Literature Report

Changbin Yu 2014-09-23 检查: 任圆圆

A catalytic asymmetric total synthesis of (-)-perophoramidine

B. M. Trost. *et al*. *Chem. Sci.* **2014***, 5,* Doi：c4sc01826e

Prof. Barry M. Trost

B.S. Degree University of Pennsylvania, **1962**

Ph.D. Degree Massachusetts Institute of Technology, **1965**

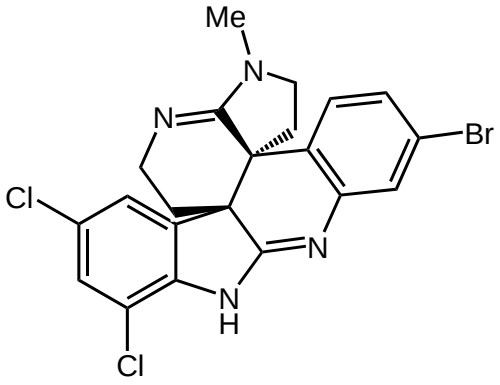
Research Interests

Our research program revolves around the theme of synthesis. There are two major activities:

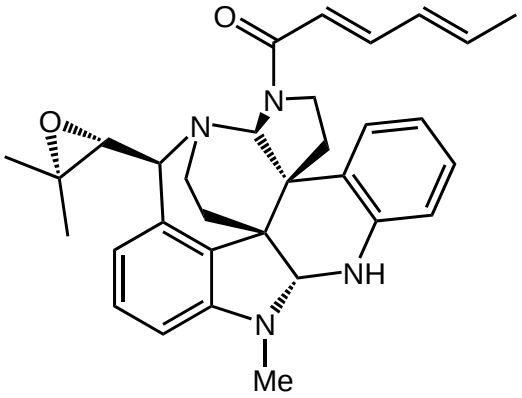
1) developing the tools, i.e., the reactions and reagents.

2) creating the proper network of reactions to make complex targets readily available from simple starting materials..

(-)-Perophoramidine (1) and (-)-communesin B (2)



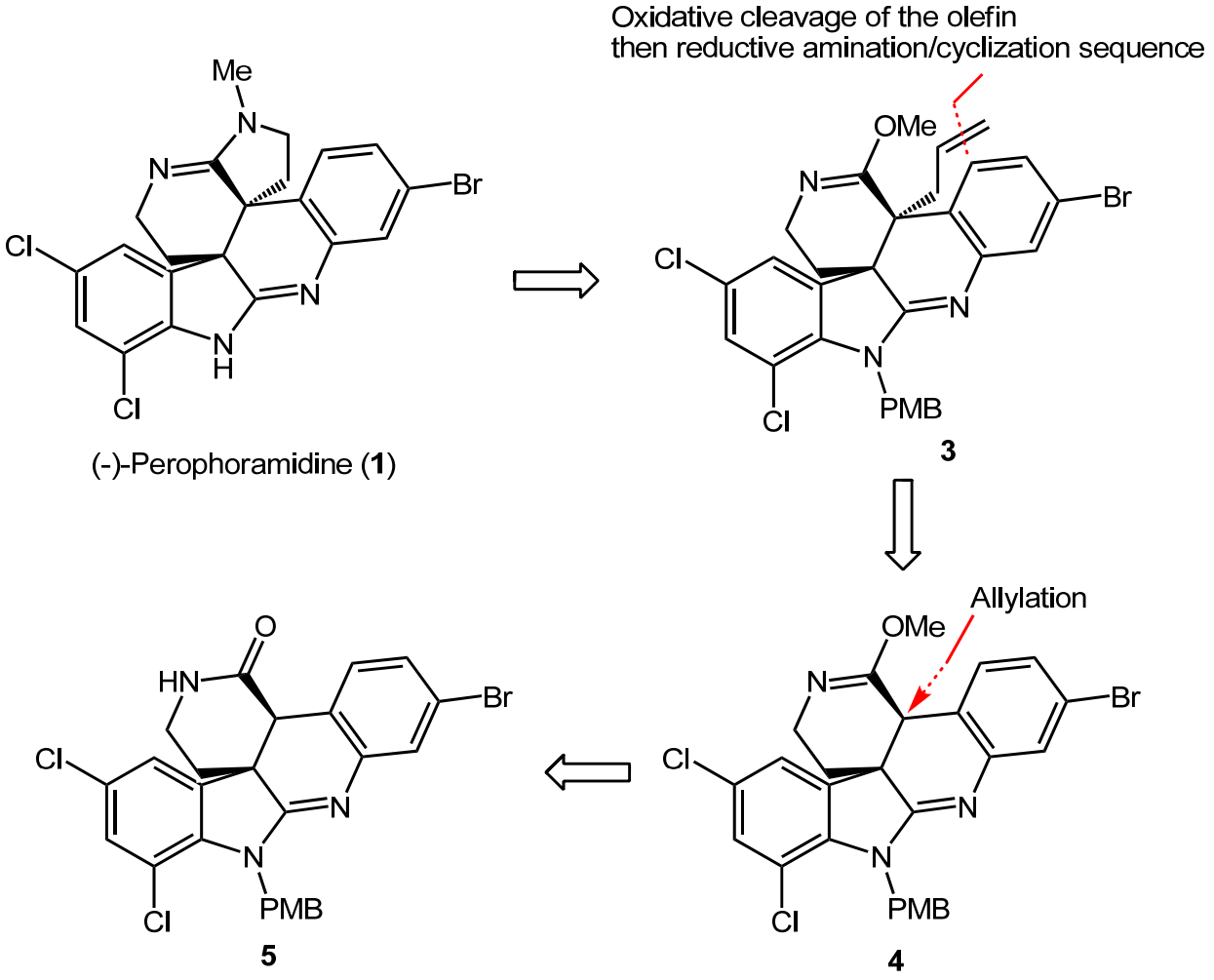
(-)-Perophoramidine (**1**)



(-)-communesin B (**2**)

