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A Concise Palladium-Catalyzed Carboamination Route to (±)-Tylophorine

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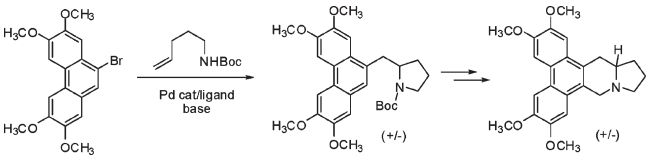
Received October 1, 2009



A total synthesis of the racemic natural product tylophorine [(±)-**1**] has been demonstrated using the palladium-catalyzed carboamination method developed by Wolfe and co-workers. In this case, an electron-rich aryl bromide **18** was prepared in four steps and subjected to palladium-catalyzed Wolfe carboamination conditions with olefinic carbamate **7** to provide the racemic 2-(arylmethyl)pyrrolidine (±)-**19** in good yield and was further elaborated to racemic tylophorine. This application of the Wolfe carboamination protocol as a key step to construct a natural product provides further evidence of the utility of the method.

Tylophorine [(*R*)-(−)-**1**, Figure 1] is a phenanthroindolizidine alkaloid that was first isolated in 1935 from the perennial climbing plant *Tylophora indica*[1] and has recently re-emerged as an alkaloid target family of interest, due largely to its cytotoxic activity by a novel mechanism of action.[2] Its synthetically derived (*S*)-(+)-antipode has generated even greater interest due to its superior cell growth inhibition activity versus its natural isomer. For instance, in three carcinoma cell lines, (*S*)-(−)-tylophorine exhibited an approximately 3- to 4-fold increase in cytotoxicity compared to its natural (*R*)-(−)-isomer (avg. GI_{50} 13 vs 43 nM, respectively).[2b]

In the past decade, a number of concise synthetic preparations of racemic tylophorine have appeared in the literature,[3] and a few approaches to the discrete *R*- and *S*-enantiomers of **1** have also been published.[4] We nevertheless sought to contribute our own novel approach, based on the palladium-catalyzed carboamination process recently established by Wolfe and co-workers.[5] As both absolute configurations of tylophorine still serve as viable starting points for structural analogue modifications for drug discovery investigations,[2] we decided to demonstrate the feasibility for a natural product synthesis of racemic tylophorine using the Wolfe carboamination strategy. This communication summarizes our results toward this goal.

A palladium-catalyzed carboamination reaction of γ-aminoalkenes **2** with aryl bromides has recently been developed by the Wolfe group to define a general synthesis of substituted pyrrolidines **3** ($n = 1$), as well as larger heterocycles (Scheme 1).[5]

This process relies on the ability of amines to form a metallo-amide species **4** with a reactive arylpalladium substrate to direct the metal toward a tethered olefinic moiety. The palladium intermediate may then undergo an insertion reaction into the olefin, generating new organometallic intermediate **5** that contains the newly formed heterocycle. Reductive elimination of the metal from the species **5** may then provide the amine heterocycle **3** and regenerate the active palladium species to perpetuate the catalytic cycle. While the earliest published method was limited to *N*-aryl nucleophiles, more recent communications have demonstrated the use of carbamate substrates **2** (e.g., PG = Cbz, Boc) to provide protected products **4** that can be easily converted into the free amine under mild conditions.[6,7]

To test the feasibility of the method toward an approach to racemic tylophorine, we first explored the carboamination reaction between the two commercially available coupling precursors 9-bromophenanthrene (**6a**, X = Br) and *tert*-butyl pent-4-enylcarbamate (**7**), as shown in Scheme 2.

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(4) For the most recent examples, see: (a) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045. (b) Wang, K.; Wang, Q.; Huang, R. *J. Org. Chem.* **2007**, *72*, 8416. (c) Fürstner, A.; Kennedy, J. W. J. *Chem.—Eur. J.* **2006**, *12*, 7398. (d) Jin, Z.; Li, S. P.; Wang, Q. M.; Huang, R. Q. *Chin. Chem. Lett.* **2004**, *15*, 1164.

