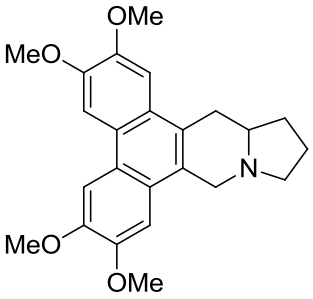
Palladium-catalysed carboamination and carboetherification

Tylophorine is an alkaloid that was first isolated in 1935 from the perennial climbing plant *Tylophora indica* and has recently re-emerged as an alkaloid target family of interest, due largely to its cytotoxic activity by a novel mechanism of action. 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).

Correlate the characterisation of the racemate to its stucture.

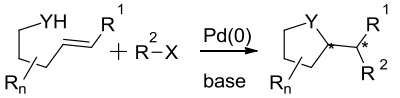


mp 230 ºC (dec); 1H NMR (500 MHz, CDCl3) δ 7.84 (s, 2H), 7.32 (s, 1H), 7.17 (s, 1H), 4.63(d, J = 14.5 Hz, 1H), 4.09 (s, 6H), 4.06 (s, 6H), 3.68 (d, J = 14.6 Hz, 1H), 3.50–3.47 (m, 1H), 3.40–3.36 (m, 1H), 2.94–2.89 (m, 1H), 2.51–2.44 (m, 2H), 2.27–2.22 (m, 1H), 2.07–2.02 (m, 1H), 1.95–1.91 (m, 1H), 1.82–1.76 (m, 1H); 13C NMR (75 MHz, CDCl3 + CD3OD) δ 148.8, 148.7, 148.6, 126.2, 125.8, 125.5, 124.3, 123.8, 123.6, 104.1, 103.6, 103.5, 103.2, 60.4, 56.1, 56.0. 55.9, 55.0, 53.9, 33.4, 31.0, 21.5; IR (KBr) 1618, 1512, 1467, 1444, 1425 cm-1; MS (ESI) m/z 394 [M+H]+; HRMS (ESI) m/z 394.1999 [M+H]+ (394.2018 calculated for C24H27NO4+H).

In the past decade, a number of concise synthetic preparations of racemic tylophorine have appeared in the literature.

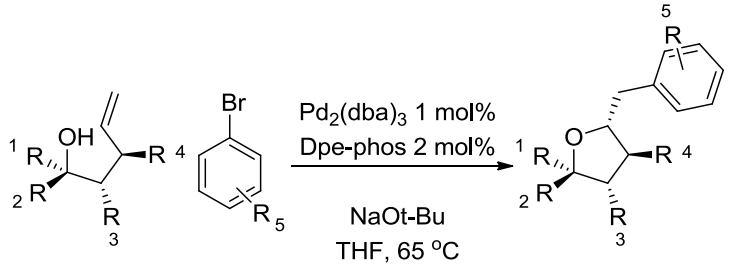
Give a retrosynthetic analysis of the racemate.

John Wolfe (U. Michigan) has been working for years on the stereoselective synthesis of saturated heterocyles *via* palladium-catalysed alkene carboetherification and carboamination.

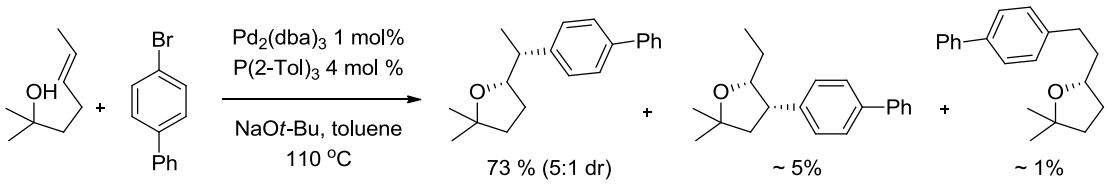


Armed with your knowledge on palladium reactivity towards the moieties present in the above example (Y = O, NR), please account for all plausible mechanisms affording the drawn product (you should find 5 of them). Explicit the stereochemistry.

Below are reported the outcome of several experiments of carboetherification.

