Lewis Acid Promoted Crystallization-Induced Diastereomer Transformations of γ-δ-unsaturated β-ketoamides

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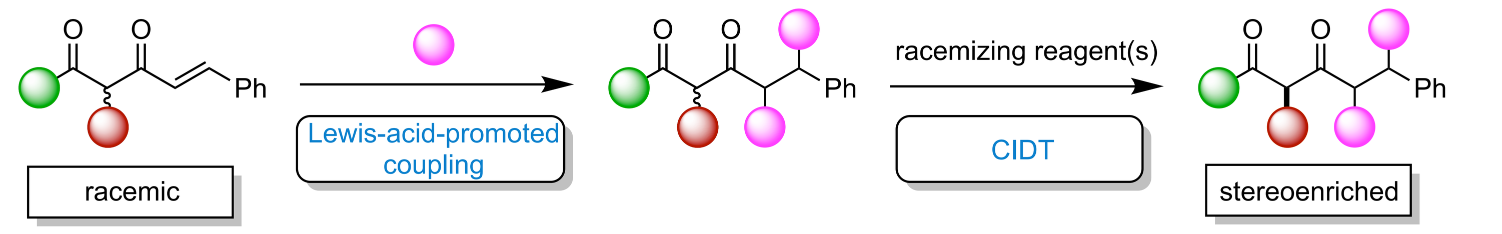
Project design and workflow

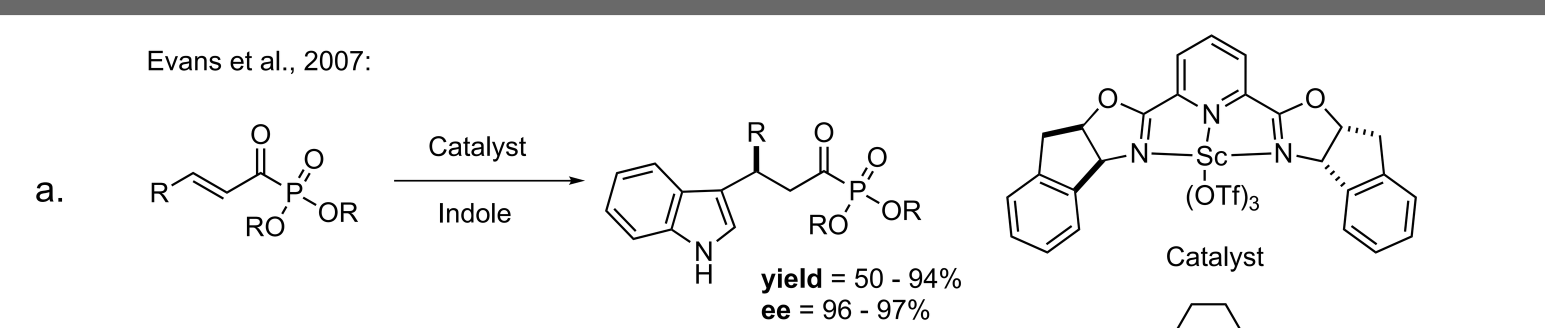
Lewis Acid Promoted Reaction of γ,δ-unsaturated β-ketoamides followed by Crystallization-Induced Diastereomer Transformations



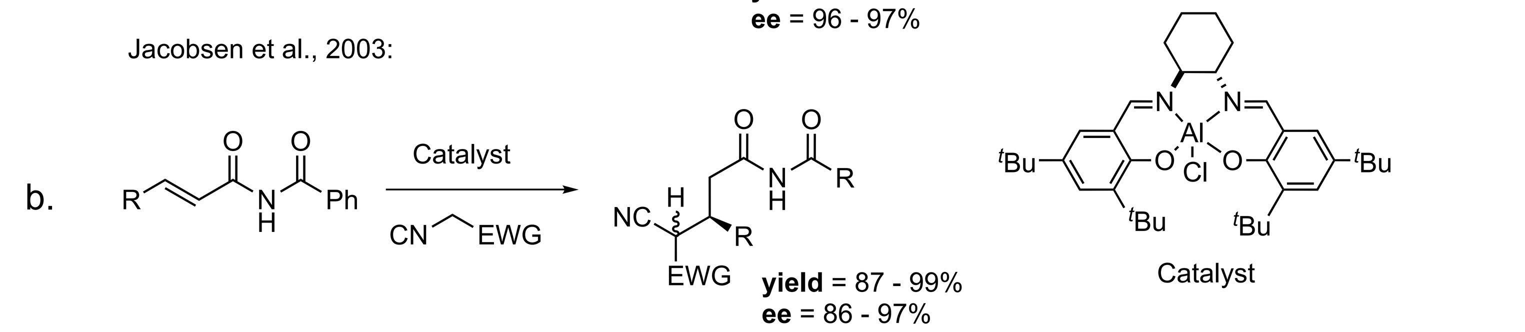
- stereoconvergent
- isolation by single filtration
- access to stereoenriched α-substituted β-dicarbonyls
- compatible with multiple functional groups

