Stereospecific Formal [3+2] Dipolar Cycloaddition of Cyclopropanes with Nitrosoarenes: An Approach to Isoxazolidines

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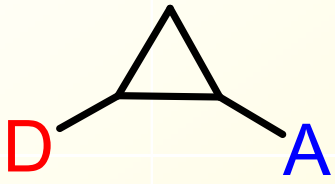
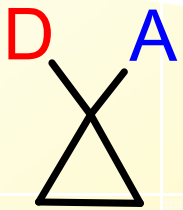
by Haiying Du

5th *May* 2014

Cyclopropanes



vicinal positioning



geminal positioning

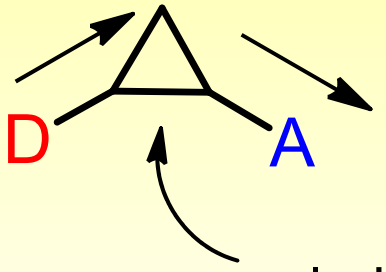
D = electron-donating group

(e.g. OR, SR, NR_2, CH_2SiR_3, Aryl, Alkyl)

A = electron-accepting group

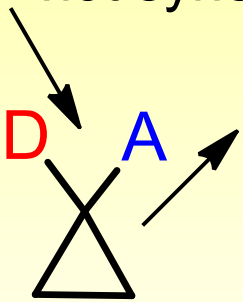
(e.g. CO_2R, COR, CN, SO_2Ph, NO_2)

