Regioselectivity Obtained by Using Non-covalent Interactions

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Today's Topics

1. Introduction
2. Regioselective Reaction Using the Ion-pair Interaction
3. Regioselective Reaction Using the Hydrogen Bonding
4. Summary

1. Introduction

Example of Non-covalent Interactions

Hydrogen bonding

Ion-pair interaction

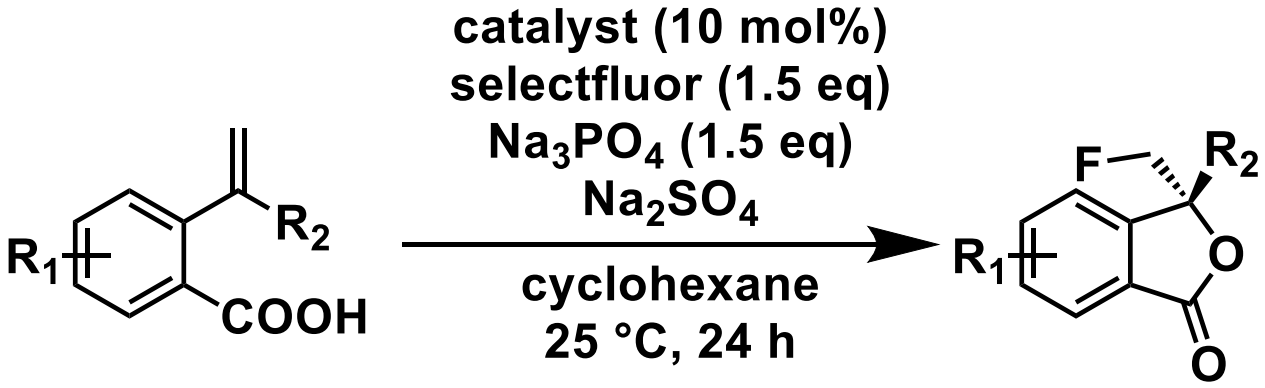
Hydrophobic interaction

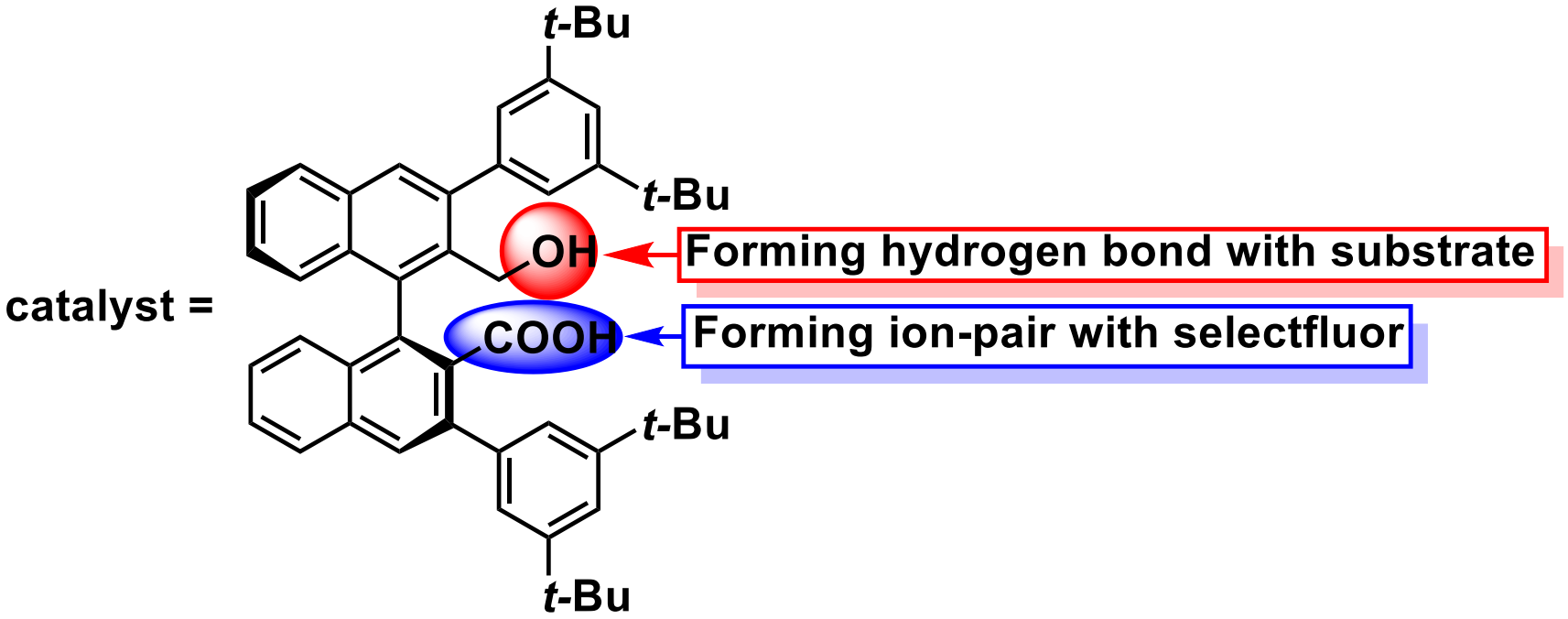
Halogen bond

⋮

These interactions were used in organic chemstry.

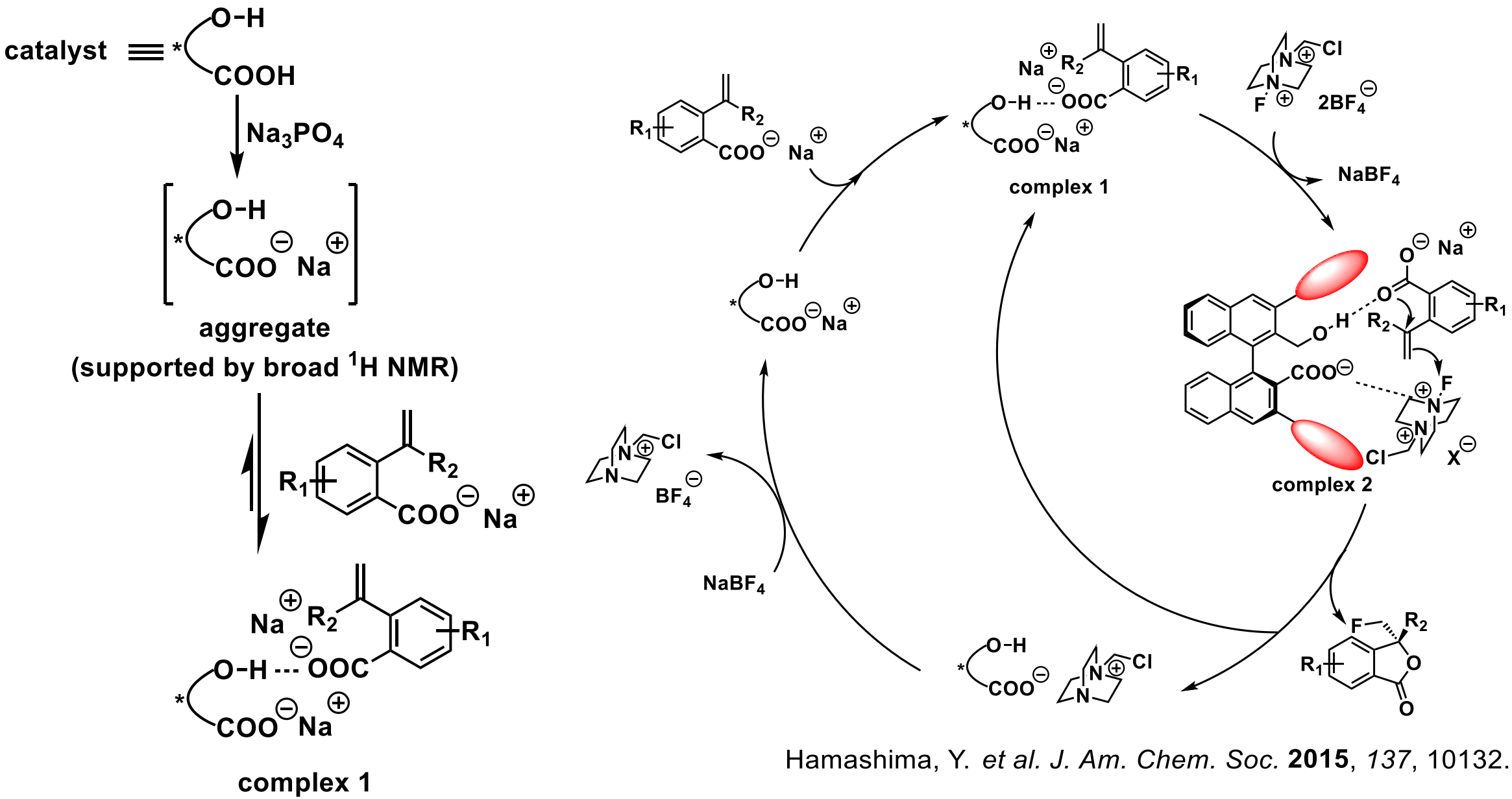
Example of Enantioselective Reaction Using Non-covalent Interaction





Hamashima, Y. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10132.

Proposed Catalytic Cycle

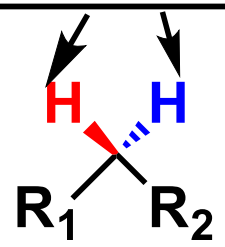


Hamashima, Y. *et al. J. Am. Chem. Soc.* **2015**, *137*, 10132.

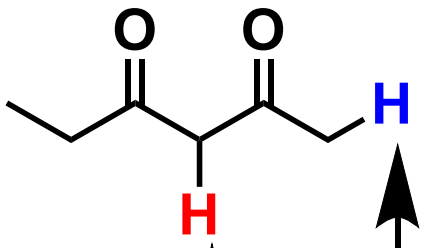
①The Presence of Innate Reactivity

Enantioselective reactions

Same innate reactivity



Regioselective reactions



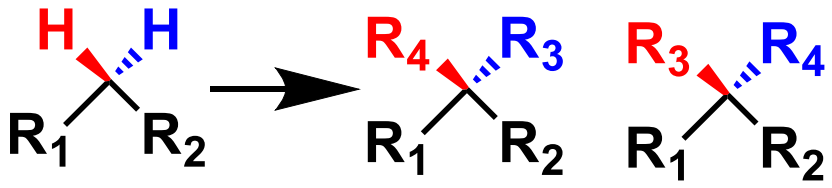
different innate reactivity

Natural selectivity may need to be overridden to get regioselectivity.

②The Number of Choices

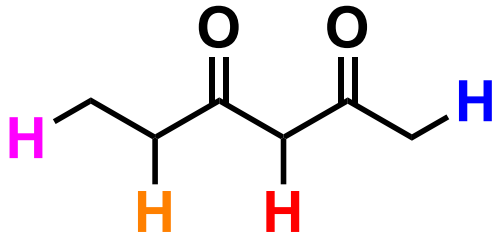
Enantioselective reactions

two choices and two products



Regioselective reactions

multiple choices and many isomers



four isomers

Acceralation of transformation at a desired reaction point may need to get a desired isomer.

Summary of Section 1

- **Regioselective reactions using non-covalent interactions are limited.**

- **Regioselective reactions may be more difficult than enantioselective reactions because of the presence of innate reactivity and many reaction points.**

2. Regioselective Catalyst Using the Ion-pair Interaction

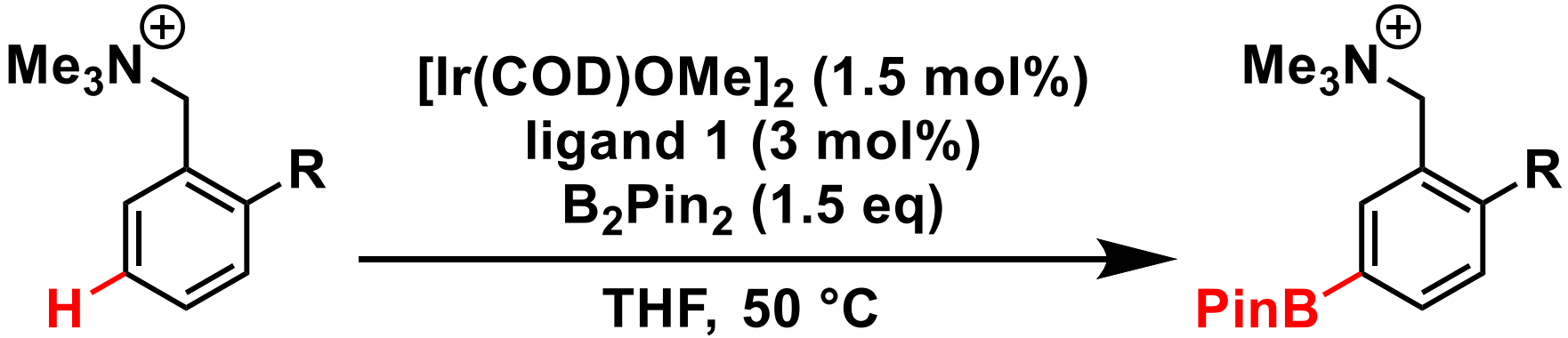
Ion-pair Interaction

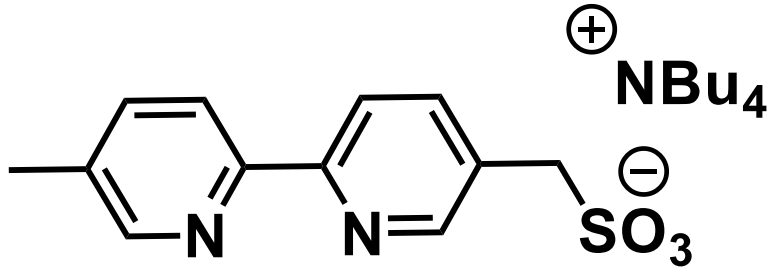
Type	distance dependency of potential energy	representative energy (kJ/mol)
ion-ion	1/r	250
ion-dipole	$1/r^2$	15
dipole-dipole	$1/r^3$ or $1/r^6$	0.6 or 2
dispersion interaction	$1/r^6$	2

Ion-pair interaction also affects distant molecules.

