ auxiliary (especially sulfinimine[3b]) controlled addition or cycloaddition to pyridyl aldehydes, ketones or imines,[3c] asymmetric reduction of similar compounds,[3d] asymmetric conjugate addition to electron-deficient pyridyl alkenes,[3e] Pd-catalyzed coupling or protonation of a chiral organometallic,[3f] or pyridine elaboration from a simple chiral precursor.[3g] None of these methods is generally applicable to the synthesis of pyridine-bearing quaternary centers.[4]

(1) (a) Ullrich, T.; Krich, S.; Mereiter, K.; Anderson, D. J.; Meyer, M. D.; Pyerin, M. *J. Med. Chem.* **2002**, *45*, 4047. (b) Lawson, E. C.; Hoekstra, W. J.; Addo, M. F.; Andrade-Gordon, P.; Damiano, B. P.; Kauffman, J. A.; Mitchell, J. A.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2619. (c) Kawata, S.; Ashzawa, S.; Hirama, M. *J. Am. Chem. Soc.* **1997**, *119*, 12012. (d) Rico, J. G.; Lindmark, J. R.; Bovy, P. R. *J. Org. Chem.* **1993**, *58*, 7948. (g) Aoki, M.; Ohtsuka, T.; Yamada, M.; Ohba, Y.; Yoshizaki, H.; Yasumo, H.; Sano, T.; Seto, H. *J. Antibiot.* **1991**, *44*, 582.

(2) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297. (b) Brunner, H.; Markus, N. *Monatsh. Chem.* **2002**, *133*, 115. (c) Chelucci, G.; Pinna, G. A.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2571. (d) Canary, J. W.; Allen, C. S.; Castagnetto, J. M.; Wang, Y. *J. Am. Chem. Soc.* **1995**, *117*, 8484. (e) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *38*, 8251. (f) Brunner, H.; Heinrich, F. *J. Organomet. Chem.* **1987**, *335*, 1.

(3) (a) For reviews, see: Chelucci, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2353. Ueinishi, J.; Aburatani, S. *Yuki Gosei Kagaku Kyokaishi* **2007**, *65*, 127. (b) Davies, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222. Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641. Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819. (c) Alvaro, G.; Boga, C.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 875. Fiore, K.; Martelli, G.; Monari, M.; Savoia, D. *Tetrahedron: Asymmetry* **1999**, *10*, 4803. Deloisy, S.; Tietgen, H.; Kunz, H. *Collect. Czech. Chem. Commun.* **2000**, *65*, 816. Kunz, H.; Pfrengle, W. *J. Org. Chem.* **1989**, *54*, 4261. Knauer, S.; Kunz, H. *Tetrahedron: Asymmetry* **2005**, *16*, 529. (d) Loh, T.-P.; Zhou, J.-R.; Li, X.-R.; Sim, K.-Y. *Tetrahedron Lett.* **1999**, *40*, 7847. Uenishi, J; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. *J. Org. Chem.* **2004**, *69*, 6781. (e) Bull, S. D.; Davies, S. G.; Fox, D. J.; Gianotti, M.; Kelly, P. M.; Pierres, C.; Savory, E. D.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1858. (f) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2005**, *128*, 3538. Prat, L.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 4515. (g) Falorni, M.; Chelucci, G.; Conti, S.; Giacomelli, G. *Synthesis* **1992**, 972. Cossu, S.; Conti, S.; Giacomelli, G.; Falorni, M. *Synthesis* **1994**, 1429. Chelucci, G.; Cabras, M. A.; Saba, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1973.

