Enantioselective Synthesis of Oseltamivir Phosphate (Tamiflu) via the Iron-Catalyzed Stereoselective Olefin Diazidation

Li, H.; Shen, S.; Zhu, C.; JACS **2018**, *xx*, xx-xx
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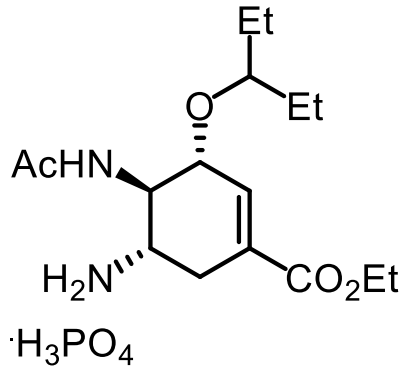
Wipf Group
Current Literature
08/11/2018

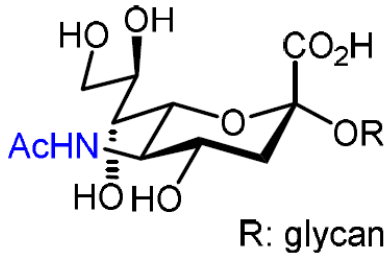
Tamiflu®

- **Oseltamivir Phosphate (Tamiflu)**



- **1996: Developed by Gilead and Hoffman-La Roche**

- **Treats and prevents influenza A and influenza B**
  - **Cells infected after enzymatic hydrolysis of terminal sialic acid from glycoconjugates**

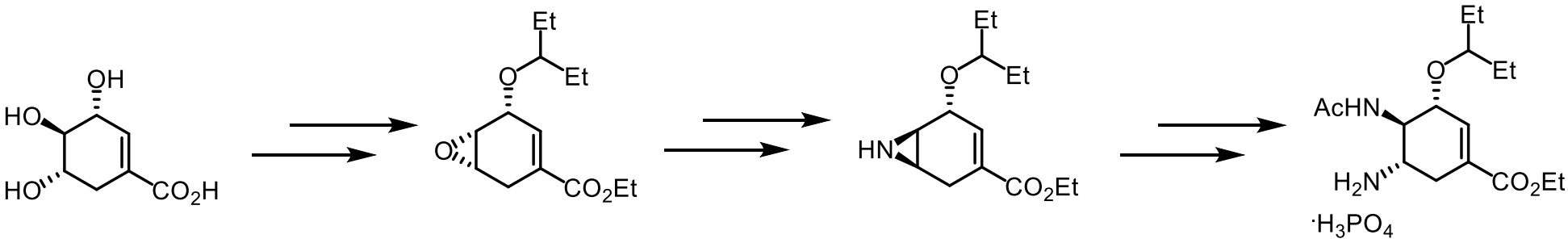


Sialic acids

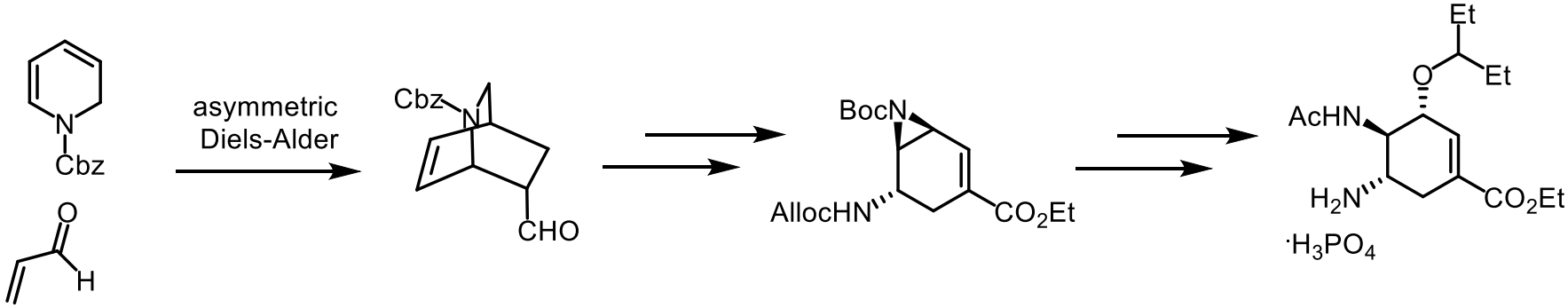
Tamiflu mimics sialic acids

Previous Syntheses of Tamiflu®

Roche:

