α-Fluorination of amide and stereodivergent synthesis of 1,4-dicarbonyls by Nuno Maulide's group

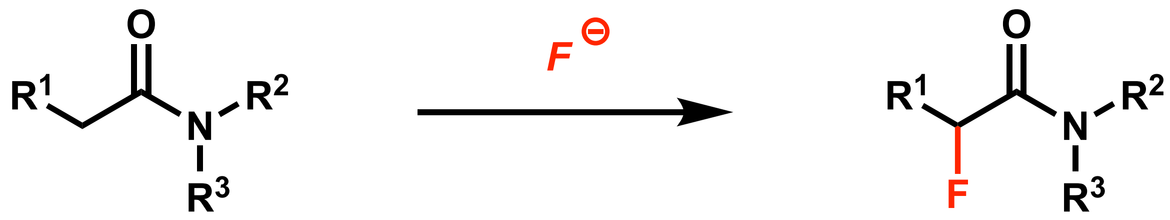
2019.06.22

Toshiya Nagai

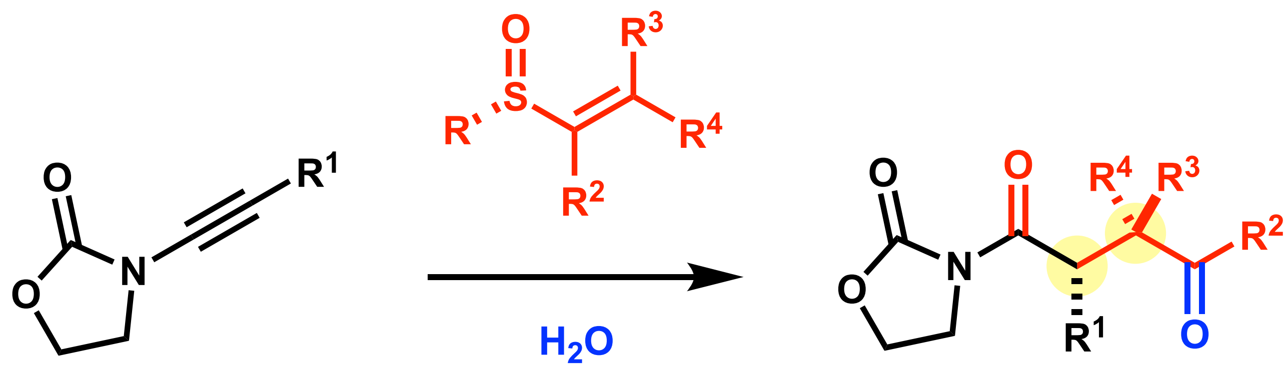
Contents

1. Introduction

2. α-Fluorination of amide with nucleophilic fluorine[1)]



3. Stereodivergent synthesis of 1,4-dicarbonyls by sulfonium rearrangement[2)]



4 possible isomers

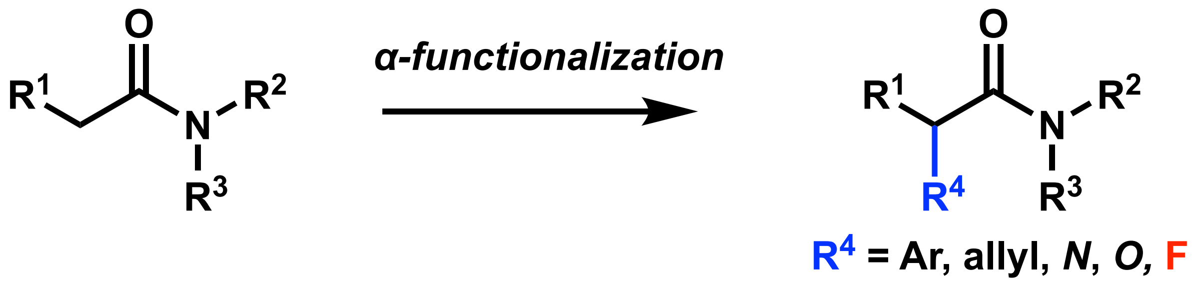
1) Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.
2) Kaldre, D.; Klose, I.; Maulide, N. *Science* **2018**, *361*, 664.

Prof. Nuno Maulide

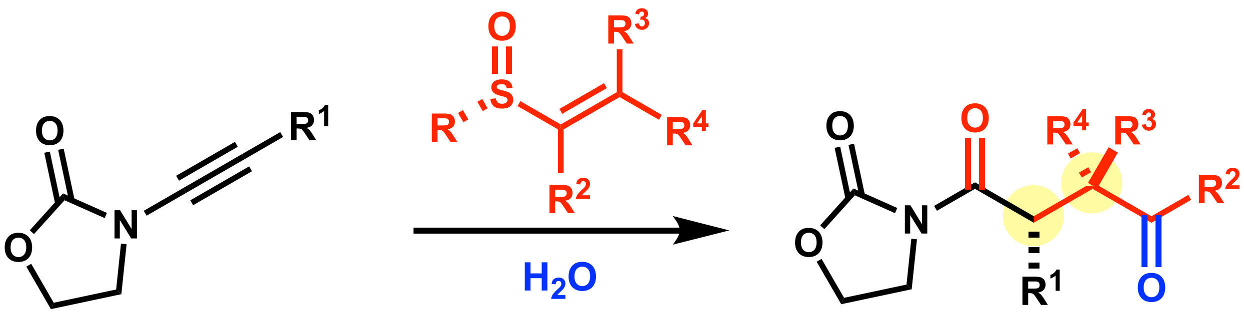
Career:
2003-2004 : Master's Degree, the Ecole Polytechnique
2004-2007 : Ph. D, the Université catholique de Louvain (Prof. István E. Markó)
2007-2008 : Postdoc, Stanford University (Prof. Barry M. Trost)
2009-2013 : Group Leader, Max-Planck Institute for Coal Research
2013- : Full Professor, the University of Vienna

Awards: Bayer Early Excellence in Science Award (2012), Heinz Maier-Leibnitz Prize (2013), EurJOC Yong Researcher Award (2015), Elisabeth Lutz Award (2016), Scientist of the Year in Austria (2019), etc.

Research topic:
Dvelopment of new reactions from amide, ynamide or sulfur (IV) and total synthesis
1. Amide or ynamide activation



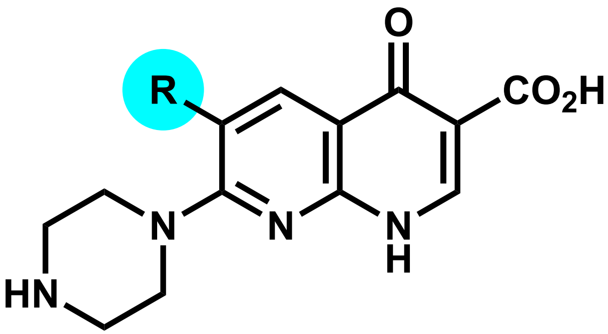
2. Reactions with sulfoxide



3. Total synthesis
(–)-quinine, macrolactin A etc.

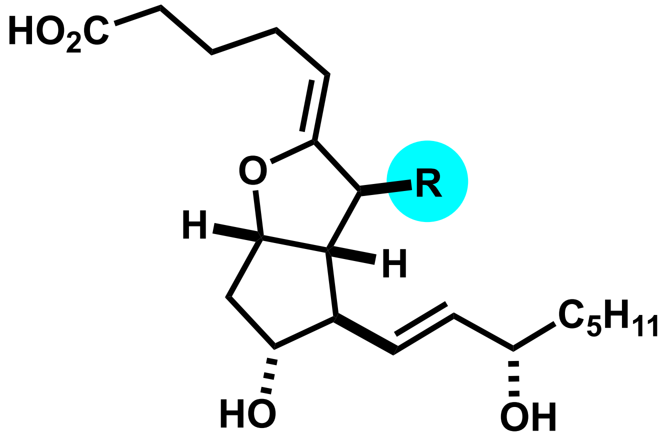
https://organicsynthesis.univie.ac.at/about-us/meet-the-group/

Fluorine Containing Biologically Active Compounds



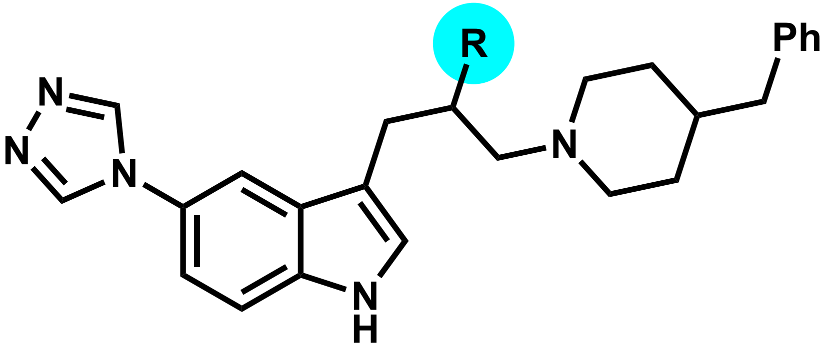
des-fluoro enoxacin (R = H)
enoxacin (R = F)

<u>greater antibacterial activity</u>



PGI_2 (R = H) ($t_{1/2}$, pH = 7.4) = 10 min
7-F-PGI_2 (R = F) ($t_{1/2}$, pH = 7.4) > 1 month

<u>longer chemical half-life</u>



5-HT_{1D} agonist (R = H)
fluorinated 5-HT_{1D} agonist (R = F)

<u>higher bioavailability</u>

	H	F
van der Waals radius	1.2 Å	1.47 Å
electronegativity*	2.1	4.0

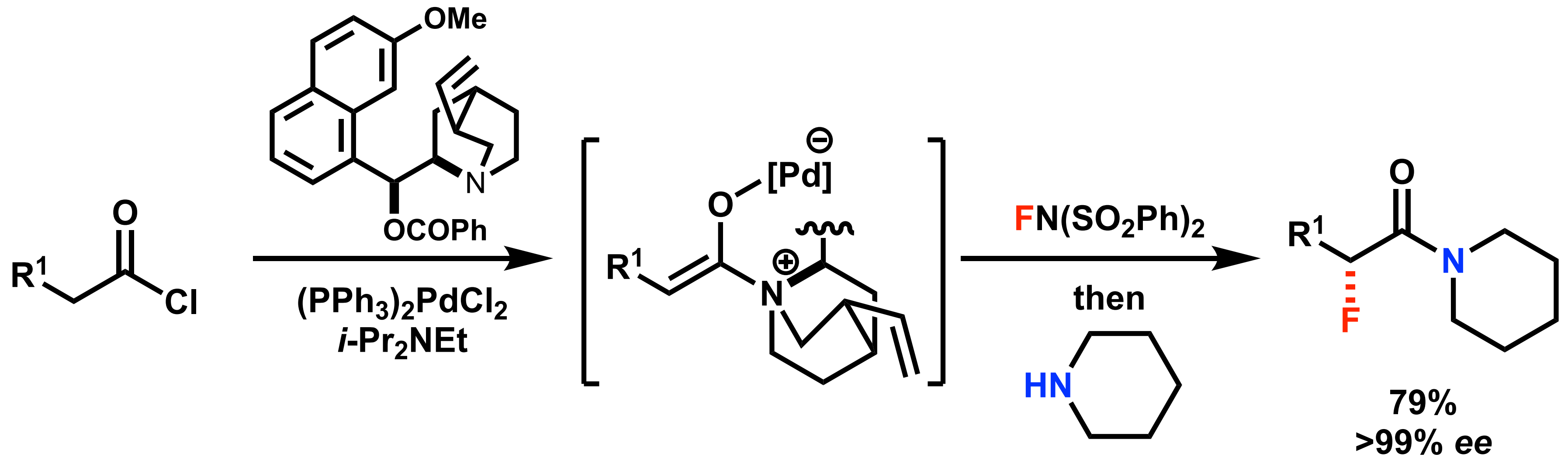
*Pauling scale

- More than <u>20%</u> of drugs approved between 2001-2011 contains at least one fluorine atom.
- 180428_LS_Takahiro_Watanabe (Enantioselective fluorination of alkene)

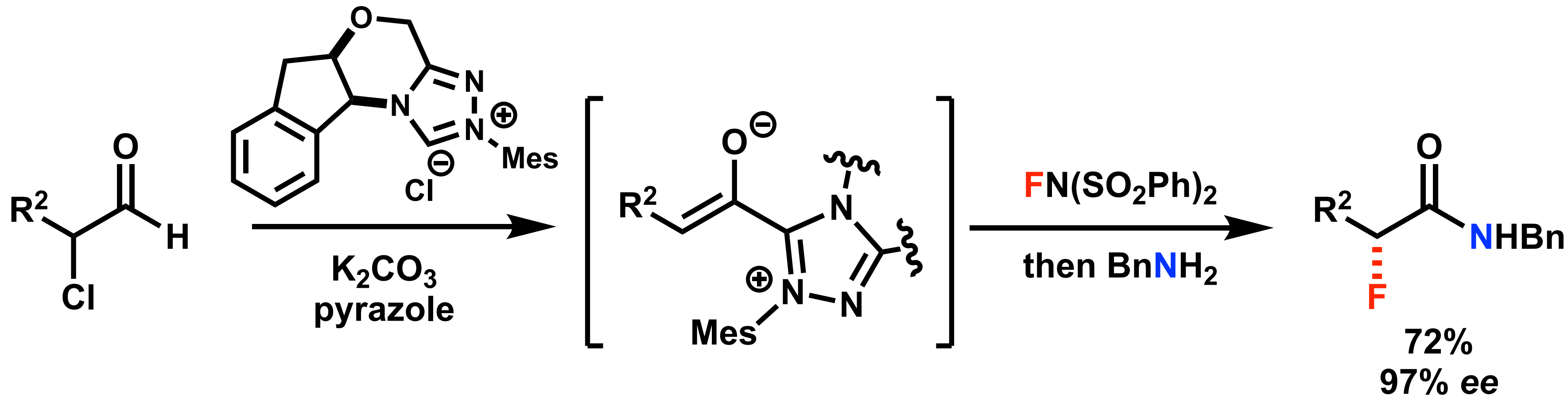
Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.. *Chem. Soc. Rev.* **2008**, *37*, 320.

Previous Approaches to Indirect Fluorination of Amides

1. Lectka's work[1)]



2. Sun's work[2)]



<u>Plobrems</u>: Preparation of substrate (steps or difficulty), Functional group tolerance

1) Paull, D. H.; Scerba, M. T.; Alden. D. E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17260.
2) Dong, X.; Yang, W.; Hu, W.; Sun, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 660.