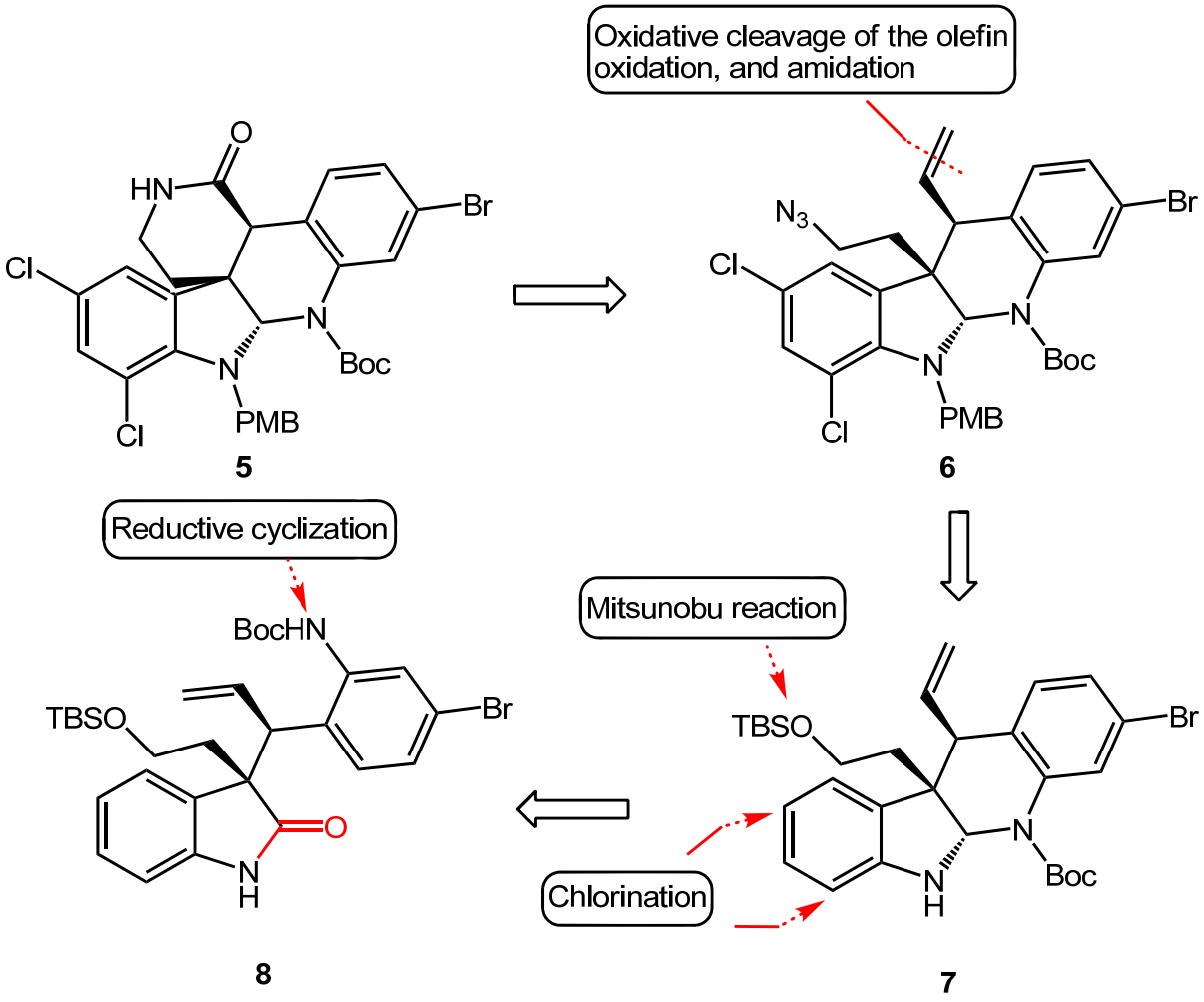
B. M. Trost. *et al*. *Chem. Sci.* **2014***, 5,* Doi：c4sc01826e

Retrosynthetic Analysis for (-)-Perophoramidine (1)



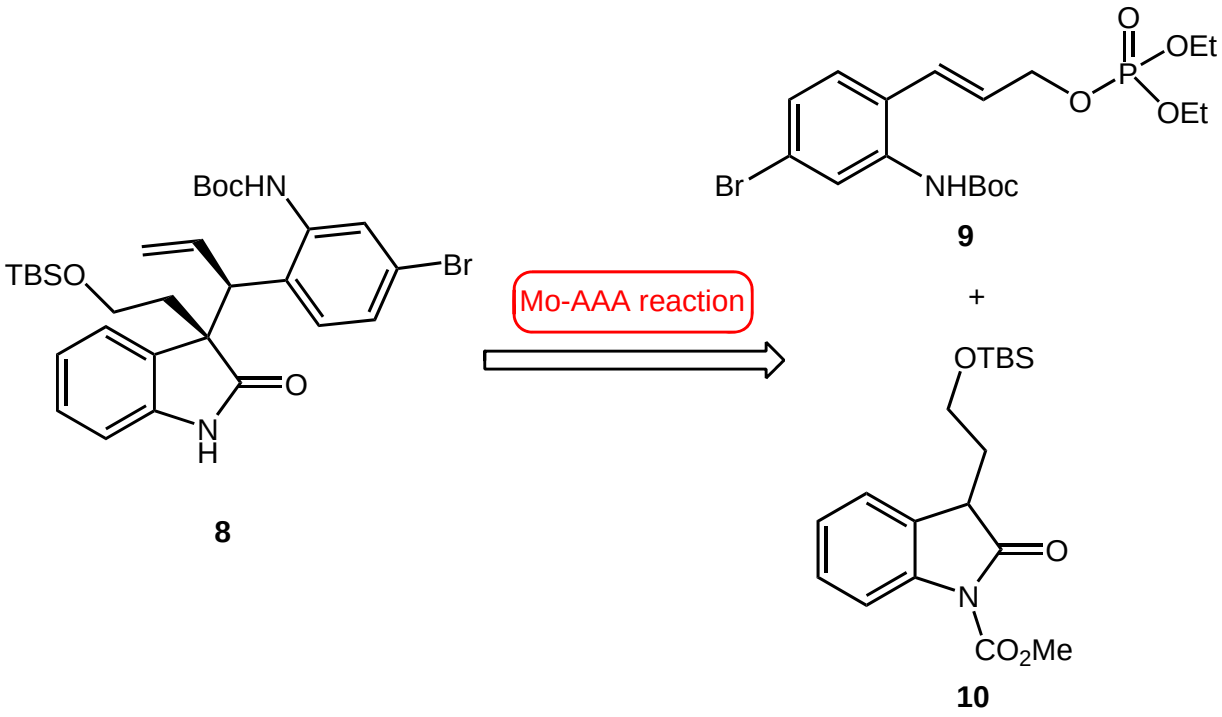
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5*, Doi：c4sc01826e

Retrosynthetic Analysis for (-)-Perophoramidine (1)



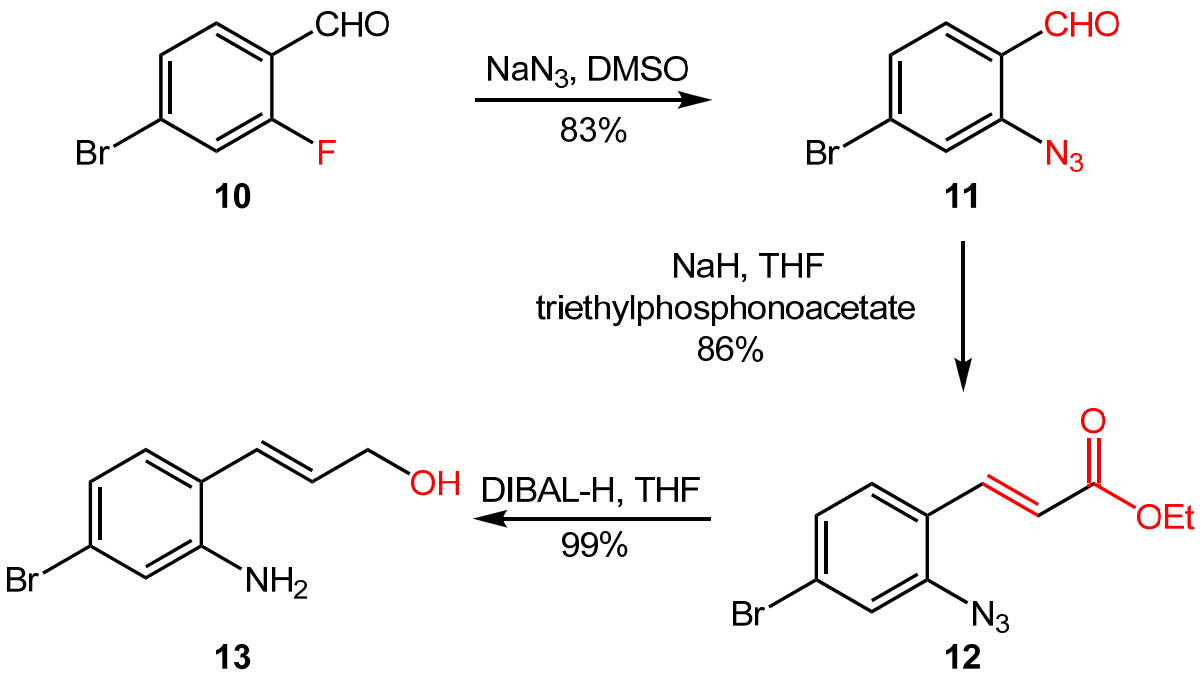
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5*, Doi：c4sc01826e