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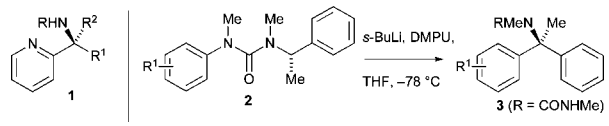
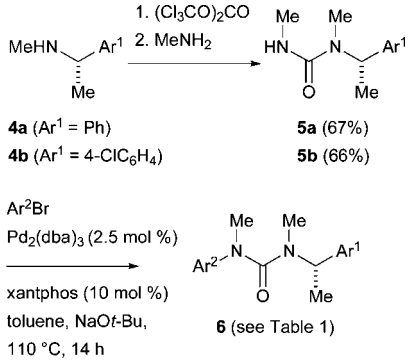
Scheme 1. Chiral Amines by Rearrangement of *N*-α-Methylbenzyl Ureas



In this paper, we now report a method which allows the introduction of a pyridyl group to a preformed stereogenic center and allows the formation of quaternary nitrogen-carrying stereogenic centers. We envisaged making pyridyl amines **1** by a modification of the urea rearrangement we recently reported[5] (Scheme 1) in which the aryl ring of urea **2**undergoes stereospecific transfer from nitrogen to carbon

Scheme 2. Synthesis of Ureas by Palladium-Catalyzed Coupling



to yield **3**. However, direct application of that method to pyridine-containing compounds was prevented by the strongly nucleophilic base needed to promote rearrangement and the electrophilic conditions required for deprotection of the product. Moreover, the synthesis of the starting pyridyl ureas required an alternative approach because of the unreactivity of appropriate pyridyl amines and/or unavailability of pyridyl isocyanates. Our solutions to all three of these problems permit for the first time the efficient enantioselective synthesis of pyridines bearing an aminated quaternary stereogenic center at the 2-, 3- or 4-position.

(4) For an isolated example, see: Shaw, A. W.; deSolms, S. J. *Tetrahedron Lett.* **2001**, *42*, 7173.

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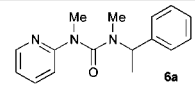
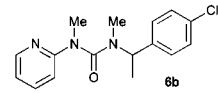
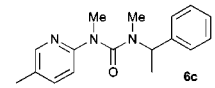
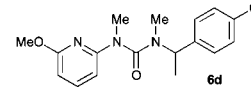
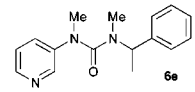
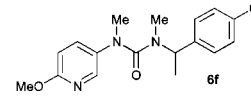
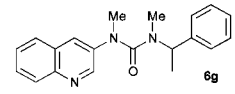
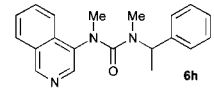
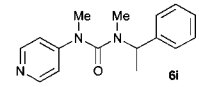
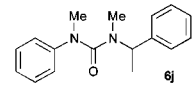
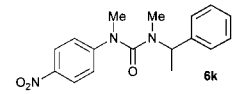
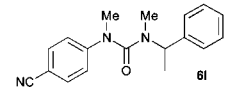
(7) Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. *Tetrahedron Lett.* **2003**, *44*, 4719. Sergeev, A. G.; Artamkina, G. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2003**, *39*, 1741. For other urea arylations, see. Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. Nandakumar, M. V. *Tetrahedron Lett.* **2004**, *45*, 1989. Popkin, M. E.; Bellingham, R. K.; Hayes, J. F. *Synlett* **2006**, 2716. Enguehard-Gueiffier, C.; Therry, I.; Gueiffier, A.; Buchwald, S. L. *Tetrahedron* **2006**, *62*, 6042. Hosseinzadeh, R.; Sarrafi, Y.; Mohadjerani, M.; Mohammadpourmir, F. *Tetrahedron Lett.* **2008**, *49*, 840. Lee, C.-C.; Wang, P.-S.; Viswanath, M. B.; Leung, M.-k. *Synthesis* **2008**, 1359.

(8) For a related discussion, see: Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734.

(9) Clayden, J.; Dufour, J. *Tetrahedron Lett.* **2006**, *47*, 6945.