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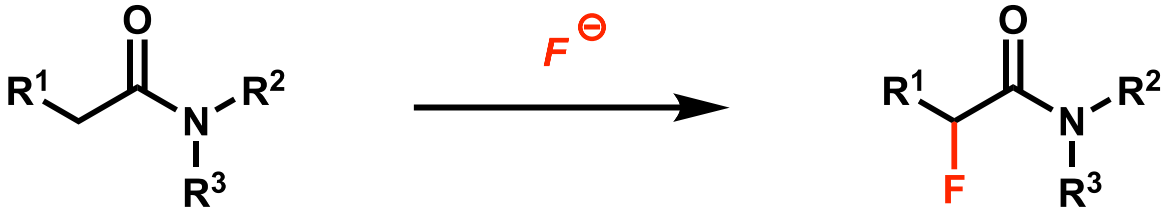

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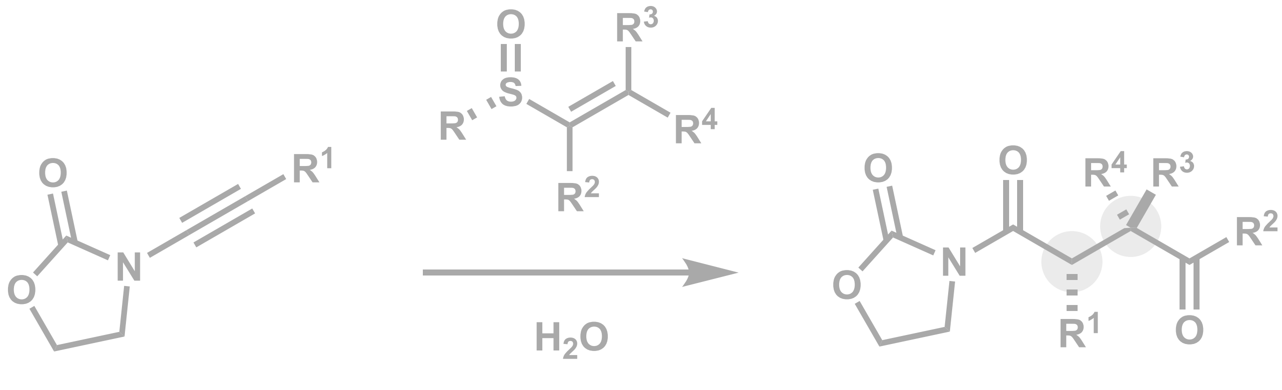
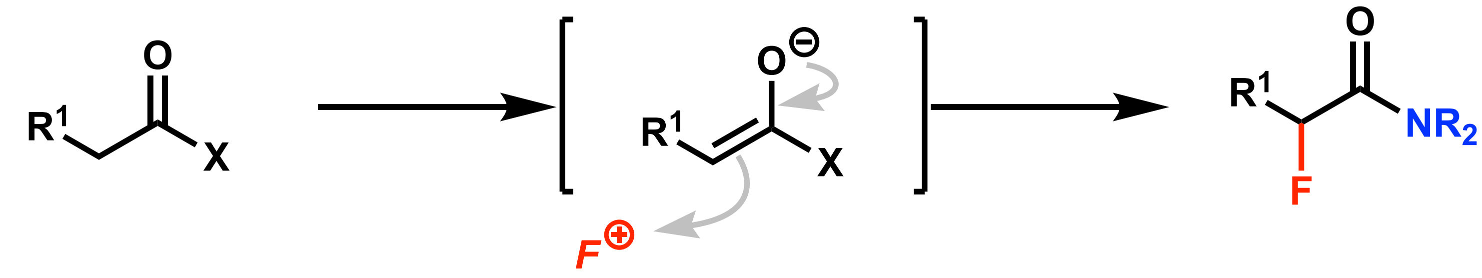


1) Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.
2) Kaldre, D.; Klose, I.; Maulide, N. *Science* **2018**, *361*, 664.

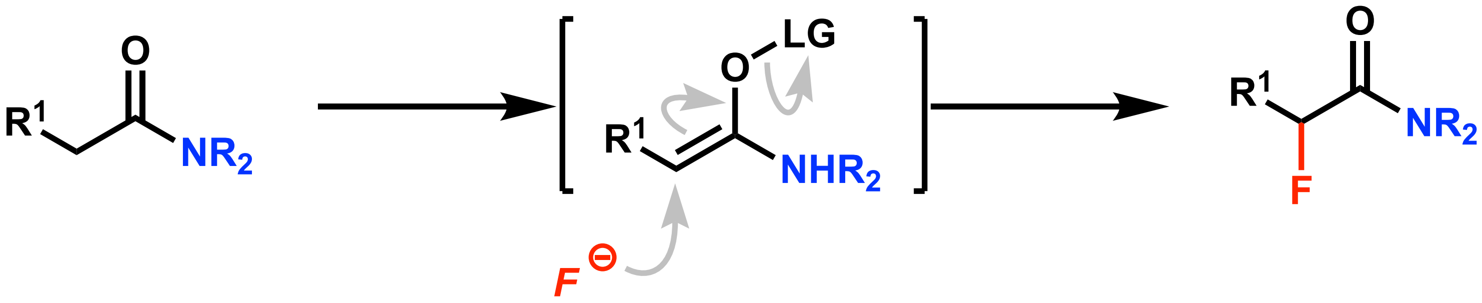
A New Approach for α-Fluorination of Amide

- **Previous methods[1),2)]**



nucleophilic enolate
+
electrophilic fluorine

- **Maulide's approach[3)]**

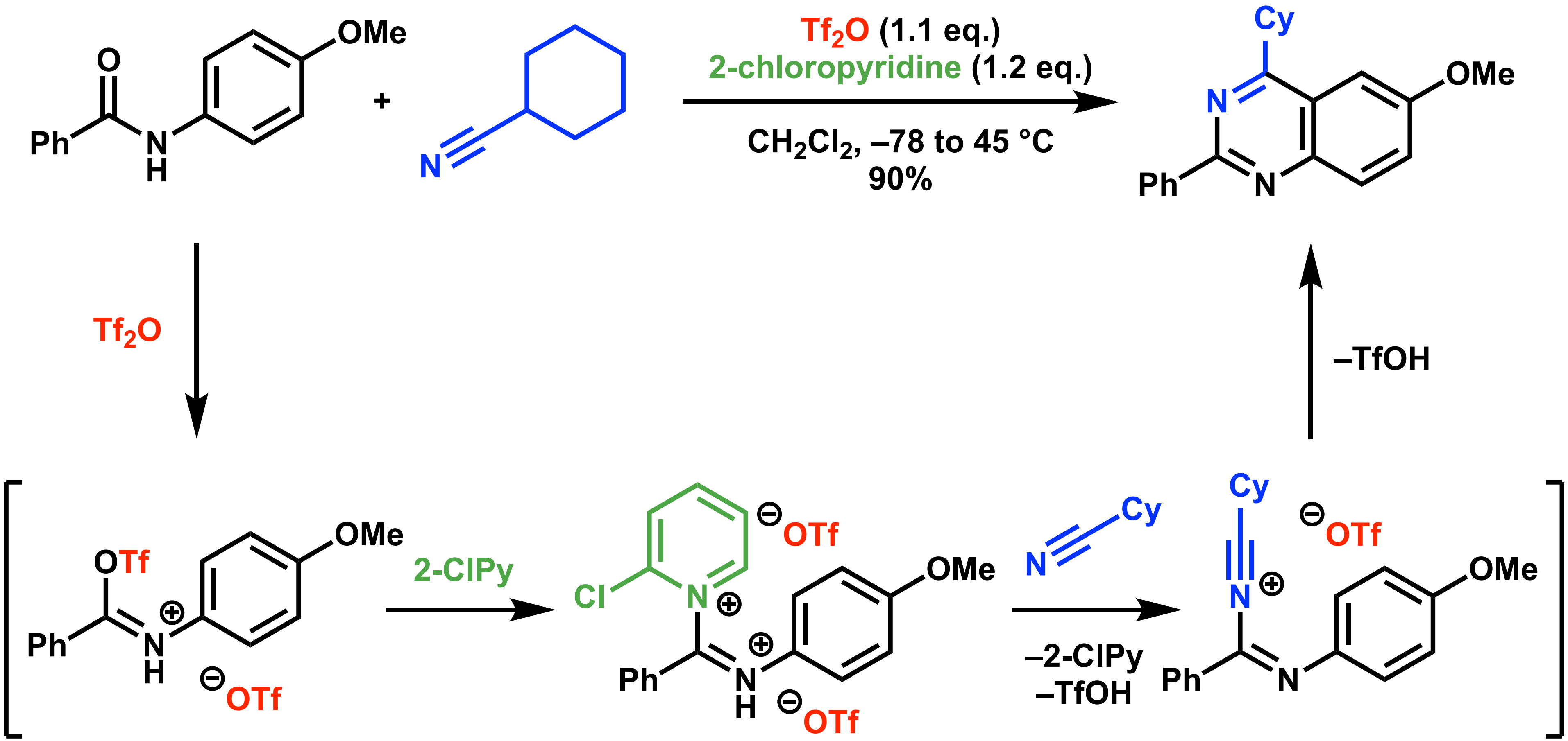


1. Activation of amide
2. Introduction of leaving group
3. Fluorine reagent

electrophilic enolonium
+
nucleophilic fluorine

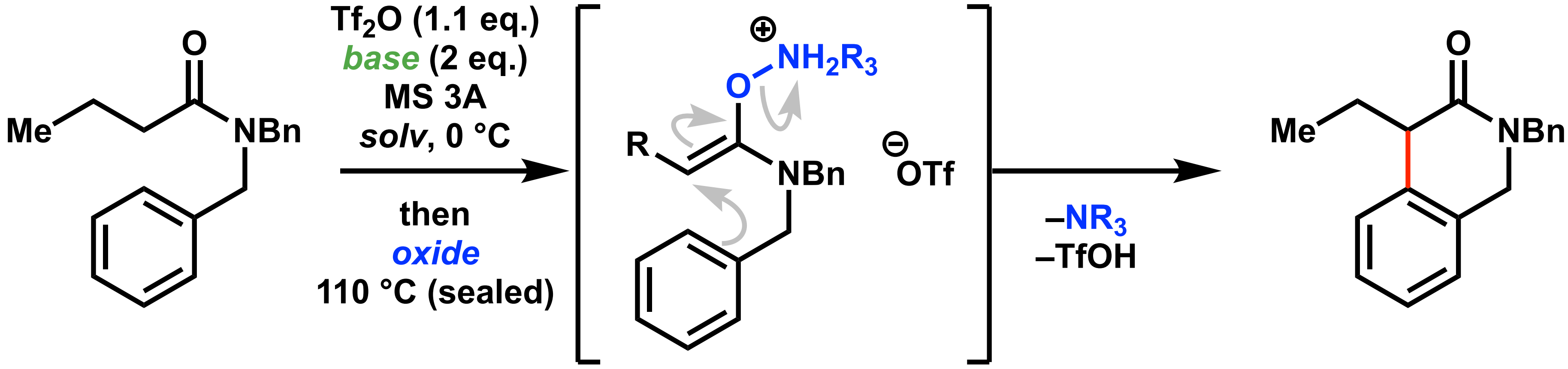
1) Paull, D. H.; Scerba, M. T.; Alden. D. E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc.* **2008**, *130*, 17260.
2) Dong, X.; Yang, W.; Hu, W.; Sun, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 660.
3) Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.

Movassaghi's Synthesis of Pyrimidine Derivatives



Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254.

Maulide's α-Arylation of Amide



entry	*base*	*solv.*	*oxide*	yield
1	pyridine	MeCN	LNO	11%
2	2-F-py	MeCN	LNO	38%
3	2-I-py	MeCN	LNO	57%
4	2-I-py	MeCN	PNO	52%
5	2-I-py	MeCN	DCPO	43%

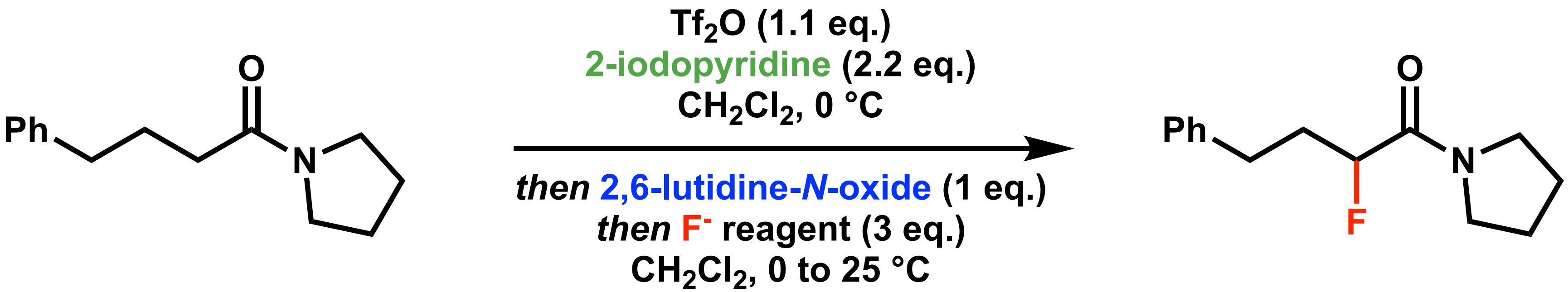
entry	*base*	*solv.*	*oxide*	yield
6	2-I-py	MeCN	NPO	30%
7	2-I-py	toluene	LNO	11%
8	2-I-py	$(CH_2Cl)_2$	LNO	14%
9	2-I-py	nitroethane	LNO	21%

NPO = 4-nitropyridine-*N*-oxide

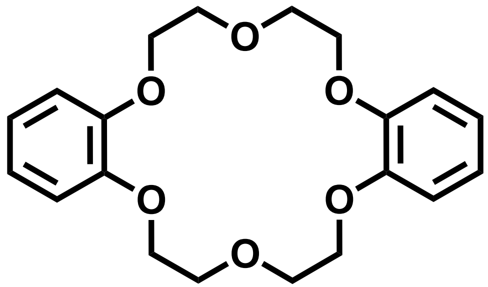
LNO = 2,6-lutidine-*N*-oxide, PNO = pyridine-*N*-oxide
DCPO = 2,6-dichloropyridine-*N*-oxide

Kaiser, D.; Torre, A.; Shaaban, S.; Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 5921.

