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链球菌是一种存在于人和动物表皮或者呼吸道的一种共生菌，其中嗜热链球菌是一种益生菌，被用来制作酸奶。而Streptide是链球菌产生的一种环状多肽链，被用来作为传递信息的物质。

Total Synthesis and Stereochemical Assignment of Streptide

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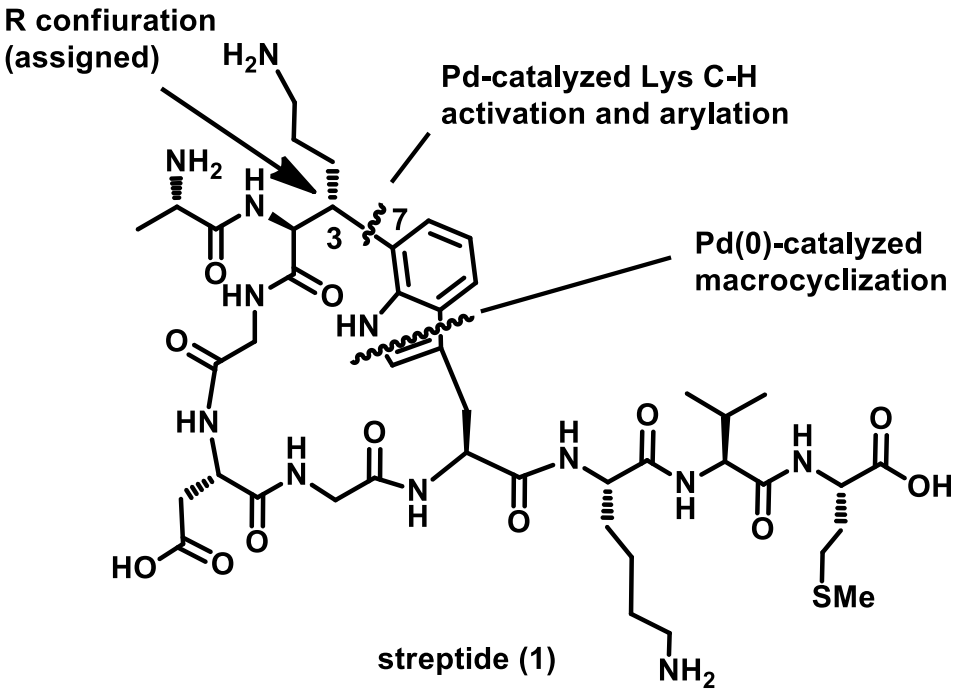
Supporting Information



链球菌是一种存在于人和动物表皮或者呼吸道的一种共生菌，其中嗜热链球菌是一种益生菌，被用来制作酸奶。而Streptide是链球菌产生的一种环状多肽链，被用来作为传递信息的物质。

DOI: 10.1021/jacs.9b09067.
J. Am. Chem. Soc. XXXX, XXX, XXX-XXX

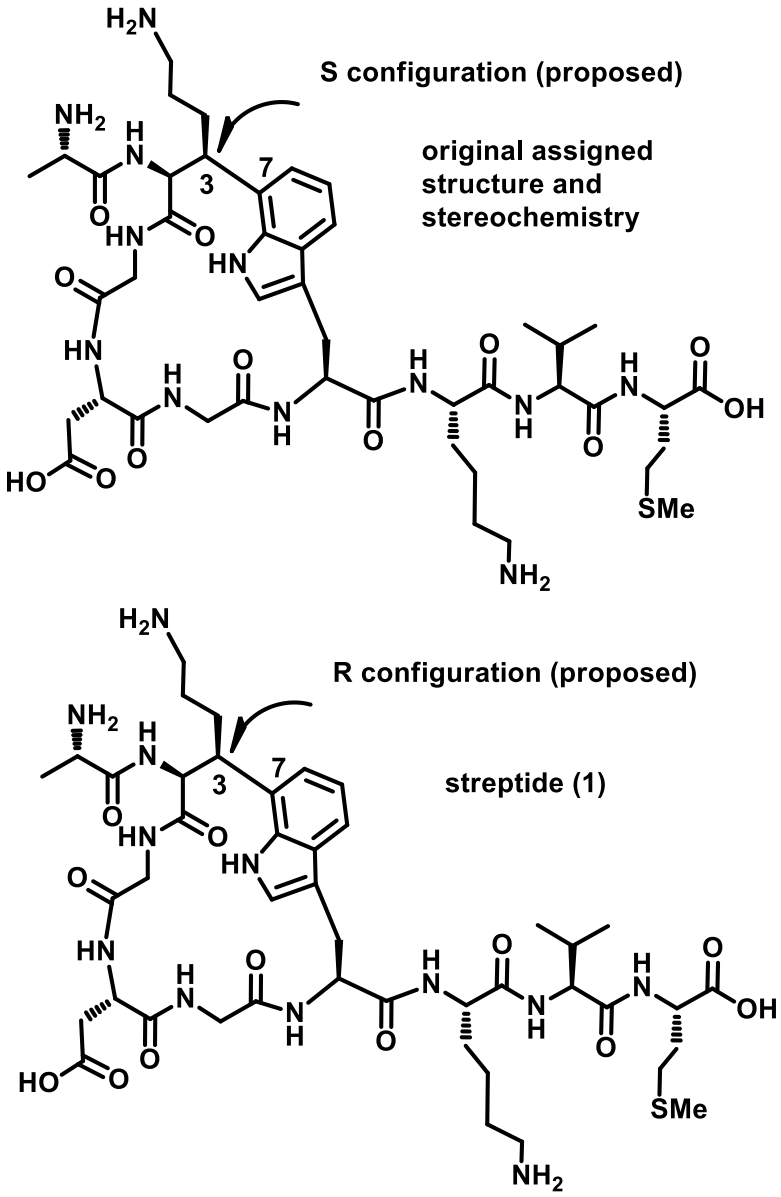


Figure 1. Originally proposed lysine (3S) and revised (3R) structure of streptide (1).

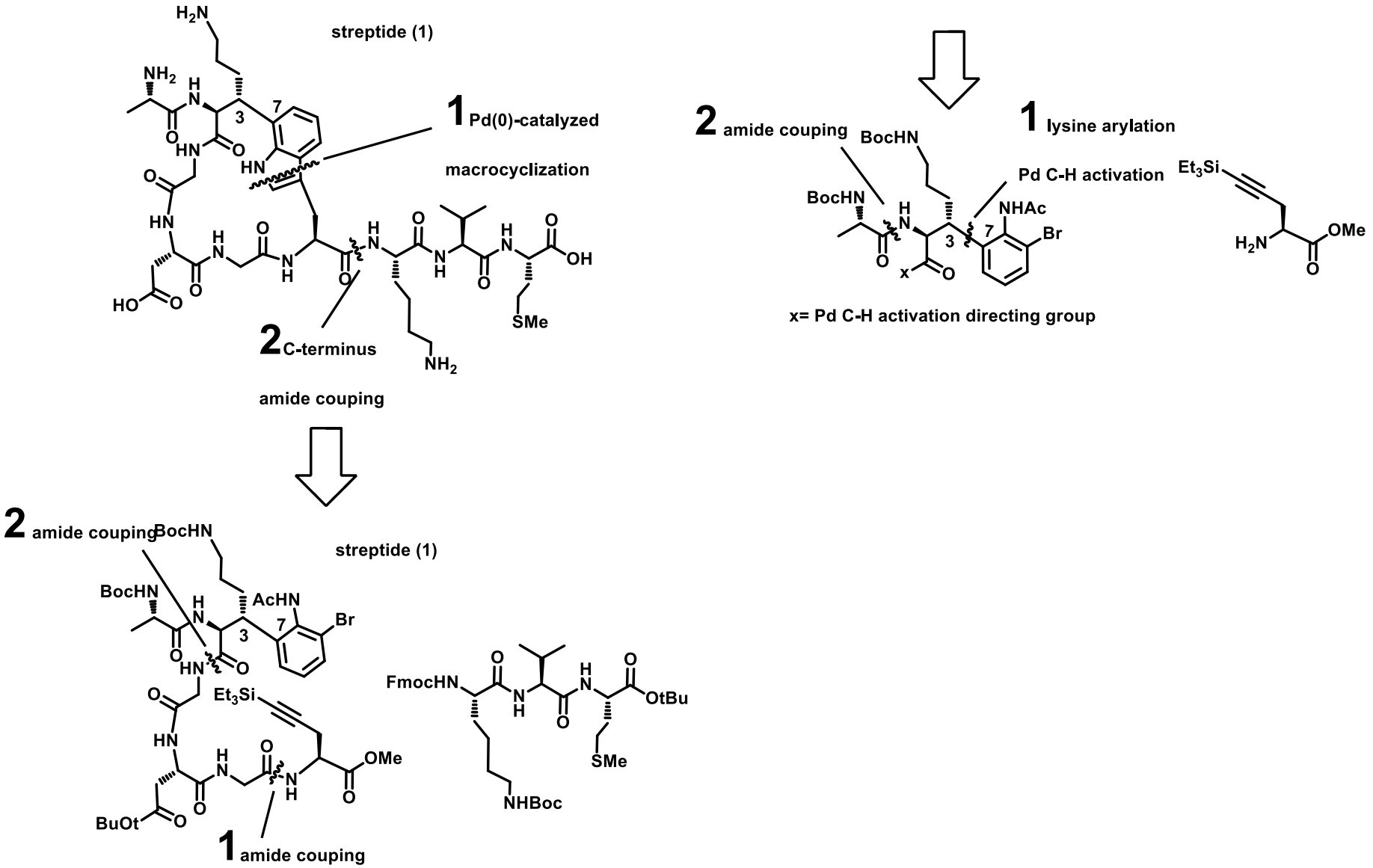


Figure 2. Key retrosynthetic steps for the total synthesis of streptide.