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Published on Web 11/17/2009 DOI: 10.1021/jo902114u

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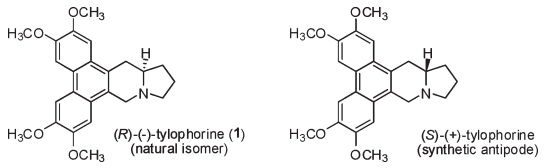
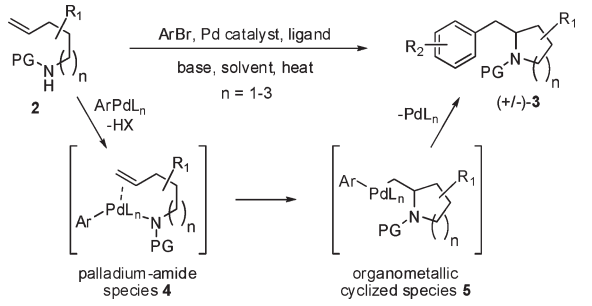


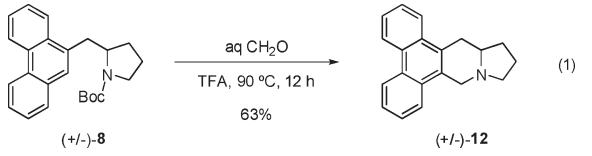
FIGURE 1. Natural product tylophorine and its unnatural antipode.

SCHEME 1. Mechanism of the Wolfe Carboamination Reaction



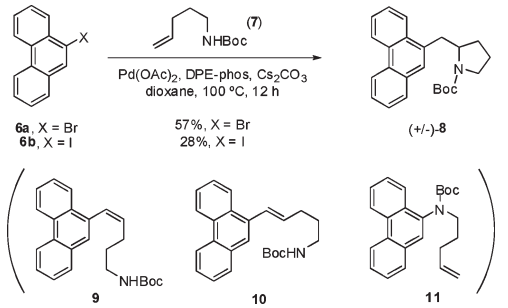
We were pleased to find that our initial attempt using the conditions reported by the Wolfe group for carbamate nucleophiles[6] produced our desired 2-benzylpyrrolidine **8** in 57% yield, a result consistent with yields reported in the literature for this process. In this case, the only other compounds isolated were small amounts of phenanthrene, resulting from the protodebromination of **6a**, and trace amounts of the byproduct **10**, originating from a Heck reaction but without cyclization. Interestingly, when we subjected commercially available 9-iodophenanthrene (**6b**, X = I) to the reaction conditions, the two major products isolated were the requisite pyrrolidine **8** in only 28% yield and substantial amounts of the protodehalogenated byproduct from the precursor **6b**. Isolated in minor amounts were both the (*Z*)- and (*E*)-olefins derived from the Heck reaction (9% of **9** and 8% of **10**) and the N-arylation byproduct **11** in 4% yield.

Formation of the pentacycle **12** from the 2-benzylic pyrrolidine carbamate **8** by nitrogen deprotection with concomitant electrophilic ring-closing reaction with formalin was achieved in 63% yield (eq 1). While this moderate conversion is typical for a Pictet−Spengler cyclomethylenation reaction of an unactivated ring system, it nevertheless provided confirmation for our proof of principle.

