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Palladium-catalyzed intramolecular arylation of an anilide enolate, application to an efficient formal total synthesis of physovenine

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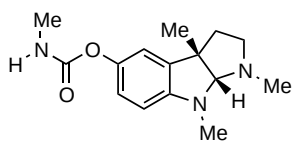
Abstract—An expedient formal total synthesis of the calabar alkaloid physovenine was reported. The key step involves an oxindole synthesis via palladium-catalyzed intramolecular arylation of *o*-bromoanilide.

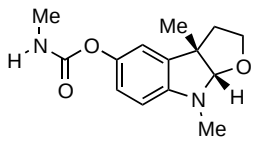
Physostigmine (**1**) and physovenine (**2**) are natural alkaloids isolated from the seeds of *Physostigma venenosum* (calabal beans). With interesting and potent biological properties, such as anticholinergic and miotic activities,[1] these compounds and derivatives have been found to be clinically useful for relieving symptoms of Alzheimer's disease. As a result of their biological activities and unique structures, they have been popular targets for total syntheses and many innovative synthetic methodologies have been developed for their preparation.[2] Reported herein are the results from our recent study on the construction of pivotal intermediate **3** using palladium-catalyzed intramolecular arylation of amides, a strategy which is similar to Overman's Heck reaction approach[3] but with a saturated substrate butananilide **4** instead of butenanilide **5**.

The direct coupling of hard enolates with aromatic halides has been a reaction of limited scope until pioneering developments by the Buldwald, Hartwig and other groups.[4] In particular, oxindoles have been prepared by this methodology.[5] During the course of our work to prepare a variety of oxindoles for medicinal chemistry, we were intrigued by the possibility of utilizing these reactions for natural alkaloid synthesis.

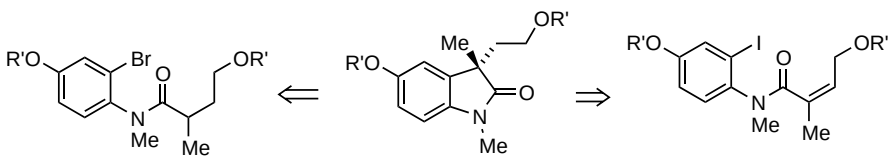
The *o*-bromobutananilde **9** was prepared in a straightforward manner (Scheme 1). Subjecting this compound to a mixture of $KN(SiMe_3)_2$, *R*-BINAP[6] and a catalytic amount of $Pd(OAc)_2$ acetate in toluene afforded oxindole **10** in 24% yield, with concomitant formation of a significant amount of elimination product 1,3-dimethyl-3-vinyl-5-methoxy-2-oxindole. However, when the reac-



1 (-) Physostigmine



2 (-) Physovenine



4 **3** **5**

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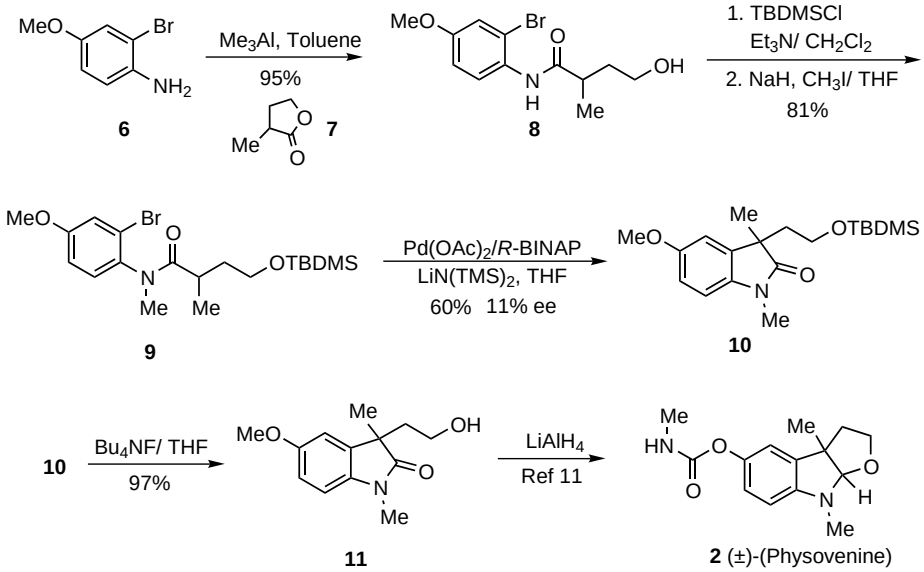