"push-pull" effect



polarized C-C bond

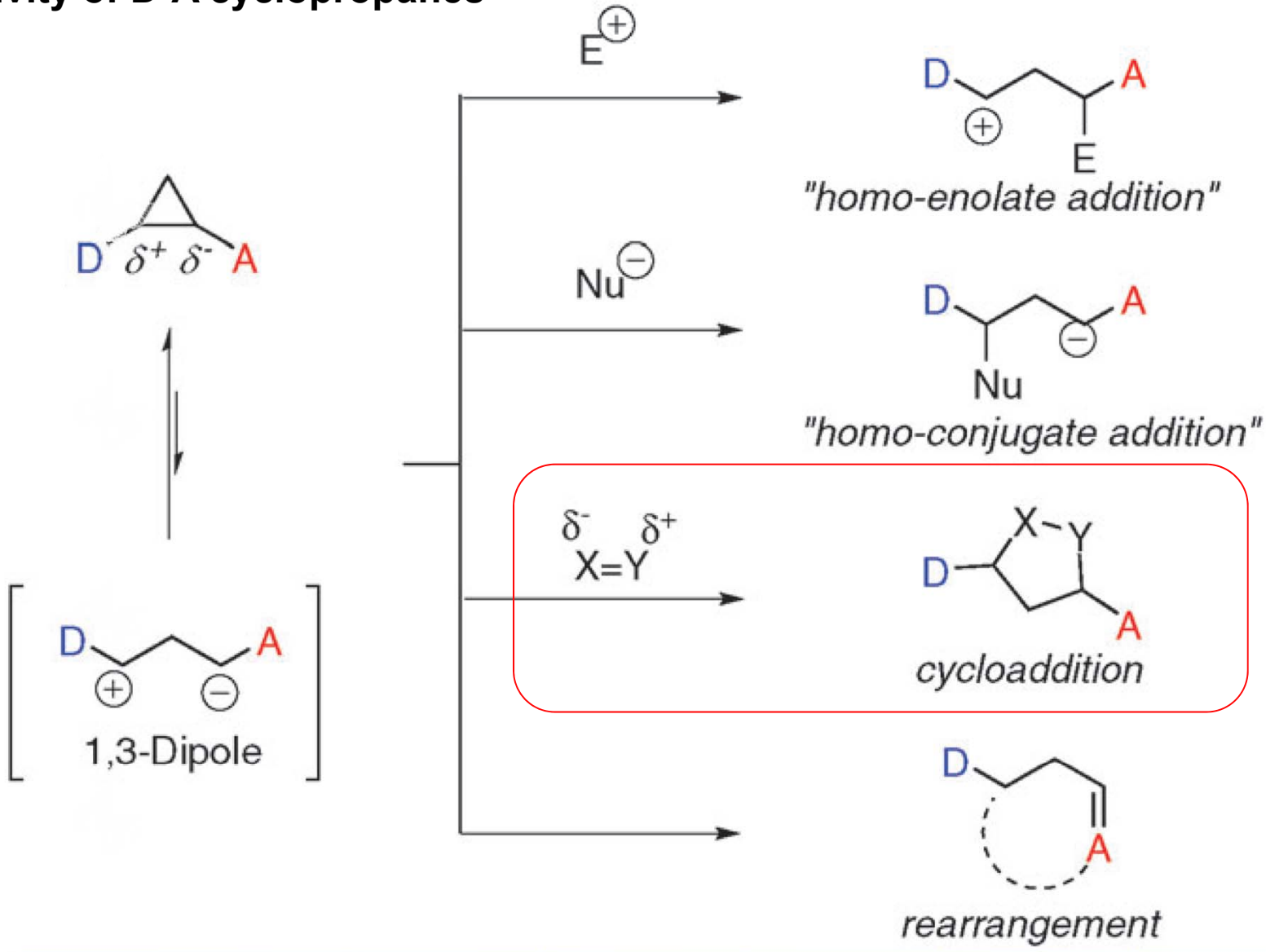
not synergistic



Cavitt, M. A., Phun, L., France, S. *Chem. Soc. Rev.*, **2014**, *43*, 804-818

Introduction