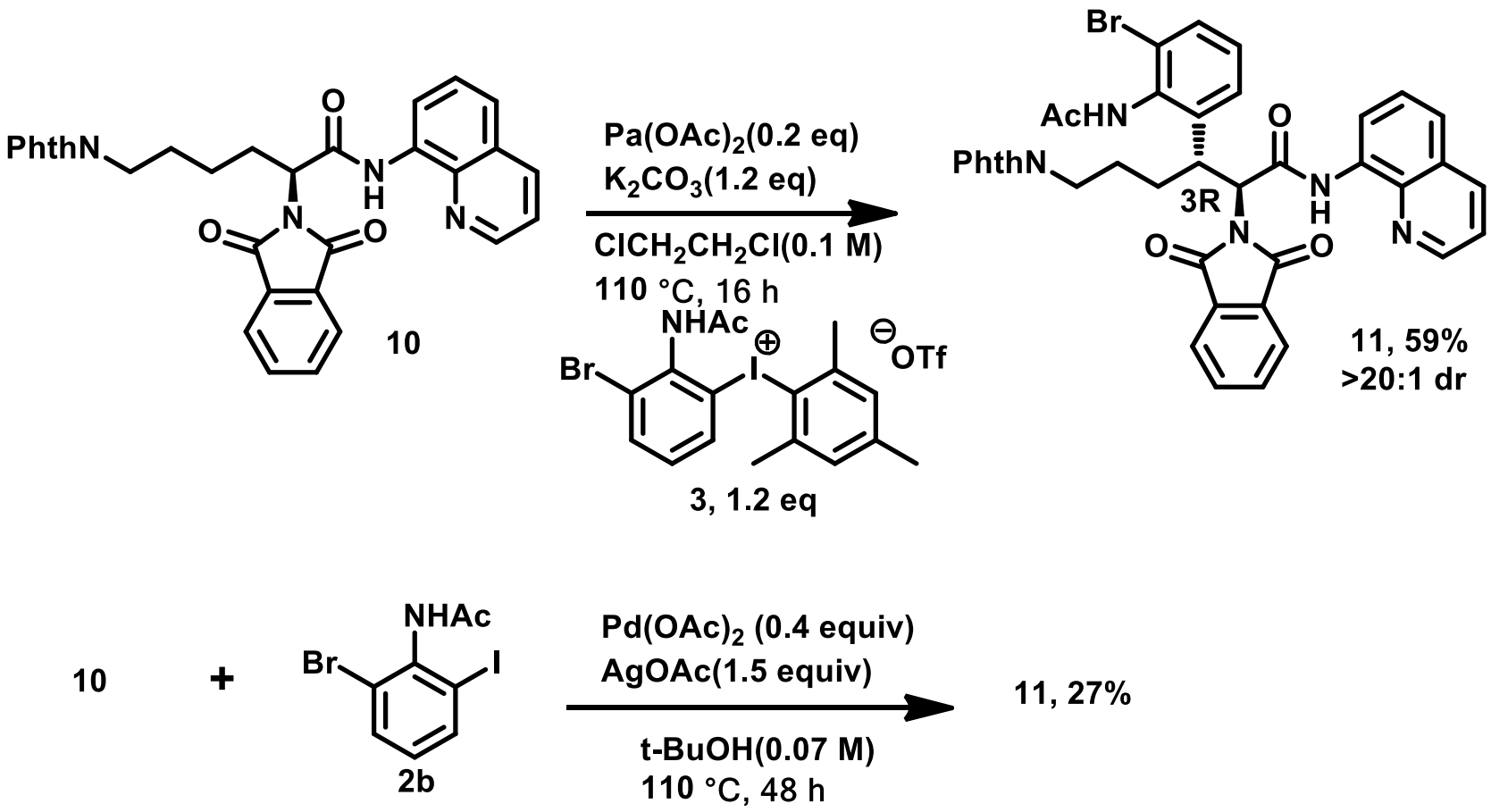
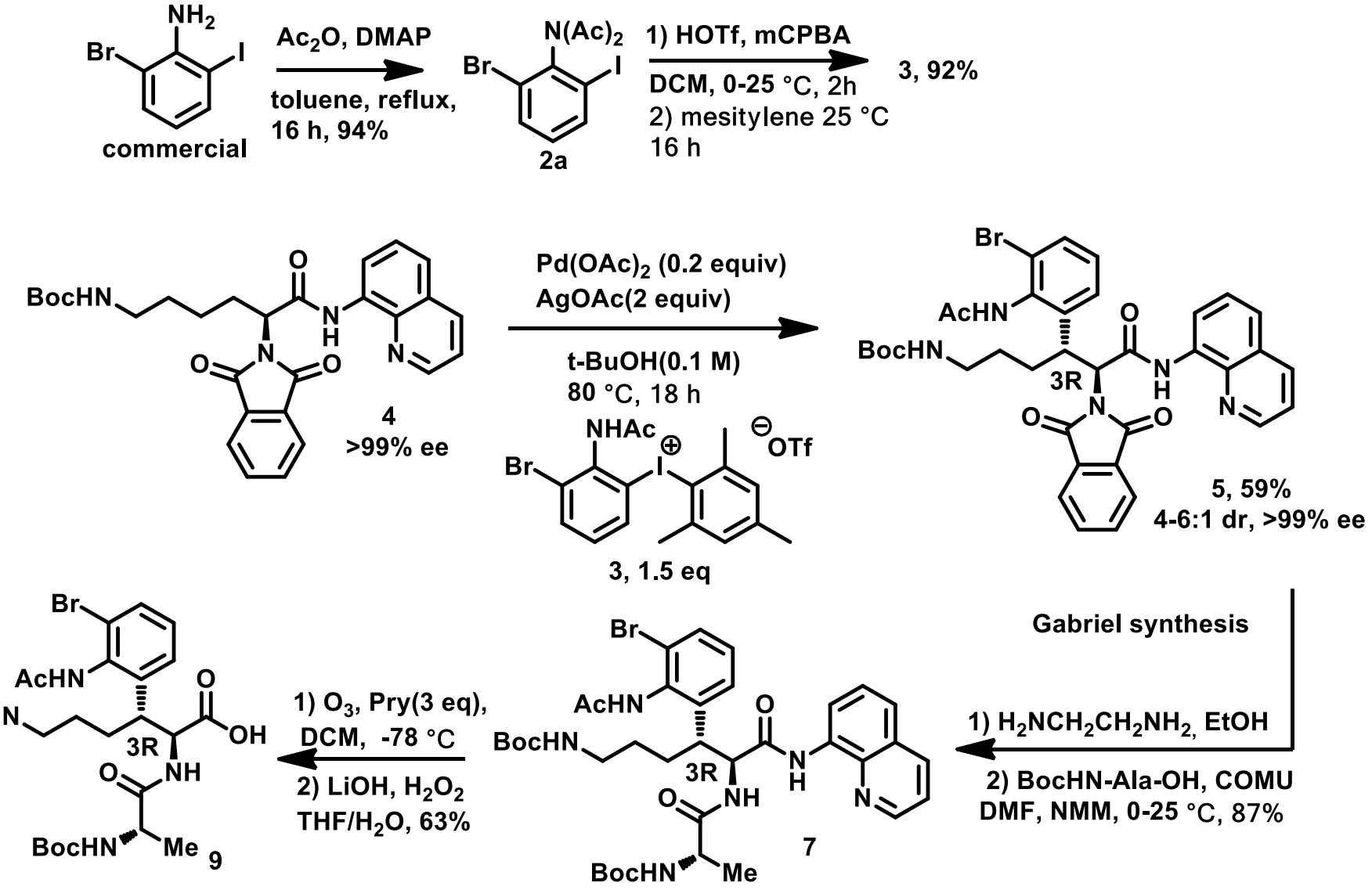
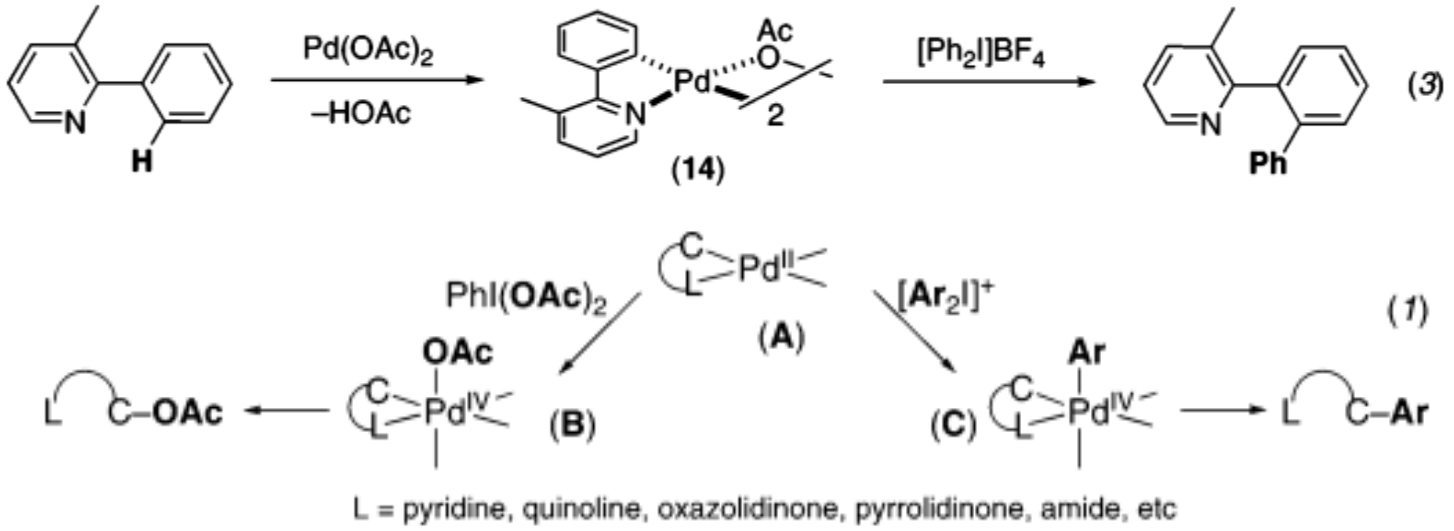


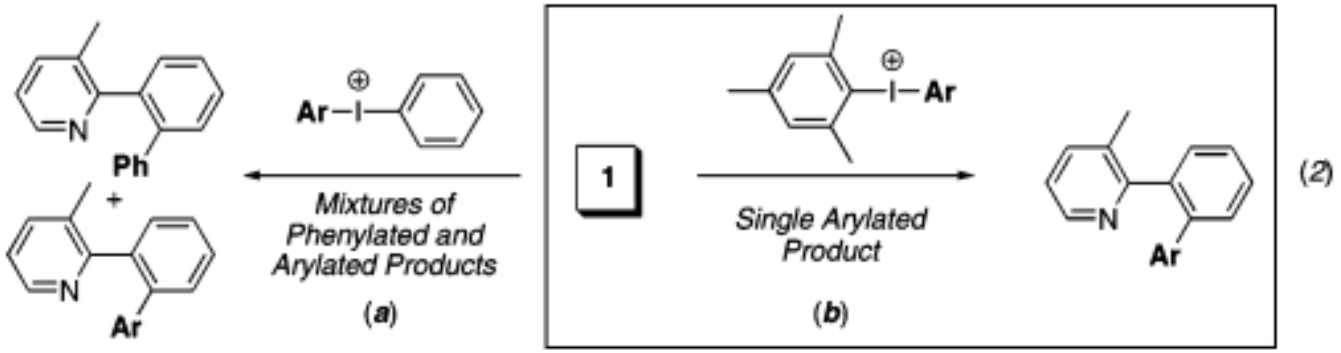
Figure 3. Initial key observations on C-H activation and subsequent arylation of alysine derivative.

