Construction of Vicinal All-Carbon Quaternary Stereocenters: Total Synthesis of (+)-Perophoramidine

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Checker: Chang-Bin Yu

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Wang, R. *et al. J. Am. Chem. Soc.* **2013**, *135*, 14098.

作者简介

1982年毕业于兰州大学；

1988年获兰州大学与日本**Kyoto university**联合培养博士学位；

1990年～**1993**年先后在兰州大学和美国**university of Kansas**从事博士后研究；

1997年**Hong Kong Polytechnic University**高级访问学者；

1997年至今，兰州大学；

2004年被聘为教育部“长江学者”特聘教授；

2005年国家杰出青年科学基金获得者；

研究方向：多肽药物和手性药物的研究

王锐教授
兰州大学

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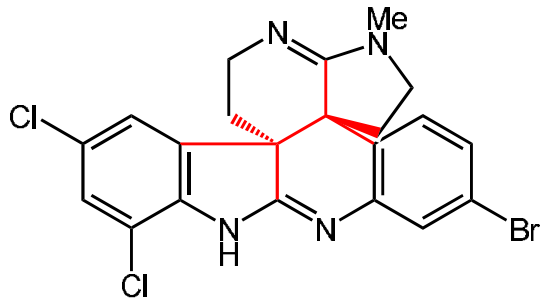
Introduction



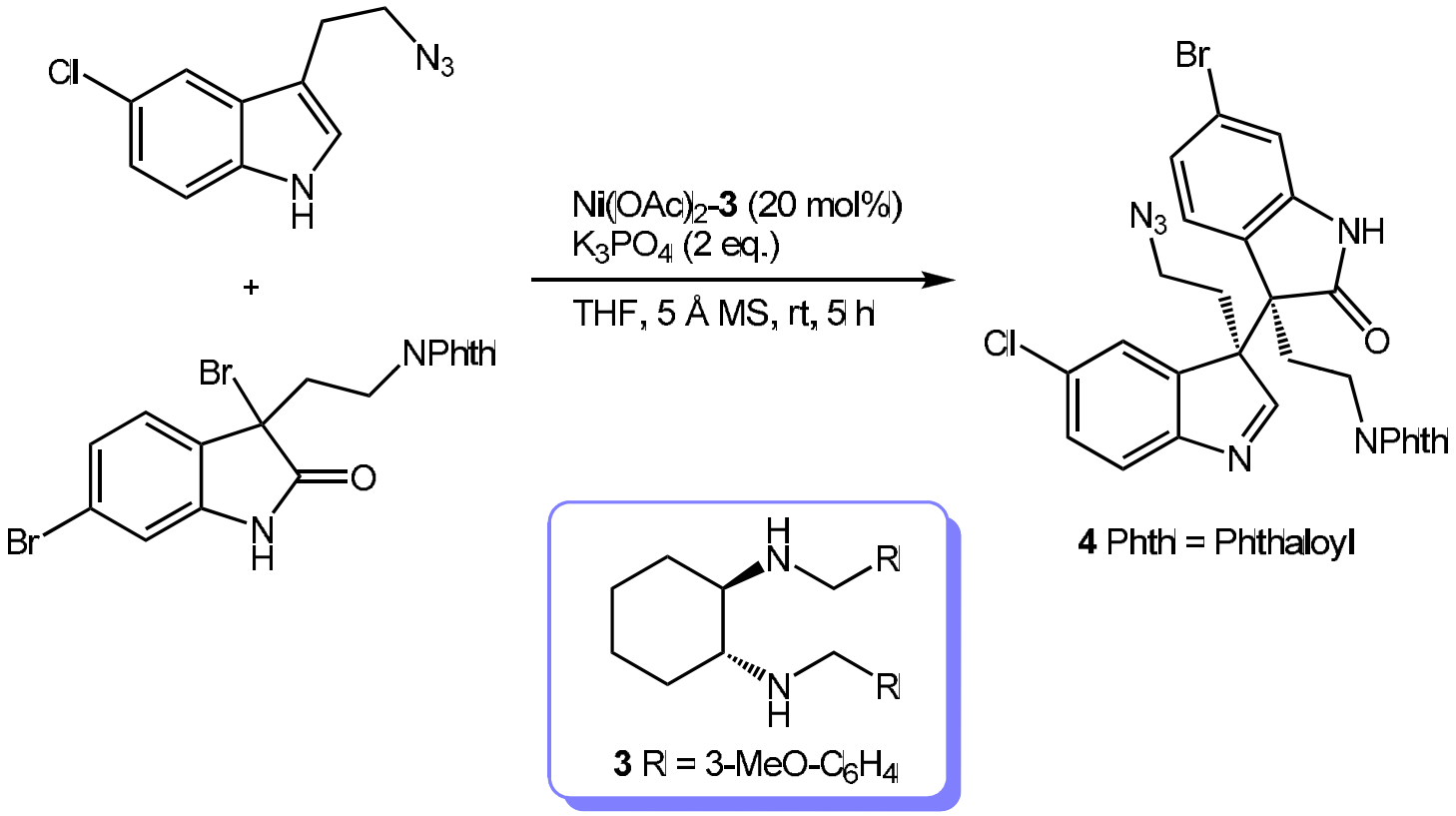
Perophoramidine

1. **Isolated from the ascidian *Perophora namei* in 2002**

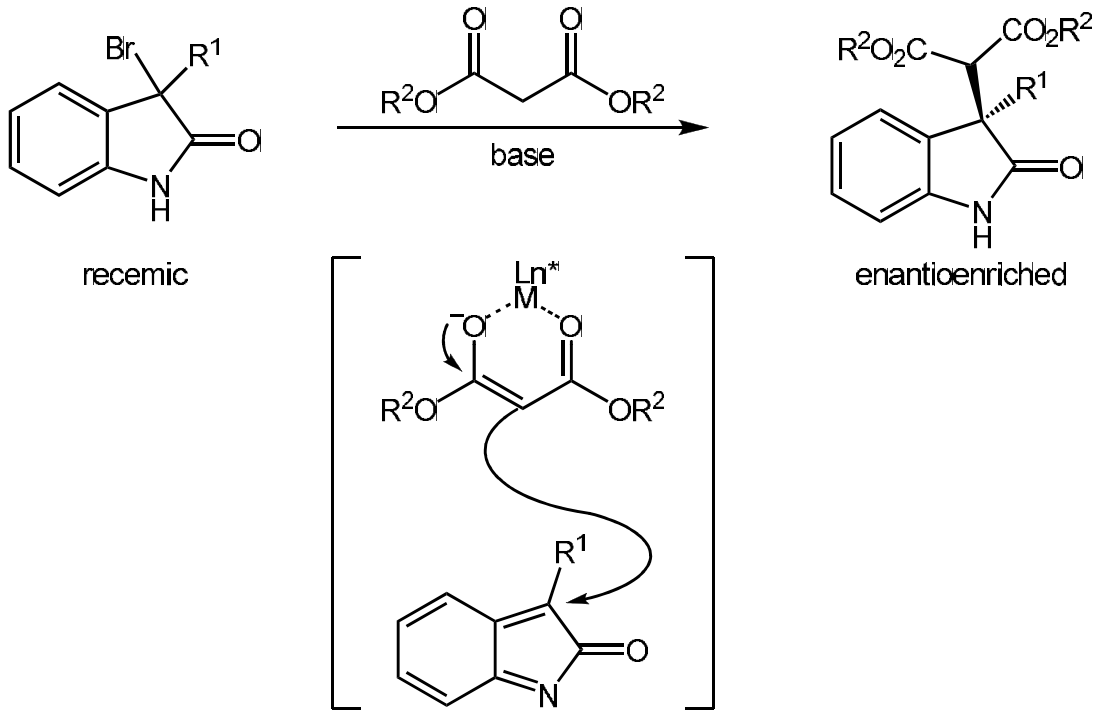
2. **(±)-(Dehalo)perophoramidine was synthesized in 2004**

