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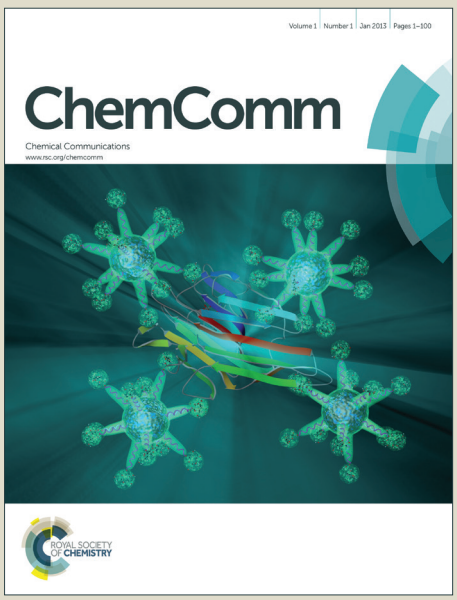

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Directed Functionalization of 1,2-Dihydropyridines: Stereoselective Synthesis of 2,6-Disubstituted Piperidines

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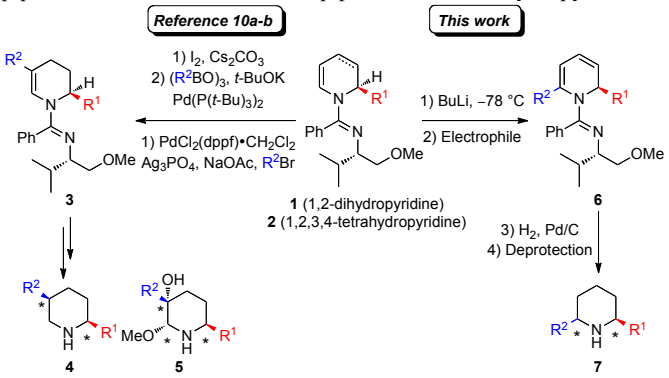
A practical and highly stereoselective approach to access to 2,6-disubstituted piperidines using an amidine auxiliary is reported. Following the diastereoselective addition of Grignard reagents at the 2-position of an activated pyridinium salt, the amidine group directs a regioselective metalation at the 6-position, enabling further functionalization. A subsequent electrophilic quench or a Negishi cross-coupling could be performed, resulting in 2,6-disubstituted dihydropyridines. These were reduced to the saturated piperidine rings with high diastereoselectivity.

Enantioenriched piperidines are often components of pharmacologically active compounds.[1] The broad interest towards these saturated heterocycles can be accounted by the fact that they are more diversified and more complex than their aromatic pyridine counterparts.[2,3] However, the full potential of chiral polysubstituted piperidines as pharmacophores is yet to be discovered. In that sense, a recent survey of SAR studies executed by different pharmaceutical companies (AstraZeneca, GlaxoSmithKline and Pfizer) demonstrated that the majority of encountered piperidines residues in drug lead candidates are either monosubstituted at the nitrogen position or 1,4-disubstituted.[4,5] One of the reasons associated to this poor representation can be attributed to the lack of reliable, stereoselective and versatile methods available for their synthesis. Therefore, rapid and general routes aimed toward generating libraries of chiral enantioenriched polysubstituted piperidines are highly desirable.

Substituted piperidines can be accessed via different approaches.[6] In this regard, our group has disclosed various asymmetric syntheses of piperidines employing either aziridinium ring expansions of prolinol derivatives,[7] Grob fragmentations of azabicyclo[2.2.2]octenes,[8] or dearomatization of *N*-activated pyridinium salts.[9] For example, we recently reported the synthesis of enantioenriched 2,5-*cis*-disubstituted piperidines (**4**) and 3-aryl-3-piperidinols (**5**) by employing the dearomatization of a chiral *N*-imidoylpyridinium salt (Scheme 1).[10]

Scheme 1. Synthesis of 2,5-*cis*-disubstituted piperidines, 3-aryl-3-piperidinol and 2,6-disubstituted piperidines from dihydropyridines.



More precisely, these units could be accessed *via* an electrophilic iodination/Suzuki cross-coupling sequence or direct arylation of 1,2,3,4-tetrahydropyridines (**2**). Following these results, we were interested in developing a divergent approach that could provide access to 2,6-disubstituted piperidines (**7**) from a common synthetic intermediate. This alternative substitution pattern is frequently found in the structure of natural alkaloids (Figure 1).[11]

