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Palladium[0]-Mediated Aminospirocyclization of Tertiary Allylic Sulfones. Stereospecific Construction of the Azabicyclic Ring System of Cephalotaxine.[1]

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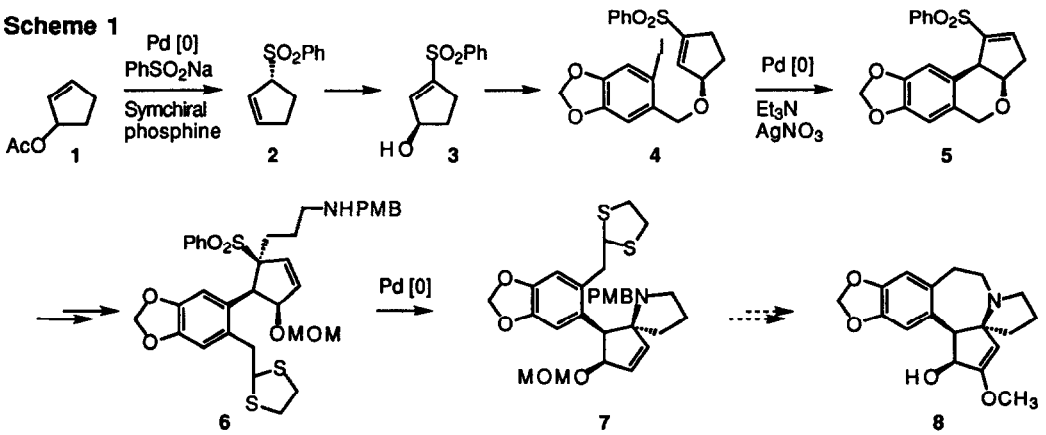
Abstract: Tertiary allylic sulfones which bear a secondary aminopropyl moiety undergo smooth palladium [0]-mediated spirocyclization. The reaction proceeds via a π-allyl intermediate and the resultant azabicyclic product is formed with net retention of sulfone stereochemistry. The use of tetramethylguanidine as companion base is required for high yielding reactions.

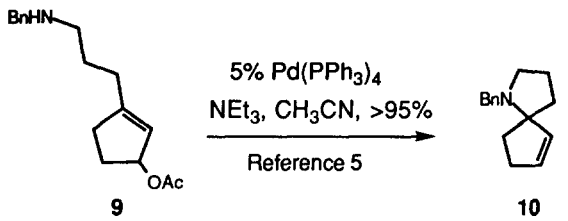
Trost, Organ, and O'Doherty have recently provided an efficient asymmetric synthesis of γ-hydroxyvinyl sulfone **3**.[2] This protocol involves enantiospecific sulfinate anion addition to the π-allyl complex derived from **1** in the presence of a symchiral palladium [0] catalyst. Epoxidation followed by treatment with DBU then affords symchiral vinyl sulfone **3**. The availability of this optically active starting material in combination with our established conversion of benzyl ether **4** to vinyl sulfone **5**[3] has inspired us to examine a new route to cephalotaxine **8** which is also based upon the intermediacy of a palladium π-allyl complex. The specific question to be determined was whether a tertiary allylic sulfone such as **6** would suffer stereospecific intramolecular capture of an amino group to afford **7**, thereby establishing the azabicyclic framework of cephalotaxine **8** (Scheme 1).

Scheme 1



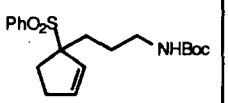
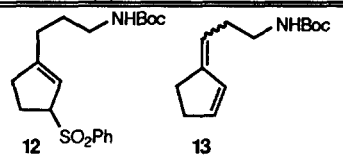
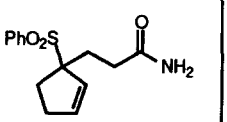
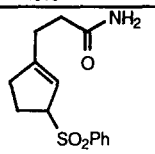
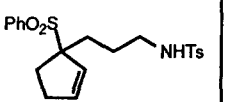
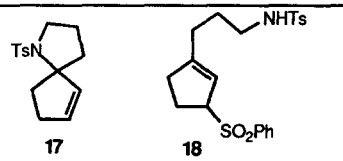
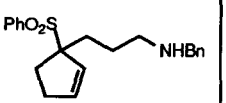
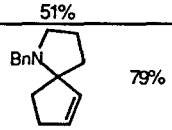
It is well known that nitrogen nucleophiles attack π-allyl palladium complexes and function efficiently in palladium [0]-catalyzed amination,[4] and the intramolecular version of this reaction has been used for the construction of 1-azaspirocycles (c.f. **9** to **10**).[5] It is also known that allyl sulfones can react with palladium [0] to form π-allyl palladium complexes.[6] Nevertheless, there was no literature precedent for palladium [0]-catalyzed allylic spirocyclic amination using allyl sulfones as the substrates (c.f. **6** to **7**). We therefore decided to explore a simple model study to examine the feasibility of this new approach (Scheme 2).