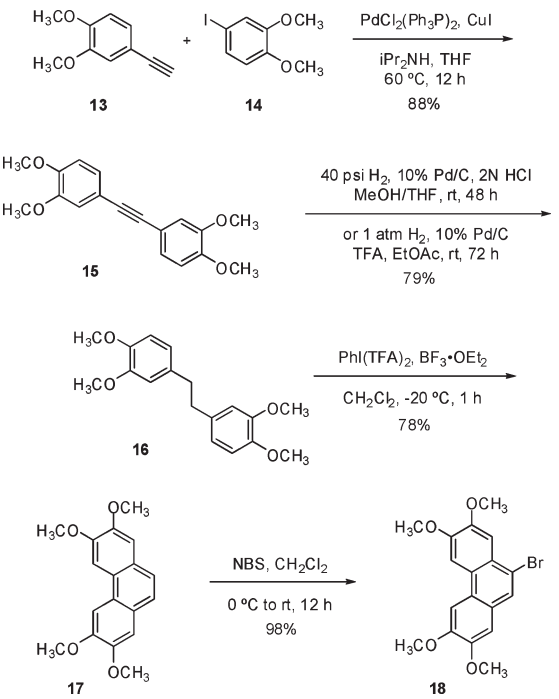


We then turned our attention to the preparation of the requisite carboamination precursor **18**, as shown in Scheme 3. Sonogashira coupling between the commercially available reagents 4-ethynyl-1,2-dimethoxybenzene (**13**) and 4-iodo-1,2-dimethoxybenzene (**14**), based on conditions for an analogous system,[8] furnished the symmetrical acetylene **15** in good isolated yields, ranging from 61 to 88%.

SCHEME 2. Model System Proof of Principle for the Key Step



SCHEME 3. Preparation of the Aryl Bromide Substrate 18



Double reduction of **15** to the corresponding bibenzyl **16** under catalytic hydrogenation conditions was problematic at first, requiring multiple subjections of fresh palladium catalyst to the reaction mixture (Scheme 3). However, after examining a number of solvent systems and additives, we found that a mixture of methanol and THF in aqueous HCl[9] worked well to effect the full reduction of **15** on a Parr shaker (40 psi of hydrogen) to **16** in yields ranging from 57 to 94%. Alternatively, we found that the reduction could be achieved under a balloon of hydrogen gas (1 atm) when the reduction of **15** to **16** was run in ethyl acetate with a small amount of TFA as a cosolvent, although the reaction took a longer time to complete (typically days rather than overnight), albeit without multiple catalyst loadings.

We surveyed several conditions for the oxidative cyclization reaction[10] of the electron-rich 1,2-diarylethane **16** to provide the symmetrical phenanthrene **17**, many of which

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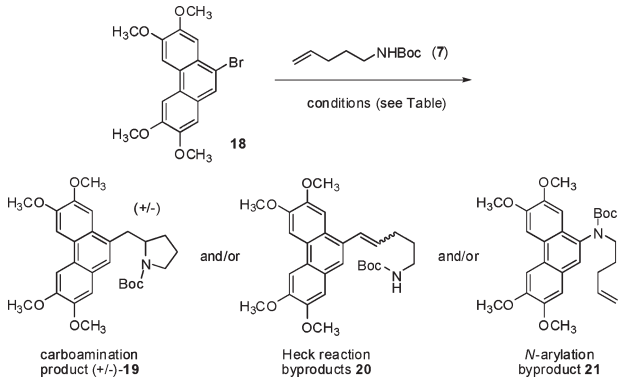
TABLE 1. Selected Results of the Wolfe Carboamination Reaction with Phenanthryl Bromide 18



entry	catalyst/ligand	base	conditions	yield of **19** (%)
1	1:1 $Pd(OAc)_2$, DPE-phos	Cs_2CO_3	dioxane, 100 °C	16
2	1:1 $Pd(OAc)_2$, DPE-phos	Cs_2CO_3	DMF, 80 °C	12
3	1:1 $Pd(OAc)_2$, DPE-phos	NaO^{t}Bu	dioxane, 100 °C	42
4	1:1 Pd_2dba_3, DPE-phos	NaO^{t}Bu	dioxane, 100 °C	67
5	1:1 Pd_2dba_3, BINAP	NaO^{t}Bu	dioxane, 100 °C	17
6	1:1 Pd_2dba_3, Xantphos	NaO^{t}Bu	dioxane, 100 °C	49
7	1:2 Pd_2dba_3, Xantphos	NaO^{t}Bu	dioxane, 100 °C	65
8	1:1 $Pd(OAc)_2$, Xantphos	Cs_2CO_3	dioxane, 100 °C	< 5
9	1:2 Pd_2dba_3, Xantphos	NaO^{t}Bu	toluene, 100 °C	61
10	1:2 Pd_2dba_3, Xantphos	NaO^{t}Bu	DME, 85 °C	56
11	1:2 Pd_2dba_3, Xantphos	NaO^{t}Bu	DMF, 100 °C	16