3. **The asymmetric version was reported via chiral auxiliary-induced strategy in 2010**

Catalytic Asymmetric Alkylation Reaction

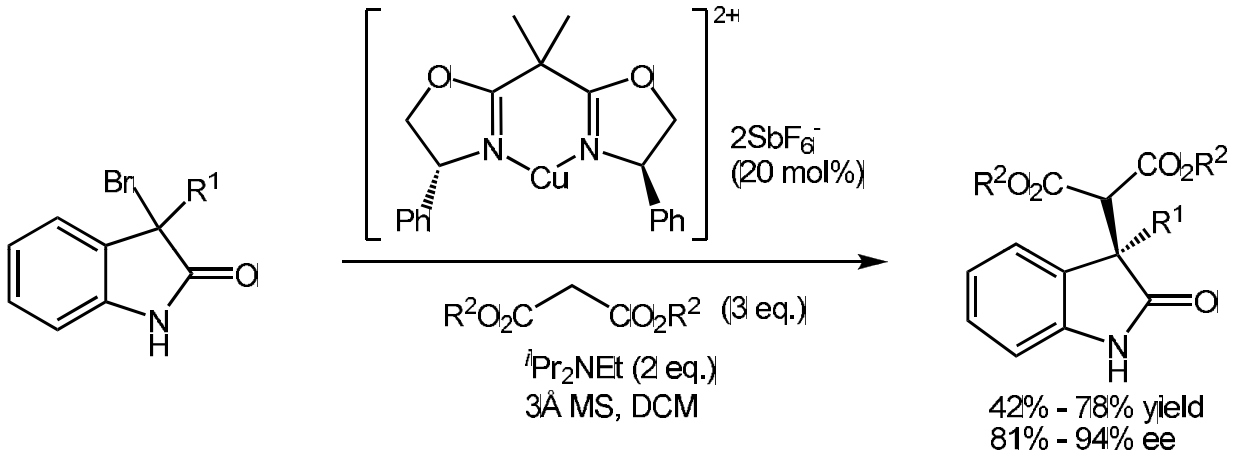


Catalytic Asymmetric Alkylation Reaction



Stoltz, B. M. *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 8037.

Catalytic Asymmetric Alkylation Reaction



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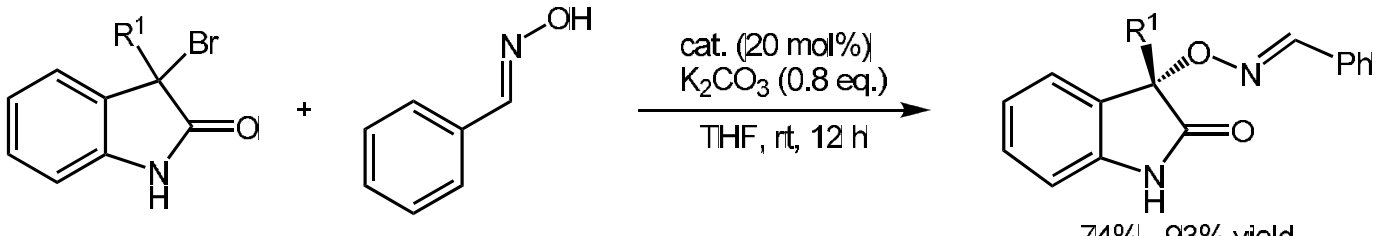
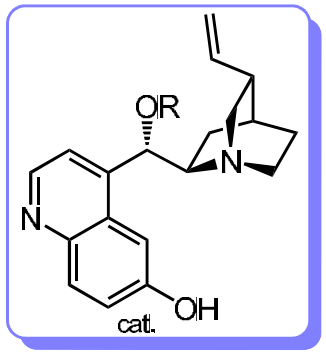
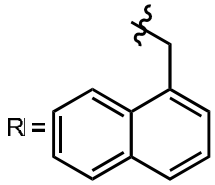
Catalytic Asymmetric Alkylation Reaction

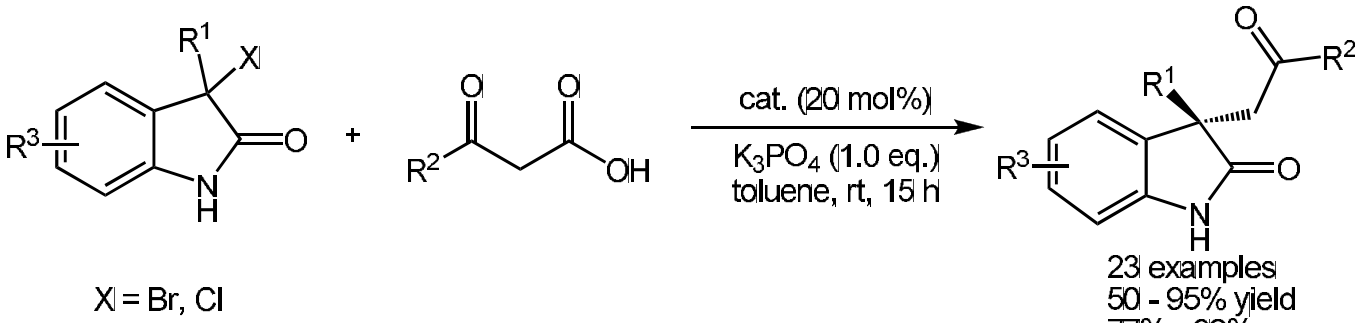


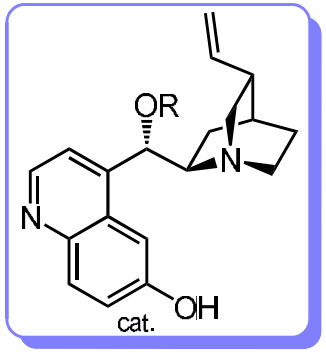


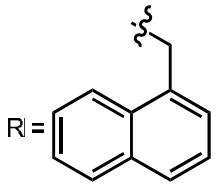


Yuan, W. C. *et al. Chem. Eur. J.* **2012**, *18*, 8916.

