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Highly Regioselective Intermolecular Arylation of 1,2,3,4-Tetrahydropyridines

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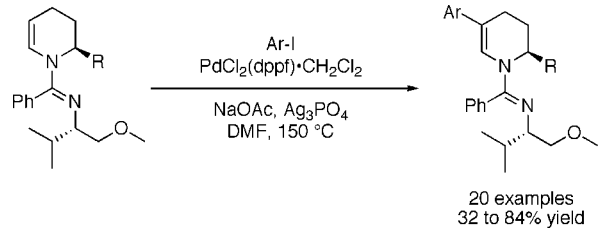
ABSTRACT

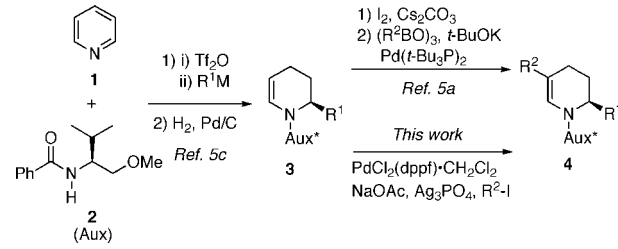


Using a catalytic amount of $PdCl_2(dppf)\cdot CH_2Cl_2$ in combination with Ag_3PO_4 and NaOAc, a range of arylated 1,2,3,4-tetrahydropyridines are synthesized in good yields and with complete selectivity at the β-position. The reaction is compatible with a variety of electron-donating and electron-withdrawing aryl iodides as well as with heteroaryl iodides. The application of these tetrahydropyridines toward the synthesis of polysubstituted piperidines is also demonstrated.

The substituted piperidine moiety is among the most encountered subunits in pharamacophores and drugs.[1] Consequently, their rapid, stereoselective formation has been the topic of numerous efforts in recent years.[2,3] Moreover, it has been demonstrated that the piperidine ring can be derivatized to the corresponding indolizidine or quinolizidine rings which are important scaffolds found in pharmaceutical targets.[4]

As part of our research program directed toward the formation of polysubstituted piperidines, we have developed a process to activate pyridine (**1**) with an amide and triflic anhydride, providing a cheap and readily available source for the nitrogen-containing six-membered cycles (Scheme 1).[5] The 1,2-addition of organometallic nucleophiles to an

Scheme 1. Formation of 5-Substituted 1,2,3,4-Tetrahydropyridines from Pyridine



N-pyridinium imidate chiral salt derived from chiral amide **2** has been applied in the synthesis of a range of enantioenriched 2-substituted dihydropyridines.[5e,f] This approach has

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(2) For recent reviews on the stereoselective syntheses of piperidines, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *19*, 3693. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.

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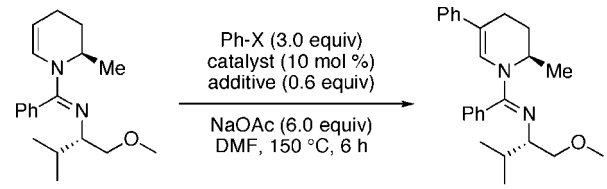
been used for the expedient stereoselective synthesis of many biologically active piperidines such as (−)-barrenazines[5b] and (−)-CP-99,994.[5e] Also, it has been reported that chemoselective hydrogenation of the resulting dihydropyridine can form 1,2,3,4-tetrahydropyridine rings **3** in excellent yields.[5c] This strategy has been employed in the stereoselective synthesis of (+)-julifloridine. More recently, we reported that the 2,5-*cis*-disubstituted piperidine moiety can be accessed in three steps from the corresponding substituted 1,2,3,4-tetrahydropyridine **3**.[5a]

The formation of the β-arylated tetrahydropyridine **4** required the activation of the starting enamidine **3** with iodine followed by a Suzuki coupling. Due to both the sensitivity of the halide and to moderate yields for the formation of the corresponding iodide intermediate, we sought to improve this sequence by using a more direct approach, namely, a palladium-catalyzed, regioselective arylation of 1,2,3,4-tetrahydropyridines. The challenge of regioselectivity in some arylation processes, especially in the Heck reaction with electron-rich olefins, is an important drawback for a potentially useful method.[6]

Ripa et al. showed that β-selectivity could be achieved with cyclic enol ethers by using a specific nitrogen-containing directing group and that cyclic enamidines give α-arylation similarly to their corresponding oxygen-containing parent.[7] Recently, Lane et al. reported a highly regioselective electrophilic substitution for the arylation of the C-3 position in indoles by increasing the steric bulk of both the ligand on the palladium and the complexing magnesium salt.[8] Also, Ge et al. showed that high regioselectivity can be achieved in a direct arylation of enaminones using organotrifluoroborates and $Cu(OAc)_2$.[9]