Scheme 1


NH2
Br
I
commercial
Ac2O, DMAP
toluene, reflux,
16 h, 94%
N(Ac)2
Br
I
2a
1) HOTf, mCPBA
DCM, 0-25 °C, 2h
2) mesitylene 25 °C
16 h
3, 92%
BocHN
O
N
H
N
O
O
N
4
>99% ee
Pd(OAc)2 (0.2 equiv)
AgOAc(2 equiv)
t-BuOH(0.1 M)
80 °C, 18 h
NHAc
I
OTf
Br
3, 1.5 eq
Br
AcHN
BocHN
3R
5, 59%
4-6:1 dr, >99% ee
Gabriel synthesis
1) H2NCH2CH2NH2, EtOH
2) BocHN-Ala-OH, COMU
DMF, NMM, 0-25 °C, 87%
7
1) O3, Pry(3 eq),
DCM, -78 °C
2) LiOH, H2O2
THF/H2O, 63%
OH
Me
9

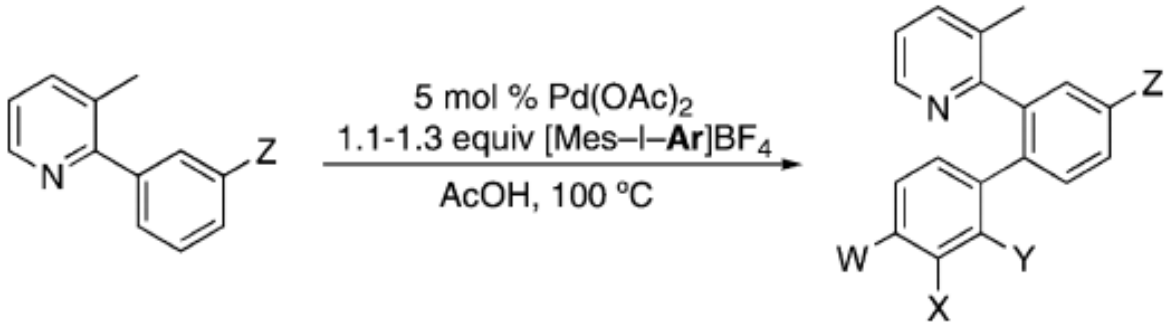


In sum, these experiments provide compelling evidence against a traditional Pd(0)/(II) catalytic cycle and are consistent with C-H activation to form a cyclometalated Pd(II) intermediate followed by (i) oxidation of Pd(II) to Pd(IV) by [Ph2I]BF4 and subsequent C-C bond forming reductive elimination (eq 1)

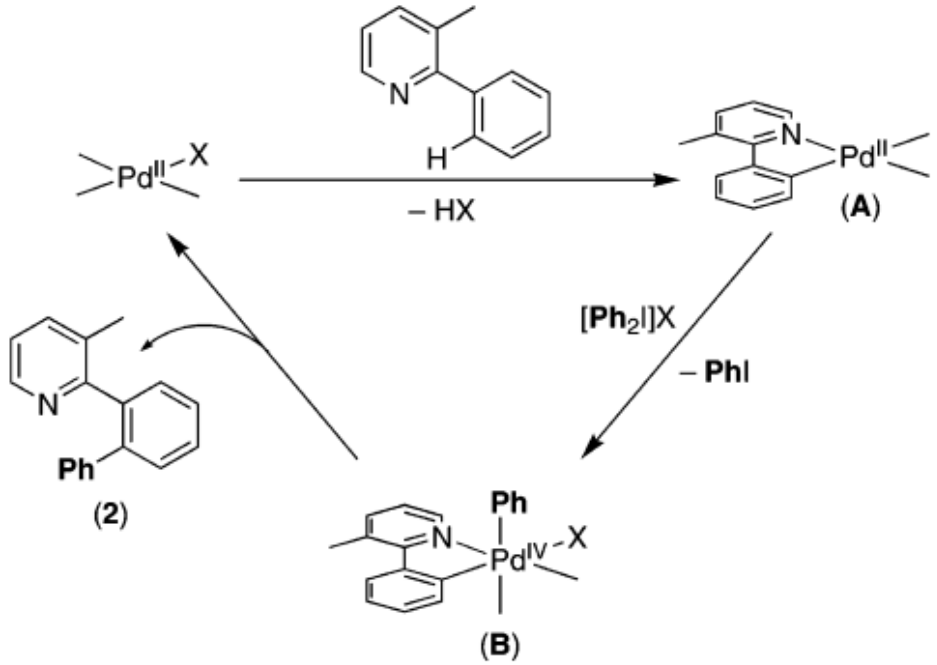


J. Am. Chem. Soc. **2005,** *127,* 7330-7331.
DOI:10.1021/ja051402f.

Table 3. Pd-Catalyzed Arylation of 3-Methyl-2-Arylpyridines with $[Mes–I–Ar]BF_4$



Scheme 1. Originally Proposed Catalytic Cycle for Pd-Catalyzed C–H Arylation[5a]



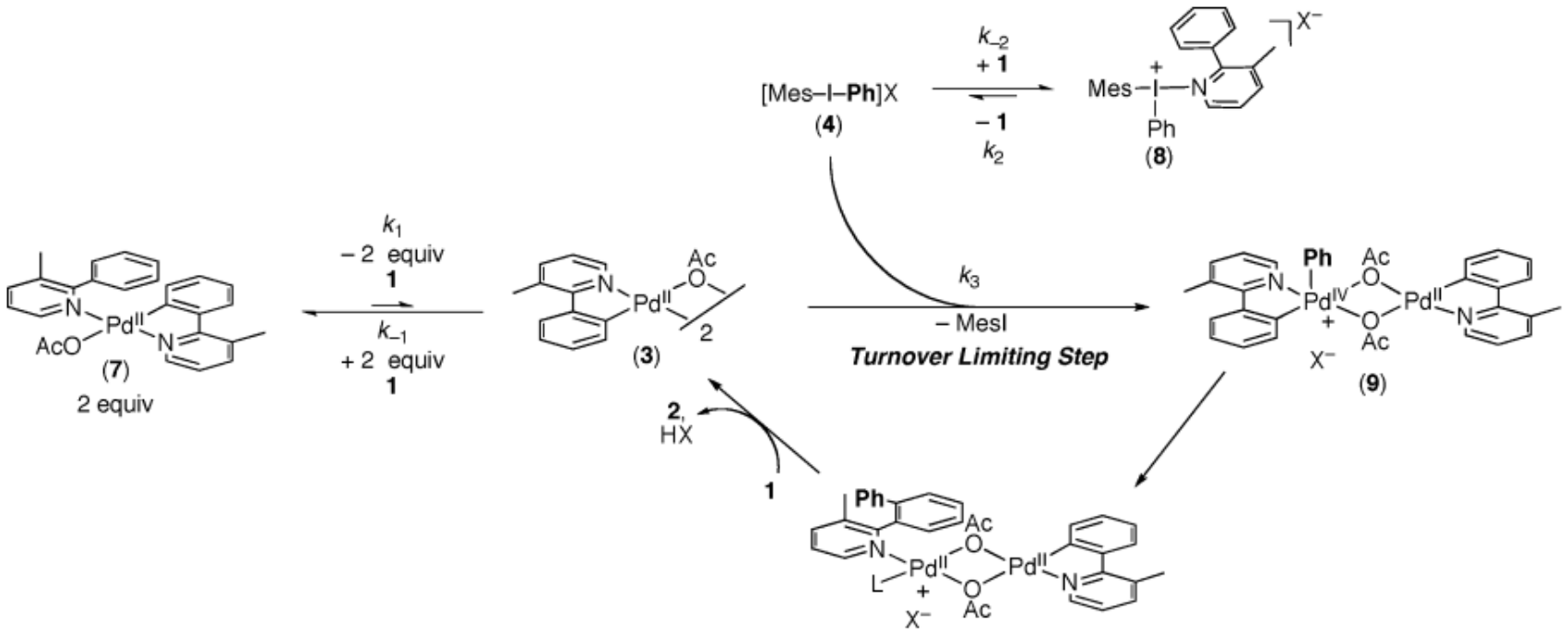
On the basis of all of these results, the general catalytic cycle shown in Scheme 1 was proposed, involving

(i) ligand-directed C-H activation to afford palladacycle A,
(ii) oxidation of A with [Ph2I]BF4 to generate a PdIV intermediate of general structure B, and finally,
(iii) C-C bond-forming reductive elimination to afford the arylated product 2.

J. Am. Chem. Soc. **2009**, *131*, 11234–11241.
DOI:10.1021/ja904116k.

Studies of reaction order in each component, **Hammett analysis**, **kinetic isotope effect data**, and **equilibrium investigations** have all been used to interrogate the resting state of the catalyst and the oxidant under the reaction conditions.

Scheme 3. Proposed Mechanism for C–H Arylation of 3-Methyl-2-phenylpyridine



As shown in Scheme 3, we propose that the **resting state** of the catalyst is the monomeric PdII species **7,** and the resting state of the oxidant is the pyridine coordinated iodine(III) reagent **8**

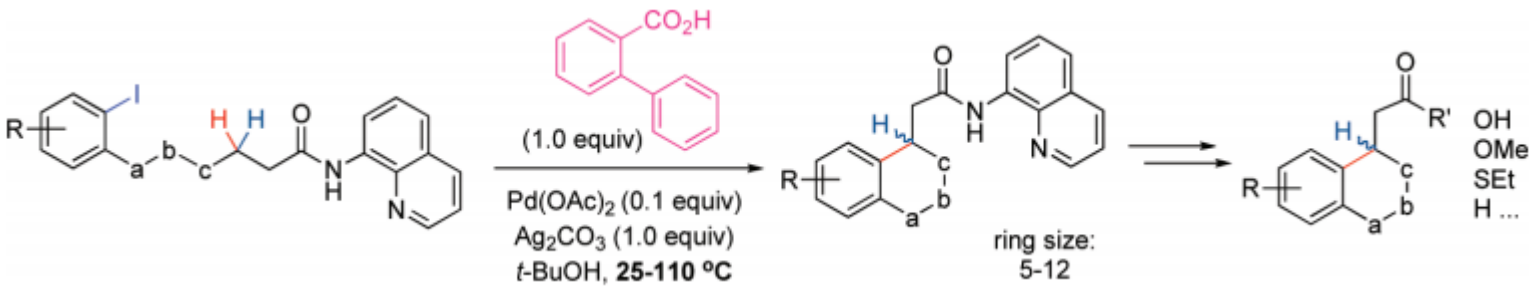
J. Am. Chem. Soc. **2009,** *131,* 11234–11241.
DOI:10.1021/ja904116k.