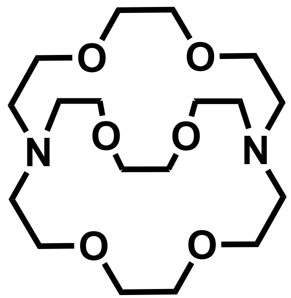
Application to α-Fluorination of Amide



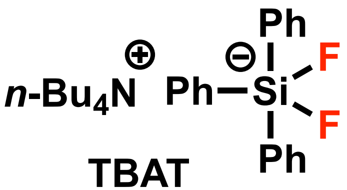
entry	F^- reagent	NMR yield
1	TBAF (1 M in THF)	54%
2	TBAF on silica	35%
3	TBAT (1 M in THF)	74%
4	TBAT (1 M in 1,2-DCE)	60%
5	**TBAT**	**84%**
6	TMAF	56%
7	HF•pyridine	0%
8	3HF•Et_3N	0%
9	TASF	0%
10	KF	0%
11	KF, dibenzo-18-crown-6	0%
12	KF, Kryptofix® 222	64%



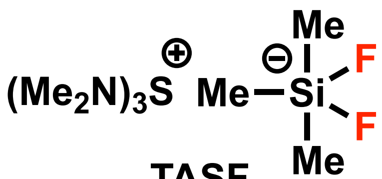
dibenzo-18-crown-6



Kryptofix® 222



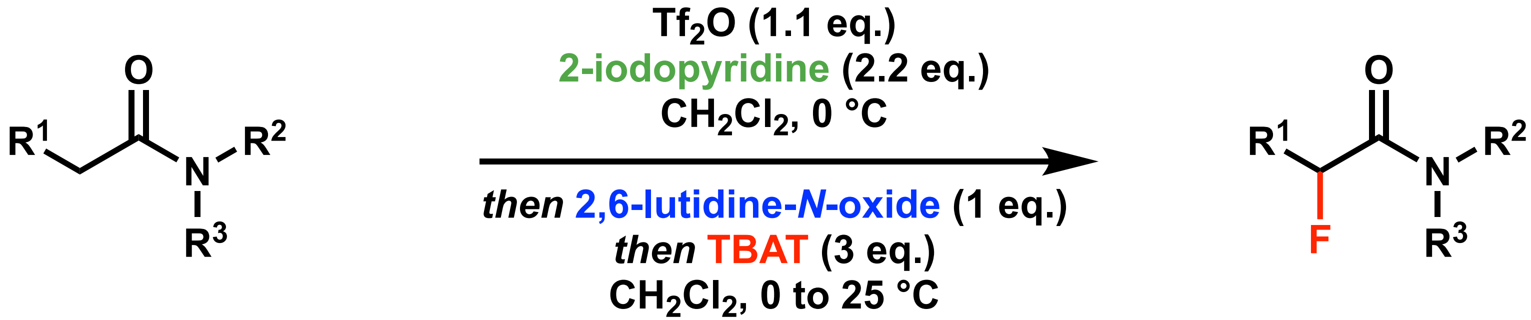
TBAT

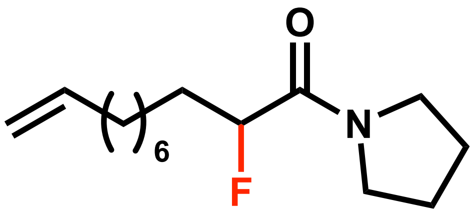


TASF

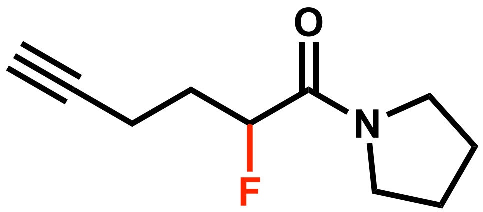
Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.

Scope of the α-Fluorination of Amides

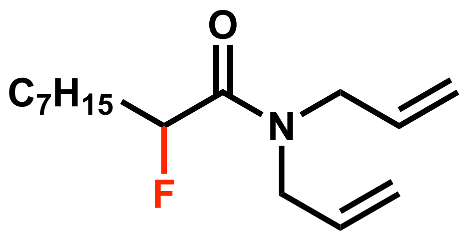




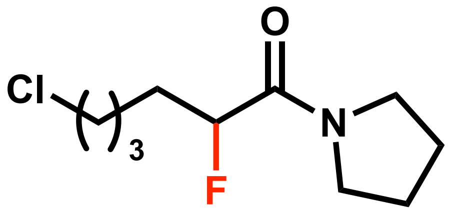
72% (89% brsm)



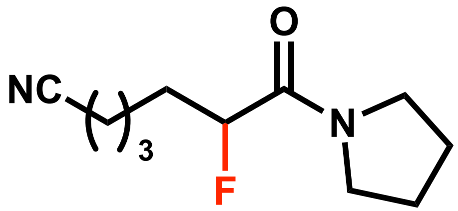
46% (59% brsm)



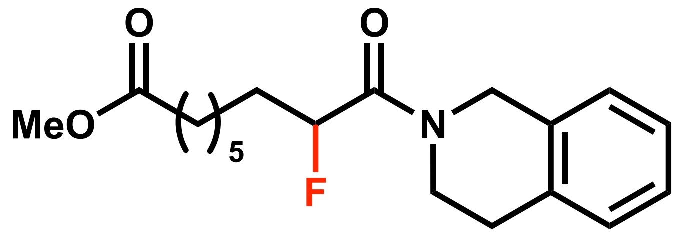
53%



70% (84% brsm)



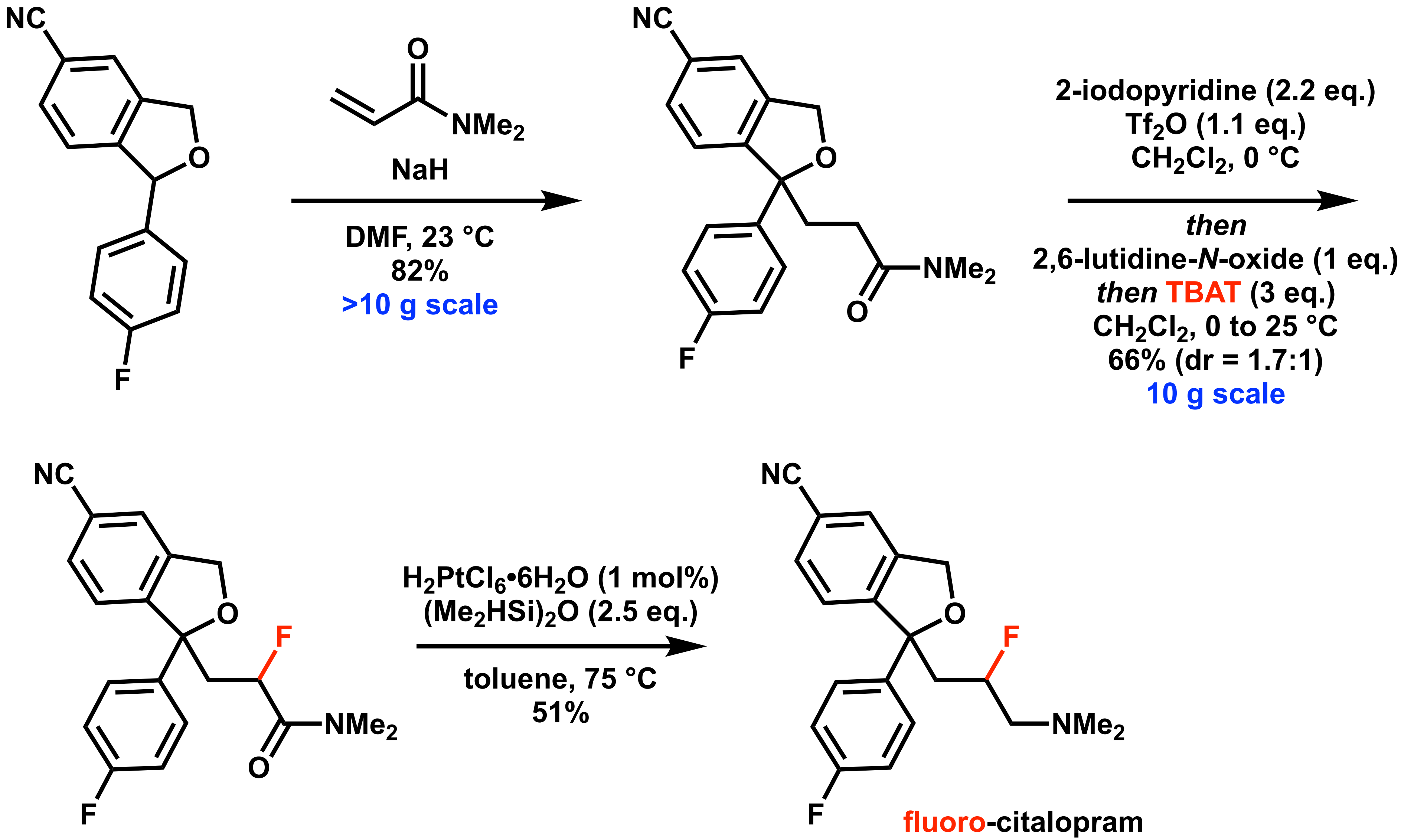
64% (82% brsm)



63%

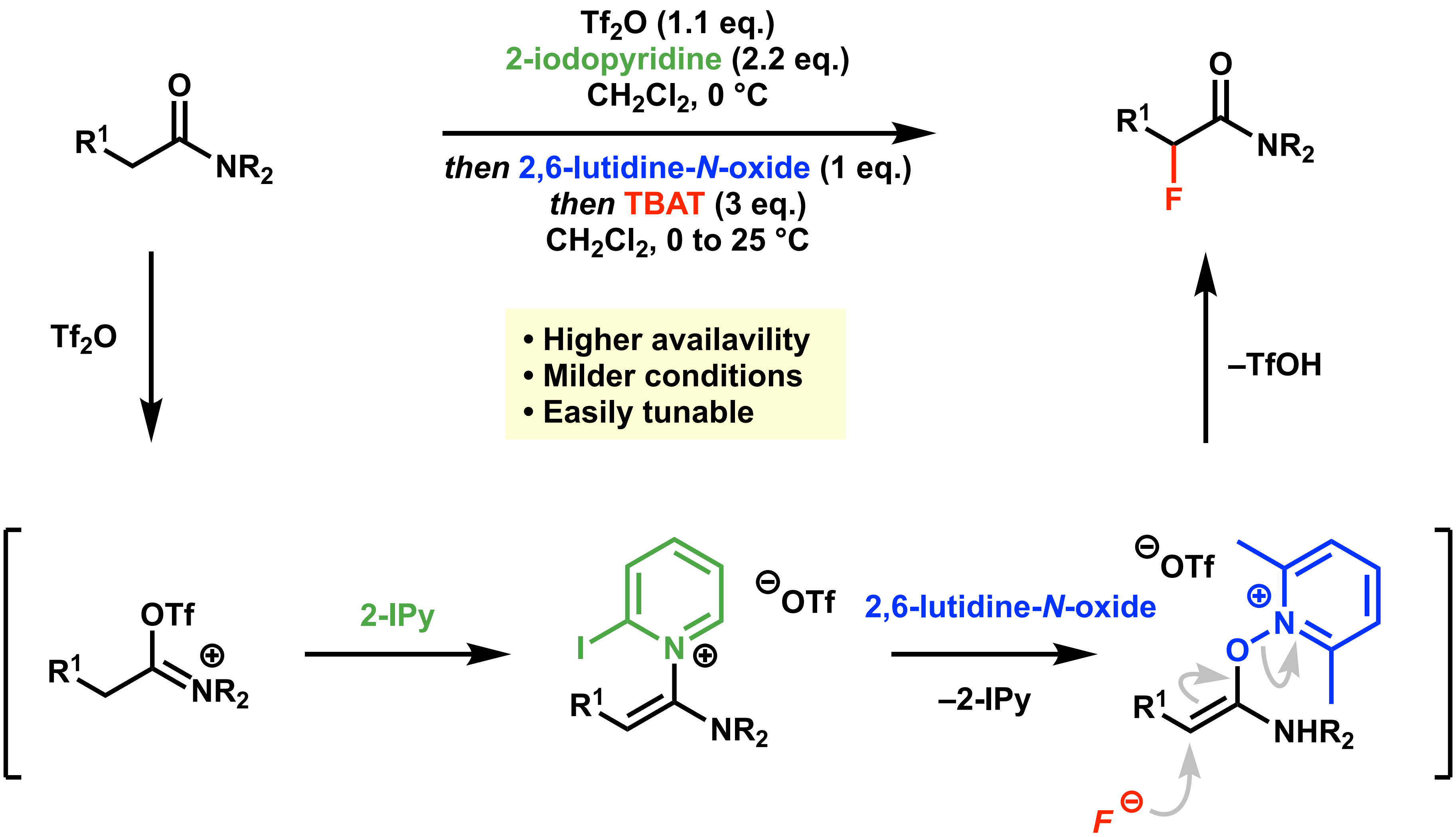
Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.

Preparation of Fluorinated Analogues



Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.

Summary-1



- Higher availavility
- Milder conditions
- Easily tunable

Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.