To arylate enamidine **5a**, we initially tested classical Heck conditions using 10 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3, NaOAc, and iodobenzene without any other metallic additive (Table 1, entry 1). This reaction gave a poor yield for the arylation (∼5%) at the β-position with large amounts of unreacted starting material. When 60 mol % of silver phosphate was added to the reaction (entry 2), a small improvement in the yield (21%) was observed. Regioselectivity problems in Heck arylation of cyclic enol-ethers have been adressed by many groups.[10] Notably, the use of stoichiometric amounts of thallium or silver salts gave satisfying results.[10c] Also, silver salts are often used to abstract halogen anions to generate cationic palladium species.[11]

Table 1. Exploration of the Different Reaction Parameters on the Arylation of 1,2,3,4-Tetrahydropyridines



5a **6a**

entry	catalyst	additive	Ph−X	yield **6a** (%)[a]
1	$Pd(OAc)_2$/2 PPh_3	none	Ph−I	5
2	$Pd(OAc)_2$	Ag_3PO_4	Ph−I	21
3	$Pd(PCy_3)_2Cl_2$	Ag_3PO_4	Ph−I	55
4	$PdCl_2$	Ag_3PO_4	Ph−I	59
5	$PdCl_2(dppf)\cdot CH_2Cl_2$	Ag_3PO_4	Ph−I	82
6	none	Ag_3PO_4	Ph−I	0
7[d]	$PdCl_2(dppf)\cdot CH_2Cl_2$	$AgClO_4$	Ph−I	26
8[d]	$PdCl_2(dppf)\cdot CH_2Cl_2$	AgOAc	Ph−I	31
9[b]	$PdCl_2(dppf)\cdot CH_2Cl_2$	Ag_3PO_4	Ph−Br	40
10[b]	$PdCl_2(dppf)\cdot CH_2Cl_2$	Ag_3PO_4	Ph−Cl	5
11[e]	$PdCl_2(dppf)\cdot CH_2Cl_2$	Ag_3PO_4	Ph−I	15
12[b]	$PdCl_2(dppf)\cdot CH_2Cl_2$	Ag_3PO_4	Ph−I	91(84)[c]

[a] Yield determined by ^1H NMR analysis of the unpurified reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b] 1.2 equiv of NaOAc used. [c] Isolated yield. [d] 1.8 equiv of additive used. [e] Reaction conducted at 100 °C.

In our case, Ag_3PO_4 could act as an oxidant since precipitation of Ag^0 was detected in the crude mixture of the reaction. Interestingly, no phosphine ligand was necessary to achieve significant conversion to the product (entry 4), as the amidine is known to be a good ligand for palladium.[7a,12] Gratifyingly, we found that the reaction proceeds with $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst to give an 82% yield as measured by ^1H NMR (entry 5). Further screening of additives (entries 7 and 8), aryl halides (entries 9 and 10), reaction temperature[13] (entry 11), and equivalents of base (entry 12) led to an optimized 84% isolated yield. In all these cases, analysis of the crude NMR showed complete regioselectivity for the β-position of the enamidine. These observations are surprising knowing that similar intramolecular Heck reactions employing enamidines as directing groups gave regioselectively α-arylated tetrahydropyridines and double bond migration.[7a]

To validate the β-regioselectivity of the reaction on a broader scope, we submitted a variety of aryl iodides to the optimized conditions (Table 2).

(4) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *n/a*, 2862.

(5) (a) Larivée, A.; Charette, A. B. *Org. Lett.* **2006**, *8*, 3955. (b) Focken, T.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2985. (c) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747. (d) Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368. (e) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517. (f) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

(6) (a) Calò, V.; Nacci, A.; Monopoli, A.; Ferola, V. *J. Org. Chem.* **2007**, *72*, 2596. (b) Phan, N. T. S.; Van der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(7) (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 7147. (b) Andersson, C.-L.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757.

(8) (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897.

(9) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708.

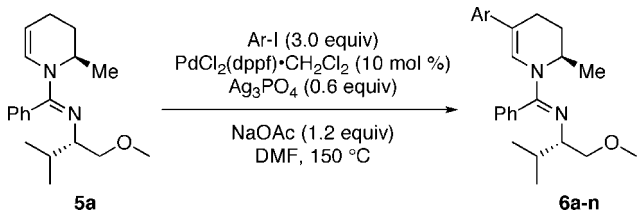
(10) (a) Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997. (b) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639. (c) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (d) Hillers, S.; Sartori, S.; Reiser, O. *J. Am. Chem. Soc.* **1996**, *118*, 2087. (e) Andersson, C.-M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529.

