

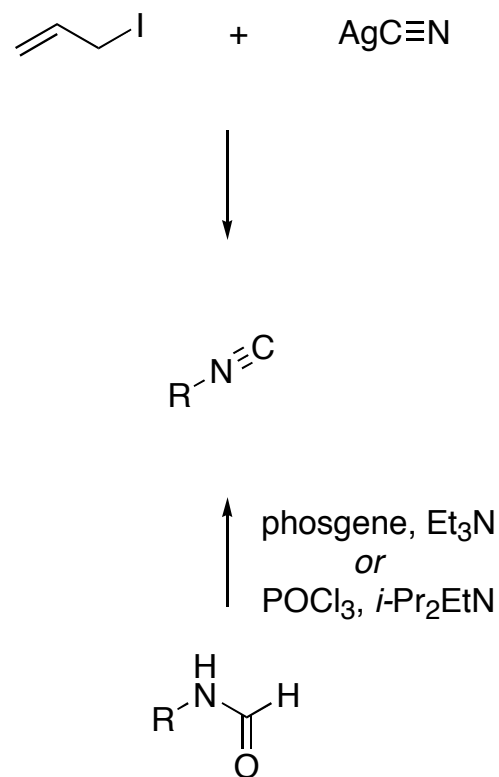
The First Catalytic, Asymmetric  $\alpha$ -Additions of Isocyanides.  
Lewis-Base-Catalyzed, Enantioselective Passerini-Type  
Reactions

*Scott E. Denmark, and Yu Fan*

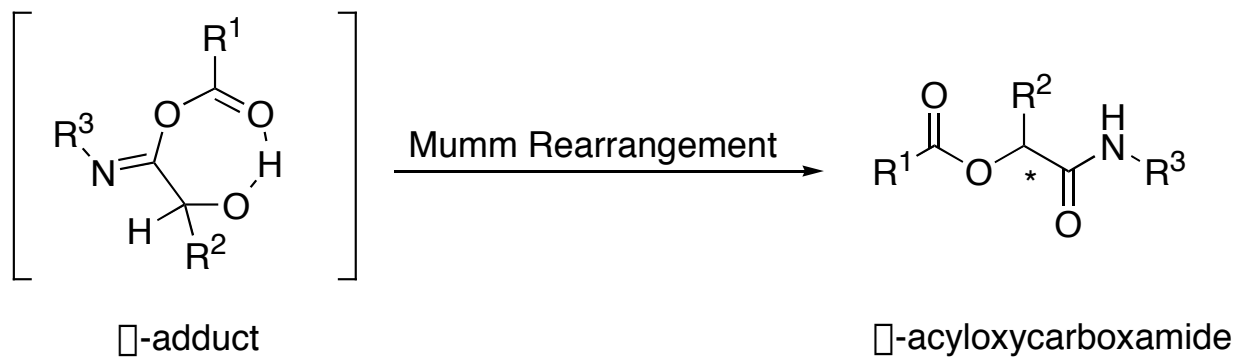
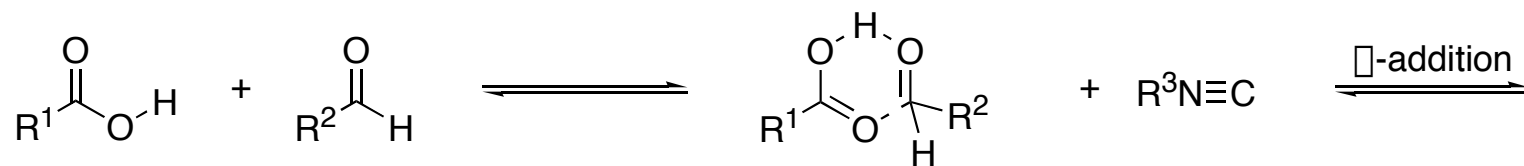
Roger Adams Laboratory  
Department of Chemistry  
University of Illinois

