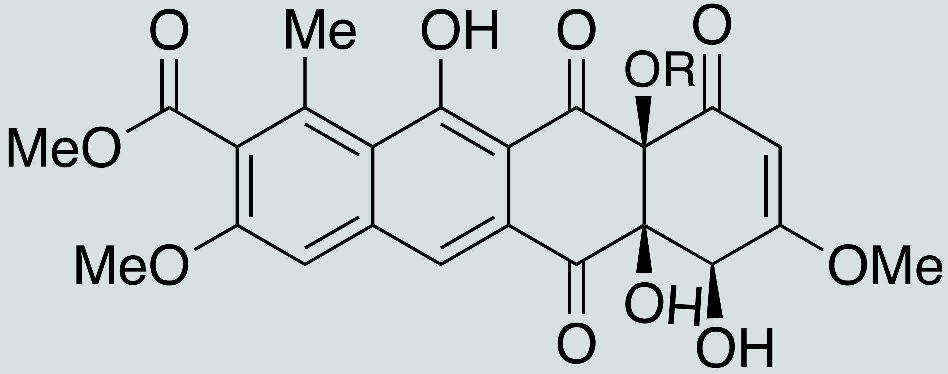
First Total Syntheses of Tetracenomycins C and X

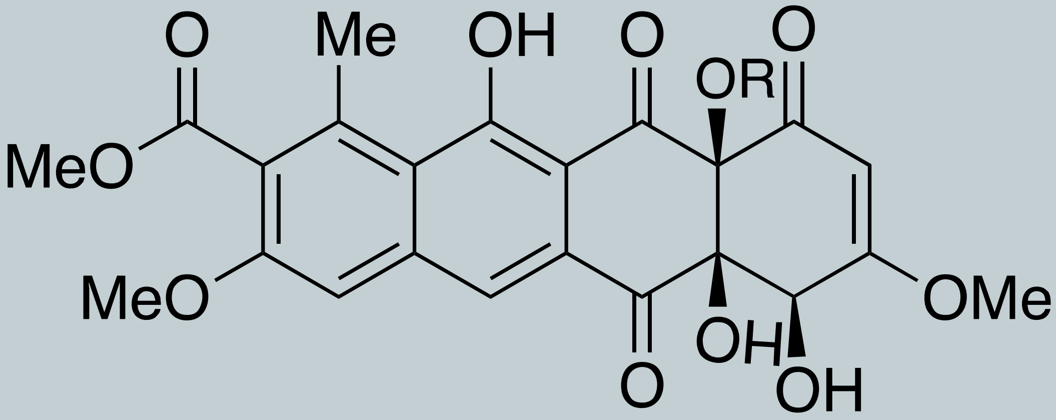
*Shogo Sato, Keiichiro Sakata, Yoshimitsu Hashimoto, Hiroshi Takikawa, and Keisuke Suzuki**

In memory of Osamu Yonemitsu



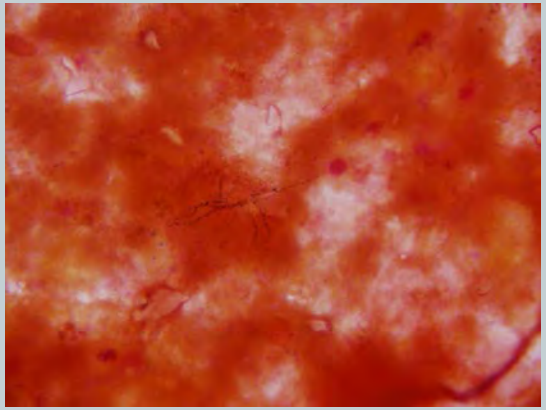
R = Me, (+)-Tetracenomycin X
R = H, (+)-Tetracenomycin C

TETRACENOMYCIN



R = Me, (+)-Tetracenomycin X
R = H,   (+)-Tetracenomycin C

Culture of Streptomyces species

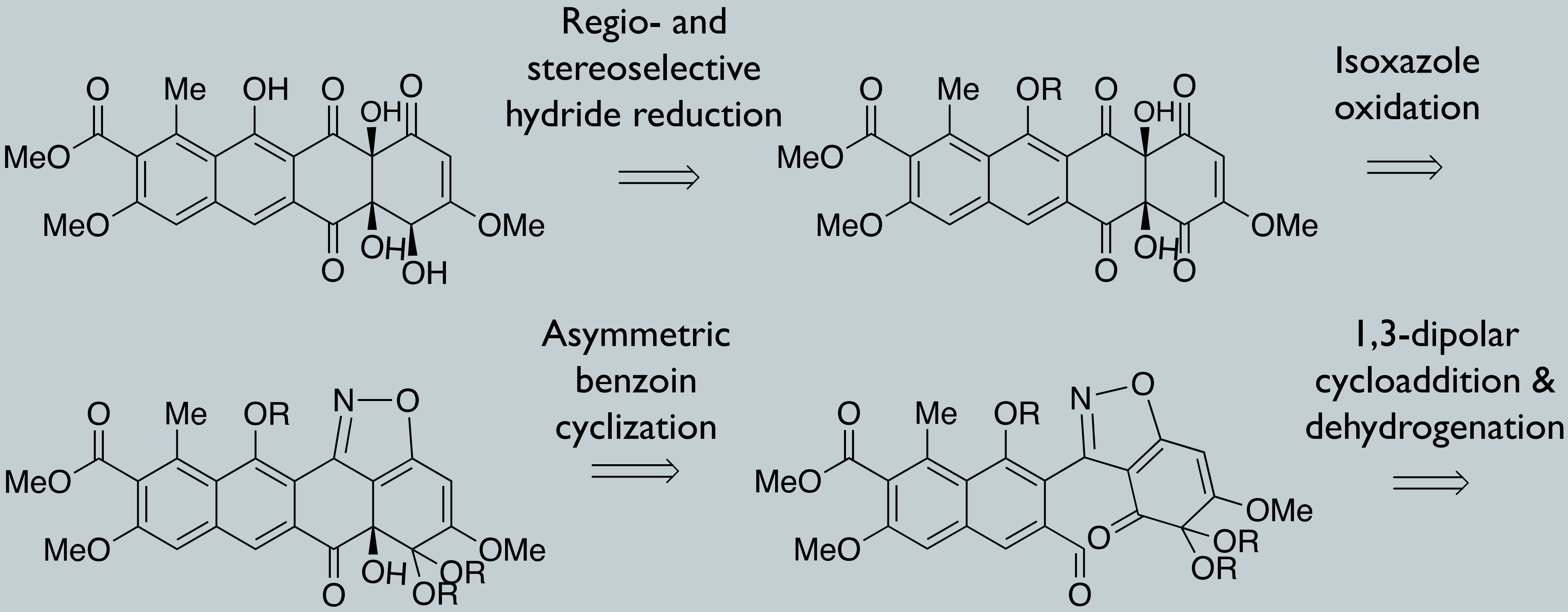


Nocardia found in a brain biopsy

- Antitumor
- Active against gram positive bacteria

J. Antibiot. **1990**, *43*, 1169.

RETROSYNTHESIS



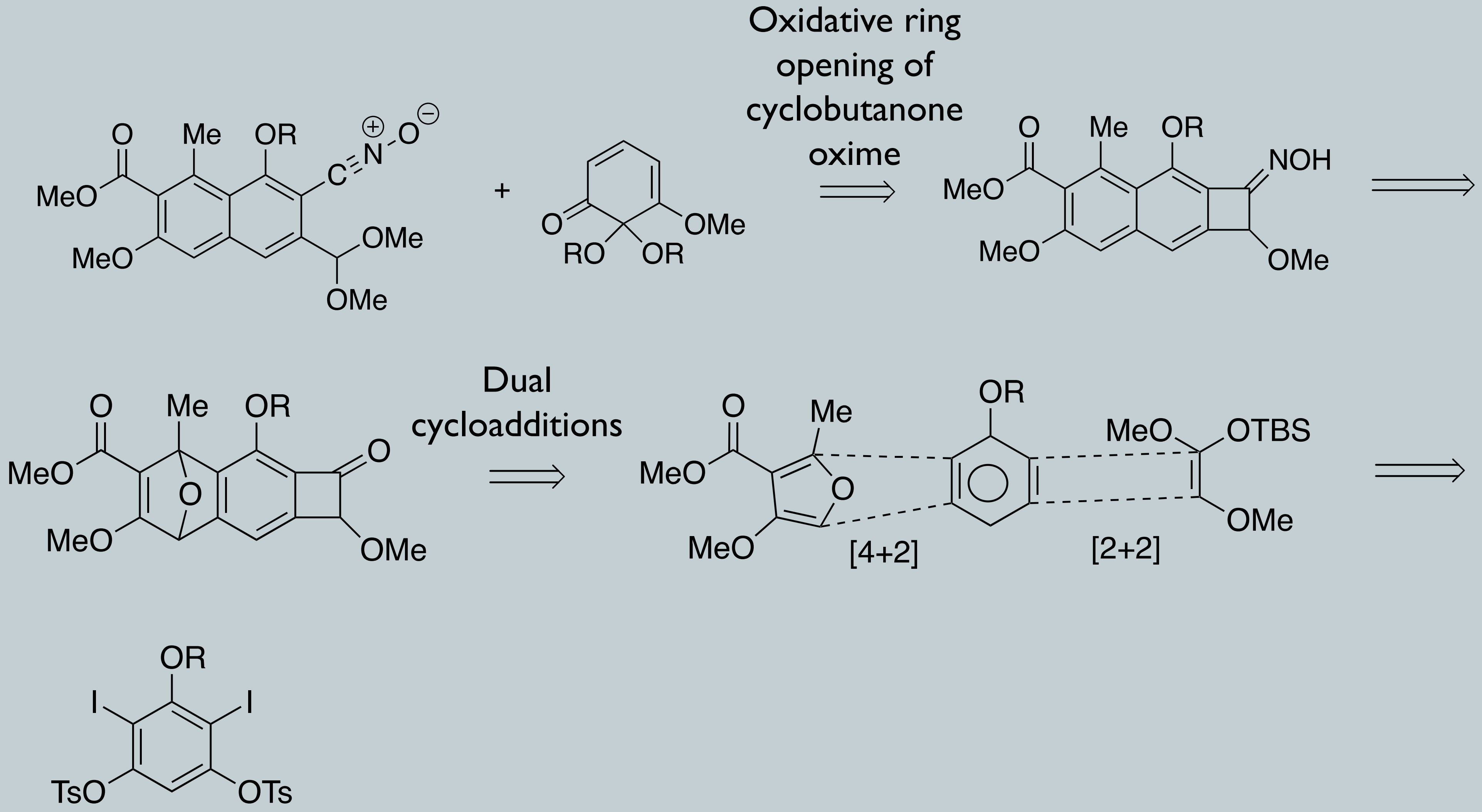
Regio- and stereoselective hydride reduction