Table 1. Coupling of Ureas with Aryl Bromides[d]

entry	starting material	Ar^2 =	product	yield (%)
1	(*S*)-**5a**	2-Py	 **6a**	86
2	(*R*)-**5b**	2-Py	 **6b**	91
3	(*S*)-**5a**	5-Me-2-Py	 **6c**	89
4	(*R*)-**5b**	6-MeO-2-Py	 **6d**	79
5	(*S*)-**5a**	3-Py	 **6e**	69[a]
6	(*R*)-**5b**	6-MeO-3-Py	 **6f**	48[a]
7	(*S*)-**5a**	3-quinolyl	 **6g**	79[a]
8	(±)-**5a**	4-isoquinolyl	 **6h**	81
9	(*S*)-**5a**	4-Py[b]	 **6i**	88
10	(*S*)-**5a**	Ph	 **6j**	41[c]
11	(±)-**5a**	4-$NO_2C_6H_4$	 **6k**	91
12	(*S*)-**5a**	4-CNC_6H_4	 **6l**	69

[a] 3 equiv aryl bromide used to ensure completion. [b] Hydrochloride salt of 4-bromopyridine was used. [c] Microwave heating, 4 h at 140 °C. [d] Conditions: urea (1 equiv), aryl bromide (1.5 equiv), NaO*t*-Bu (2 equiv), $Pd_2(dba)_3$ (2.5 mol %) and xantphos (10 mol %) were heated in toluene at 110 °C for 14 h.

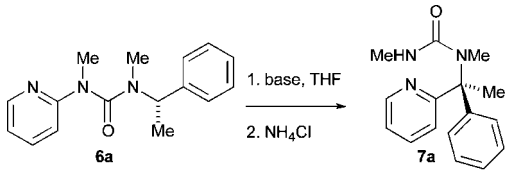
Bromopyridines are much more readily available than pyridyl isocyanates, so we sought a new, coupling-based route from these compounds to the urea starting materials. Starting with the amines **4**, treatment with triphosgene and subsequently methylamine gave the urea **5** (Scheme 2). This urea was coupled (Scheme 2) under the standard *N*-arylation conditions reported for amides[6] and simple unsubstituted ureas[7] ($Pd_2(dba)_3$, xantphos, toluene, NaO*t*-Bu) with a series of bromopyridines, along with a further selection of electron-deficient bromoarenes, to yield ureas **6** as detailed in Table 1.

The urea coupling was successful with all bromopyridines, substituted bromopyridines, 3-bromoquinoline and 4-bromoisoquinoline, and could be extended to bromoarenes in

general, but clearly performs best with more electron deficent aryl bromide partners (see entries 10−12). 2- (Entries 1−4) and 4- (entry 9) bromopyridines couple faster than 3-bromopyridines (entries 5−7), which were used in excess to ensure acceptable yields. Coupling is slow and low-yielding with bromobenzene (entry 10), leading to incomplete reaction even on microwave irradiation.[8]

The arylation shown in Scheme 1 involves nucleophilic attack of an organolithium center on the *N*-aryl ring, and given the electrophilicity of pyridines we hoped that a corresponding rearrangement of *N*-benzyl-*N*′-pyridyl ureas would be successful. However, under the conditions previously used for deprotonation (*s*-BuLi in THF), the products isolated from the reaction of *N*-pyridyl-urea **6a** contained alkyl groups arising from nucleophilic attack on the pyridine ring by the organolithium. Deprotonation of the urea by a less nucleophilic base, LDA, was therefore attempted (Scheme 3). The rearrangement now took place and yielded

Scheme 3. Rearrangement of an *N*-2-Pyridyl Urea



[a]Products of nucleophilic attack on pyridyl ring observed by ^{1}H NMR.

the urea **7a** cleanly but with poor stereospecificity (er = 60:40), presumably because of extensive racemisation of the intermediate benzyllithium[10] before rearrangement. Adding 10% DMPU, which has been shown previously to accelerate related rearrangements[5] and cyclizations,[11] to the THF solvent increased both the rate and stereospecificity of the pyridine transfer reaction, yielding the product **7a** with 98:2 er.[12]

