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Synthesis of 4-Arylpiperidines from 1-Benzyl-4-piperidone: Application of the Shapiro Reaction and Alkenylsilane Cross-Coupling

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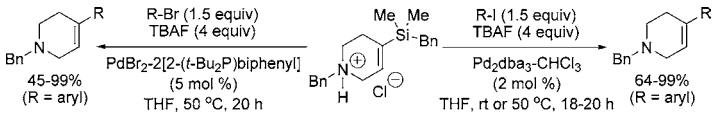
ABSTRACT



1-Benzyl-3,4-unsaturated-4-piperidinyl benzyldimethylsilane has been prepared and observed to readily undergo palladium-catalyzed cross-coupling reactions with a variety of aryl iodides and aryl bromides to generate 3,4-unsaturated 4-arylpiperidines, often at ambient temperature.

The 4-arylpiperidine moiety is commonly employed as a structural unit in numerous drug discovery programs, including those with potential application for the treatment of asthma,[1] hypertension,[2] depression,[3] migraines,[4] bacterial infections,[5] prostate gland enlargement,[6] estrogen-related disorders,[7] Alzheimer's disease,[8] neuronal excitotoxicity (e.g., epilepsy, Parkinson's disease),[9] cocaine abuse,[10] and allergic rhinitis.[11] Both the 4-aryl group and the N-substituent are frequently used as points of structural diversification.[1,3−5,9,11]

Because few 4-arylpiperidines are commercially available, new synthetic routes are desirable. The most common synthetic methods include the condensation of a 4-piperidone derivative with an aryl organometallic species (Scheme 1, eq 1),[3−4,8−12] the cross-coupling of a fully saturated piperidine reagent (eq 2),[13] and the cross-coupling of a 3,4-unsaturated piperidine reagent (eq 3).[1−2,5−7,14] The first method is often undesirable due to its use of strong nucleophiles and acids.

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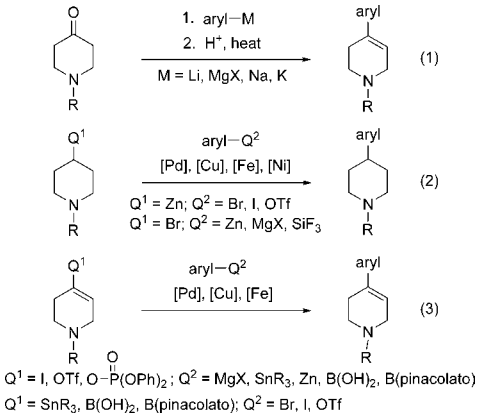
Scheme 1. Common Methods to Synthesize 4-Arylpiperidines



The latter two methods represent more general procedures because they involve mild reaction conditions.

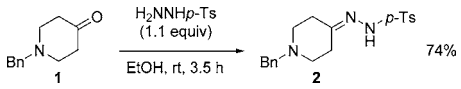
One disadvantage, however, of the methods represented in eqs 2 and 3 is that the requisite piperidine reagents generally cannot be carried through multiple synthetic steps. They must undergo cross-coupling immediately following their preparation. Thus, the manner in which a 4-arylpiperidine unit can be diversified within a drug discovery program is limited. This situation exists primarily because tin reagents introduce issues of toxicity and difficult byproduct removal, whereas triflate, zinc, and boron reagents introduce issues of reagent instability and incompatibility.

Organosilanes have recently emerged as alternative cross-coupling reagents that possess the advantages of low toxicity *and* high stability.[15] Benzyldimethylsilyl reagents in particular exhibit notable stability toward acids and bases,[16] and they can be carried through multiple synthetic steps.[17] We wanted to ascertain whether a 3,4-unsaturated piperidine reagent containing a benzyldimethylsilyl moiety could be readily synthesized and successfully employed in cross-coupling reactions. Herein, we report (1) the application of the Shapiro reaction to efficiently convert 1-benzyl-4-piperidone into a benzyldimethylsilyl reagent and (2) the use of cross-coupling chemistry to subsequently transform this reagent into a variety of 3,4-unsaturated 4-arylpiperidines.