Isoxazole oxidation

Asymmetric benzoin cyclization

1,3-dipolar cycloaddition & dehydrogenation

RETROSYNTHESIS

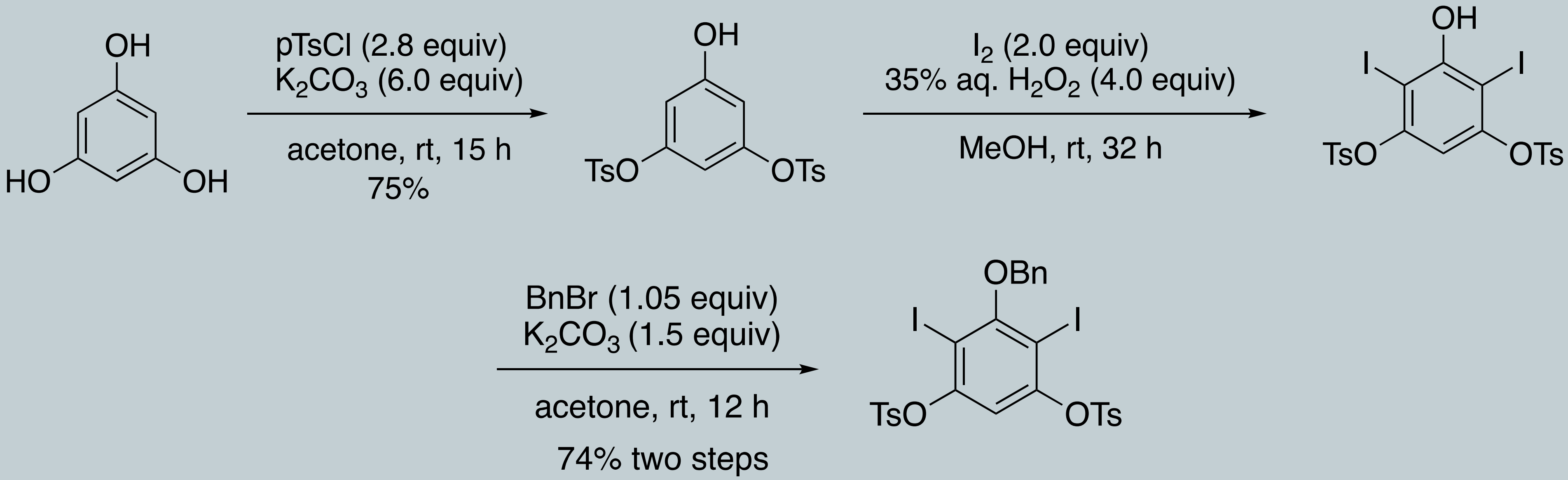


Oxidative ring opening of cyclobutanone oxime

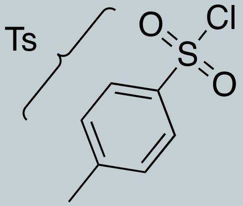
Dual cycloadditions

TOTAL SYNTHESIS

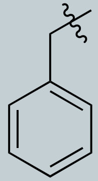
Generation of the benzdiyne equivalent



pTsCl

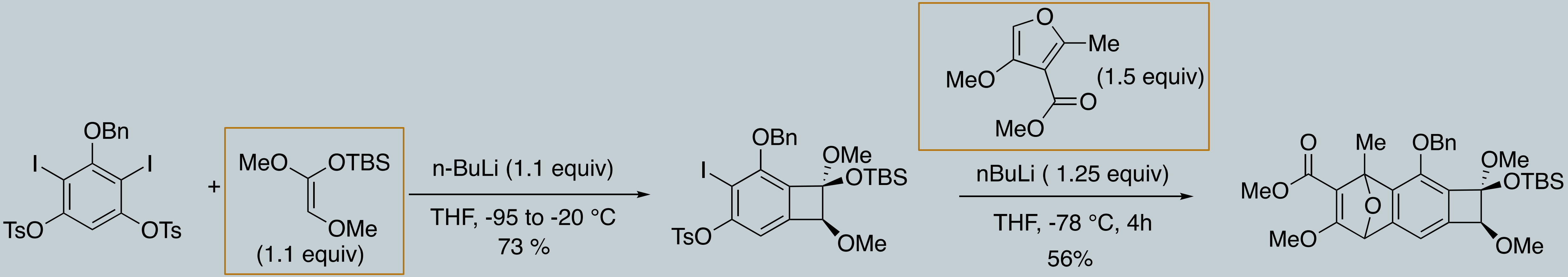


Bn



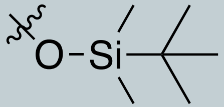
TOTAL SYNTHESIS

[2+2] and [4+2] cycloaddition

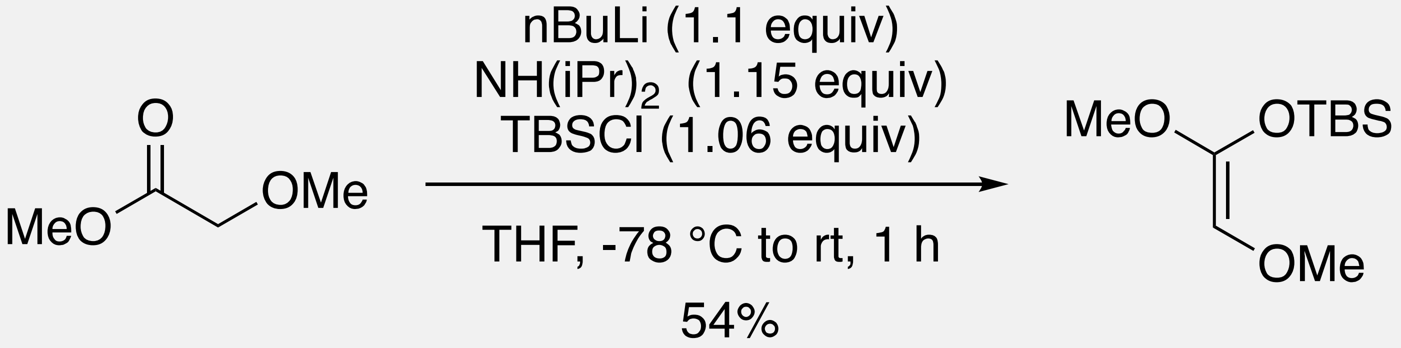


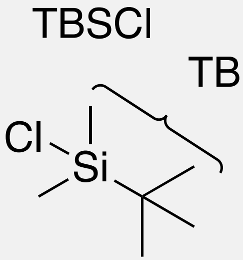
They were also able to do this reaction as a one pot synthesis