Catalytic Asymmetric Alkylation Reaction

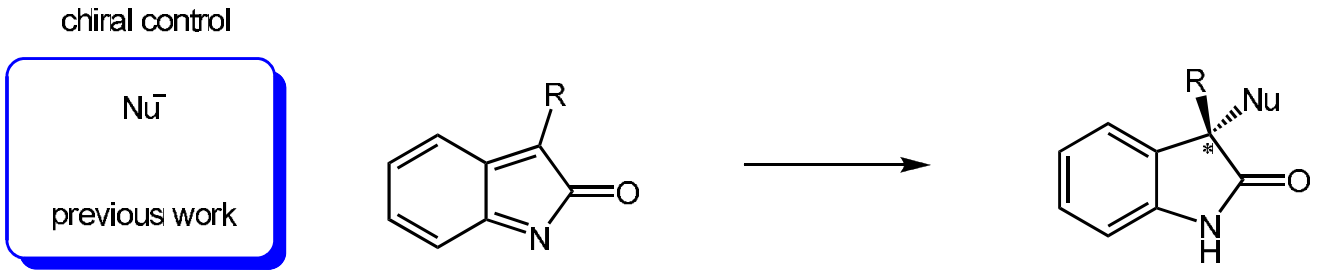




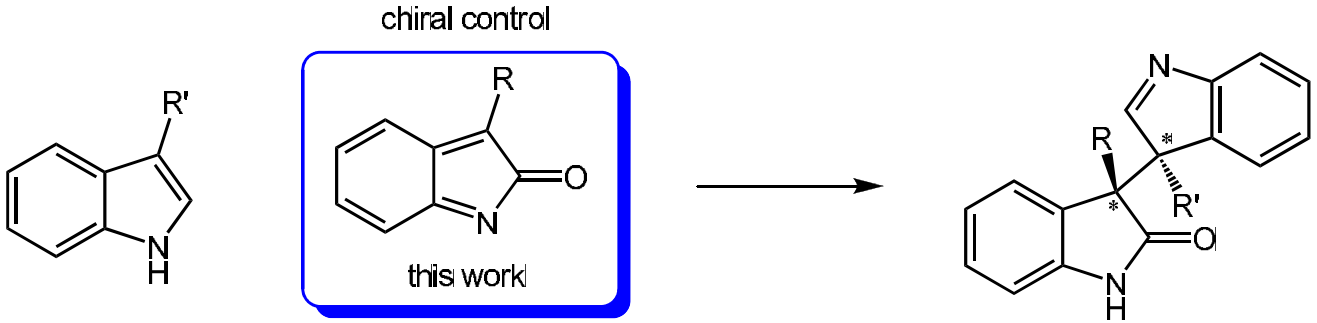


Yuan, W. C. *et al. J. Org. Chem.* **2012**, *77*, 11325.

Catalytic Asymmetric Alkylation Reaction



Chiral control by the activation of nucleophiles
One quaternary stereocenter



Chiral control by the activation of electrophiles
Vicinal all-carbon quaternary stereocenters

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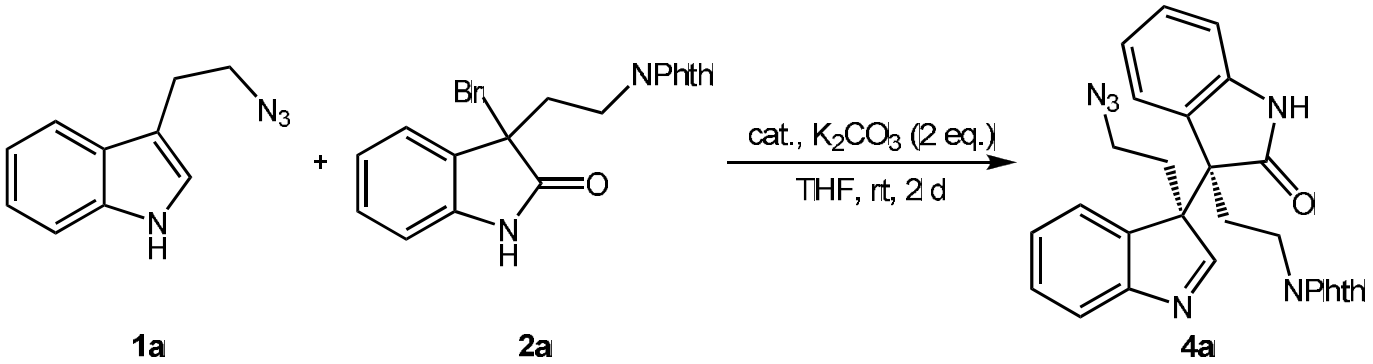
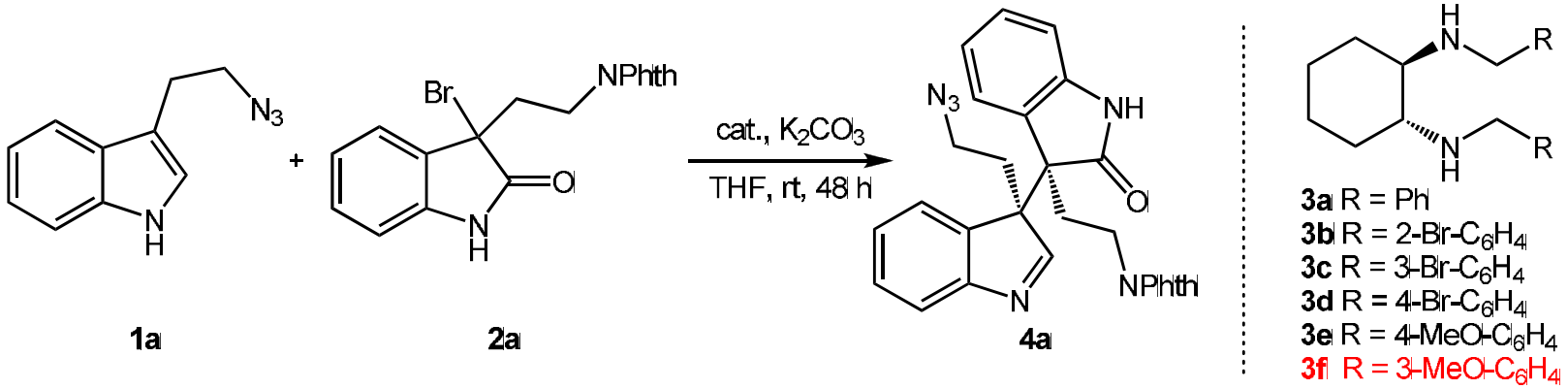
Optimization of the Reaction



1a **2a** **4a**

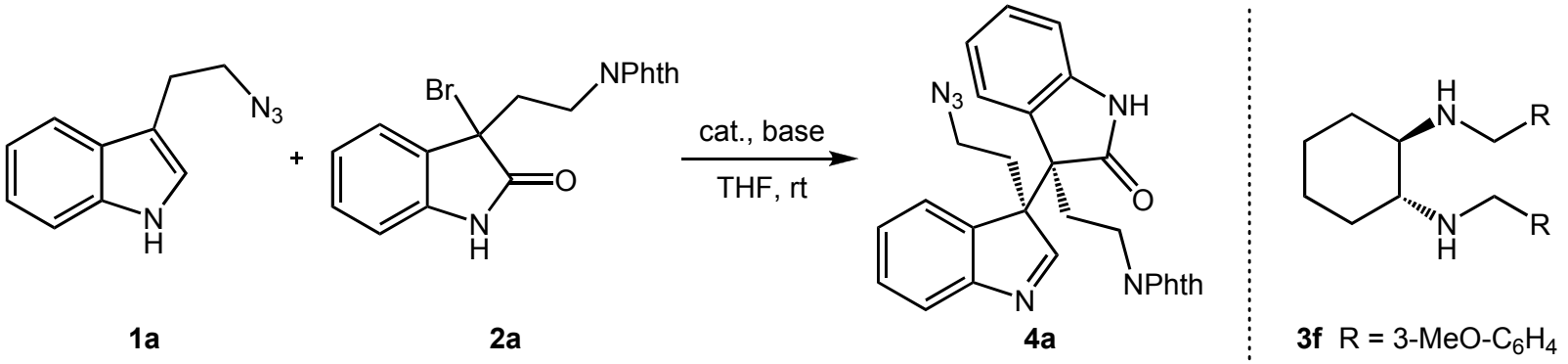
entry	cat. (20% mol)	yield (%)	dr	ee (%)
1	-	-	-	-
2	$Cu(OAc)_2$	trace	-	-
3	$La(OTf)_3$	-	-	-
4	$NiCl_2$	45	7:1	-
5	**$Ni(OAc)_2 \cdot H_2O$**	**75**	**9:1**	**-**