Scheme 2



9 **10**

The model study showed that palladium [0] did form a π-allyl complex upon reacting with allyl sulfones, but Boc-urethane **11**[7] and amide **14**[7] failed to cyclize (Table, entries 1,2). Although amine **16**[7] protected by a sulfonamide group did cyclize, the yield was only 51% and further ionization of secondary allylic sulfone **18** under the same conditions was extremely slow and produced only trace amounts of **17** (Table entry 3). The most successful cyclization took place in the case of a simple secondary benzylamine **19**[7]. Although the reaction was slow compared to Godleski's cases,[5] the yield was good (Table entry 4). The advantage of this new protocol is that it changes the polarity of the sulfonyl-bearing carbon, and enables the formation of two carbon-carbon single bonds at that site.

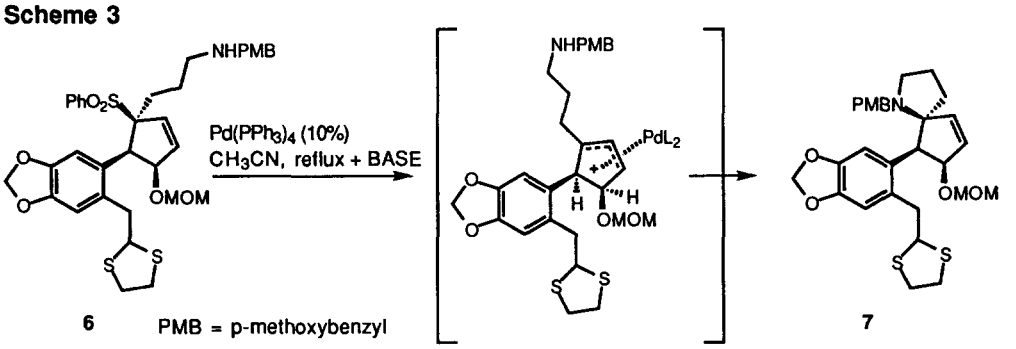
Entry	Substrate	Conditions	Product(s)
1	 **11**	$Pd(PPh_3)_4$, 10% NEt_3, CH_3CN, reflux, 12 h.	 **12** 40% **13** 30%
2	 **14**	$Pd(PPh_3)_4$, 10% NEt_3, CH_3CN, reflux, 12 h	 **15** 73%
3	 **16**	$Pd(PPh_3)_4$, 10% NEt_3, CH_3CN, reflux, 12 h	 **17** 51% **18** 46%
4a 4b	 **19**	$Pd(PPh_3)_4$, 10% NEt_3, CH_3CN, reflux, 18 h. $Pd(PPh_3)_4$, 10% TMG* (1.1 eq), CH_3CN, reflux, 4.5 h	 **10** 79% 91%

*See scheme 3.

We next turned to examination of racemic tertiary allyl sulfone **6**.[7] Reaction of **6** in the presence 10% $Pd(PPh_3)_4$ and 1.1 eq NEt_3 gave 64% of **7** along with an unknown polar byproduct which appears to be a secondly amine (Scheme 3, reaction 1). Based on mechanistic considerations, base promoted β-elimination might be one of the sources for side reactions, so the insoluble base Ag_2CO_3 was used in the hope of avoiding the postulated β-elimination. Unfortunately, the reaction was appreciably slower and the yield was even lower (Scheme 3, reaction 2). The TLC of this reaction was not as clean as the previous reaction.

Both reactions were quite clean and rapid at the outset, and reached ~50% completion after the first 30 minutes. It took 1.5-2 hours for the first reaction to complete; but it required 12 hours for the second reaction to fully consume starting material. The most reasonable explanation for this observation was that secondary amine **6** was competitively serving as a base in both reactions. By the time the reactions reached 50% completion, the remaining 50% of the amine moiety of **6** was partially protonated in the case of NEt_3; and almost completely protonated in the case of Ag_2CO_3, thereby rendering the remaining starting material non-nucleophilic even though the π-allyl palladium complex was being formed. Therefore, it seemed logical to consider using a stronger base rather than NEt_3. However, the base cannot be too strong, otherwise it will foster β-elimination. In addition, the base itself should not be a nucleophile, or it will add to the π-allyl palladium complex. After considering a multitude of bases, tetramethylguanidine[8] (TMG) appeared most attractive. It is about 2-3 pKa units more basic than triethylamine, but is not generally regarded as being a good nucleophile. In the event, when the reaction was run in the presence of 1.1 eq of TMG, the reaction was complete within 30 minutes and the yield of the desired product was nearly quantitative.[9] This appears to be the first example of using TMG as a base in palladium-mediated amination reactions, and clearly deserves further investigation (also see Table, entry 4b). The stereochemistry of compound **7** was based upon nOe experiments of a tetracyclic derivative.[10]

