



**A TRADITION OF  
INDEPENDENT  
THINKING**

---



**UCC**

**University College Cork, Ireland**  
Coláiste na hOllscoile Corcaigh



# SSPC

SYNTHESIS AND SOLID STATE PHARMACEUTICAL CENTRE  
Innovation Through Collaboration



University College Cork, Ireland  
Coláiste na hOllscoile Corcaigh

# Taming Diazo Chemistry in Flow

Anita Maguire

Dial-a-Molecule Annual Meeting 2019

– Sustaining Chemical Synthesis

*York*

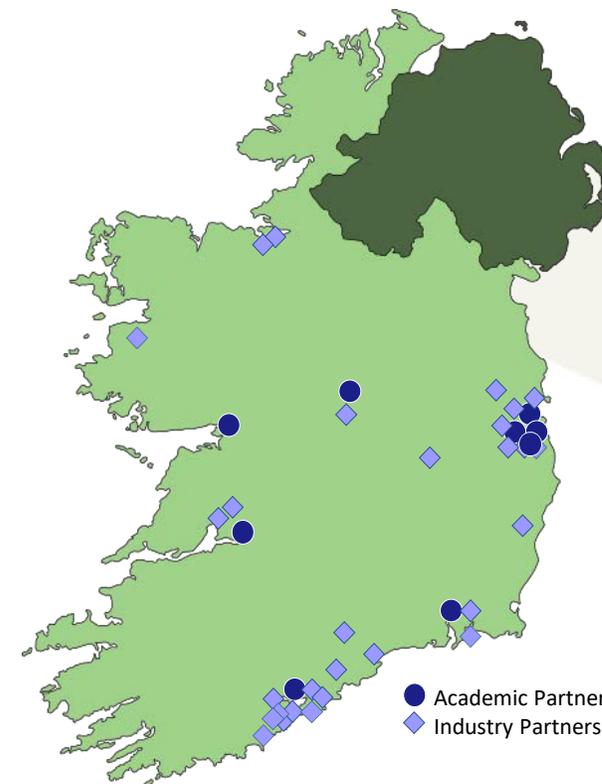
*4th July 2019*



# Synthesis & Solid-State Pharmaceutical Centre

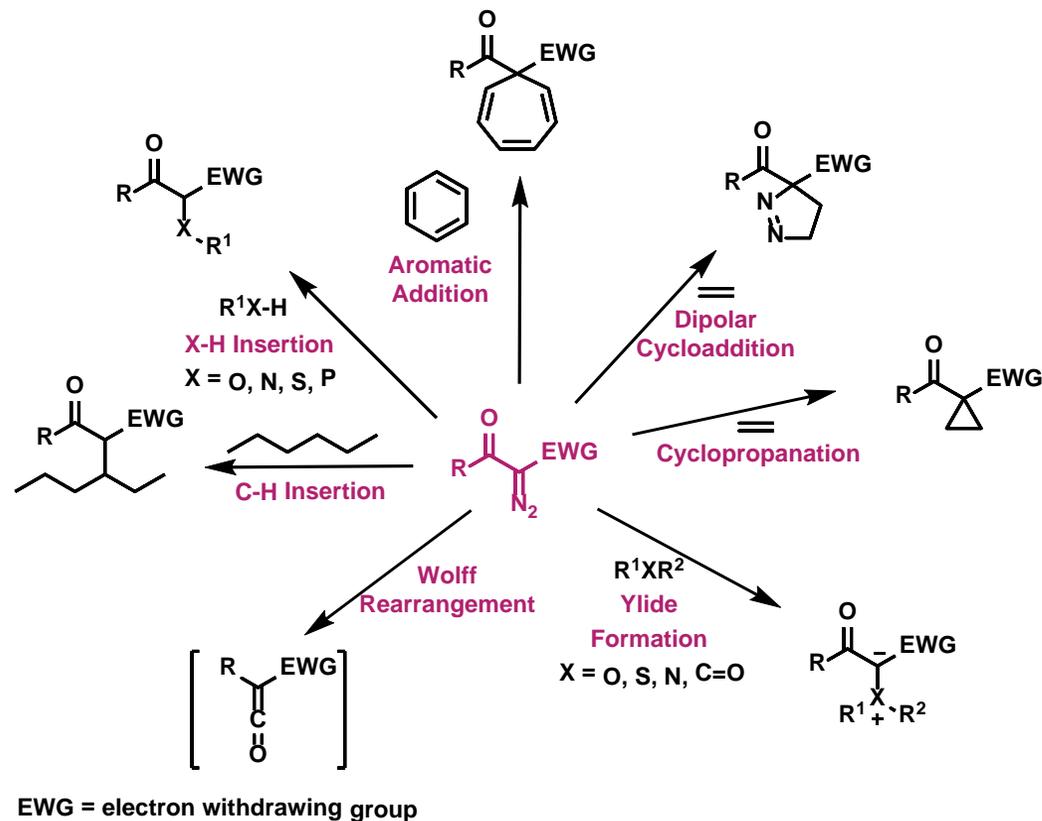
## “SSPC Centre”

- Multidisciplinary academic-industrial collaboration focused on innovating Pharmaceutical products and processes
- €80M; 68 Academics; 115 PhD students; 87 PDRA over 6 years
- Exemplar of academia-industry collaboration (24 industry partners)
- Facilitates inter-industry collaboration in the precompetitive space
- Community of Practice & Open Innovation