Optimization of the Reaction



entry	cat. (20% mol)	yield (%)	dr	ee (%)
1	$Ni(OAc)_2$-**3a**	81	10:1	40
2	$Ni(OAc)_2$-**3b**	79	10:1	37
3	$Ni(OAc)_2$-**3c**	81	10:1	68
4	$Ni(OAc)_2$-**3d**	77	10:1	67
5	$Ni(OAc)_2$-**3e**	75	10:1	83
6	**$Ni(OAc)_2$-3f**	**87**	**10:1**	**86**

Optimization of the Reaction

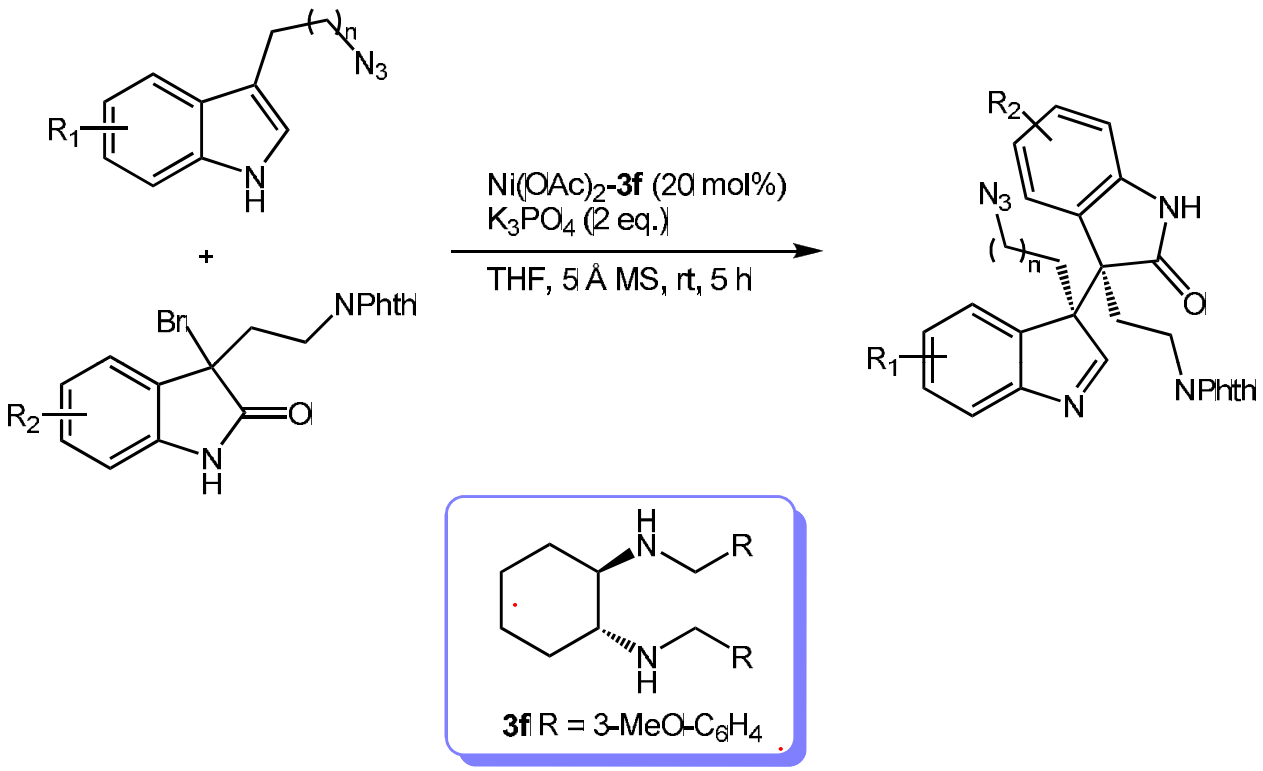


1a **2a** **4a** **3f** R = 3-MeO-C_6H_4

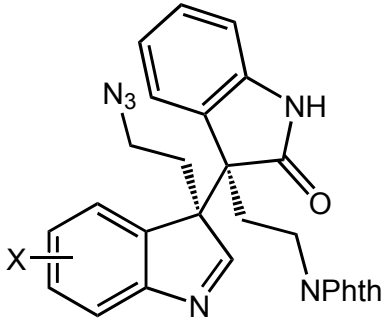
entry	cat. (20% mol)	Base (2 eq.)	time (h)	yield (%)	dr	ee (%)
1	$Ni(OAc)_2$-**3f**	K_3PO_4	5	91	10:1	89
2	$Ni(OAc)_2$-**3f**	Cs_2CO_3	2	88	10:1	83
3[a]	**$Ni(OAc)_2$-3f**	**K_3PO_4**	**5**	**94**	**10:1**	**92**

[a] 5 Å MS was added.

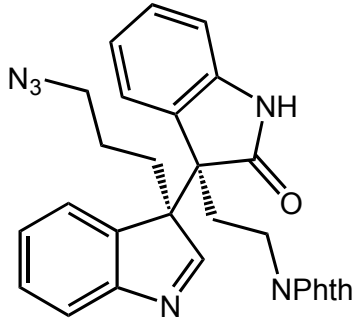
Substrate Scopes



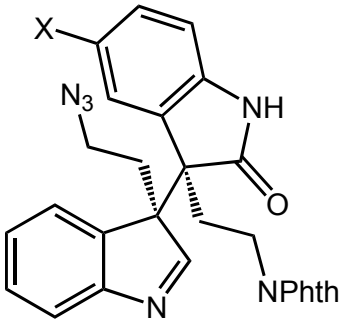
Substrate Scopes



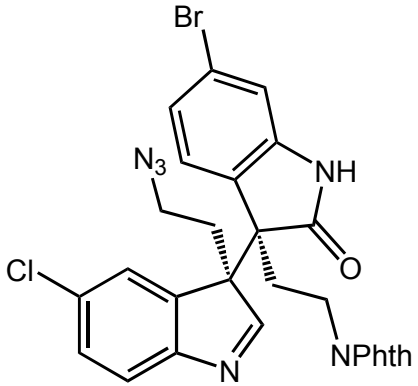
4a - **4l** X = H, Me, MeO, Halo-
73% - 94% yield
9:1 - >20:1 dr
85% - 99% ee