# Isocyanides in Organic Chemistry

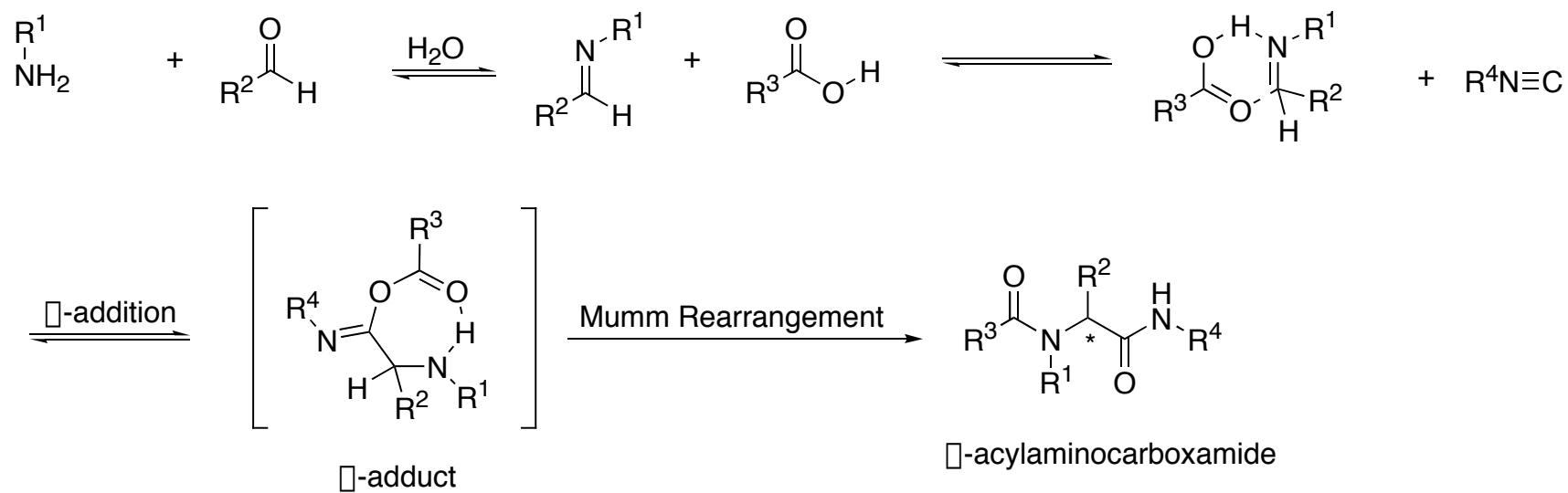
- Only functional moiety with a formally divalent carbon atom which provides a unique pattern of chemical reactivity.
- Allyl isocyanide, the first synthetic isocyanide, was generated in 1859 by Lieke from allyliodide and silver cyanide.
- Modern preparation of isocyanides usually entails the dehydration of formamides with numerous reagents