Scheme 3



6 PMB = p-methoxybenzyl **7**

	BASE	
Reaction 1	NEt_3 (1.1 eq), 2 h	**7** 64% + unidentified product
Reaction 2	Ag_2CO_3 (2 eq), 12 h	**7** 50% + many side products
Reaction 3	TMG (1.1 eq), 0.5 h	**7** 98%

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References and Notes

[1] Syntheses via vinyl sulfones 66.

[2] Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

[3] Jin, Z.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 5205.

[4] Inami, H.; Ito, T.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1993**, *34*, 5919 and references cited therein.

[5] (a) Godleski, S. A.; Meinhart, J. D.; Miller, D. J.; Van Wallendael, S. *Tetrahedron Lett.* **1981**, *22*, 2247; (b) Godleski, S. A.; Heacock, D. J.; Meinhart, J. D.; Van Wallendael, S. *J. Org. Chem.* **1983**, *48*, 2101; (c) Carruthers, W.; Cumming, S. A. *J.Chem.Soc. Chem. Commun.* **1983**, 360.

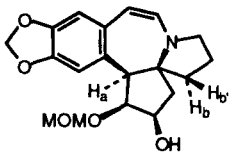
[6] (a) Trost, B. M.; Schmuff, N. R.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 5979; (b) Mandai, T.; Matsumoto, T.; Tsuji, J. *Synlett.* **1993**, 113 and references cited therein.

[7] Tertiary sulfones bearing the aminopropyl moiety were prepared via base-catalyzed phase transfer isomerative alkylation of the corresponding vinyl sulfones via reaction of acrylonitrile followed by nitrile reduction and reductive amination: See Jin, Z., Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 0000, preceding paper.

[8] Angyal, S. J.; Warburton, W. K. *J. Chem. Soc.* **1951**, 2492.

[9] **Experimental:** Secondary amine **6** (0.0264 mmol, 18 mg), $Pd(PPh_3)_4$ (0.1 eq, 0.00264 mmol, 3 mg), and tetramethyl guanidine (1.0 eq, 0.0264 mmol, 0.38M in CH_3CN, 0.069 mL) was dissolved in 2 mL of degassed CH_3CN. The reaction mixture was heated to reflux for 30 min. After removal of the solvent, the crude residue was purified by flash column chromatography on silica gel (15% ethyl acetate in hexanes) to afford 14 mg of product **7** (98%). ^1H NMR (300 MHz, C_6D_6): δ 7.38 (1H, s), 6.92 (1H, s), 6.88 (1H, d, *J*=8.6 Hz), 6.82 (1H, d, *J*=8.6 Hz), 5.94 (1H, m), 5.81 (1H, m), 5.21 (1H, s), 5.19 (1H, s), 4.85 (1H, t), 4.72 (1H, d, *J*=6.5 Hz), 4.37 (1H, AB, *J*=6.7 Hz), 4.26 (1H, AB, *J*=6.7 Hz), 4.03 (1H, AB, *J*=13.2 Hz), 3.71 (1H, d, *J*=6.5 Hz), 3.34 (1H, ABX), 3.27 (3H, s), 3.17 (1H, AB, *J*=13.2 Hz), 3.13 (1H, ABX), 2.95 (3H, s), 2.85-2.55 (5H, m), 2.17 (1H, m), 1.78-0.78 (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$):δ 158.5 (e), 146.0 (e), 145.7 (e), 139.1 (o), 133.5 (e), 133.1 (e), 132.6 (o), 129.6 (o), 113.7 (o), 112.8 (o), 110.3 (o), 101.1 (e), 96.7 (e), 81.9 (o), 78.4 (e), 56.3 (e), 56.0 (o), 55.7 (o), 55.5 (o), 55.1 (o), 54.4 (e), 43.5 (e), 40.1 (e), 39.2 (e), 38.9 (e), 24.1 (e). MS (EI): 541 (M^+), 121 (base peak). MS (CI): 542 (M+H, base peak), 510 (M+H-$HOCH_3$).HRMS (EI): calculated for $C_{29}H_{35}O_5S_2$ 541.1957, found 541.1946.

[10] Z. Jin, unpublished results. The synthesis of derivative **11** will be eventually published in a subsequent full paper discussing the total synthesis of symchiral cephalotaxine **8**.



11 nOe irr. $H_a \Rightarrow H_bH_{b'}$ = 38%

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