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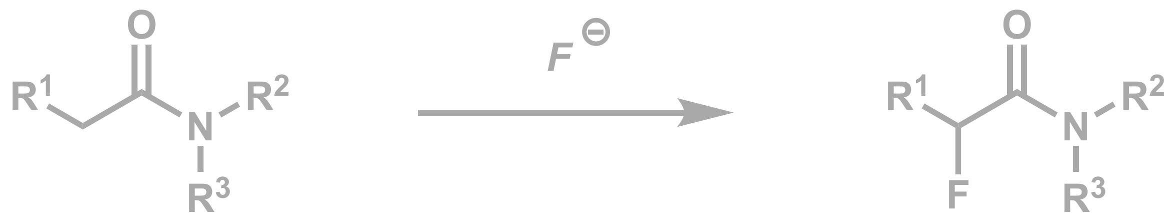

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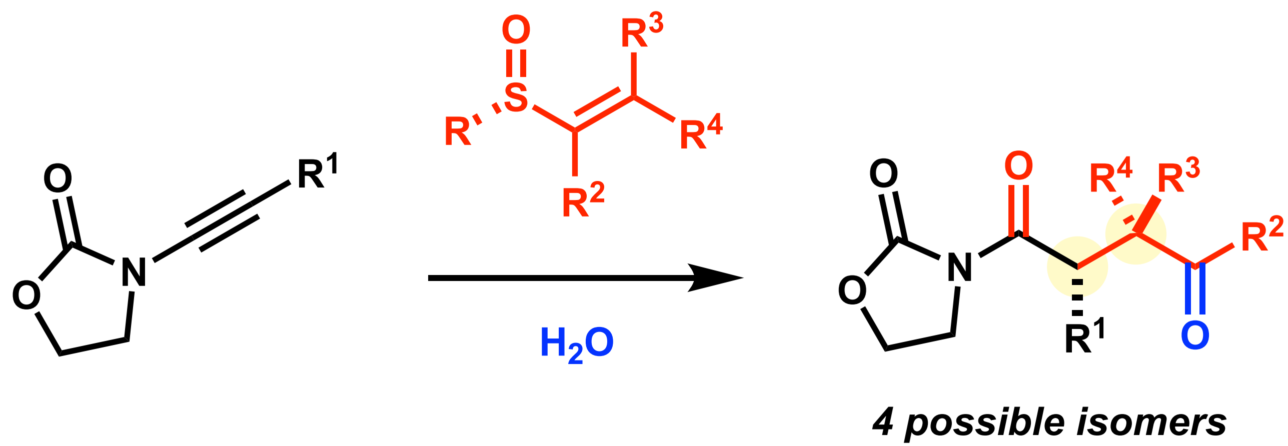
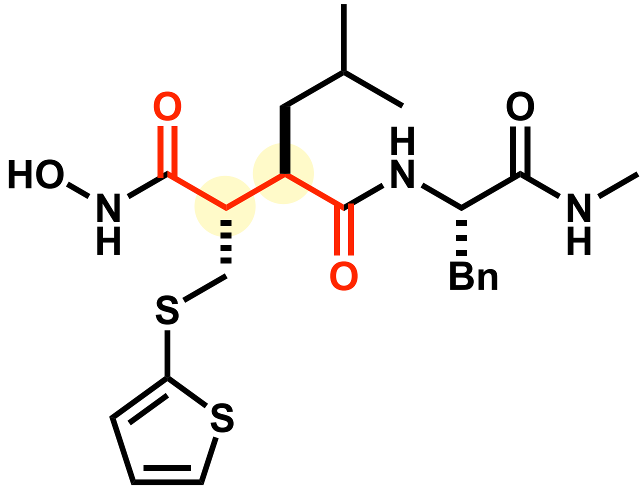
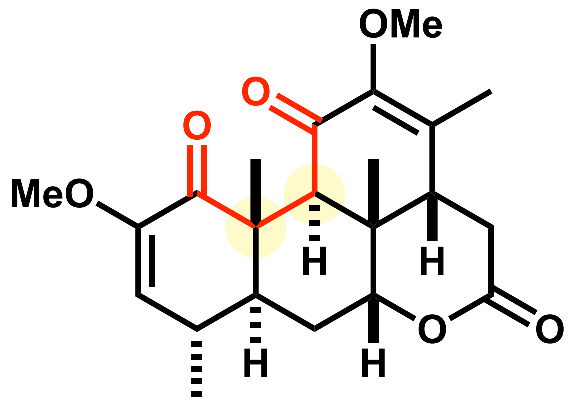


1) Adler, P.; Teskey, C. J.; Kaiser, D.; Holy, M.; Sitte, H. H.; Maulide, N. *Nature Chemistry* **2019**, *11*, 329.
2) Kaldre, D.; Klose, I.; Maulide, N. *Science* **2018**, *361*, 664.

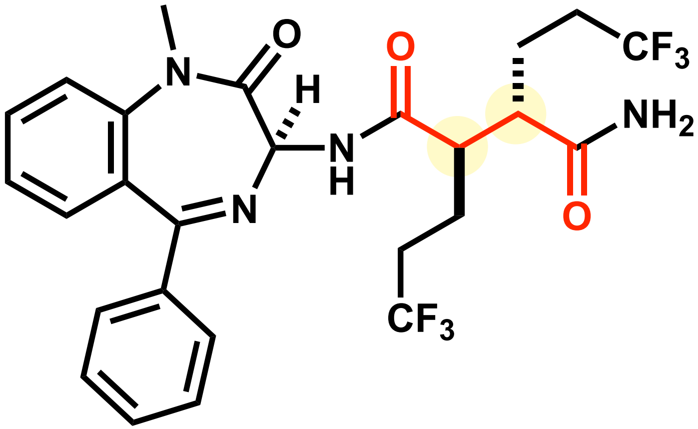
Natural Products and Drug Scaffolds Containing 1,4-Dicarbonyl Moiety



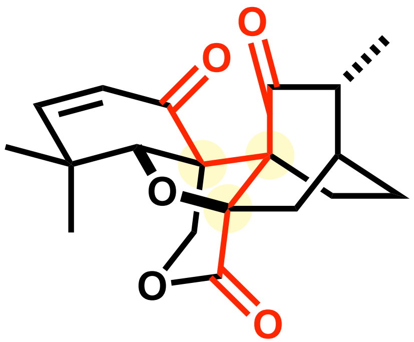
batimastat
anticancer



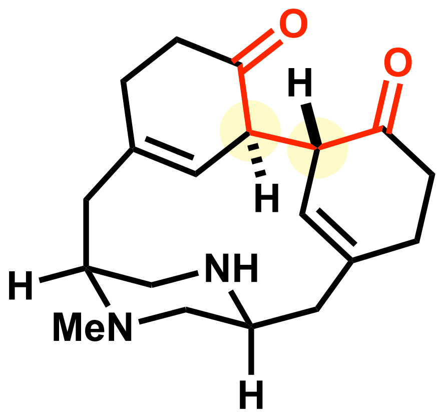
quassin
antineoplastic



BMS-906024
anticancer

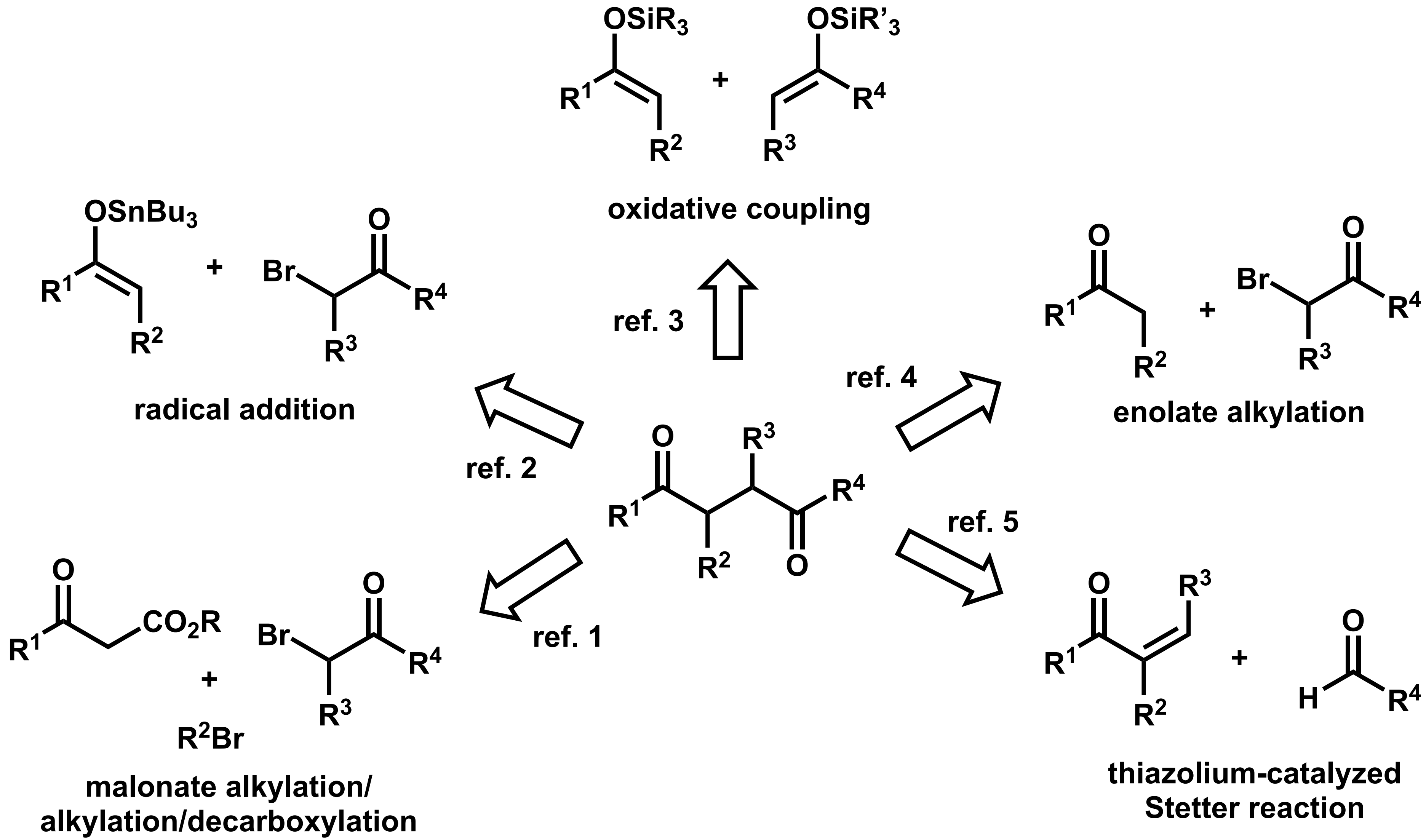


maoecrystal V
anticancer



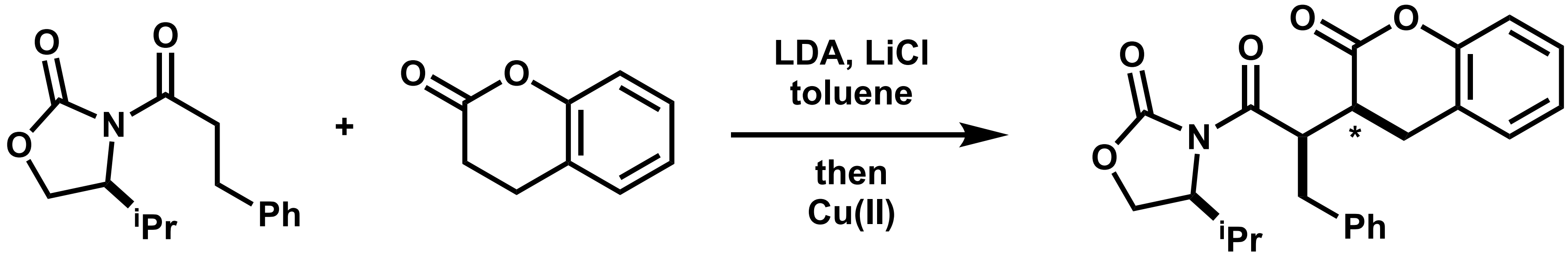
herquline C

Previous Syntheses of 1,4-Dicarbonyls

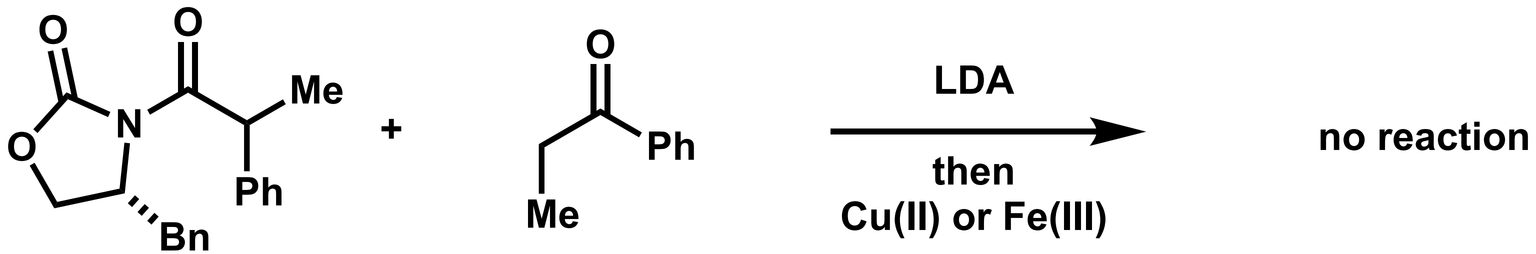


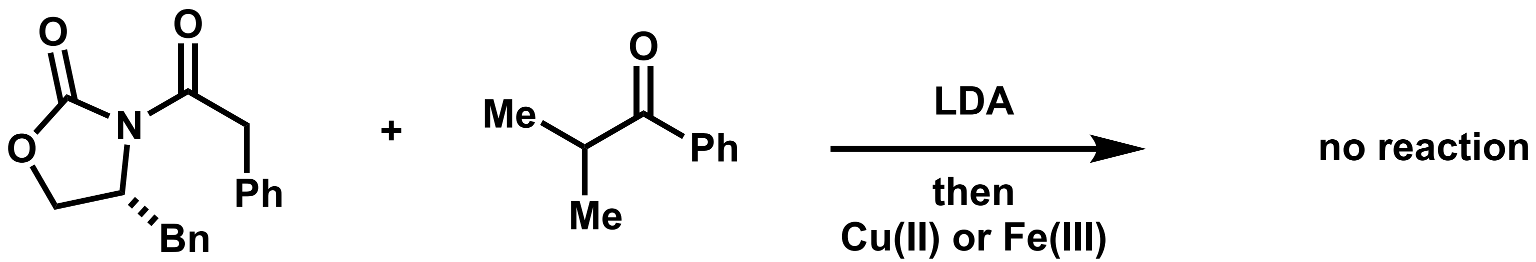
1. Morikawa, T. *et al*. *Bioorg. Med. Chem.* **2002**, *10*, 2569. 2. Hosomi, A. *et al. Org. Lett.* **2001**, *3*, 2591. 3. Ryter, K; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 2658. 4. Wong, W. Y. *et al. Tetrahedron* **1999**, *55*, 13983. 5. Sulsky, R. *et al. Bioorg. Med. Chem.* **2007**, *17*, 3511.