Ion-pair interaction has high potential energy.

Regioselective Reaction Using Ion-pair Interaction



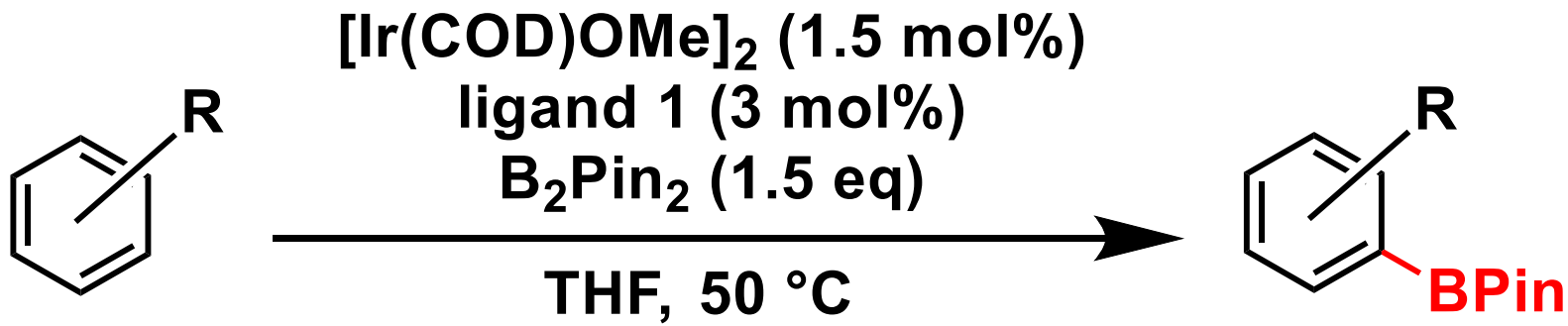


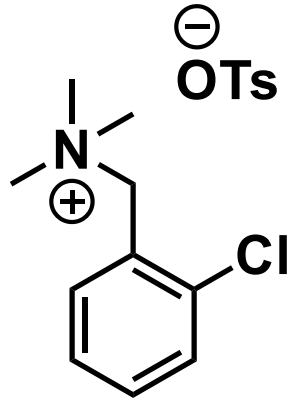
ligand 1

Phipps, R. J. *et al. J. Am. Chem. Soc.* **2016**, *138*, 12759.

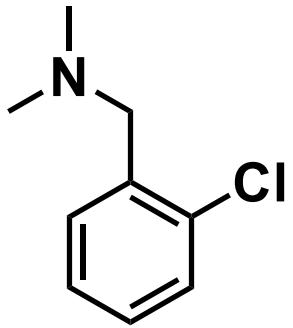
Unlike enantioselective reactions, regioselective reactions are limited.

Importance of the Presence of Cation Charge

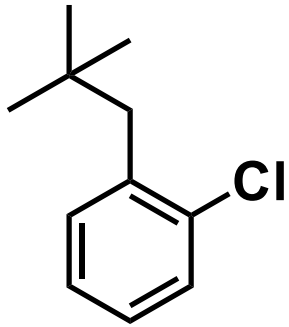




m:*p* = 10:1
selective



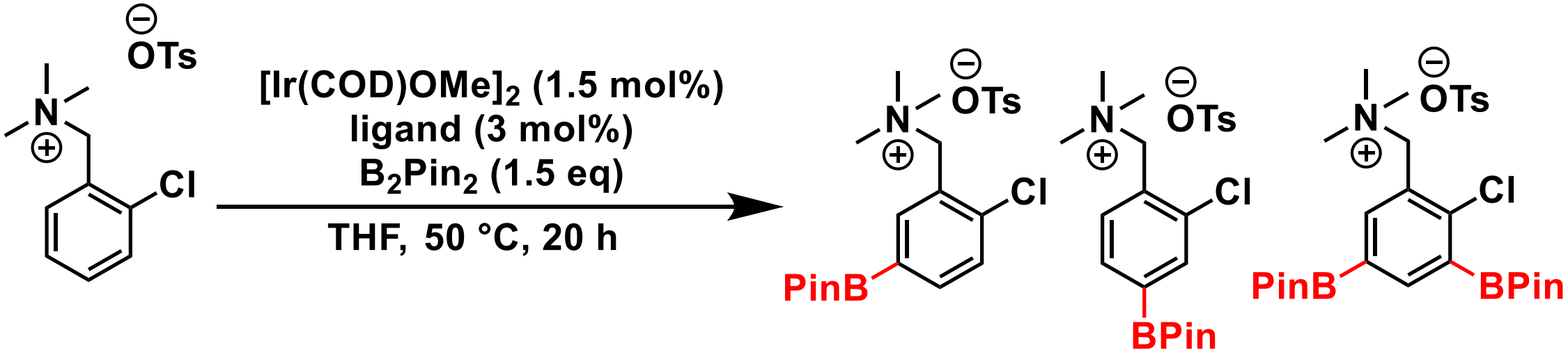
m:*p* = 1:1
non-selective

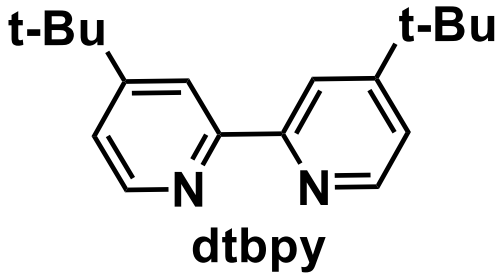


m:*p* = 1:1
non-selective

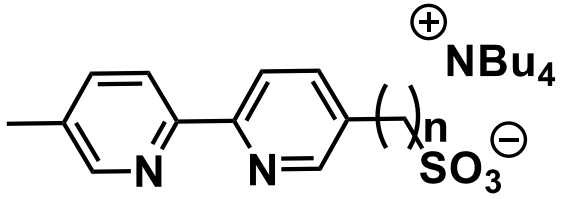
Cation charge was important for regioselectivity.

Importance of the Presence of Anion Charge

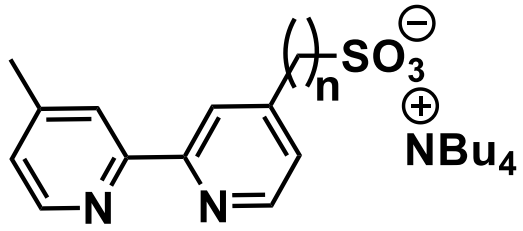




dtbpy



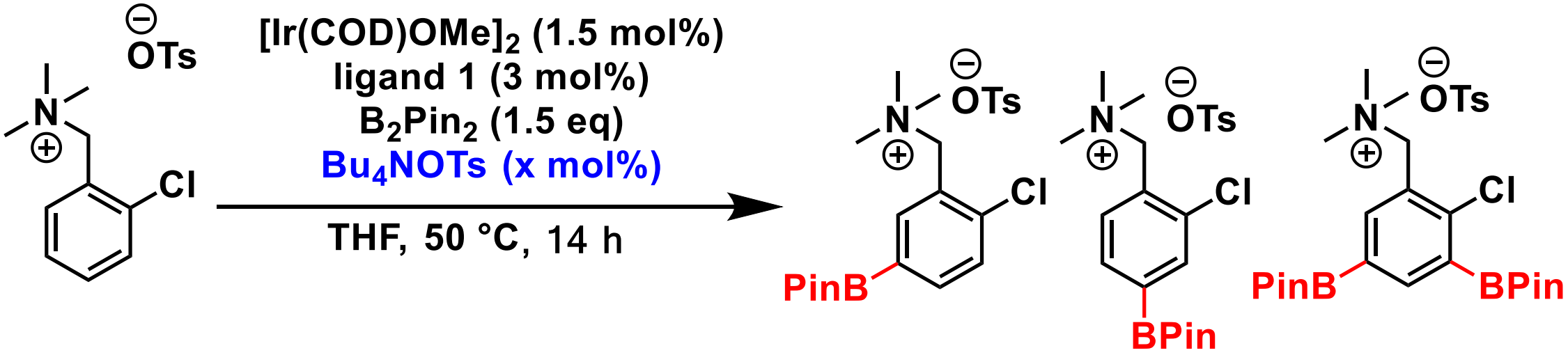
n=1; ligand 1
n=2; ligand 2



n=1; ligand 3
n=2; ligand 4

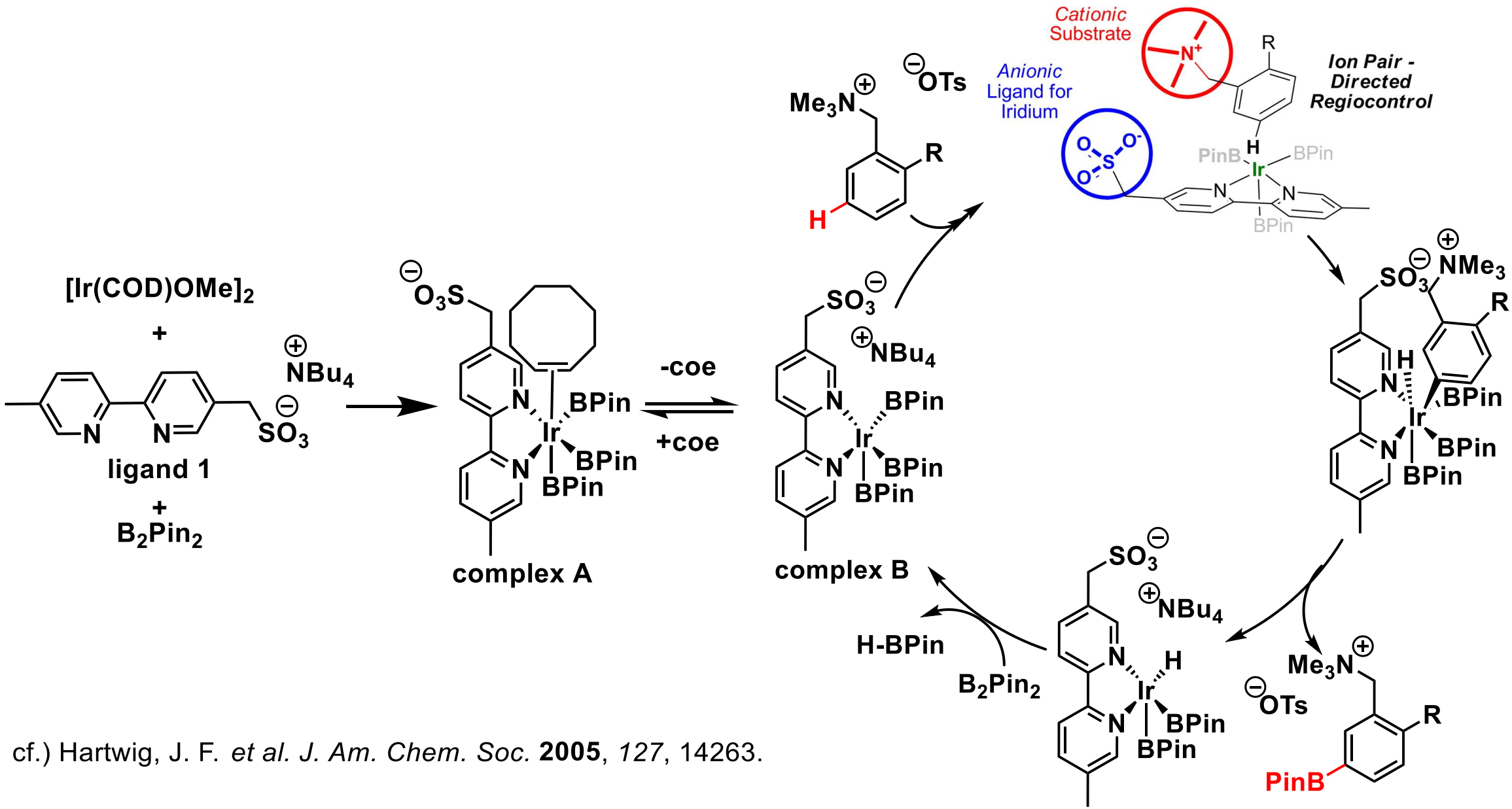
entry	ligand	NMR yield (%) meta	para	dimeta	regioselectivity (meta:para)
1	dtbpy	28	64	1	1:2.2
2	ligand 1	77	8	4	10.1:1
3	ligand 2	77	22	1	3.5:1
4	ligand 3	51	31	6	1.8:1
5	ligand 4	46	43	3	1.1:1

Importance of Substrate and Ligand Interaction



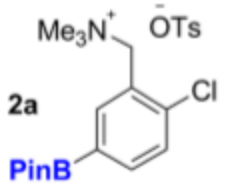
entry	x mol%	NMR yield (%) meta	para	dimeta	regioselectivity (meta:para)
1	0	77	8	4	10.1:1
2	50	71	10	5	7.6:1
3	100	66	13	3	5.3:1
4	200	66	14	2	4.9:1
5	300	66	14	6	5.1:1
6	400	65	14	0	4.6:1

Assumed Reaction Mechanism

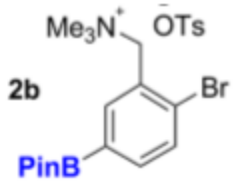


cf.) Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2005**, *127*, 14263.