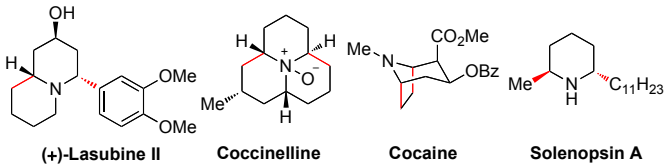
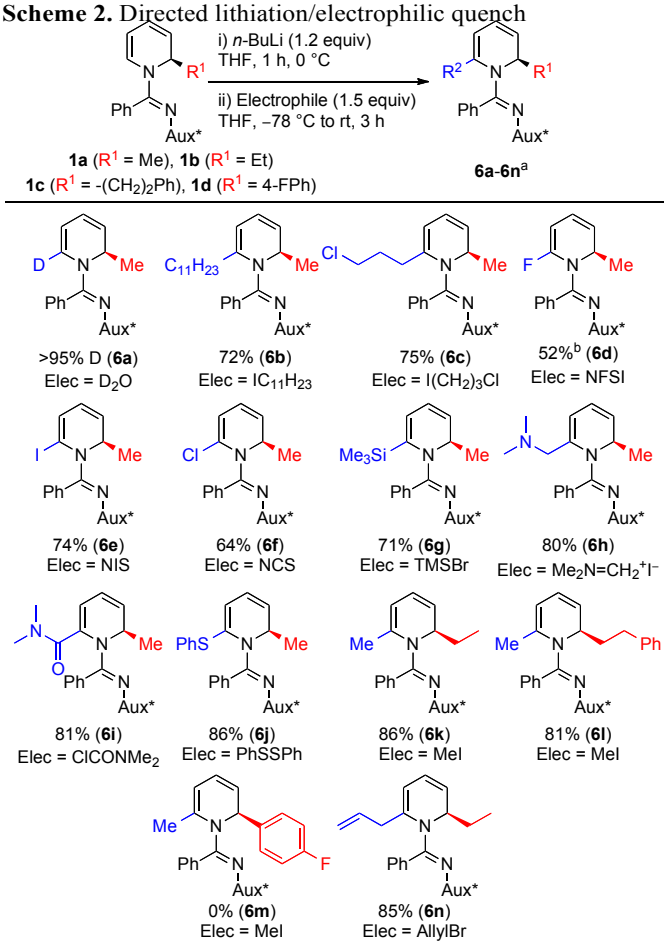


Figure 1. Naturally occurring 2,6-disubstituted piperidines

To do so, we initially recognized that the amidine protecting group on the 1,2-dihydropyridines (**1**) could be an efficient directing tether for lithiation of aryl and alkyl C–H bonds[12] and direct α-arylation of pyrrolidines and piperidines.[13] In particular, we anticipated that a chiral Schiff base variant, developed by Meyers,[12] could be used to direct a deprotonation at the 6 position of **1** using *n*-BuLi, where the transient 6-lithio-1,2-dihydropyridine could be trapped with various electrophiles in order to diversify the heterocycle substitution pattern.[14] This hypothesis can be closely associated to a previously popularized strategy developed by Comins *et al.* using variously substituted *N*-Boc α-lithiated dihydropyridines.[15] The latter technique was applied successively in total synthesis of many nitrogen containing alkaloids such as (+)-myrtine,[15e] (+)-epi-myrtine,[15f] and spirolucidine.[15c]

This strategy was explored by deprotonating the model 1,2-dihydropyridine **1a**[9c] at 0 °C with a slight excess of *n*-BuLi (1.2 equiv), and then quenching the anion with D_2O. Analysis of the crude reaction mixture by ^{1}H NMR showed complete deuterium incorporation at the 6 position (**6a**, >95% D incorporation). Deuterium oxide was then substituted by different electrophiles in order to evaluate the reactivity of the 6-lithio-1,2-dihydropyridine (Scheme 2). Alkyl iodides and activated alkyl bromides reacted well with the anion of **1a**, as the corresponding 2,6-dialkyl-1,2-dihydropyridines **6b**, **6c** and **6n** were isolated in good yields (72%, 75%, and 85%).

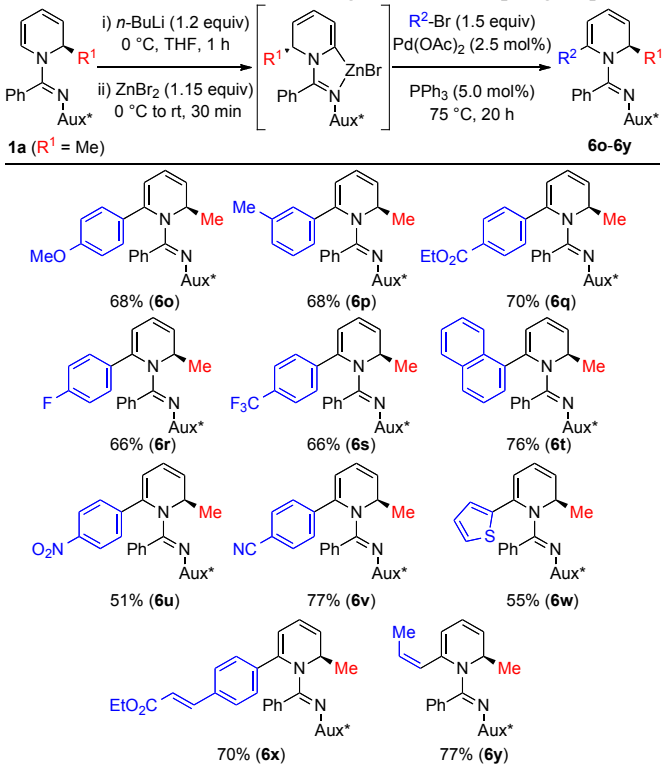
Scheme 2. Directed lithiation/electrophilic quench



[a] Reaction performed on a 1.0 mmol scale. Isolated yield. [b] 1.1 equiv. of electrophile was used instead of 1.5 equiv. NFSI *N*-fluorobenzenesulfonimide; NIS : *N*-iodosuccinimide. NCS : *N*-chlorosuccinimide; Elec = Electrophile.