Retrosynthetic Analysis for (-)-Perophoramidine (1)



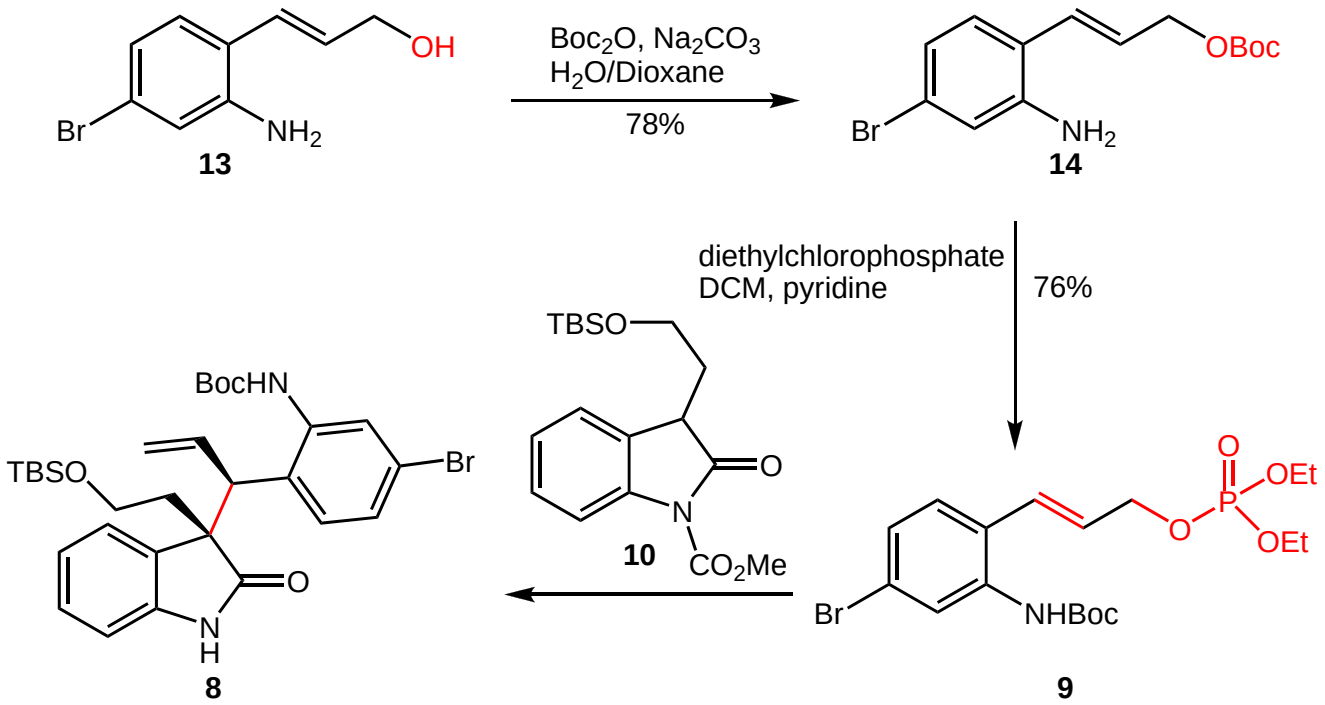
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5,* Doi：c4sc01826e

Synthesis of allylic phosphate 9



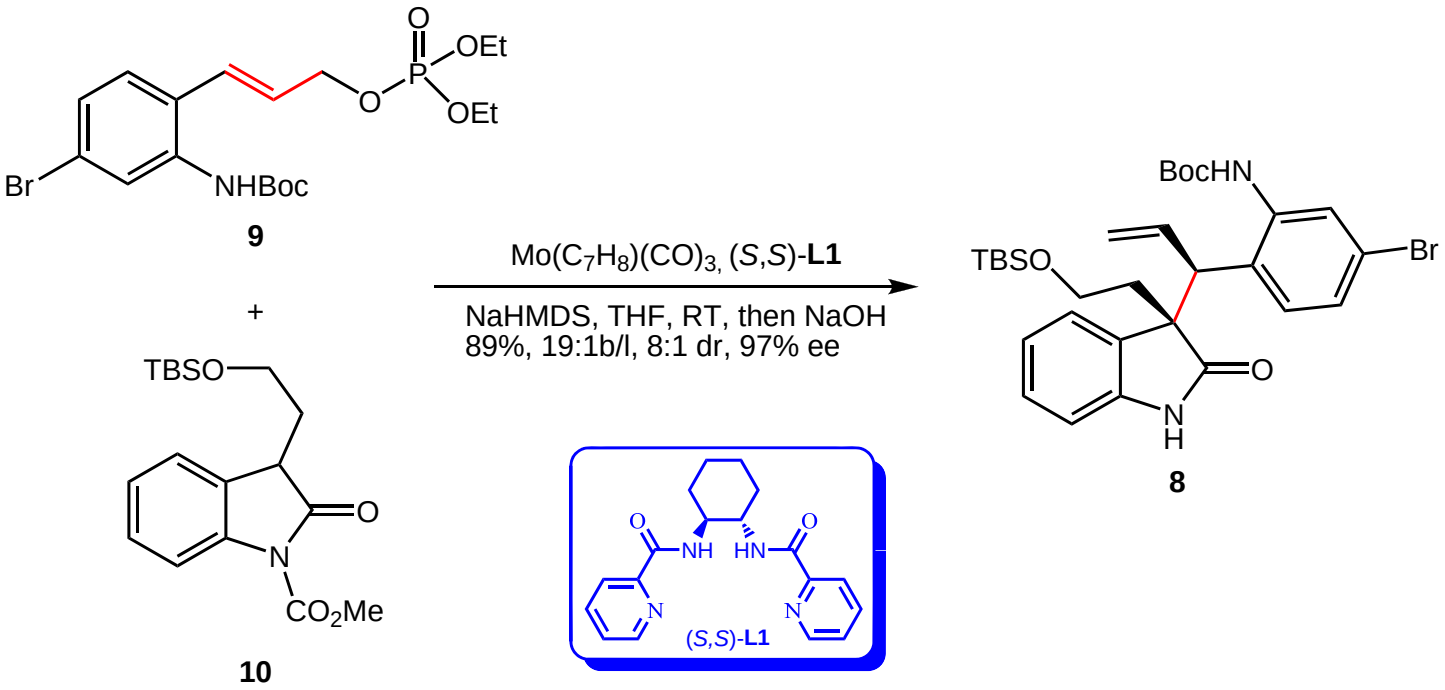
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5,* Doi：c4sc01826e