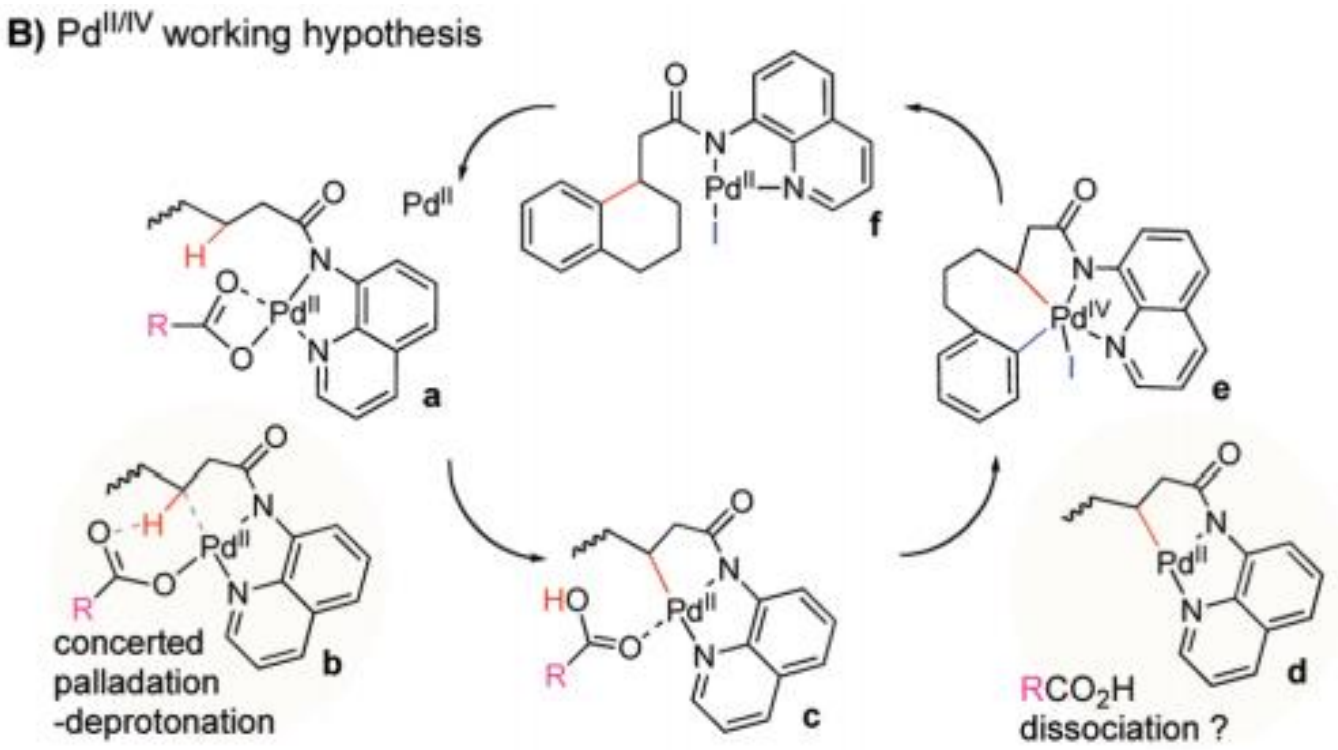
Pd (II/IV)循环的Pa催化C-H活化反应的优点：

- PdII/IV sequences should tolerate important functional groups (e.g., **aryl halides and enolizable ketones**) **that can be reactive with the low-valent Pd intermediate**s and/or **strong bases** often required in Pd0/II processes.

- In addition, high oxidation state Pd species are known to **be stable toward air and moisture,7,8** obviating the need for special glassware and/ or for rigorous purification of solvents and reagents.

J. Am. Chem. Soc. **2009,** *131*, 11234–11241.
DOI:10.1021/ja904116k.





Org. Lett., Vol. 12, No. 15, **2010**
DOI:10.1021/ol101220x.

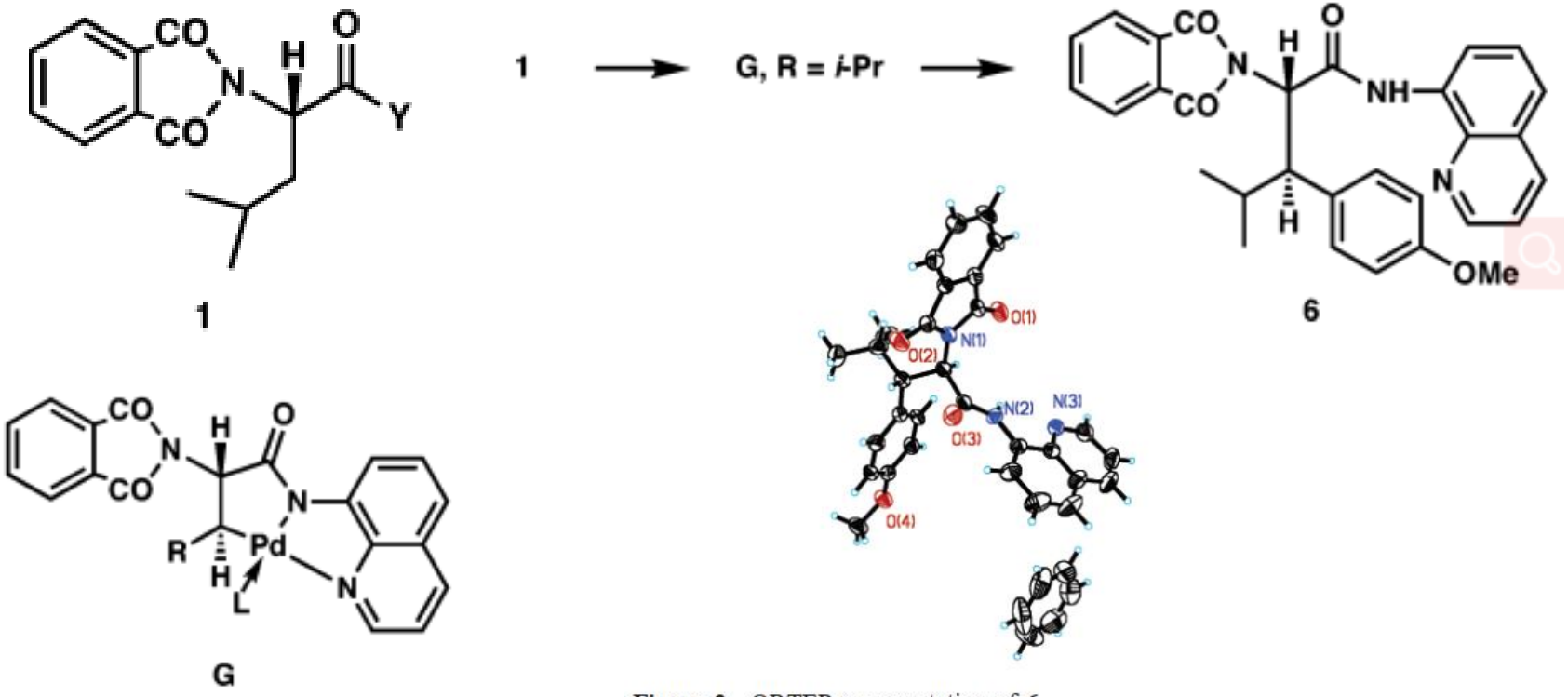


Figure 2. ORTEP representation of **6**.

The palladacycle **G**, R) *i*-Pr, could be generated, trapped, and defined structurally by the reaction of **1** with ***p*iodoanisole (4 equiv p-碘苯甲醚), Pd(OAc)2 (20 mol %), and AgOAc (1.5 equiv, to remove HI) at 110 ° C for 30 min** (without solvent) which afforded the crystalline 2*S*,3*S*-3-*p*-anisyl derivative **6** in 95% yield.6

The observed stereochemistry of the *β*-functionalization can be understood in terms of a preference for forming the **sterically more favored intermediate** *trans*-palladacycle **G**.

Org. Lett., Vol. 8, No. 15, **2006**
10.1021/ol061389j .

