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# 2,2- and 2,6-Diarylpiperidines by Aryl Migration within Lithiated Urea Derivatives of Tetrahydropyridines

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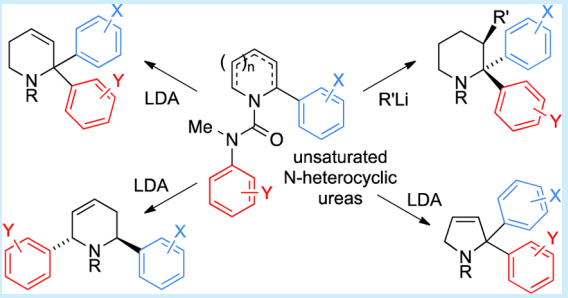
Supporting Information

**ABSTRACT:** 2-Aryltetrahydropyridines formed by anionic cyclization or ring-closing metathesis were converted to their N′-aryl urea derivatives. Depending on the position of the unsaturation within the tetrahydropyridine ring, metalation by deprotonative lithiation or carbolithiation led to migration of the N′-aryl substituent to the 2- or 6-position via intramolecular nucleophilic attack of a benzylic organolithium on the aryl ring. The products are a range of 2,2-, 2,2,3-, and 2,6-polysubstituted piperidine derivatives. Related chemistry was observed in pyrroline homologues.




2-Arylpiperidines are a valuable class of biologically active saturated heterocycles[1] and have found particular utility as orally active NK1 receptor antagonists, PARP inhibitors, TGR5 agonists, and bradykinin B1 antagonists, and as treatments for erectile dysfunction (tadalafil) and urinary incontinence (solifenacin).[2−4] Among the wide range of strategies that have been employed for their synthesis,[5] the organolithium chemistry[6] of piperidines features highly because deprotonation adjacent to nitrogen may be facilitated by N-acylation.[7−13] Nonetheless, lithiated piperidines typically suffer from the limitation of reacting only with "polar" electrophiles: introduction of aryl or vinyl substituents typically requires transmetalation to an organozinc followed by Negishi coupling.[10,14−17]

We have previously reported that acyclic organolithiums may be arylated[18] or vinylated[19] intramolecularly with a broad scope of trigonal "electrophiles" if they are stabilized by a functional group XCONRAr (a urea X = NR;[18,20] a carbamate X = O;[21−23] a thiocarbamate X = S[24−26]) that delivers the "electrophile" intramolecularly. We now report the use of a similar organolithium arylation, initiated by either deprotonation or carbolithiation, to the direct $\alpha$-arylation of cyclic amines,[27,28] allowing the synthesis of otherwise synthetically challenging 2,2- and 2,6-diaryl piperidine and 2,2-diarylpyrrolidine derivatives.

The intramolecular organolithium arylation has shown the most generality when applied to allylic[29,30] or benzylic[18,20] ureas. The *N*-carboxamidotetrahydropyridines **1**−**4** (Figure 1)[31] were thus made as suitable starting materials for the synthesis of the arylated piperidines. The three strategies outlined in Scheme 1 and detailed in full in the Supporting Information were used. In the first, 5-bromopentanenitrile **5** was treated with an aryllithium to give imine **6**.[32] N-Acylation[33] with a series of aryl isocyanates and methylation gave the urea derivatives **1**, in which a vinyl urea is embedded within the tetrahydropyridine ring.

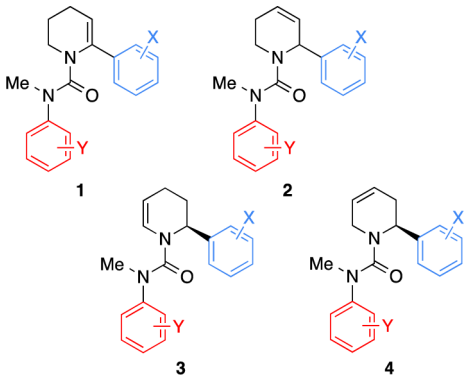



**Figure 1.** Tetrahydropyridines used as starting materials for arylation.

In the other approaches to the starting materials, the tetrahydropyridines were formed by ring-closing metathesis. A vinylzinc addition[34] to imines **7** gave a secondary amine that was converted to the unsaturated urea **8**, from which the Grubbs I catalyst provided racemic 1,2,5,6-tetrahydropyridines **2**. Alternatively, adding allylmagnesium bromide to a range of *tert*-butyl sulfinimine derivatives[35] **9** gave the sulfonamides **10** in excellent yield as single diastereoisomers. Hydrolysis of the sulfonamide followed by conversion to the ureas **11** was achieved under standard conditions. Ring closing metathesis with the Grubbs I catalyst gave the 1,2,3,6-tetrahydropyridines **4** as single enantiomers. Isomerization of the unsaturation in **4** using $RuHCl(CO)(PPh_3)_3$ returned vinylurea **3** without loss of enantiomeric purity.[33] This regioisomer was surprisingly also formed exclusively (as a racemic mixture) from **2** under the same conditions; isomerization to **1** was achieved by deprotonation of