(11) For a discussion on the Heck mechanism see ref 6c.

(12) For some examples of ligand-free Heck reactions, see: (a) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 7528. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(13) Similar experiments performed in other polar solvents such as DMA, NMP, and DME gave significantly lower yields.

Table 2. Palladium-Catalyzed Arylation of Various Aryl and Heteroaryl Iodides with 1,2,3,4-Tetrahydropyridines



entry	product	Ar	time (h)	yield (%)[a]
1	**6a**	Ph	6	84
2	**6b**	2-Me-C_6H_4	6	80
3	**6c**	3-Me-C_6H_4	6	75
4	**6d**	4-MeO-C_6H_4	6	85
5	**6e**	3,4-OCH_2O-C_6H_3	8	71
6	**6f**	4-F-C_6H_4	12	76
7	**6g**	3-Br-C_6H_4	12	68
8	**6h**	3-Cl-C_6H_4	12	64
9	**6i**	4-CO_2Et-C_6H_4	16	68
10	**6j**	3-CF_3-C_6H_4	24	55
11	**6k**	1-naphthyl	6	75
12	**6l**	2-thiophene	12	46
13[b]	**6m**	3-pyridine	24	32
14[b]	**6n**	2-benzofuran	16	50

[a] Isolated yield. [b] Reaction was conducted with 15 mol % of $PdCl_2(dppf)•CH_2Cl_2$.

Aryl iodides bearing electron-rich substituents underwent regioselective β-arylation in good yields after 8 h of reaction (entries 2−5). Aryl iodides possessing electron-withdrawing groups required longer reaction times, and slightly lower yields (55−76%) were obtained (entries 6−10). The more hindered 1-naphthyl iodide underwent the arylation smoothly in 75% yield (entry 11). We then tested the reaction with different heteroaryl iodides, and we were pleased to find that 2-iodothiophene (entry 12, 46% yield), 3-iodopyridine (entry 13, 32% yield), and 2-iodobenzofuran (entry 14, 50% yield) gave the desired β-arylated product with moderate yields to afford a range of valuable 5-heteroaryl 1,2,3,4-tetrahydropyridines that are difficult to synthesize using other methods. A variety of 2-substituted 1,2,3,4-tetrahydropyridines **5b**−**5d** (Table 3) were also viable substituents for β-arylation.

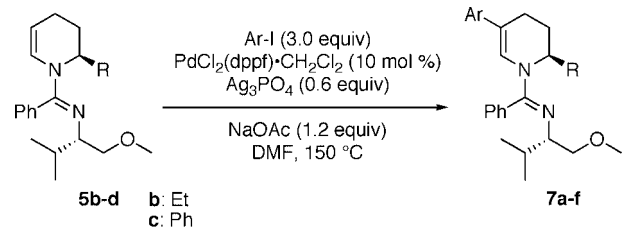
The yields were relatively constant with different 2-substituted tetrahydropyridines; 2-ethyl (**5b**), 2-phenyl (**5c**), and 2-furyl (**5d**) tetrahydropyridines all yielded β-arylation products in 71−73% (entries 1−3). The reaction with the 2-phenyl-substituted starting material **5c** also tolerated a variety of functional groups on the aryl coupling partner, such as an electron-rich 4-MeO (entry 4) and an electron-poor 3-CF_3 (entry 6), with yields comparable to when the enamidine **5a** was used.

(14) For a detailed discussion on arylation mechanisms involving enamines or indoles, see refs 8 and 9.

(15) See Supporting Information for NOE spectra analysis.

(16) (a) Macchia, B.; Macchia, M.; Martinelli, A.; Martinotti, E.; Orlandini, E.; Romagnoli, F.; Scatizzi, R. *Eur. J. Med. Chem.* **1997**, *32*, 231. (b) Balsamo, A.; Barili, P. L.; Gagliardi, A.; Lapucci, A.; Macchia, B.; Macchia, F.; Bergamaschi, M. *Eur. J. Med. Chem.* **1982**, *17*, 285.

Table 3. Palladium-Catalyzed Arylation of Various 2-Substituted 1,2,3,4-Tetrahydropyridines

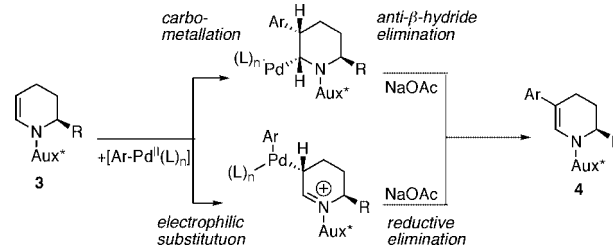


entry	product	R	Ar	time (h)	yield (%)[a]
1	**7a**	Et	Ph	6	71
2	**7b**	Ph	Ph	6	73
3	**7c**	2-Furyl	Ph	6	73
4	**7d**	Ph	4-MeO-C_6H_4	6	83
5	**7e**	Ph	3-Me-C_6H_4	6	75
6	**7f**	Ph	3-CF_3-C_6H_4	20	58

[a] Isolated yield.