Synthesis of allylic phosphate 9



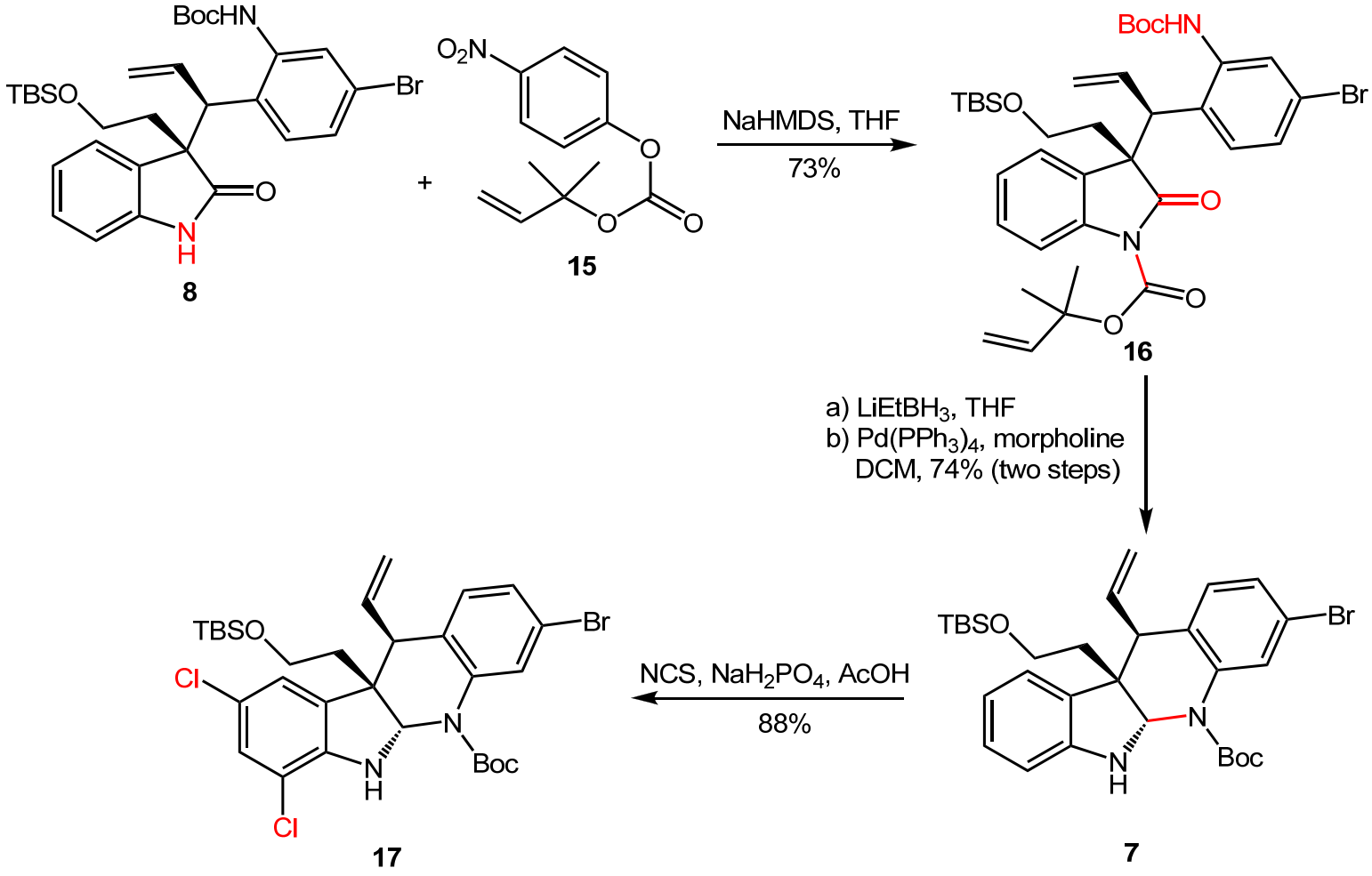
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5,* Doi：c4sc01826e

Mo-AAA



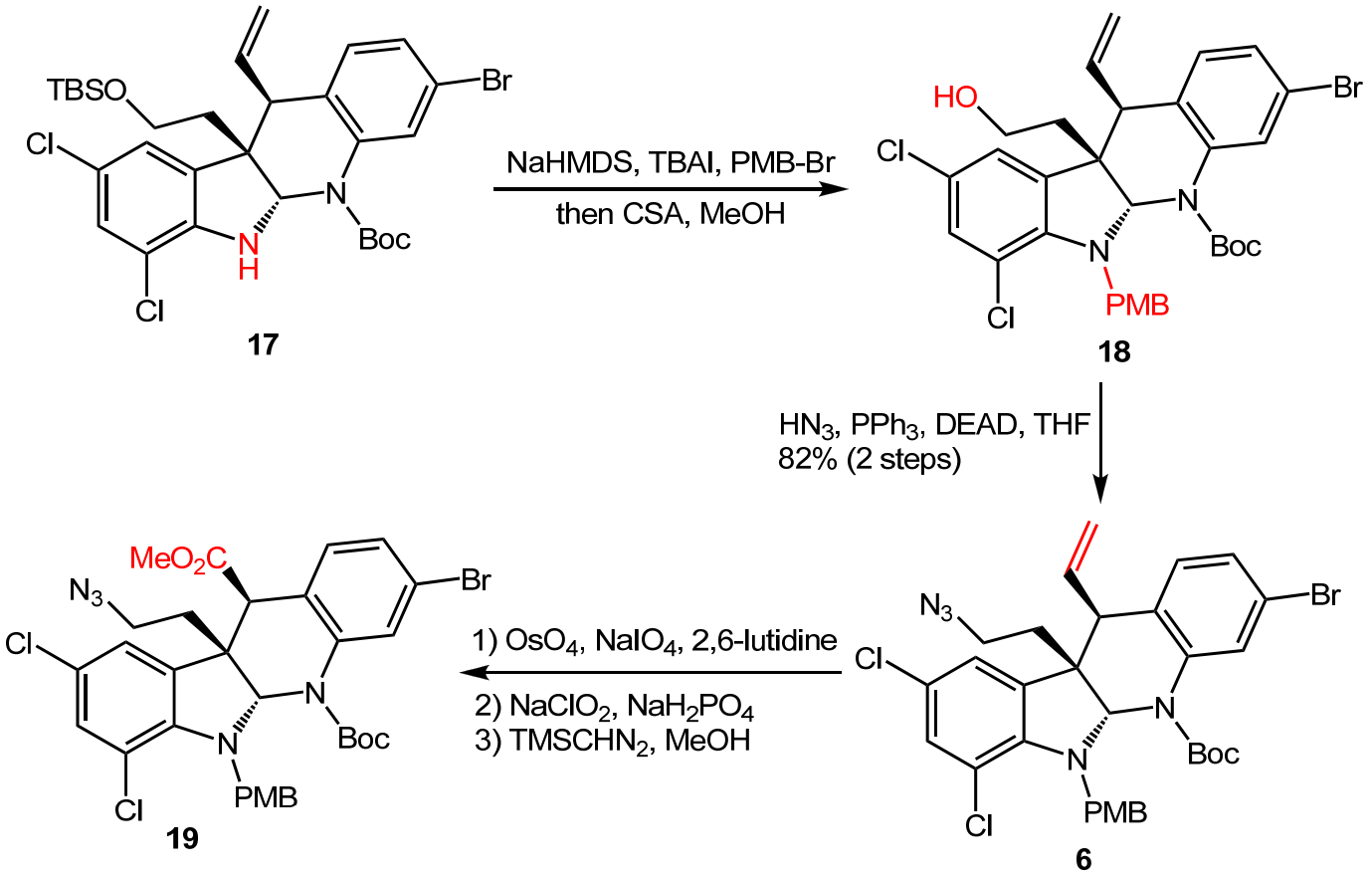
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5,* Doi：c4sc01826e