The Shapiro reaction[18] was employed to synthesize the desired alkenylsilane reagent. This strategy involved the fragmentation of a tosylhydrazone to generate an alkenyllithium species, which was then trapped with benzyldimethylsilyl chloride ($BnMe_2SiCl$). This synthetic route appeared to be more direct compared to routes involving precursors such as alkynes or alkenyl halides, which would have likely involved additional synthetic steps, as well as problems of regioselectivity.

The first step in this synthesis converted 1-benzyl-4-piperidone (**1**) into tosylhydrazone **2** (Scheme 2). The benzyl protecting group was utilized because of its relatively high stability toward organometallic reagents such as *n*-butyllithium (*n*-BuLi).[19] Tosylhydrazone **2** was isolated by filtration as a crystalline, white solid that was stable for at least 6 months on the bench top. This material was used without further purification.

Scheme 2. Synthesis of Tosylhydrazone **2**



The second step involved the Shapiro reaction of **2**. Previous reports described the Shapiro reaction of carbocyclic tosylhydrazones using excess *n*-BuLi (4.0−4.3 equiv) and trimethylsilyl chloride (3.4−4.0 equiv) in TMEDA/hexanes.[20] The use of these literature-recommended conditions in the reaction of **2** with $BnMe_2SiCl$ resulted in only a 60% isolated yield of alkenylsilane **4** (Scheme 3). HPLC and ^1H NMR spectroscopy studies indicated that this low yield was *not* the result of either (1) incomplete consumption of **2** or (2) premature protonation of intermediate **3**.

Scheme 3. Syntheis of **4** Using Literature Conditions

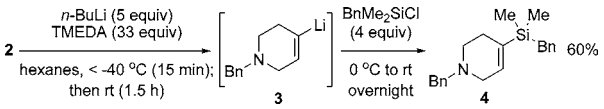


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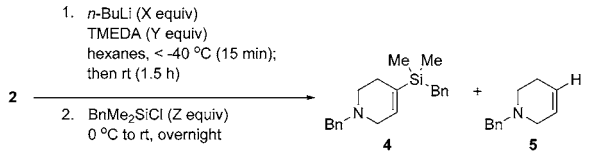
Table 1. Optimization of the Shapiro Reaction of **2**[a]



entry	X	Y	Z	isolated yield: **4**	isolated yield: **5**
1	5	33	4	60%	0%
2	4	33	4	49%	10-20%[b]
3	3	33	4	5%	47%
4	5	5	4	65%	0%
5	5	5	1.5	81%	0%
6	5	5	1.1	62%	10%

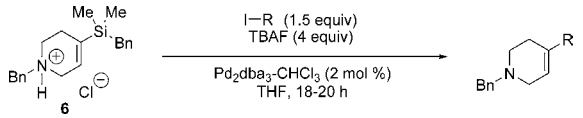
[a] 0.2 M; 26 mmol scale. [b]Contaminated with unknown impurities.

Further optimization involved varying the reagent stoichiometries (Table 1). Entry 1 shows the initial reaction conditions. As the literature suggests,[18,20,21] at least 5 equiv of *n*-BuLi was required to prevent the formation of **5** (entries 1−3). Moreover, TMEDA was not needed as a cosolvent; the reaction could be carried out in hexanes with only 5 equiv of TMEDA (entry 4). Finally, the use of only 1.5 equiv of $BnMe_2SiCl$ significantly *increased* the isolated yield of **4** (compare entries 4−6). This observation contradicts literature reports, which suggest that similar amounts of the electrophile and *n*-BuLi must be employed.[18,20,21] The use of less $BnMe_2SiCl$ also greatly facilitated the isolation of **4**. The aqueous workup and purification of the reactions shown in entries 1−4 were plagued with emulsions and abundant byproducts, but the workup and purification of the reactions shown in entries 5 and 6 were not. Using the optimized conditions (entry 5), this reaction was successfully performed on scales of up to 18 g.

Alkenylsilane **4** was purified by silica gel chromatography, but it still contained minor impurities. Further purification was achieved by the conversion of **4** into HCl salt **6** through reaction with concentrated HCl in isopropanol. Analytically pure **6** precipitated from the solution overnight, and it was isolated by filtration in 65% yield as a crystalline, white solid that was stable for at least 6 months on the bench top.