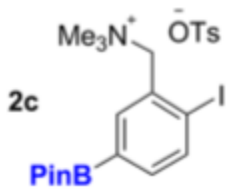
Substrate Scope 1 (disubstituted)



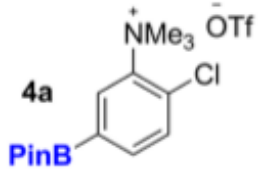
L1, THF: 11:1, 77%
dtbpy, THF: 1:2, 80%



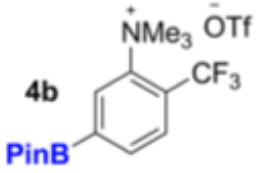
L1, THF: 8:1, 82%
dtbpy, THF: 1:2.6, 51%



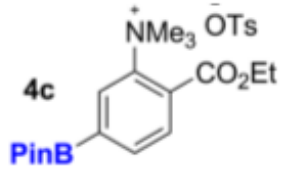
L1, THF: 5.5:1 (82%)
dtbpy, THF: 1:2.5 (73%)



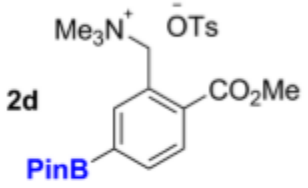
L1, THF: 8:1, 88%
dtbpy, THF: 1:2, 91%



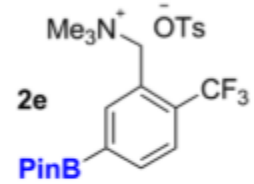
L1, THF: 9:1, 90%
dtbpy, THF: 1:1.2, 88%



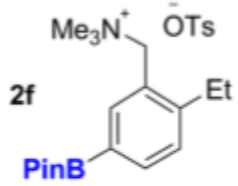
L1, THF: 7:1, (91%)
dtbpy, THF: 1:1, (98%)



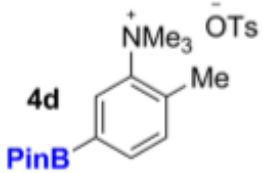
L1, THF: 13:1 (71%)
dtbpy, THF: 1.5:1 (100%)



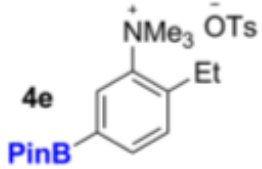
L1, THF: 8:1, 78%
dtbpy, THF: 1:1.4, 63%



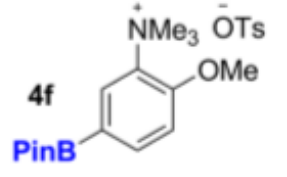
L1, THF: 9:1, 59%
dtbpy, THF: 1:1.1, 53%



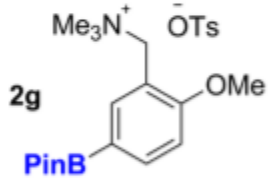
L1, THF: 8:1, 85%
dtbpy, THF: 1.7:1, (21%)



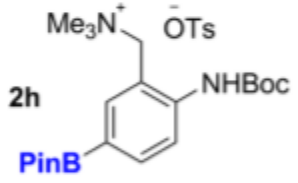
L1, THF: 14:1, 93%
dtbpy, THF: 1.4:1, 87%



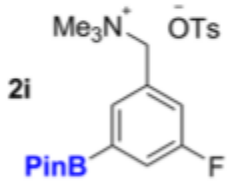
L1, THF: 4:1, 75%
dtbpy, THF: 1:1.2, 95%



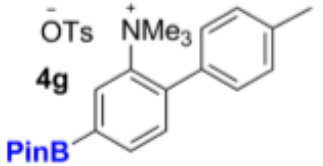
L1, THF: 9:1, 74%
dtbpy, THF: 1:1.7, 80%



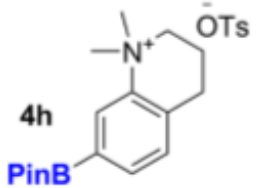
L1, THF: 20:1, 59%
dtbpy, THF: 1.5:1 (52%)



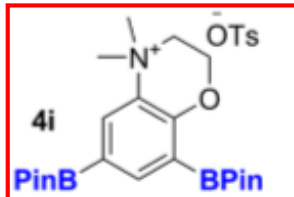
L1, THF: 20:1, 76%
dtbpy, THF: 1.3:1, 52%



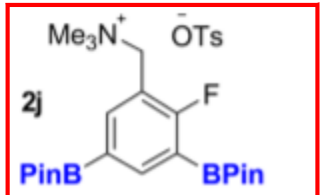
L1, THF: 9:1, 79%
dtbpy, THF: 1:1, 86%



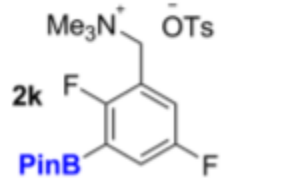
L1, THF: >20:1, 80%
dtbpy, THF: 2.1:1, (67%)



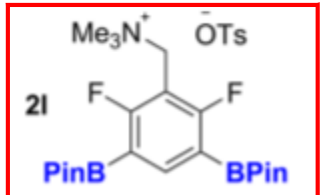
L1, THF: 20:1, 89%
dtbpy, THF: 1.4:1, 73%



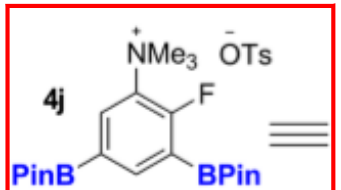
L1, THF: 12:1, 61%
dtbpy, THF: 2.2:1, 69%



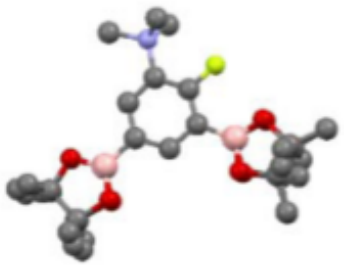
L1, THF: 11:1, 76%
dtbpy, THF: 1.7:1, 70%



L1, THF: 7:1 (90%)
dtbpy, THF: 1.7:1 (82%)



L1, THF: >20:1, 81%
dtbpy, THF: 5:1, 87%



L1, THF: >20:1, 87%
dtbpy, THF: 2:1, 87%

Some substrates were diborylated.

Substrate Scope 2 (monosubstituted)

L1, THF: >20:1, 92%
dtbpy, THF: 3.3:1 (82%)

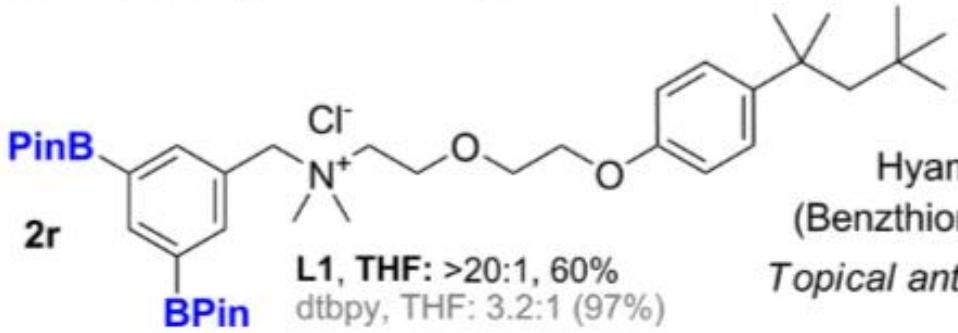
L1, THF: >20:1, 80%
dtbpy, THF: 5.3:1 (88%)

L1, THF: >20:1, 86%
dtbpy, THF: 1.3:1 (95%)

L1, THF: >20:1, 52%
dtbpy, THF: 5:1 (92%)

L1, THF: >20:1, 96%
dtbpy, THF: 5:1 (94%)

L1, THF: >20:1, 97%
dtbpy, THF: 3.2:1 (99%)

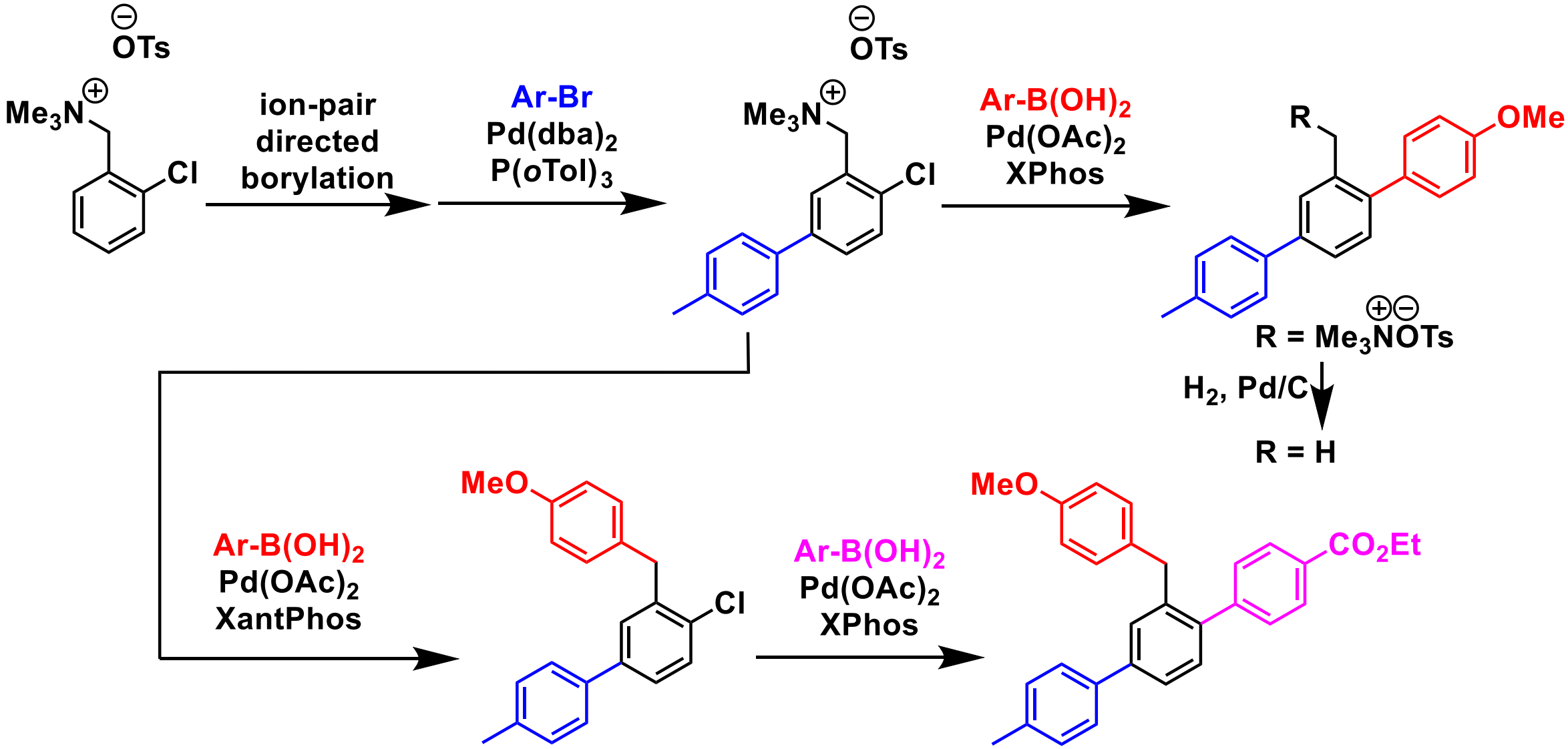


L1, THF: >20:1, 60%
dtbpy, THF: 3.2:1 (97%)

Hyamine® 1622
(Benzthionium Chloride)
Topical antimicrobial agent

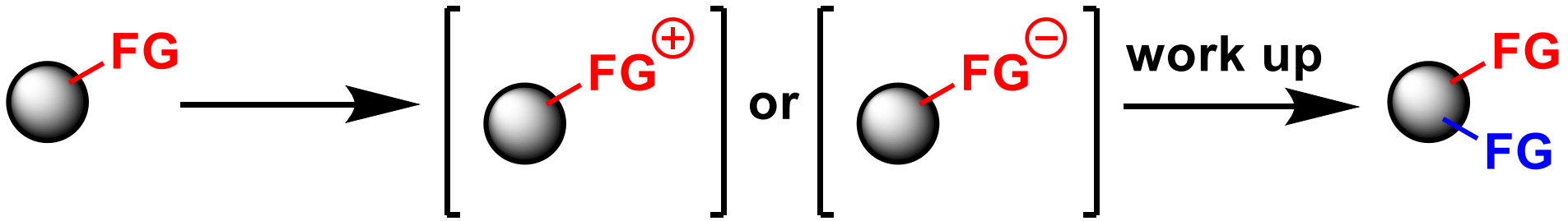
Double functionalization couldn't be avoided.