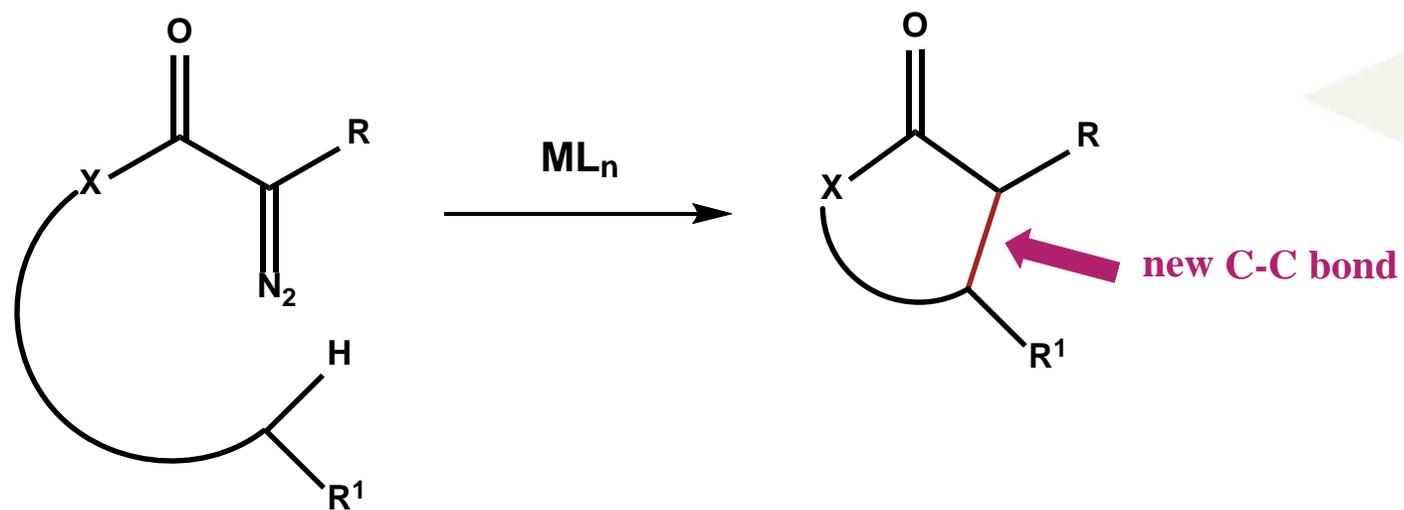
● Academic Partners  
◆ Industry Partners

# $\alpha$ -Diazocarbonyl Compounds – *Versatile Synthetic Intermediates*



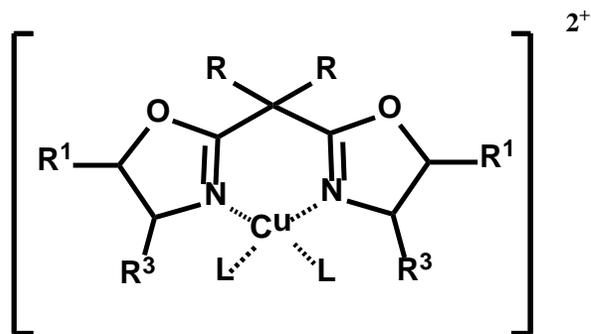
Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKerver, M. A. *Chem. Rev.*, **2015**, *115*, 9981.