Previous Work

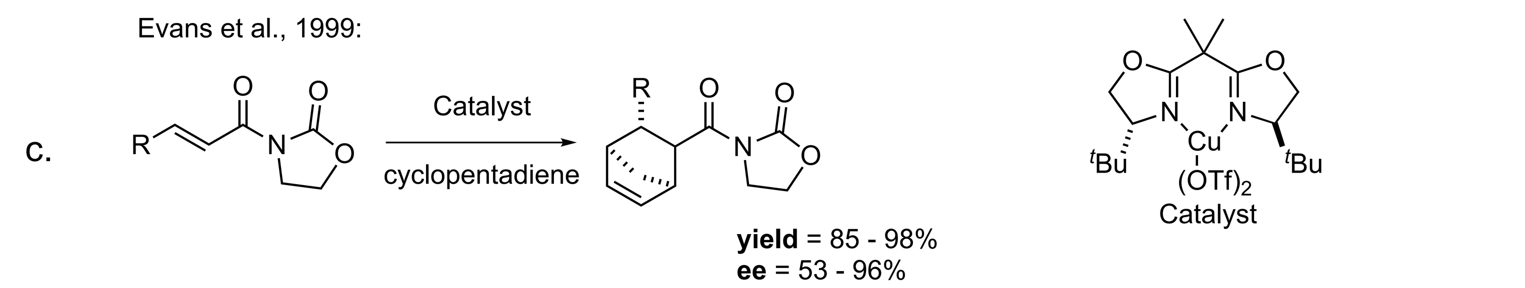
Evans et al., 2007:



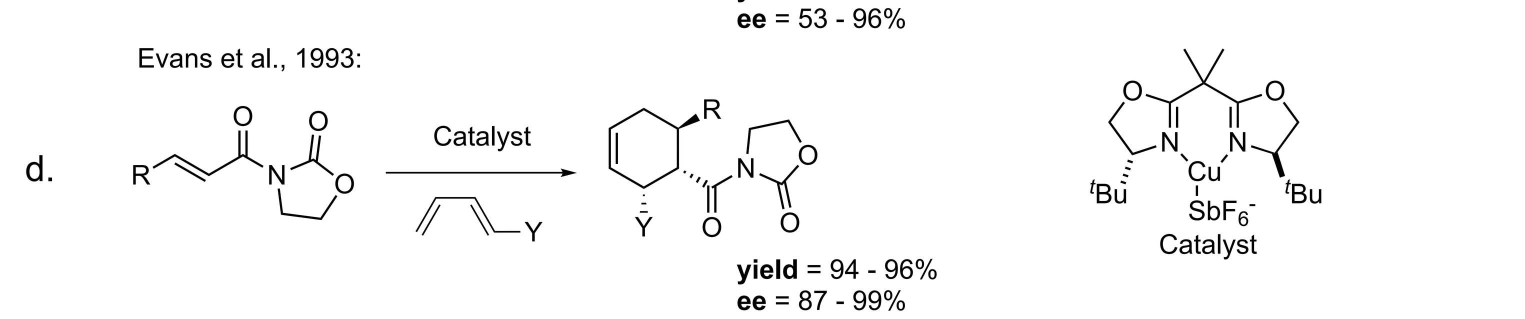
Jacobsen et al., 2003:



Evans et al., 1999:

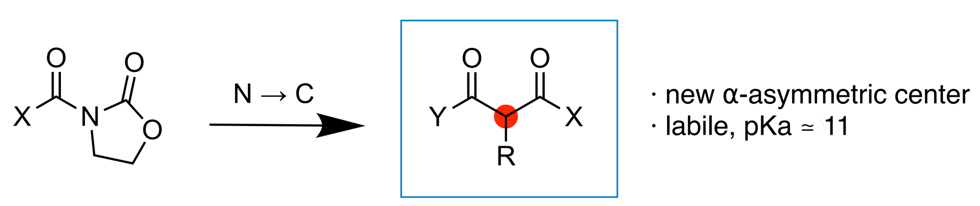


Evans et al., 1993:



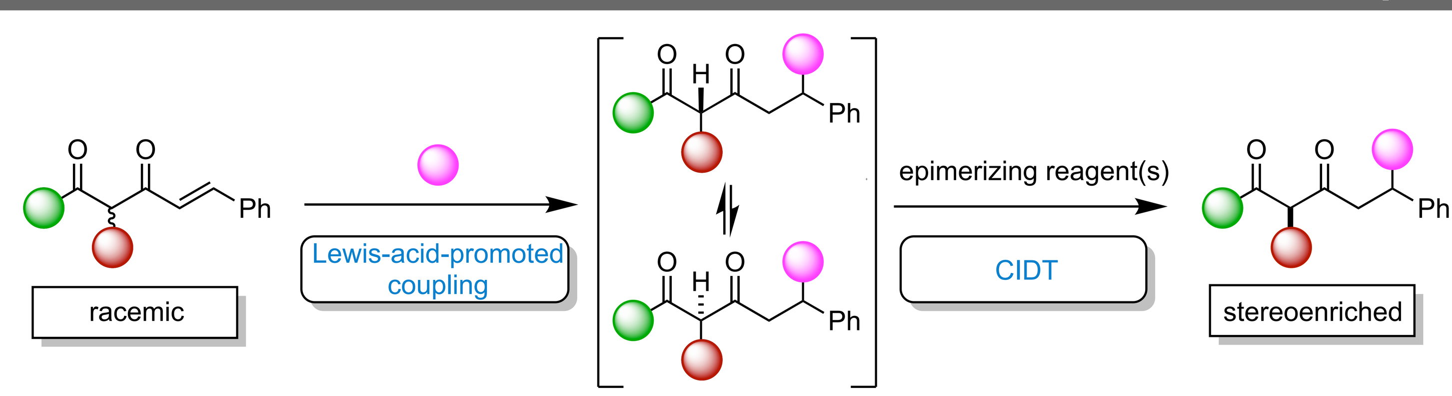
Common Theme to Note:

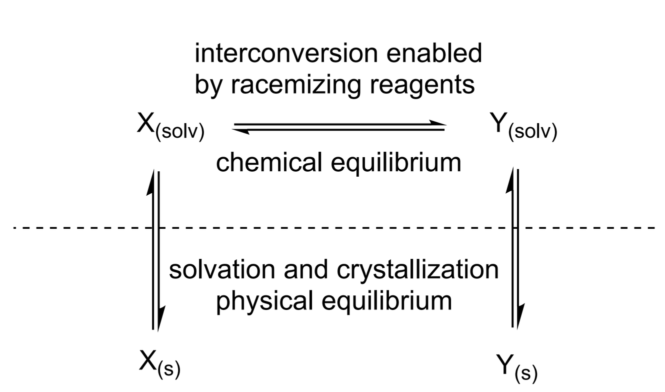
1. β-dicarbonyl motif in substrates
2. C_2-symmetric bidentate ligands
3. Transition metals as catalysts
4. **Product doesn't contain α-asymmetric centers**



How to control
2 asymmetric centers?