Application? Limitation?



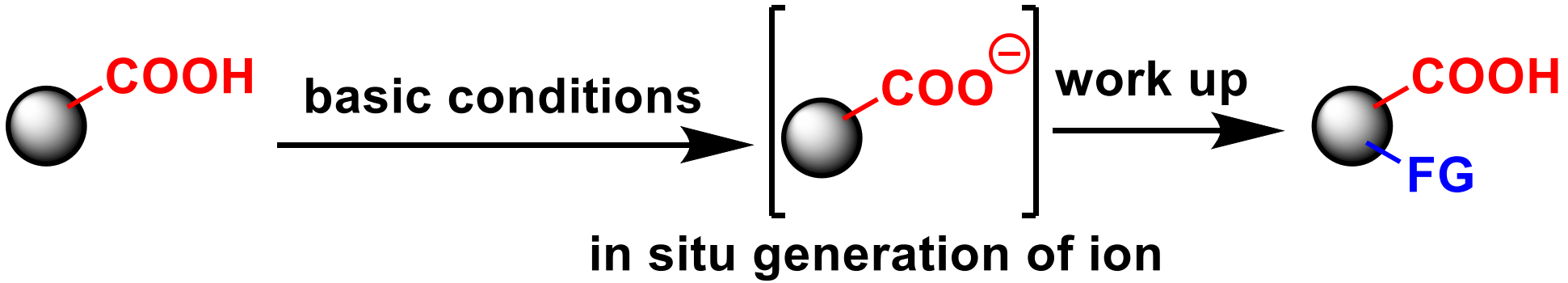
Quaternary ammonium salts may need to be converted to various structure.

A Solution of the Problem



Some acidic FG and basic FG may act as above FG.

For example

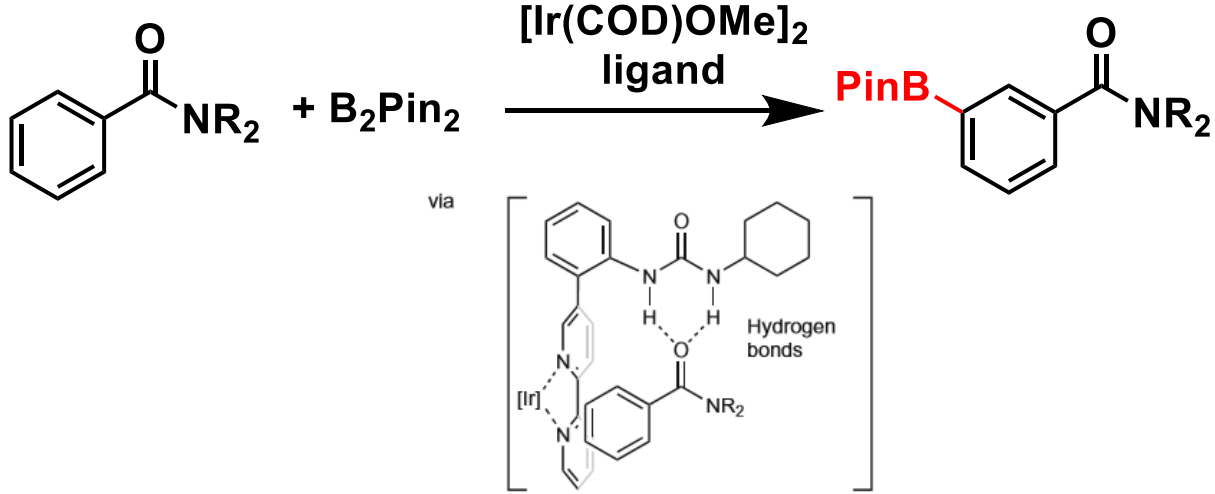


Summary of Section 2

- **Regioselective reactions using ion-pair interaction are limited.**
- **Current regioselective reactions using ion-pair interaction leave a problem in the structure of substrates.**
- **Some FG such as -COOH may solve the problem.**

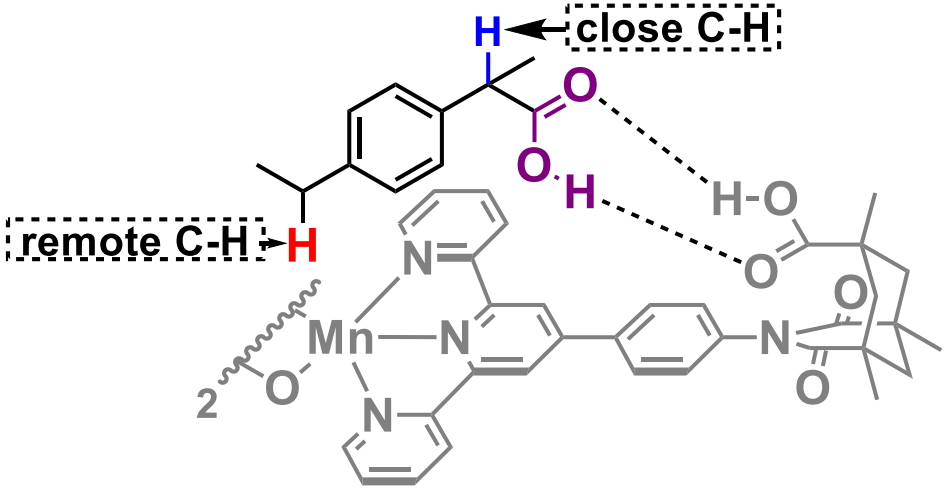
3. Regioselective Catalyst Using the Hydrogen Bonding

Regioselective Reactions Using Hydrogen Bonding



Special directing group required.

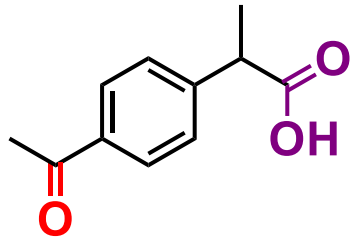
Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712.



Oxone (5 eq)

Mn cat. (1 mol%)

CH_3CN, 20 °C



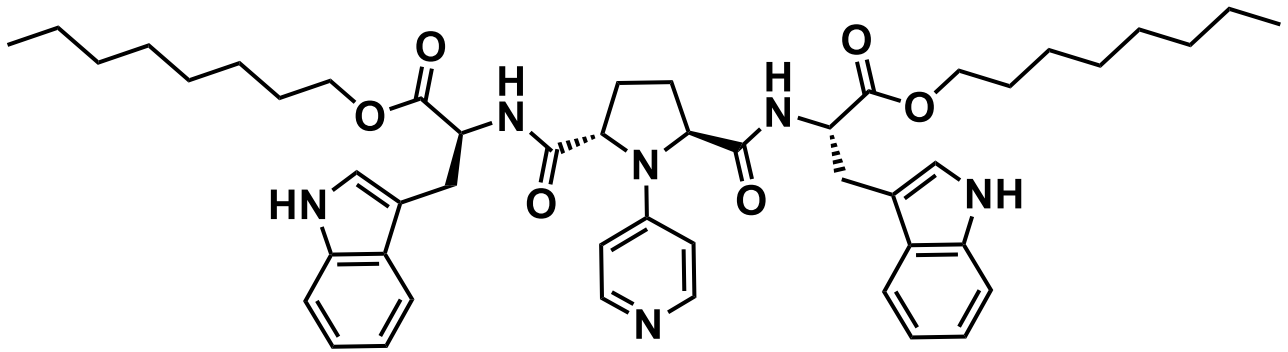
remote selective oxidation

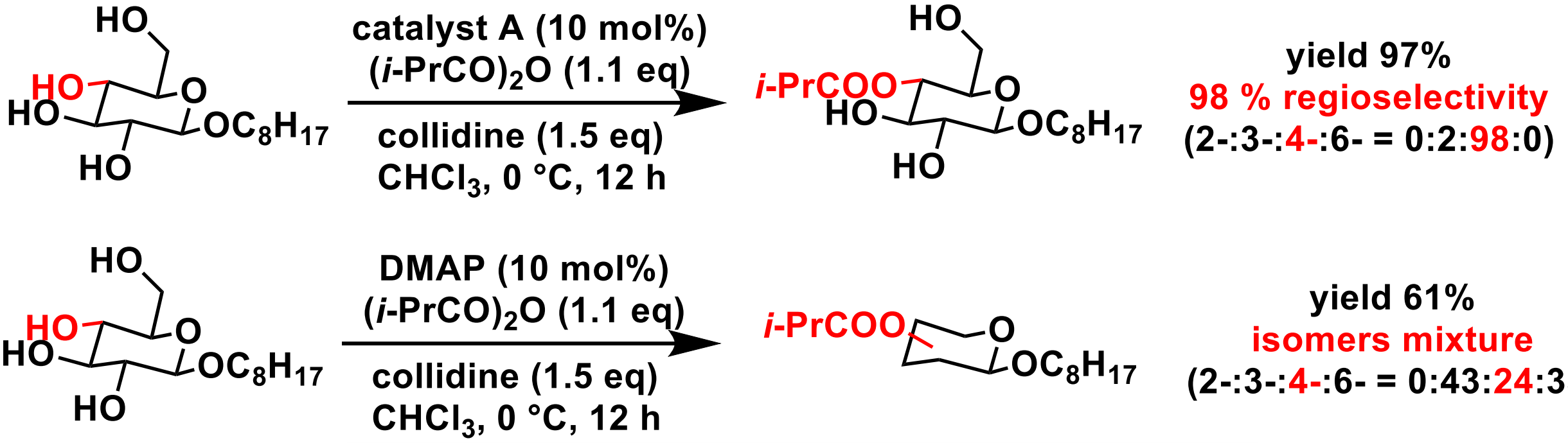
(remote / close = 97.5 / 2.5)

Lack of substrate generality

Crabtree, R. H.; Brudvig, G. W. *et al. Science* **2006**, *312*, 1941.

Regioselective Acylation of Polyol

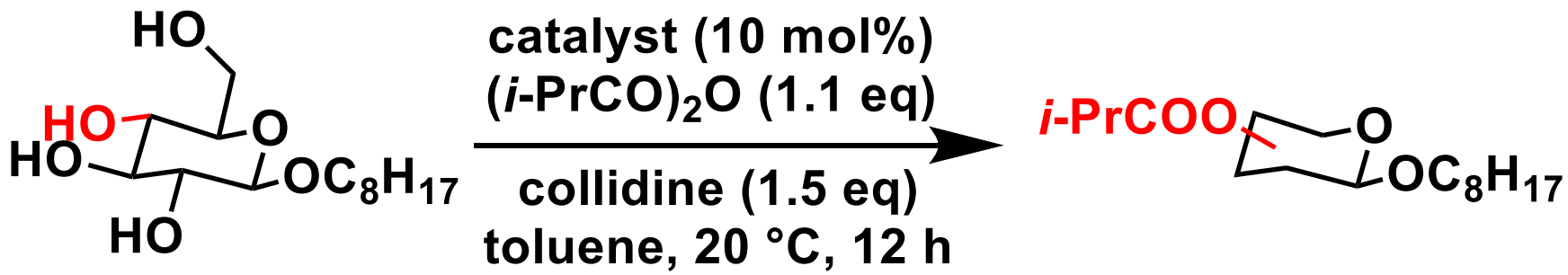


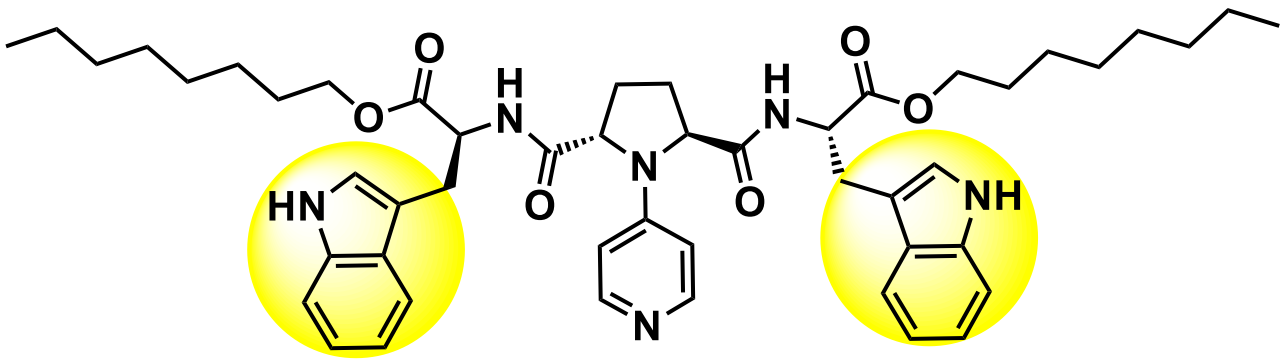


✓ ***Catalyst-controled regioselectivity was observed.***

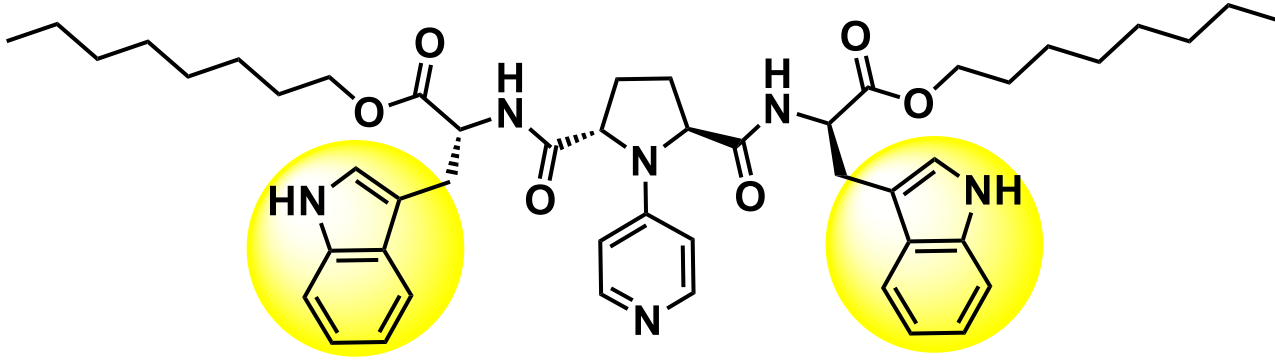
Kawabata, T. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12890.