# $\alpha$ -Diazocarbonyls: *Intramolecular C–H Insertion Reactions*



# Copper Bis(oxazoline) Complexes

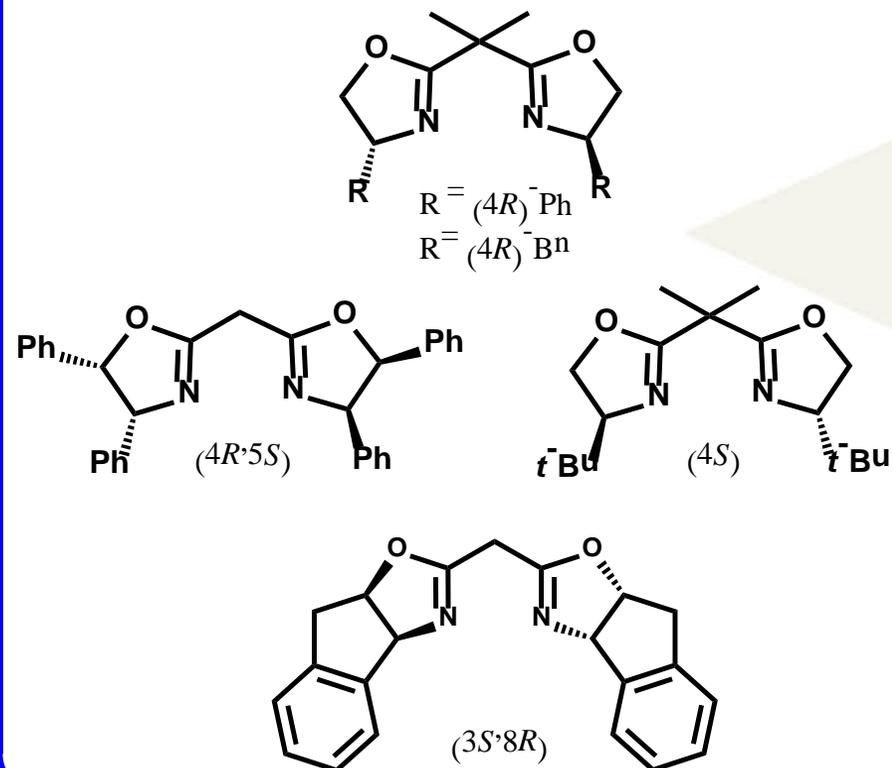
## Copper bis(oxazoline) catalysts



## Copper source



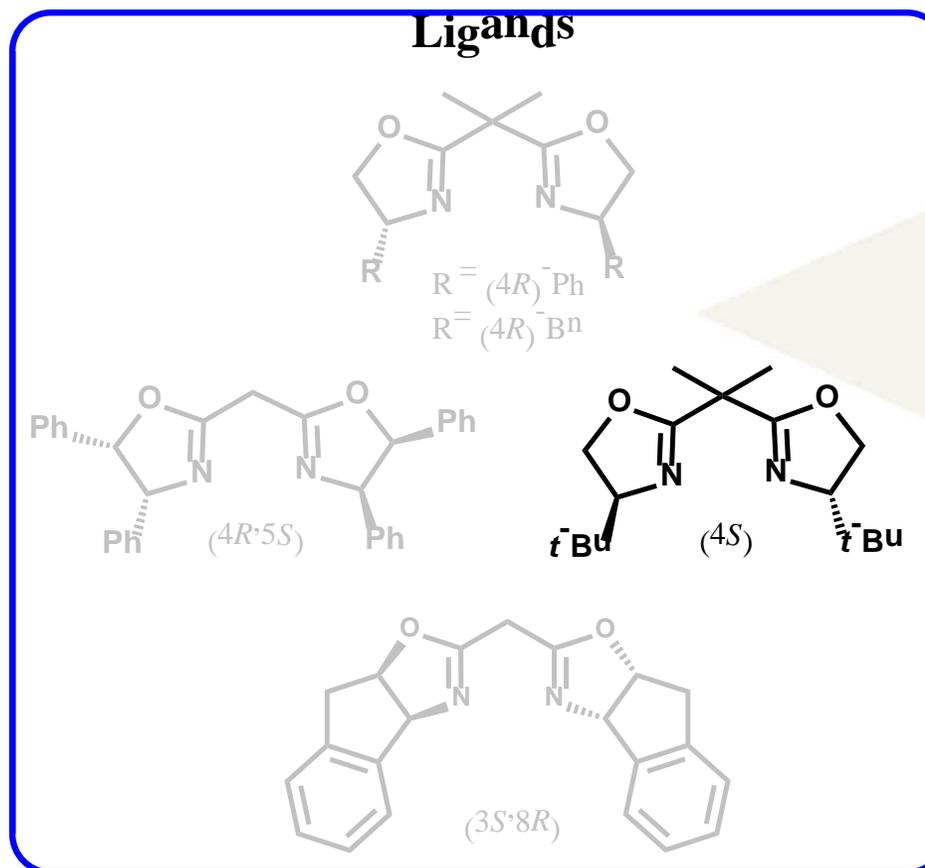
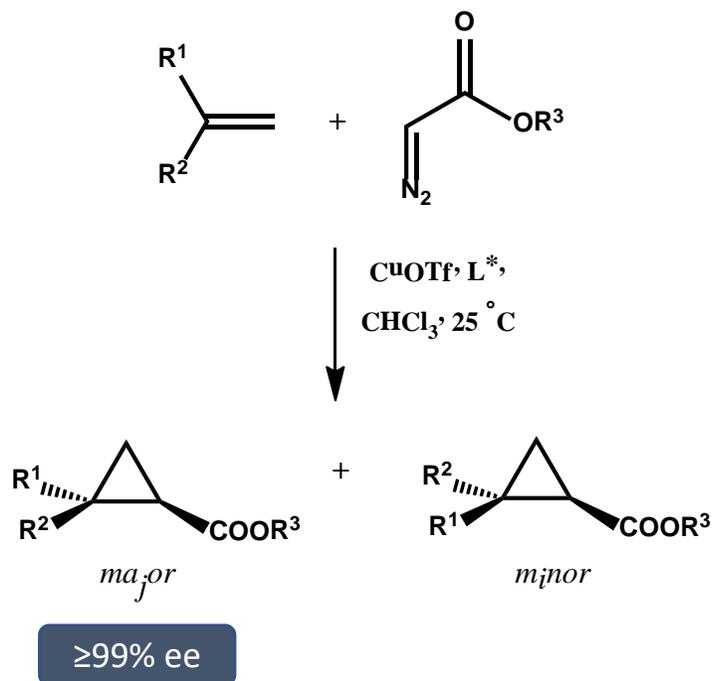
## Ligands



Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505.

Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

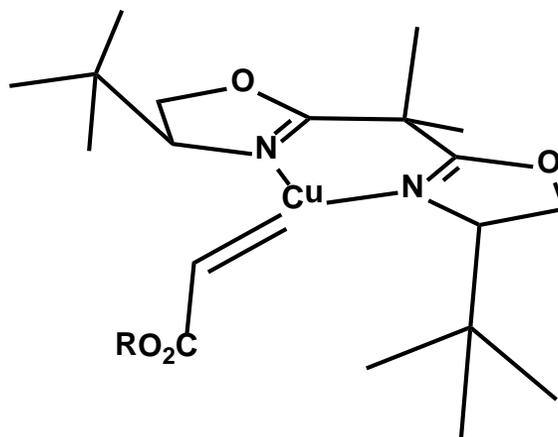
# Copper Bis(oxazoline) Complexes



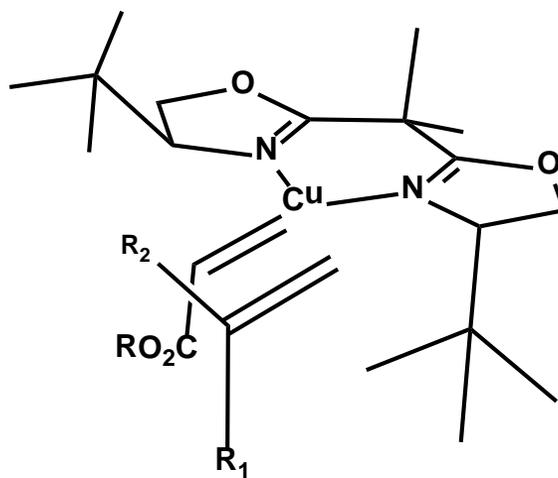
Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed.* **1992**, *31*, 430.

Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

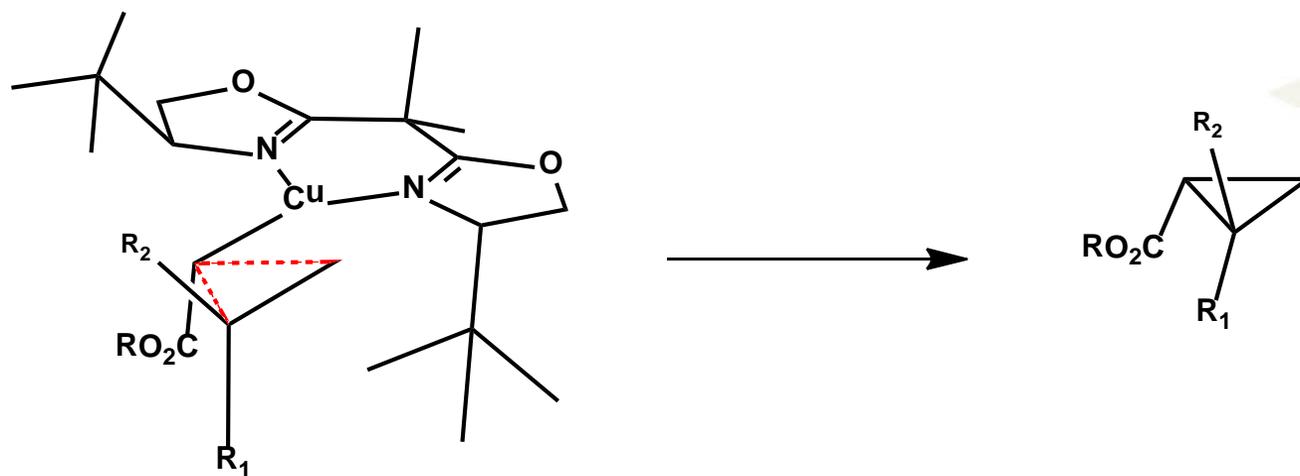
# Copper Bis(oxazoline)-Catalysed Cyclopropanation



