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Palladium catalyzed α-arylation of methyl isobutyrate and isobutyronitrile: an efficient synthesis of 2,5-disubstituted benzyl alcohol and amine intermediates

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Abstract—Several 2,5-disubstituted benzyl alcohols containing a functionalized *t*-butyl moiety were synthesized via palladium catalyzed α-arylation of methyl isobutyrate and butyronitrile on synthetically useful scales. The resulting benzyl alcohols could then be further elaborated to benzyl amines or other desirable intermediates.

Locus Pharmaceuticals uses a fragment based approach which utilizes a proprietary set of computational methods to discover leads in generating new therapies for various diseases. As a result, some of the compounds that come out of our computational efforts are structurally more elaborated than traditional lead starting materials or intermediates. In order to access these intermediates, methods must be found to efficiently construct these more complex compounds to support the synthesis of novel drug-like leads.

One such series of intermediates is a set of 2,5-substituted benzyl amines where a *t*-butyl derived substituent was to be incorporated as shown in Figure 1. Such an arrangement of substitution and functionality led us to evaluate several synthetic schemes.

The first route envisioned the alkylation of 4-hydroxyphenyl acetonitrile followed by hydroxyl or alkoxy directed formylation as the key step (Scheme 1). The formyl moiety could then undergo reductive amination to give the desired benzyl amine. Examination of this strategy using 4-hydroxyphenyl acetonitrile under a variety of conditions,[1] however, was unsuccessful in giving the desired formylated product (Scheme 2). Either

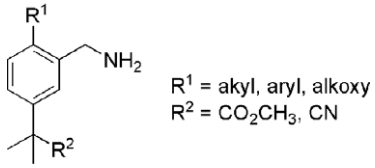
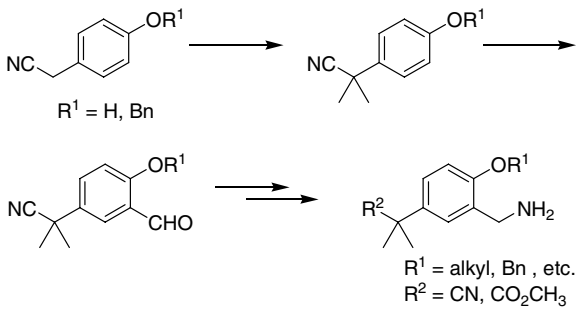
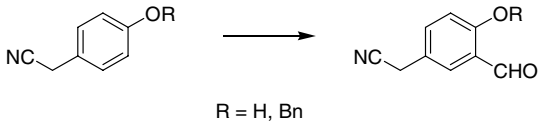


Figure 1. 2,5-Substituted benzyl amines containing a *t*-butyl derived moiety.



Scheme 1. Synthesis involving formylation as the key step.



Scheme 2. Reagents and conditions: R = H (a) paraformaldehyde, $SnCl_4$, DIEA, CH_3CN, 120 °C microwave; (b) paraformaldehyde, $MgCl_2$, DIEA, CH_3CN, reflux; (c) NaOH, H_2O, $CHCl_3$, reflux; R = Bn and (d) dichloromethyl methyl ether, $TiCl_4$, 0°–rt.

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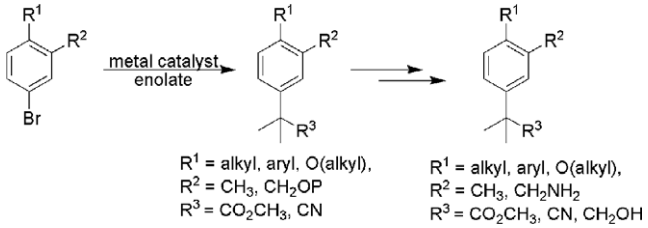


Scheme 3. Synthesis involving palladium catalyzed enolate addition as the key step.

starting material was recovered or other unidentifiable material was obtained.

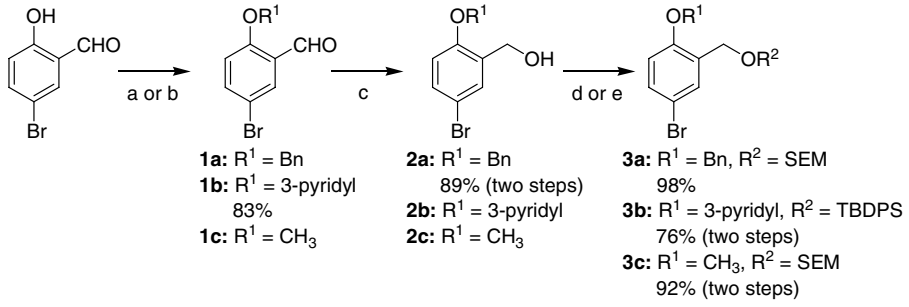
Our second approach envisioned using a metal mediated coupling of an enolate to an appropriately functionalized aryl bromide (Scheme 3). A search of the literature revealed that Pd^0 complexes could be used to catalyze the addition of enolates to aryl halides.[2] The desired functionalized *t*-butyl group could be introduced via this chemistry using isobutyl ester and nitrile enolates. The appropriate chemistries could then be used to arrive at the desired benzyl amines.