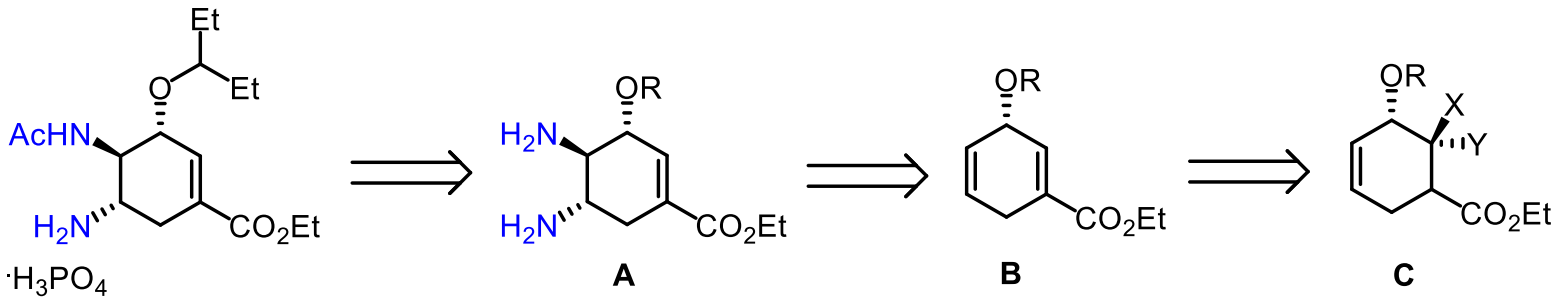


Fukuyama:



J. Org. Chem., **1998**, *63* Vol. 63, 4545-4550
Angew. Chem., Int. Ed. **2007**, *46*, 5734

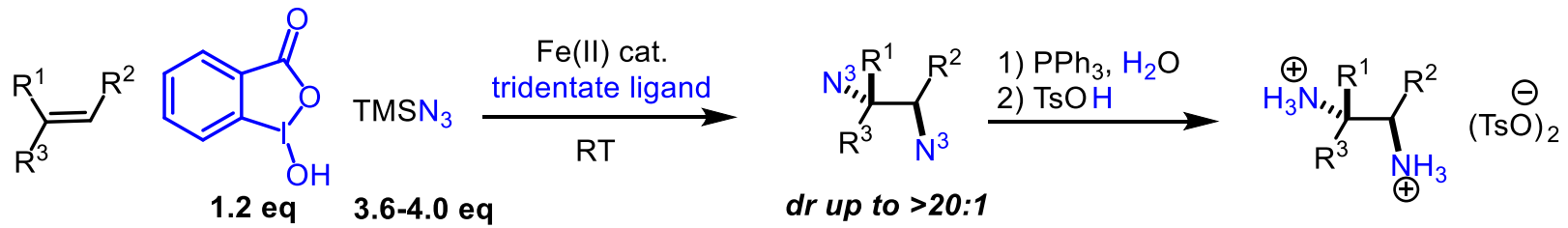
Proposed Functionalization



R = H, acyl, or aryl
X, Y= H and leaving group

Xu's Previous work on stereoselective diamination

Diamination by benziodoxole activation:

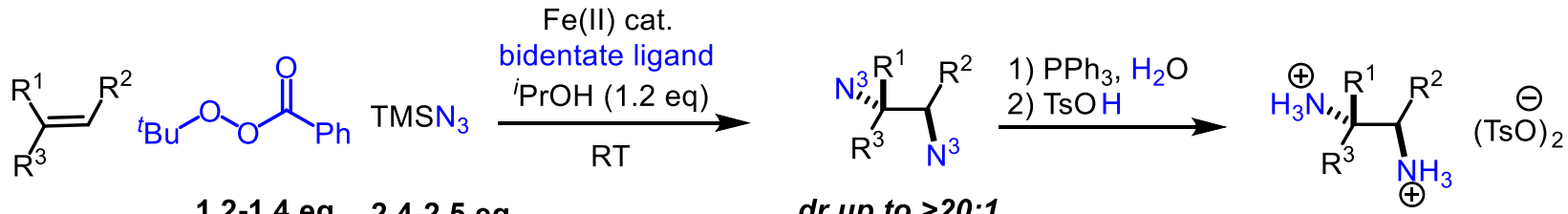


1.2 eq **3.6-4.0 eq**

dr up to >20:1

R^1, R^2 , R^3 = H, alkyl, aryl

Diamination by peroxyester activation:



1.2-1.4 eq **2.4-2.5 eq**

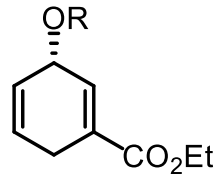
dr up to >20:1

R^1, R^2 , R^3 = H, alkyl, aryl

Angew. Chem. Int. Ed. **2016**, *55*, 534 –538

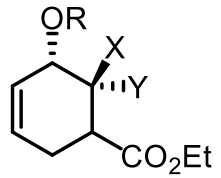
ACS Catal. **2018**, *8*, 4473−4482

Proposed Functionalization



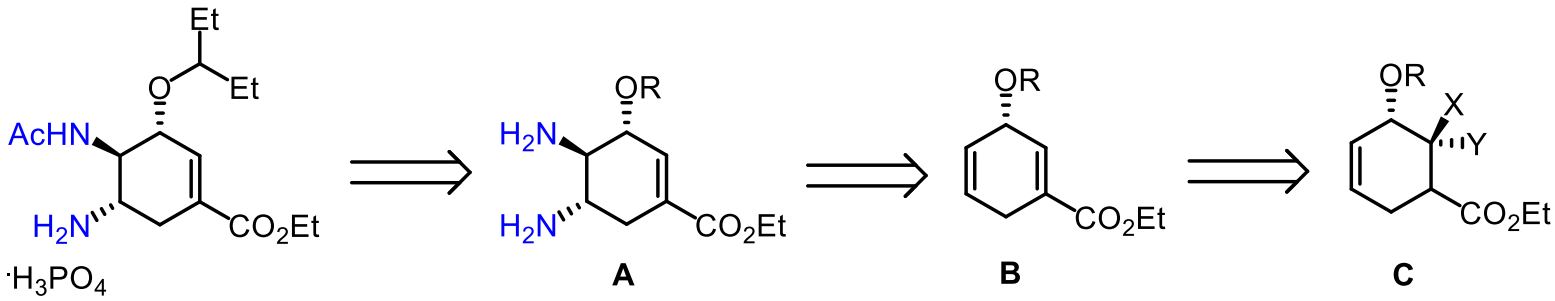
B

underwent aromatization



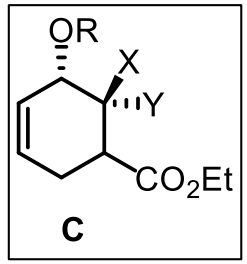