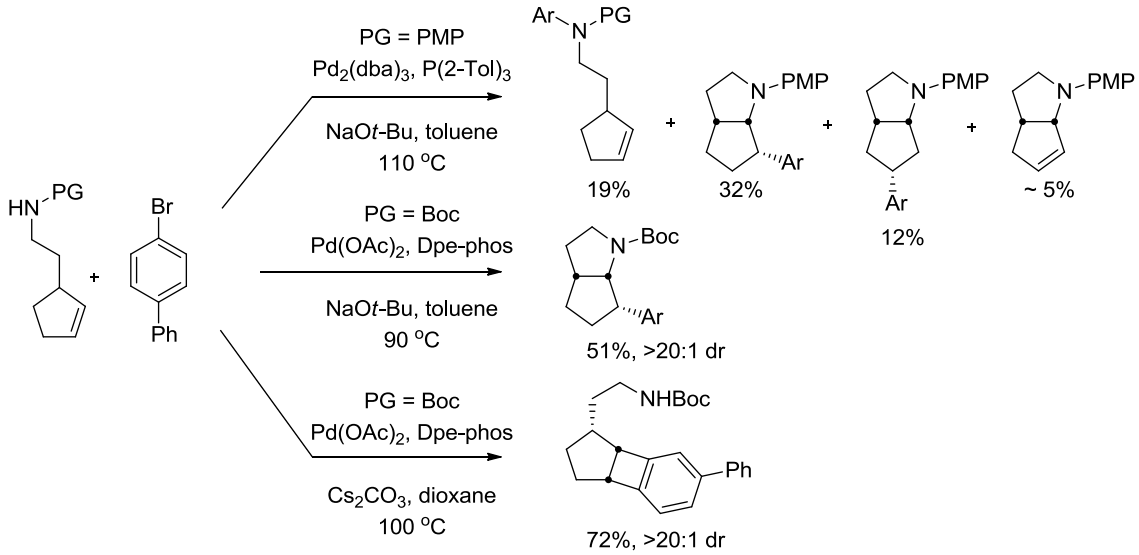


Entry	R^1	R^2	R^3	R^4	R^5	Diast. Ratio	Yield (%)
1	H	Ph	H	H	4-OMe	>20:1	62
2	Me	Ph	H	H	4-*t*-Bu	>20:1	77
3	Me	Me	H	Me	4-Ph	8:1	78
4	H	H	Ph	H	3-OMe	2:1	84
5	$(CH_2)_4$		H	H	2-Me	-	60
6	H	$(CH_2)_4$		H	4-Ph	>20:1	70



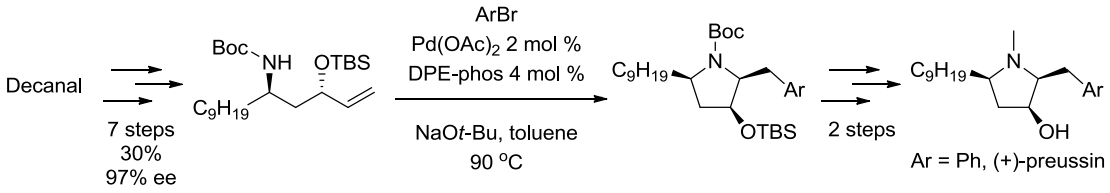
From this, rule out 4 of the mechanisms you have found in the previous question to keep only one.

In many aspects, Pd-catalysed carboaminations are quite similar to carboetherifications, but not completely. When Wolfe *et al.* examined the transformation of *N*-protected 2 cyclopent-2-enylethanamine, they obtained the following:



Account for the mechanisms affording these different products. How would you choose the ligands if you wanted to tune the top reaction to yield mainly each of the product?