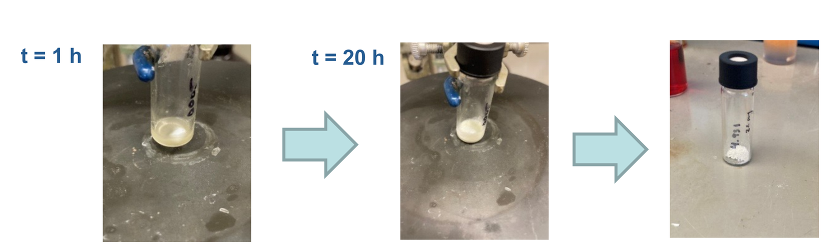
Crystallization Induced Diastereomer Transformations (CIDTs)





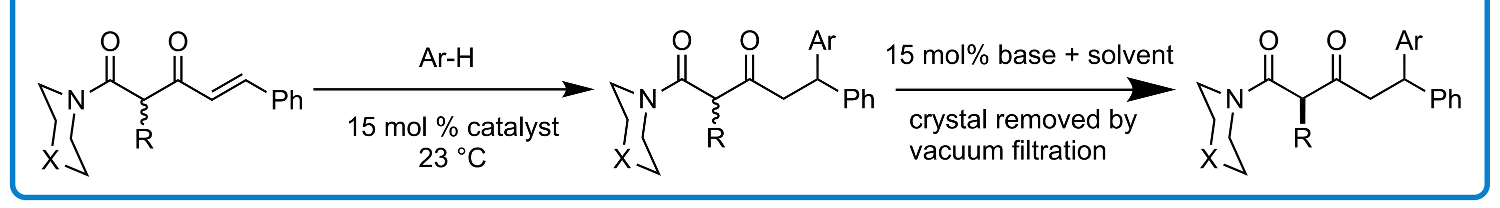
Enantiomers: Same Physical Properties

Diastereomers: Different Physical Properties

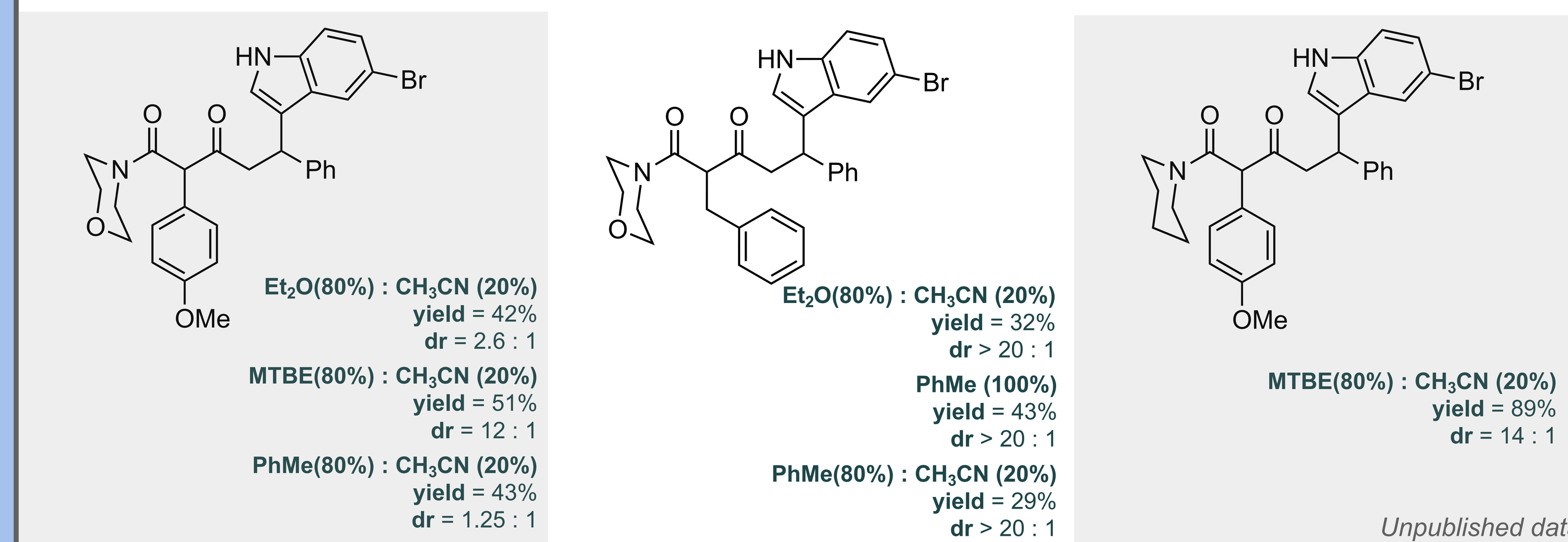


Application to Friedel-Crafts Reactions

Friedel-Crafts Arylation

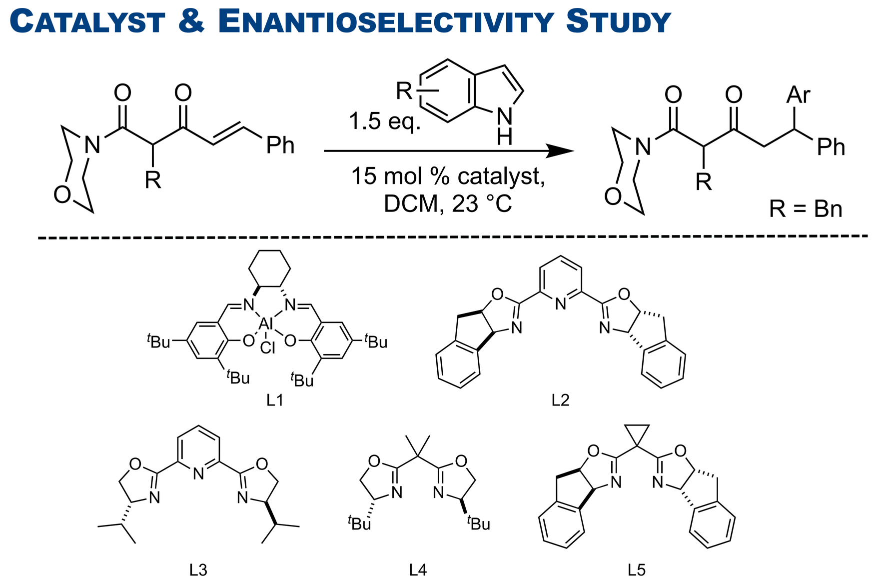