The synthesis of the necessary intermediates proceeded as shown in Scheme 4. Commercially available 5-bromo-2-hydroxybenzaldehyde was alkylated with benzyl bromide or 3-(chloromethyl)pyridine to give **1a** and **1b**. These aldehydes, along with commercially available **1c**, were reduced to the alcohol and protected to provide intermediates **3a**–**c**.

With the aryl bromides **3a**–**c** and commercially available 4-bromo-2-methylbiphenyl in hand, we proceeded to explore the palladium catalyzed enolate coupling. We chose a catalyst preparation utilizing the easily handled and air stable $Pd_2(dba)_3/Pd(^tBu_3P)_2$ system.[2b,3] As seen in Table 1, the reaction of aryl bromides with methyl isobutyrate enolate (generated using lithium dicyclohexylamide) in the presence of $Pd_2(dba)_3$ and $Pd(^tBu_3P)_2$ provided the corresponding esters **4**–**7** in excellent yields. We were able to carry out these transformations on synthetically useful scales (1–5 mmol of starting material). The reaction rates were much faster than those reported (3 h for most reactions compared to 8–24 h) with no reduction in yields.[2b]

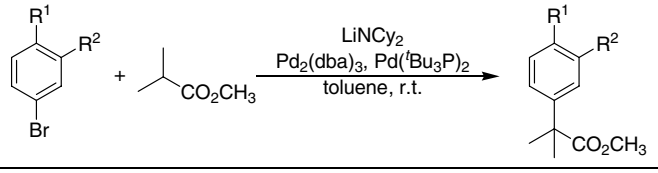
The corresponding reaction with isobutyronitrile was performed using the reported conditions[2a] giving a good yield of the desired nitrile **8** (Scheme 5).

Compound **6** was converted into ether **10** (Scheme 6) via hydrogenolysis of the benzyl group followed by alkylation of the resulting phenol **9**. Using this methodology,



Scheme 4. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, 60 °C; (b) 3-(chloromethyl)pyridine, Cs_2CO_3, DMF, 100 °C; (c) $NaBH_4$, THF, MeOH, 0 °C–rt; (d) SEMCl, DIEA, DCM and (e) TBDPSCl, imidazole, DCM, DMF.

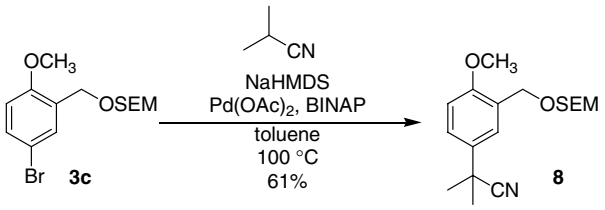
Table 1. Palladium catalyzed coupling of methyl isobutyrate enolate to aryl bromides[a]



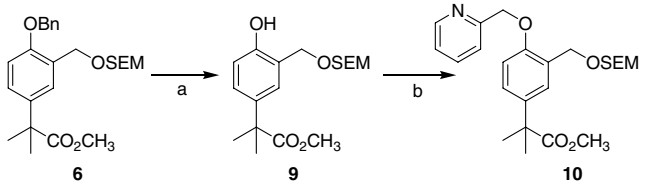
Entry	R^1	R^2	$Pd_2(dba)_3$ (mol %)	$Pd(^tBu_3P)_2$ (mol %)	Compound	Yield[b] (%)
1	OCH_2(3-Pyridyl)	$CH_2OTBDPS$	0.8	3.5	**4**	87
2	OCH_3	CH_2OSEM	0.7	3.0	**5**	74
3	OBn	CH_2OSEM	2.0	3.2	**6**	72
4	Ph	CH_3	0.8	3.8	**7**	94

[a] Typical conditions: To a flask containing 2.5 M *n*-BuLi (1.3 mmol) in hexanes under argon at 0 °C was added dicyclohexylamine (1.3 mmol). The ice bath was removed and the mixture was stirred at rt. (Alternatively, $LiNCy_2$ can be made separately and stored as a solid until use.) To the mixture was added a solution of ester (1 mmol) in 1 mL toluene. This second mixture was stirred at rt for at least 10 min, then was added to a flask containing aryl bromide, $Pd_2(dba)_3$ and $Pd(^tBu_3P)_2$ in 1.5 mL toluene under argon. The final mixture was stirred at rt. After 3–24 h, the reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated. Purification was by flash column on silica gel using EtOAc:hexanes.

[b] Isolated yields.



Scheme 5. Isobutylnitrile enolate addition.[4]



Scheme 6. Reagents and conditions: (a) Pd/C, H_2, MeOH, 98% and (b) 2-chloromethylpyridine HCl, acetone, 60 °C, 78%.

a large amount of the advanced intermediate **6** could potentially be synthesized and used as the starting point for a diverse set of substituted phenyl ethers. Indeed, **6** could be used as a common intermediate for the synthesis of **4** (albeit with the SEM group instead of TBDPS) and **5** as well as **10**.

