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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 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 in these saturated heterocycles can be accounted for 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 piperidine residues in drug lead candidates are either monosubstituted at the nitrogen position or 1,4-disubstituted.^{4,5} One of the reasons associated with 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



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

employing the dearomatization of a chiral *N*-imidoylpyridinium salt (Scheme 1).¹⁰

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 (Fig. 1).¹¹

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 bonds¹² 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 deprotonation at the 6 position of 1 using





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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 with a previously popularized strategy developed by Comins *et al.* using variously substituted *N*-Boc α -lithiated dihydropyridines.¹⁵ The latter technique was applied successively for the total synthesis of many nitrogen containing alkaloids such as (+)-myrtine,^{15*e*} (+)-*epi*-myrtine,^{15*f*} and spirolucidine.^{15*c*}

This strategy was explored by deprotonating the model 1,2-dihydropyridine $1a^{9f}$ at 0 °C with a slight excess of *n*-BuLi (1.2 equiv.), and then quenching the anion with D₂O. Analysis of the crude reaction mixture by ¹H 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%).

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, $Me_2N = CH_2^+\Gamma^-$, ClCONMe₂ and



Scheme 2 Directed lithiation/electrophilic quench.^a Reaction performed on a 1.0 mmol scale. Isolated yield.^b 1.1 equiv. of the electrophile was used instead of 1.5 equiv. NFSI *N*-fluorobenzenesulfonimide; NIS: *N*-iodosuccinimide. NCS: *N*-chlorosuccinimide; Elec = electrophile.

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-arylsubstituted dihydropyridine 1d afforded a complex mixture of products when treated with n-BuLi. In order to access aryl-substituted dihydropyridines, we performed 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 palladiumcatalyzed Negishi conditions (Scheme 3).18 After transmetallation with ZnBr₂ at rt, the resulting organozinc reagent derived from 1a was treated with Pd(OAc)₂ (2.5 mol%) and PPh₃ (5.0 mol%) in the presence of 1.5 equiv. of 4-bromoanisole, which furnished the desired 6-aryl-1,2-dihydropyridine 60 in 68% yield. To explore the scope of this reaction, we replaced 4-bromoanisole by different arvl bromides. In general, any bromides bearing electron withdrawing or electron donating substituents gave modest to good yields for the corresponding 6-aryl-1,2-dihydropyridines. Interestingly, ¹H NMR analysis of compounds 60-6x revealed that the protons associated with the phenyl ring of the amidine broaden in comparison with 1a. Alternatively, with a 6-cis-prop-1-envl substituent (6y), or with the previous examples depicted in Scheme 2, this phenomenon was not observed.

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)



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



 a Diastereoselective ratios were determined by analysis of the crude reaction mixture. b Isolated yield.

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 deuterium (2:1 *trans*: *cis*, **8d**). The relative stereochemistry of the centers at the 2 and 6 positions was confirmed by selective nOe analysis.¹⁸

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 diastereoselective hydrogenation to generate 2,6-*cis*-disubstituted piperidines.

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Notes and references

- 1 S. Duttwyler, S. Chen, M. K. Takase, K. B. Wiberg, R. G. Bergman and J. A. Ellman, *Science*, 2013, **339**, 678.
- (a) F. Lovering, J. Bikker and C. Humblet, J. Med. Chem., 2009, 52, 6752; (b) T. J. Ritchie and S. J. F. MacDonald, Drug Discovery Today, 2009, 14, 1011; (c) T. J. Ritchie, S. J. F. MacDonald, R. J. Young and S. D. Pickett, Drug Discovery Today, 2011, 16, 164; (d) M. D. Burke and S. L. Schreiber, Angew. Chem., Int. Ed., 2004, 43, 46; (e) P. Arya, R. Joseph, Z. Gan and B. Rakic, Chem. Biol., 2005, 12, 163.
- 3 (a) P. Selzer, H.-J. Roth, P. Ertl and A. Schuffenhauer, *Curr. Opin. Chem. Biol.*, 2005, 9, 310; (b) A. Schuffenhauer, N. Brown, P. Selzer, P. Ertl and E. Jacoby, *J. Chem. Inf. Model.*, 2006, 46, 525.
- 4 S. D. Roughley and A. M. Jordan, J. Med. Chem., 2011, 54, 3451.
- 5 A recent review correlates the profound effect of installing a chiral methyl group on a piperidine ring with an increased activity of a

given drug: H. Schönherr and T. Cernak, Angew. Chem., Int. Ed., 2013, 52, 12256.