Baran's Synthesis of 1,4-Dicarbonyls



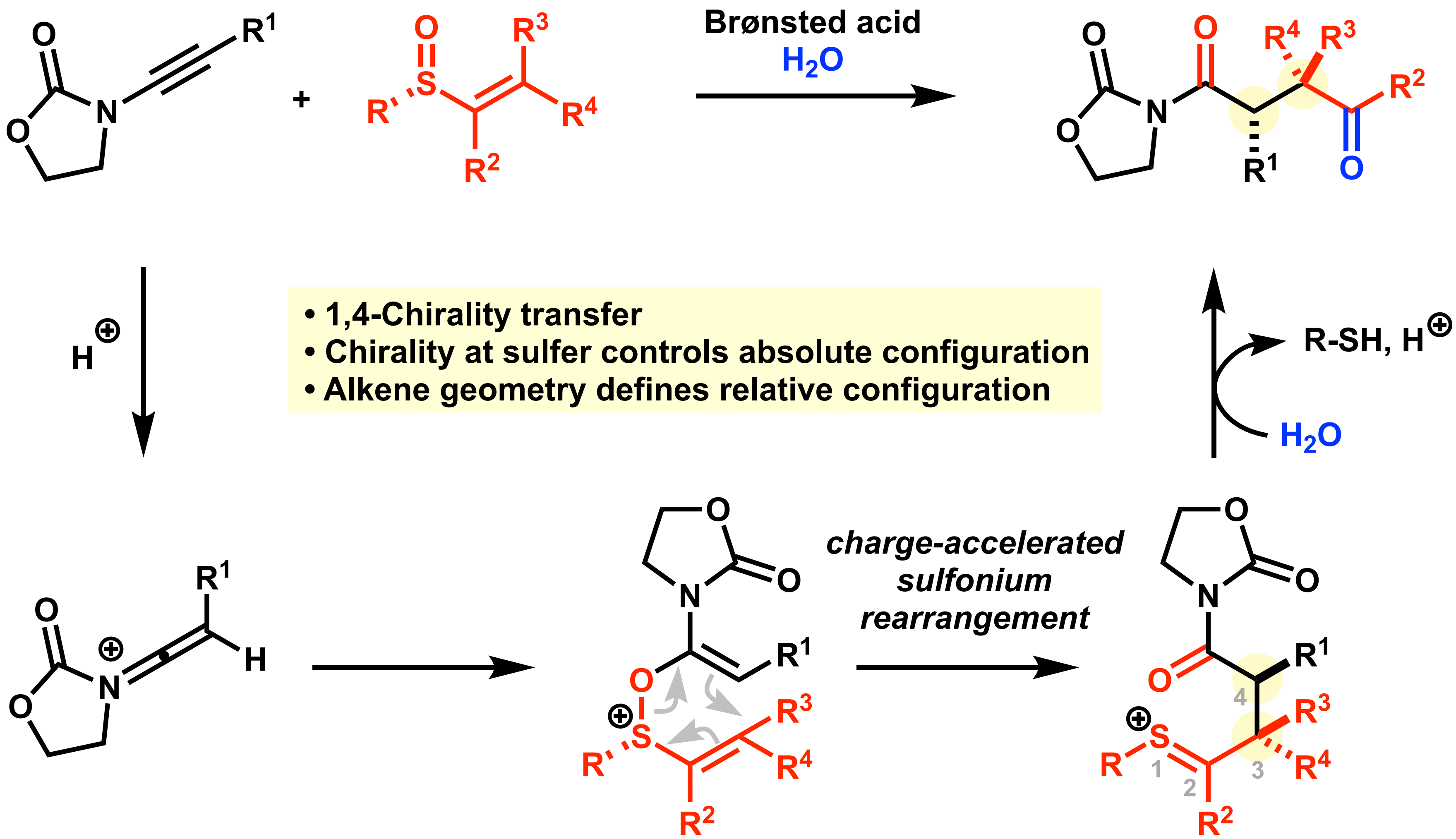
54%, dr 2.4:1





DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc* **2008**, *130*, 11546.

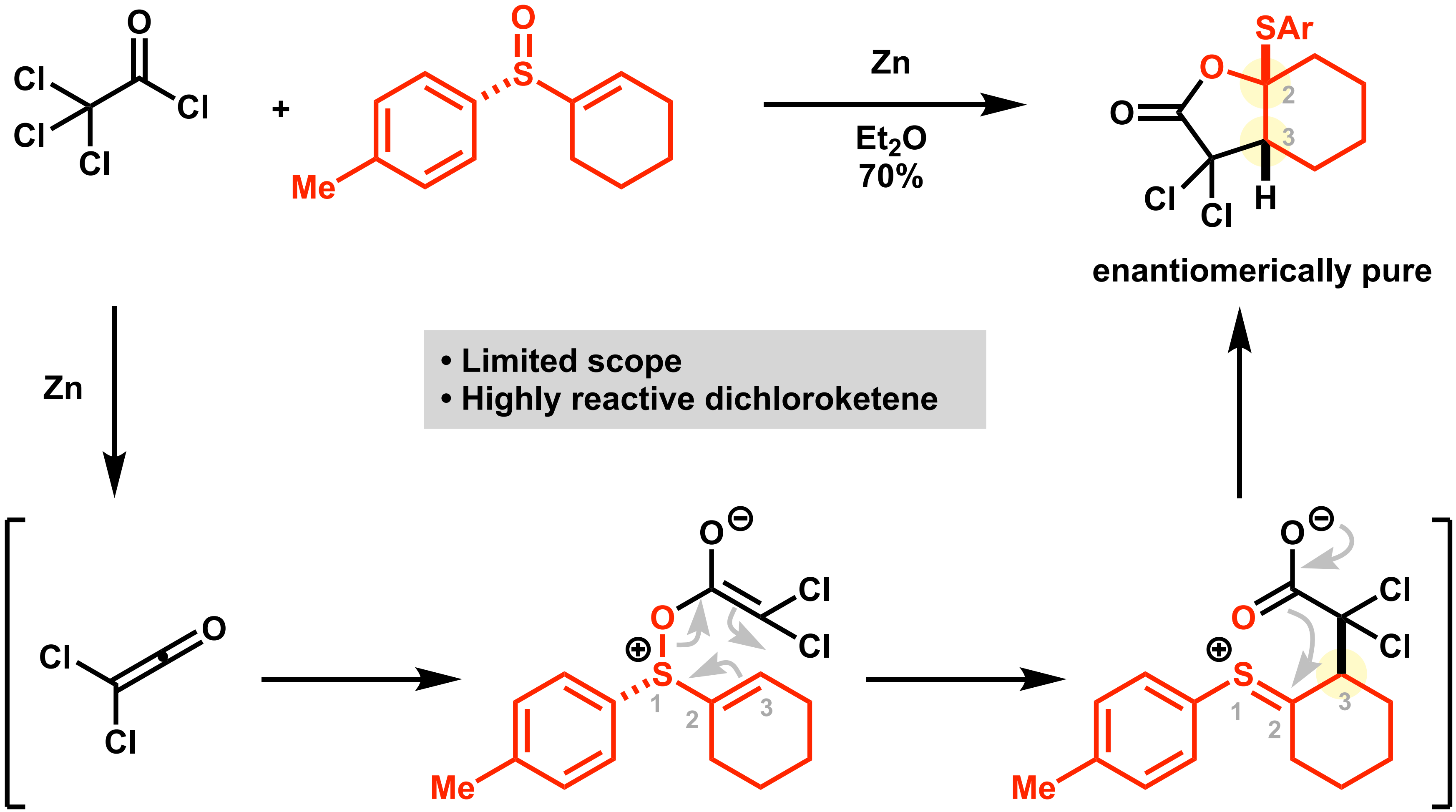
Stereodivergent Approach for The Enantio- and Diastereoselective Synthesis of 1,4-Dicarbonyls



- 1,4-Chirality transfer
- Chirality at sulfer controls absolute configuration
- Alkene geometry defines relative configuration

Kaldre, D.; Klose, I.; Maulide, N. *Science* **2018**, *361*, 664.

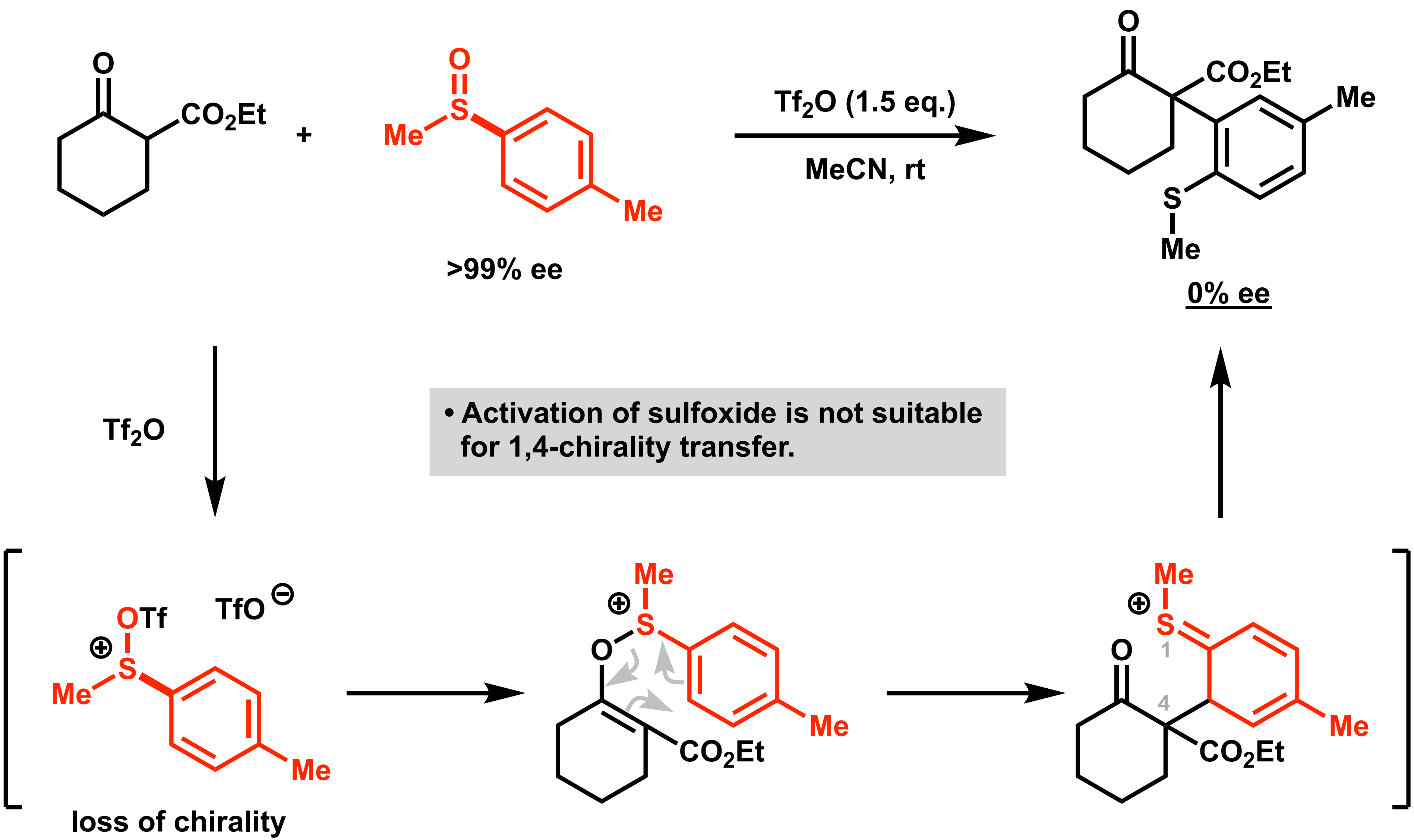
1,3-Chirality Transfer by Slufonium [3,3]-Sigmatropic Rearrangement



• Limited scope
• Highly reactive dichloroketene

Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7644.

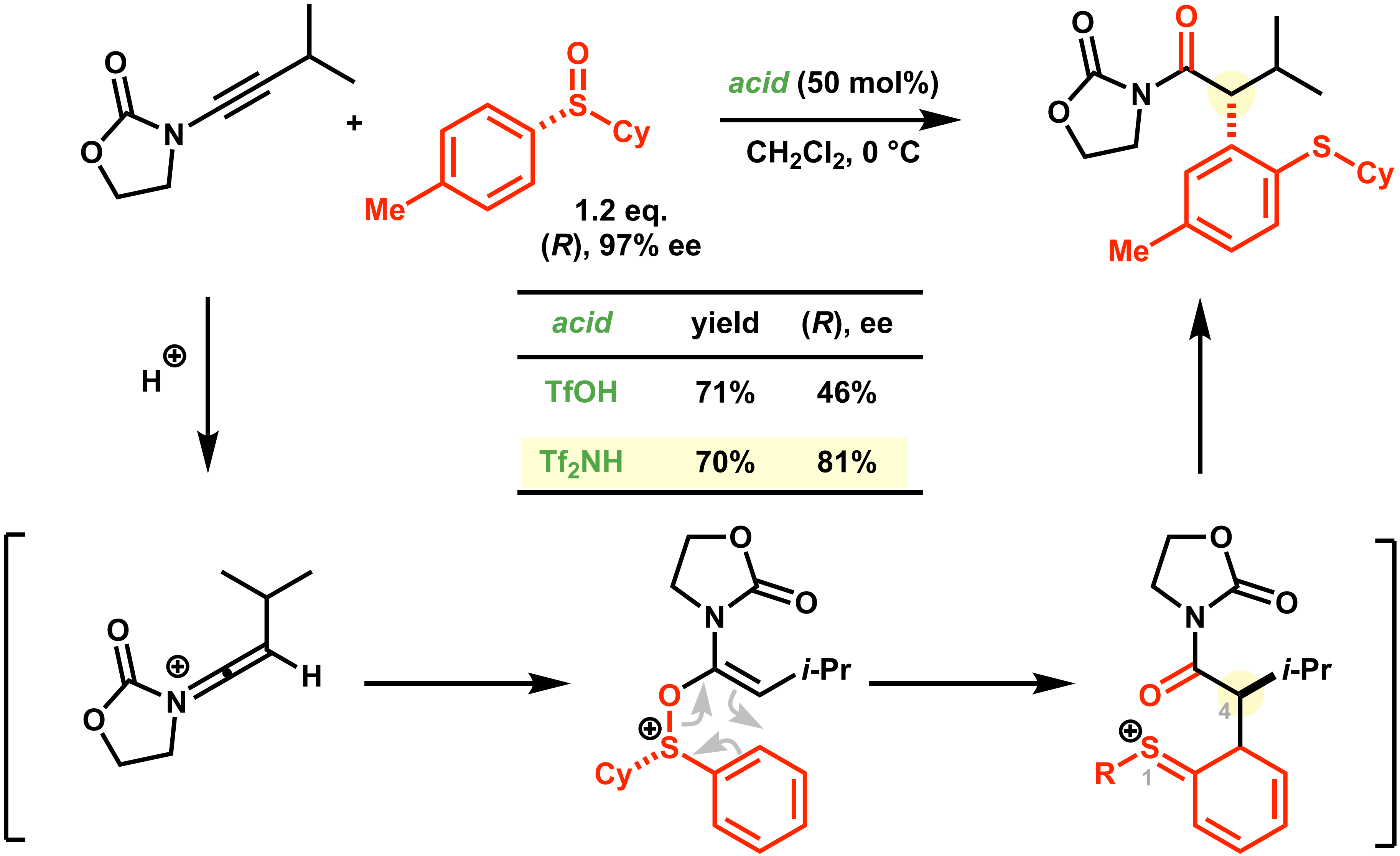
Unsuccessful Attempts of 1,4-Chirality Transfer



- **Activation of sulfoxide is not suitable for 1,4-chirality transfer.**

Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 2212.