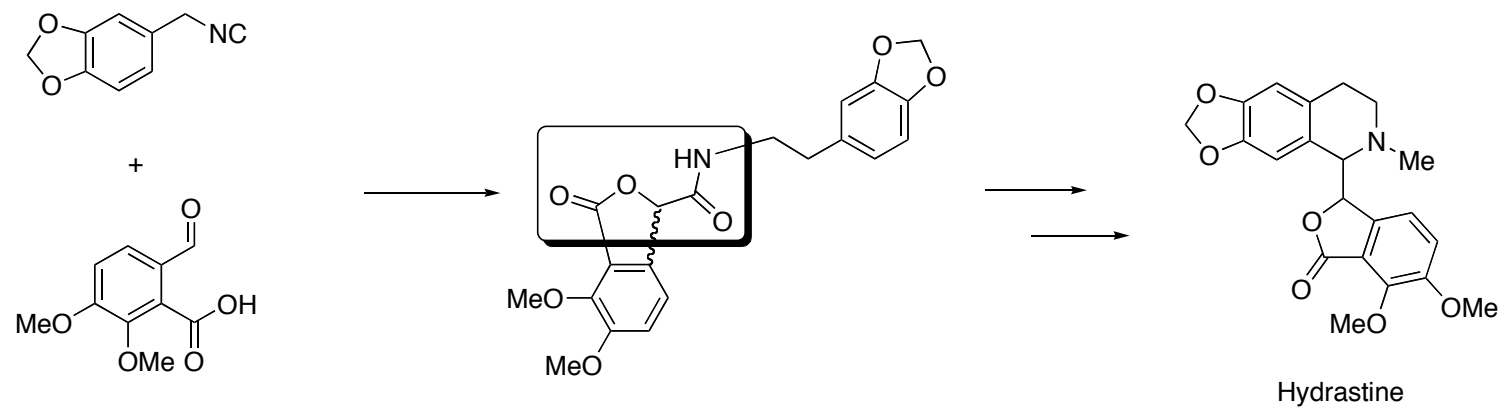
# The Passerini Reaction



# The Ugi Reaction

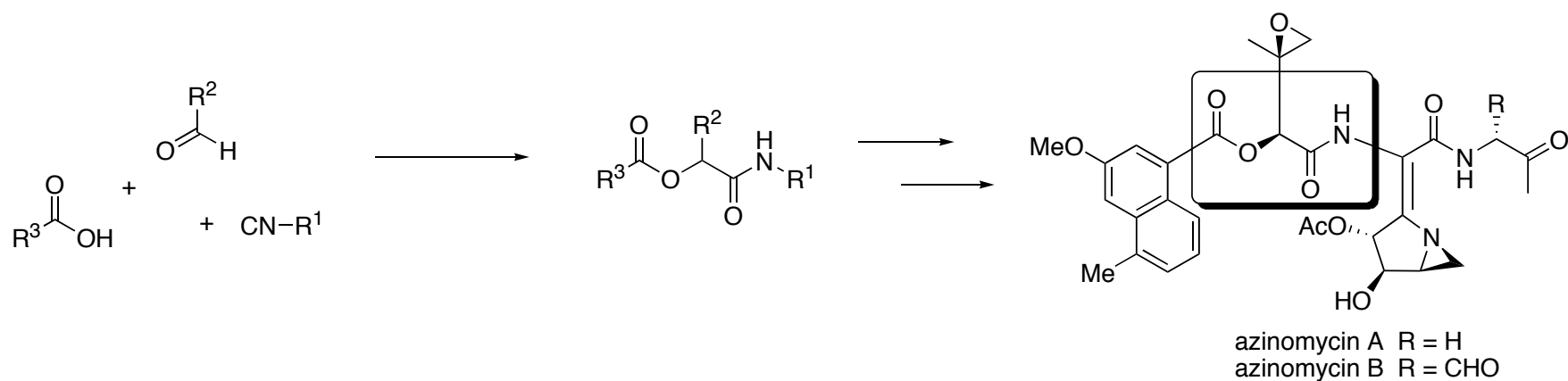


## Synthesis of (+/-) hydrastine



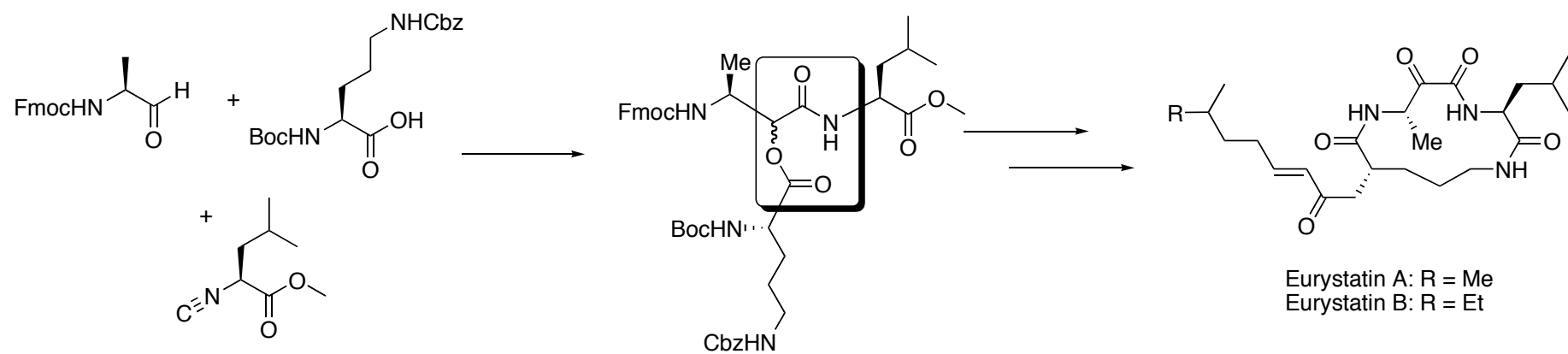
Falck, J. R.; Manna, S. *Tetrahedron Lett.* **1981**, *22*, 619-620.