- 6 For recent reviews concerning the synthesis of enantioenriched piperidines, see: (a) C. Escolano, M. Amat and J. Bosch, Chem. Eur. J., 2006, 12, 8198; (b) J. Cossy, Chem. Rec., 2005, 5, 70; (c) M. G. P. Buffat, Tetrahedron, 2004, 60, 1701; (d) P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcherding, Tetrahedron, 2003, 59, 2953; (e) S. Laschat and T. Dickner, Synthesis, 2000, 1781; (f) A. Mitchinson and A. Nadin, J. Chem. Soc., Perkin Trans. 1, 2000, 2862.
- 7 (a) S. B. D. Jarvis and A. B. Charette, Org. Lett., 2011, 13, 3830. See also: (b) J. Cossy, O. Mirguet and D. G. Pardo, Synlett, 2001, 1575; (c) J. L. Bilke, S. P. Moore, P. O'Brien and J. Gilday, Org. Lett., 2009, 11, 1935.
- 8 (a) G. Lemonnier and A. B. Charette, J. Org. Chem., 2012, 77, 5832;
 (b) G. Lemonnier and A. B. Charette, J. Org. Chem., 2010, 75, 7465;
 (c) G. Barbe, M. St-Onge and A. B. Charette, Org. Lett., 2008, 10, 5497.
- 9 (a) A. Lemire and A. B. Charette, J. Org. Chem., 2010, 75, 2077; (b) A. Lemire and A. B. Charette, Org. Lett., 2005, 7, 2747; (c) C. Legault and A. B. Charette, J. Am. Chem. Soc., 2005, 125, 8966; (d) C. Legault and A. B. Charette, J. Am. Chem. Soc., 2005, 125, 6360; (e) A. Lemire, M. Grenon, M. Pourashraf and A. B. Charette, Org. Lett., 2004, 6, 3517; (f) A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf and J. Martel, J. Am. Chem. Soc., 2001, 123, 11829. For recent reviews of the literature, see: (g) D. L. Comins, K. Higuchi and D. W. Young, Adv. Heterocycl. Chem., 2013, 110, 175; (h) E. M. P. Silva, P. A. M. M. Varandas and A. M. S. Silva, Synthesis, 2013, 3053; (i) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, Chem. Rev., 2012, 112, 2642; (j) R. J. Lavilla, J. Chem. Soc., Perkin Trans. 1, 2002, 1141; (k) D. L. Comins and S. O'Connor, in Progress in Heterocyclic Chemistry, ed. G. Gribble and J. Joule, Elsevier Ltd., Oxford, U.K., 2004, vol. 16, p. 309.
- 10 (a) G. Pelletier, A. Larivée and A. B. Charette, Org. Lett., 2008, 10, 4791; (b) A. Larivée and A. B. Charette, Org. Lett., 2006, 8, 3955.
- 11 For potent biologically active 2,6-disubstituted piperidines, see: (a) S. Leclercq, J. C. Braekman, D. Daloze and J. M. Pasteels, *Prog. Chem. Org. Nat. Prod.*, 2000, **79**, 115; (b) A. Pianaro, E. G. P. Fox, O. C. Bueno and A. J. Marsaioli, *Tetrahedron: Asymmetry*, 2012, 23, 635; (c) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139.
- 12 (a) A. I. Meyers and J. Guiles, *Heterocycles*, 1989, 28, 295. For reviews on α-lithiation of piperidines, see: (b) P. Beak and A. I. Meyers, *Acc. Chem. Res.*, 1986, 19, 356; (c) A. I. Meyers, *Tetrahedron Lett.*, 1992, 48, 2589; (d) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, 29, 552; (e) P. Beak, D. R. Anderson, M. D. Curtis, J. M. Laumer, D. J. Pippel and G. A. Weisenburger, *Acc. Chem. Res.*, 2000, 33, 715.
- 13 (a) S. J. Pastine, D. V. Gribkov and D. Sames, *J. Am. Chem. Soc.*, 2006, 126, 14220; (b) H. Prokopcová, S. D. Bergman, K. Aelvoet, V. Smout, W. Herrebout, B. Van der Veken, L. Meerpoel and B. U. W. Maes, *Chem. Eur. J.*, 2010, 16, 13063.
- 14 V. Snieckus, Chem. Rev., 1990, 90, 879.
- (a) J. J. Sahn and D. L. Comins, J. Org. Chem., 2010, 75, 6728;
 (b) D. W. Young and D. L. Comins, Org. Lett., 2005, 7, 5661; (c) D. L. Comins and A. L. Williams, Org. Lett., 2001, 3, 3217; (d) D. L. Comins and M. A. Werglarz, J. Org. Chem., 1988, 53, 4437; (e) D. L. Comins and D. H. LaMunyon, Tetrahedron Lett., 1989, 30, 5053; (f) D. L. Comins, M. A. Werglarz and S. O'Connor, Tetrahedron Lett., 1988, 29, 1751; (g) D. L. Comins, Tetrahedron Lett., 1983, 24, 2807. See also: (h) R. Schmidt and G. Berger, Chem. Ber., 1976, 109, 2936; (i) D. M. Stout, T. Takaya and A. I. Meyers, J. Org. Chem., 1975, 40, 563; (j) A. I. Meyers, D. M. Stout and T. Takaya, J. Chem. Soc., Chem. Commun, 1972, 1260; (k) P. Beak, W. J. Zajdel and D. B. Reitz, Chem. Rev., 1984, 84, 471.
- 16 We suspect that the 6-halo-2-alkylsubstituted dihydropyridines **6d–6f** are easily oxidized by the electrophile used in the reaction or by air, thus lowering the yield of the reaction.
- 17 This procedure was inspired by related transformations reported by the Coldham, Gawley and Knochel groups using N-Boc-2-lithiopiperidines: (a) I. Coldham and D. Leonori, Org. Lett., 2008, 10, 3923; (b) T. K. Beng and R. E. Gawley, Org. Lett., 2011, 13, 394; (c) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer and P. Knochel, J. Am. Chem. Soc., 2011, 133, 4774.
- 18 See ESI[†] for more information and for optimization tables.
- 19 G. Barbe, G. Pelletier and A. B. Charette, Org. Lett., 2009, 11, 3398.