1,4-Arylation Promoted CIDT of Nazarov Amide – Full Scope



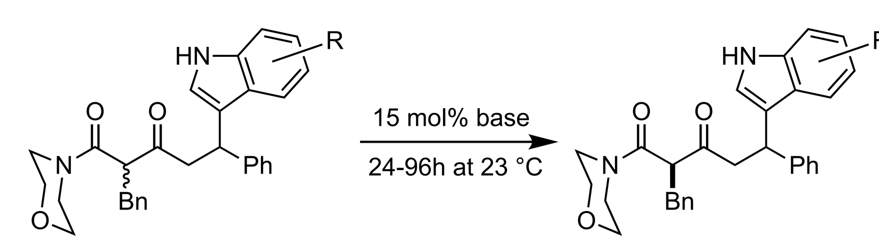
Unpublished data

Catalyst & Enantioselectivity Study



Entry	R	Catalyst	Ligand	yield	dr	er
1	n/a	$Sc(OTf)_3$	L2	78%	2:1	52:48
2	n/a	$Sc(OTf)_3$	L3	54%	2:1	50:50
3	n/a	$Sc(OTf)_3$	L4	61%	2:1	49:51
4	n/a	$Mg(OTf)_2$	L5	2%	2:1	n/a
5	n/a	L1	--	7%	1:1	n/a
6	5-Br	$Sc(OTf)_3$	L3	31%	3:1	n/a
7	5-Br	$Sn(OTf)_2$	L3	22%	3:1	n/a