C

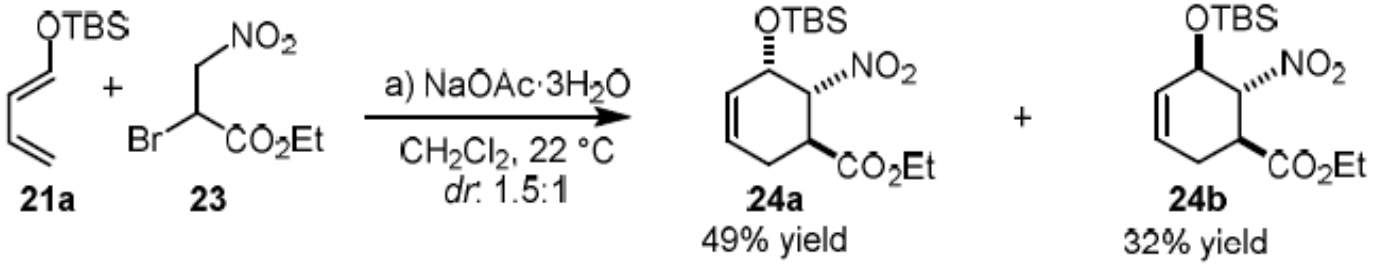
more suitable substrate

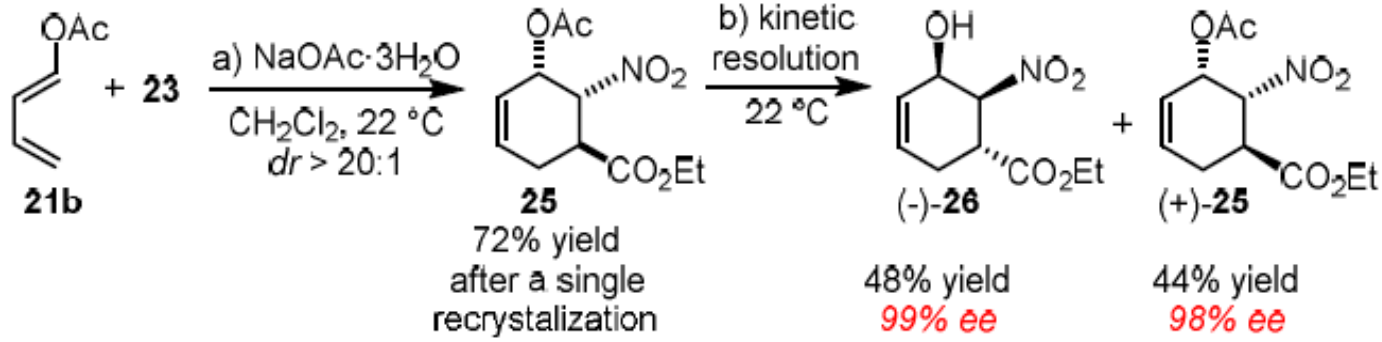


R = H, acyl, or aryl
X, Y= H and leaving group

Diels Alder Synthesis of **C**

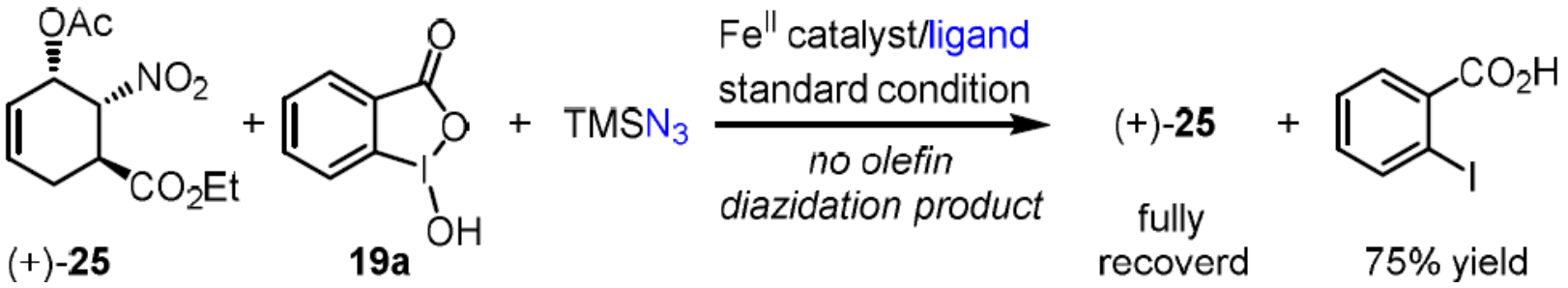






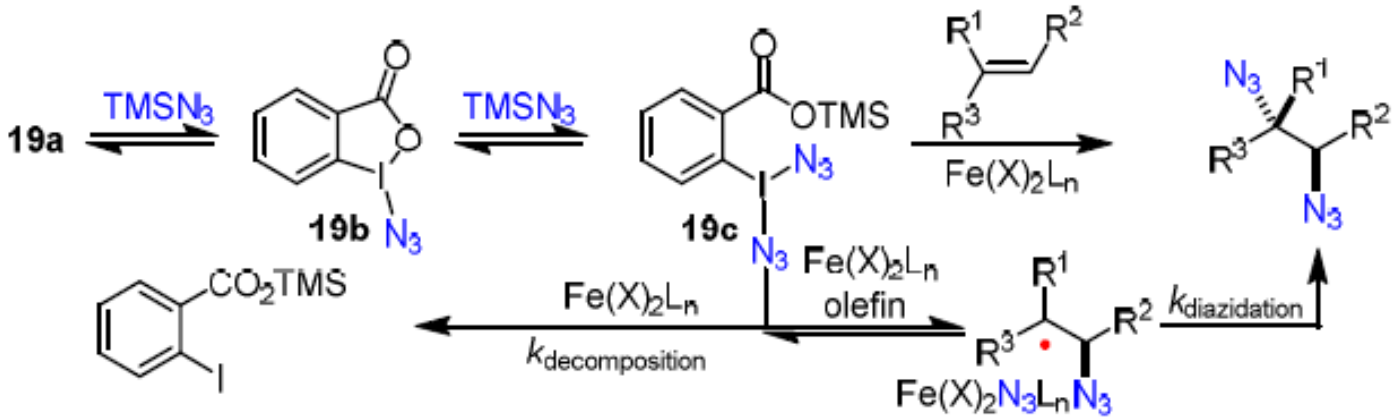
Kinetic Resolution using Amano Lipase from *Pseudomonas fluorescens*