4m: 83%, >20:1 dr, 80% ee

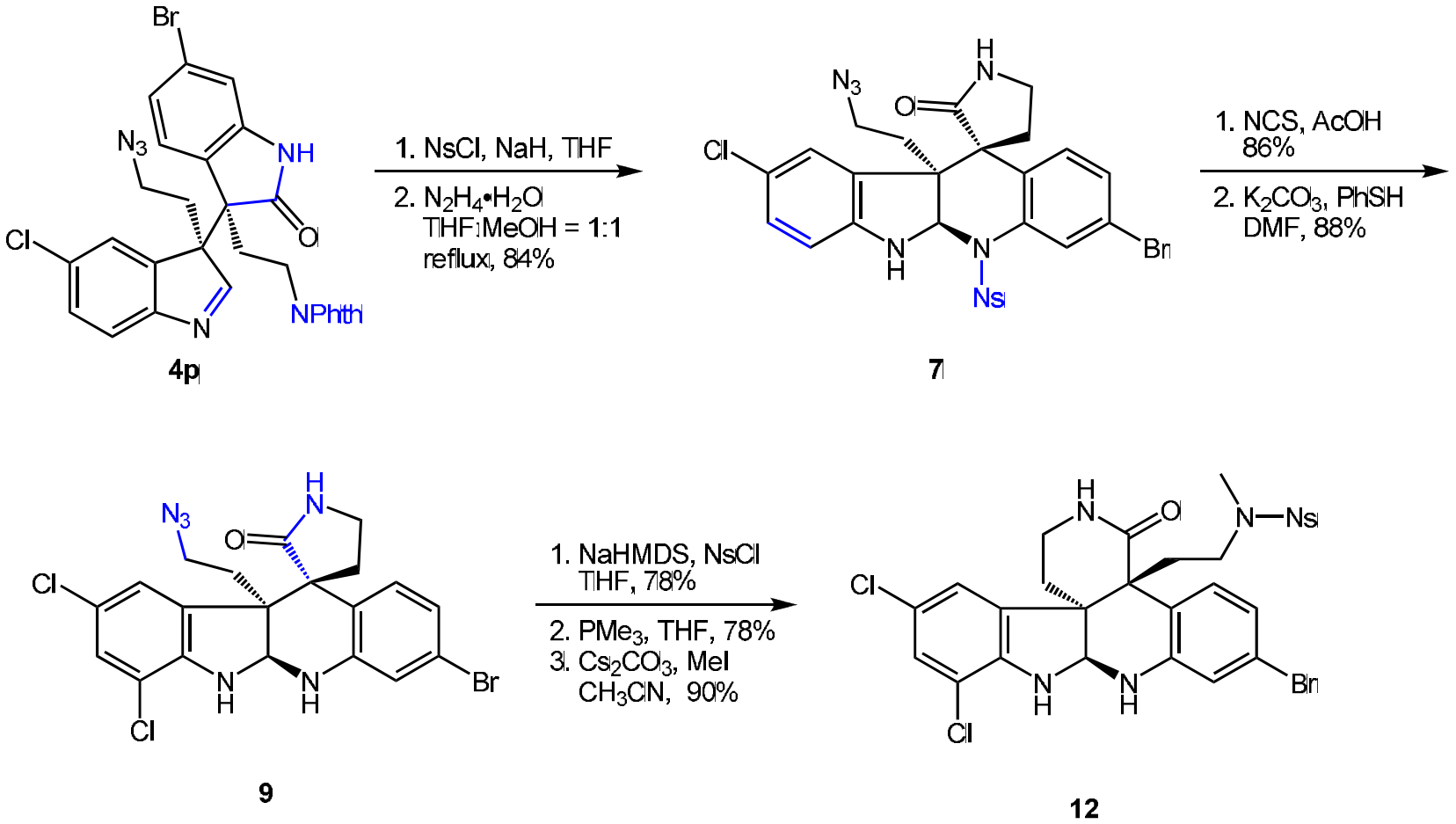


4n: X = OMe, 91%, 17:1 dr, 94% ee
4o: X = Br, 45%, 4:1 dr, 60% ee



4p: 51%, >12:1 dr, 90% ee

Total Synthesis of (+)-Perophoramidine



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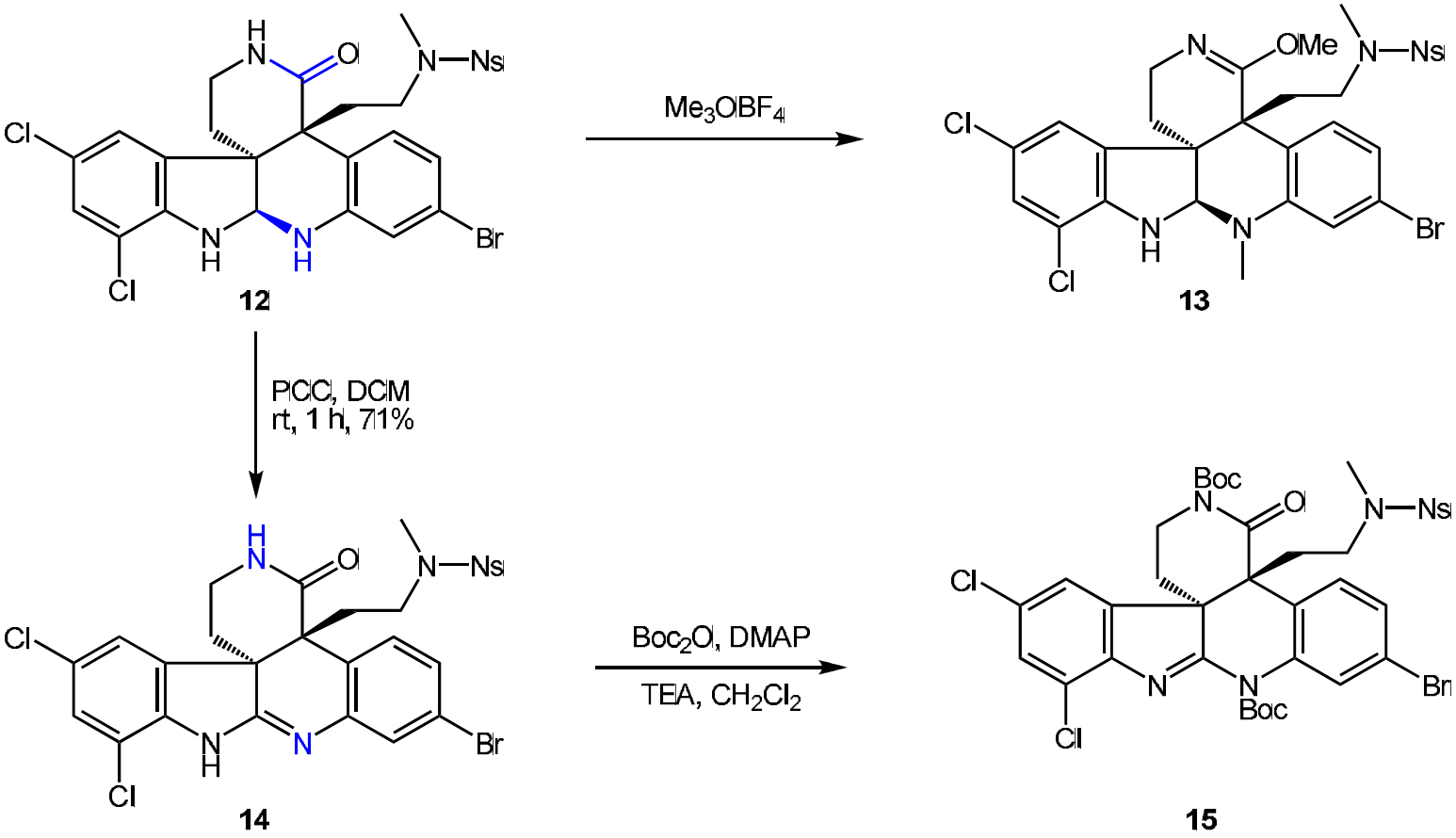