OTBS



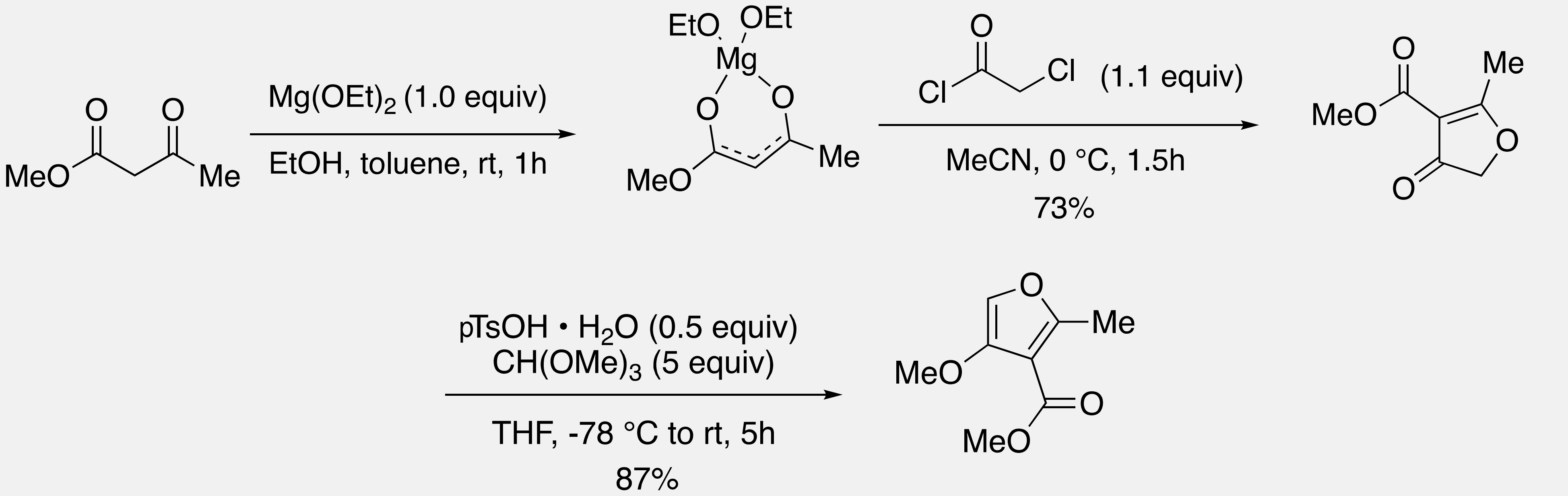
NON-LINEAR SYNTHESIS - 1



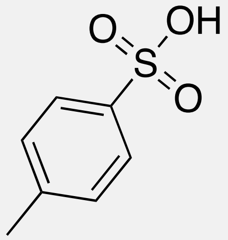


Ang. Chem. Int. Ed. **2007**, *46*, 6502-6504

NON-LINEAR SYNTHESIS – 2



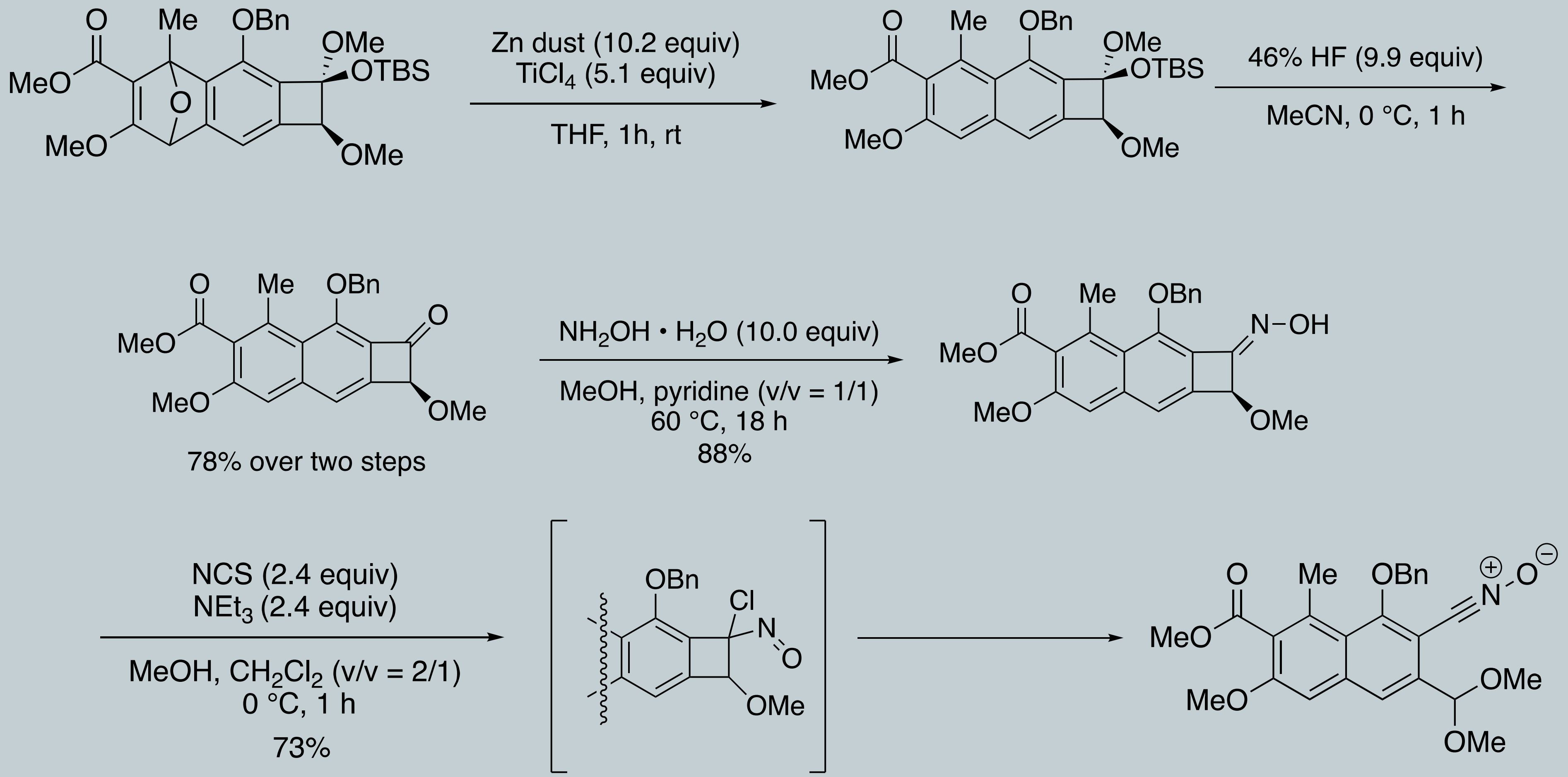
pTsOH

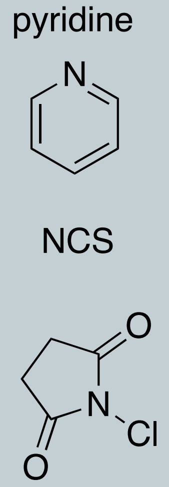


Syn. Lett.. **2017**, *28*, 1719.

TOTAL SYNTHESIS

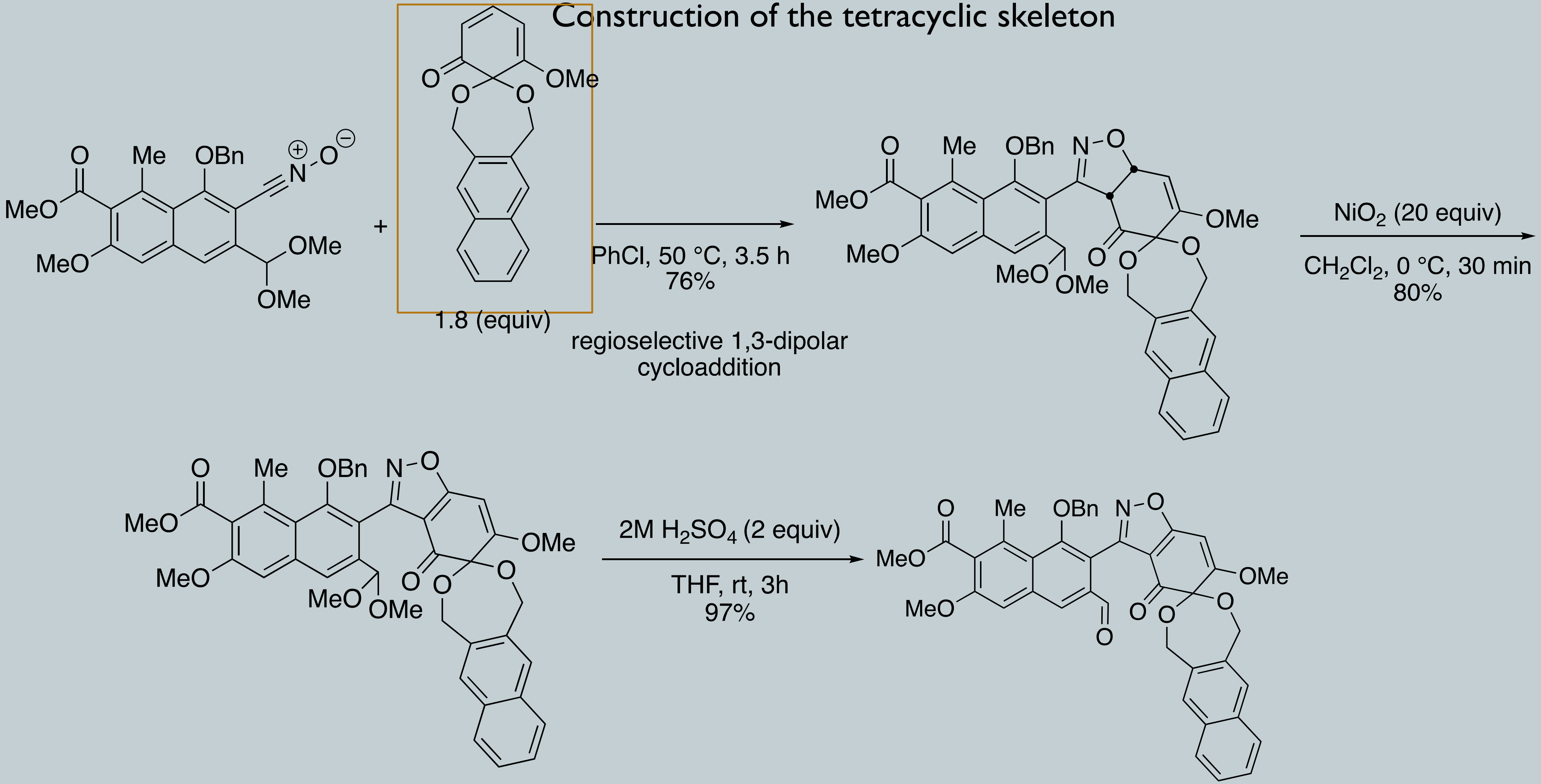
Establishing unsymmetrical functionality by unique oxidative ring opening





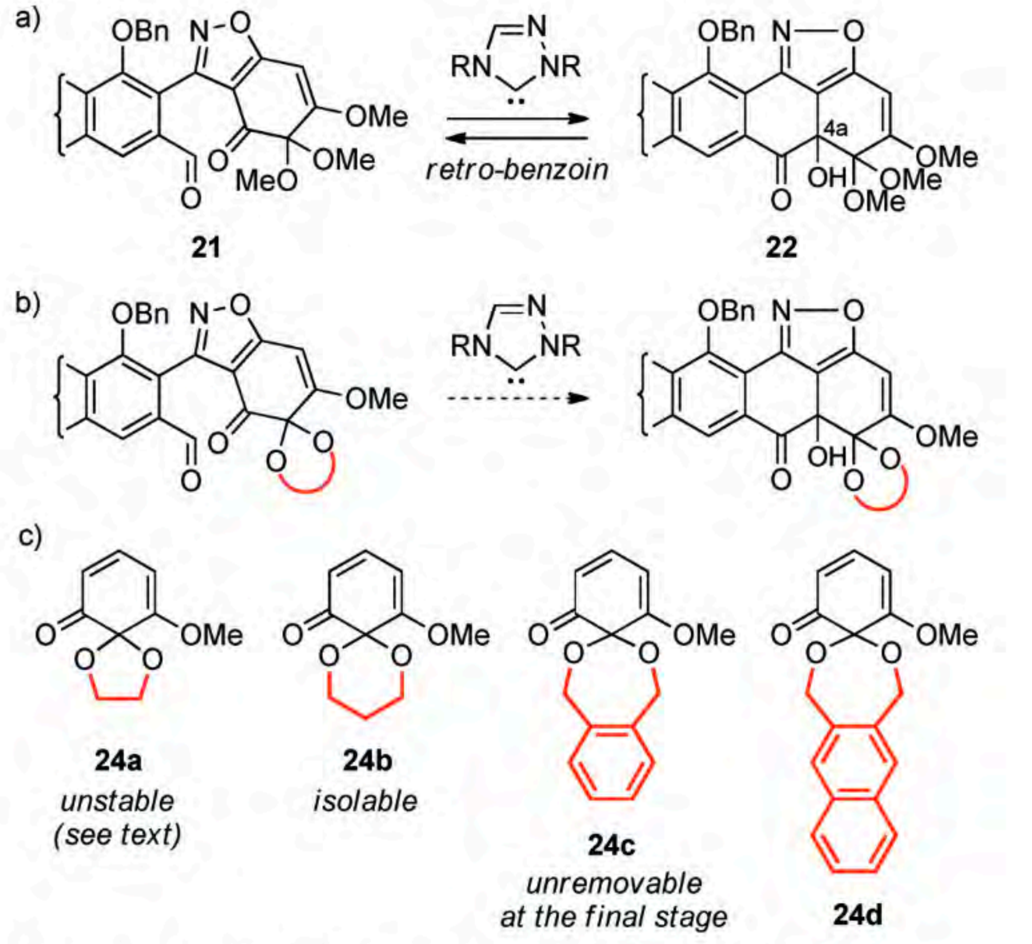
TOTAL SYNTHESIS

Construction of the tetracyclic skeleton



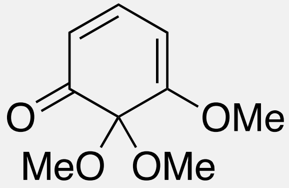
regioselective 1,3-dipolar cycloaddition

COMPLICATIONS WITH ADDITION OF THE MONO-ACETAL



Scheme 5. Problem and solution for the benzoin cyclization.