# Synthesis of Azinomycin A, B



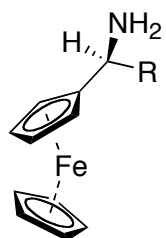
Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123-131

# Synthesis of Eurystatin A



Owens, T. D.; Araldi, G.-O.L.; Nutt, R. F.; Semple, J. E. *Tetrahedron Lett.* **2001** 42, 6271-6274.

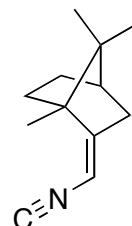
# Some diastereoselective approaches to the $\alpha$ -addition of isocyanates in Passerini and Ugi chemistry



## $\alpha$ -ferrocenylalkylamines

Early chiral auxiliaries used in the Ugi reaction provided poor product yields and modest diastereoselectivities

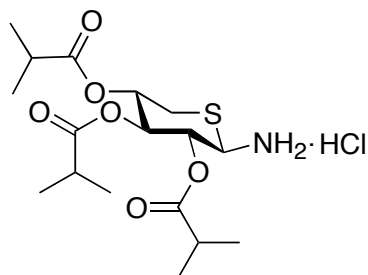
Demharter, A.; Ugi, I. *J. Prakt. Chem.* **1993**, 335, 244.



## Camphor-2-*cis*-methylidene-isocyanide

Effective auxiliary for the Passerini reaction  
Reported reaction yields of 84-96%  
Reported %de 92-93%  
Auxiliary was not effective in the Ugi reaction.

Bock, H.; Ugi, I. *J. Prakt. Chem.* **1997**, 385-9.



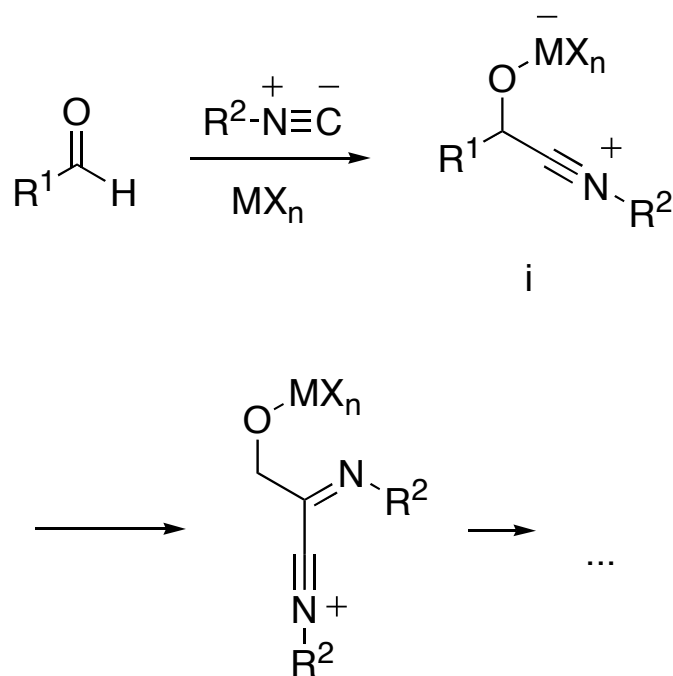
## 1-amino-5-deoxy-5-thio-2,3,4-*O*-isobutonyl- $\beta$ -D-xylopyranose · HCl

Recently applied chiral auxiliary for the Ugi reaction  
Reported reaction yields and %de of up to 92%  
Simple removal with TFA and Hg(OAc)<sub>2</sub> in methanol

Ross, G. F.; Herdtweck, E.; Ugi, I. *Tetrahedron* **2002**, 58, 6127-6133.