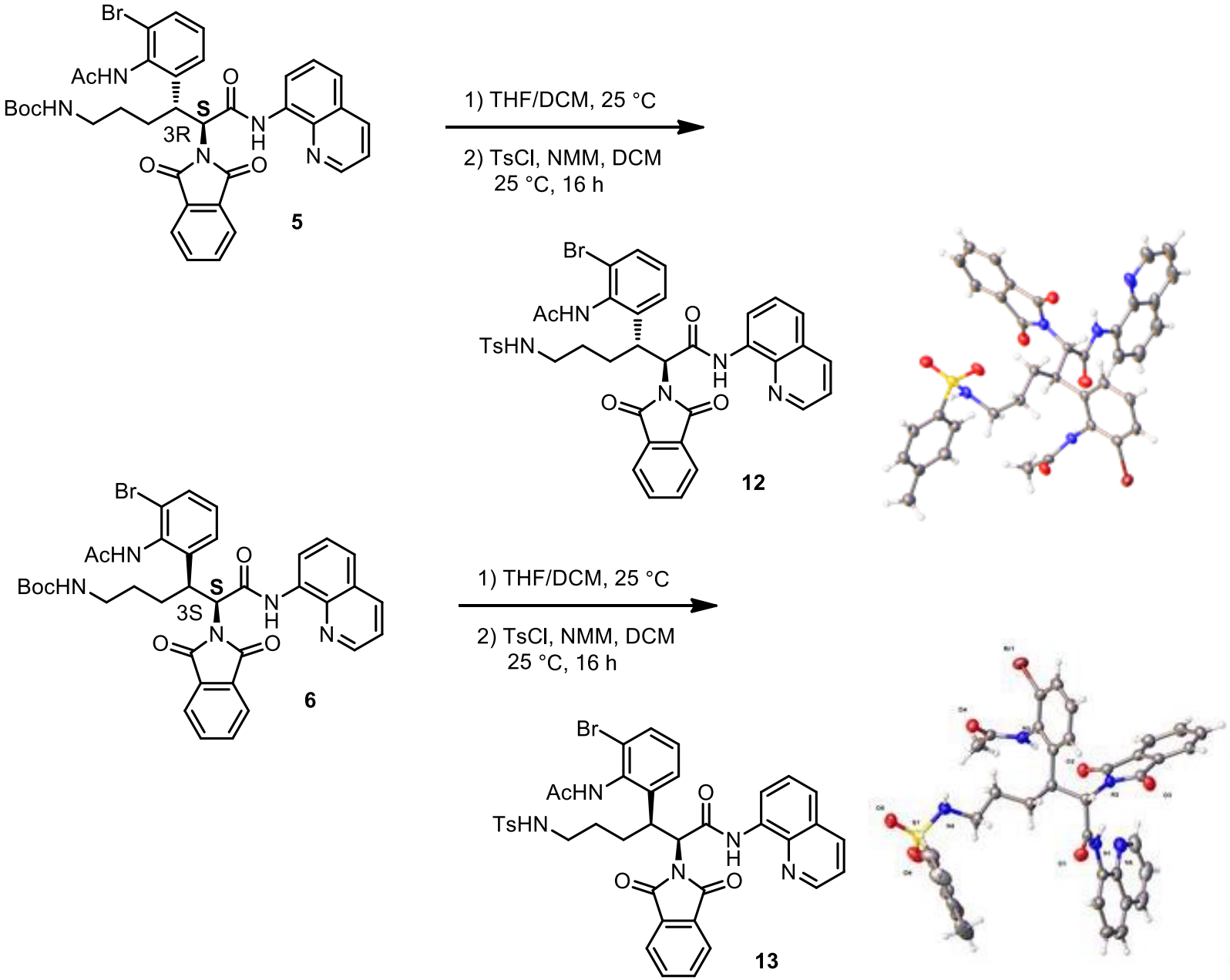
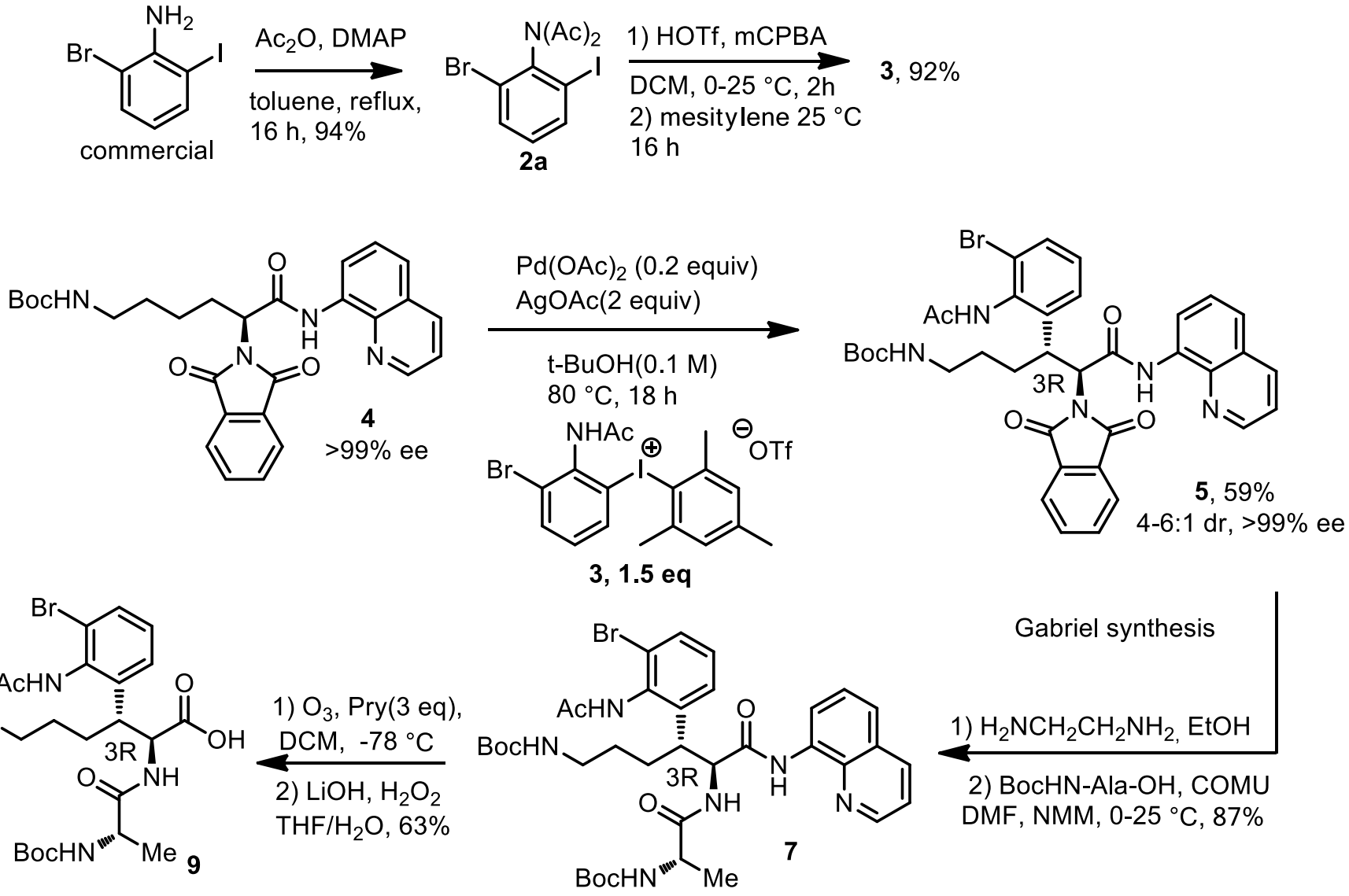
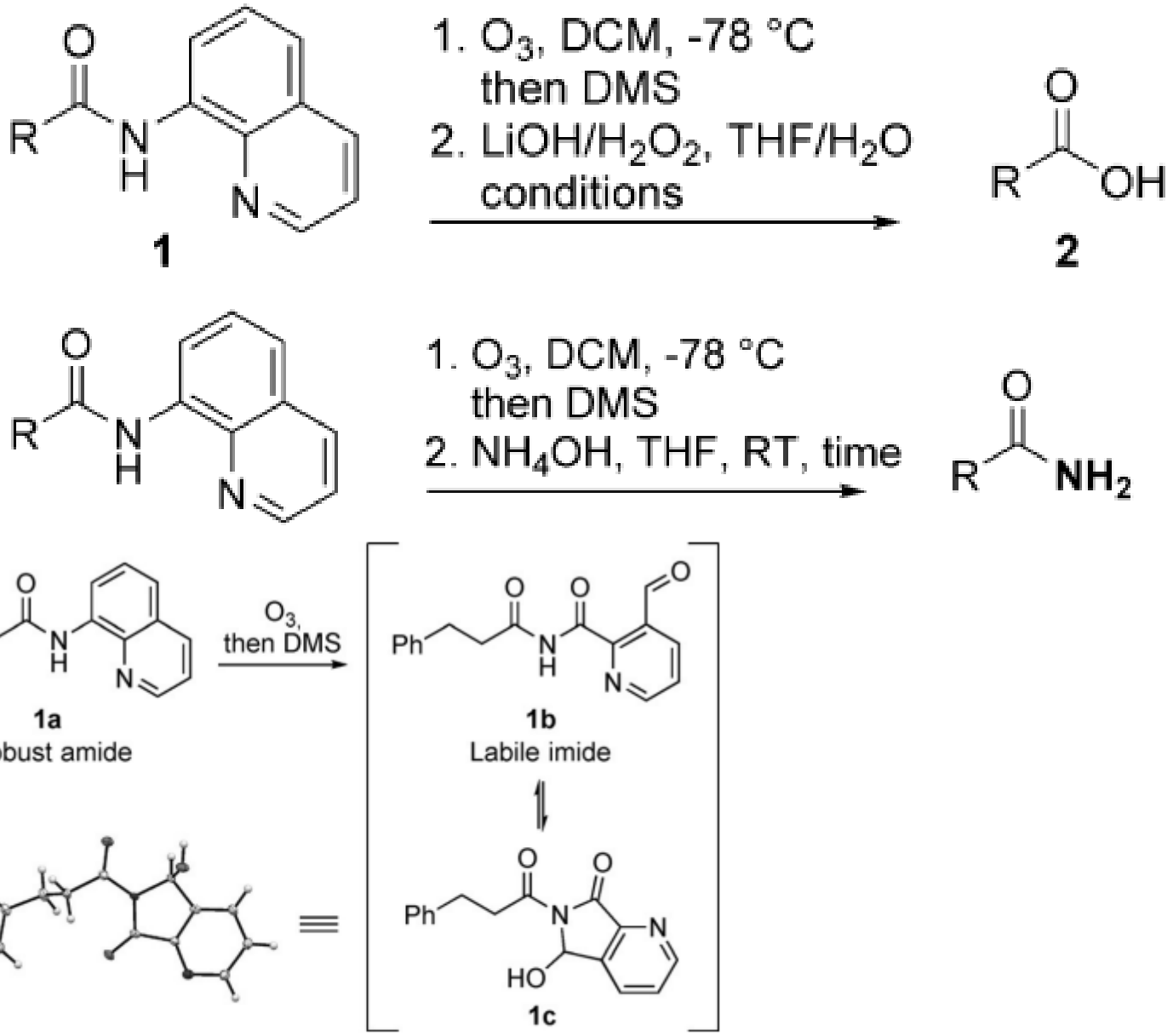


Figure 4. Relative and absolute stereochemistry of 5 and 6 established by X-ray diffraction analysis.20

Scheme 1


NH2
Br
I
commercial
Ac2O, DMAP
toluene, reflux,
16 h, 94%
N(Ac)2
2a
1) HOTf, mCPBA
DCM, 0-25 °C, 2h
2) mesitylene 25 °C
16 h
3, 92%
BocHN
4
>99% ee
Pd(OAc)2 (0.2 equiv)
AgOAc(2 equiv)
t-BuOH(0.1 M)
80 °C, 18 h
NHAc
OTf
3, 1.5 eq
AcHN
3R
5, 59%
4-6:1 dr, >99% ee
Gabriel synthesis
1) H2NCH2CH2NH2, EtOH
2) BocHN-Ala-OH, COMU
DMF, NMM, 0-25 °C, 87%
7
1) O3, Pry(3 eq),
DCM, -78 °C
2) LiOH, H2O2
THF/H2O, 63%
OH
Me
9



Scheme 2. Ozonolytic weakening of the robust AQ–amide into a labile imide. X-ray crystallographic structure of **1c** is shown.