The Side-chain Effect

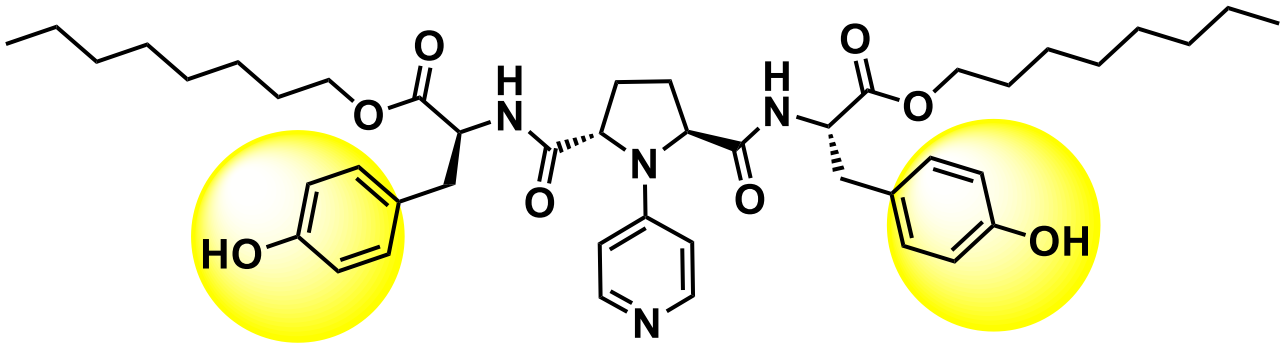




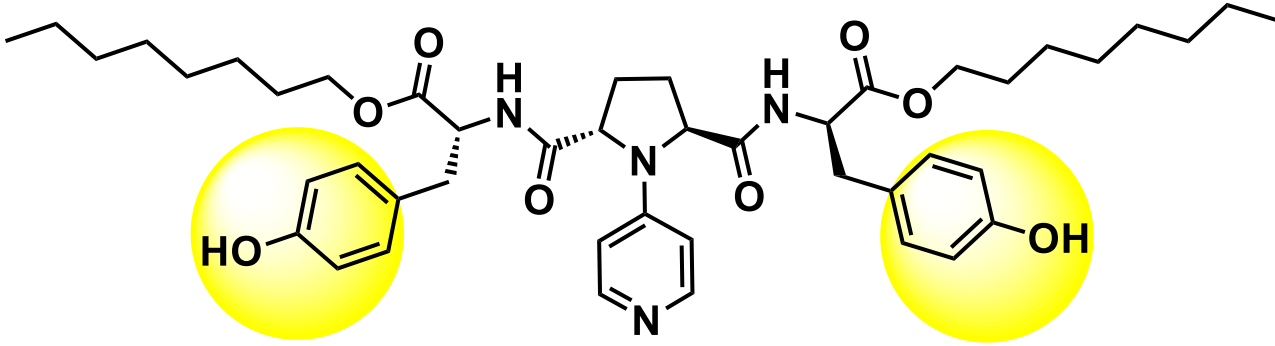
catA; yield 84%, selectivity 2-:3-:4-:6- = 0:3:86:11



catB; yield 71%, selectivity 2-:3-:4-:6- = 0:7:73:20

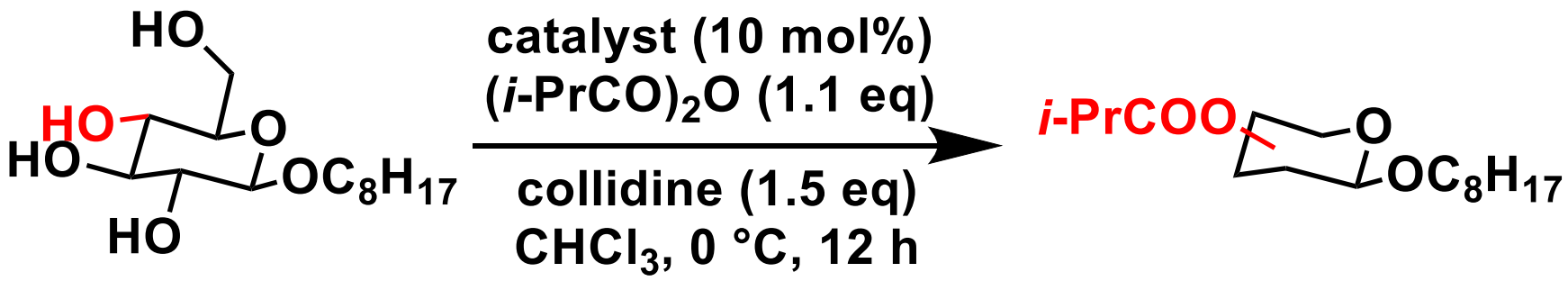


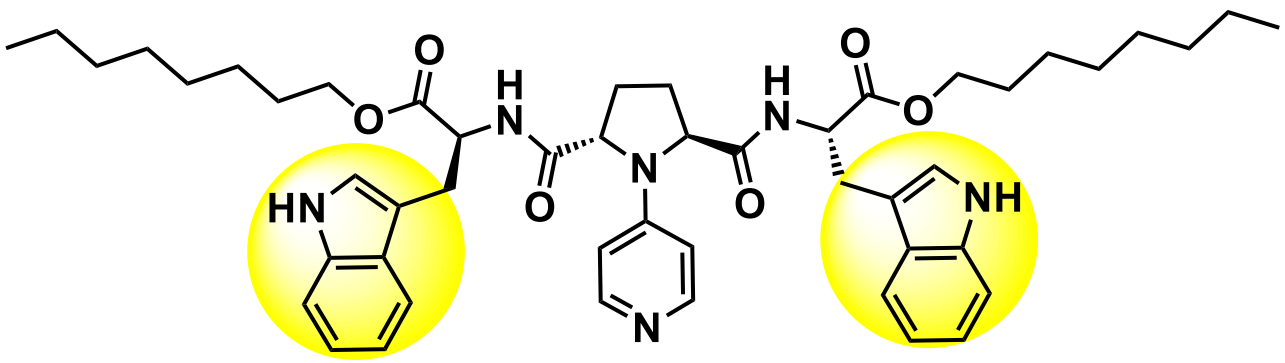
catC; yield 60%, selectivity 2-:3-:4-:6- = 0:19:58:23



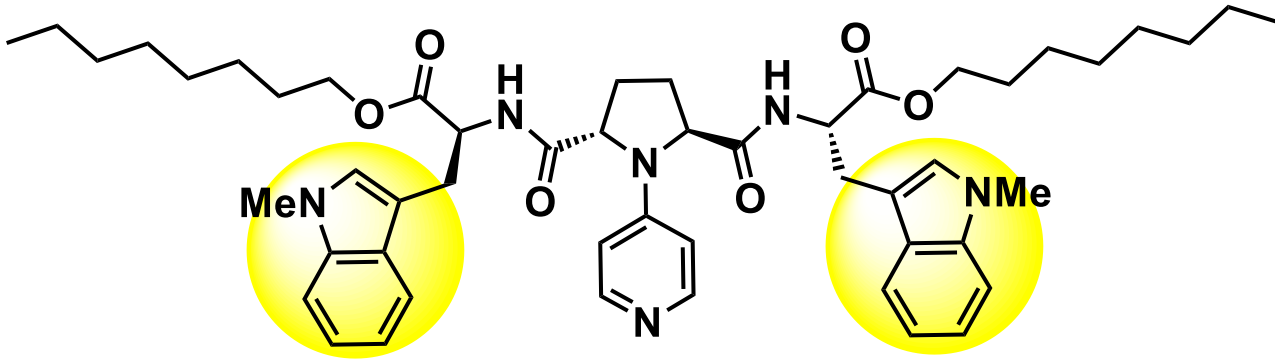
catD; yield 80%, selectivity 2-:3-:4-:6- = 1:16:59:24