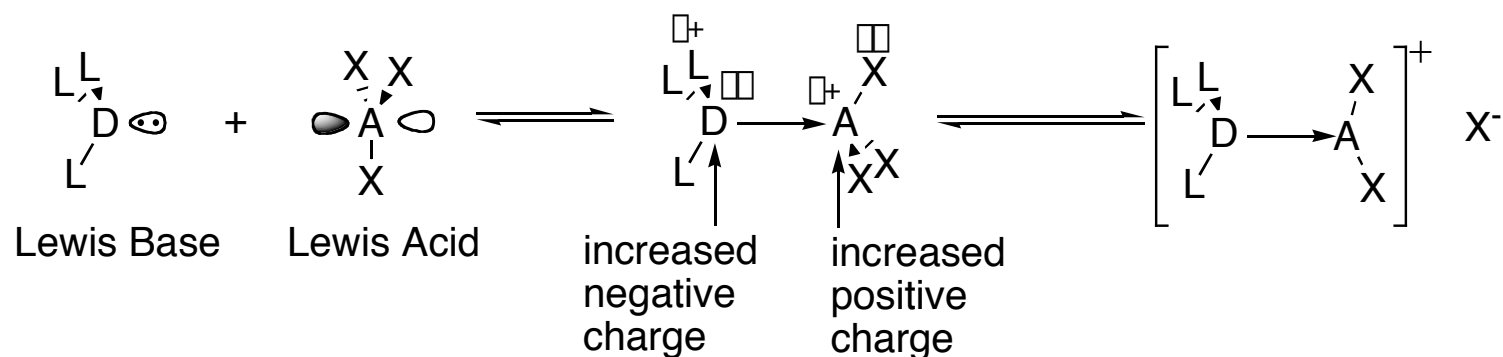


## Why have asymmetric variants of these reactions failed to develop?



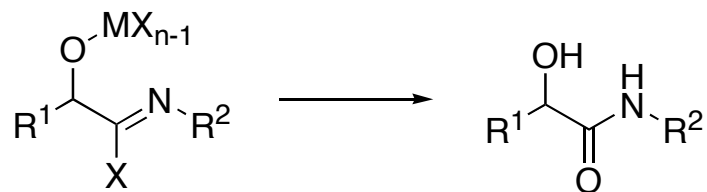
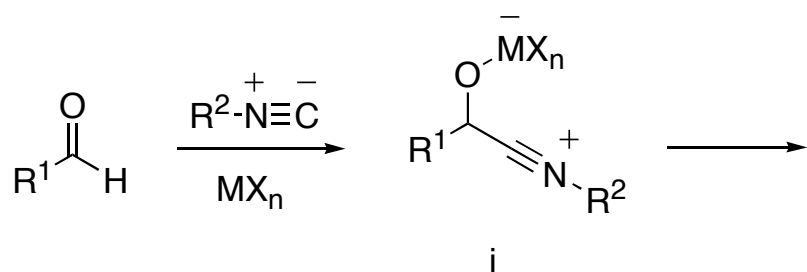
- Following Lewis acid activation of the aldehyde and  $\pi$ -addition of the first equivalent of isocyanide, additional equivalents can add to the zwitterionic intermediate i... What a mess!
- In order for catalyst turnover to occur, cleavage of the bond between  $MX_n$  and the product must be facile. Often not the case in  $\pi$ -additions.
- Asymmetric modification of Lewis acids often leads to deactivation with respect to their unmodified counterparts.

## Potential Solution: Lewis base activation of the Lewis Acid



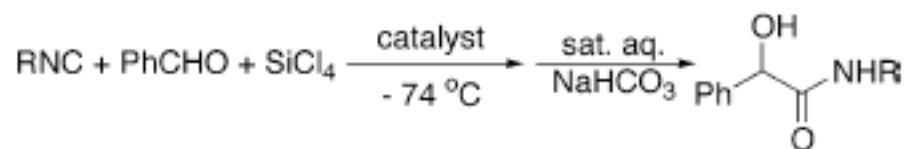
- Gutmann's 4th rule:  
*"...although a donor-acceptor interaction will result in a net transfer of electron density from a donor species to an acceptor species, it will, in the case of polyatomic species, actually lead to a net increase or "pileup" of electron density at the donor atom of the donor species and to a net decrease or "spillover" of electron density at the acceptor atom of the acceptor species..."*