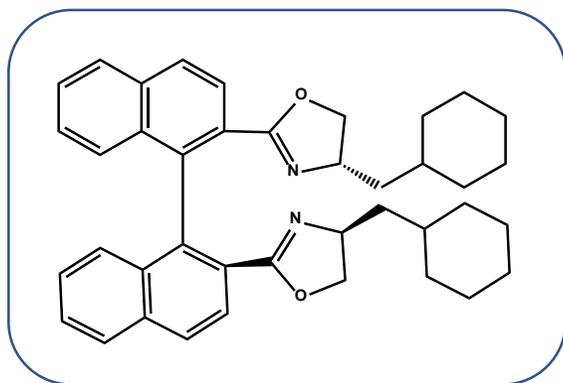
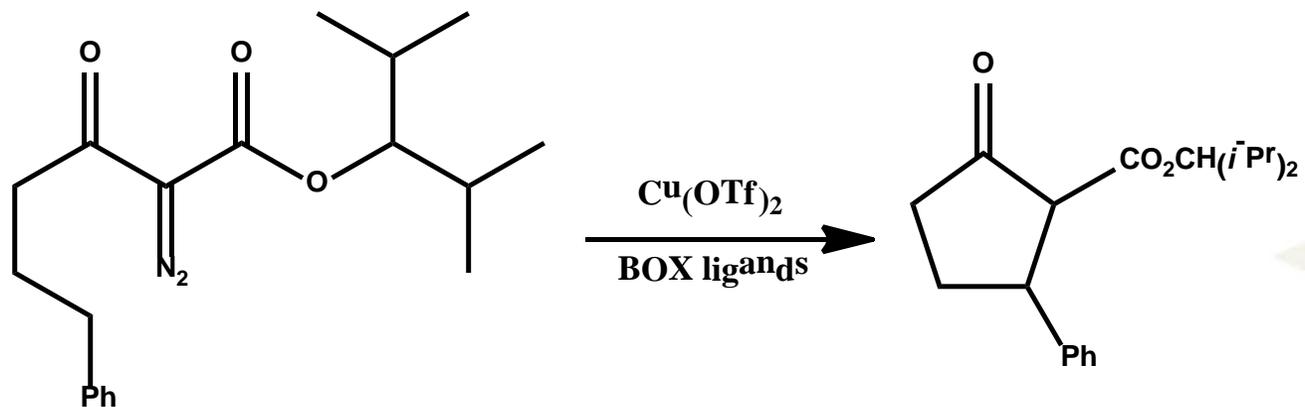
# Copper Bis(oxazoline)-Catalysed Cyclopropanation



# Copper Bis(oxazoline)-Catalysed Cyclopropanation



# Copper Bis(oxazoline)-Catalysed C–H Insertion

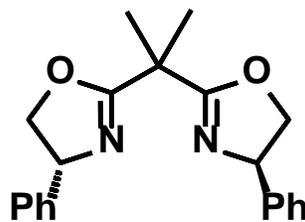


17-38% yield

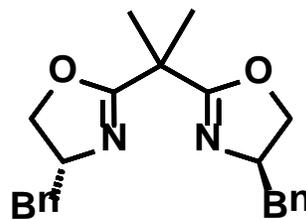
15-60% ee

Müller, P.; Boléa, C. *Molecules* **2001**, *6*, 258.

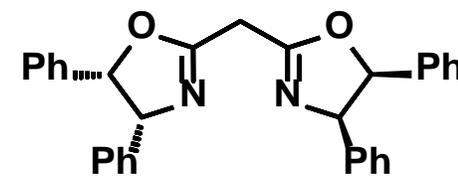
# C–H Insertion: *Enantioselective Copper Catalysis*