Reactivity of D-A cyclopropanes



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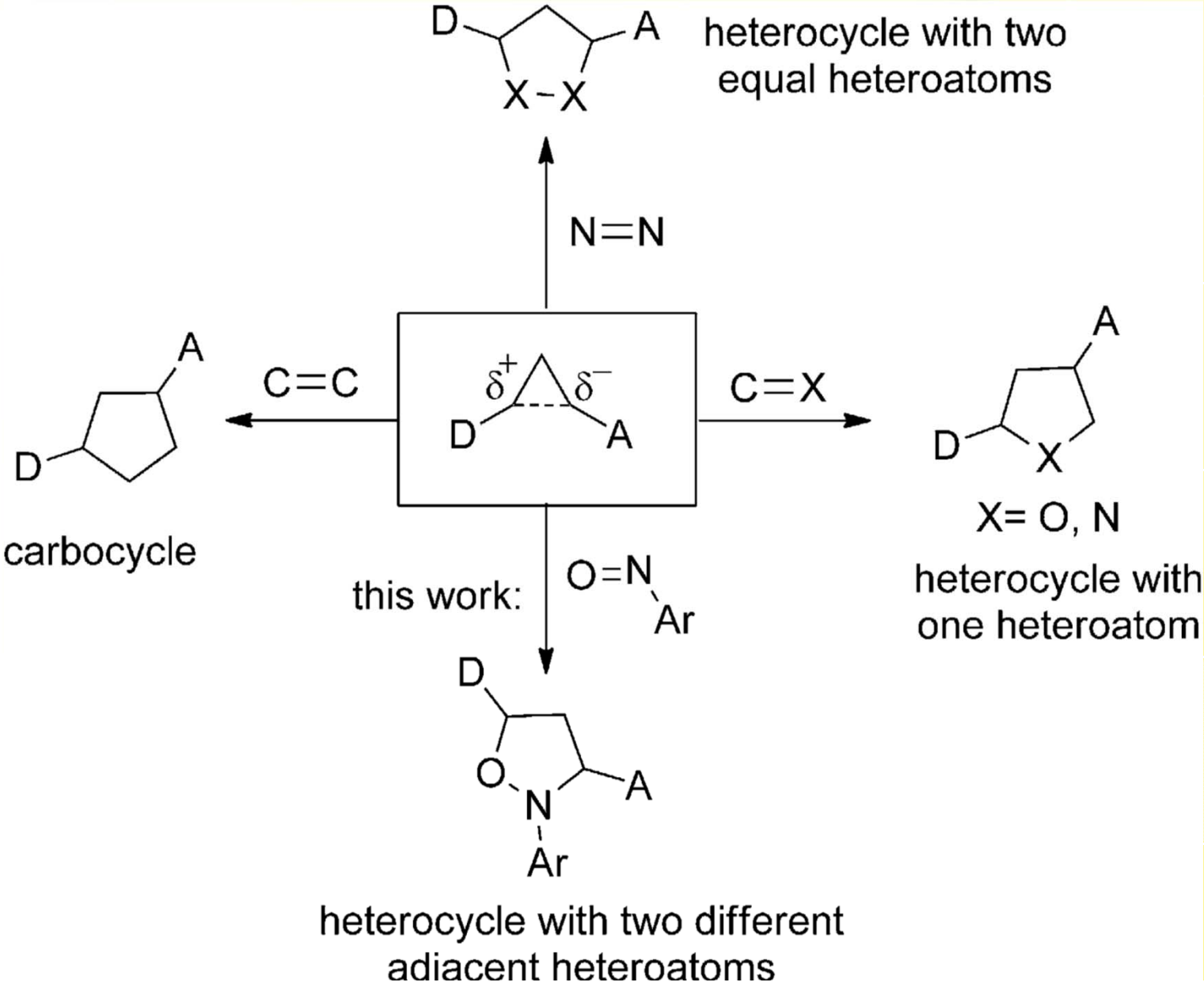
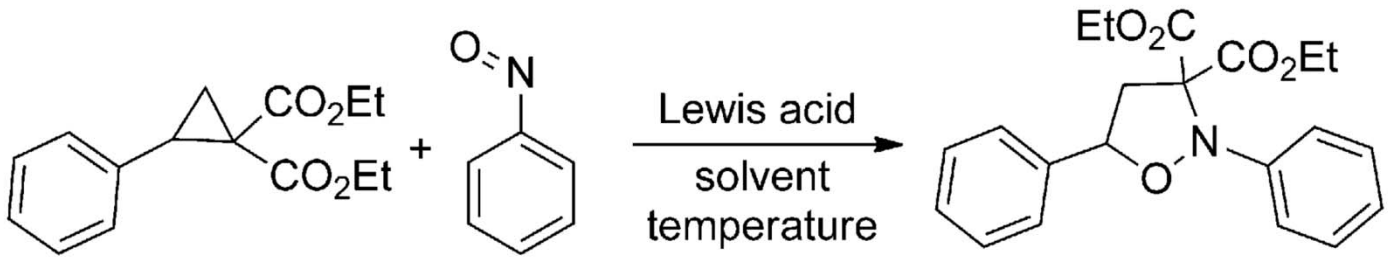
Introduction