## Advantages of the Lewis base activation of Lewis acids in the Passerini and Ugi reactions

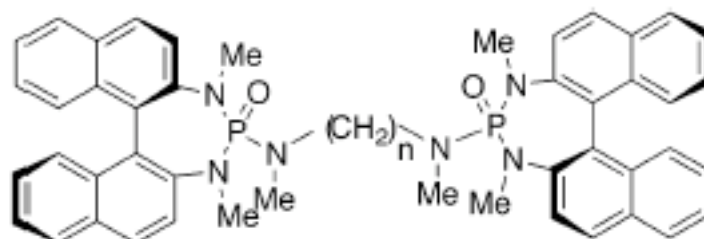
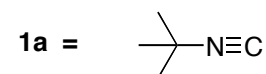


- Nitrilium ion can capture the now dissociated halide ion following carbonyl activation and isonitrile addition
- The attenuated activity of the Lewis acid-substrate complex should promote dissociation of the complex and activation of a new molecule of  $\text{SiCl}_4$ .

## Addition of Isocyanides to Benzaldehyde

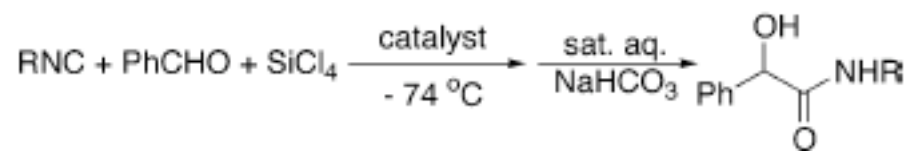


entry	isocyanide	product	catalyst	yield, % <sup>a</sup>	er <sup>b</sup>
1 <sup>c</sup>	<b>1a</b>	<b>3a</b>		79	
2 <sup>d</sup>	<b>1a</b>	<b>3a</b>	<b>4a</b>	90	
3 <sup>e</sup>	<b>1a</b>	<b>3a</b>	<b>4b</b>	94	
4 <sup>f,g</sup>	<b>1a</b>	<b>3a</b>	<b>5a</b>	83	90.2/9.8
5 <sup>f,h</sup>	<b>1a</b>	<b>3a</b>	<b>5a</b>	94	94.3/5.7
6 <sup>f,i</sup>	<b>1a</b>	<b>3a</b>	<b>5a</b>	89	98.1/1.9
7 <sup>f,j</sup>	<b>1a</b>	<b>3a</b>	<b>5a</b>	96	> 99/1 <sup>k</sup>

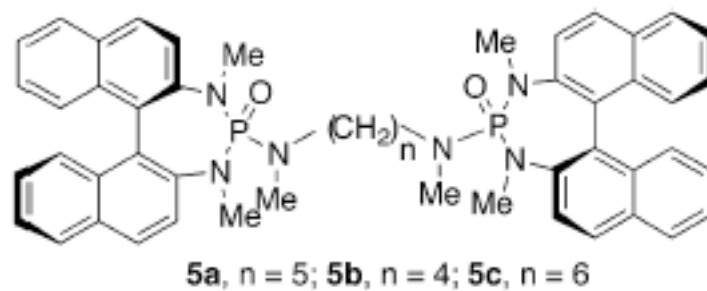
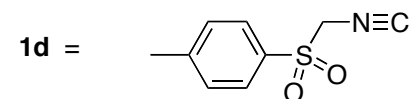
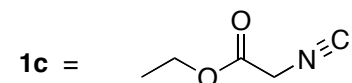
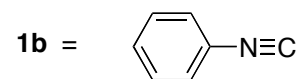
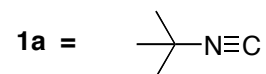


**5a**,  $n = 5$ ; **5b**,  $n = 4$ ; **5c**,  $n = 6$

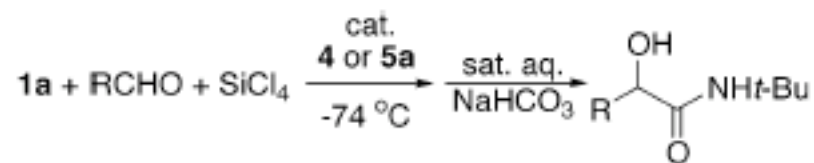
## Reaction Scope I (modified isonitriles)



entry	isocyanide	product	catalyst	yield, % <sup>a</sup>	er <sup>b</sup>
8 <sup>e,l</sup>	<b>1b</b>	<b>3n</b>	<b>4b</b>	76	
9 <sup>f,j</sup>	<b>1b</b>	<b>3n</b>	<b>5a</b>	82	73.2/26.8
10 <sup>e,m</sup>	<b>1c</b>	<b>3o</b>	<b>4b</b>	72	
11 <sup>f,m</sup>	<b>1c</b>	<b>3o</b>	<b>5a</b>	83	83.3/16.7
12 <sup>e,m</sup>	<b>1d</b>	<b>3p</b>	<b>4b</b>	69	
13 <sup>f,m</sup>	<b>1d</b>	<b>3p</b>	<b>5a</b>	80	88.5/11.5