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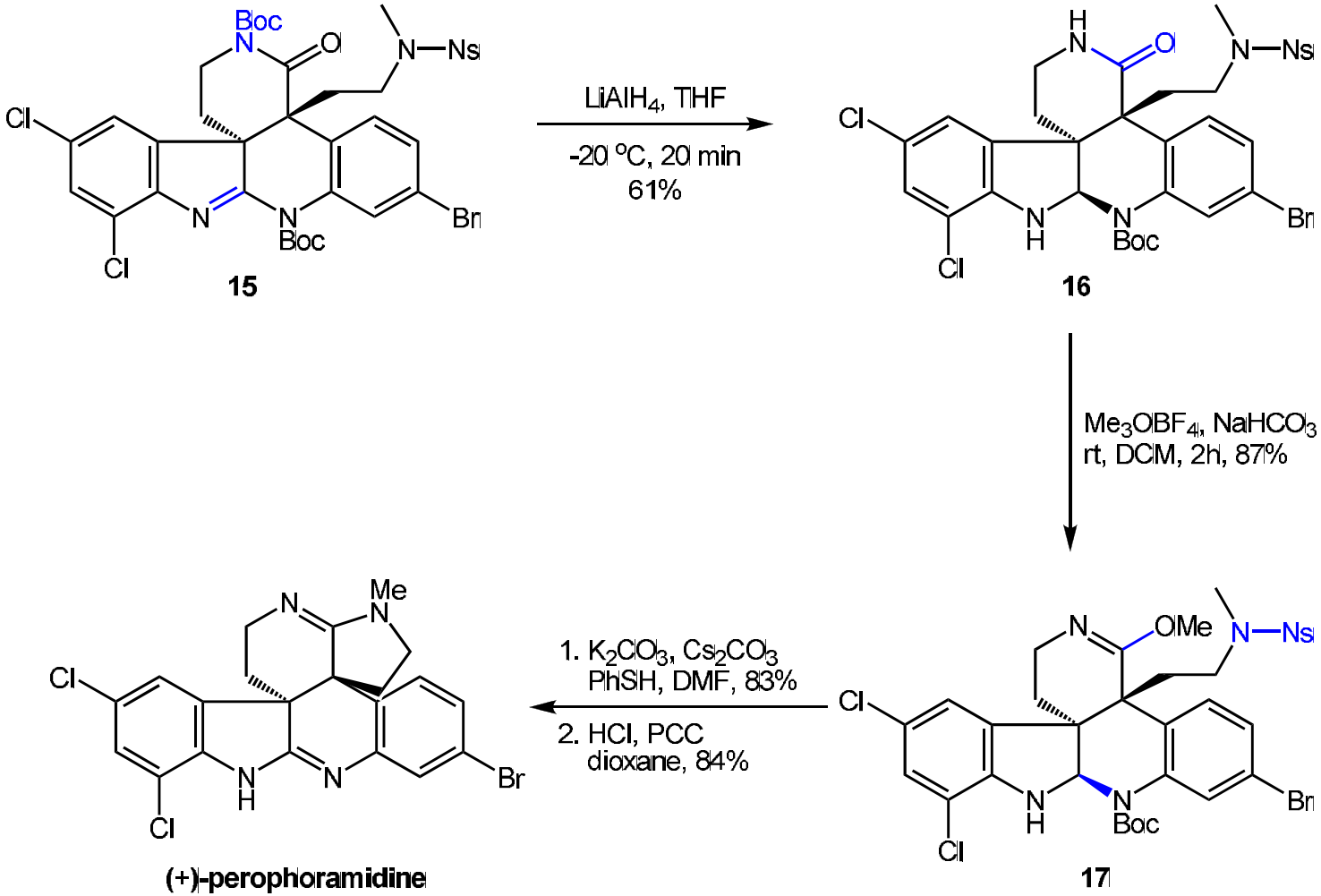
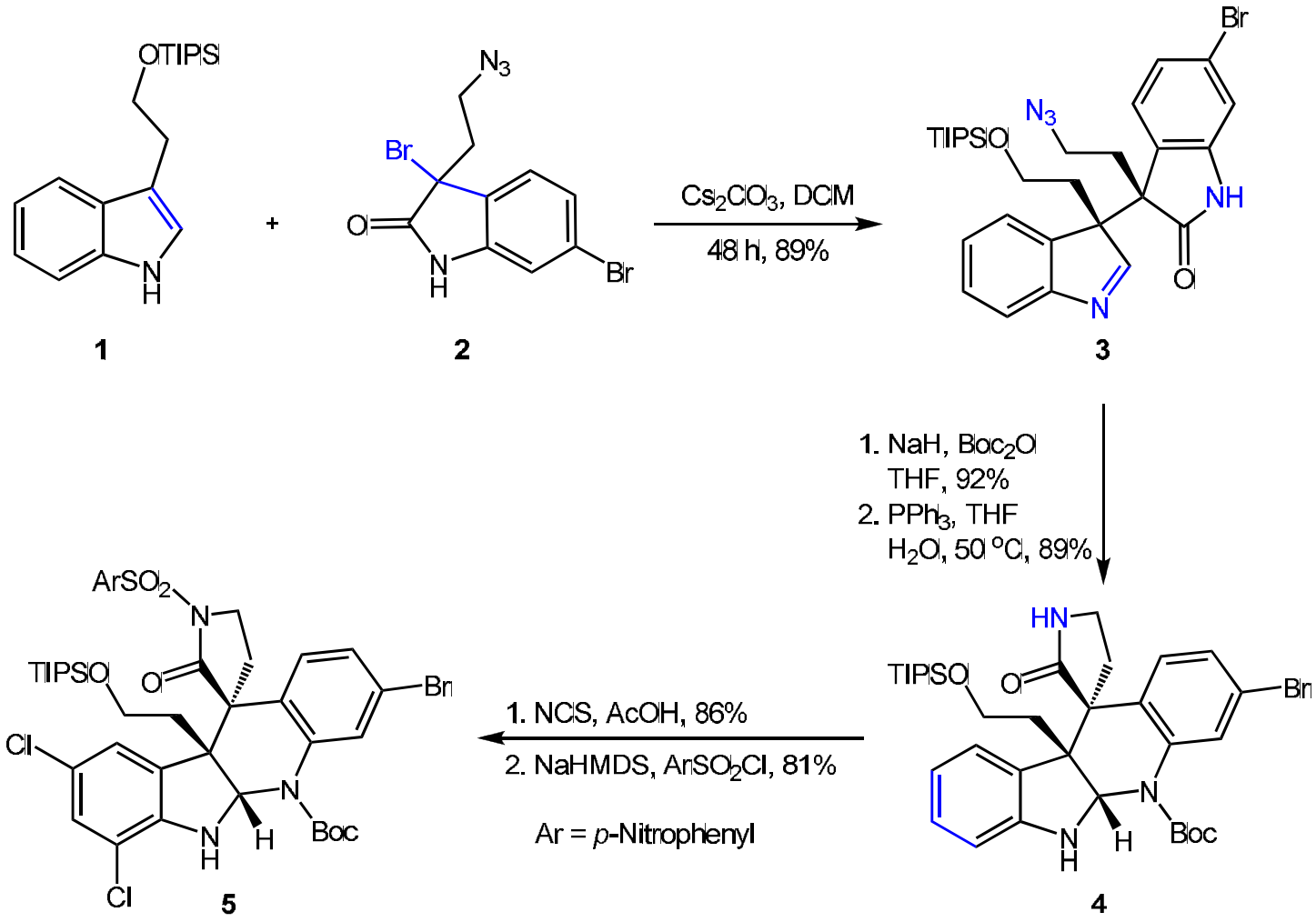
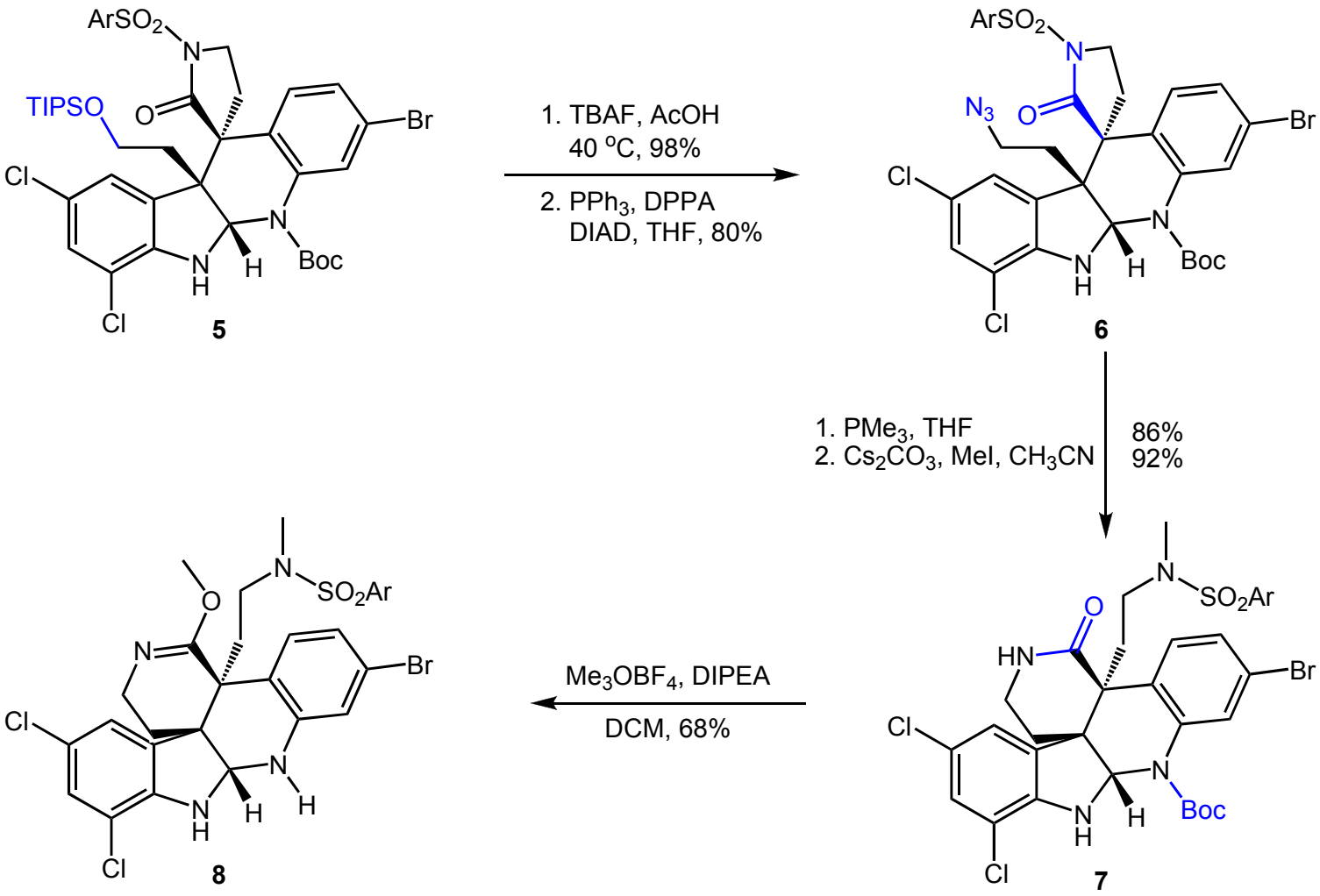