Scheme 1.

tion was conducted in THF instead of toluene and using $LiN(SiMe_3)_2$ as a base, **10** was isolated in 60% yield, albeit with low ee.[7] In addition to solvent, the reaction was also sensitive to the ligand employed (Table 1). Surprisingly, some of the ligands reported to be useful in promoting oxindole formation[5] proved to be unsatisfactory for **9**.

Compound **10** was deprotected uneventfully to the free alcohol **11**, which has been previously converted to physovenine via straightforward transformations, as demonstrated by Clark et al.[8] The enantiomerically pure form of **11** was also reported by Overman and co-workers in their enantioselective synthesis of phytosigmine.[3]

In summary, we have demonstrated the utility of palladium-catalyzed oxindole formation through intramolecular arylation of *o*-bromoanilide. This has been applied to the formal total synthesis of physovenine. While the current enantioselectivity is relatively low, the potential of a more suitable chiral ligand affording higher ee's is being explored.

Table 1. Cyclization of *o*-bromoanilide **9** to oxindole **10**

Catalysts	Reaction conditions	**10**
BINAP, $Pd(OAc)_2$ or $Pd_2(dba)_3$	$LiN(TMS)_2$, THF, 68°C	50–60% (isolated yield)
BINAP, $Pd_2(dba)_3$	$KN(TMS)_2$, toluene, 70°C	<5%, complex mixture
DPPF, $Pd_2(dba)_3$	$LiN(TMS)_2$, THF, 68°C	<1%
t-Bu_3P, $Pd_2(dba)_3$	$LiN(TMS)_2$, THF, 68°C	<1%
No catalyst	$LiN(TMS)_2$, THF, 68°C	<1%

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7. Experimental procedure: **1,3-Dimethyl-5-methoxy-3-(2′-*tert*-butyldimethylsiloxyethyl)oxindole (10).** Palladium acetate (23 mg, 0.1 mmol) and *R*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (78 mg, 0.125 mmol) in dry THF (20 mL) were stirred at room temperature under nitrogen for 60 minutes. The bromoanilide (**9**, 430 mg, 1 mmol) in THF (5 mL) was added via a syringe. $LiN(TMS)_2$ in THF (1.0 M, 2 mL, 2 mmol) was added dropwise and the resultant dark-purple mixture was stirred at 68°C for 16 h. The reaction mixture was cooled to room temperature before treating with 1N HCl (2 mL) and water (50 mL). The mixture was extracted with ethyl acetate (3×25 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. After removal of the solvents, the residue was chromatographed on silica gel (heptane:ethyl acetate = 8:1→4:1) to afford compound **10** (210 mg, 60%) as pale yellow oil: IR (cm^{-1}) 3016(m); 2951(m); 2928(m); 2854(w); 1696(s); 1597(w); 1499(m); 1470(m); 1288(w); 1249(w); 1111(m); 1085(m); 1030(w); 835(m). ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (1H, dd, J = 0.9, 3.0 Hz); 6.78 (1H, dd, J = 3.0, 8.4 Hz); 6.70 (1H, dd, J = 0.6, 8.4 Hz); 3.79 (3H, s, OCH_3); 3.35 (2H, m); 3.16 (3H, s, NCH_3); 2.21 (1H, ddd, J = 7.4, 7.5, 13.5 Hz); 1.94 (1H, ddd, J = 5.4, 6.9, 13.8 Hz); 1.34 (3H, s, CH_3); 0.75 (9H, s, 3×CH_3); −0.13 (6H, s, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.81; 155.70; 136.67; 134.93; 111.52; 110.34; 107.98; 59.53; 55.81; 47.01; 40.40; 26.33; 25.88; 24.98; 18.24; −5.49. MS m/z 350 (M^++1); 271; 119. HRMS (FIA): calcd for $C_{19}H_{32}NO_3Si$ (M^++1) 350.2152. Found 350.2138.
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