Synthesis of Lactam 5



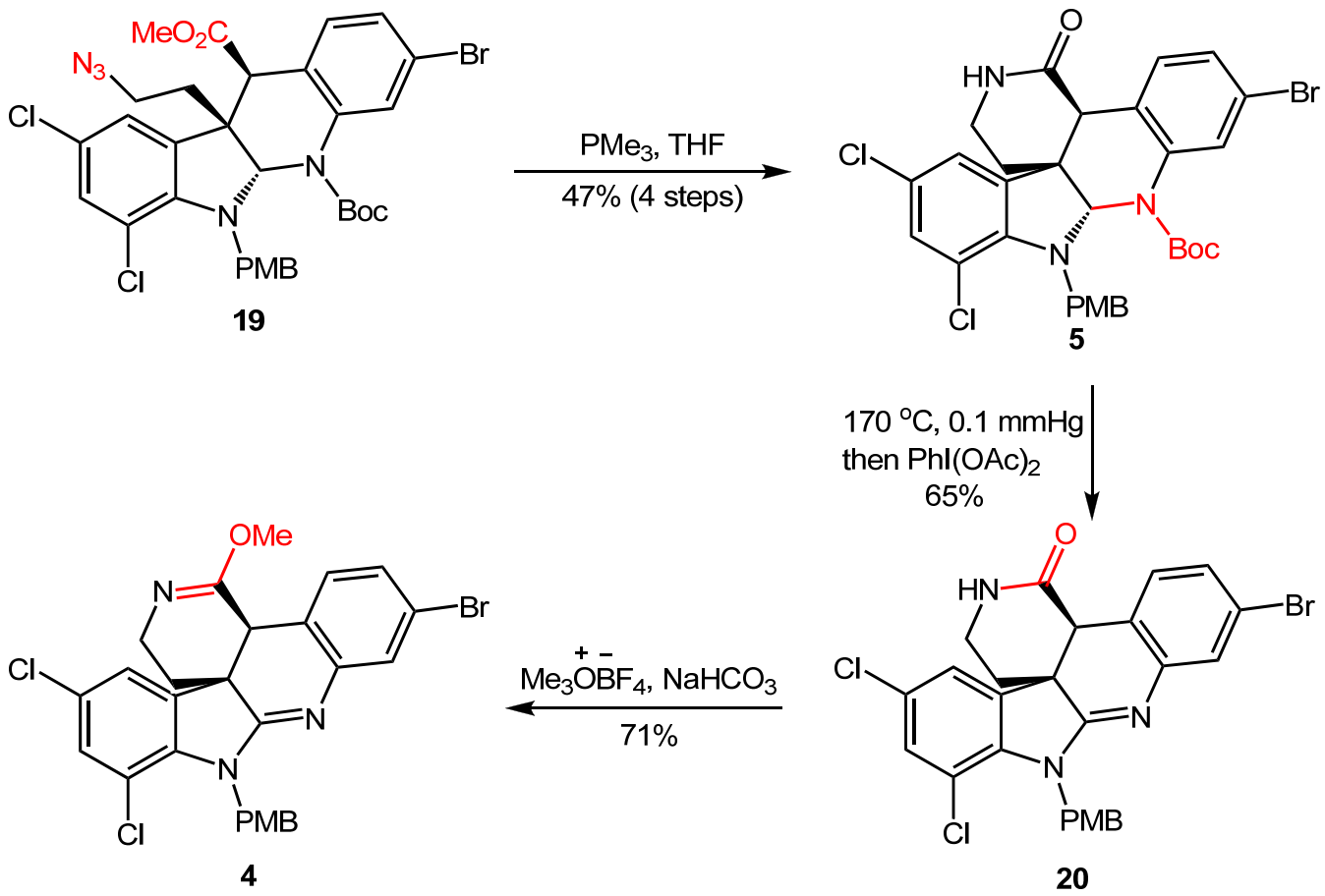
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5,* Doi：c4sc01826e

Synthesis of Lactam 5



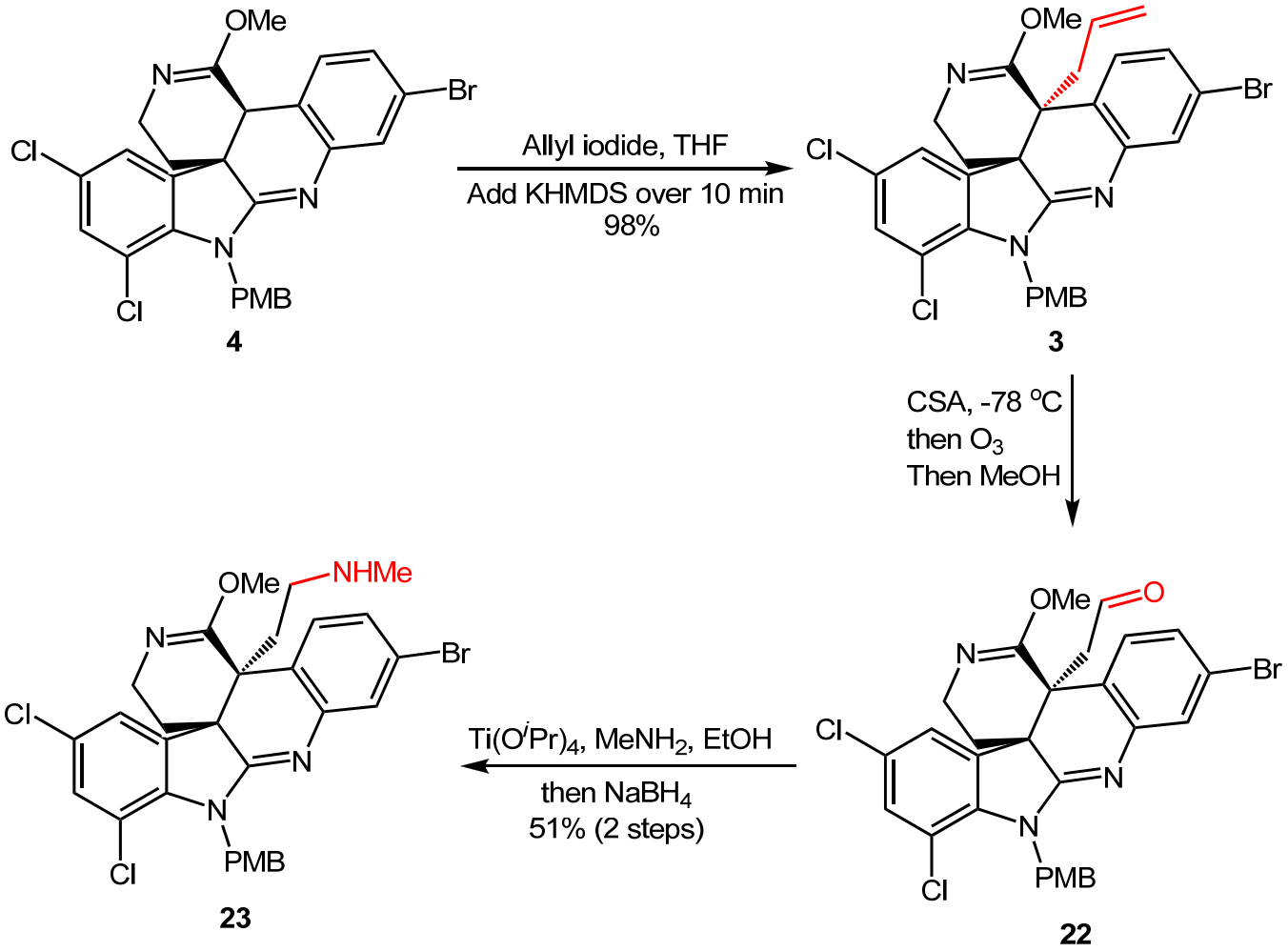
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5,* Doi：c4sc01826e