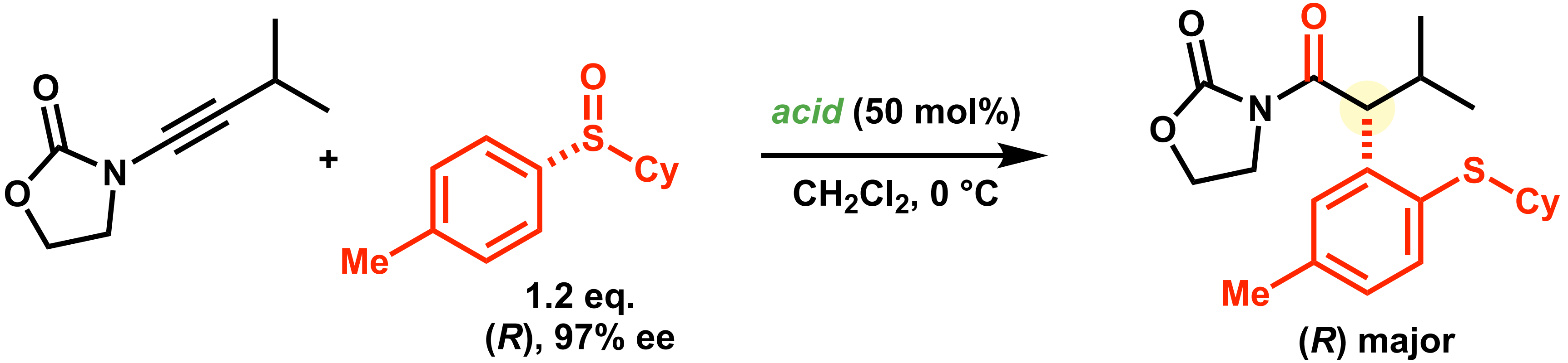
1,4-Chirality Transfer by Slufonium [3,3]-Sigmatropic Rearrangement

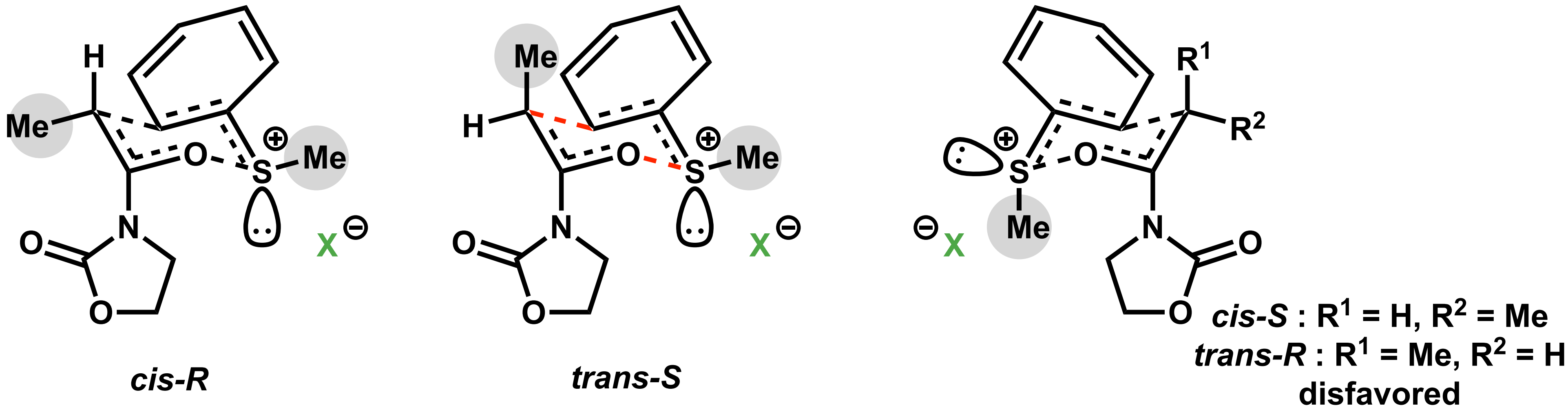


acid	yield	(R), ee
TfOH	71%	46%
Tf_2NH	70%	81%

Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 2212.

Enantioselectivity of 1,4-Chirality Transfer





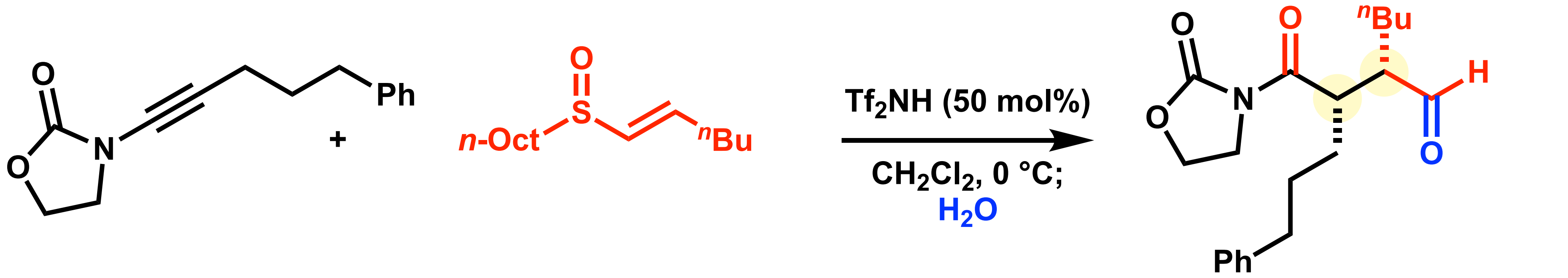
X	$\Delta G_{298,DCM}^{\ddagger}$		X	$\Delta G_{298,DCM}^{\ddagger}$
OTf	: 5.4 kcal/mol	−0.1 →	OTf	: 5.3 kcal/mol
NTf_2	: 3.7 kcal/mol	+2.3	NTf_2	: 6.0 kcal/mol

bond length (Å)
C-C: 3.147, S-O: 2.135
C-C: 3.140, S-O: 2.094

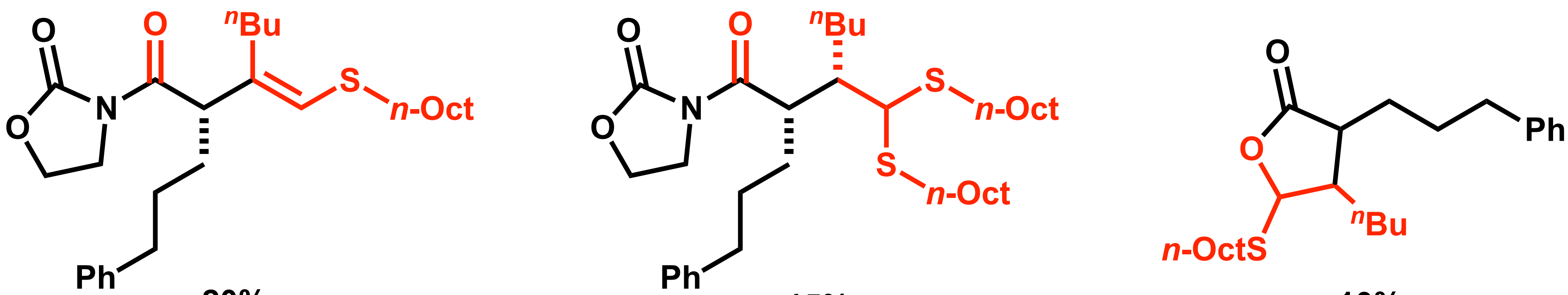
calculation level:
RI-MP2/def2-TZVP//
B3LYP-D3/6-31+G(d,p)

Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 2212.

Attempted Synthesis of 1,4-Dicarbonyls by Sulfonium Rearrangement



26%



20% 15% <10%

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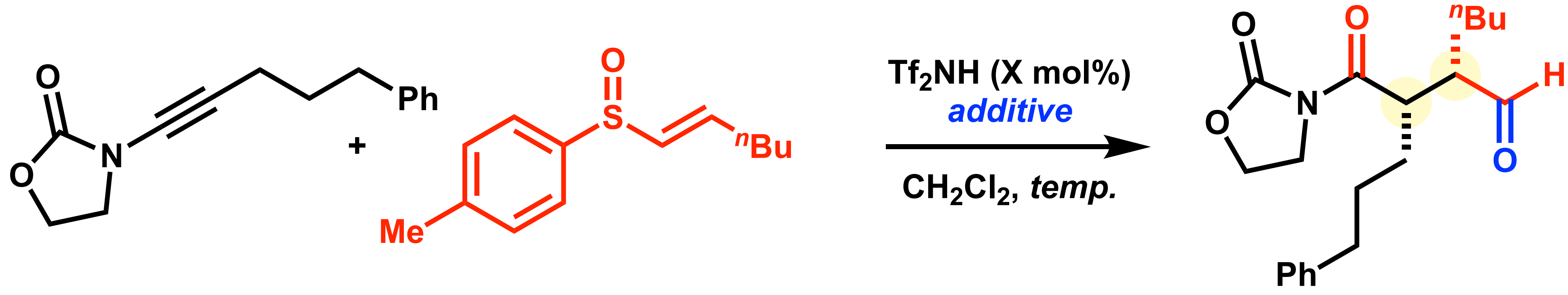
Optimization of Synthesis of 1,4-Dicarbonyls by Sulfonium Rearrangement



entry	X	*additive*	yield	dr
1	50	none	12%	10:1
2	50	H_2O (3 eq.)	34%	11:1
3	50	H_2O, *i*-PrCHO (3 eq.)	67%	8:1
4	50	H_2O, *i*-PrCHO (6 eq.)	80%	8:1
5	50	H_2O, *i*-PrCHO (10 eq.)	79%	8:1

entry	X	*additive*, *temp*	yield	dr
6	50	entry 4, –10 °C	68%	15:1
7	50	entry 4, –30 °C	55%	20:1
8	100	entry 4	69%	5.5:1
9	35	entry 4	82%	8:1
10	20	entry 4	63%	16:1

*The reactions were conducted at 0 °C, except for entry 6 and 7.

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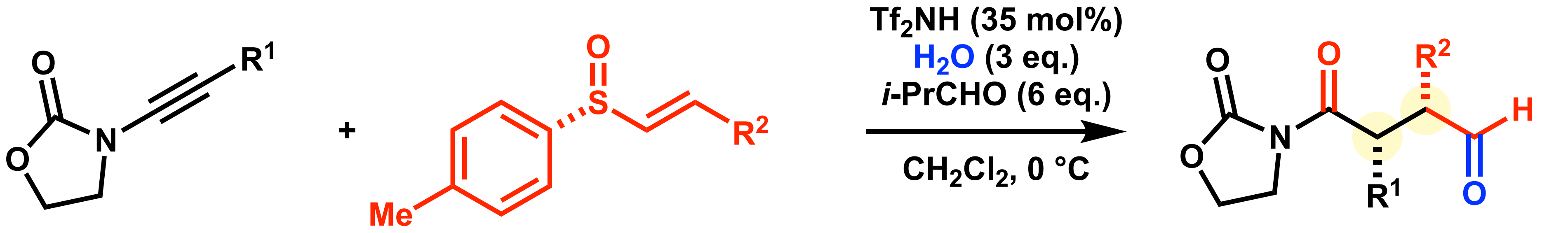
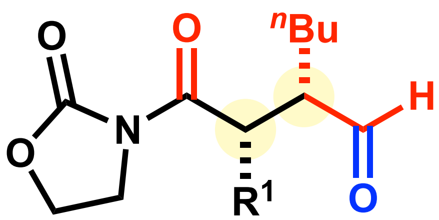
Substrate Scope for *Syn*-1,4-dicarbonyls-1

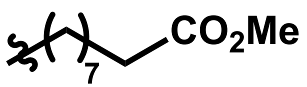


(*R*)-*E*-vinylsulfoxide

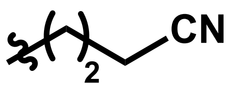
syn-1,4-dicarbonyl



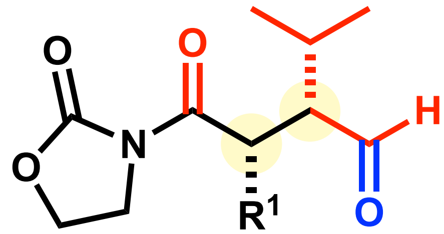
R^1 = Cy : 78%, dr 8:1, ee >98%
R^1 = Ph : 54%, dr 13:1, ee >98%
R^1 = 3,4-dichloro phenyl : 66%, dr 12:1, ee >99%