Azidation of (+)-**25**



Mechanistic studies of azidation

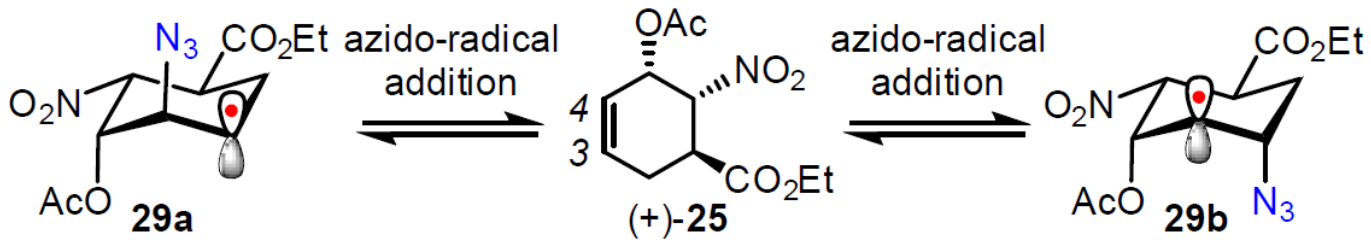
19a is stable towards TMSN3 without an iron catalyst



First C–N_3 bond forming step is reversible
Second C–N_3 bond forming step is rate-limiting