Synthesis of Lactam 4



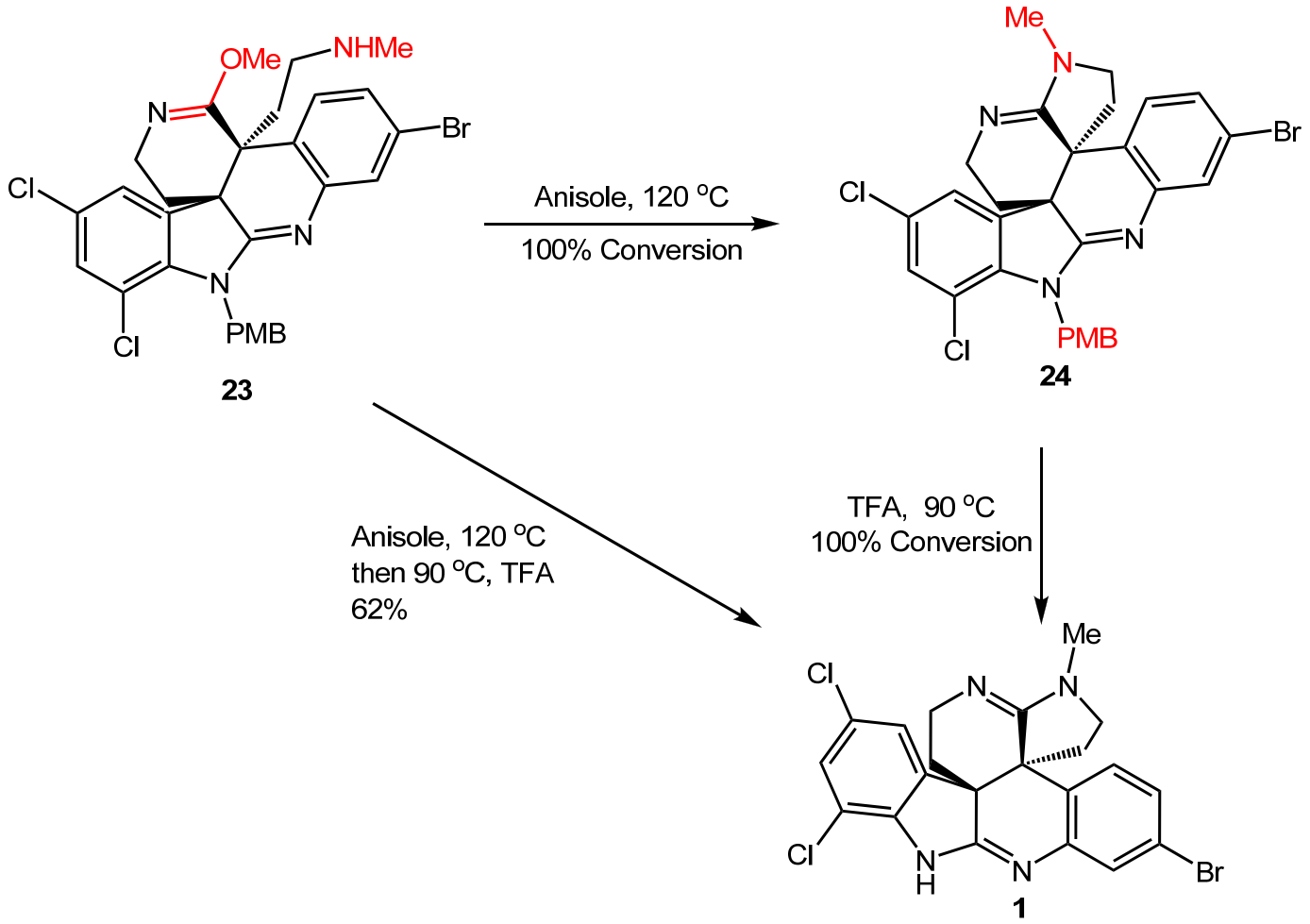
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5*, Doi：c4sc01826e