Although 6-halo-2-alkyl-1,2-dihydropyridines **6d–6f** could be synthesized effectively, they were found to be unstable on silica gel and decomposed after a few hours if stored at room temperature.[16] Electrophiles such as TMSBr, $Me_2N{=}CH_2{}^+I^-$, $ClCONMe_2$ and PhSSPh reacted well under the optimal conditions. The methyl substituent at the 2-position could be varied for other alkyl groups (**1b–1c**) without a significant effect on the yield. Unfortunately, 2-aryl-substituted dihydropyridine **1d** afforded a complex mixture of products when treated with *n*-BuLi. In order to access to aryl-substituted dihydropyridines, we elaborated an alternative sequence where the 6-lithio-1,2-dihydropyridines would undergo a transmetallation/Negishi cross-coupling.[17] We initially optimized the 2-step, 1-pot sequence with 4-bromoanisole and **1a** under classic palladium-catalyzed Negishi conditions (Scheme 3).[18] After transmetallation with $ZnBr_2$ at rt, the resulting organozinc reagent derived from **1a** was treated with $Pd(OAc)_2$ (2.5 mol%), PPh_3 (5.0 mol%) in presence of 1.5 equiv of 4-bromoanisole, which furnished the desired 6-aryl-1,2-dihydropyridine **6o** in 68% yield. To explore the scope of this reaction, we replaced 4-bromoanisole by different aryl bromides. In general, aryl bromides bearing electron withdrawing or electron donating substituent gave modest to good yields for the corresponding 6-aryl-1,2-dihydropyridines. Interestingly, ^{1}H NMR analysis of compounds **6o–6x** revealed that the protons associated to the phenyl ring of the amidine broaden in comparison with **1a**. Alternatively, with a 6-*cis*-prop-1-enyl substituent (**6y**), or with the previous examples depicted in Scheme 2, this phenomenon was not observed.

Scheme 3. Directed lithiation/Negishi cross-coupling sequence

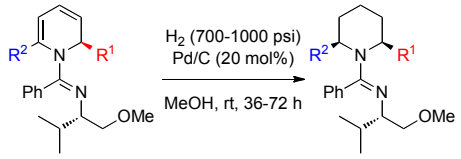


[a] Reaction performed on a 1.0 mmol scale. Isolated yield.

To demonstrate the utility of the 2,6-disubstituted 1,2-dihydropyridine derivatives synthesized as precursors of chiral

polysubstituted piperidines, various hydrogenation conditions were explored. This strategy was employed in some of our previous studies directed toward the synthesis of indolizidines, quinolizidines and other piperidine rings.[10,19] However, treating different 2,6-disubstituted dihydropyridines (**6**) under ambient pressure of hydrogen (1 atm) with Pd/C resulted only in partial hydrogenation of the 3,4-unsaturation to the 1,2,3,4-tetrahydropyridines. In order to have complete conversion to the fully saturated piperidines, an atmosphere of 700 to 1000 psi of hydrogen was needed (Table 1). Fortunately, high diastereoselectivity for the *cis* isomer was observed for the piperidines synthesized (17:1 to >20:1). Curiously, poor selectivity favoring the *trans* isomer was observed when the 6-substituent is a deuterium (2:1 *trans*:*cis*, **8d**). The relative stereochemistry of the centers at the 2 and 6 positions were confirmed by selective nOe analysis.[18]

Table 1. Diastereoselective hydrogenation of the 1,2-dihydropyridine diene



6 **8**

Entry	R^1	R^2	d.r. (*cis*:*trans*)[a]	Yield (%)[b]
1	Me	4-FPh	>20:1	57 (**8a**)
2	Me	4-MeOPh	17:1	62 (**8b**)
3	Et	Me	>20:1	70 (**8c**)
4	Me	D	1:2	73 (**8d**)

[a] Diastereoselective ratio were determined by analysis of the crude reaction mixture. [b] Isolated yield.

Conclusions

A rapid and stereoselective synthetic method for the generation of 2,6-*cis*-disubstituted piperidines was developed. Regioselective lithiation at the 6-position of 1,2-dihydropyridines was enabled by a chiral amidine directing group. The *in situ* generated anions were treated with various electrophiles or used in a transmetallation/Negishi coupling sequence. The obtained 2,6-disubstituted 1,2-dihydropyridines underwent a diastereoselective hydrogenation to generate 2,6-*cis*-disubstituted piperidines.

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Notes and references

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† Electronic Supplementary Information (ESI) available: on the web or form the author. See DOI: 10.1039/c000000x/

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