[a]Isolated yields. All reactions were conducted at the temperatures shown for 16 h, and all starting materials were consumed unless otherwise noted.

worked moderately well (Scheme 3). However, we found that the best results were achieved when we subjected **16** to the PIFA-mediated oxidative cyclization conditions reported by Zeng and Chemler.[4a] Our modification of running the reaction at −20 °C rather than at room temperature successfully generated phenanthrene **17** in good yields (64−78% range), with only a trituration of the crude reaction residue necessary to isolate the purified product. As our preliminary experiments suggested that an aryl bromide would be a more suitable coupling partner versus the analogous aryl iodide (Scheme 2), we decided to explore the halogenation of **17** to prepare phenanthryl bromide **18**. Thus, careful addition of 1.0 equiv of NBS[11] to **17** at 0 °C cleanly formed the monobrominated adduct **18** in excellent isolated yields (98−99%), whereas the use of greater than an equimolar amount of NBS led to unsymmetrical bisbromination byproducts that were inseparable from the desired product.

Finally, the phenanthryl bromide **18** was subjected to the Wolfe carboamination cross-coupling/cyclization conditions with the commercially available olefinic carbamate **7** (Table 1). We set up our first set of conditions for the palladium-catalyzed protocol as described by the Wolfe group for carbamate internal nucleophiles, using palladium acetate as a precatalyst, DPE-phos as a ligand, and cesium carbonate as a base in refluxing 1,4-dioxane.[6] We observed that our desired benzylic pyrrolidine (±)-**19** was isolated, albeit in only 16% yield, although the starting phenanthryl bromide **18** was completely consumed (Table 1, entry 1). Upon closer examination of the reaction byproducts, we also isolated and identified a 24% yield of a mixture of (*E*)- and (*Z*)-olefinic byproducts **20** resulting from a Heck coupling reaction between **18** and **7**, but without the cyclization process having taken place, an observation also made by Wolfe and co-workers in various instances. We also isolated a significant amount of the phenanthrene **17**, resulting from the protodebromination of **18** in the reaction environment. However, as we set about optimizing the reaction parameters, we were eventually able to increase the yield of desired (±)-**19**, as described by the representative experiments summarized in Table 1.

We next subjected phenanthryl bromide **18** and olefinic carbamate **7** to the reaction conditions using DMF as a solvent at 80 °C (Table 1, entry 2), as we were initially concerned about the apparent insolubility of aryl bromide **18** in refluxing dioxane. However, no increase in the isolated yield of (±)-**19** was observed. Returning to the use of refluxing dioxane but using sodium *tert*-butoxide as a base (entry 3) provided a significant increase in yield of (±)-**19**, although it was accompanied by the isolation of 18% of a new byproduct **21** resulting from a palladium-catalyzed N-arylation process. Using these new conditions with a change to Pd_2dba_3 as an active catalyst (entry 4) increased the isolated of (±)-**19** even further to 67%, although the formation of N-arylation byproduct **21** only increased to 21%.

Investigation of other bidentate ligands for palladium, including BINAP (entry 5) and Xantphos (entry 6), led to diminished isolated yields of **19**, although it was found that increasing the ratio of catalyst to Xantphos ligand from 1:1 to 1:2 brought the isolated yield back to a synthetically useful process and virtually eliminated the formation of byproduct **21** (entry 7). Interestingly, the switch back to the initial reaction conditions, but using Xantphos as a ligand (entry 8), did not provide any significant amounts of the desired product.

Investigations using the entry 7 conditions in other solvents including toluene (entry 9) and DME (entry 10) led to yields that were roughly equivalent, although the use of DMF (entry 11) led to a decrease in the amount of **19** isolated and a significant increase in the protodebromination of **18**.

To complete the total synthesis of (±)-tylophorine, the benzylic pyrrolidine (±)-**19** was first subjected to anhydrous deprotection conditions to generate the free pyrrolidine (±)-**22** as a hydrochloride salt (Scheme 4). This material was typically not isolated, but instead formalin and ethanol were added and the resulting mixture was heated at reflux to effect the Pictet−Spengler cyclomethylenation reaction,[3c,4a,12] providing the pentacyclic product (±)-**1** in near-quantitative isolated yields for the two-step process. While there is one example in the literature for the one-step deprotection/cyclization sequence from **19** (prepared by a different strategy) to tylophorine,[4c] we found the protocol to be fairly low-yielding in our hands.