Synthesis of amine 23

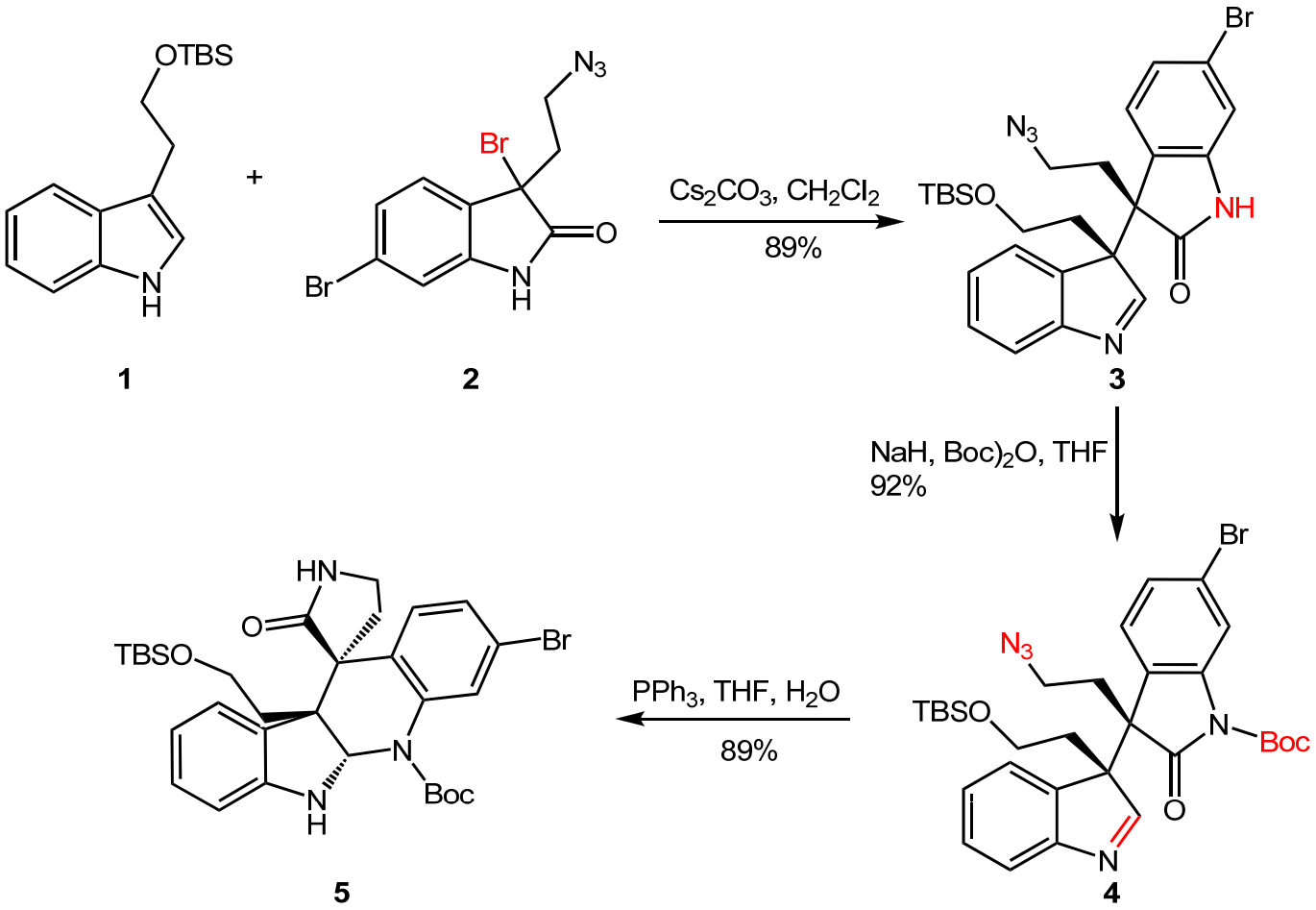


B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5*, Doi：c4sc01826e

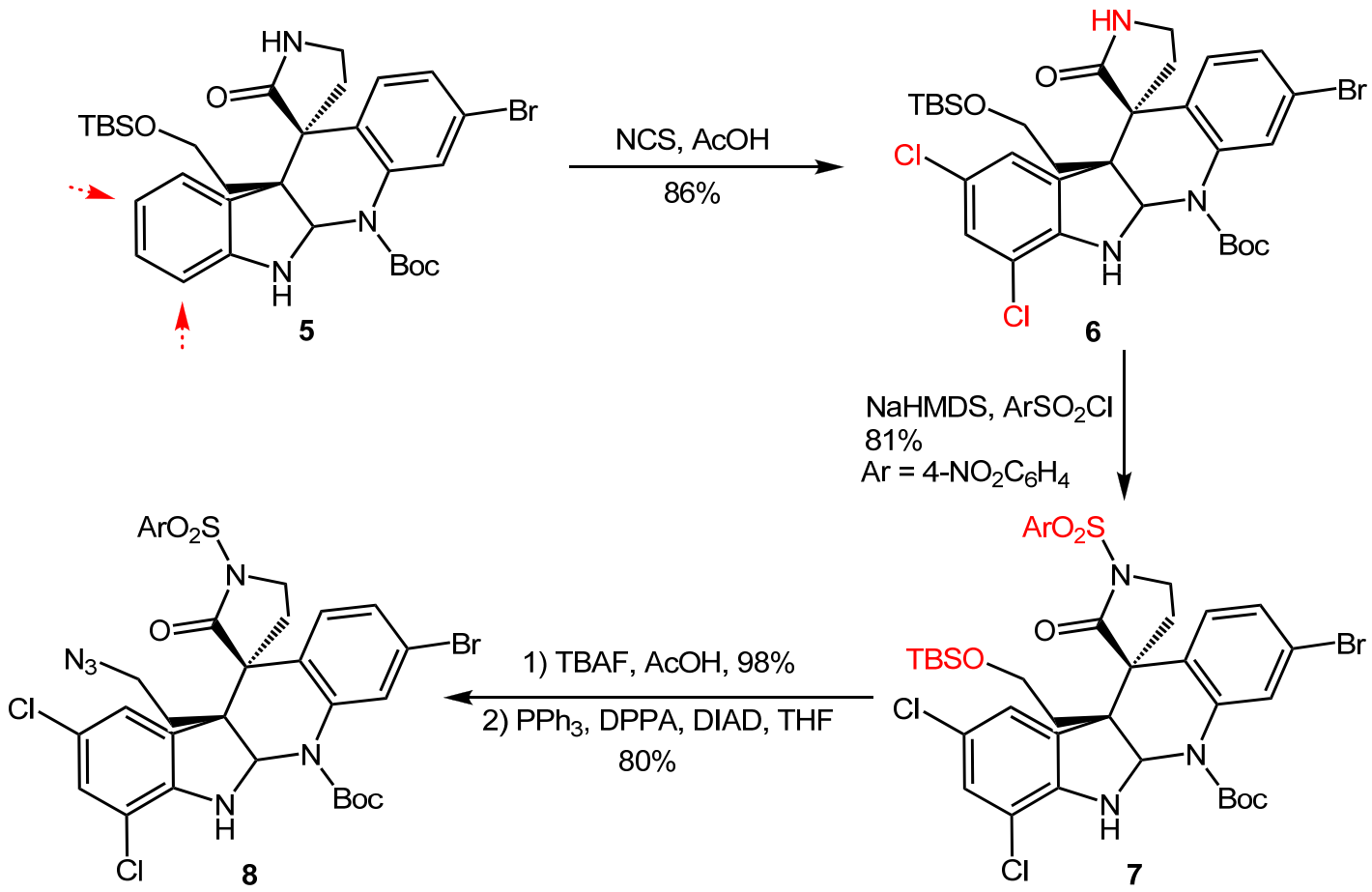
Completion of the total synthesis



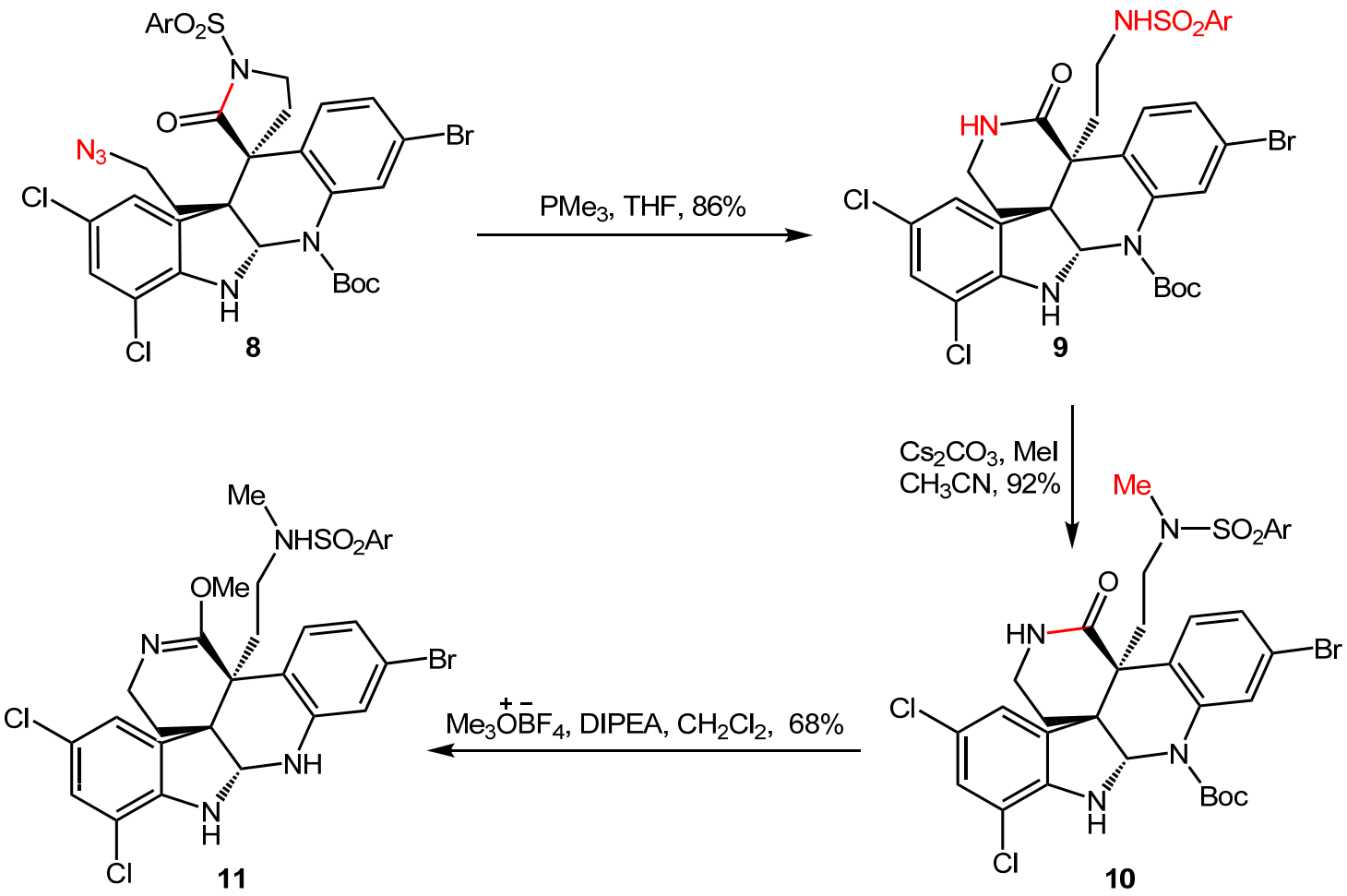
B. M. Trost. *et al*. *Chem. Sci.* **2014**, *5,* Doi：c4sc01826e