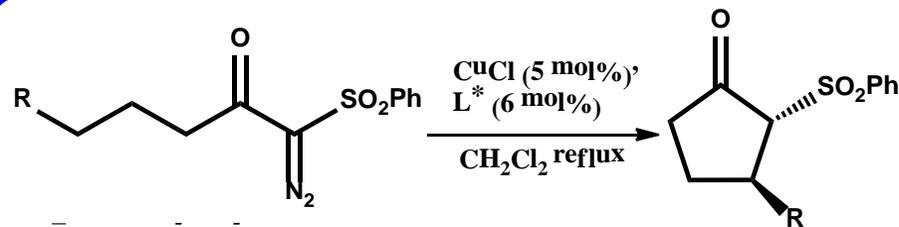
0–5% ee



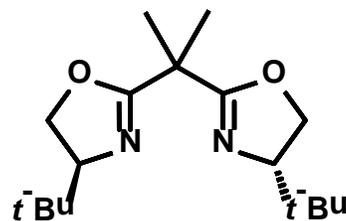
0–8% ee



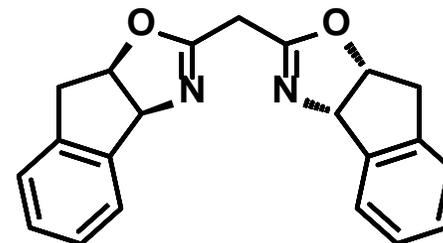
0–33% ee



$R = \text{Me, Et, } i\text{-Pr, } t\text{-Bu, Ph, Bn}$



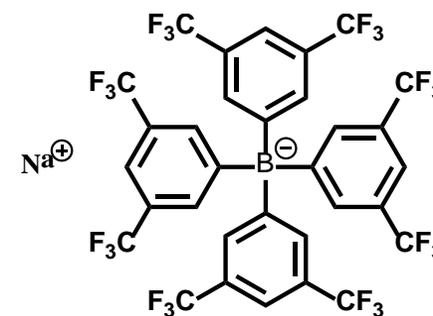
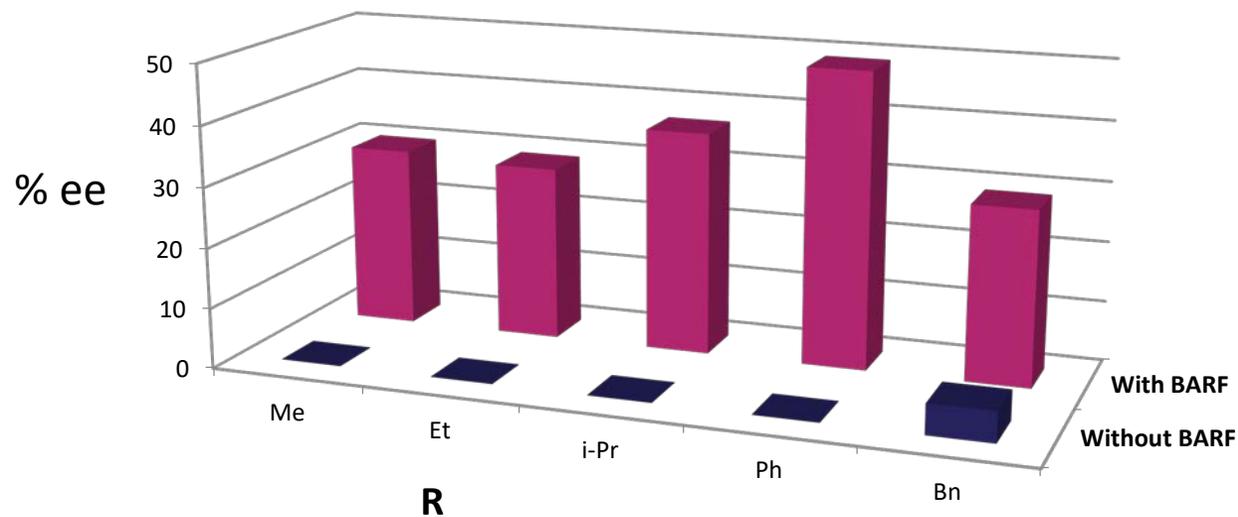
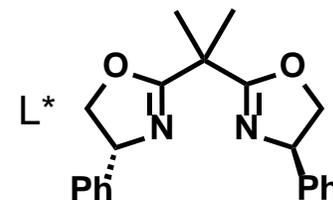
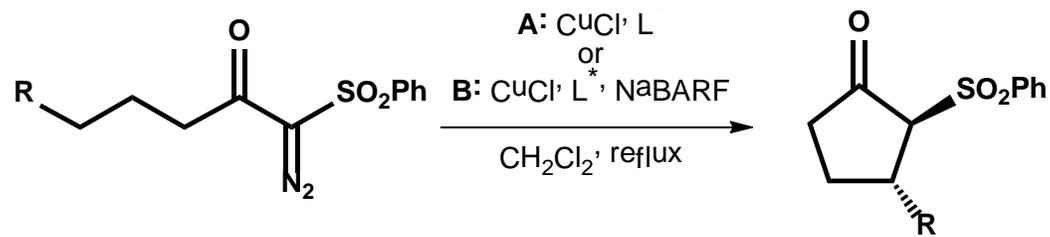
0% ee



0–14% ee

Slattery, C. N.; Maguire, A. R. *Org. Biomol. Chem.* **2011**, *9*, 667.

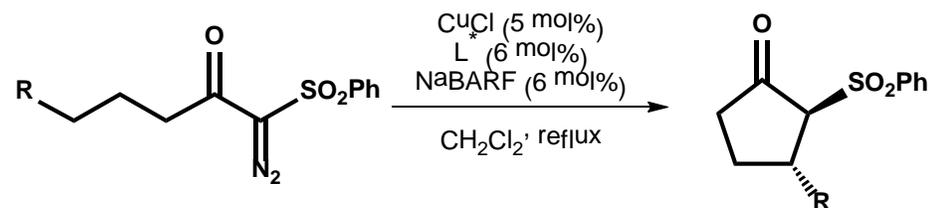
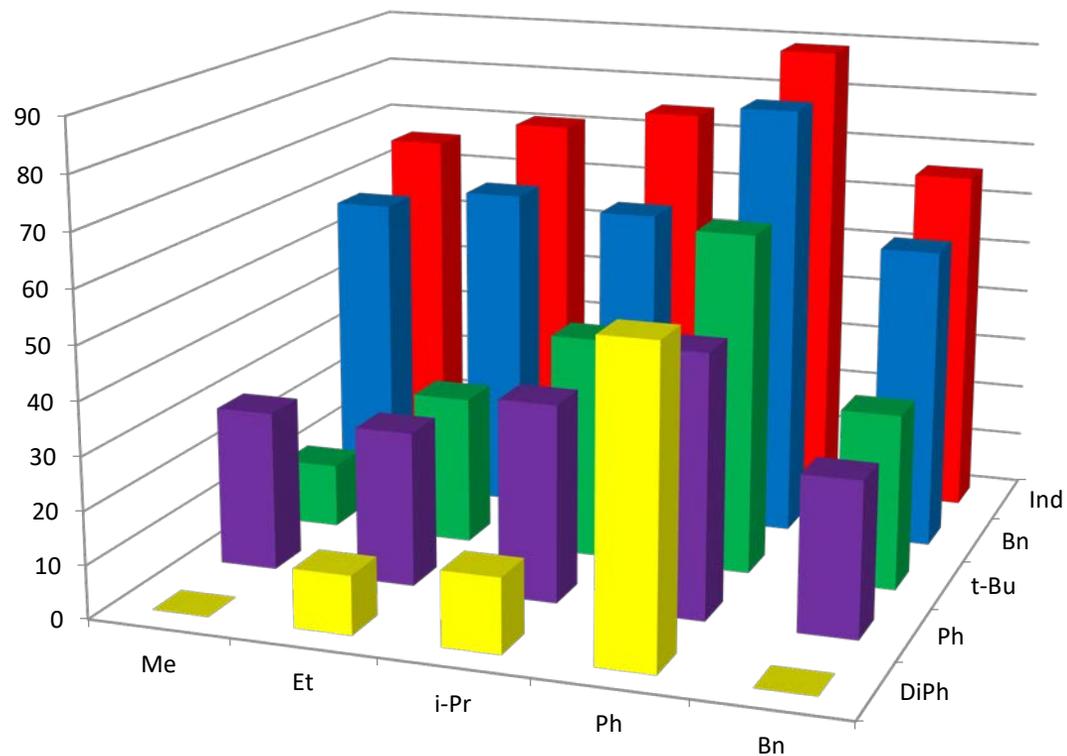
# Cyclopentanone Synthesis: *Effect of NaBARF*