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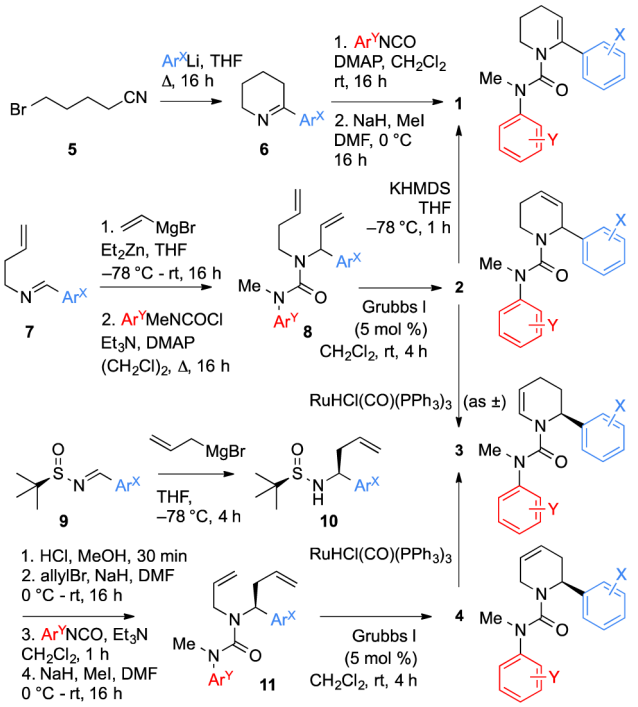
**Scheme 1. Synthesis of the Starting Tetrahydropyridines**

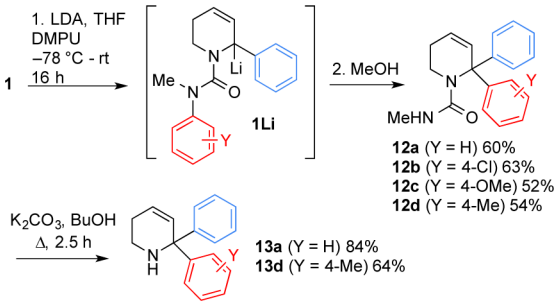


2 under conditions not promoting aryl migration (KHMDS at −78 °C in THF).[33]

Each of the three substrates **1**, **3**, and **4** was deprotonated with LDA to generate a urea-stabilized organolithium.

In **1**, deprotonation by LDA at the 4-position of the tetrahydropyridine ring in a mixture of THF and DMPU led to migration of the aryl ring to the benzylic 2-position of the piperidine system, presumably via the intermediate cinnamyllithium **1Li**,[29] which selectively reacted at the position $\alpha$ to N (Scheme 2).[36] The 2,2-diaryltetrahydropyridine products **12** were readily solvolyzed under our standard conditions to yield the 2,2-diaryl-1,2,5,6-tetrahydropyridines **13**.[37]

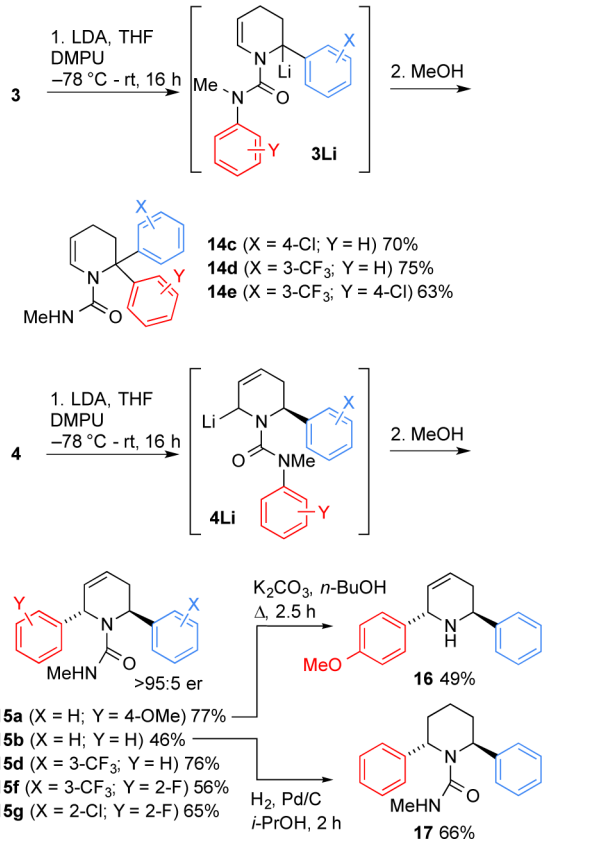
**Scheme 2. Arylation of Tetrahydropyridines 1 by Rearrangement of Their Organolithium Derivatives**