Originally the reaction was run with



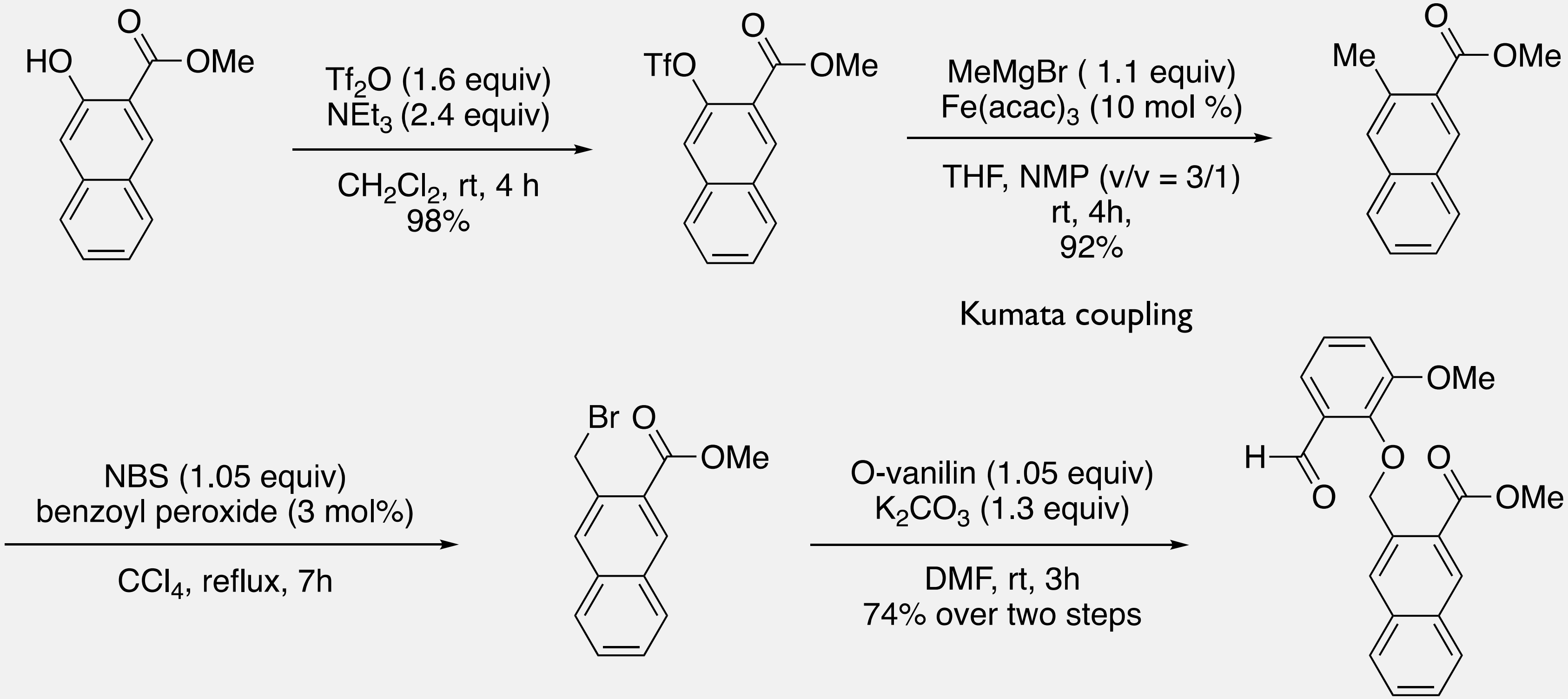
Which lead to the desired product but in the benzoin cyclization led to low yields.

This was proposed to be due to unfavorable steric interactions at the C-4 carbon leading to retro-benzoin

So they tried cyclic, less rotatable, acetal moietys

NON-LINEAR SYNTHESIS - 3

Construction of the acetal moiety



Tf_2O (1.6 equiv)
NEt_3 (2.4 equiv)
CH_2Cl_2, rt, 4 h
98%

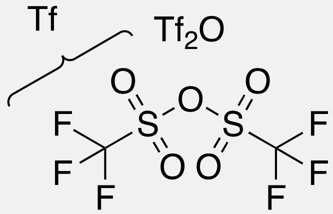
MeMgBr (1.1 equiv)
$Fe(acac)_3$ (10 mol %)
THF, NMP (v/v = 3/1)
rt, 4h,
92%

Kumata coupling

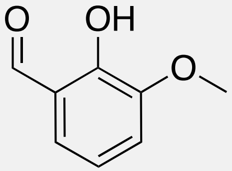
NBS (1.05 equiv)
benzoyl peroxide (3 mol%)
CCl_4, reflux, 7h