Two possible mechanisms account for the regioselectivity observed (Scheme 2).[14] The first possible pathway illustrates

Scheme 2. Proposed Mechanisms for the Arylation of 1,2,3,4-Tetrahydropyridines



a mechanism where the reaction proceeds via a Heck-type carbo-metalation followed by an *anti*-β-hydride elimination to form the product **4**. The second possible pathway involves an electrophilic substitution from the enamidine **3**. Subsequent deprotonation mediated by NaOAc, followed by reductive elimination, can lead to the formation of the observed tetrahydropyridine **4**.

Having a range of substituted tetrahydropyridines in hand, these products were subjected to hydrogenation conditions (Table 4). Treatment of cyclic enamidines with Pd/C and a strong Lewis acid ($BF_3•OEt_2$) under a hydrogen atmosphere produced piperidines in high yields and good stereocontrol (4:1−6:1) favoring the *cis* isomer (entries 1−4).

Additionally, the cyclic enamidines were found to be efficiently transformed to 3-aryl-3-piperidinols upon treatment with dimethyldioxirane (DMDO) at −78 °C (Table 5, entries 1−3). The relative stereochemistry was confirmed by an NOE study of piperidinol **9b**.[15] Only one diastereoisomer was detected by ^{1}H NMR analysis of the crude

Table 4. Hydrogenation of Various 2,5-Substituted 1,2,3,4-Tetrahydropyridines

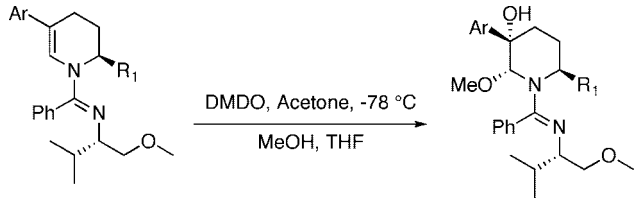
7 8a-d

entry	product	Ar	yield (%)[a]	dr (*cis*:*trans*)[b]
1	**8a**	Ph	98	6:1
2	**8b**	4-MeO-C_6H_4	76	5:1
3	**8c**	3-Me-C_6H_4	90	5:1
4	**8d**	3-CF_3-C_6H_4	81	4:1

[a] Isolated yield of the mixture of diastereoisomers. [b] Determined by ^{1}H NMR analysis of the crude mixture.

mixture. 3-Aryl-3-piperidinols are found in non-natural polysubstituted piperidinols that are agonists of α-adrenergic receptors.[16]

Table 5. Formation of Polysubstituted 3-Aryl-3-piperidinol Using a Tandem Epoxidation−Methanol Opening Reaction



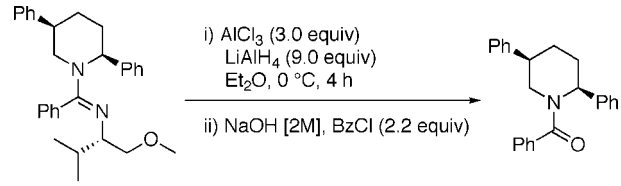
6 or 7 9a-c

entry	product	R_1	Ar	yield (%)[a]
1	**9a**	Ph	Ph	87
2	**9b**	Et	Ph	91
3	**9c**	Me	3-Cl-C_6H_4	81

[a] Isolated yield. Only one diastereoisomer was observed.

The amidine group can be removed by treatment with in situ generated AlH_3 and one-pot protection of the free amine with benzoyl chloride (Scheme 3). This cleavage sequence was performed without epimerization in 81% yield for product *cis*-**10a**.

Scheme 3. Synthesis of a Benzoylated 2,5-*cis*-Piperidine



***cis*-8a**
dr = >10:1

***cis*-10a**
81% yield
98% ee
dr = >10:1

In summary, we developed a regioselective intermolecular arylation for the synthesis of a broad variety of 5-aryl and 5-heteroaryl 1,2,3,4-tetrahydropyridines that avoids the preactivation of the enamidine with iodine. These products were smoothly transformed into highly functionalized piperidines by a diastereoselective hydrogenation and a tandem epoxidation−nucleophile opening sequence. Mechanistic investigations to explain the regioselectivity of this reaction are ongoing 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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