In **3** and **4**, there is potential competition for deprotonation between the allylic position(s) and the benzylic position, and a different outcome was observed with each of the two sets of compounds. On lithiation with LDA, the 5,6-unstaturated isomers **3** rearranged to the 2,2-diaryl-1,2,3,4-tetrahydropyridines **14** via the benzylic organolithium **3Li** (Scheme 3).

The 4,5-unsaturated isomers **4** by contrast gave the 2,6-diaryl-1,2,3,6-tetrahydropyridines[38] **15** by rearrangement of the intermediate allylic organolithium **4Li**. Since **4Li** could in

**Scheme 3. 2- and 6-Arylation of Tetrahydropyridines 3 and 4**



principle also be formed from **3** by deprotonation at the 4-position, it must be that the regioselectivities of the rearrangement arise from kinetic control over the relative rates of deprotonation at the three possible sites: allylic 2-CH > benzylic 2-CH > allylic 4-CH. Differing reactivities of equilibrating organolithiums are not responsible for the selectivity because the products **15** are formed stereospecifically: there is no racemization at the benzylic carbon atom. An unoptimized solvolysis of a representative example **15a** gave the 2,6-diaryltetrahydropyridine **16** in moderate yield.

The formation of the products **15** was also completely diastereoselective (>95:5 by NMR).[17] The relative configuration of **15b** was established by hydrogenation over Pd in isopropyl alcohol[39] to give the symmetrical 2,6-diphenylpiperidinyl urea **17**. Its optical rotation $[\alpha]^{25}_{D}$ = +40.4 ($c$ = 1.0, $CHCl_3$) proved this compound to be the chiral, rather than the meso, diastereoisomer, and hence *trans* relative stereochemistry was assigned to the entire series **15**.[40]

Rearrangement to the 2-position of **3** was however not stereospecific: the products were formed as racemic mixtures. We have previously noted[41] that while rearrangements of acyclic lithiated ureas proceed with high levels of stereospecificity, rearrangements that pass through fused bicyclic transition states tend to be poorly stereospecific.

Organolithiums may be generated connectively by carbolithiation of alkenes.[6,42] We have previously reported a carbolithiation−rearrangement sequence for the 1,2-difunctionalization of acyclic vinyl ureas,[43,44] and after considerable optimization we found that the best way to form the 2,2,3-trifunctionalized products **19** in good yield was to carbolithiate **1** in toluene or (for primary alkyllithiums, which deprotonate toluene) cumene and then immediately to add DMPU to



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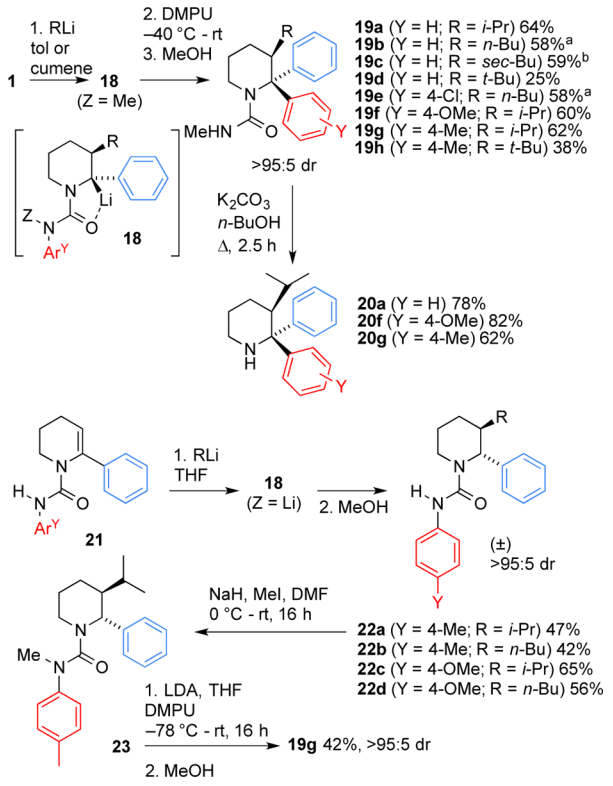
**Scheme 4. Carbolithiation–Rearrangement of Ureas 1**