Chem. Eur. J. **2016,** *22,* 16805 – 16808.
DOI: 10.1002/chem.201604344.

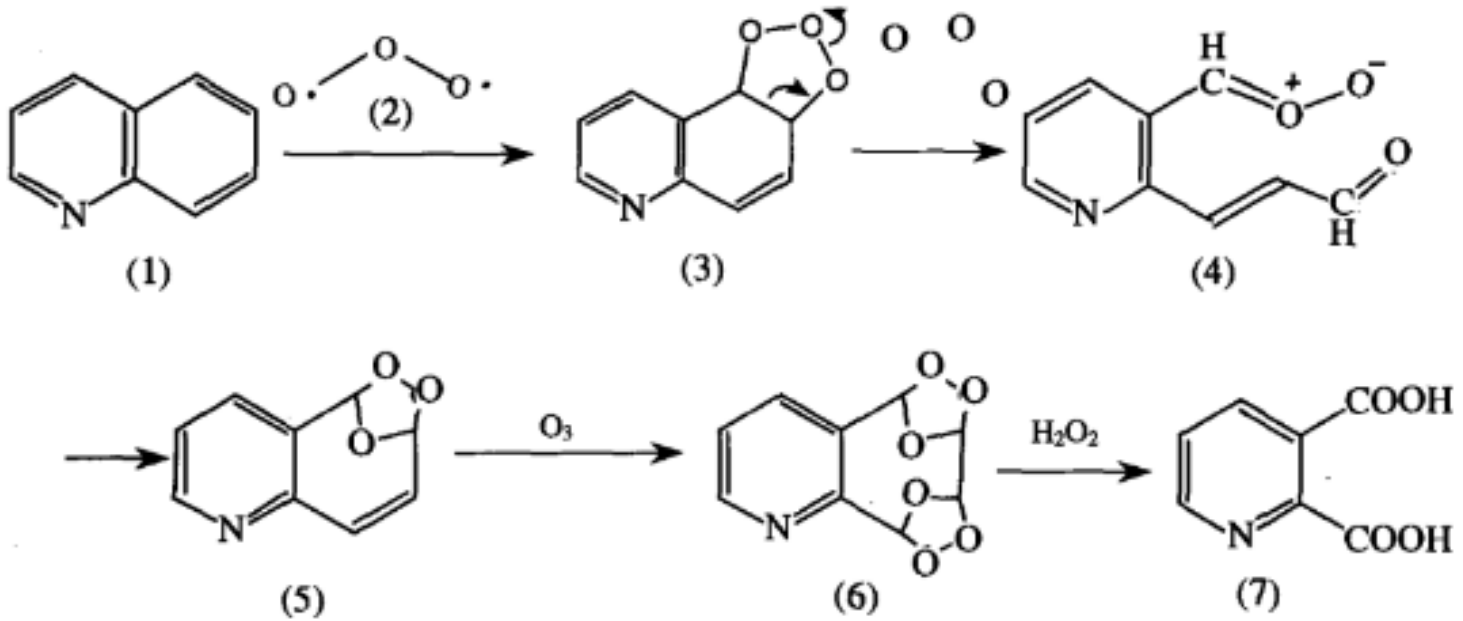
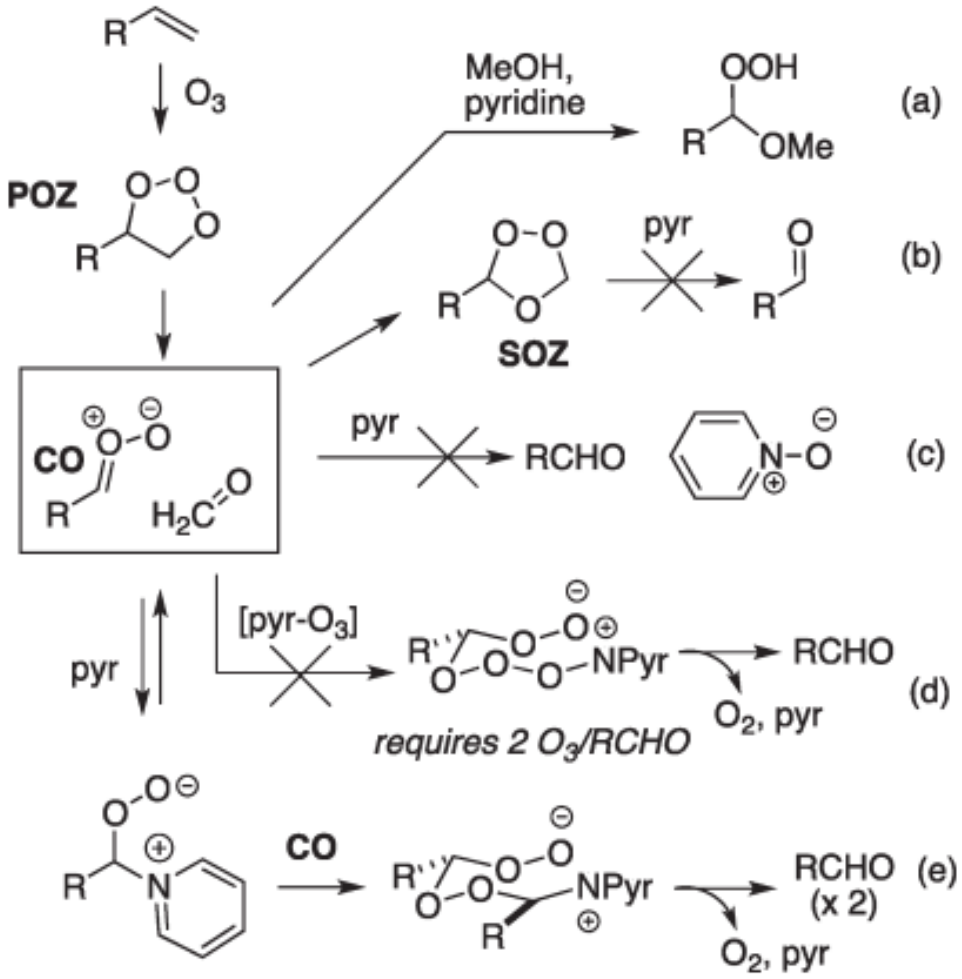


图 1　喹啉臭氧化

参考文献：“preparing nicotinic acid by ozonolysis-decarboxylation of quinoline”