CIDT Conditions

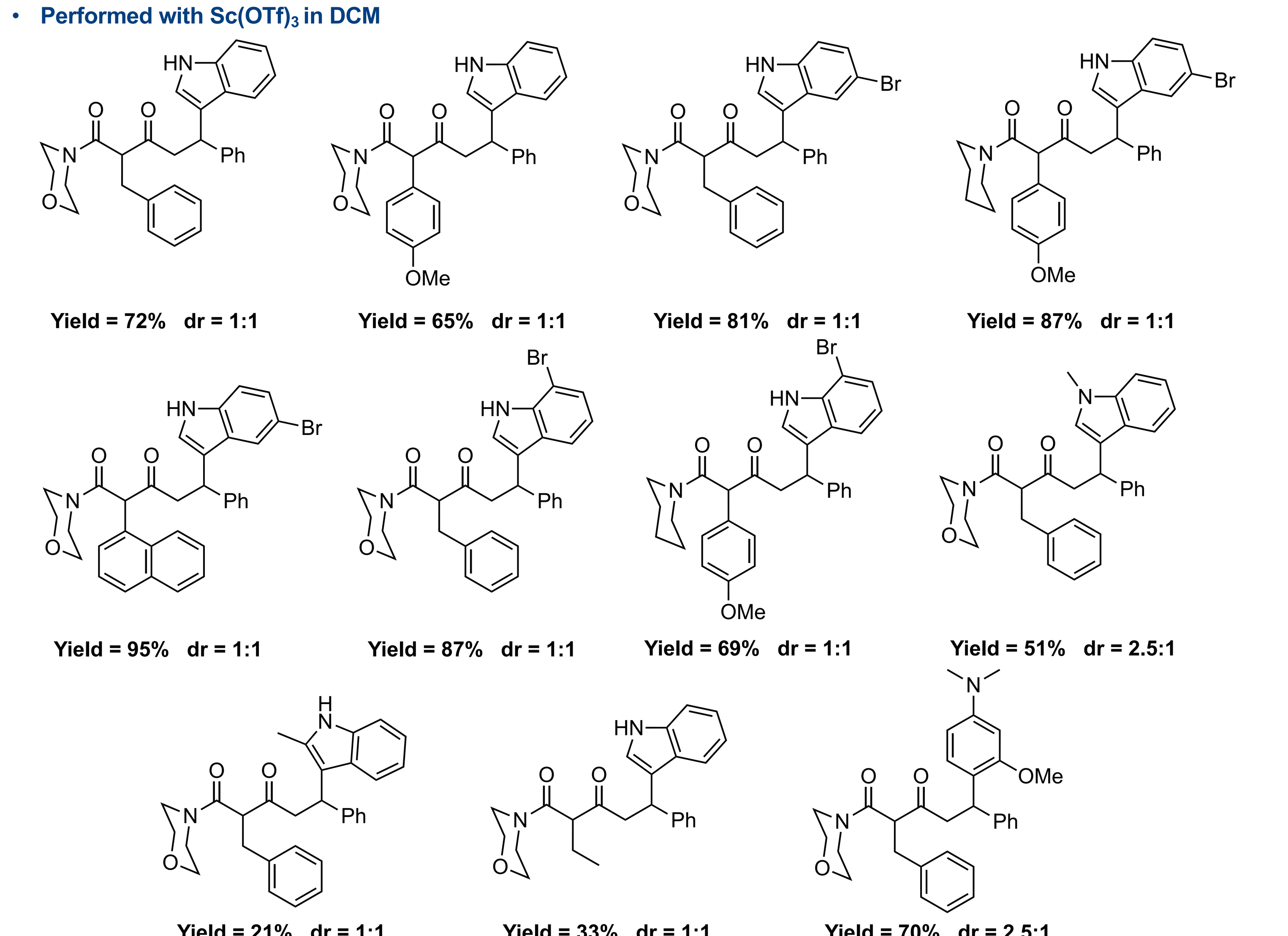


All reactions were carried out on a 0.200 mmol scale. Yield refers to ^1H NMR yield using phenanthrene as an internal standard.

Entry	R	Base	Solvent	dr	recovery
1	n/a	TEA	Et_2O	~1:1	48%
2	n/a	TEA	MTBE	~1:1	45%
3	n/a	TEA	PhMe	3:1	80%
4	n/a	DBU	PhMe	3:1	53%
5	n/a	Pyrrolidine	PhMe	3:1	63%

Substrate Survey

- Performed with $Sc(OTf)_3$ in DCM



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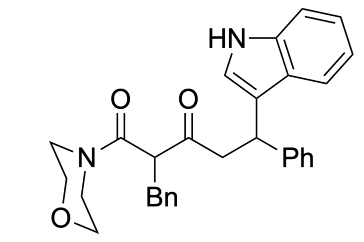
Unpublished data