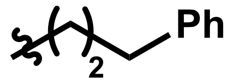
R^1 = 

: 81%, dr 7:1, ee >96%

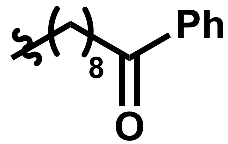
R^1 = 

: 83%, dr 8:1, ee >98%



R^1 = 

: 78%, dr 16:1, ee >99%

R^1 = 

: 88%, dr 15:1, ee >99%

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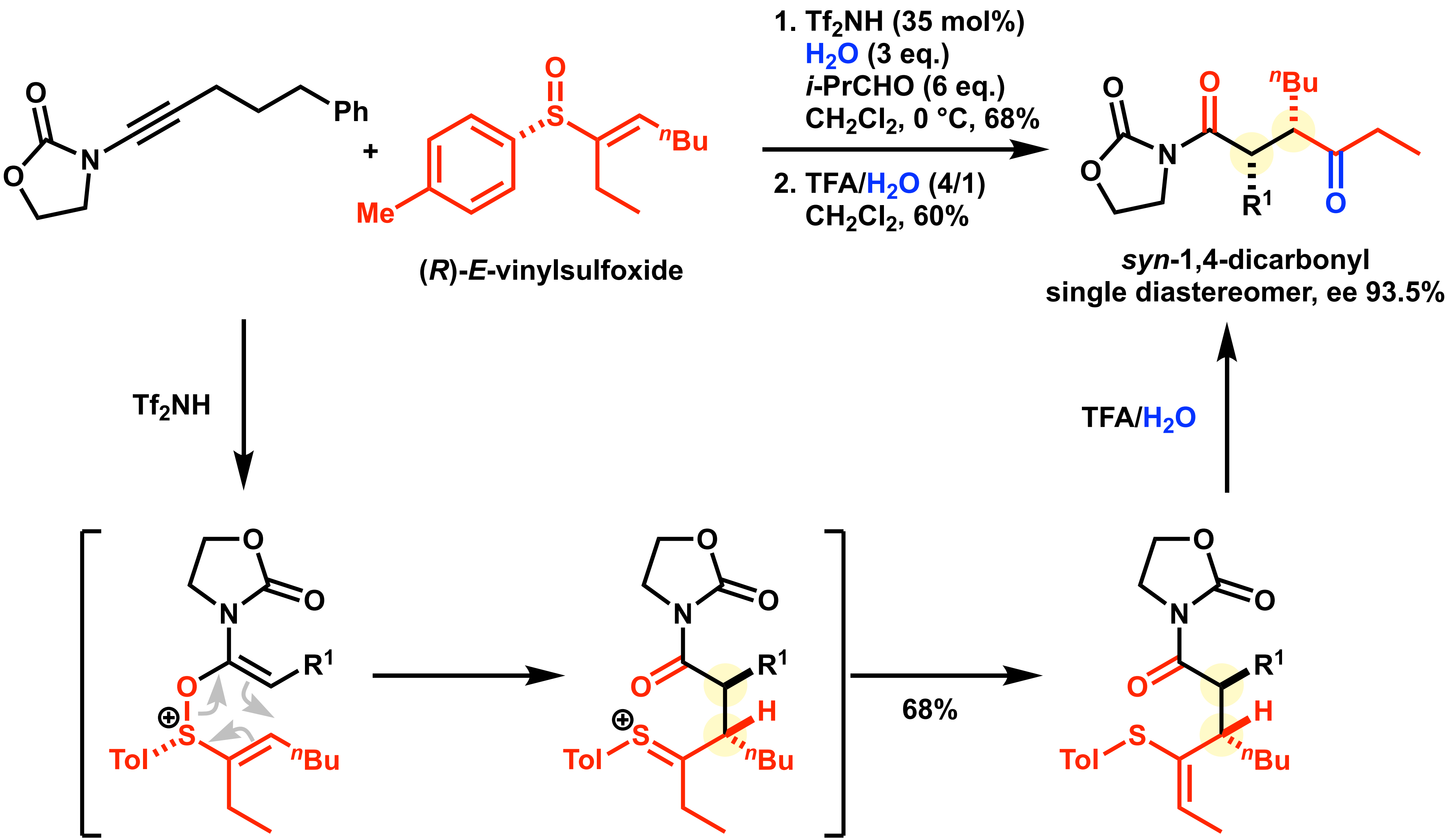
Substrate Scope for *Syn*-1,4-dicarbonyls-2



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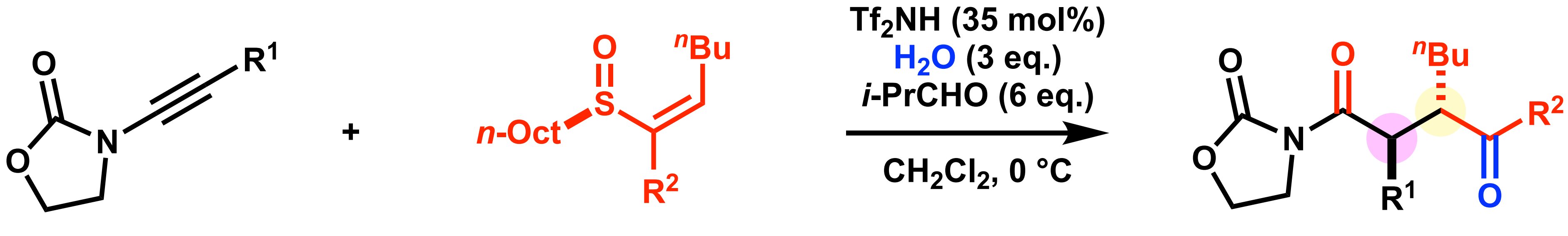
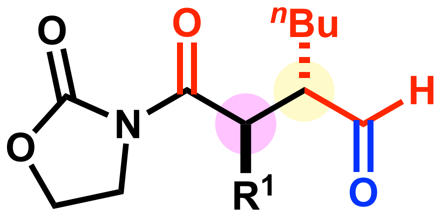
Substrate Scope for *Anti*-1,4-dicarbonyls

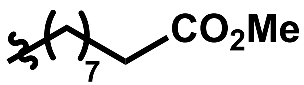


(*R*)-*Z*-vinylsulfoxide

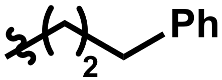
anti-**1,4-dicarbonyl**



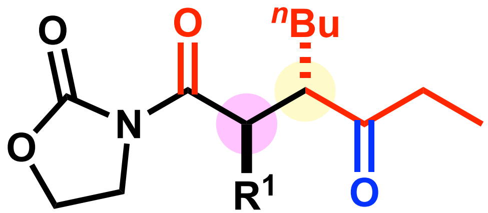
R^1 = Cy : 80%, dr 8:1, ee >99%
R^1 = Ph : 60%, dr 14:1, ee >99%

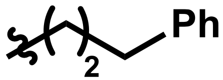
R^1 = 

: 62%, dr 8:1, ee >99%

R^1 = 

: 75%, dr 8:1, ee >99%



R^1 = 

: 76%*, dr 11:1, ee >99%

***The modified condition (TFA/H_2O) was used.**

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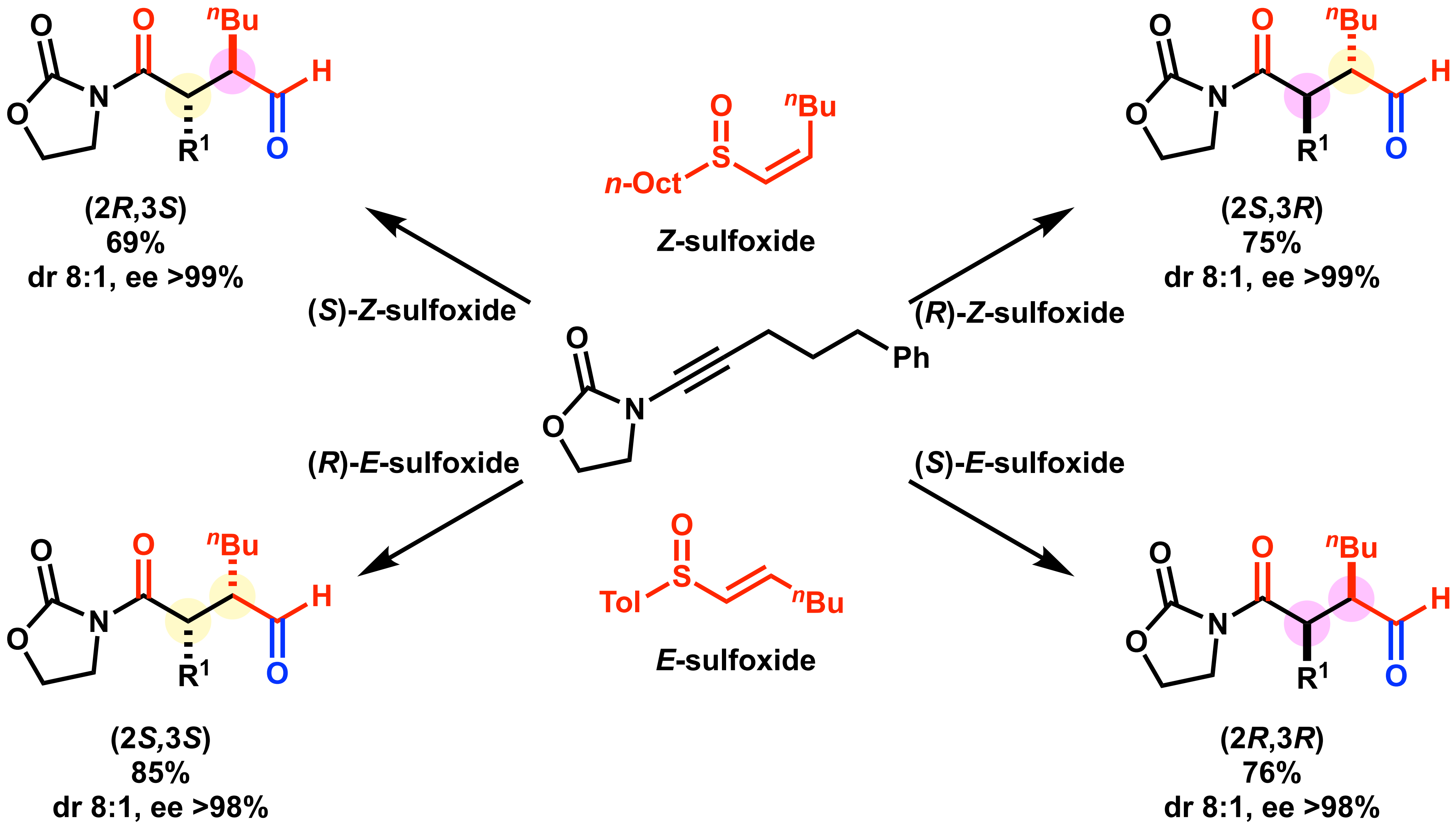
Access to All Stereoisomers



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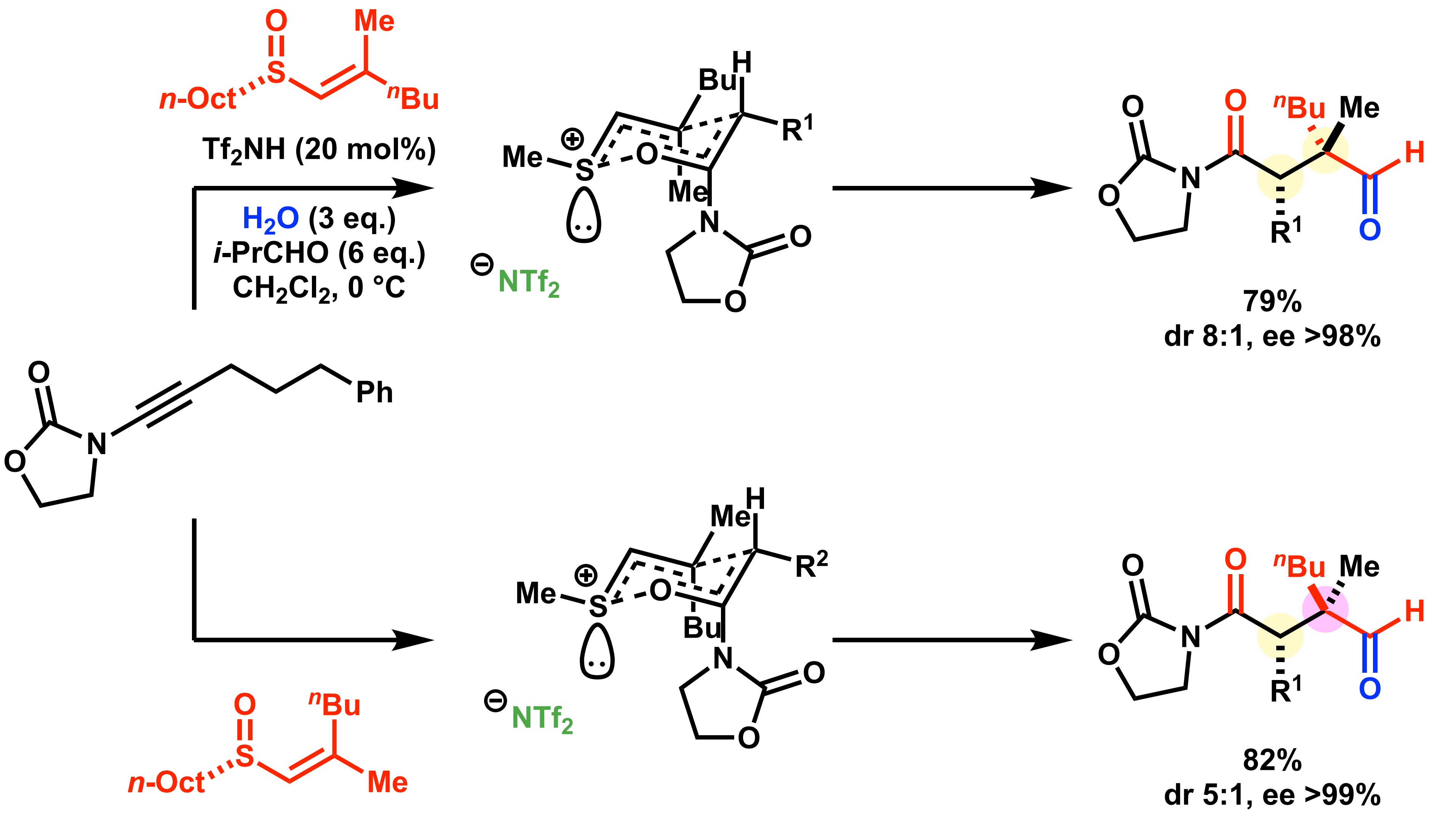
Synthesis of All-carbon Quaternary Products