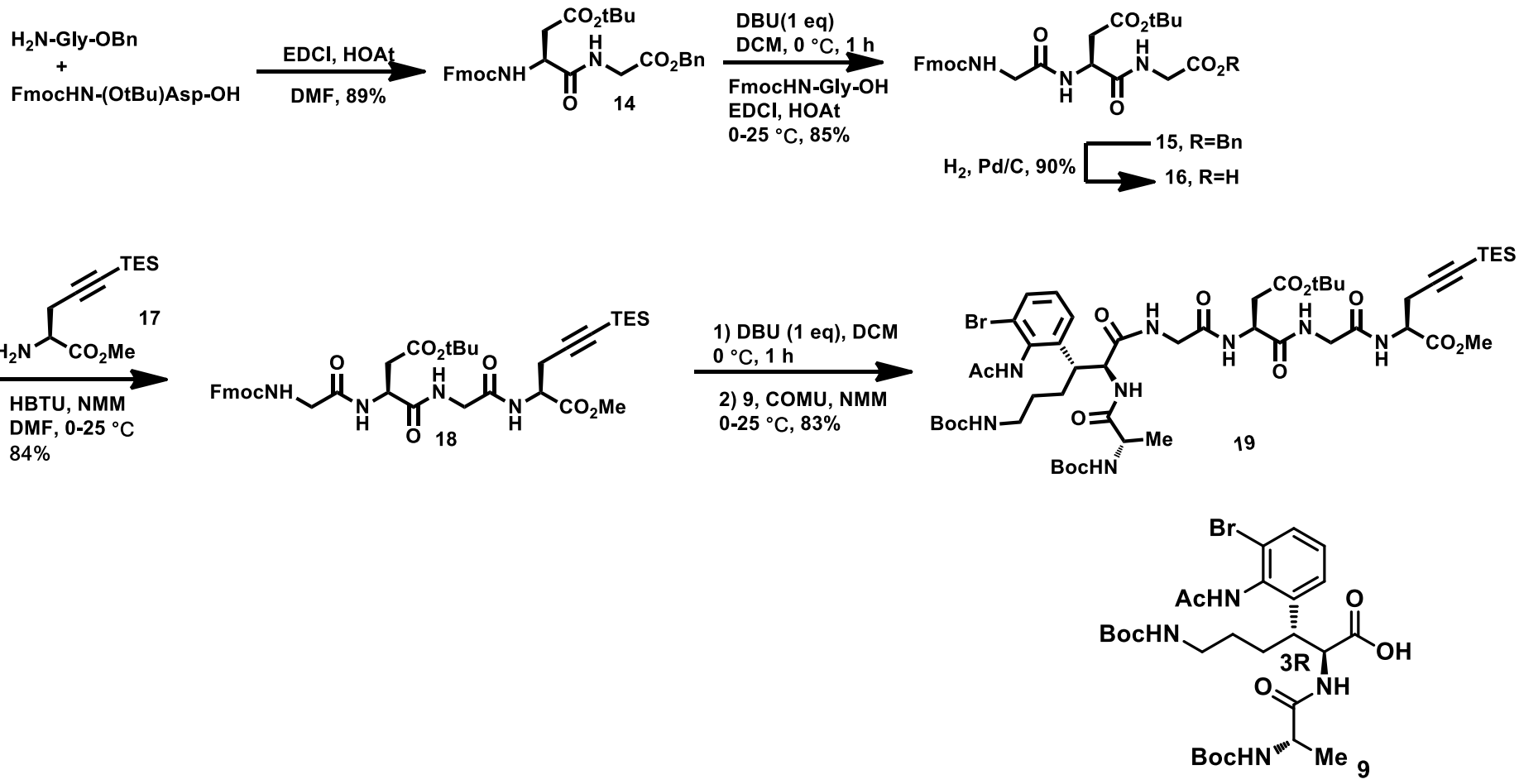
Scheme 1. Mechanistic Possibilities

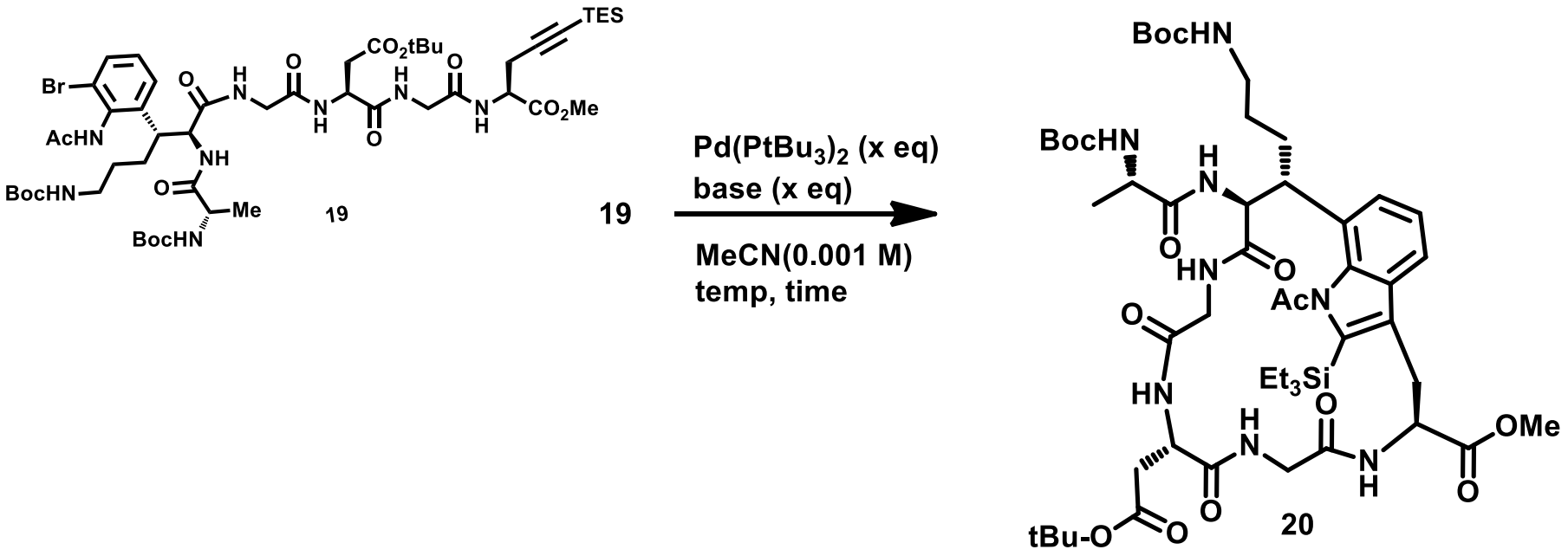


CO could trap pyridine to generate the nucleophilic zwitterion（两性离子）.

10.1021/ol300617r
Org. Lett., Vol. 14, No. 9, 2012

Scheme 2

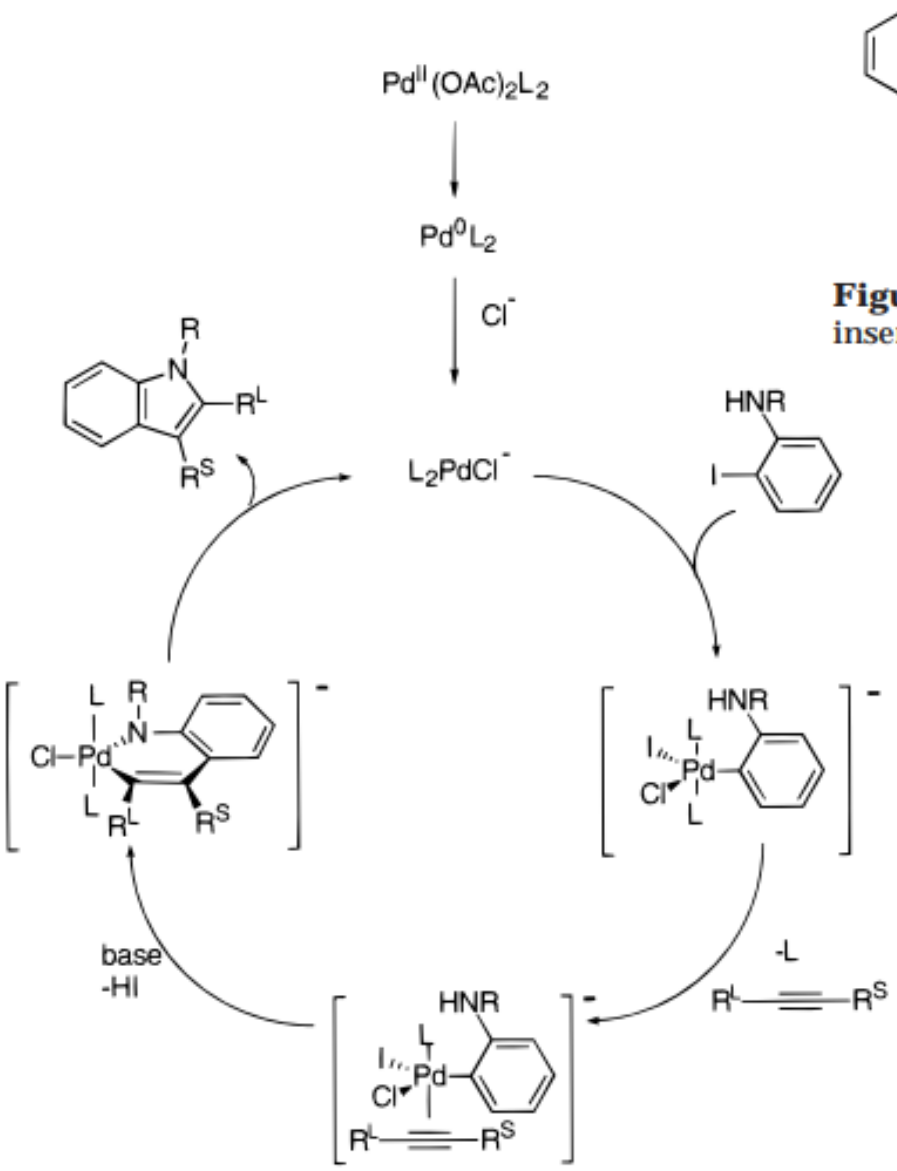

H2N-Gly-OBn
+
FmocHN-(OtBu)Asp-OH
EDCI, HOAt
DMF, 89%
FmocNH
CO2tBu
CO2Bn
14
DBU(1 eq)
DCM, 0 °C, 1 h
FmocHN-Gly-OH
EDCI, HOAt
0-25 °C, 85%
CO2R
15, R=Bn
H2, Pd/C, 90%
16, R=H
TES
17
H2N
CO2Me
HBTU, NMM
DMF, 0-25 °C
84%
18
1) DBU (1 eq), DCM
0 °C, 1 h
2) 9, COMU, NMM
0-25 °C, 83%
Br
AcHN
BocHN
NH
Me
19
3R
OH
9



entry	Pd (equiv)	base (equiv)	temp (°C)	time	yield
1	$Pd(OAc)_2$ (1.1)[a]	Et_3N (1.3)	100	1 h	50%
2	$Pd(OAc)_2$ (1.1)[a,b]	Et_3N (1.3)	100	1 h	45%
3	$Pd(P\textit{t}\text{-}Bu_3)_2$ (1.1)	Et_3N (1.3)	100	1 h	28%
4	$Pd(P\textit{t}\text{-}Bu_3)_2$ (1.2)	Et_3N (1.3)	80	1 h	58%
5	$Pd(P\textit{t}\text{-}Bu_3)_2$ (0.2)	Cy_2NMe (2.5)	80	4 h	34%
6	$Pd(P\textit{t}\text{-}Bu_3)_2$ (0.6)	Cy_2NMe (2.5)	80	2 h	58%
7	$Pd(P\textit{t}\text{-}Bu_3)_2$ (1.2)	Cy_2NMe (2.5)	80	4 h	50%
8	**$Pd(P\textit{t}\text{-}Bu_3)_2$ (1.1)**	**Cy_2NMe (1.3)**	**80**	**1 h**	**60%**
9	$Pd(P\textit{t}\text{-}Bu_3)_2$ (1.1)	Cy_2NMe (1.3)	80	2 h	54%

[a]1.3 equiv dtbpf, toluene/MeCN (1:1). [b]1 equiv Bu_4NBr.

Figure 5. Representative results of the macrocyclization optimization.



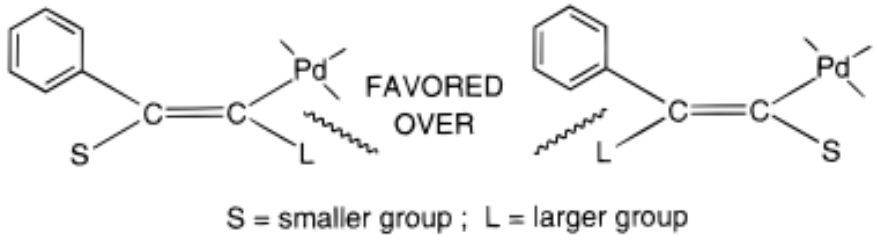


Figure 1. Steric effects on the regiochemistry of alkyne insertion.

J. Org. Chem. **1998,** *63,* 7652-7662.

"Synthesis of 2,3-Disubstituted Indoles via Palladium-Catalyzed Annulation of Internal Alkynes"