Using these conditions, the other pyridyl ureas **6a**−**e** and **6i** also underwent efficient rearrangement, yielding the products **7** as shown in Table 2. When the starting materials were enantiomerically pure, the rearrangement proceeded with high stereospecificity, the product ureas **7** being obtained in >96:4 er in every case where er was measurable. Previous

Scheme 4. "Deprotection" of the Product Ureas

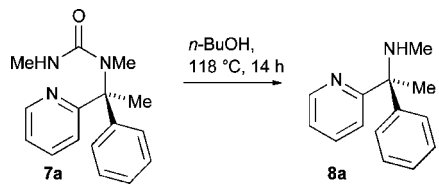
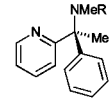
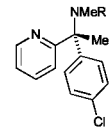
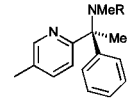
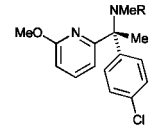
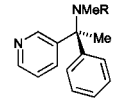
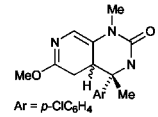
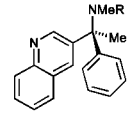
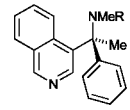
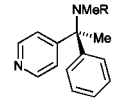
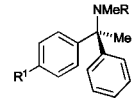


Table 2. Ureas **7** and Aminopyridines **8** by Stereospecific Rearrangement and Hydrolysis

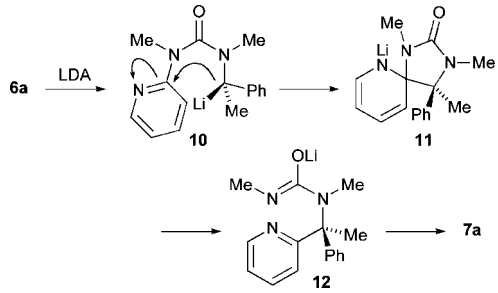
entry	starting material	product **7** (R = CONHMe) and **8** (R = H))	urea **7**, yield (%)[a]	er[b]	amine **8**, yield (%)[c]
1	(*S*)-**6a**		(*S*)-**7a**, 65	98:2	(*S*)-**8a**, 76
2	(*R*)-**6b**		(*R*)-**7b**, 73	98:2	(*R*)-**8b**, 81
3	(*S*)-**6c**		(*S*)-**7c**, 66	>99:1	–
4	(*R*)-**6d**		(*R*)-**7d**, 80	n.d.	–
5	(*S*)-**6e**		(*S*)-**7e**, 74	99:1[d]	(*S*)-**8e**, 78
6	(*R*)-**6f**		**9**, 63[e] (dr = 4:3).	n.d.	–
7	(*S*)-**6g**		(*S*)-**7g**, 40	n.d.	–
8	(±)-**6h**		0	–	–
9	(*S*)-**6i**		**7i**, 83	96:4[d]	(*S*)-**8i**, 65
10	(*S*)-**6k**		(*S*)-**7k** (R^1 = NO_2), <5%	n.d.	–
11	(*S*)-**6l**		(*S*)-**7l**, (R^1 = CN), 67	97:3	(*S*)-**8k** (R^1 = CN), 91

[a] Rearrangement conditions: LDA (2 equiv) in 10:1 THF/DMPU, −78 °C, 1−4 h. [b] Determined by HPLC on a chiral stationary phase. [c] Deprotection conditions: 118 °C for 14 h in *n*-BuOH. [d] Determined after deprotection to amine **8**. [e] Estimated yield of impure material: oxidizes rapidly to **15** in air.

related rearrangements of *N*-aryl ureas have proceeded with retention of stereochemistry and we assume the same is the case here. The rearrangement of quinoline substituted urea **6g** (entry 7) showed minor side products but still gave **7g** in 40% yield. The isoquinoline substituted urea **6h** (entry 8) failed to rearrange in good yield, but the only pyridyl urea not to give the expected product was the 6-methoxy-

(10) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002; pp 169−213.
(11) Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett* **2003**, 1701.