Importance of Free NH of Catalyst





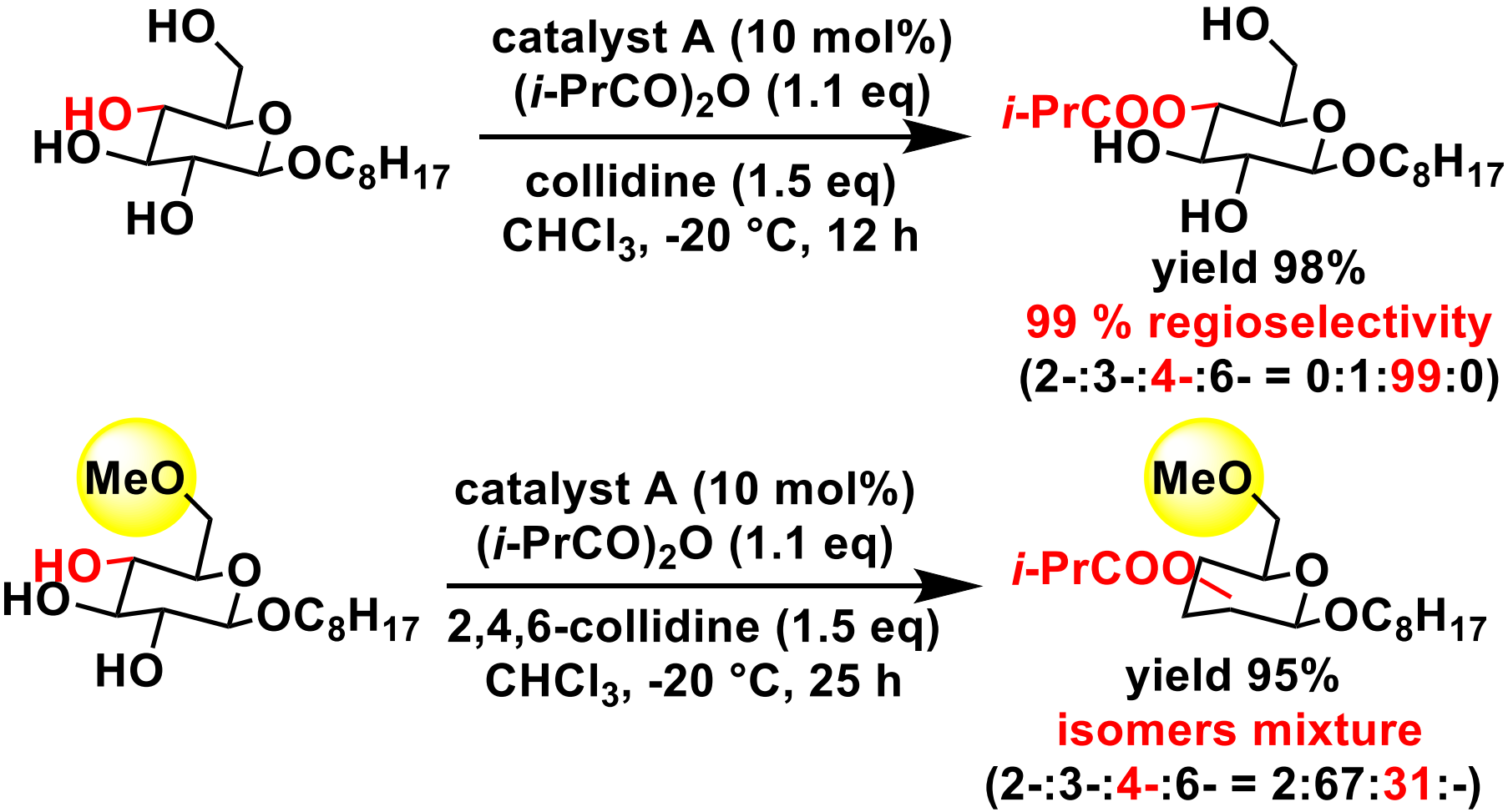
catalyst A



catalyst E

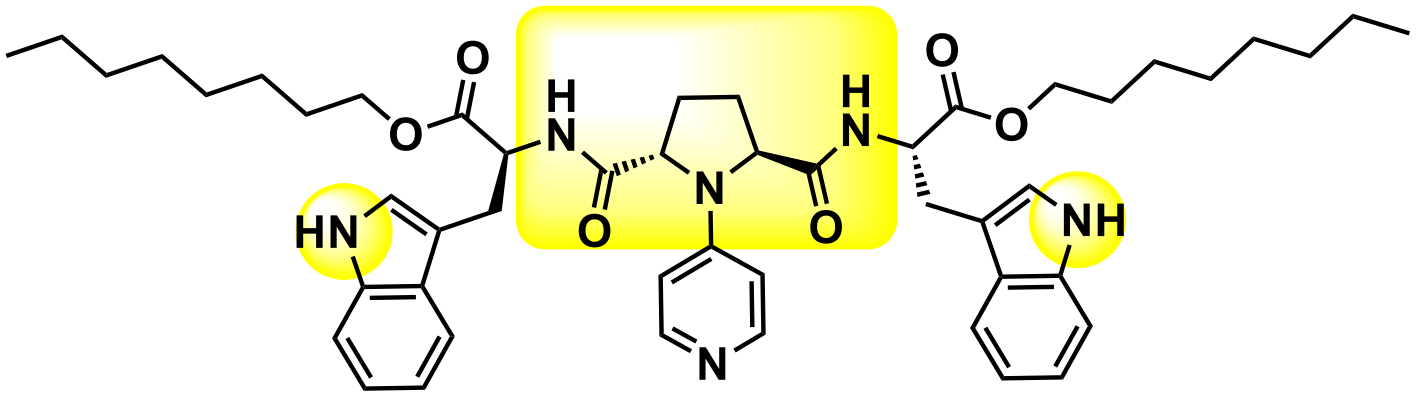
entry	catalyst	yield (%)	regioselectivity (2-:3-:4-:6-)
1	A	97	0: 2 :98:0
2	E	69	0:26:60:14

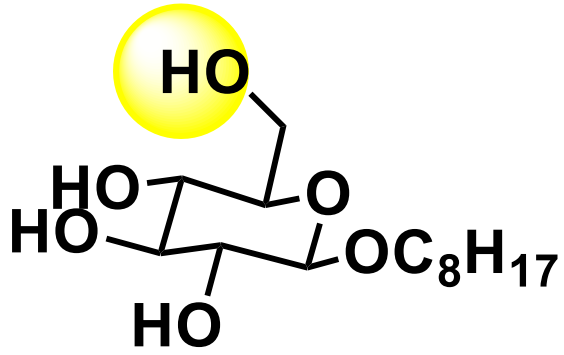
Importance of Free OH of Substrate



✓ *6-OH group of the substrate was important for regioselectivity.*

Important Sites for Regioselectivity Expression

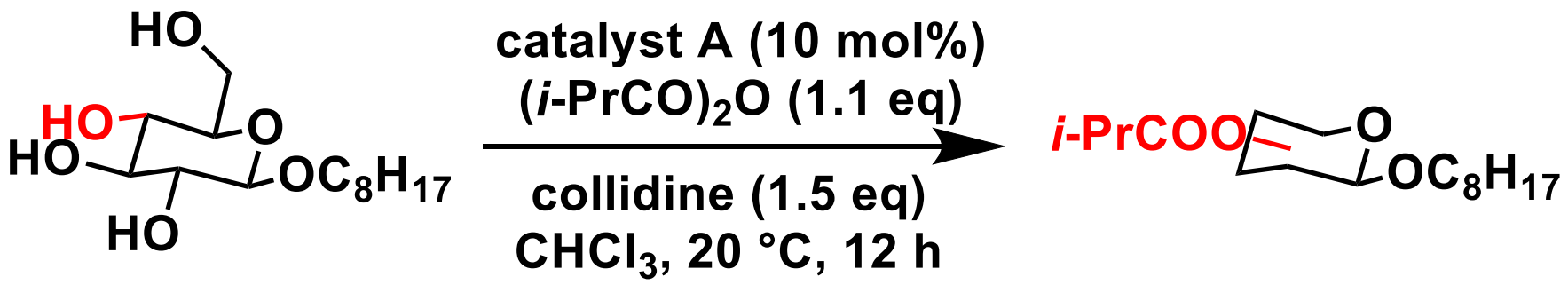




Free NH, -OH, structure including amide bonds was important for regioselectivity.

Hydrogen bonding involved?

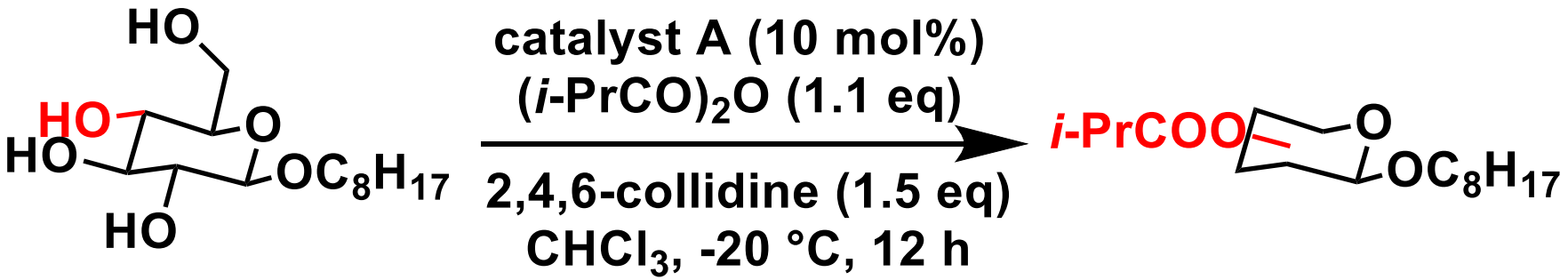
Solvent Effect



entry	solvent	yield (%)	regioselectivity (2-:3-:4-:6-)
1	toluene	84	0: 3 :86:11
2	$CHCl_3$	90	0: 5 :91:4
3	THF	51	0:22:51:27
4	DMF	46	1:24:12:63

✓ *Polar solvent decreased yields and regioselectivity.*

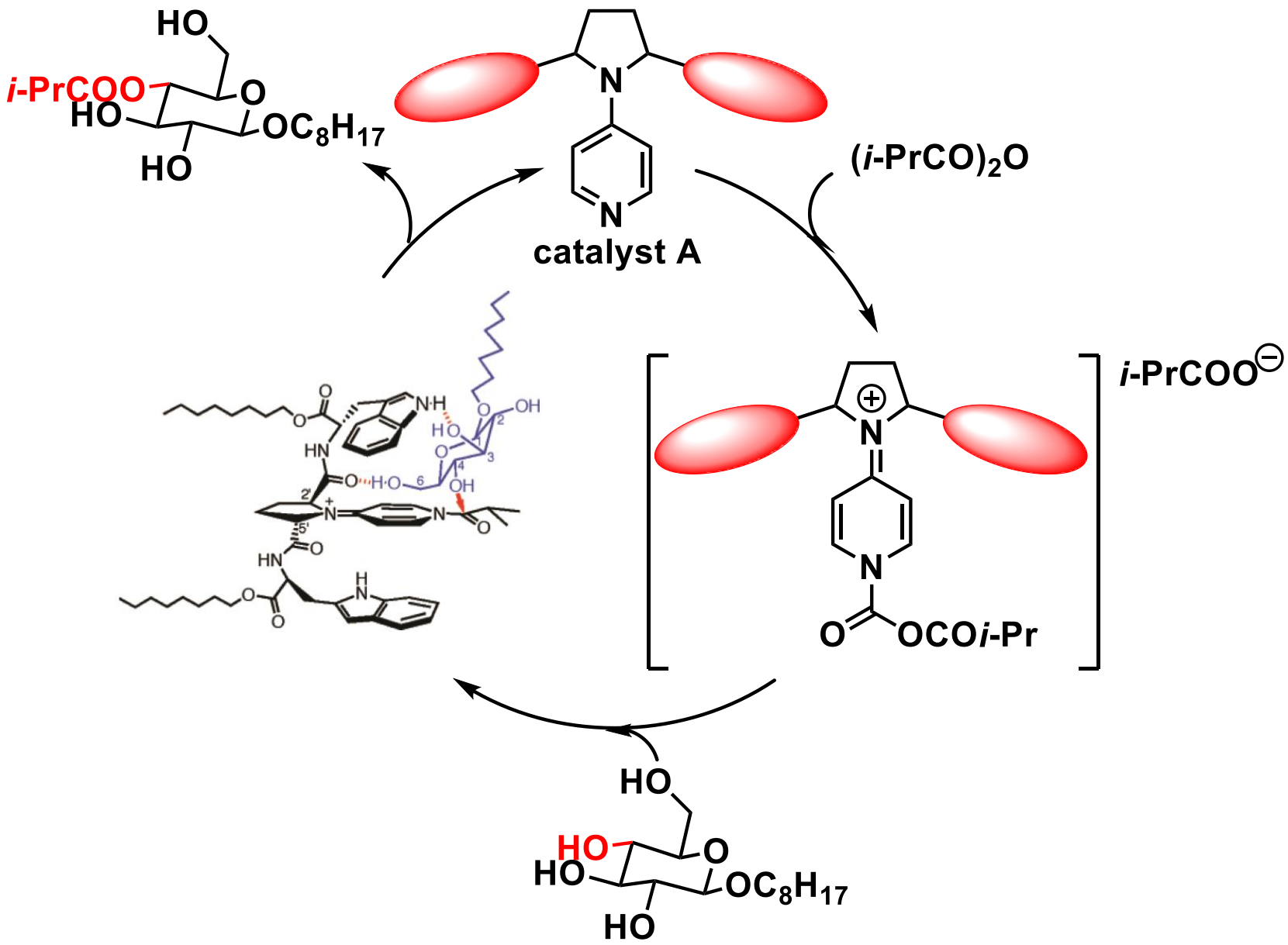
No Effect of Additives



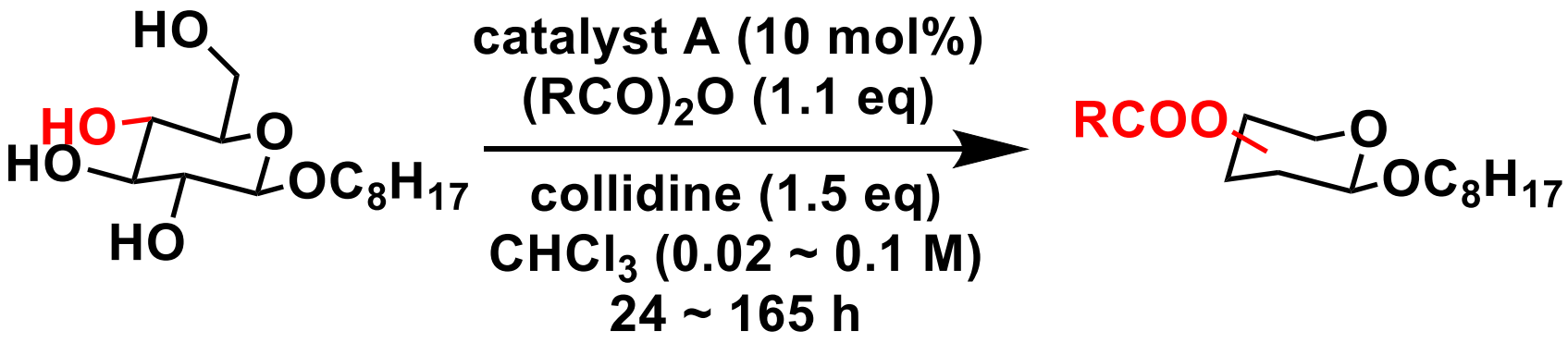
entry	additive	yield (%)	regioselectivity (2-:3-:4-:6-)
1	-	98	0: 1 : 99 :0
2	2-phenylethanol	98	0: 1 : 99 :0
3	1-phenylethanol	99	0:<1:>99:0