[3+2] cycloaddition of cyclopropane with different 2π components

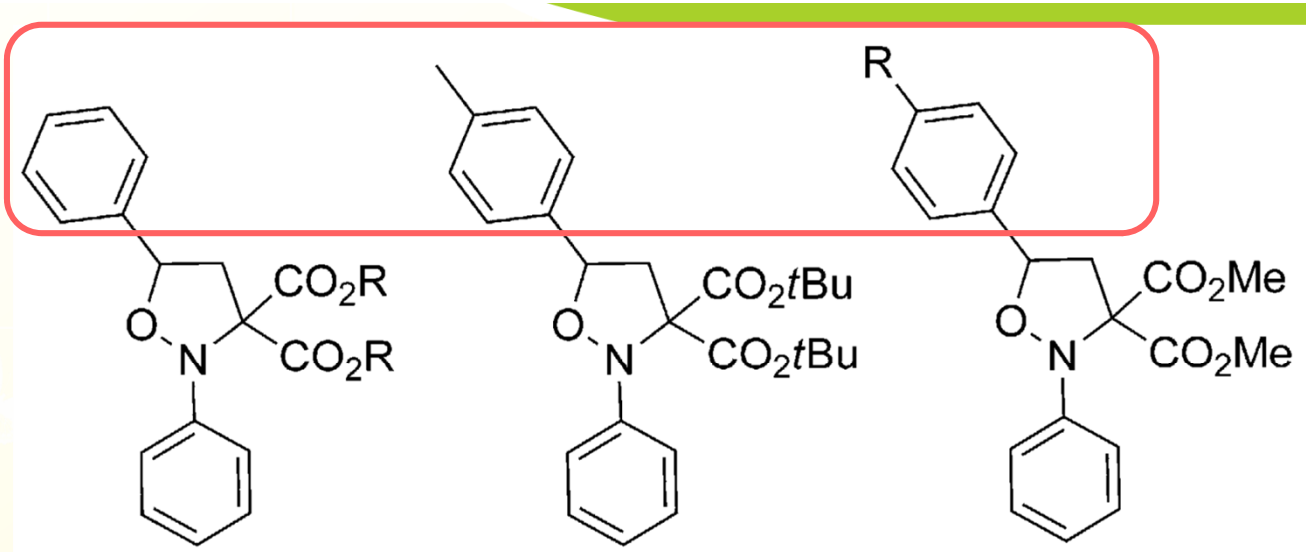




1a **2a** (1.5 equiv) **3a** isoxazolidine

Entry	Lewis acid	LA [mol%]	*T* [°C]	Solvent	Yield [%]
1	$Cu(OTf)_2$	20	20	CH_2Cl_2	25
2	$Sc(OTf)_3$	20	20	CH_2Cl_2	10
3	$Sn(OTf)_2$	15	20	$ClCH_2CH_2Cl$	20
4	$InBr_3$	20	20	CH_2Cl_2	< 10
5	$FeCl_3$	20	20	$ClCH_2CH_2Cl$	40
6	$MgCl_2$	20	20	CH_2Cl_2	40
7	MgI_2	20	20	CH_2Cl_2	40
8	MgI_2	20	20	$ClCH_2CH_2Cl$	60
9	MgI_2	20	90	$ClCH_2CH_2Cl$	20
10	$MgBr_2$	20	20	CH_2Cl_2	50
11	$MgBr_2$	20	20	$ClCH_2CH_2Cl$	70
12	**$MgBr_2$**	**20**	**90**	**$ClCH_2CH_2Cl$**	**92**
13	$MgBr_2$	10	90	$ClCH_2CH_2Cl$	50
14	$MgBr_2$	20	20	CCl_4	10
15	$MgBr_2$	20	20	THF	40

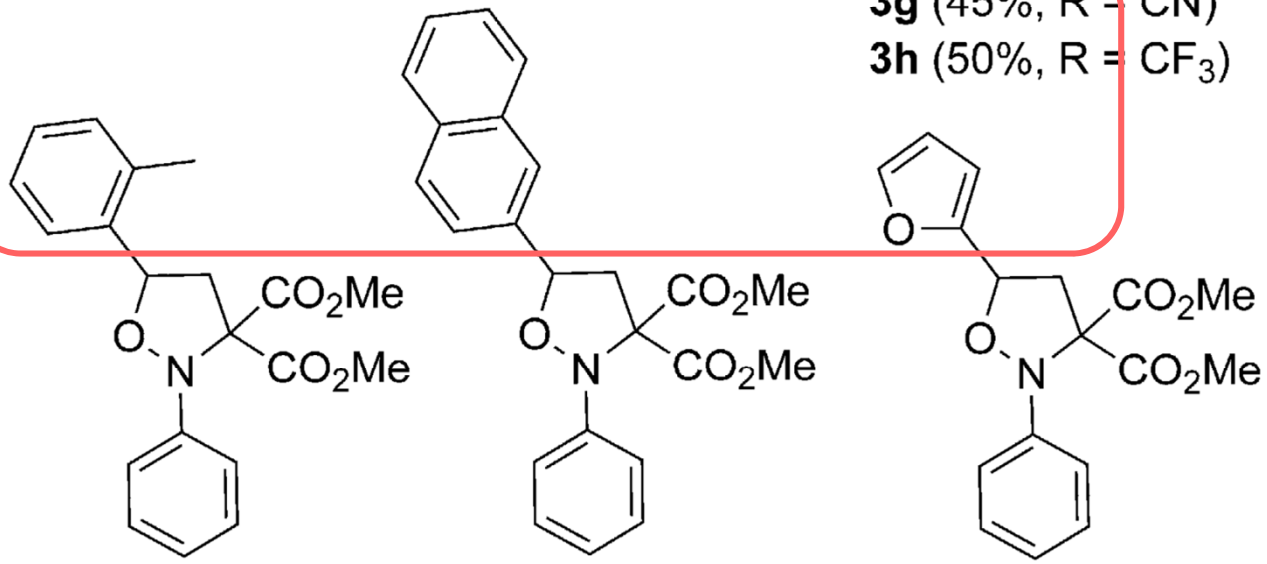
Scope



3b (82%, R = Me)
3d (60%, R = Allyl)

3c (51%)

3e (70%, R = OAc)
3f (75%, R = OMe)
3g (45%, R = CN)
3h (50%, R = CF_3)

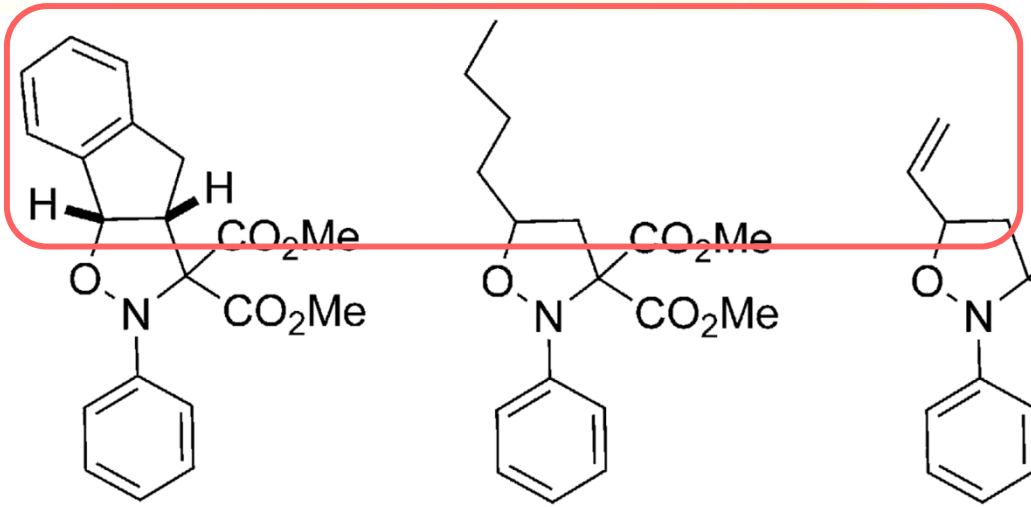


3i (70%)