O-vanilin (1.05 equiv)
K_2CO_3 (1.3 equiv)
DMF, rt, 3h
74% over two steps

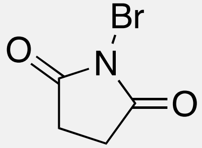
Tf_2O



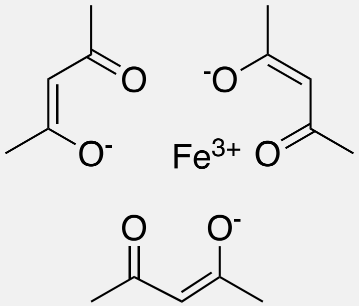
O-vanilin



NBS

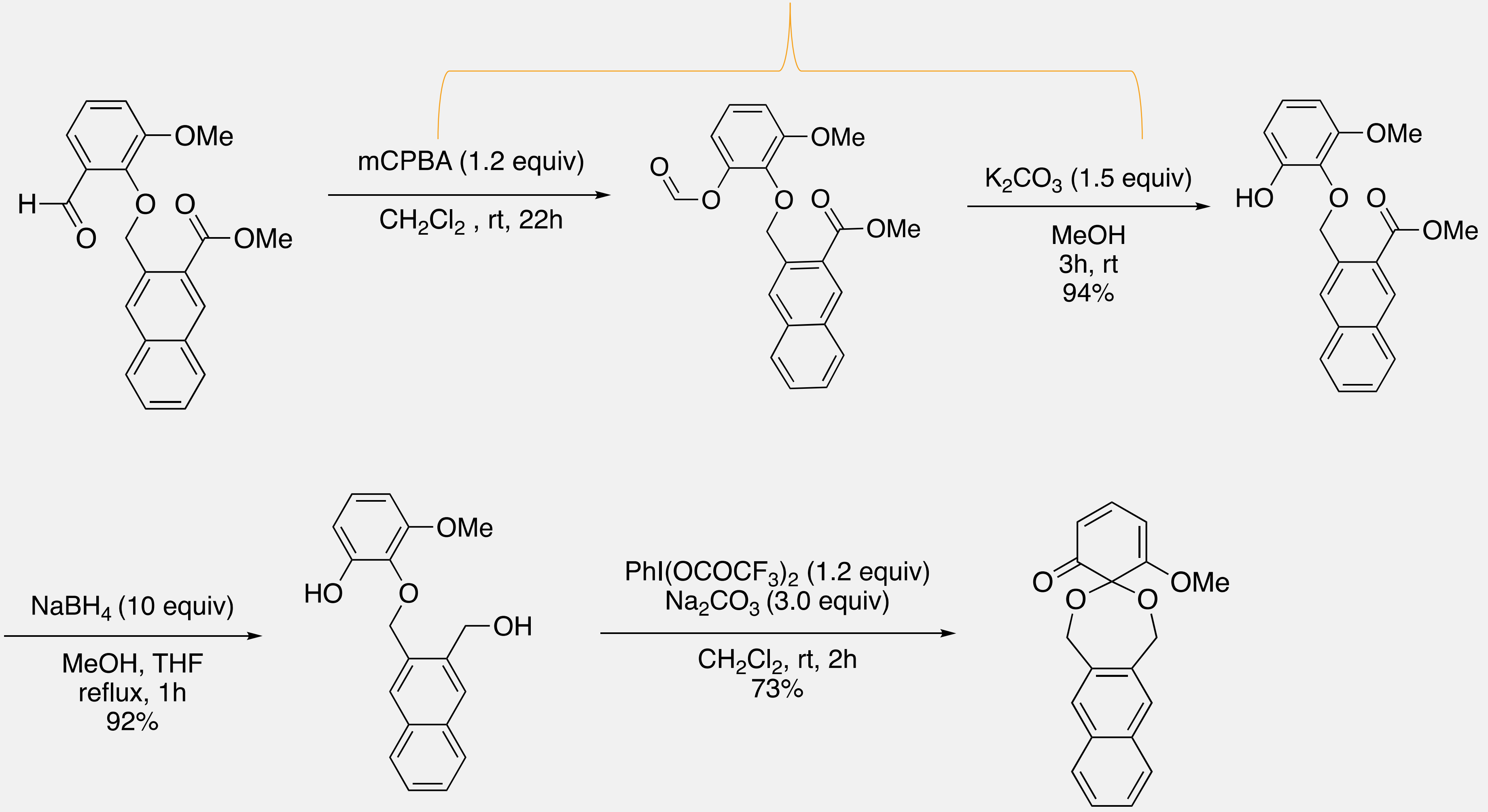


$Fe(acac)_3$

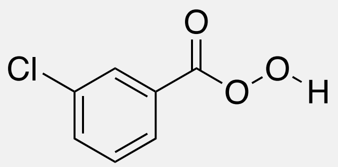


NON-LINEAR SYNTHESIS – 3 CONT'D

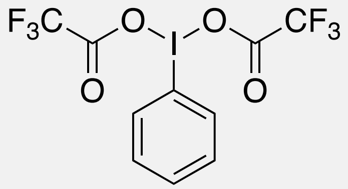
Dakin Oxidation



m-CPBA

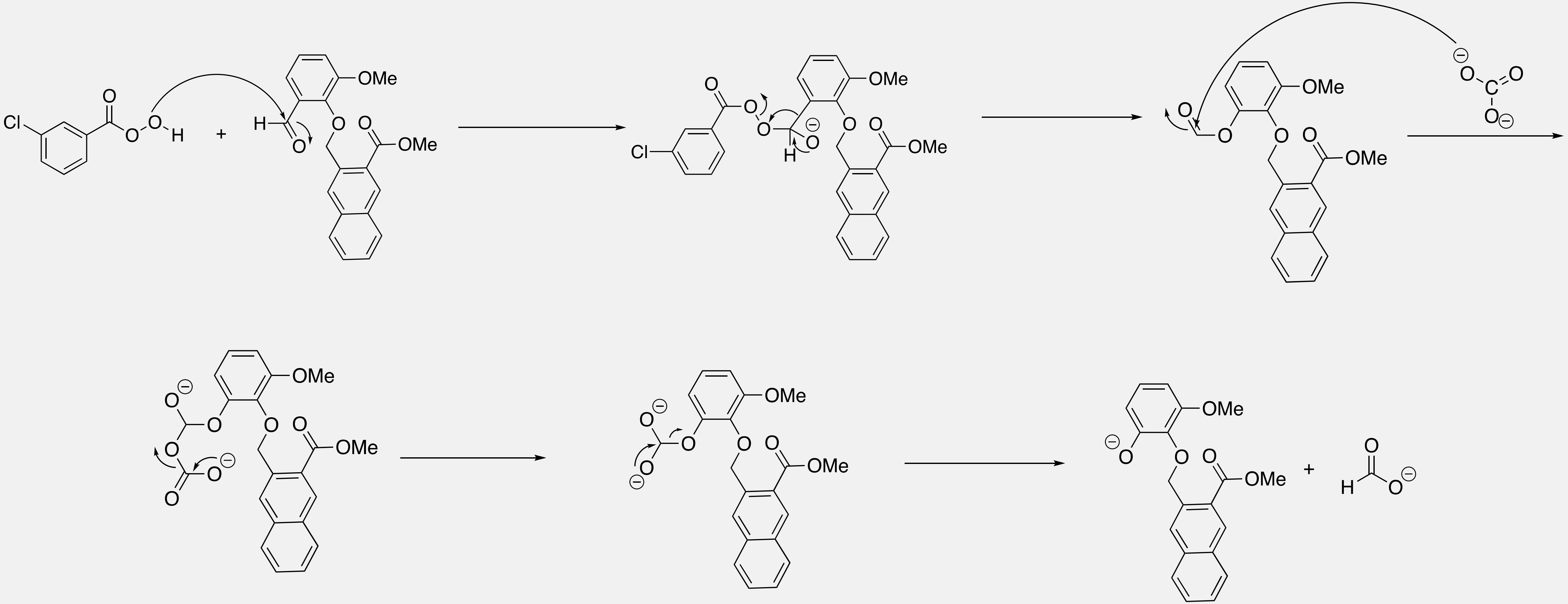


$PhI(OCOCF_3)_2$



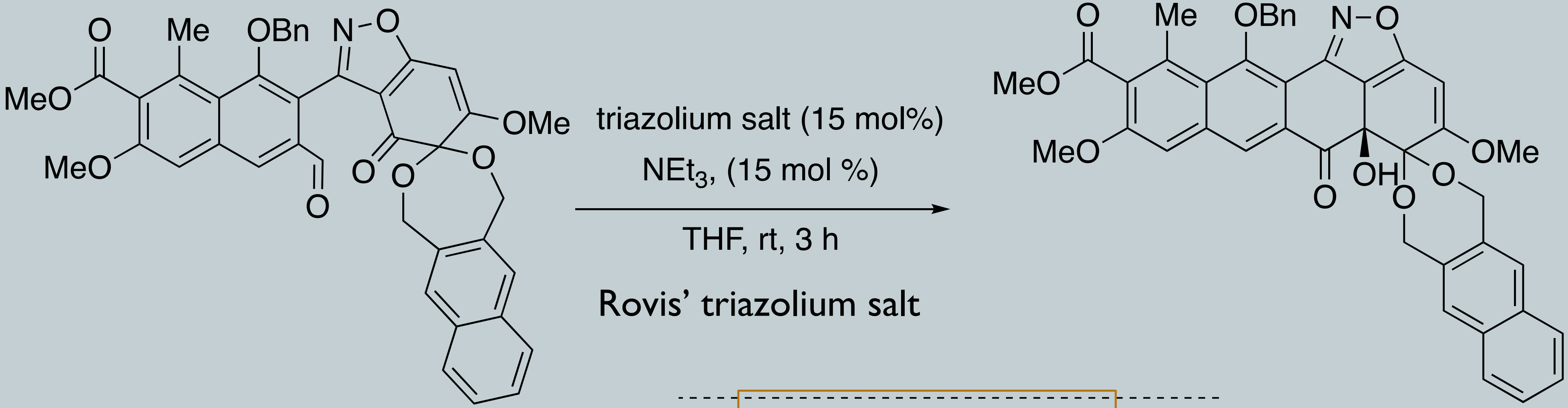
DAKIN OXIDATION

- Very similar to Baeyer-Villiger
- Oxidation of aromatic aldehydes to phenols



TOTAL SYNTHESIS

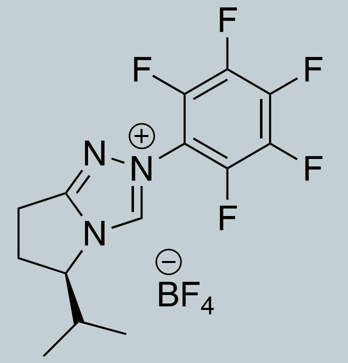
Key benzoin cyclization



triazolium salt (15 mol%)
NEt_3, (15 mol %)
THF, rt, 3 h

Rovis' triazolium salt

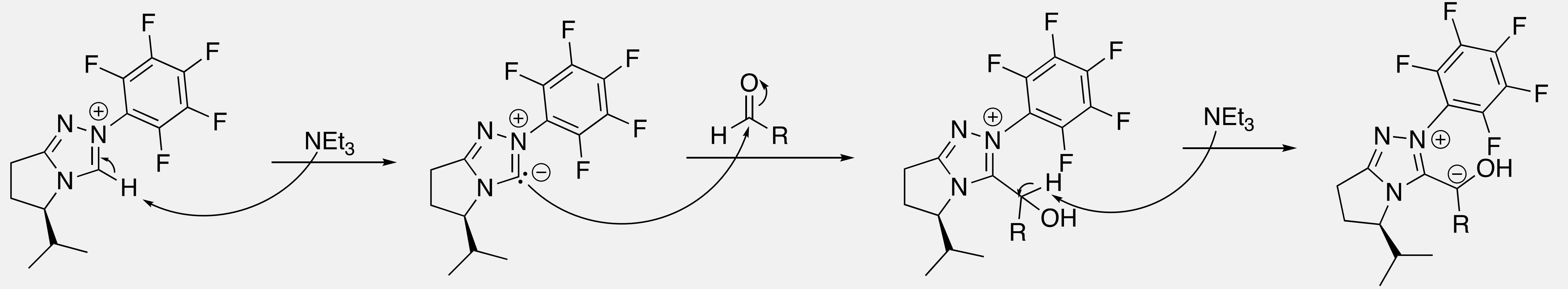
triazolium salt



What does the triazolium salt do?

J. Am. Chem. Soc. **2009**, *131*, 10872.

TRIAZOLIUM SALTS IN BENZOIN CONDENSATIONS

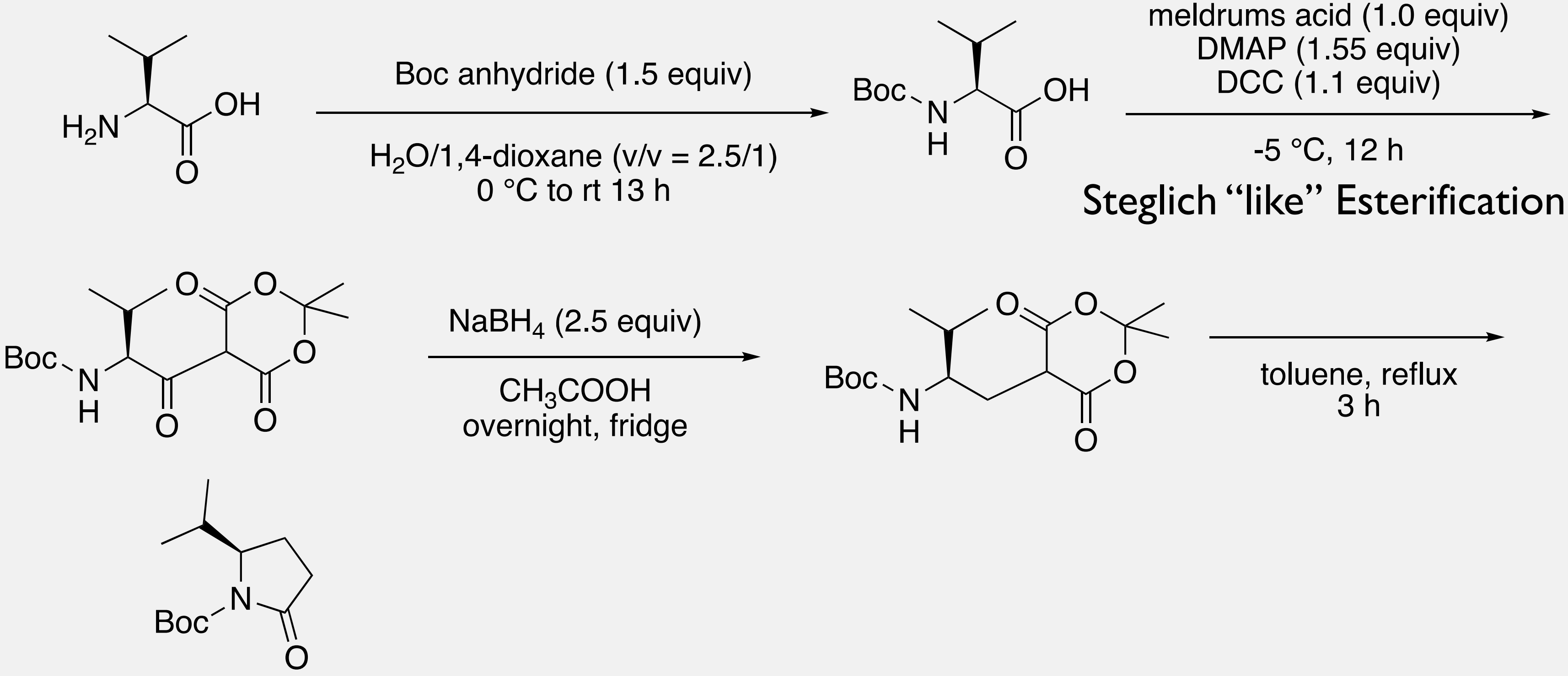


Why Triazolium salts and not just CN-?