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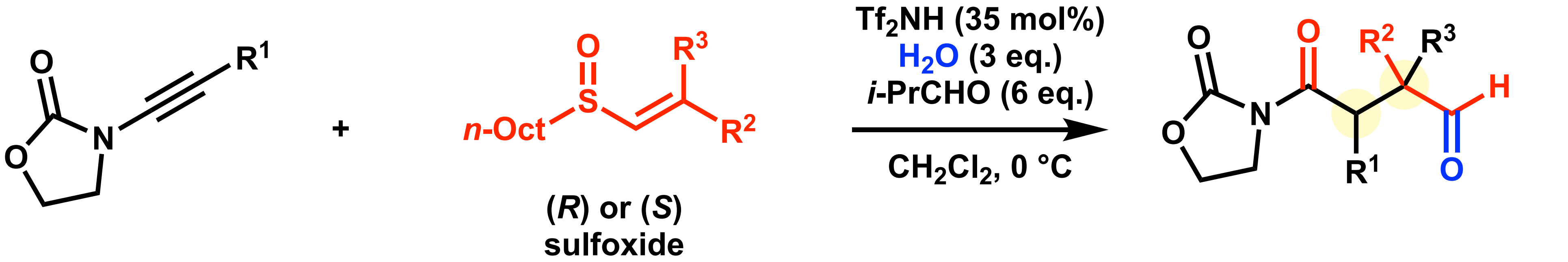
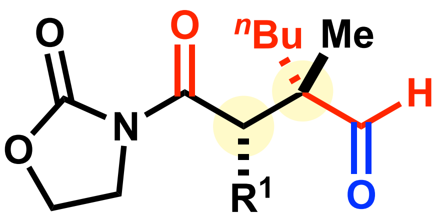
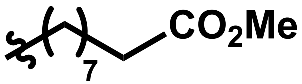
Scope of Ynamides and Vinyl Sulfoxides

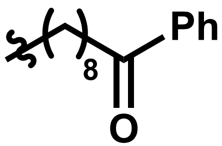




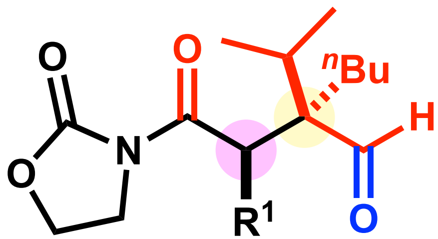
R^2 = ^{n}Bu, R^3 = Me, (*S*)-sulfoxide
R^1 = Cy : 93%, dr 8:1, ee >98%
R^1 = Ph : 55%, dr 9:1, ee >97%

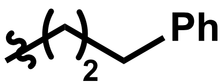
R^1 = 

: 79%, dr 8:1, ee >98%

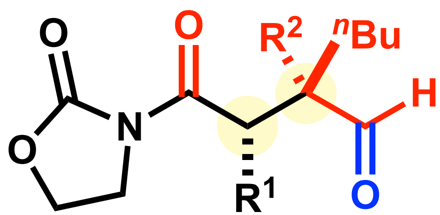
R^1 = 

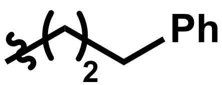
: 83%, dr 7:1, ee >98%



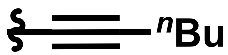
R^1 = 

R^2 = ^{i}Pr, R^3 = ^{n}Bu, (*R*)-sulfoxide
: 63%, dr 6:1, ee >98%



R^1 = 

R^3 = ^{n}Bu, (*S*)-sulfoxide

R^2 = F : 58%, dr 6:1, ee >97%
R^2 = CF_3 : 68%, dr 7:1, ee >98%
R^2 = 

: 55%, dr 6:1, ee >99%

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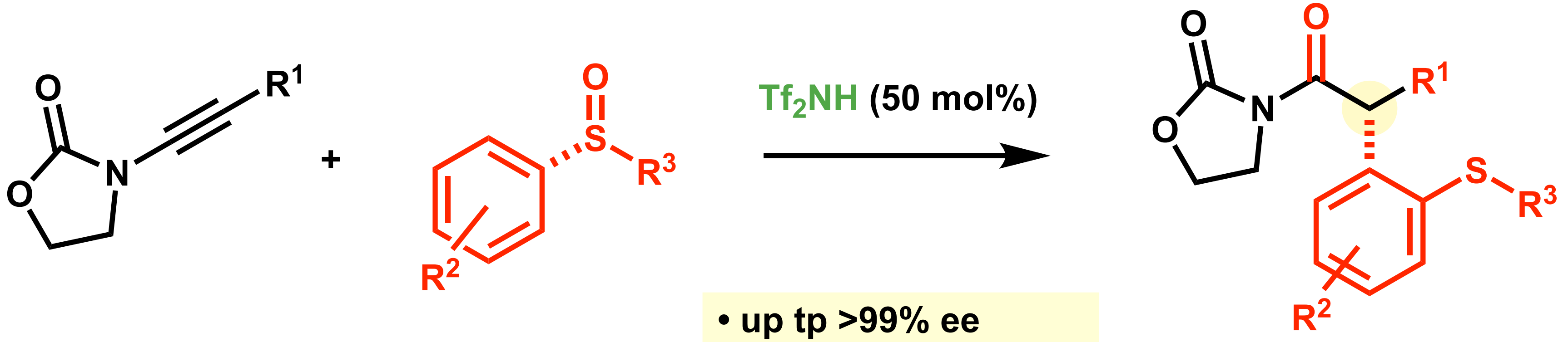
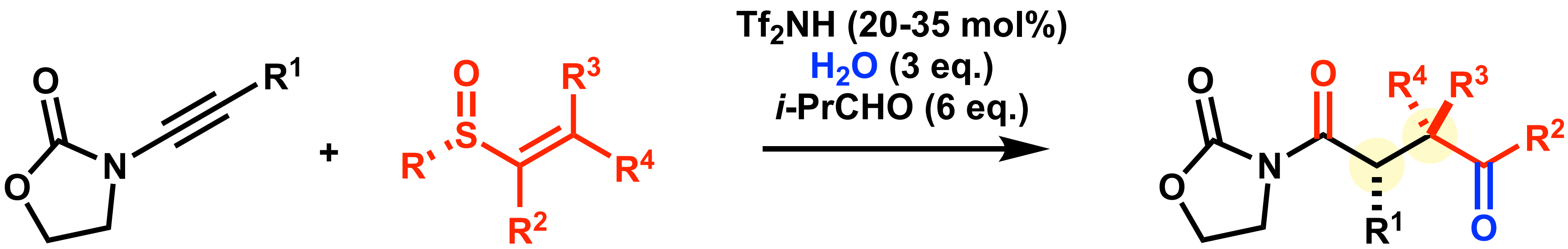
Summary-2



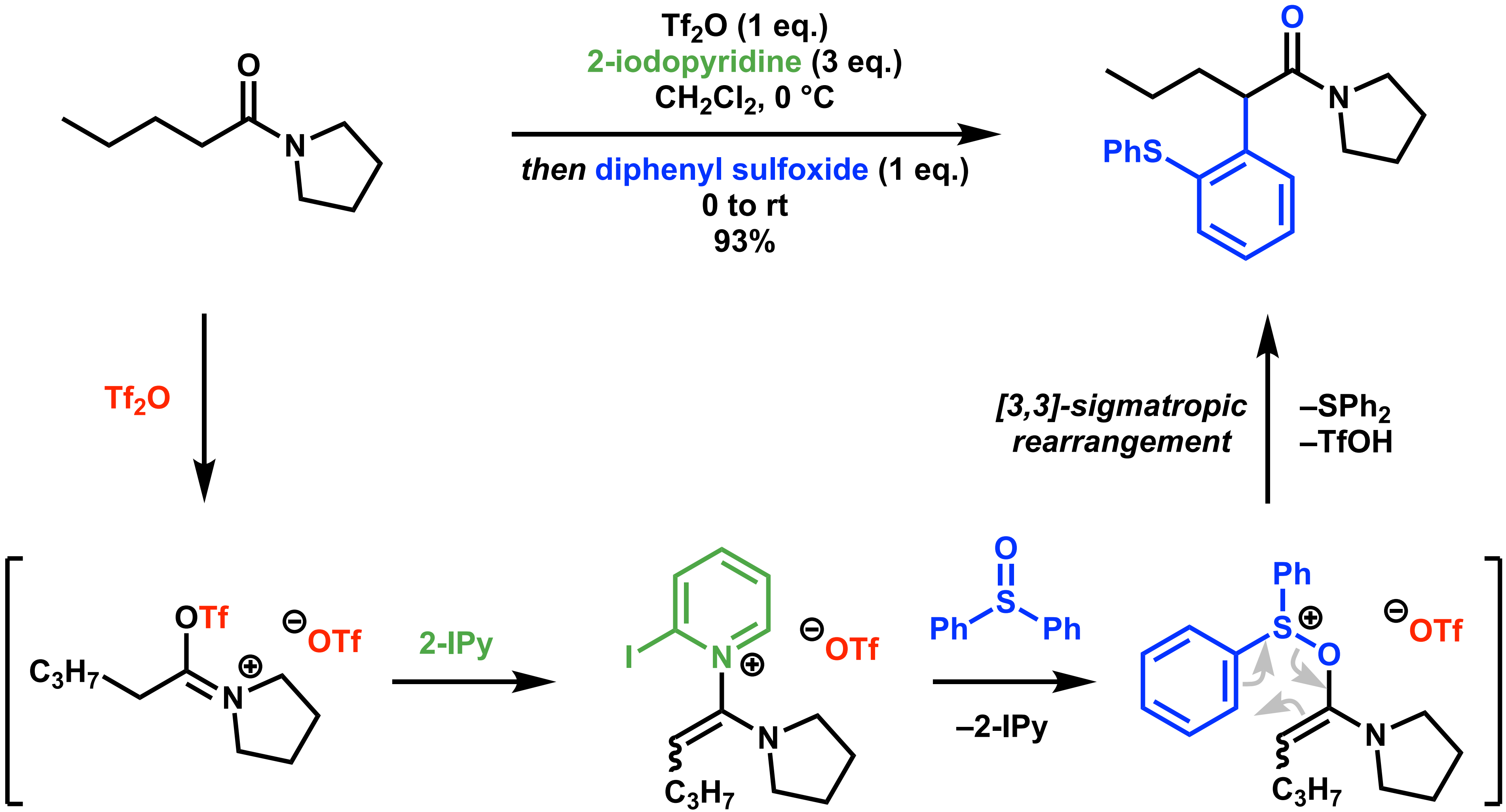
• up tp >99% ee
• 1,4-chirality transfer



• up tp >99% ee
• stereodivergent method
• quaternary stereocenters
• traceless sulfer moiety

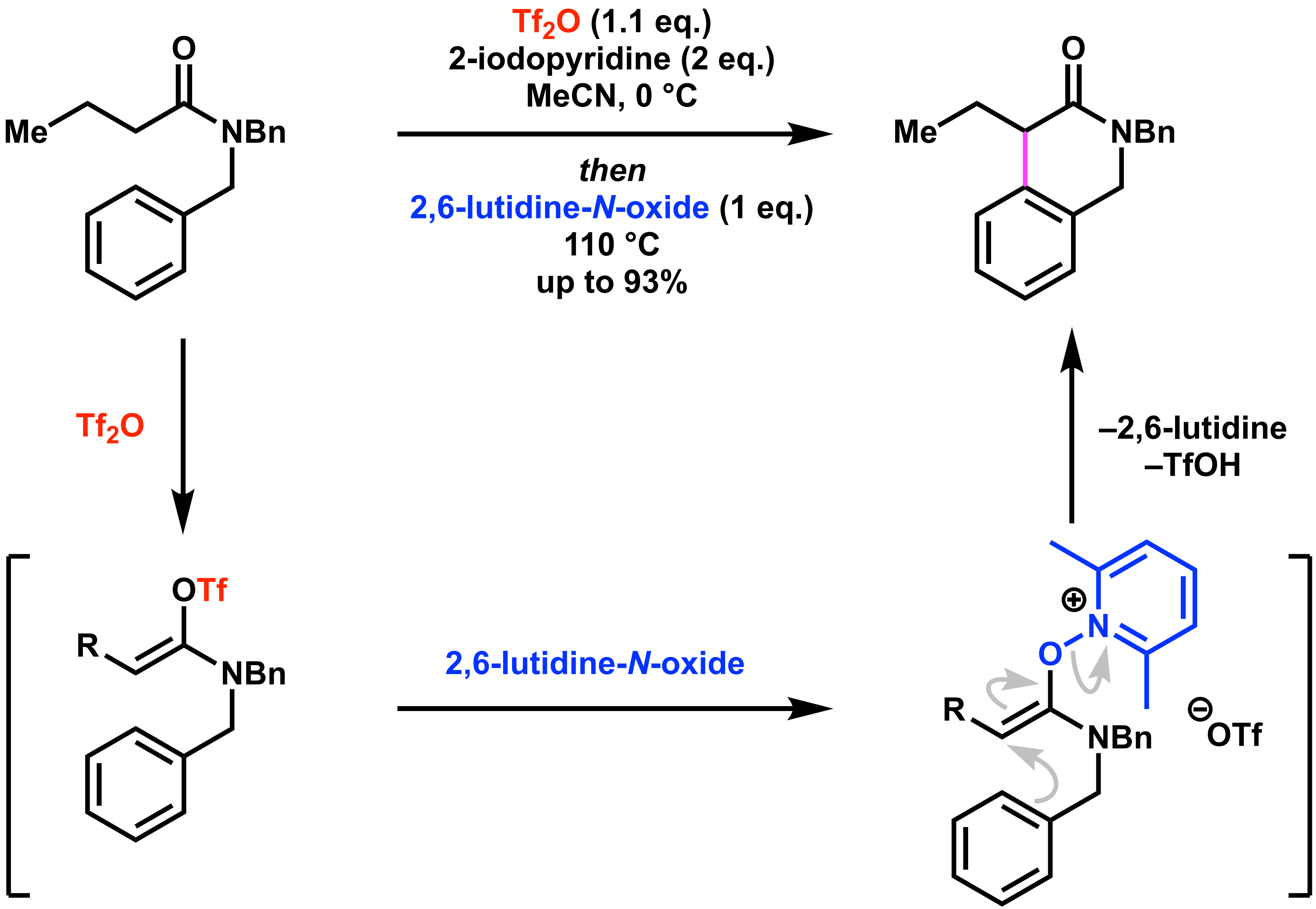
Appendix

Charge-Accelerated Sulfonium Rearrangement



Peng, B.; Geerdink, D.; Farés, C.; Maulide, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 5462.

Maulide's α-Arylation of Amide



Kaiser, D.; Torre, A.; Shaaban, S.; Maulide, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 5921.