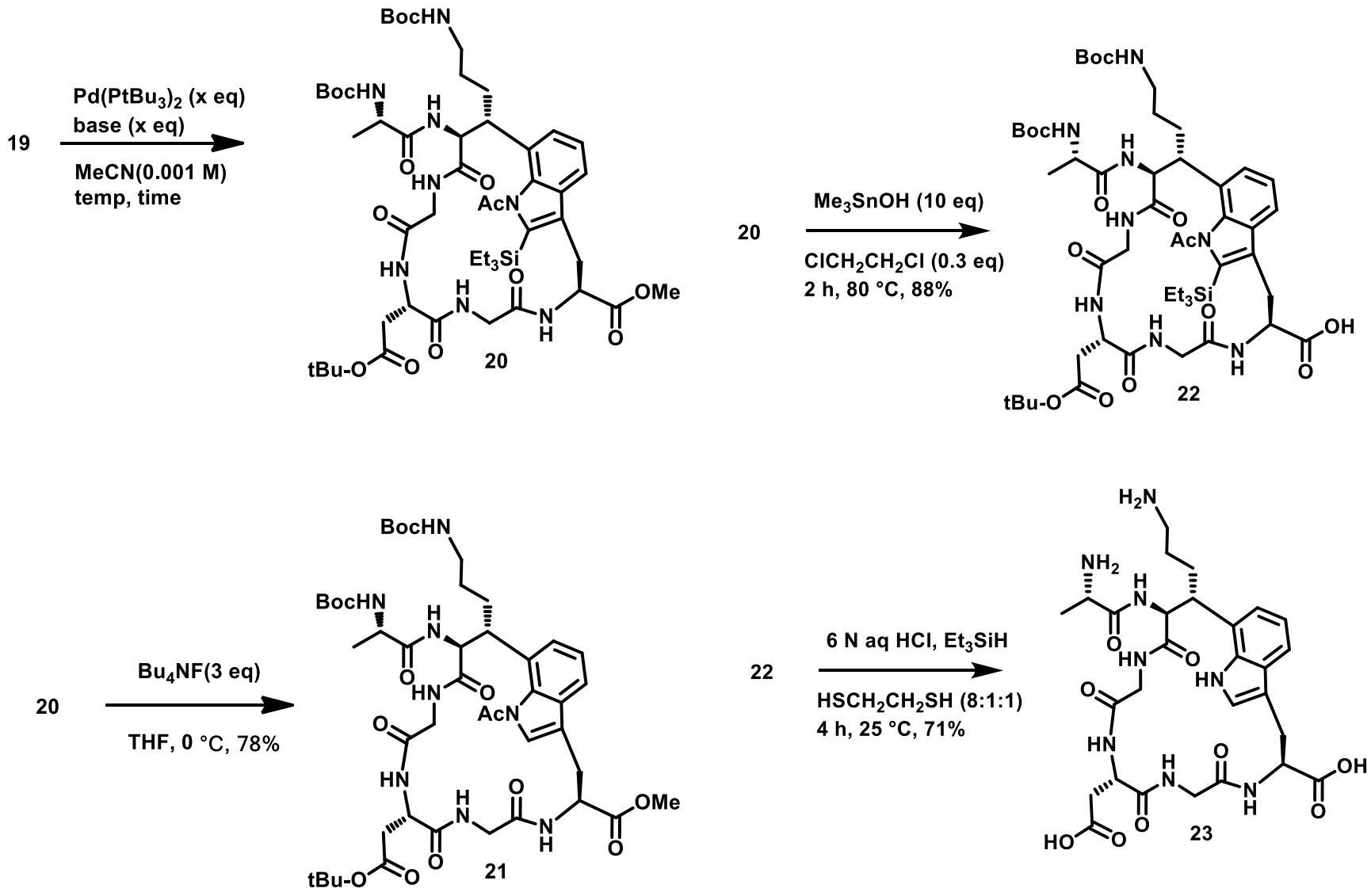


Figure 6. Deprotection studies on the macrocyclic core.

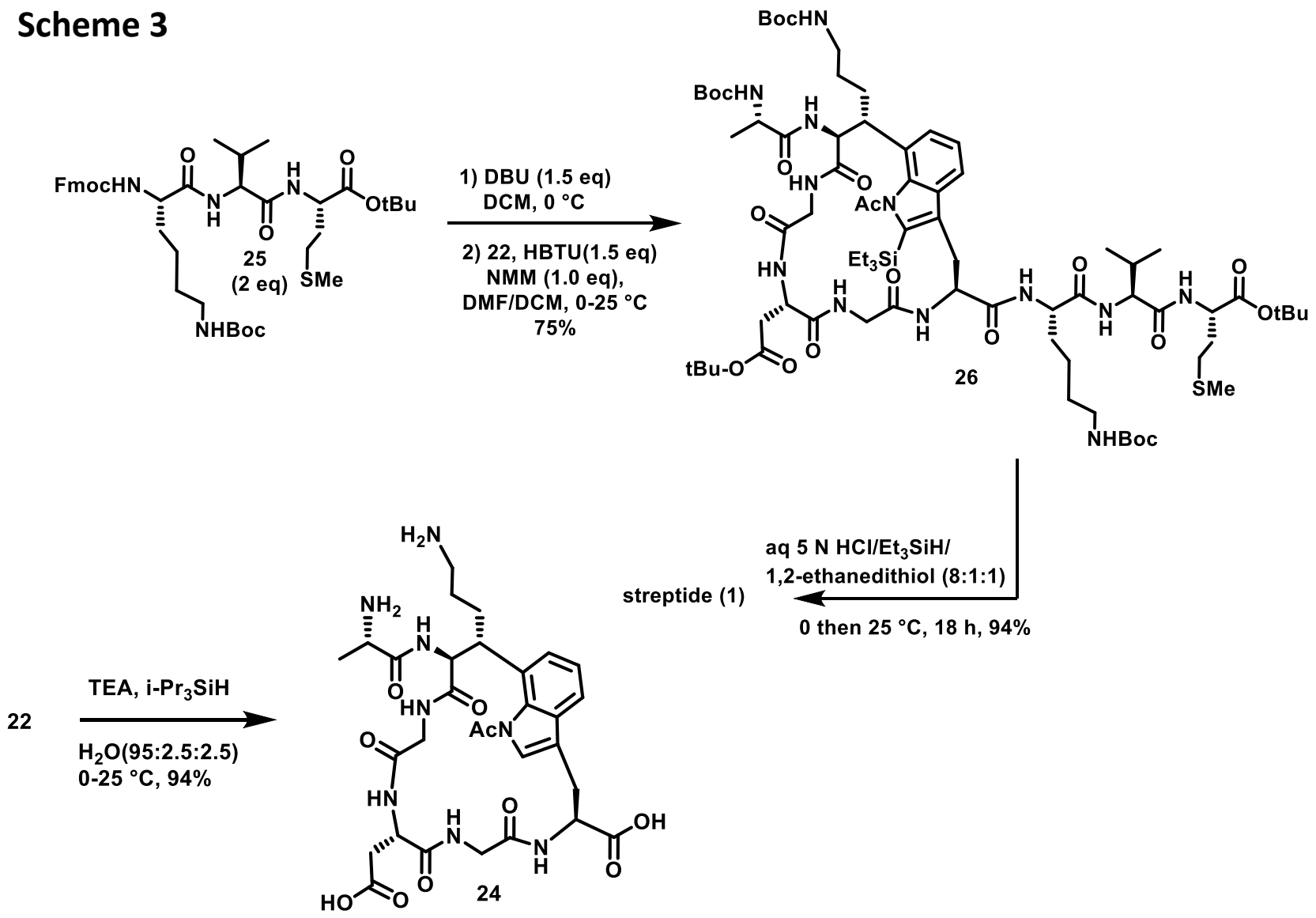


Figure 6. Deprotection studies on the macrocyclic core.

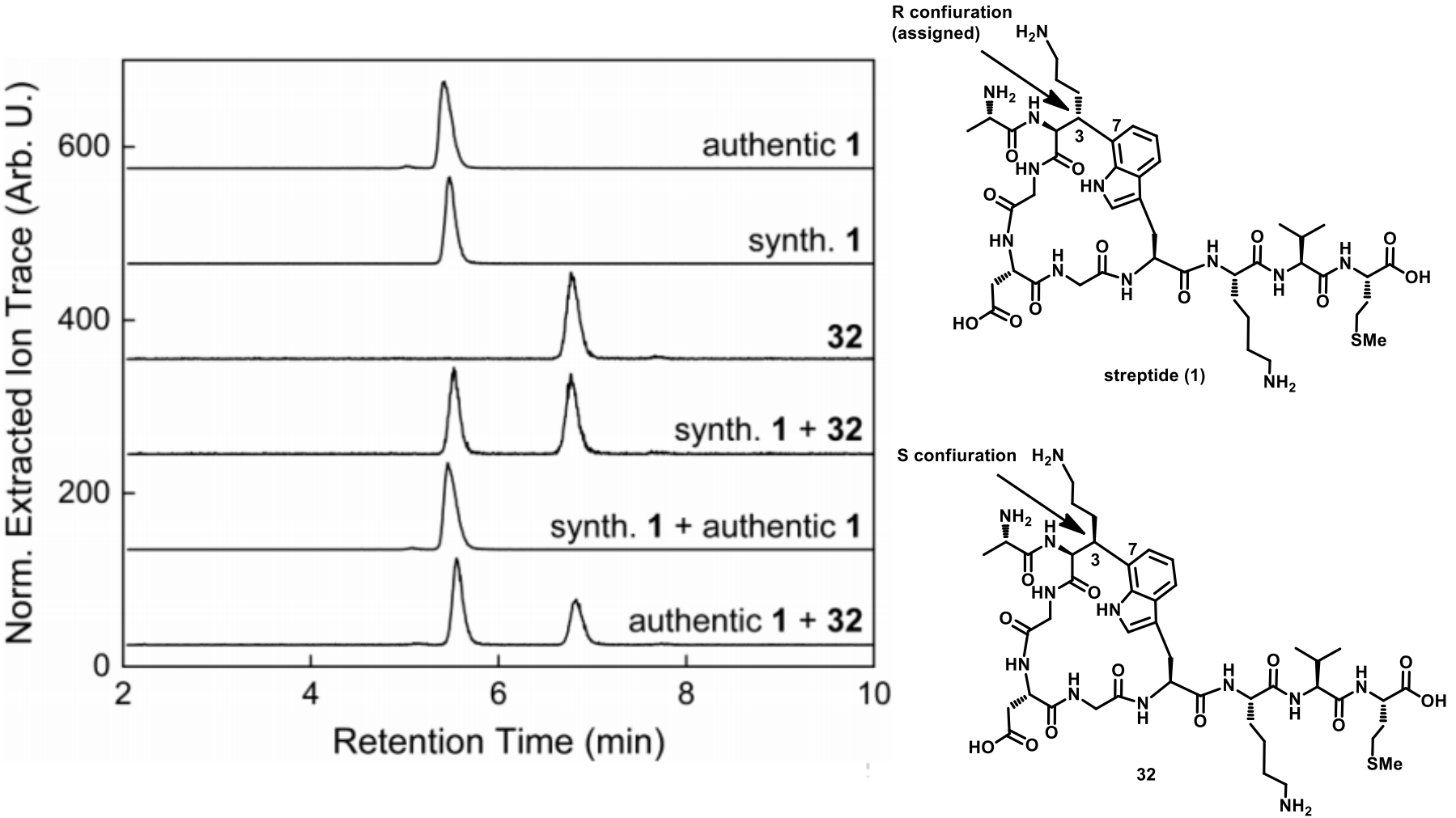


Figure 7. HR-HPLC-MS analysis of authentic and synthetic streptides. The sample loaded is labeled on top of the resulting elution profile. Streptide elution was monitored by absorbance at 280 nm (not shown) and by MS total ion count. Shown is the HR-MSextracted ion chromatogram for streptide (m/z 989.489) in each trace. Authentic streptide coelutes with lysine-2 C3 diastereomer 1 (3R) but not with 32 (3S).
See Supporting Information for details.

THANK YOU!