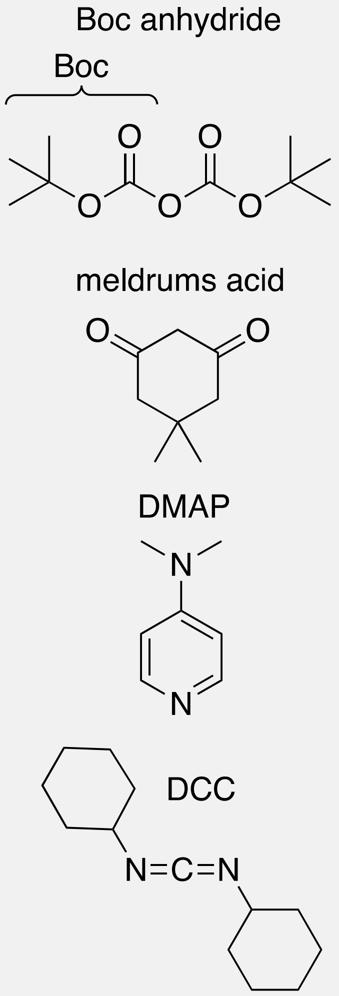
- Ability to insert a chiral auxiliary into the mechanism to control the stereochemical outcome
- More powerful at increasing the acidity of the proton, so generally more applicable
- However, they are more complicated

NON-LINEAR SYNTHESIS - 4

Synthesis of the chiral triazolium salt



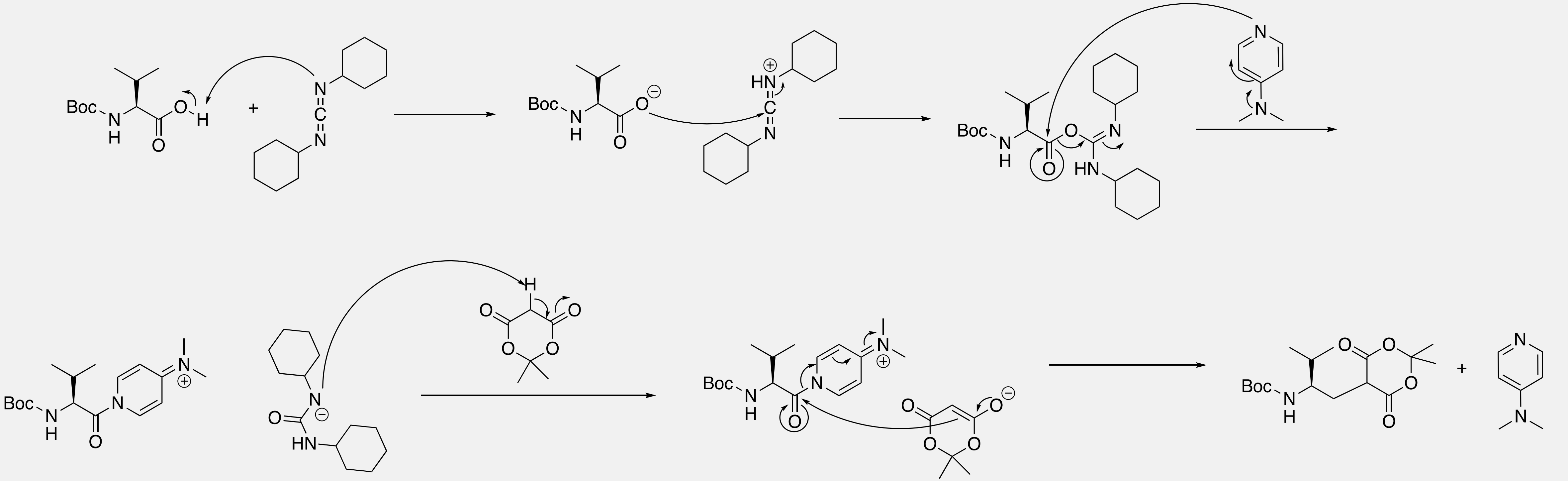
Steglich “like” Esterification



Acta Pharm. Sin. B **2012,** *2*, 213.

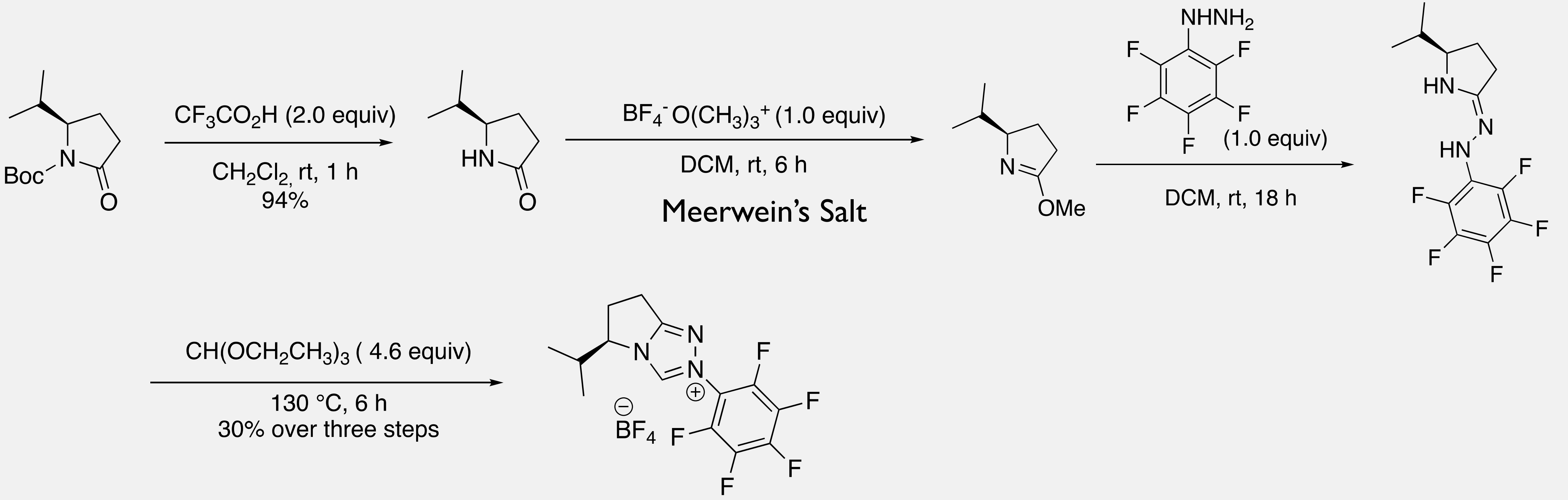
Tetrahedron. **1997**, *53*, 12867.

STEGLICH ESTERIFICATION



Classic Steglich esterification would then be attacked
By an alcohol to make an ester. However here we have
nucleophilic attack of an enolate from Meuldrum’s acid

NON-LINEAR SYNTHESIS – 4 CONT'D

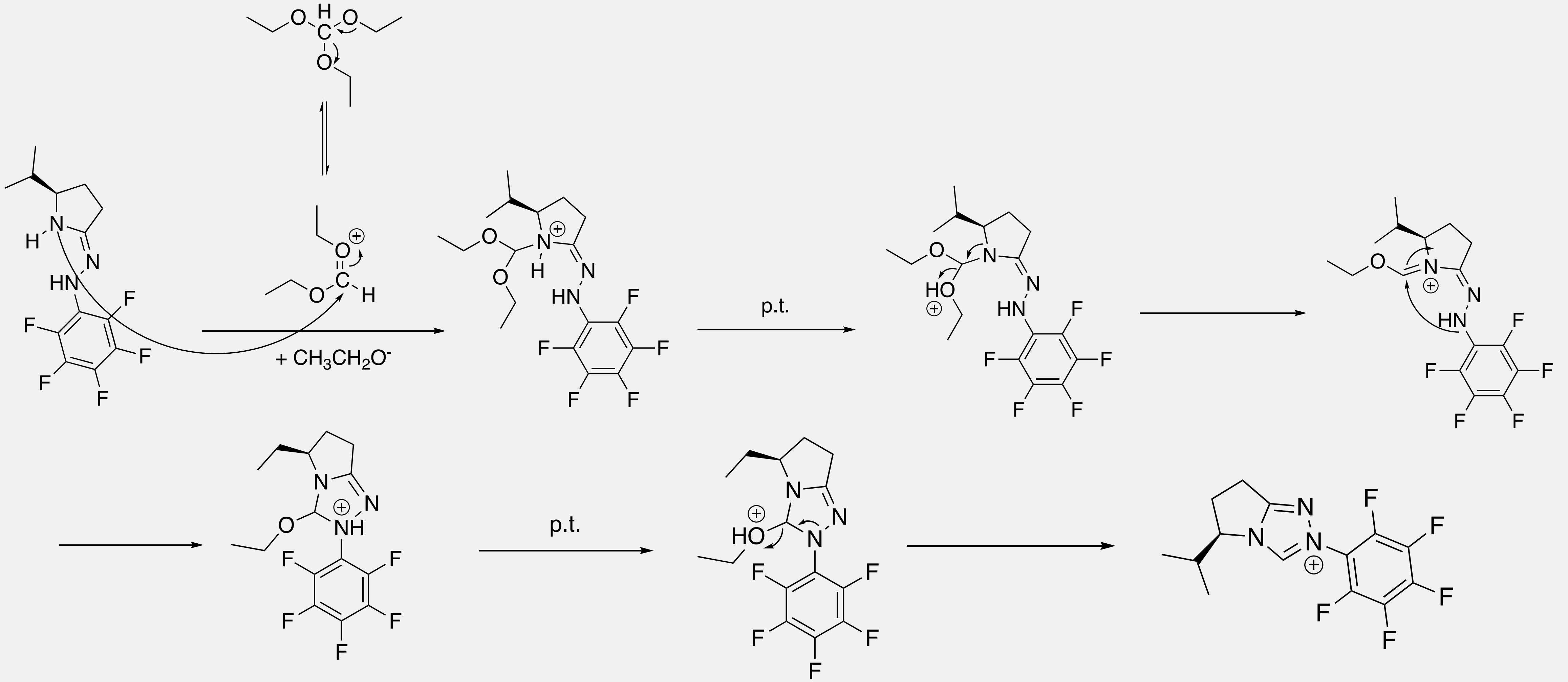


J. Amer. Chem. Soc. **2009,** *131*, 10872.

Org. Biomol. Chem., **2014,** *12*, 7537.