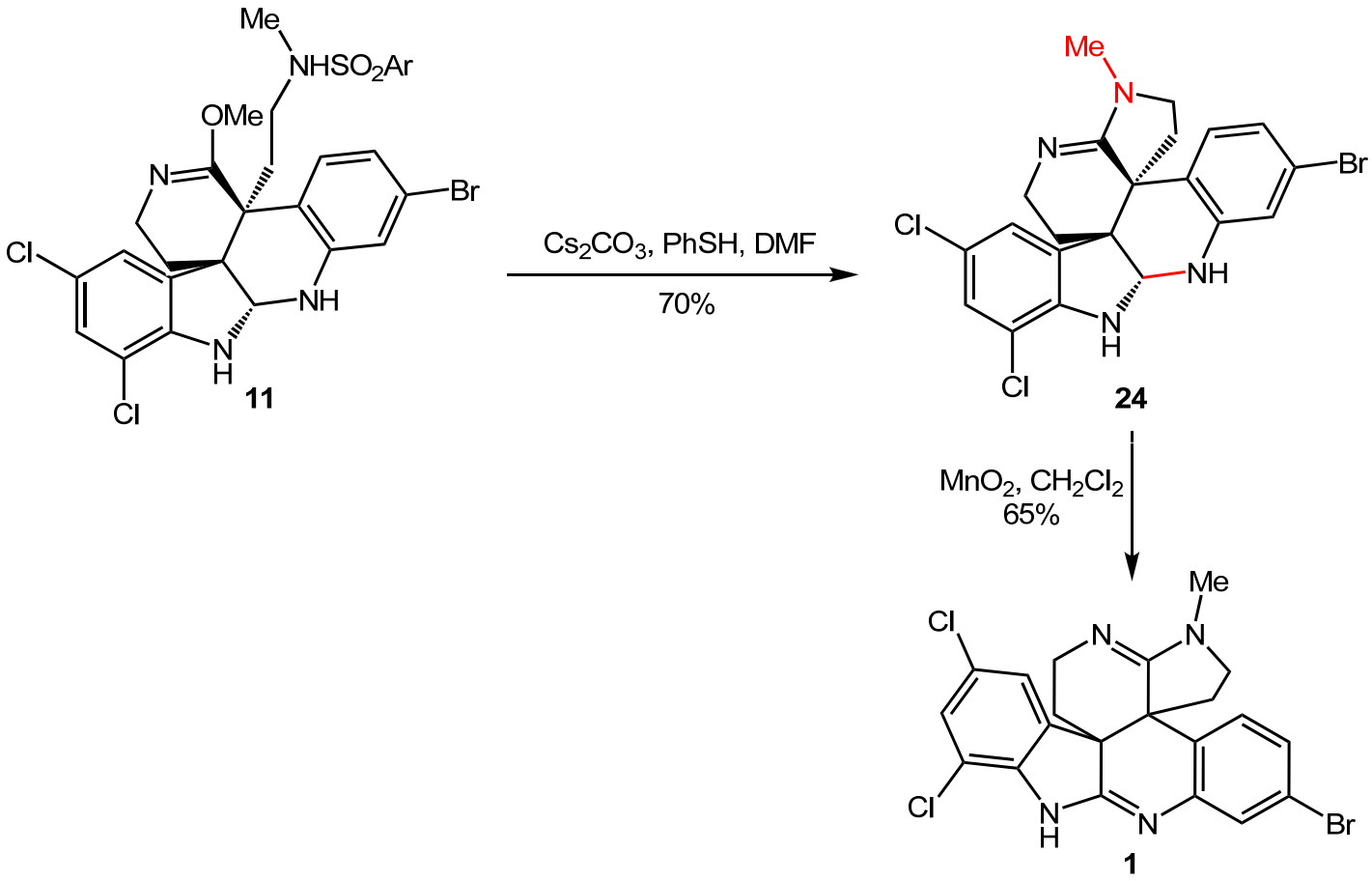
R. L. Funk. *et al*. *J. Am. Chem. Soc.* **2004**,*126*, 5068-5069



R. L. Funk. *et al*. *J. Am. Chem. Soc.* **2004**,*126*, 5068-5069



R. L. Funk. *et al*. *J. Am. Chem. Soc.* **2004**,*126*, 5068-5069



R. L. Funk. *et al*. *J. Am. Chem. Soc.* **2004**,*126*, 5068-5069

In 2002, Ireland and coworkers reported the isolation and structural elucidation of a novel polycyclic alkaloid, (+)-perophoramidine (**1**) from the Philippine ascidian organism Perophora namei. The structure of (+)-perophoramidine (**1**) was established using multidimensional NMR techniques, and the molecule was found to contain a densely functionalized hexacyclic structure containing two vicinal quaternary all carbon stereocenters, two amidines, and several points of halogenation on the aromatic nuclei. The skeletal connectivity of perophoramidine (**1**) is related to the Penicillium derived communesin alkaloids, such as communesin B (**2**). Unlike perophoramidine (**1**), the communesin alkaloids contain a benzazepine ring and bear two aminal functionalities in place of two amidines. Additionally, the relative relationship of the vicinal quaternary stereocenters in perophoramidine (**1**) is *trans* while that of the communesins is *cis*. From a biological perspective, perophoramidine (**1**) displays cytotoxicity against the HCT116 colon carcinoma cell line with an IC_{50} of 60 mM. The combination of its complex, densely functionalized structure and cytotoxic properties make perophoramidine (**1**) an attractive target for asymmetric total synthesis.

In summary, we have developed a catalytic asymmetric total synthesis of the alkaloid natural product (-)-perophoramidine (**1**). The route utilizes a regio- diastereo- and enantioselective Mo-AAA to construct one of the two vicinal quaternary carbon stereocenters present in the target. The second quaternary carbon stereocenter is constructed employing a regio- and diastereoselective allylation of an imino ether anion, which shows an unprecedented dependence of regioselectivity on the nature of the metal cation. With the potassium salt the reaction proceeds with complete regio- and diastereoselectivity for the desired product. Manipulation of the allyl moiety *via* oxidative cleavage, reductive amination, cyclization and protecting group cleavage are used to complete the synthesis. The strategy permits structural flexibility particularly at the quaternary stereocenters for analog synthesis.