The cross-coupling reactions of alkenylsilane **6** were evaluated under the conditions that have been previously reported for the cross-coupling of alkenyl benzyldimethylsilanes.[16] Reagent **6** efficiently coupled with a variety of aryl iodides (Table 2). The only necessary modifications to the literature procedure were: (1) the use of 4, instead of 2, equiv of TBAF, presumably to ensure neutralization of **6** and (2) reaction times of >12 h, as opposed to ≤4 h. We suspect that the tertiary amine, which could potentially coordinate to palladium, is responsible for the longer reaction times.

Table 2. Cross-Coupling of **6** with Aryl Iodides[a]



entry	R	temp	isolated yield
1	C_6H_5	rt	90%
2	4-MeC_6H_5	rt	91%
3	2-MeC_6H_5	rt	62%
4	2-MeC_6H_5	50 °C	91%
5	4-$MeOC_6H_5$	rt	88%
6	2-$MeOC_6H_5$	rt	36%
7	2-$MeOC_6H_5$	50 °C	75%
8	2-thienyl	rt	64%
9	2-thienyl	50 °C	60%
10	3-thienyl	rt	83%
11	4-FC_6H_5	rt	92%
12	4-$(CF_3)C_6H_5$	rt	99%
13	4-$(MeOC)C_6H_5$	rt	99%
14	4-$(MeO_2C)C_6H_5$	rt	93%
15	4-NCC_6H_5	rt	90%
16	4-BrC_6H_5	rt	65%[b]
17	4-BrC_6H_5	50 °C	61%[b]

[a] 0.2 M in THF; 0.3 mmol scale. [b]No bromo-coupled product isolated.

Alkenylsilane **4** also efficiently underwent cross-coupling: its reaction with iodobenzene, using only 2 equiv of TBAF, resulted in an 89% yield of the isolated cross-coupled product. However, because **6** was more readily obtained in pure form, it was used to evaluate the full substrate scope of this reaction.

The observed trends matched those previously reported in alkenylsilane cross-coupling reactions.[15,16] Thus, electron-rich substrates (Table 2, entries 5−10) gave lower yields than electron-deficient ones (entries 11−15), and ortho-substituted substrates (entries 3 and 6) gave lower yields than para-substituted ones (entries 2 and 5). Lower reaction yields could be improved by raising the temperature to 50 °C in some cases (entries 4 and 7) but not in others (entries 9 and 17). Finally, entries 16 and 17 show that an aryl iodide is significantly more reactive than an aryl bromide under these conditions.

The cross-coupling of **6** with aryl bromides was also investigated (Table 3). Under the reaction conditions employed for the aryl iodide couplings, the aryl bromides afforded extremely low isolated yields (entries 1 and 5). Attempts to improve these yields by raising the temperature led to only marginal improvement (entries 2 and 3), except in the case of a highly electron-deficient substrate bearing a *para*-trifluoromethyl group (entries 6 and 7). However, the use of a $PdBr_2$/2-(di-*tert*-butylphosphino)biphenyl catalyst system, which facilitated the cross-coupling of a vinylpolysiloxane reagent with aryl bromides,[22] led to greatly improved yields (entries 4 and 8). These reaction conditions promoted the efficient cross-coupling of **6** with a variety of aryl

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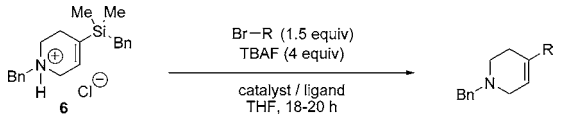
Table 3. Cross-Coupling of **6** with Aryl Bromides[a]