3j (60%)

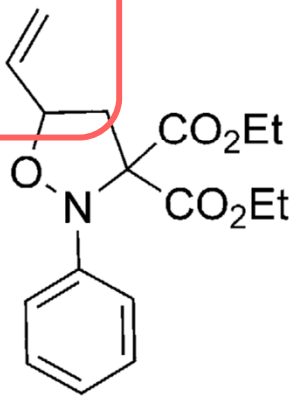
3k (40%)

Scope

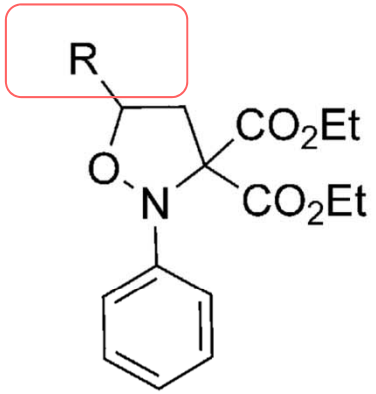


3l (82%)

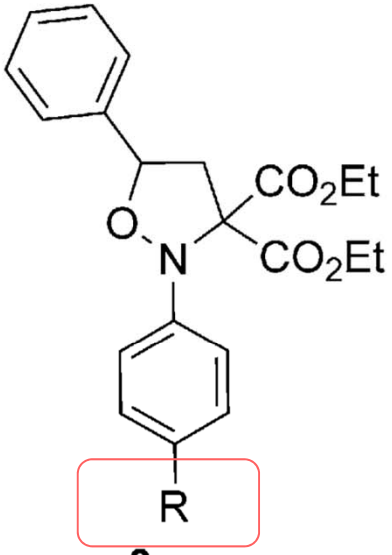
3m (65%)



3n (82%)



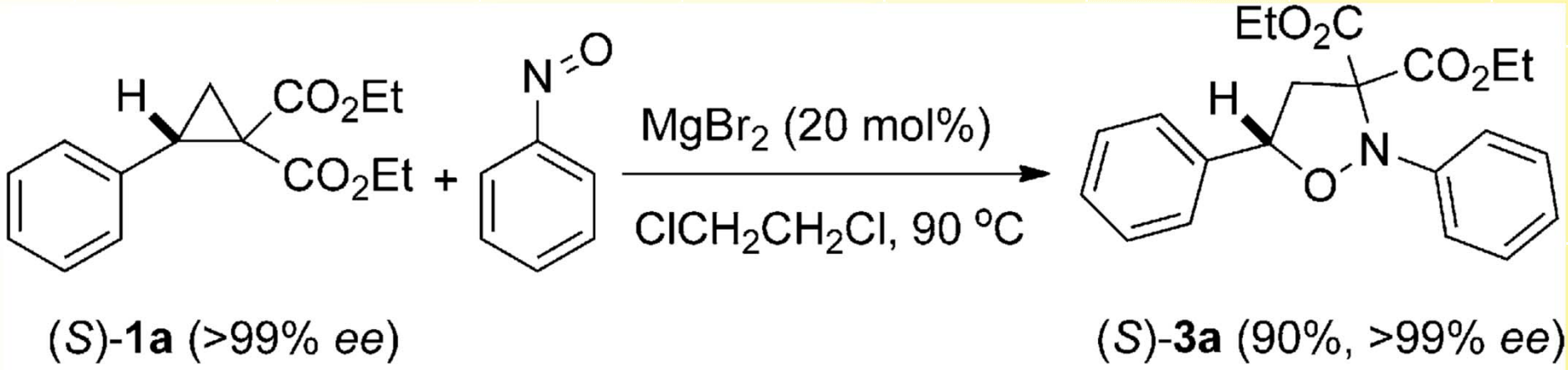
3o (90%, R = PhthN)
3p (45%, R = AcO)