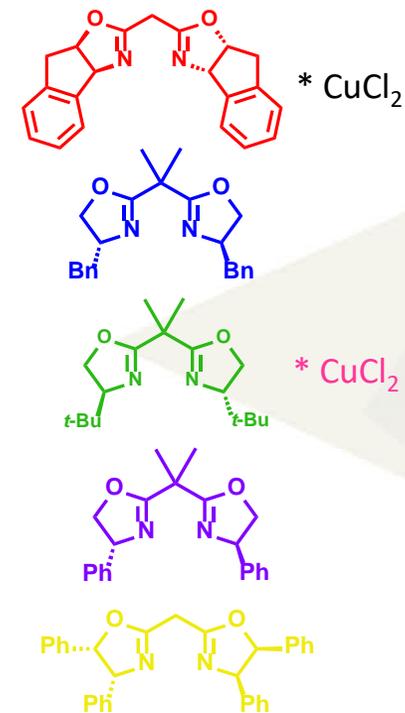
*Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate*

Slattery, C. N.; Maguire, A. R. *Org. Biomol. Chem.* **2011**, *9*, 667.

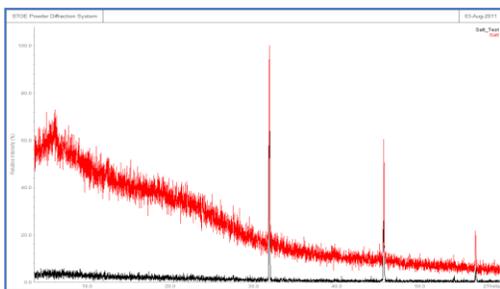
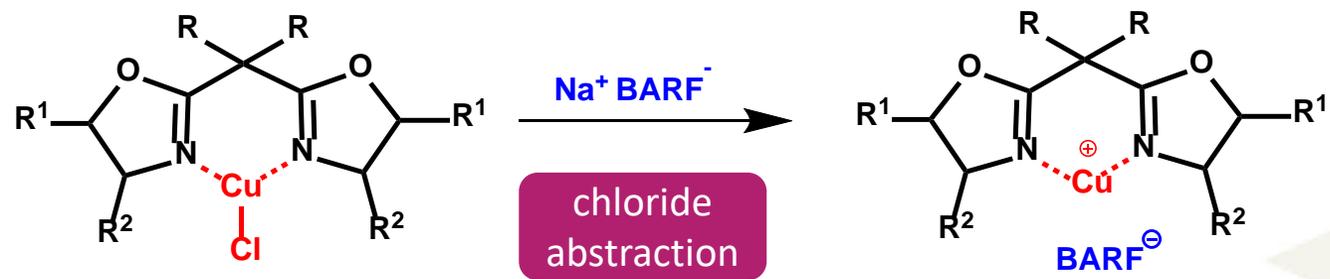
# Observed Trends in Enantioselectivity



Slattery, C. N.; Maguire, A. R. *Org. Biomol. Chem.* **2011**, *9*, 667.



# Enantiocontrol in C–H Insertion Reactions: *Additive Effects*

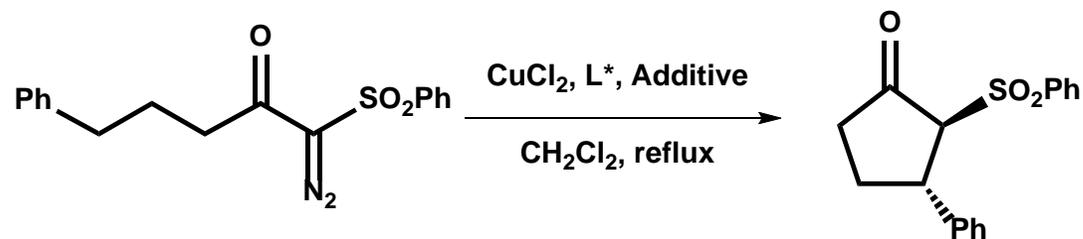


***PXRD of isolated NaCl***



Slattery, C. N.; Clarke, L-A.; O'Neill, S.; Ring, A.; Ford, A.; Maguire, A. R. *Synlett* **2012**, 23, 765.  
Slattery, C. N.; Clarke, L-A.; Ford, A.; Maguire, A. R. *Tetrahedron*, **2013**, 69, 1297.

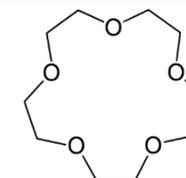
# Enantiocontrol in C–H Insertion Reactions: *Additive Effects*



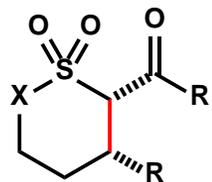
Additive	Time (h)			Yield <sup>a</sup> (%)			ee <sup>b</sup> (%)		
<b>L*</b>									
–	21	21	30	62	57	48	14 (2 <i>R</i> ,3 <i>R</i> )	9 (2 <i>S</i> ,3 <i>S</i> )	~0
NaBARF	2	2	2	87	65	69	89 (2 <i>R</i> , 3 <i>R</i> )	79 (2 <i>S</i> , 3 <i>S</i> )	57 (2 <i>S</i> , 3 <i>S</i> )
NaBARF + 15-crown-5 <sup>c</sup>	20	48	20	63	50	62	25 (2 <i>R</i> , 3 <i>R</i> )	28 (2 <i>S</i> , 3 <i>S</i> )	20 (2 <i>S</i> , 3 <i>S</i> )

<sup>a</sup> Isolated after flash chromatography, <sup>b</sup> Determined by chiral HPLC, <sup>c</sup> 8 mol% 15-crown-5 added to catalytic complex

15-crown-5

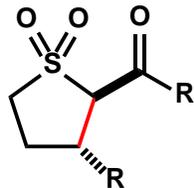


Slattery, C. N.; Clarke, L-A.; O'Neill, S.; Ring, A.; Ford, A.; Maguire, A. R. *Synlett* **2012**, 23, 765.  
Slattery, C. N.; Clarke, L-A.; Ford, A.; Maguire, A. R. *Tetrahedron*, **2013**, 69, 1297.