entry	R	catalyst/ligand	temp	isolated yield
1	C_6H_5	Pd_2dba_3-$CHCl_3$/none	rt	0%
2	C_6H_5	Pd_2dba_3-$CHCl_3$/none	50 °C	26%
3	C_6H_5	Pd_2dba_3-$CHCl_3$/none	90 °C	42%
4	C_6H_5	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	74%
5	4-(CF_3)C_6H_5	Pd_2dba_3-$CHCl_3$/none	rt	21%
6	4-(CF_3)C_6H_5	Pd_2dba_3-$CHCl_3$/none	50 °C	64%
7	4-(CF_3)C_6H_5	Pd_2dba_3-$CHCl_3$/none	90 °C	74%
8	4-(CF_3)C_6H_5	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	80%
9	4-MeC_6H_5	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	89%
10	4-$MeOC_6H_5$	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	78%
11	3-thienyl	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	45%
12	4-FC_6H_5	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	69%
13	4-(MeOC)C_6H_5	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	99%
14	4-(MeO_2C)C_6H_5	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	84%
15	4-NCC_6H_5	$PdBr_2$/2-(^{t}Bu_2P)biphenyl	50 °C	94%

[a] 0.2 M in THF or 0.1 M in 1,4-dioxane/THF (for 90 °C reactions), 2 mol % of Pd_2dba_3-$CHCl_3$, 5 mol % of $PdBr_2$, 10 mol % of 2-(*t*-Bu_2P)biphenyl; 0.3 mmol scale.

bromides (entries 9−15). Both electron-rich substrates (entries 9−11) and electron-deficient substrates (entries 8 and 12−15) gave yields comparable to those of the corresponding aryl iodides, with the exception of the thiophene substrate (entry 11). Common functional groups such as ketones, esters, and nitriles were tolerated.

The N-substituent of **4** and **6** can be manipulated prior to undergoing cross-coupling. For example, the *N*-benzyl group of **4** was selectively removed through reaction with 1-chloroethyl chloroformate.[23] The resultant secondary amine was subsequently converted into Boc-protected amine **7**, which readily underwent cross-coupling to form **8** (Scheme 4). Such a transformation would be challenging with the corresponding boronic acid or pinacol boronic ester reagents.

In summary, we have demonstrated that piperidine reagent **6**, which contains a benzyldimethylsilyl moiety, can be easily synthesized from 1-benzyl-4-piperidone via the Shapiro

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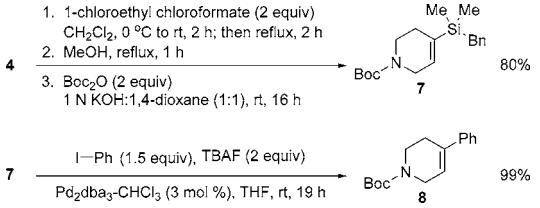
Scheme 4. Transformation of **4** into **7** and Then of **7** into **8**



reaction. Reagent **6** readily undergoes palladium-catalyzed cross-coupling reactions with a variety of aryl iodides and aryl bromides to generate 3,4-unsaturated 4-arylpiperidines.[24] Many of these coupling reactions proceed at ambient temperature. It is also noteworthy that **6** undergoes efficient cross-coupling, despite its basic tertiary amine. Piperidine-derived coupling reagents usually possess nonbasic, carbamate-, or amide-protected amines.[1,2,5−7,13b−e,14]

Because of the low toxicity and high stability of silyl reagent **6**, the coupling reactions of **6** hold some advantages over those involving analogous tin and boron reagents. Most notably, because benzyldimethylsilanes can easily be carried through multiple synthetic steps, piperidenyl silanes such as **6** can be further manipulated prior to undergoing cross-coupling. Thus, the chemistry demonstrated herein presents a useful alternative method for 4-arylpiperidine synthesis. Because 4-arylpiperidines are one of the basic heterocyclic building blocks for drug candidates, this chemistry provides new opportunities for drug discovery programs.

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Supporting Information Available: Experimental details and characterization data for compounds **2**, **4**, **6**, **7**, and all compounds reported in Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Procedures to convert 1-benzyl-4-aryl-1,2,3,6-tetrahydropyridines into their 4-arylpiperidine analogues with retention of the *N*-benzyl protecting group have been reported. See: (a) Sakamuri, S.; Enyedy, I. J.; Kozikowski, A. P.; Zaman, W. A.; Johnson, K. M.; Wang, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 495−500. (b) Czibula, L.; Nemes, A.; Sebök, F.; Szántay, C., Jr.; Mák, M. *Eur. J. Org. Chem.* **2004**, 3336−3339.