✓ *The presence of alcohol didn't inhibit the selective acylation.*

Proposed Reaction Mechanism



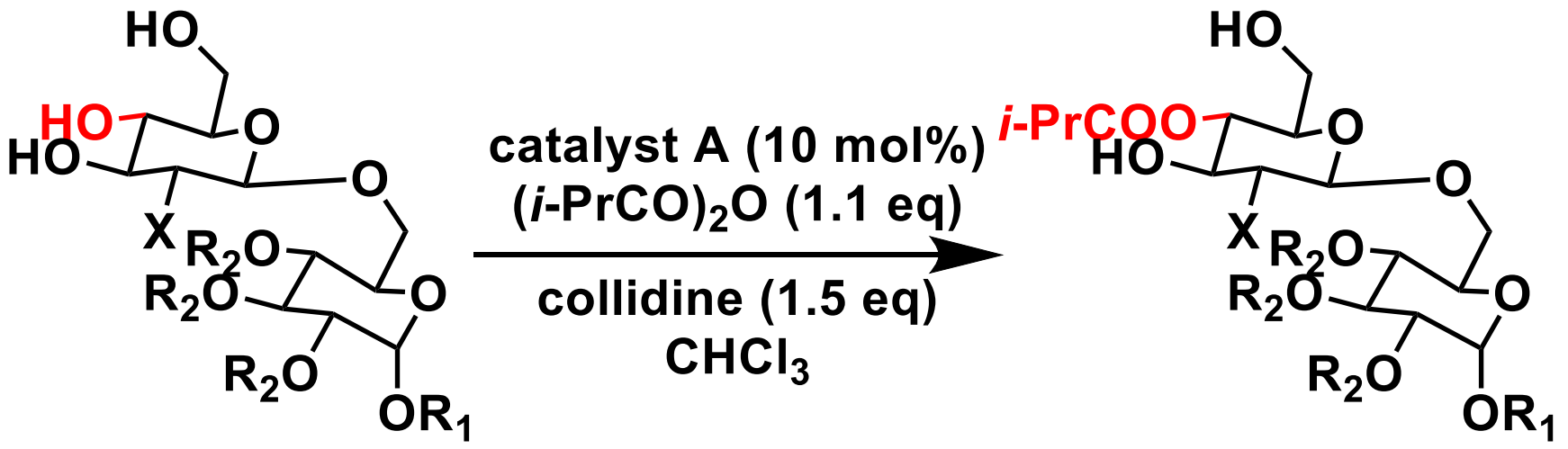
Various Acyl Donor

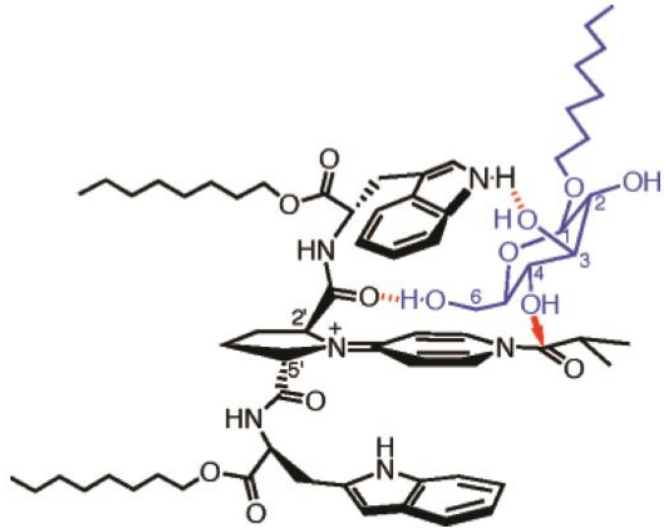


entry	$(RCO)_2O$	T (°C)	yield (mono) (%)	regioselectivity (2-:3-:4-:6-)	yield (di) (%)
1	$(Cbz\text{-}(L)\text{-}Phe\text{-}CO)_2O$	-20	93	0: 1 :94:5	2
2	$(Cbz\text{-}(D)\text{-}Phe\text{-}CO)_2O$	-20	82	0: 4 :88:8	10
3	$(Fmoc\text{-}(L)\text{-}Ala\text{-}CO)_2O$	-50	75	0:13:86:1	17
4	$(Cbz\text{-}(L)\text{-}Trp\text{-}CO)_2O$	-20	76	6: 3 :70:27	10
5	$(Cbz\text{-}(L)\text{-}Gly\text{-}CO)_2O$	-50	76	0:10:67:23	15
6	cinnamic anhydride	-30	88	0: 3 :94:3	6
7	triacetoxybenzoic anhydride	-50	78	0: 2 :87:11	-

Kawabata, T. *et al. J. Org. Chem.* **2009**, *74*, 8802.

Acylation of Other Structures

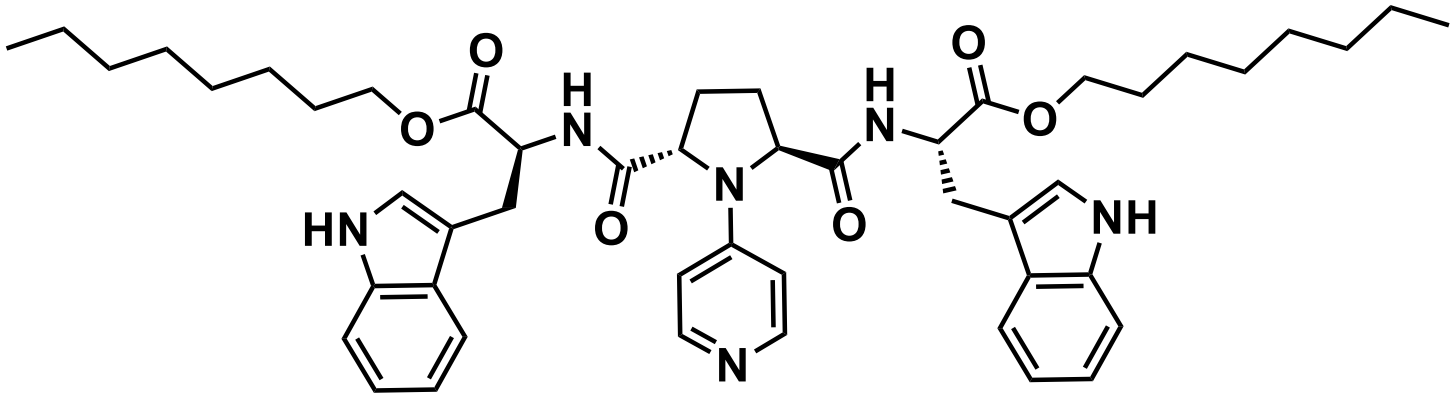


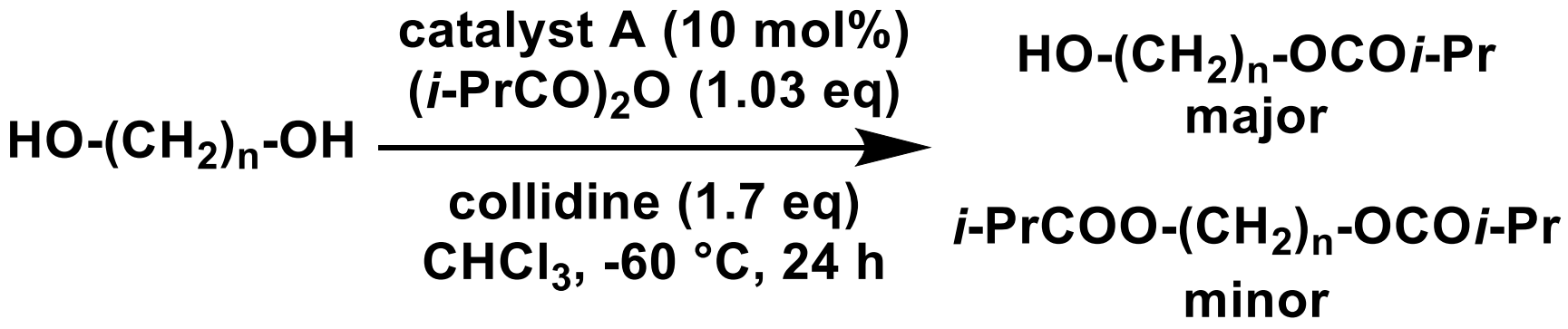


entry	X	R_1	R_2	yield (mono) (%)	selectivity (%)
1	N_3	Me	Bn	92	93
2	NHCbz	Me	Bn	83	89
3	OH	$CH_2CH(C_6H_{13})_2$	OH	36	78

Kawabata, T. *et al. J. Org. Chem.* **2009**, *74*, 8802.

Chemoselective Acylation of 1,n-diol (1)

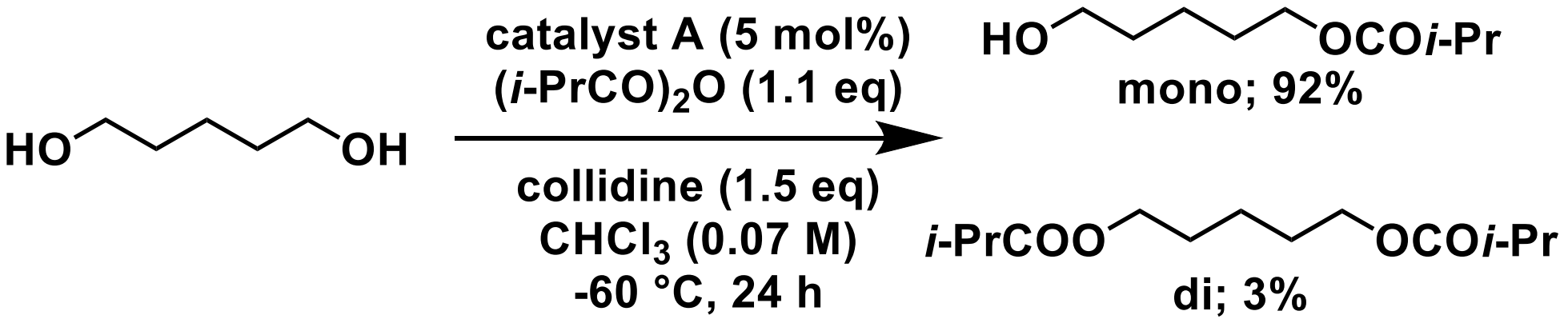




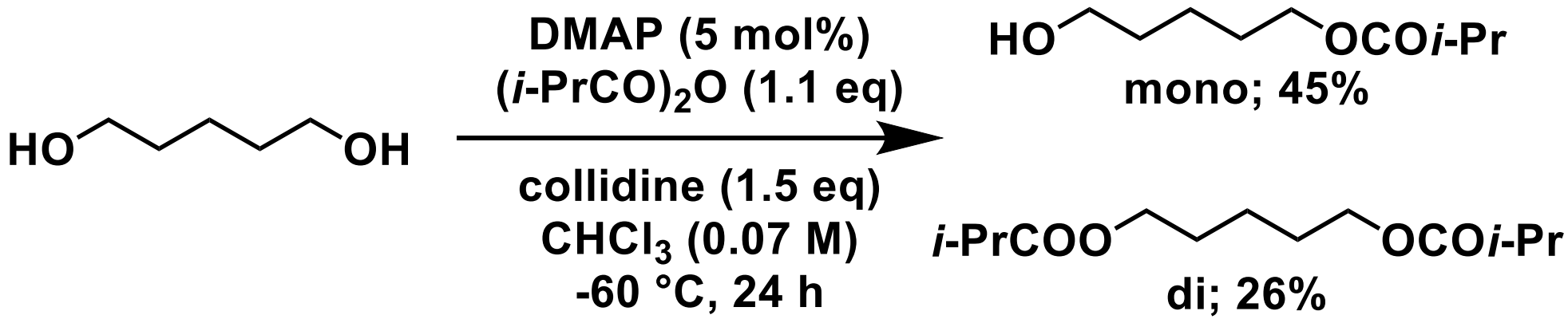
✓ ***It was difficult to suppress the double acylation in the previous method.***

Kawabata, T. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 4888.

Chemoselective Acylation of 1,n-diol (2)



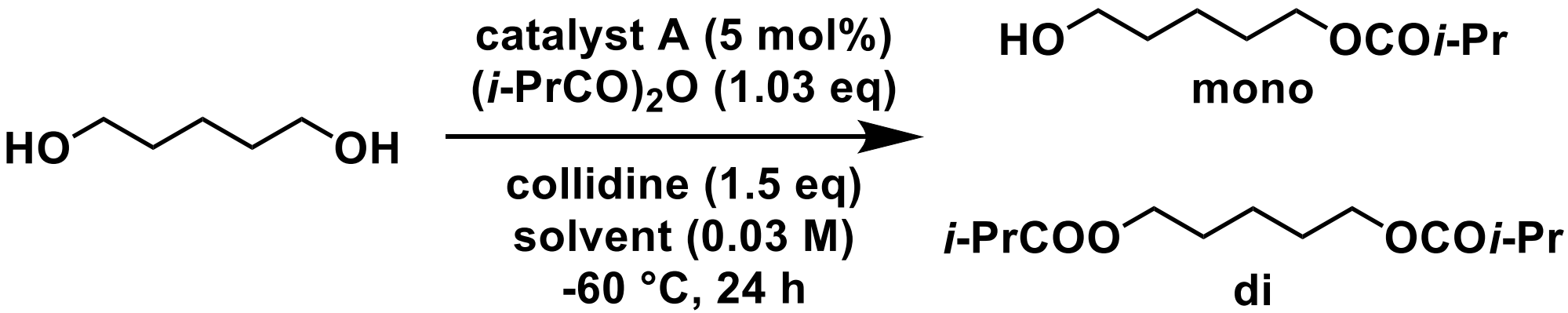
mono / di = 31
high selectivity



mono / di = 1.7
no selectivity

✓ ***Acylation with catalyst A avoided double functionalization.***

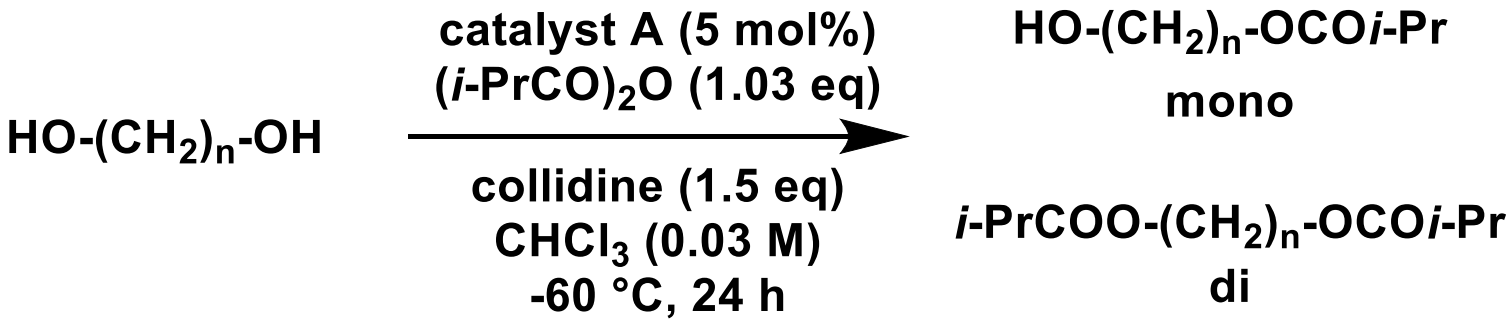
Solvent Effect on Chemoselectivity



entry	solvent	mono (%)	di (%)	rSM (%)	mono / di
1	DMF	48	29	23	1.7
2	toluene	74	9	15	8.2
3	$CHCl_3$	71	< 1	23	> 71