Solution: increase [25] and decrease [19c]. Slow addition of 19c

Stereoselectivity of azide addition



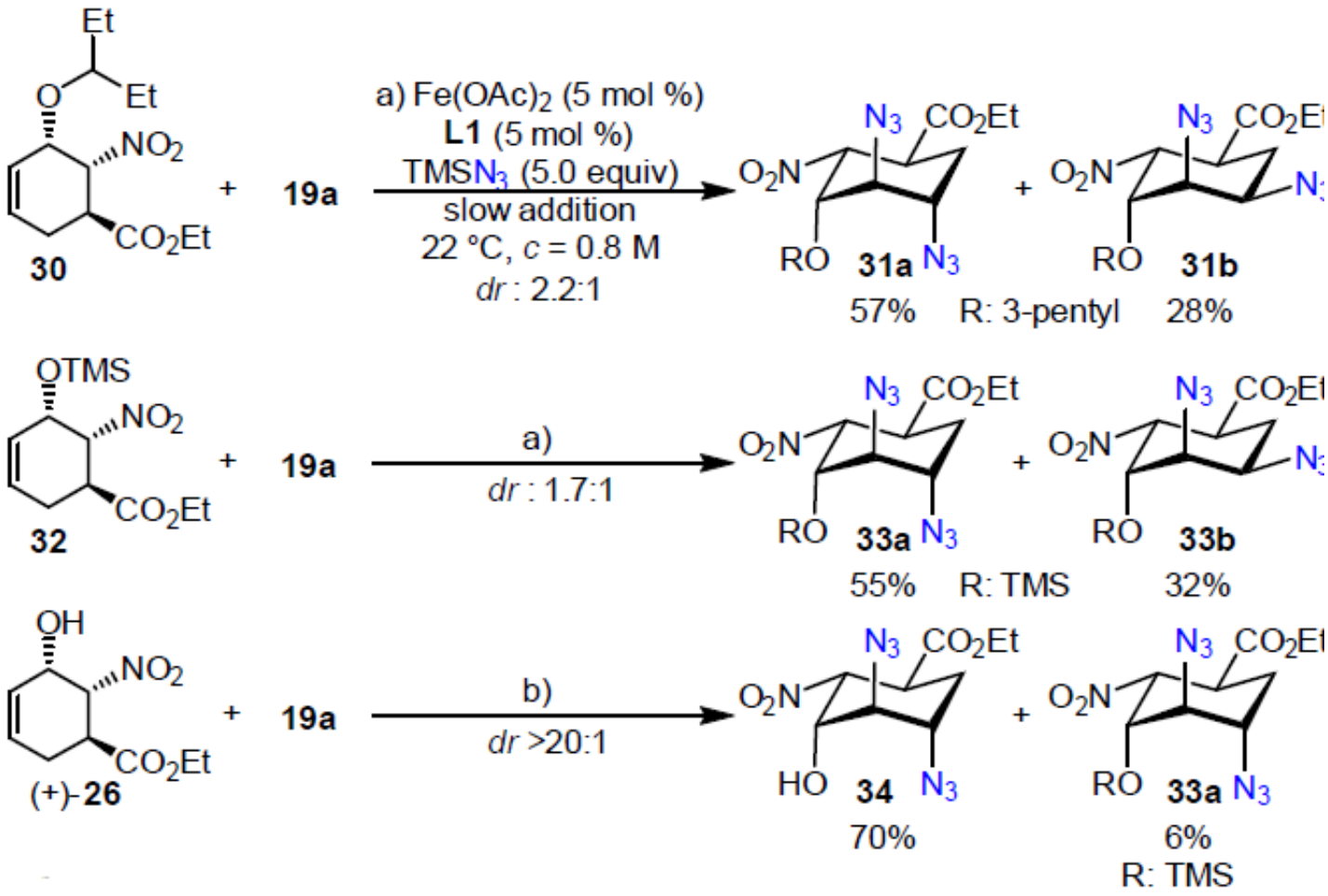
C4 azide addition: dr >20:1

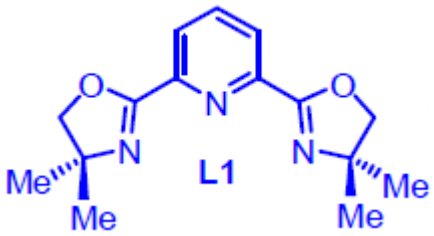
C3 azide addition: dr = 7.4: 1

More reactive

dr not improved by iron catalysts used

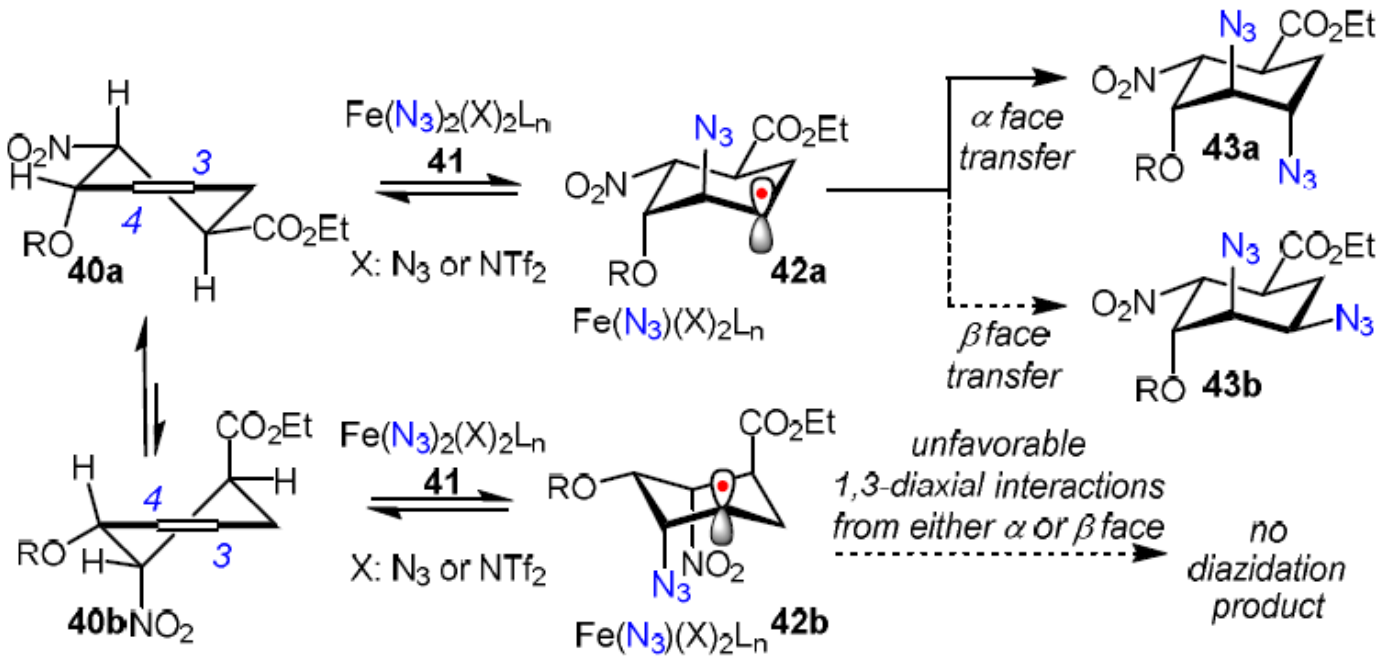
Stereoselectivity through Substrate Control



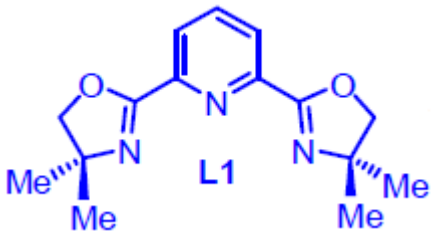


[a]$Fe(OAc)_2$ (5 mol %), **L1** (5 mol %), **19a** (2 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C, $TMSN_3$ (5 equiv) added gradually within 8 h. [b]$Fe(OAc)_2$ (5 mol %), **L1** (5 mol %), **19a** (1.5 equiv), CH_2Cl_2/MeCN (10:1), 0.8 M, 22 °C, $TMSN_3$ (3.6 equiv) added gradually within 8 h. The reactions were subsequently quenched with saturated $NaHCO_3$ solution.