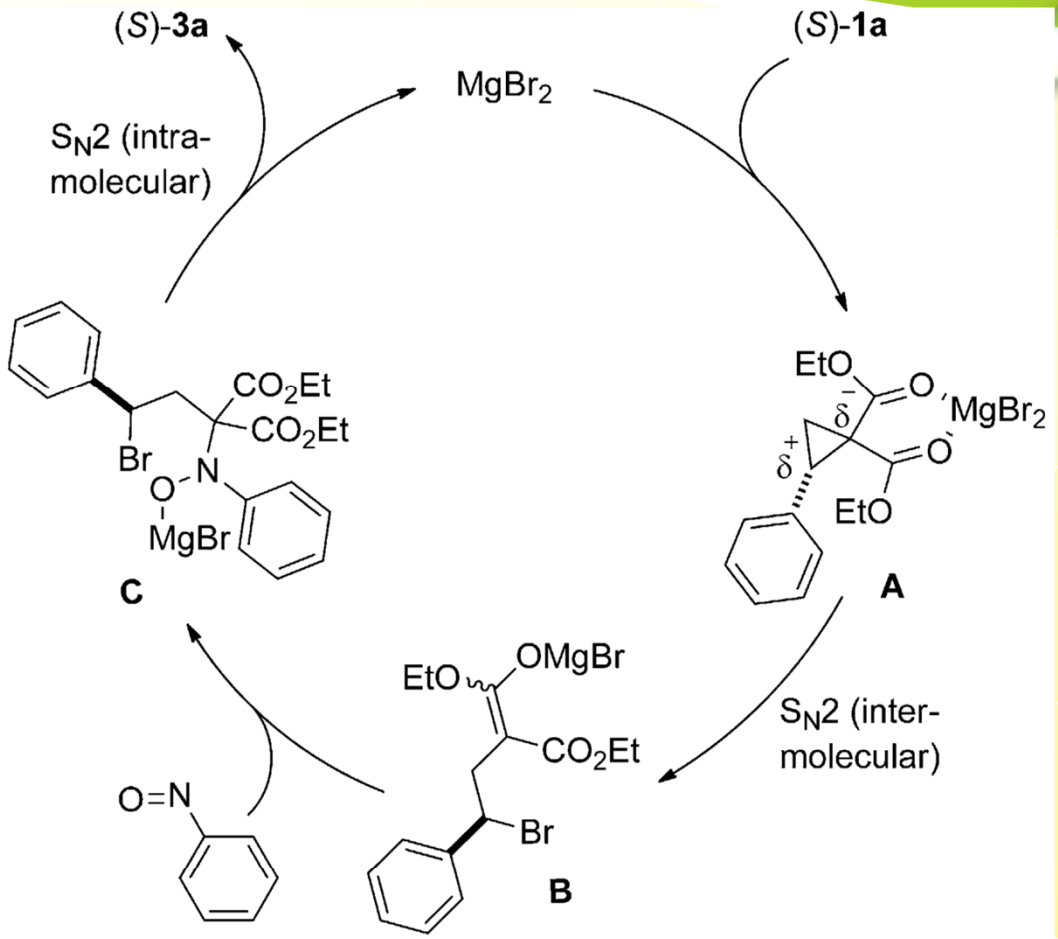
3q–v

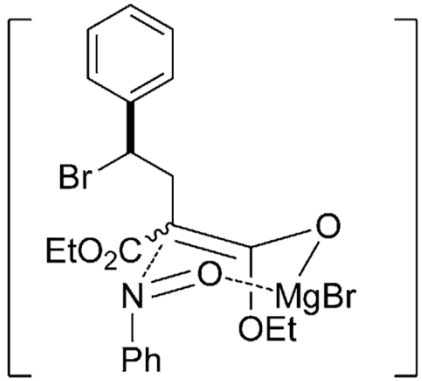
3q (50%, R = Me)
3r (95%, R = CO_2Et)
3s (90%, R = COMe)
3t (90%, R = Br)
3u (99%, R = NO_2)
3v (78%, R = OCF_3)

Testing stereospecificity of the cycloaddition of nitrosobenzene with enantiopure cyclopropane