Total Synthesis of (±)-Perophoramidine

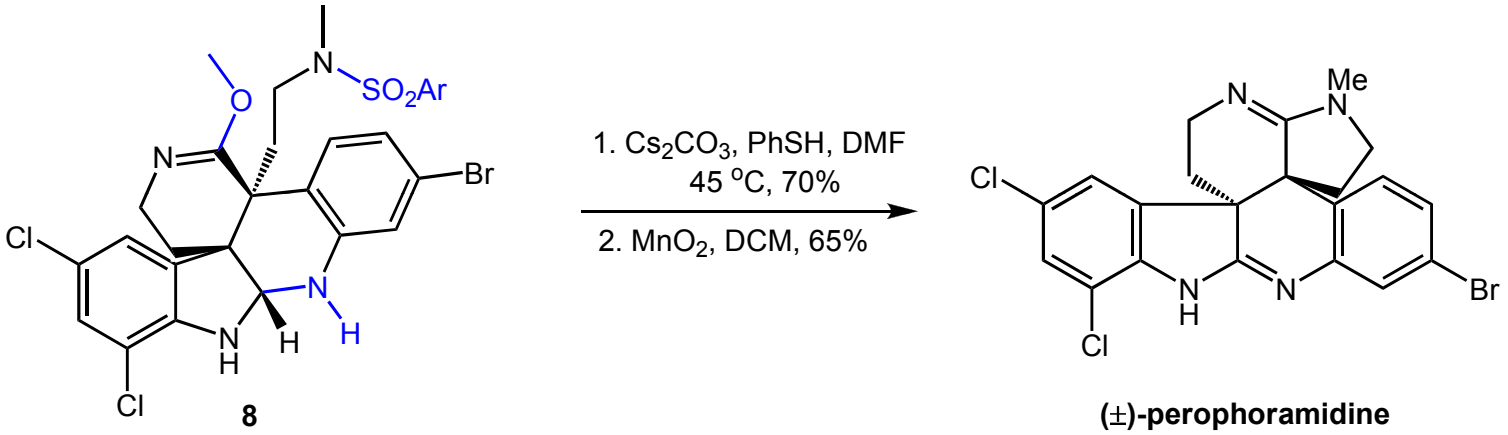


Funk, R. L. *et al. J. Am. Chem. Soc.* **2004**, *126*, 5068.