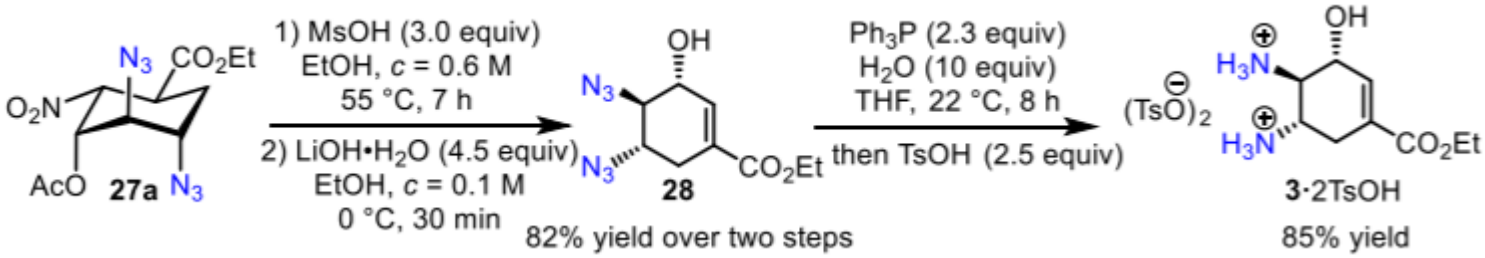
Proposed Stereochemical Model

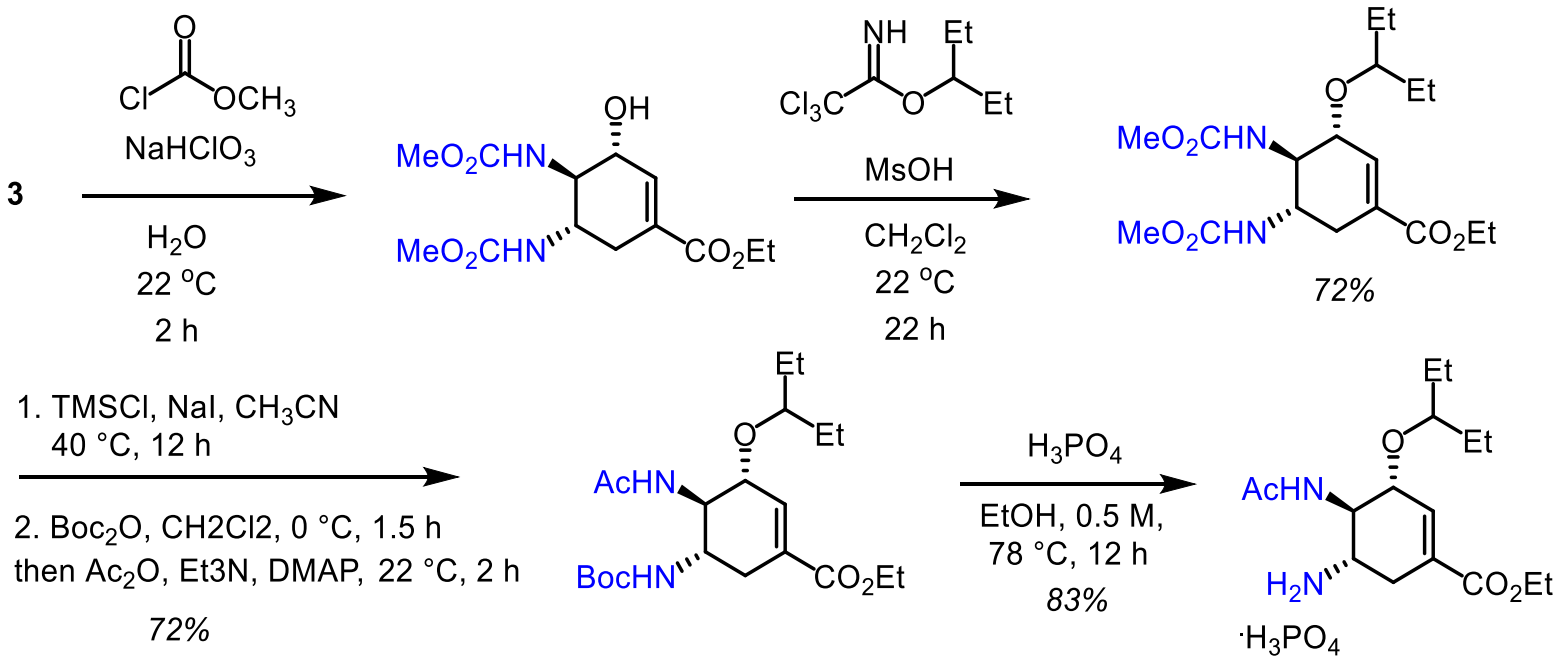


R group needs to be small to avoid β face transfer

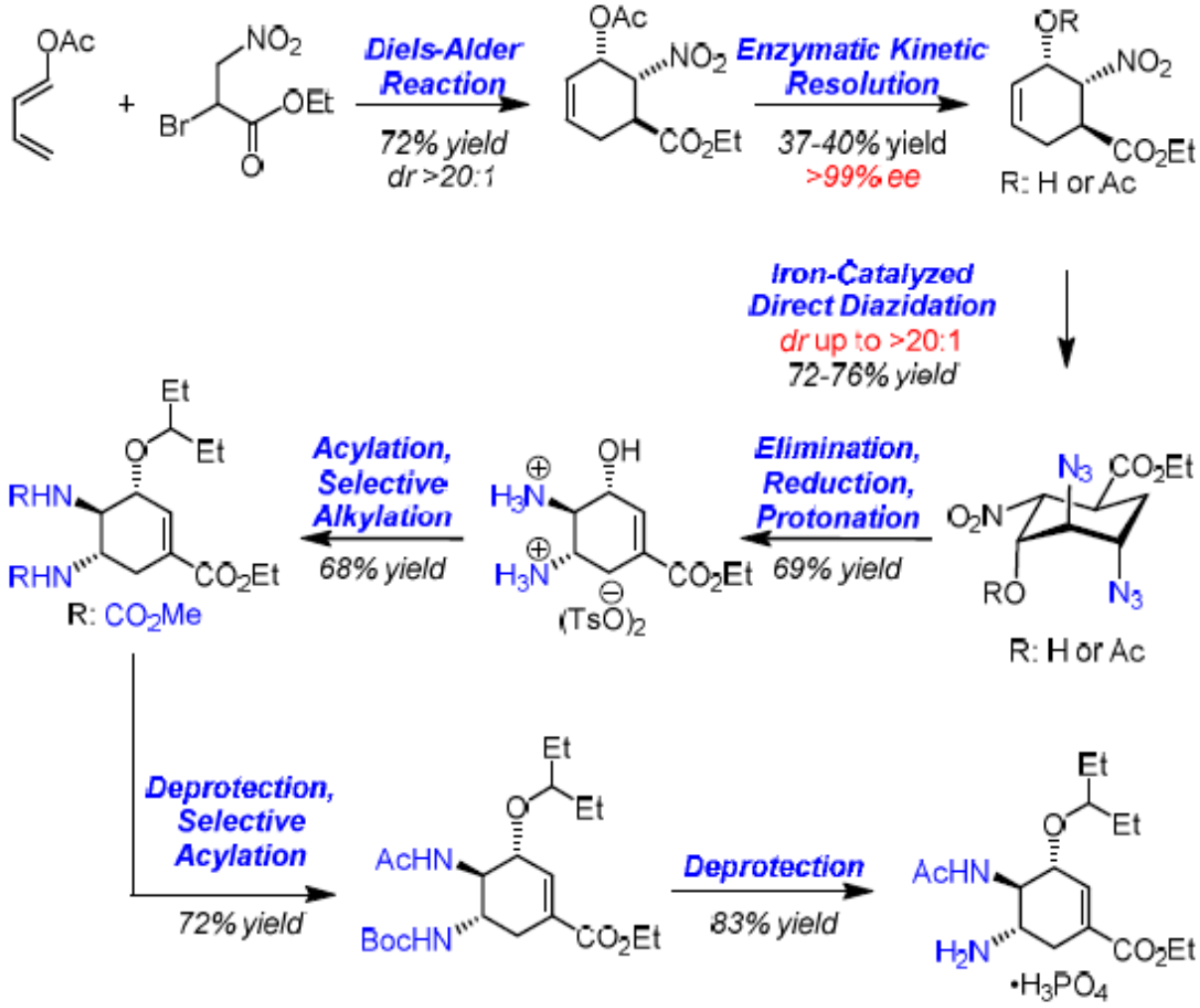


Synthesis of Tamiflu from the deamination intermediate





Conclusion


Diels-Alder Reaction
72% yield
dr >20:1
Enzymatic Kinetic Resolution
37-40% yield
>99% ee
R: H or Ac
Iron-Catalyzed Direct Diazidation
dr up to >20:1
72-76% yield
Elimination, Reduction, Protonation
69% yield
Acylation, Selective Alkylation
68% yield
R: H or Ac
R: CO2Me
Deprotection, Selective Acylation
72% yield
Deprotection
83% yield
•H3PO4