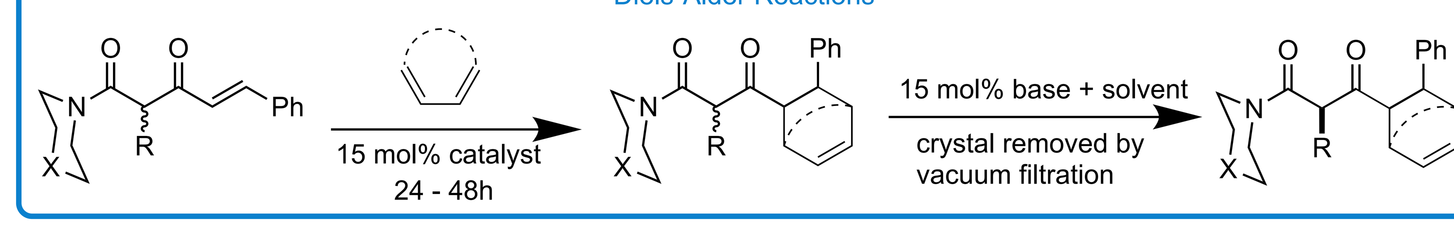
Solvent and Equivalence Optimization



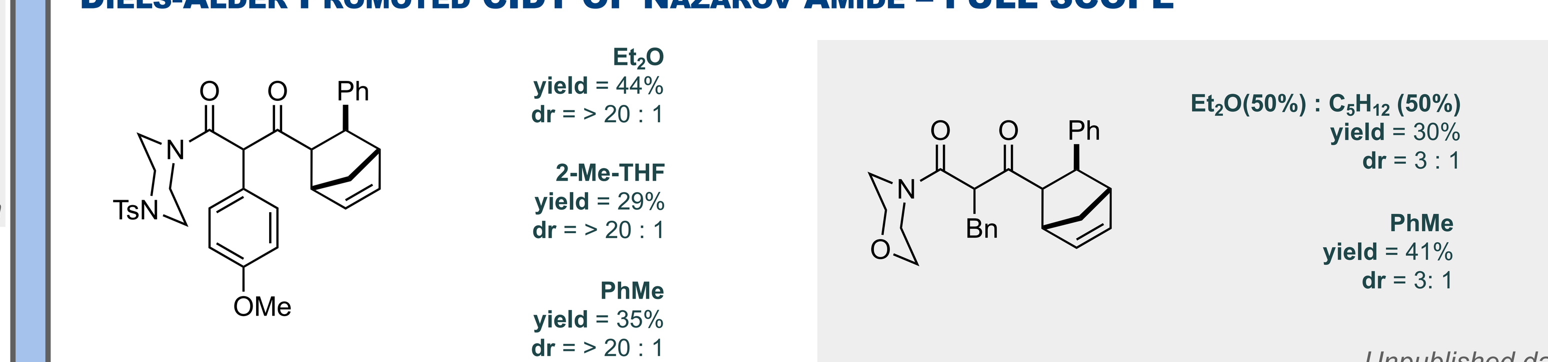
Entry	Equiv Indole	Solvent	yield	dr
1	1.0	DCM	39%	1:1
2	1.2	DCM	61%	1:1
3	1.5	DCM	72%	1:1
4	1.5	PhMe	77%	3:1

Application to Diels-Alder Reactions

Diels-Alder Reactions

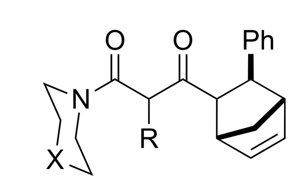


Diels-Alder Promoted CIDT of Nazarov Amide – Full Scope



Unpublished data

Temperature Dependence of Reaction

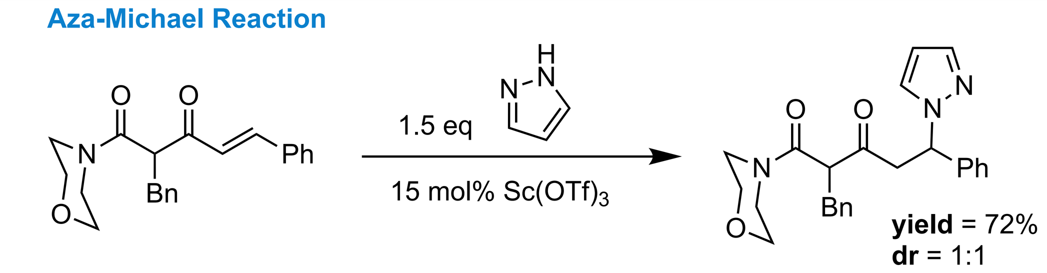


Entry	X	R	Equiv. Cp	Temperature	Yield	endo : exo	dr
1	O	Bn	5	23 °C	82%	3 : 1	1 : 1
2	O	Bn	5	-30 °C	64%	10 : 1	1 : 1
3	O	Bn	5	-40 °C	81%	>20 : 1	1 : 1
4	NTs	p-MeO-C_6H_4	5	-40 °C	48%	> 20 : 1	1 : 1