The conversion of **4**–**6**, **8** and **10** to the corresponding benzyl alcohols and the subsequent amines also proceeded smoothly (Scheme 7). Silyl deprotection, either with HCl for the SEM group or TBAF for the TBDPS group, gave benzyl alcohols **11a**–**e** which were converted to azides **12a**–**e** using diphenylphosphoryl azide (DPPA). The subsequent reduction of the azides with triphenylphosphine gave the desired amines **13a**–**e** in an overall good yield. As noted, the attempted palladium catalyzed enolate additions on an aryl bromide containing the azide resulted in the displacement of the azide through O-alkylation of the ester enolate.

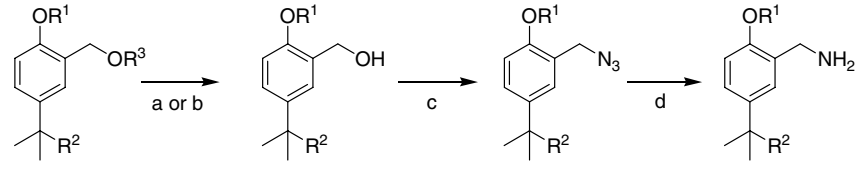
The biphenyl ester **7** (Table 1, entry 4) was converted to amine **16** by first brominating the benzylic methyl using *N*-bromosuccinimide and benzoyl peroxide (Scheme 8). The bromide of **14** was then displaced by azide, giving **15**, which was reduced by triphenylphosphine to give the desired amine **16**.

The benzyl amines **13a**–**e** and **16** were subsequently used as building blocks in the synthesis of more complex, drug-like molecules.

We have demonstrated the use of palladium catalyzed addition of enolates to aryl bromides to synthesize highly fiunctionalized benzyl amines and alcohols with several points of potential diversity as intermediates for further elaboration. Utilizing these catalyst systems, we achieved good overall yields and increased reaction rates. This coupling strategy combined with robust, well established chemistries allowed us to efficiently synthesize the desired intermediates which we elaborated further to synthesize drug-like molecules.

References and notes

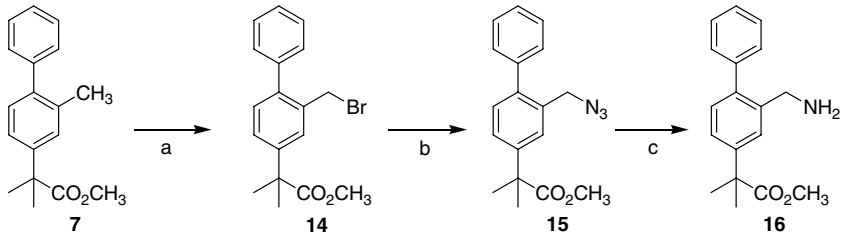
1. Conditions were used or modified from the following: (a) Hofslokken, N. U.; Skattebol, L. *Acta Chem. Scand.* **1999**, *53*, 258; (b) Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1997**, *62*, 1553; (c) Miyachi, H.; Nomura, M.; Tanase, T.; Suzuki, M.; Muralami, K.; Awano, K. *Bioorg. Med. Chem.*



4: $R^1 = CH_2$(3-pyridyl), $R^2 = CO_2CH_3$, R^3 = TBDPS
5: $R^1 = CH_3$, $R^2 = CO_2CH_3$, R^3 = SEM
6: R^1 = Bn, $R^2 = CO_2CH_3$, R^3 = SEM
8: $R^1 = CH_3$, R^2 = CN, R^3 = SEM
10: $R^1 = CH_2$(2-pyridyl), $R^2 = CO_2CH_3$, R^3 = SEM

11-13a: $R^1 = CH_2$(3-pyridyl), $R^2 = CO_2CH_3$
11-13b: $R^1 = CH_3$, $R^2 = CO_2CH_3$
11-13c: R^1 = Bn, $R^2 = CO_2CH_3$
11-13d: $R^1 = CH_3$, R^2 = CN
11-13e: $R^1 = CH_2$(2-pyridyl), $R^2 = CO_2CH_3$

Scheme 7. Reagents and conditions: (a) **5**, **6**, **8** and **10**, HCl, 1,4-dioxane, 0 °C, 64–89%; (b) **4**, TBAF, THF, 93%; (c) DPPA, DBU, 0 °C–rt and (d) PPh_3, 20:1 THF:H_2O; 65–75% (two steps).



Scheme 8. Reagents and conditions: (a) NBS, Bz_2O_2, CCl_4, 90 °C, 89%; (b) NaN_3, DMF, 70 °C and (c) PPh_3, 20:1 THF:H_2O, rt, 82% (two steps).

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2. (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330; (b) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.
3. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
4. Isobutyronitrile (1.15 equiv) was added to a vial containing a stirred solution of NaHMDS (1.3 equiv) in 5.0 mL of toluene. The solution was stirred for 10 min and then added to a stirred suspension of $Pd(OAc)_2$, BINAP and the aryl bromide (4.9 mmol) in 5.0 mL of toluene. The reaction mixture was heated at 100 °C for 3 h, cooled to room temperature, diluted with water and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and the crude chromatographed on silica gel using 10:1 hexanes:EtOAc to give 1.0 g of the desired nitrile.