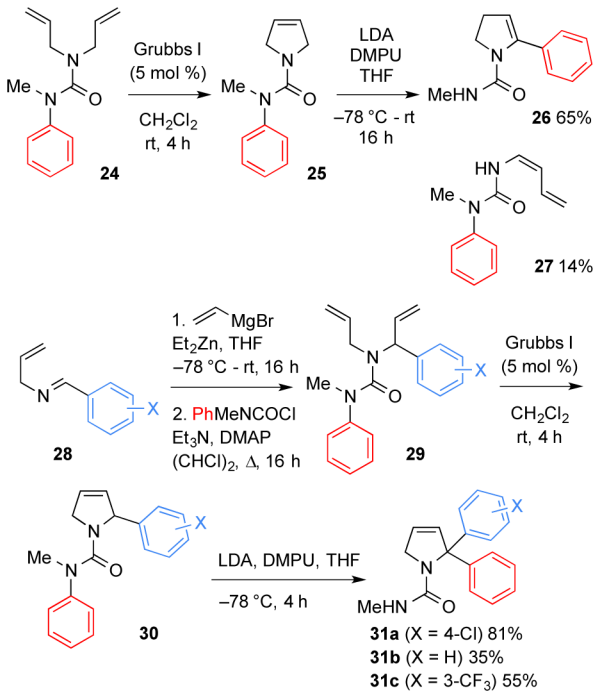

[a]Using cumene. [b]2:1 dr at the exocyclic center.

promote efficient rearrangement of the intermediate **18** on warming (Scheme 4). Other conditions (including the use of THF) led in various degrees to competing allylic deprotonation in the manner of Scheme 2, or to incomplete rearrangement. The products were typically formed in around 60% yield as single diastereoisomers by NMR spectroscopy, and solvolysis of a selection of ureas **19** by heating in *n*-BuOH gave 2,2-aryl-3-alkylpiperidines **20**, also as single diastereoisomers, in good yield.

It was difficult to ascertain the relative configuration of **19** or **20** directly. A series of related unsaturated ureas **21** were thus made by N-acylation of imine **6** with aryl isocyanates. Carbolithiation of these ureas with an excess of alkyllithium gave the ureas **22** via **18** (Z = Li), which cannot undergo rearrangement due to the anionic nitrogen adjacent to the ring. Products **22** were formed as single diastereoisomers and their relative configuration was deduced from the strong NOE correlation between the protons of the new alkyl group and the benzylic proton. *N*-Methylation of **22a** followed by deprotonation under the conditions used for carbolithiation recreates **18** (Z = Me) with known configuration, which rearranges to yield the same diastereoisomer of **19g** as that obtained directly from **1**.

Due to their structural relationship to nicotine, 2-arylpyrrolidines form another important group of valuable targets,[14,16,45] and we extended the metathesis/rearrangement sequence as a method for the 2-arylation of heterocycles to some 5-membered cyclic substrates. The pyrrolinyl urea starting material **25** was formed readily by metathesis of the *N*,*N*-diallylurea **24** (Scheme 5). Treatment with LDA in THF with DMPU as a cosolvent led to rearrangement, accompanied by double bond migration (presumably due to a second deprotonation of the first-formed product of this reaction), to return the 2-arylpyrroline **26** in 65%

**Scheme 5. Arylation of Pyrrolines**




yield.[46] Also obtained was a small amount of the ring-fragmentation product **27**, which presumably arises from the electrocyclic ring opening of the anionic derivative of **25**.

Substituted analogues **30** were made by an analogous metathesis strategy, this time forming the starting doubly allylic urea **29** by addition of a vinyl nucleophile to the imine **28**. Pyrrolines **30** were rearranged to **31a–c** by treatment with LDA in DMPU and THF.

In summary, 2- and 6-arylated piperidine and pyrrolidine derivatives containing unsaturation ripe for further functionalization may be synthesized by anionic migration of aryl rings from an N-aryl urea at the ring nitrogen.

## ■ ASSOCIATED CONTENT

### Supporting Information

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

## ■ AUTHOR INFORMATION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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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