Total Synthesis of (±)-Perophoramidine

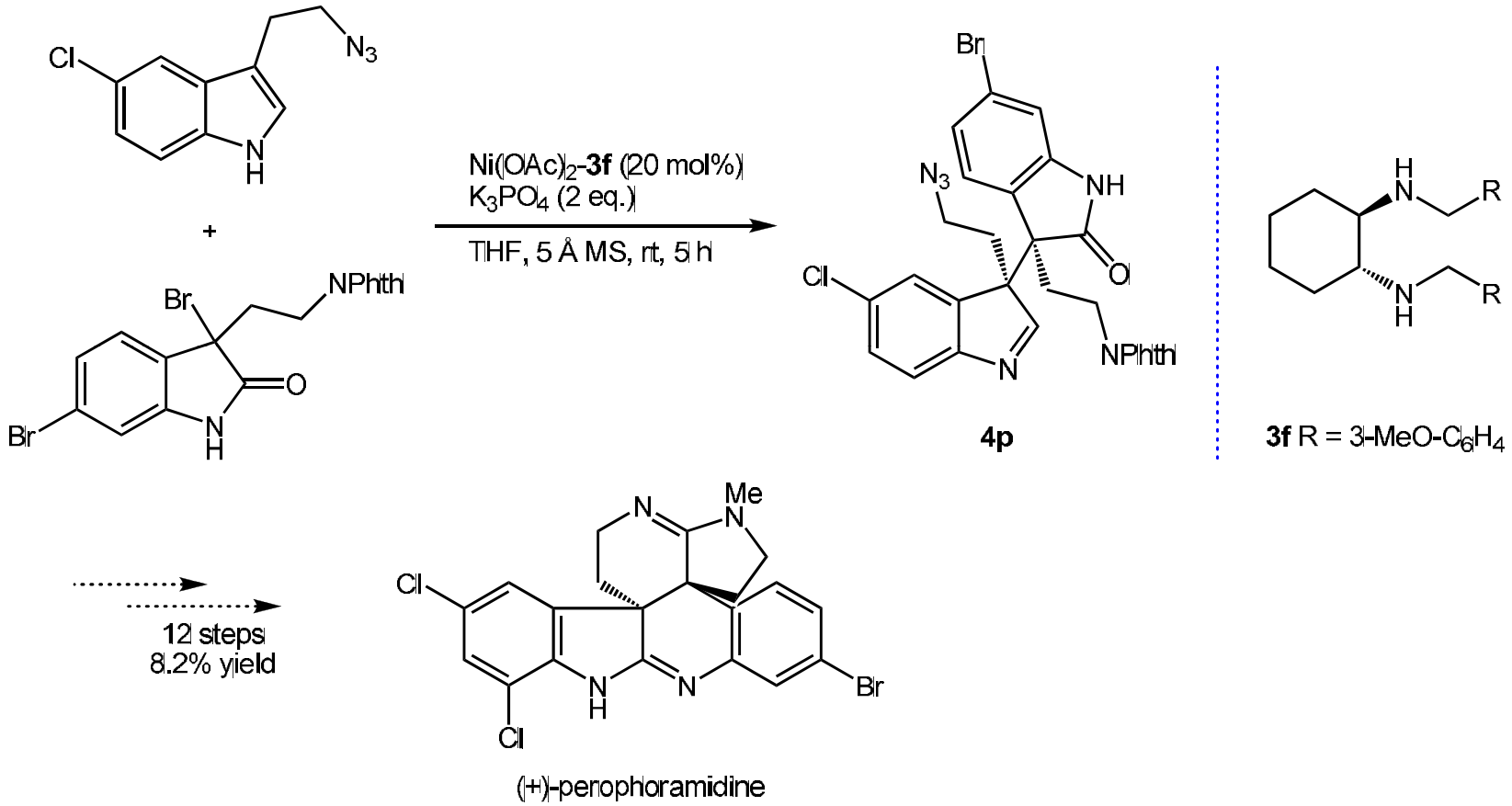


Total Synthesis of (±)-Perophoramidine



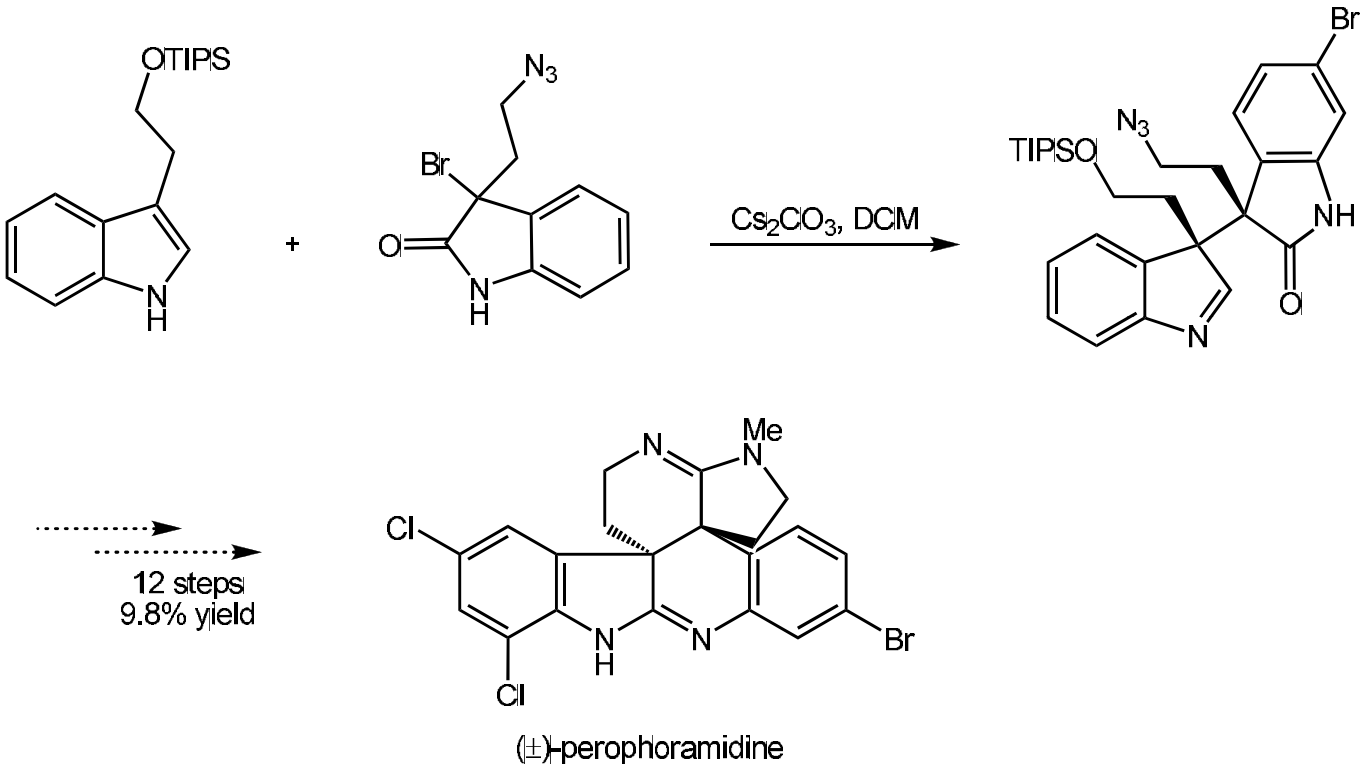
Summary

1. Total Synthesis of (+)-Perophoramidine



Summary

2. Total Synthesis of (±)-Perophoramidine



(−)-Communesins and (+)-perophoramidine are two architecturally intriguing natural products, which contain a complex multiring system with two crucial vicinal all-carbon quaternary stereocenters. To date, a number of elegant protocols for assembling these indole alkaloids have been developed. In the case of perophoramidine, Funk et al. and Rainier et al. reported the total synthesis of (±)-(dehalo)perophoramidine. Subsquently, Qin et al. achieved the asymmetric total synthesis of (+)-perophoramidine by a chiral auxiliary-induced strategy. However, the catalytic asymmetric synthesis of (+)-perophoramidine has never been reported, probably due to the challenge of catalytic asymmetric construction of the sterically congested vicinal all-carbon quaternary stereocenters.

In summary, we have developed a successful strategy for the construction of indolenines containing two vicinal all-carbon quaternary stereocenters with high diastereoselectivity and excellent enantioselectivity by using a nickel(II)-catalyzed asymmetric alkylation reaction of 3-bromooxindoles with 3-substituted indoles. This methodology facilitated the first catalytic asymmetric total synthesis of the cytotoxic agent (+)-perophoramidine. Additional applications of this methodology are underway.