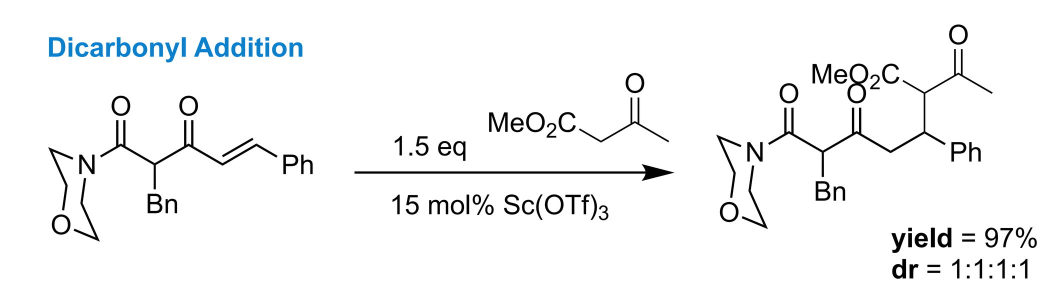
All reactions were carried out on a 0.200 mmol scale. Yield refers to ^1H NMR yield using phenanthrene as an internal standard.

Efforts Towards Lewis Acid Activation of Nazarov Amides

Aza-Michael Reaction

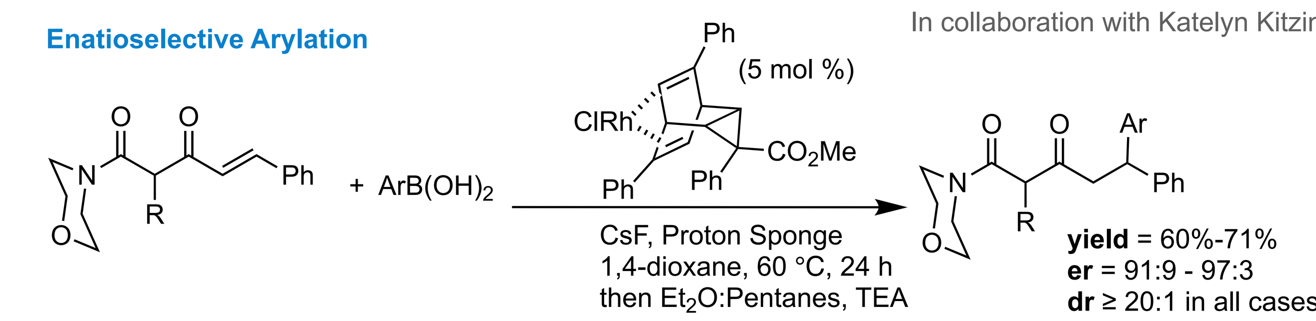


Dicarbonyl Addition

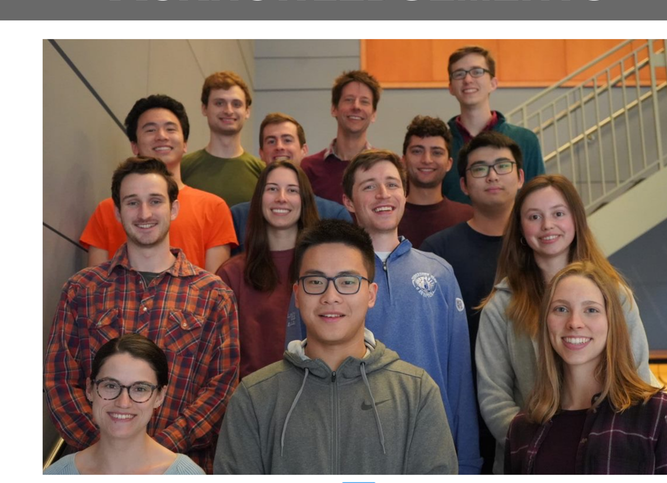


In collaboration with Katelyn Kitzinger

Enatioselective Arylation



Acknowledgements



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