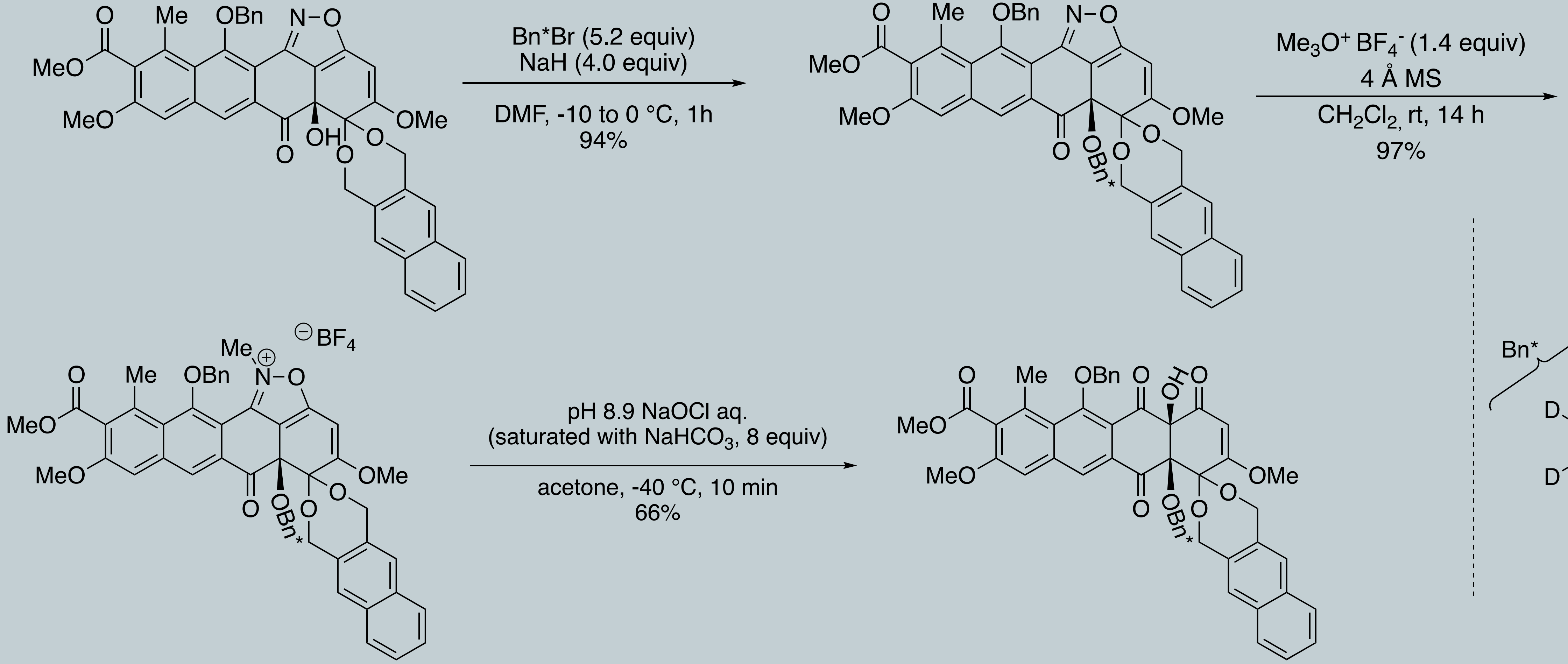
J. Chem. Soc., Perkin Trans. 1, **1998,** 1891. (Leeper Method)

MECHANISM OF HETEROCYCLE FORMATION



TOTAL SYNTHESIS

Series of imperative protections/deprotections to lead to the desired product

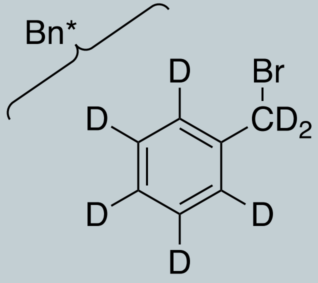


Bn*Br (5.2 equiv)
NaH (4.0 equiv)
DMF, -10 to 0 °C, 1h
94%

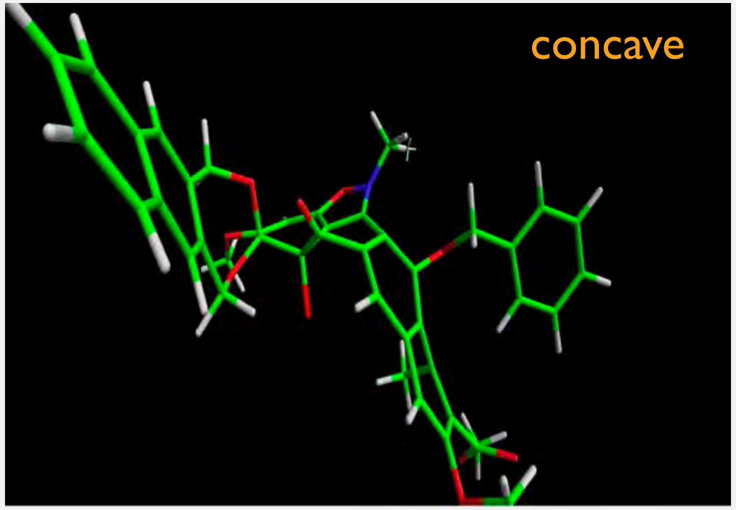
$Me_3O^+ BF_4^-$ (1.4 equiv)
4 Å MS
CH_2Cl_2, rt, 14 h
97%

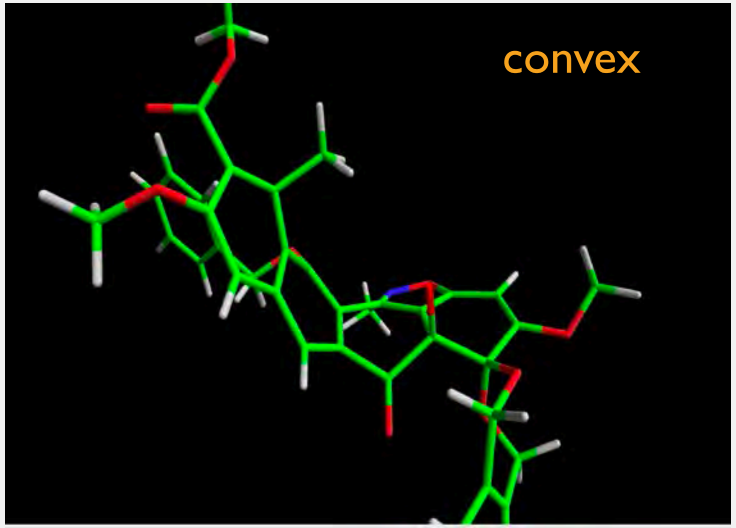
pH 8.9 NaOCl aq.
(saturated with $NaHCO_3$, 8 equiv)
acetone, -40 °C, 10 min
66%