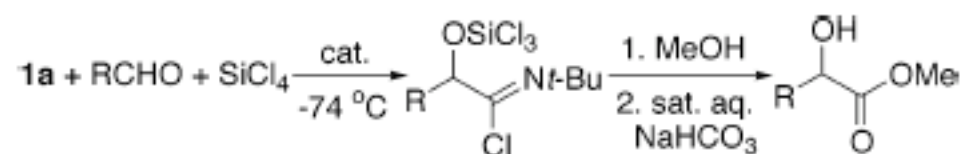
## Reaction Scope II (modified aldehydes)



entry	R	product	catalyst		er <sup>d</sup>
			4b yield, % <sup>a,b</sup>	5a yield, % <sup>a,c</sup>	
1	4-CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> ( <b>2b</b> )	<b>3b</b>	87	91	99.9/0.1
2	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	<b>3c</b>	92	89	98.3/1.7
3	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	<b>3d</b>	87	89	96.5/3.5
4	2-naphthyl ( <b>2e</b> )	<b>3e</b>	90	93	99.7/0.3
5	1-naphthyl ( <b>2f</b> )	<b>3f</b>	87	92	92.2/7.8 <sup>e</sup>
6	2-furyl ( <b>2g</b> )	<b>3g</b>	76	83	95.9/4.1 <sup>f</sup>
7	( <i>E</i> )-PhCH=CH ( <b>2h</b> )	<b>3h</b>	73	81	97.8/2.2
8	( <i>E</i> )-PhCH=CH(CH <sub>3</sub> ) ( <b>2i</b> )	<b>3i</b>	86	86	67.4/32.6
9	phenylpropargyl ( <b>2j</b> )	<b>3j</b>	85	76	77.0/23.0
10	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>2k</b> )	<b>3k</b>	89	92	81.9/18.1
11	cyclohexyl ( <b>2l</b> )	<b>3l</b>	72	53	87.1/12.9 <sup>f</sup>
12 <sup>g</sup>	PhCH <sub>2</sub> CH <sub>2</sub> ( <b>2k</b> )	<b>3m</b>	84	87	70.0/30.0

<sup>a</sup> Yields of chromatographically homogeneous material. <sup>b</sup> With 10 mol % of pyridine-*N*-oxide. <sup>c</sup> With 5 mol % of **5a**. <sup>d</sup> Determined by CSP-SFC. <sup>e</sup> Determined by CSP-HPLC. <sup>f</sup> Determined by CSP-GC. <sup>g</sup> 1,1,3,3-Tetra-methylbutyl isocyanide (**1e**) served as the nucleophile.

## Facile Conversion of Imidoyl Chlorides to Methyl Esters



aldehyde	product	catalyst		config	er <sup>d</sup>
		4b yield, % <sup>a,b</sup>	5a yield, % <sup>a,c</sup>		
<b>2a</b>	<b>6</b>	83	97	<i>S</i>	> 99/1
<b>2h</b>	<b>7</b>	74	71	<i>S</i>	97.9/2.1 <sup>e</sup>
<b>2k</b>	<b>8</b>	83	88	<i>S</i>	81.8/18.2

<sup>a</sup> Yields of chromatographically homogeneous material. <sup>b</sup> With 10 mol % of pyridine-*N*-oxide. <sup>c</sup> With 5 mol % of **5a**. <sup>d</sup> Determined by CSP-SFC. <sup>e</sup> Determined by CSP-GC.

## Summary and Conclusions

- The first catalytic, enantioselective  $\alpha$ -additions of isocyanides to aldehydes has been described
- Activation of a weak Lewis acid with a chiral Lewis base was demonstrated to catalyze asymmetric Passerini-type reactions