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New Methodology Toward Chiral, Non-Racemic 2,5-*cis*-Substituted Piperidines via Suzuki Cross-Coupling

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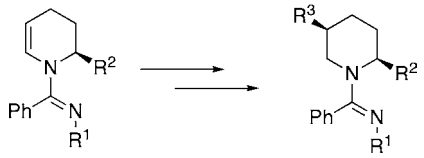
ABSTRACT



1,2,3,4-Tetrahydropyridines were halogenated upon treatment with iodine to obtain the desired cross-coupling precursors. Diastereoselective hydrogenation of Suzuki cross-coupling adducts allowed the facile asymmetric synthesis of 2,5-*cis*-substituted piperidines in five steps from readily available pyridine.

Piperidine units are found in many natural products and are key pharmacophores in several biologically active compounds. Their stereoselective synthesis remains a great challenge.[1,2] During our studies on the enantioselective synthesis of piperidines with different substitution patterns from readily available pyridine derivatives,[3] we have been interested in the preparation of the 2,5-*cis*-substituted adducts.

An increasing number of non-natural 2,5-substituted piperidines has sparked the interest of the scientific community in the recent years due to their abilities to interact with adrenergic receptors (**1**), their anti-inflammatory properties (**3**), and their herbicidal activities (**3**, **4**; Figure 1).[4,5] For example, octahydropyrido-1,2-pyrazine **6** is an advanced intermediate in the synthesis of a serotonin receptor agonist patented by Pfizer.[4h]

We have previously reported that the addition of organometallic reagents to 3-substituted *N*-pyridinium imidate salts bearing an electron-donating group (EDG) resulted in the

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(4) For examples of non-natural 2,5-substituted piperidines of interest, see: (a) Houlihan, W. J. U.S. Patent 3,334,104. (b) Houlihan, W. J. German Patent, DE 1 964 441 (in German); U.S. Patent 3,709,677. (c) Tilles, H. French Patent FR 2 095 399 (in French). (d) Balsamo, A.; Barili, P. L.; Gagliardi, M.; Lapucci, A.; Macchia, B.; Macchia, F.; Bergamaschi, M. *Chim. Ind.* **1976**, *58*, 222−222. (e) Balsamo, A.; Barili, P. L.; Gagliardi, M.; Lapucci, A.; Macchia, B.; Macchia, F.; Bergamaschi, M. *Eur. J. Med. Chem.* **1982**, *17*, 285−289. (f) Desai, M. C.; Stramiello, L. M. S. *Tetrahedron Lett.* **1993**, *34*, 7685−7688. (g) Macchia, B.; Macchia, M.; Martinelli, A.; Martinotti, E.; Orlandini, E.; Romagnoli, F.; Scatizzi, R. *Eur. J. Med. Chem.* **1997**, *32*, 231−240. (h) Bright, G. M. World Patent WO 9952907.

(5) For examples of recent synthesis of 2,5-substituted piperidines, see: (a) Gnecco, D.; Marazano, C.; Das, B. C. *Chem. Commun.* **1991**, 625−626. (b) Varea, T.; Dufour, M.; Micouin, L.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1035−1038. (c) Kuethe, J. T.; Brooks, C. A.; Comins, D. L. *Org. Lett.* **2003**, *5*, 321−323.

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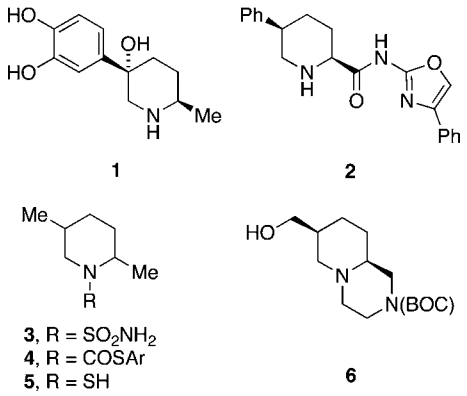
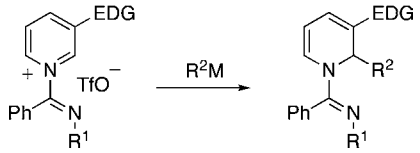


Figure 1. 2,5-Substituted piperidines of importance.

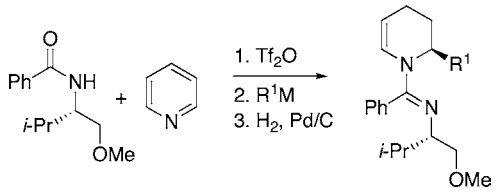
highly regioselective formation of 2,3-substituted 1,2-dihydropyridines (Scheme 1).[3f]

Scheme 1. Organometallic Reagent Addition to 3-Substituted Pyridinium Salts



We also reported that, *N*-imidate 1,2,3,4-tetrahydropyridines can be synthesized in good yields and high diastereoselectivities in two steps from chiral pyridinium salts (Scheme 2).[3c] We envisioned that their iodination, followed

Scheme 2. Preparation of 1,2,3,4-Tetrahydropyridines from Chiral Pyridinium Salts

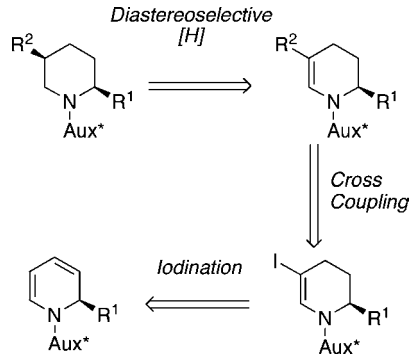


by their cross-coupling and their diastereoselective reduction, would afford the 2,5-*cis*-disubstituted piperidines (Scheme 3).