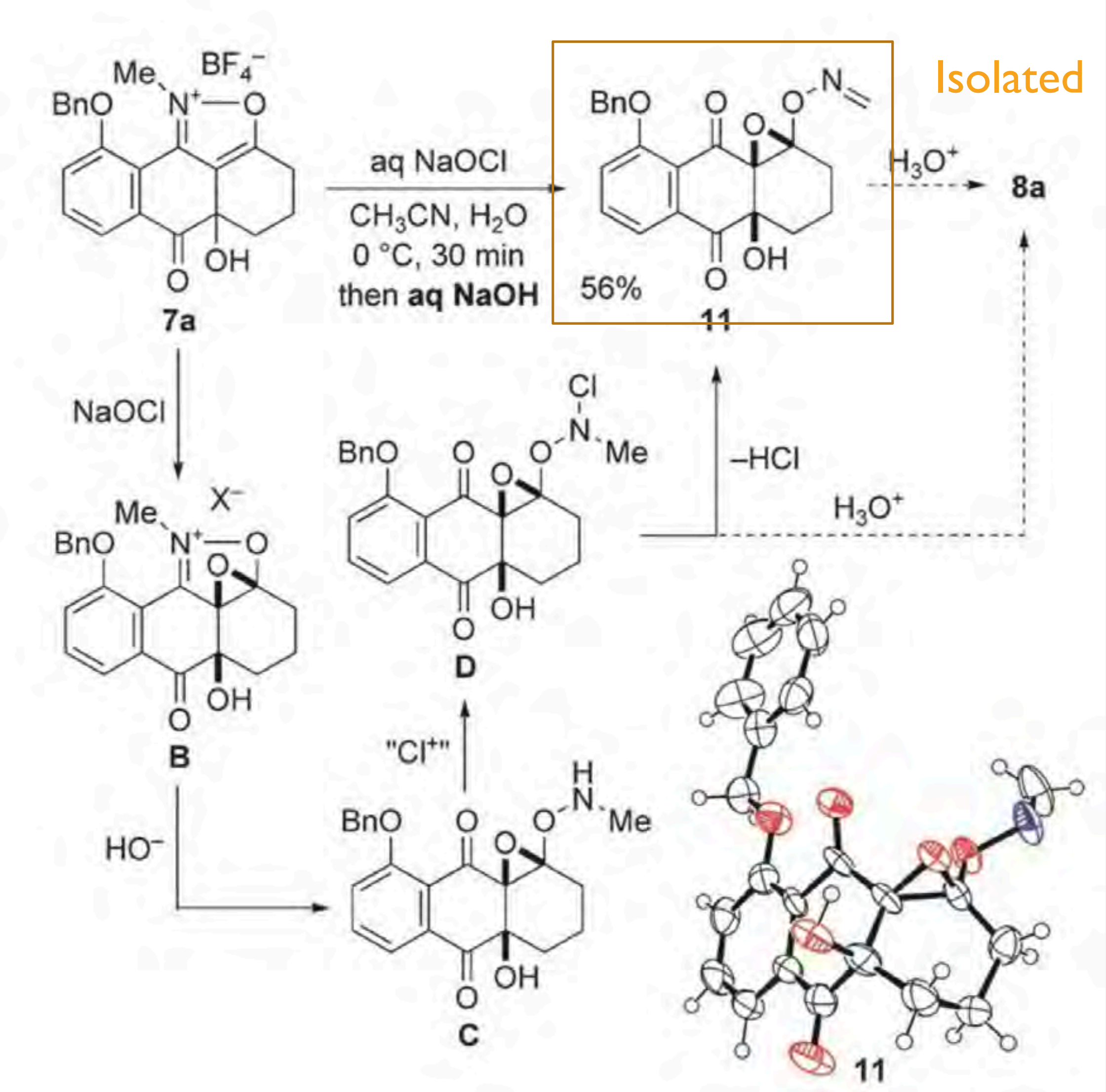
Bn*Br



ISOXAZOLE TWO STEP HYDROXYLATION



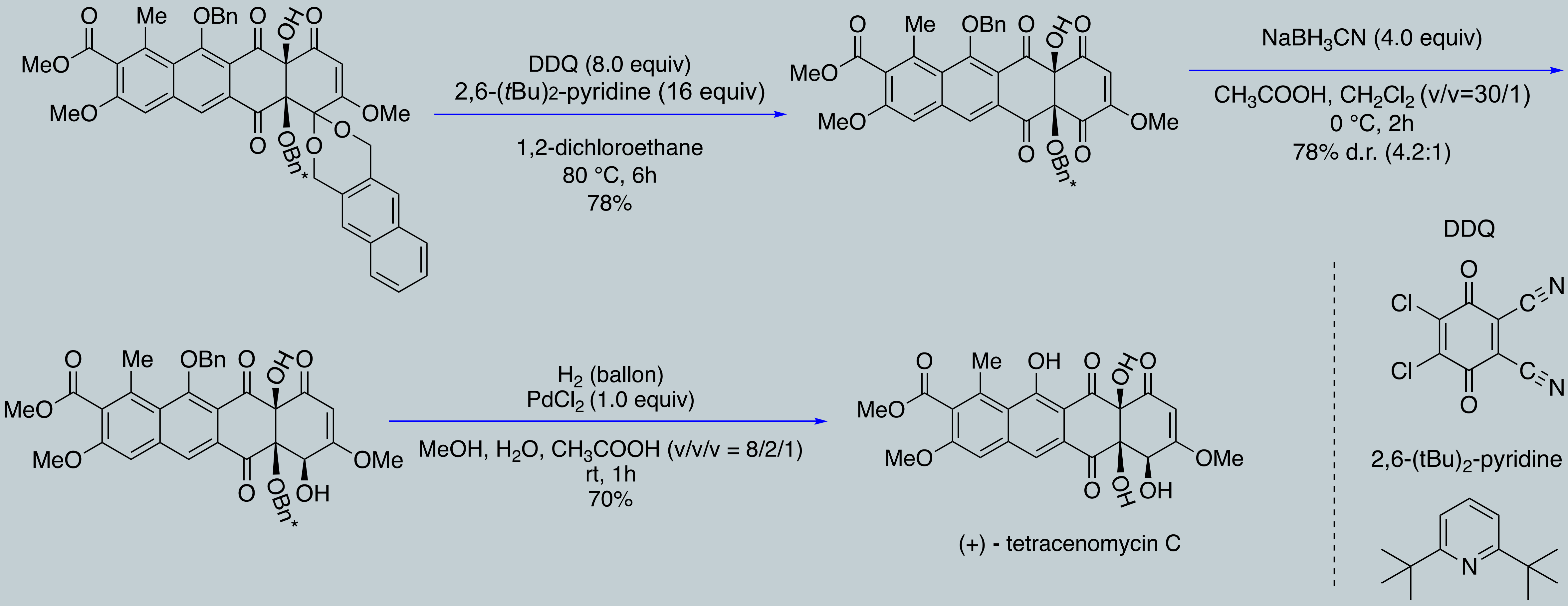




Ang. Chem. Int. Ed. **2008**, *47*, 7446.

TOTAL SYNTHESIS

Regioselective hydride reduction & divergence of synthesis Tetraceomycin C/ Tetracenomycin X



DDQ (8.0 equiv)
2,6-(tBu)2-pyridine (16 equiv)
1,2-dichloroethane
80 °C, 6h
78%

NaBH$_3$CN (4.0 equiv)
CH$_3$COOH, CH$_2$Cl$_2$ (v/v=30/1)
0 °C, 2h
78% d.r. (4.2:1)

H$_2$ (ballon)
PdCl$_2$ (1.0 equiv)
MeOH, H$_2$O, CH$_3$COOH (v/v/v = 8/2/1)
rt, 1h
70%

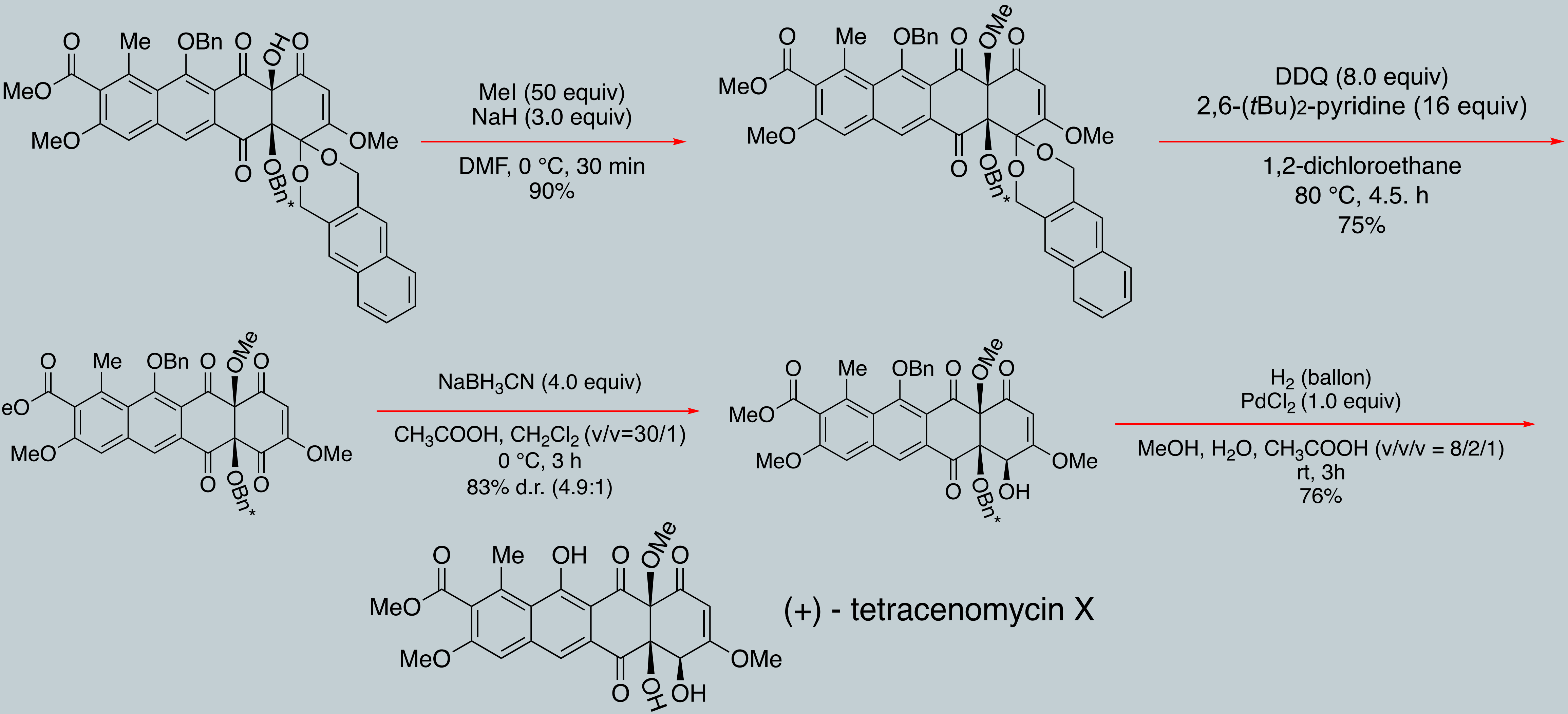
(+) - tetracenomycin C

DDQ

2,6-(tBu)$_2$-pyridine

TOTAL SYNTHESIS

Slightly longer synthesis of Tetracenomycin X

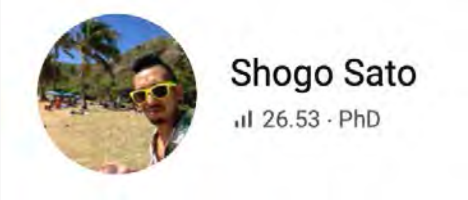


(+) - tetracenomycin X

OVERVIEW

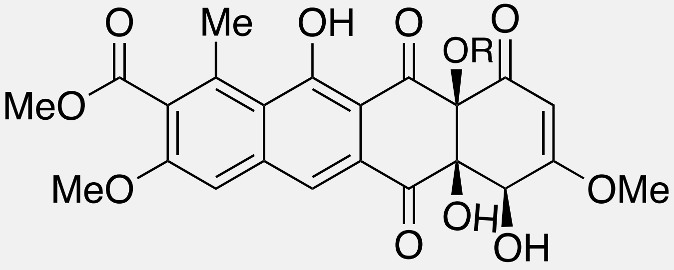

Keisuke Suzuki


Hiroshi Takikawa
27.94 · PhD


Shogo Sato
26.53 · PhD


Yoshimitsu Hashimoto
23.62 · PhD (Doctor of Science in Chemistry)

Not pictured: Keiichiro Sakata



R = Me, (+)-Tetracenomycin X
R = H, (+)-Tetracenomycin C

C- 20 total steps, 2.2% yield
X- 19 total steps, 2.2% yield