✓ *Hydrogen bonds may be involved in this reaction.*

The Effect of Chain Length

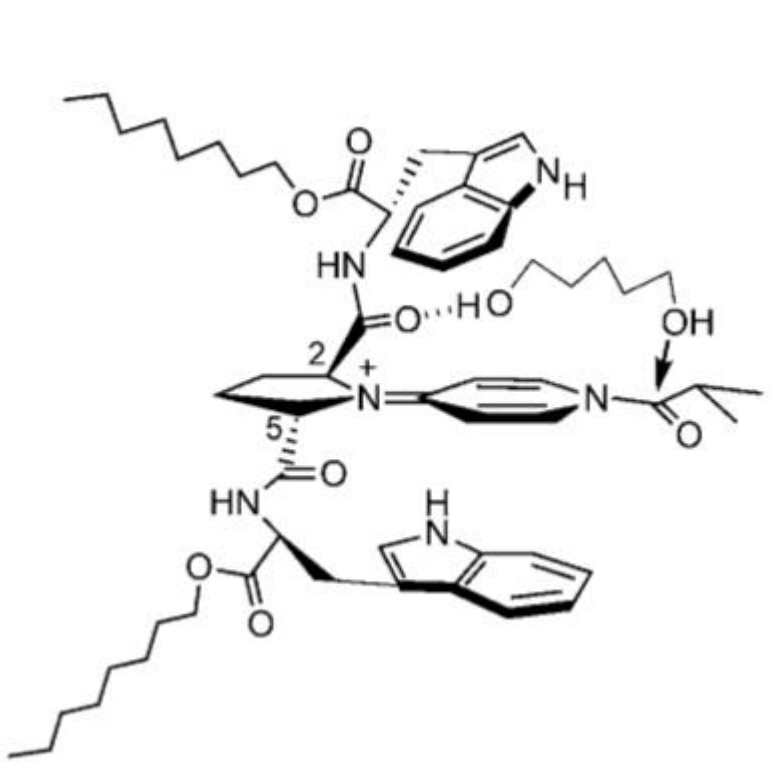


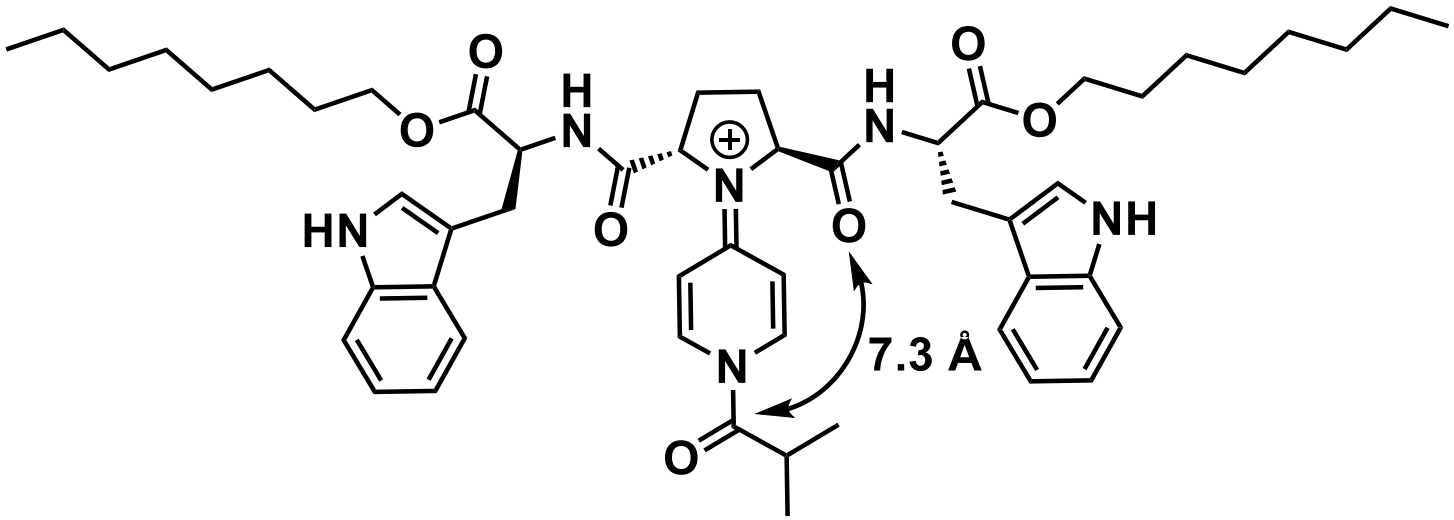
entry	n	yield (mono) (%)	yield (di) (%)	rSM (%)	selectivity (mono / di)
1	2	66	< 1	24	> 66
2	3	81	< 1	16	> 81
3	4	77	4	15	19.3
4	5	86	< 1	12	> 86
5[a]	(5)	71	< 1	22	> 71
6	6	70	15	12	4.7
7	7	73	11	13	6.6

[a] Diethylene glycol (HO-$(CH_2)_2O(CH_2)_2$-OH) was employed as a substrate.

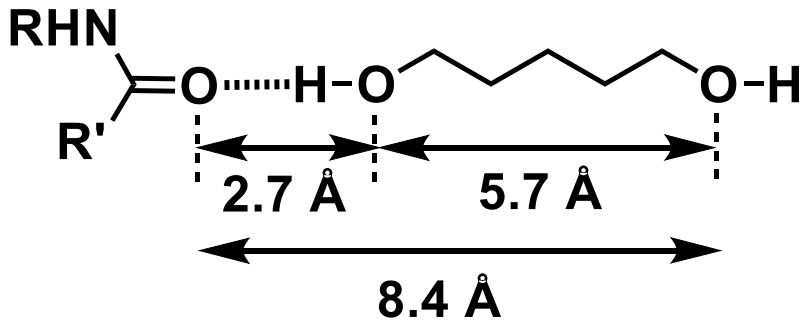
✓ *Long chain decreased selectivity.*

Proposed Mechanism of the Phenomenon

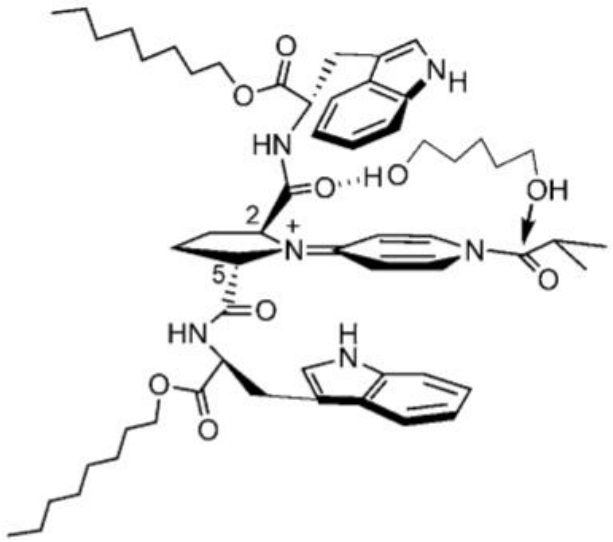


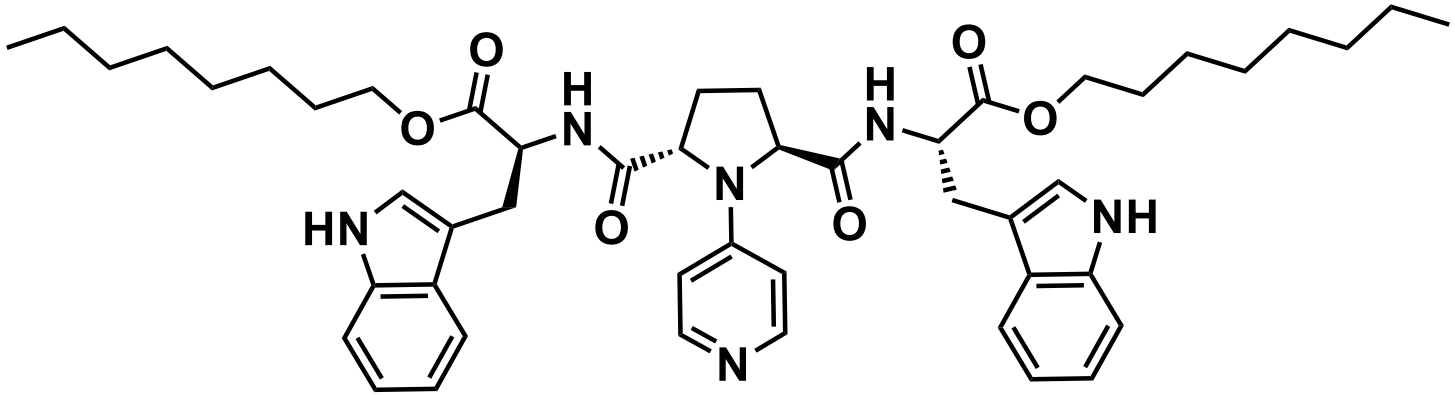


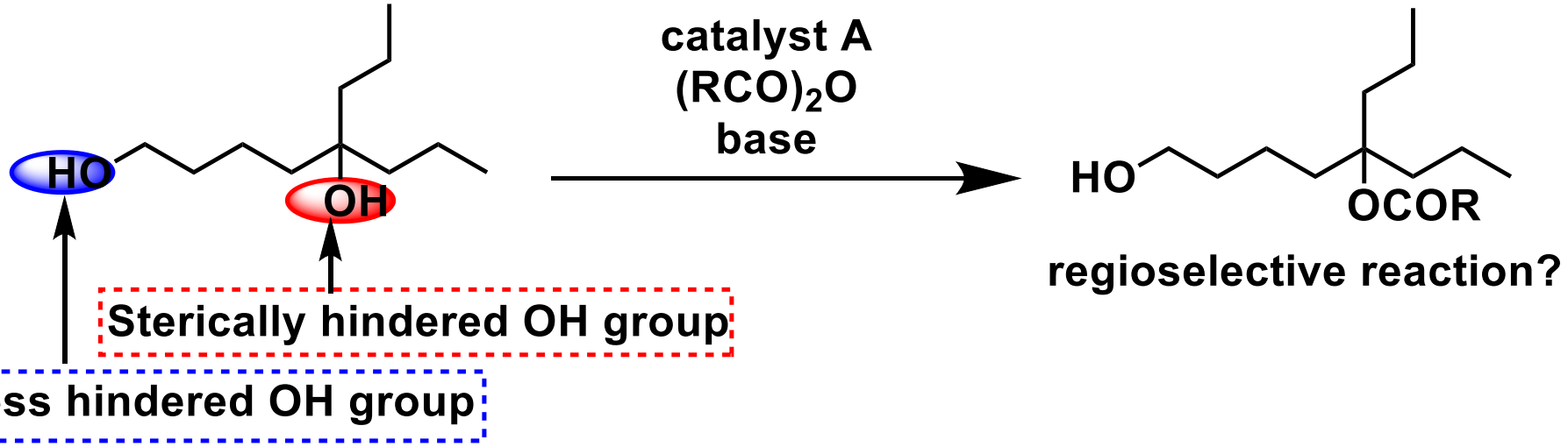
A possible transition-state model for monoacylation



My Idea: Regioselective Acylation of 1,n-diol ?







✓ *May such regioselective reaction be possible?*

Summary of Section 3

- There are several advantages of hydrogen bonds for use in regioselective reactions.
- Sometimes regioselectivity is improved by forming hydrogen bonds at multiple sites.
- Challenges may remain in substrate generality.

4. Summary

Summary of Today's Literature Seminar

- Regioselective reactions using non-covalent interactions are limited.
- Ion-pair interactions and hydrogen bonds are used to obtain regioselectivity.
- A special structure requiring conversion after the reaction may be necessary to obtain regioselectivity.
- New reactions which needn't such special structure will develop organic synthesis.