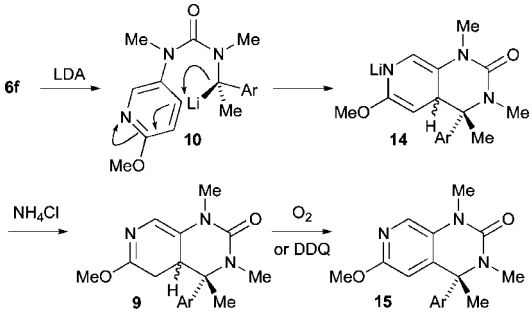
Scheme 5. Proposed Mechanism for the Rearrangement of **6a**



substituted[13] **6f** (entry 9) whose cyclization product **9** is discussed below. Demonstrating that these new rearrangement conditions are more generally applicable to other functionalized ureas, starting materials **6k** carrying an *N*-*p*-cyanophenyl group also rearranged under these conditions, although the *p*-nitrophenyl-substituted **6l** failed to rearrange cleanly.

Removal of the −CONHMe substituent carried by the urea products of the rearrangement has been accomplished either by reductive cleavage or, more generally, hydrolysis of the ureas' *N*-nitroso derivatives.[5] However, the electrophilicity of the pyridine ring and the nucleophilicity of its nitrogen atom posed problems with these methods. We therefore developed an alternative method for urea cleavage. We found that simply heating the urea product **7a** to reflux in neutral ethanol over a period of several days led to clean elimination of methyl isocyanate (which is presumably trapped by the alcohol solvent) to return the secondary amine **8a**. Deprotection was slow under these conditions, but replacing ethanol by *n*-butanol, and heating to 118 °C overnight served to accomplish the transformation cleanly and reliably (Scheme 4 and Table 2).

Scheme 6. Cyclisation of **6f**[a]



[a]Ar = *p*-ClC$_6$H$_4$−.

The rearrangement presumably proceeds by the mechanism shown in Scheme 5: deprotonation at the benzylic position[9] generates an organolithium **10** which (given the er's of the products) is evidently configurationally stable on the time scale of the reaction. *Ipso* attack of this organolithium center on the pyridyl ring gives a dearomatised intermediate **11** which then collapses with regeneration of aromaticity to provide lithiourea **12**.

The lack of regioisomeric pyridine products shows that even the 3-pyridyl substituents are attacked α to the urea nitrogen, overriding the usual regiochemistry of nucleophilic attack on a pyridine ring. However, when electron-density is loaded onto the 3-position by incorporation of a 6-methoxy substituent, an alternative pathway takes over. The product of attempted rearrangement of **6f** was identified as a diastereoisomeric mixture of the unstable 3,4-dihydropyridine **9**, which must arise by attack of organolithium **13** at the 4-position of the pyridine (Scheme 6). The dearomatized product **14** now has no possibility to regain aromaticity by elimination of the urea nitrogen: instead it remains in the reaction mixture until trapped by protonation, and rearomatises by oxidation in air to give **15**.[14] Treatment of **9** with DDQ yields **15** in 24% yield from **6f**.

In summary, a simple four-step sequence from **4** to **8** provides functionalized aminopyridines containing a fully substituted quaternary stereogenic center adjacent to the pyridine ring.

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Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For the reasons put forward by Gawley (Gawley, R. E. *J. Org. Chem.* **2006**, *71*, 2411), we prefer the term "enantiomeric ratio" to "enantiomeric excess".

(13) The difficulty of attacking an aromatic ring para to a methoxy group with an organolithium is noted in ref 11.

(14) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673. Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325.