Halogenation of vinylogous amides and indoles at the 3 position are well-documented and normally straightforward reactions.[5c,6]

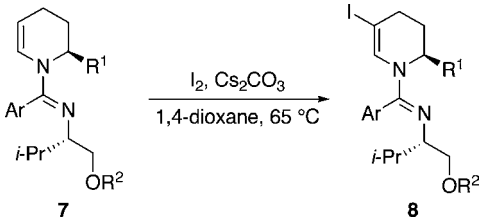
However, iodination of simple enamines is difficult because of the higher pK_a of the proton to be removed. Under the reaction conditions, the generated iminium intermediate can react with a nucleophilic base, the solvent, or dimerize.[7] Fortunately, formation of the vinyl iodide **8** proceeds cleanly

Scheme 3. Retrosynthetic Approach to 2,5-Substituted Piperidines



when the 1,2,3,4-tetrahydropyridines **7** are added over 6 h to a mixture of iodine and cesium carbonate (Table 1).

Table 1. Preparation of Vinyl Iodides[a]



entry	Ar	R^1	R^2	yield (%)	product
1	Ph	Me	Me	80	**8a**
2	Ph	Ph	Me	84	**8b**
3	Ph	Me	Bn	66	**8c**
4	2-(CH_2OTBS)Ph	Me	Me	73	**8d**

[a] 3 equiv of iodine and cesium carbonate were used.

With the vinyl iodide adducts in hand, we turned our attention to the Suzuki cross-coupling reaction. A screening of palladium catalysts showed that the commercially available bis(tri-*tert*-butylphosphine) palladium complex[8] catalyzes the coupling of 1,2,3,4-tetrahydro-5-iodopyridines **8** and aryl boroxins **9** to generate in high yields 2,5-substituted 1,2,3,4-tetrahydropyridines (Table 2).

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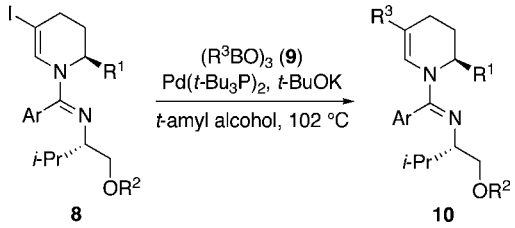
(8) (a) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662−13663. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

Table 2. Suzuki Cross-Coupling with 1,2,3,4-Tetrahydro-5-iodopyridines



8 **10**

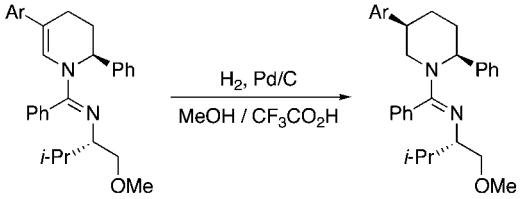
entry	substrate	R^3	yield (%)	product
1	**8a**	4-(MeO)Ph (**9a**)	92	**10a**
2	**8a**	4-(Cl)Ph (**9b**)	85	**10b**
3	**8a**	3,4-$(BnO)_2$Ph (**9c**)	83	**10c**
4	**8b**	4-(MeO)Ph (**9a**)	85	**10d**
5	**8b**	4-(Cl)Ph (**9b**)	70	**10e**
6	**8b**	Ph (**9d**)	91	**10f**
7	**8b**	2-(Me)Ph (**9e**)	80	**10g**
8[a]	**8b**	4-(NC)Ph (**9f**)	84	**10h**
9[b]	**8b**	*n*-Bu (**9g**)	65	**10i**
10	**8c**	3,4-$(BnO)_2$Ph (**9c**)	97	**10j**
11	**8d**	3,4-$(BnO)_2$Ph (**9c**)	74	**10k**

[a] CsF was used instead of *t*-BuOK in this case. [b] $Pd_2(dba)_3$ and P(*t*-Bu)$_2$Me were used instead of the Pd(*t*-Bu$_3$P) complex in this case.

Electron-rich boroxins were efficient coupling partners for these Suzuki cross-couplings when *t*-BuOK was used as a base. However, an improved yield was obtained if the base was switched to CsF for cross-coupling with boroxins bearing electron withdrawing substituents (entry 8). $Pd_2(dba)_3$ and P(*t*-Bu)$_2$Me forms an active complex for the cross-coupling of alkyl boroxin, as opposed to Pd(P(*t*-Bu)$_3$)$_2$ which mostly led to dehalogenation products **7** (entry 9).

Conformational analysis of *N*-imidate tetrahydropyridines **10** indicates that the R^1 substituent rests in a pseudo-axial conformation due to $A^{1,3}$ allylic strain interactions with the amidine group. We, therefore, expected this substituent to shield one face of the cyclic alkene. Gratifyingly, subjecting tetrahydropyridines **10f** and **10d** to standard hydrogenation conditions afforded the corresponding piperidines in a good ratio of diastereomers favoring the cis isomer (Scheme 4).

Scheme 4. Stereocontrolled Hydrogenation of 5-Substituted 1,2,3,4-Tetrahydropyridines



10f Ar = Ph
10d Ar = 4-(MeO)Ph

11a Ar = Ph, 98% (dr 6:1)
11b Ar = 4-(MeO)Ph, 76% (dr

In conclusion, we have developed a new methodology for the stereoselective synthesis of 2,5-*cis*-disubstituted piperidines. For example, **11a** was synthesized in 5 steps from pyridine in 57% overall isolated yield demonstrating that the halogenation of 1,2,3,4-tetrahydropyridines forms a versatile vinyl iodide intermediate. Previous studies showed that reduction of amidine in high yields is straighforward.[3] The application of this methodology to the synthesis of biologically active compounds is under examination and will be reported in due course.

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Supporting Information Available: Experimental procedures and data for each reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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