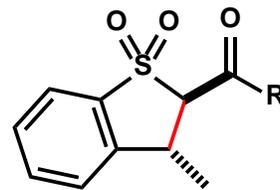


X = CH<sub>2</sub>, O

Up to 98% ee

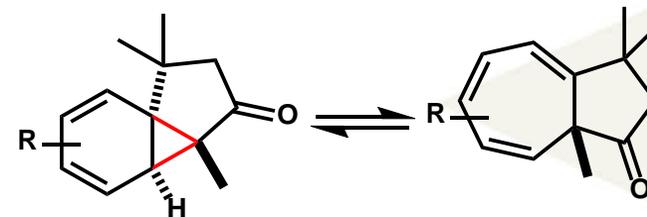
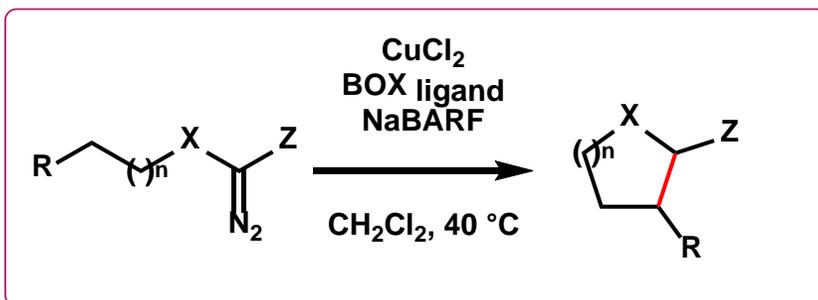


Up to 77% ee

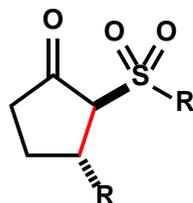


Up to 80% ee

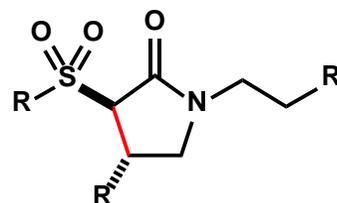
Flynn, C. J.; Elcoate, C. J.; Lawrence, S. E.; Maguire, A. R. *J. Am. Chem. Soc.*, **2010**, *132*, 1184.



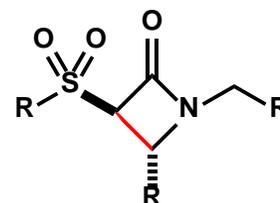
Up to 95% ee



Up to 91% ee



Up to 91% ee

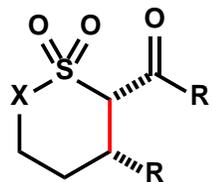


Up to 84% ee

Slattery, C. N.; Maguire, A. R. *Org. Biomol. Chem.* **2011**, *9*, 667-669.

Clarke, L. A.; Ring, A.; Ford, A.; Sinha, A. S.; Lawrence, S. E.;

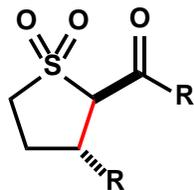
Maguire, A. R. *Org. Biomol. Chem.* **2014**, *12*, 7612.



X = CH<sub>2</sub>, O

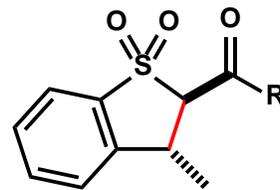
Up to 98% ee

Best ligand: Ph/diPh



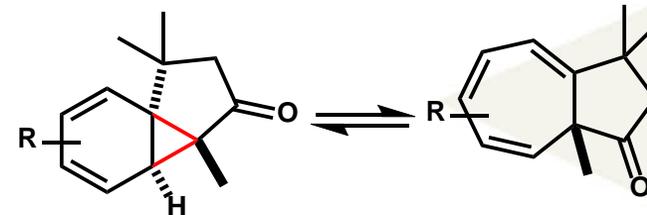
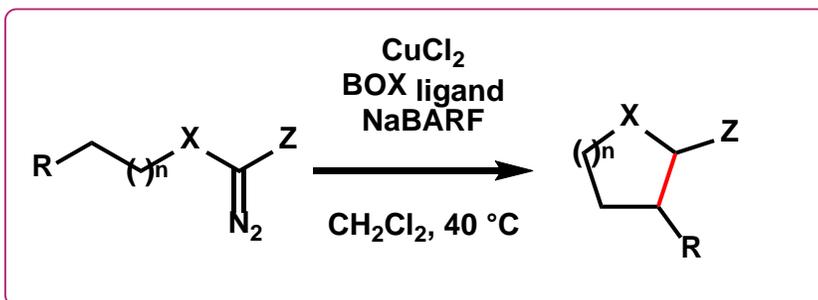
Up to 77% ee