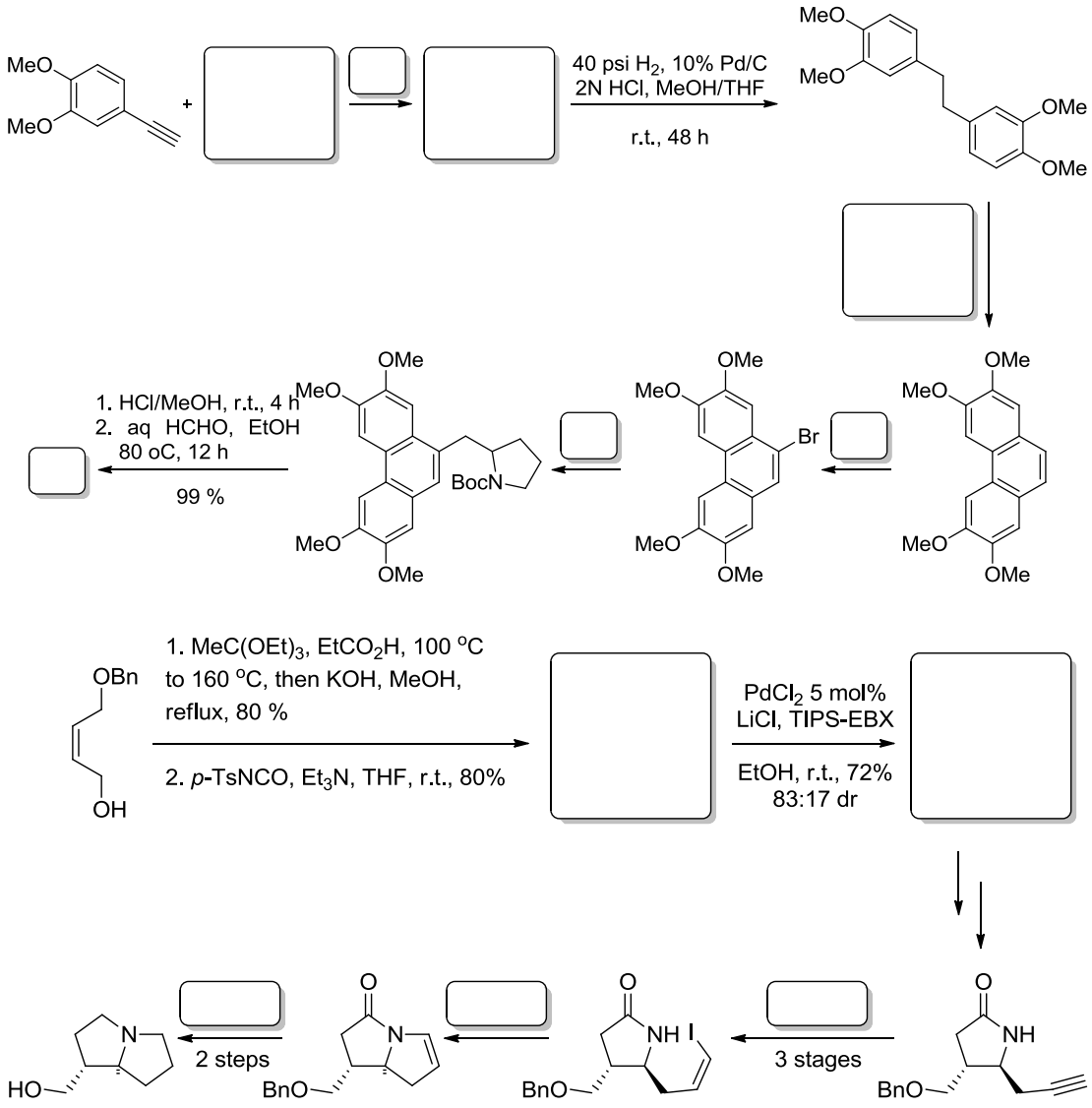
The synthesis of (+)-Preussin and its analogues raise interesting questions about the stereocontrol in the carboamination reaction of complex subtrates.



Rationalise the stereochemical outcome of the carboamination reaction. How would you complete the rest of the synthesis?

The two following racemic natural products were also synthesised *via* this strategy.

Complete the synthesis pathway and account for mechanisms. Give the name of the transformations if they have one.



TIPS-EBX = 1-{[Tris-(1-methylethyl)silyl]ethynyl]}-1,2-benziodoxol-3(1H)-one

References: Wolfe, 10.1055/s-0028-1087339; Wolfe, 10.1021/ol0606435; Waser, 10.1002/anie.201100718; Herr, 10.1021/jo902114u