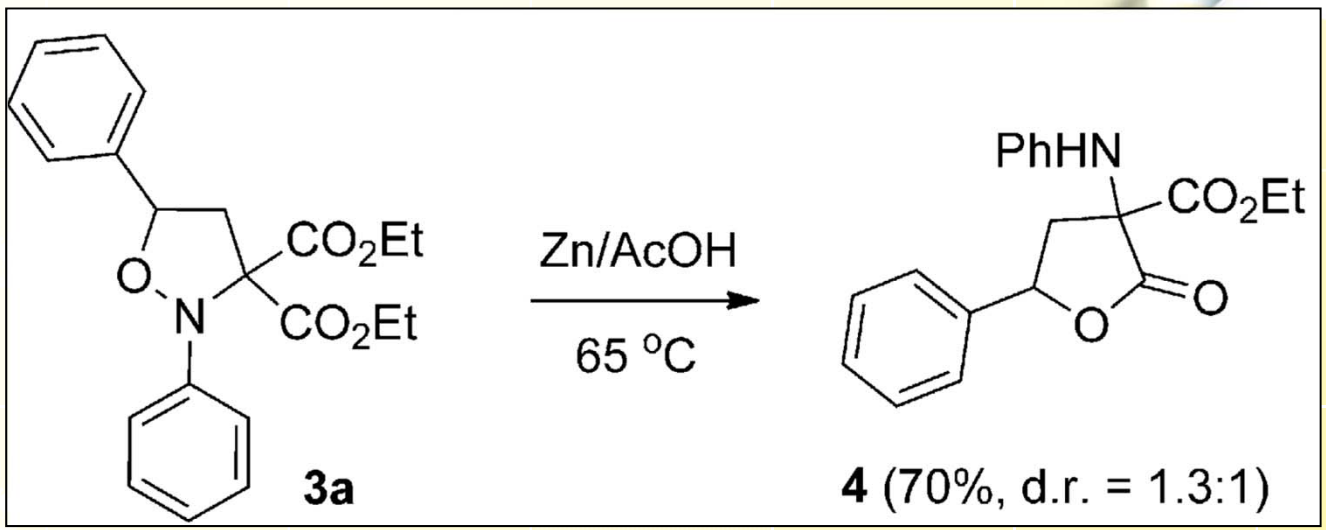
Proposed catalytic cycle

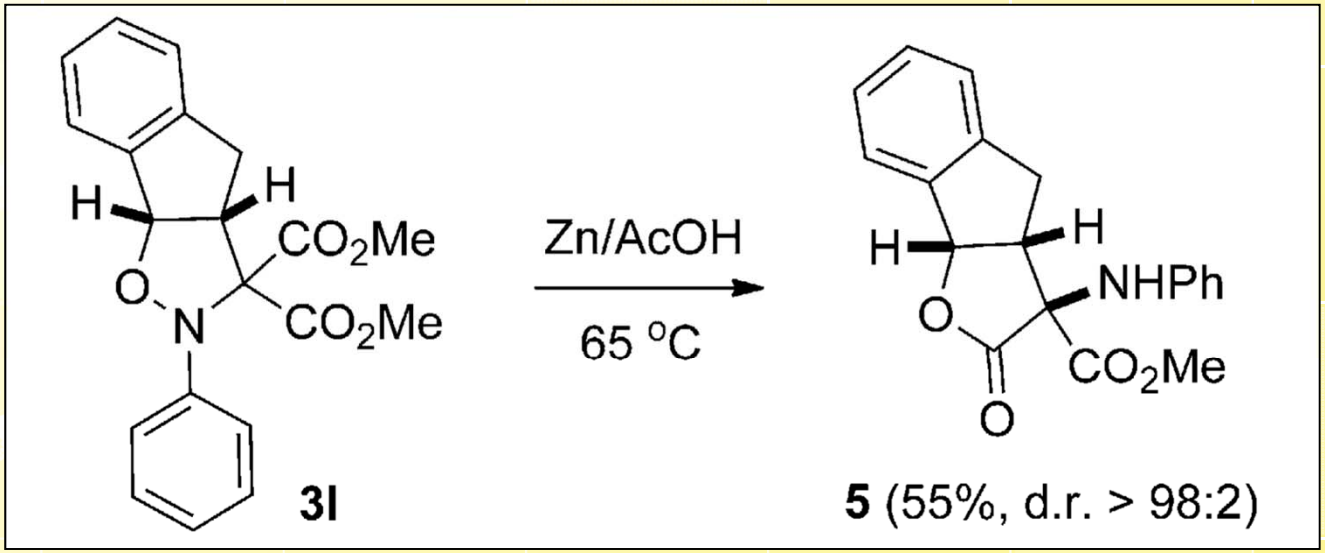




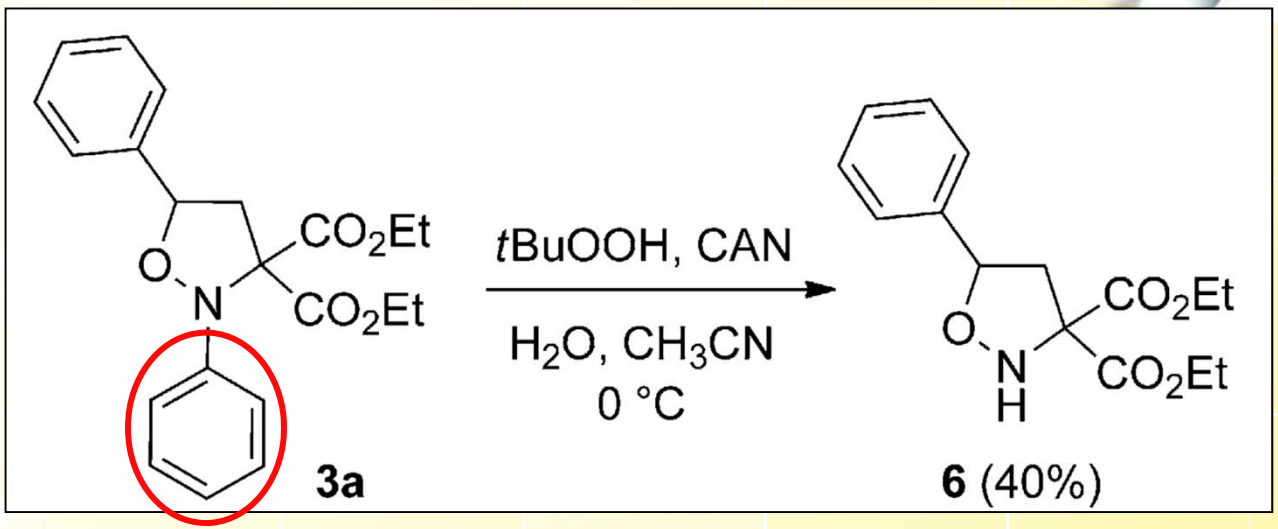
six-membered cyclic transition state **D**

Post-functionalization

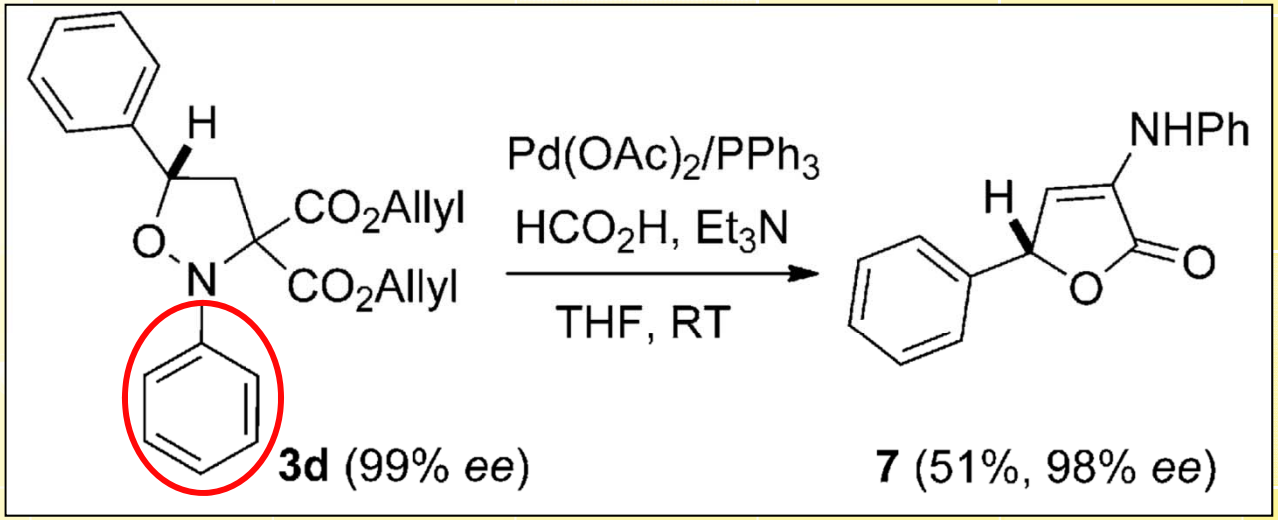




Post-functionalization



CAN = ceric ammonium nitrate



Conclusions

- **[3+2] cycloaddition** of **nitrosoarenes** with **DA-cyclopropanes** to give valuable **isoxazolidines** with high yields and complete regioselectivity.
- the cycloaddition with an enantiomerically pure cyclopropane gave the product isoxazolidine with **complete stereospecificity**.
- transformed into **α-amino lactones** and subsequent **lactonisation**.

Thank You for Your Attention