In summary, the present work further demonstrates the synthetic utility of the Wolfe carboamination reaction as an application to the construction of the natural product

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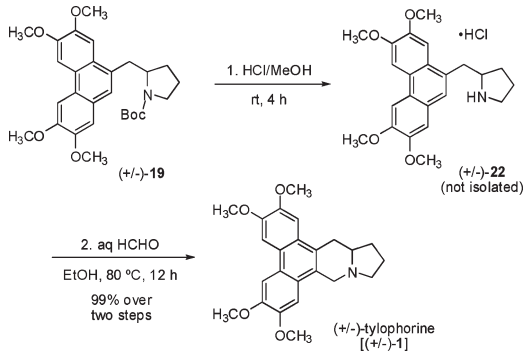
SCHEME 4. Elaboration of Pyrrolidine 19 to (±)-Tylophorine



tylophorine. The preparation of the requisite aryl bromide precursor **18** was achieved in four steps, followed by a palladium-catalyzed cross-coupling/cyclization reaction with the commercially available olefinic carbamate **7** to provide the 2-(2-arylmethyl)pyrrolidine (±)-**19** in 67% isolated yield for the key step. A one-pot deprotection and Pictet−Spengler cyclomethylenation of **19** with formalin provided a near-quantitative yield of racemic tylophorine [(±)-**1**], providing an overall 35% yield of the natural product over the six-step process. This application of the Wolfe carboamination protocol as a key step to construct a natural product provides further evidence of the utility of the method, and further work is under investigation in our laboratory to establish a catalytic asymmetric variant for the preparation of nonracemic natural products.

Experimental Section

9-Bromo-2,3,6,7-tetramethoxyphenanthrene (18). *N*-Bromosuccinimide (NBS, 98 mg, 0.55 mmol) was added to a solution of 2,3,6,7-tetramethoxyphenanthrene (**17**, 172 mg, 0.58 mmol) in anhydrous methylene chloride (5 mL) at 0 °C under nitrogen, after which the mixture was stirred for 1 h and then slowly warmed to room temperature, stirring for a total of 7 h. The mixture was diluted with 5% $Na_2S_2O_3$ solution (50 mL) and extracted with methylene chloride (2 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and brine solutions (20 mL each), dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure to provide 9-bromo-2,3,6,7-tetramethoxyphenanthrene (**18**) as a brown solid (204 mg, 98%): see Supporting Information for spectroscopic and characterization data.

(±)-*tert*-Butyl 2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)-pyrrolidine-1-carboxylate [(±)-19][4a,c]. A degassed mixture of 9-bromo-2,3,6,7-tetramethoxyphenanthrene (**18**, 101.9 mg, 0.27 mmol), *tert*-butyl pent-4-enylcarbamate (**7**, 65.1 mg, 0.35 mmol), tris(dibenzylideneacetone)dipalladium(0) (51.2 mg, 0.06 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 62.0 mg, 0.11 mmol), and sodium *tert*-butoxide (68.4 mg, 0.71 mmol) in anhydrous 1,4-dioxane (5.0 mL) was heated at 100 °C under nitrogen for 12 h. The cooled mixture was diluted with ethyl acetate (25 mL) and partially purified by filtration through a plug of Celite, eluting with ethyl acetate, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/methylene chloride (gradient of 1:99 to 15:85), to provide racemic *tert*-butyl 2-((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)pyrrolidine-1-carboxylate [(±)-**19**] as an off-white solid (89.9 mg, 65%): see Supporting Information for spectroscopic and characterization data.

Acknowledgment. The authors wish to thank AMRI scientists Paul E. Zhichkin and Larry Yet for many helpful discussions, and Kent Kaltenborn for acquiring high-resolution mass spectrometry data.

Supporting Information Available: Full experimental procedures as well as spectroscopic and characterization data for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.