Best ligand: variable



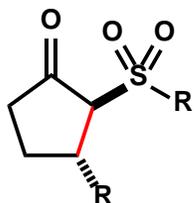
Up to 80% ee

Best ligand: Ph/diPh



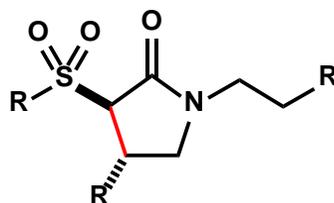
Up to 95% ee

Best ligand: Ph



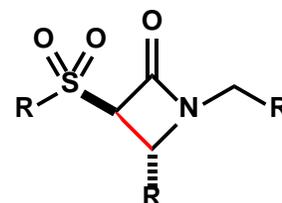
Up to 91% ee

Best ligand: Bn/Ind



Up to 91% ee

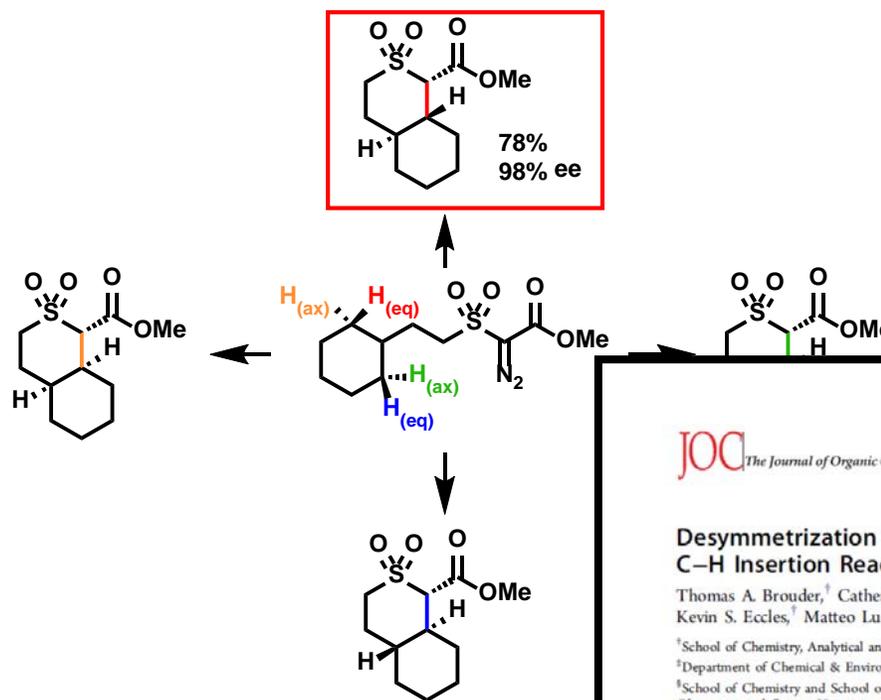
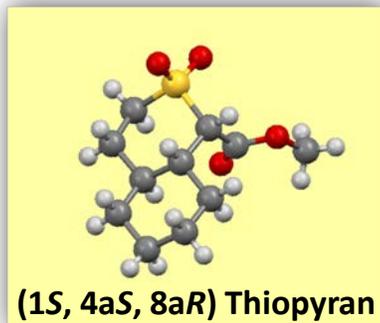
Best ligand: *t*-Bu/Ind



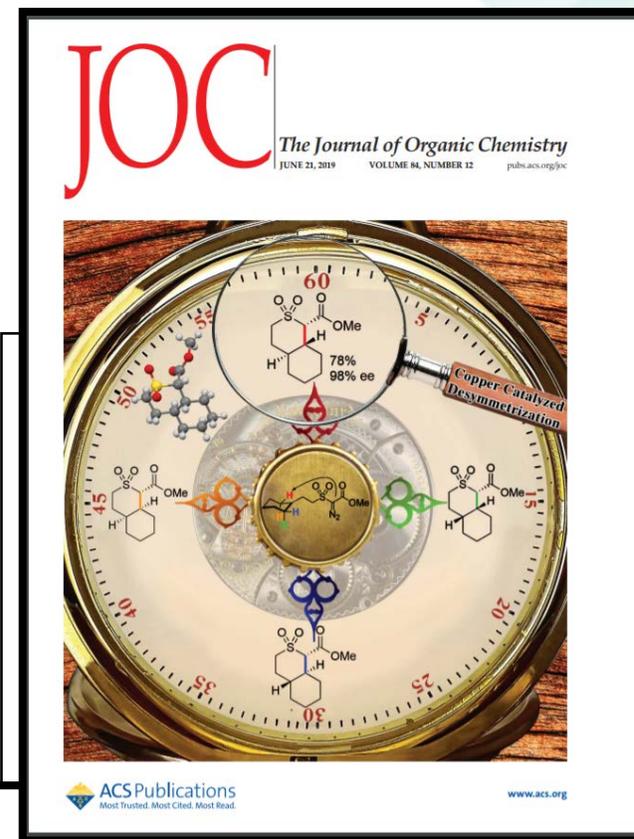
Up to 84% ee

Best ligand: Ph/Bn

# Desymmetrisation



Brouder, T. A.; Slattery, C. N.; Ford, A.; Khandavilli, U. B. R.; Skorepova, E.; Eccles, K. S.; Lusi, M.; Lawrence, S. E.; Maguire, A. R. *J. Org. Chem.* **2019**, *84*, 7543.



JOC The Journal of Organic Chemistry

Cite This: *J. Org. Chem.* XXXX, XXX, XXX-XXX

Featured Article  
pubs.acs.org/joc

## Desymmetrization by Asymmetric Copper-Catalyzed Intramolecular C–H Insertion Reactions of $\alpha$ -Diazo- $\beta$ -oxosulfones

Thomas A. Brouder,<sup>†</sup> Catherine N. Slattery,<sup>†</sup> Alan Ford,<sup>†</sup> U. B. Rao Khandavilli,<sup>†</sup> Eliška Skorepová,<sup>†</sup> Kevin S. Eccles,<sup>†</sup> Matteo Lusi,<sup>‡</sup> Simon E. Lawrence,<sup>†</sup> and Anita R. Maguire<sup>\*-§</sup>

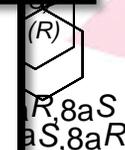
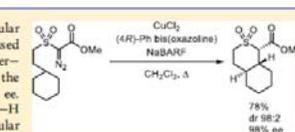
<sup>†</sup>School of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork T12 K8AF, Ireland

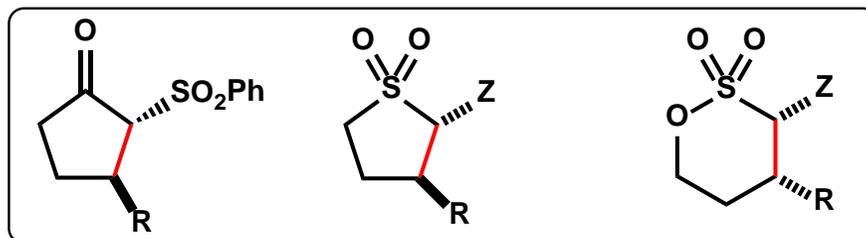
<sup>‡</sup>Department of Chemical & Environmental Sciences, University of Limerick, Limerick V94 T9PX, Ireland

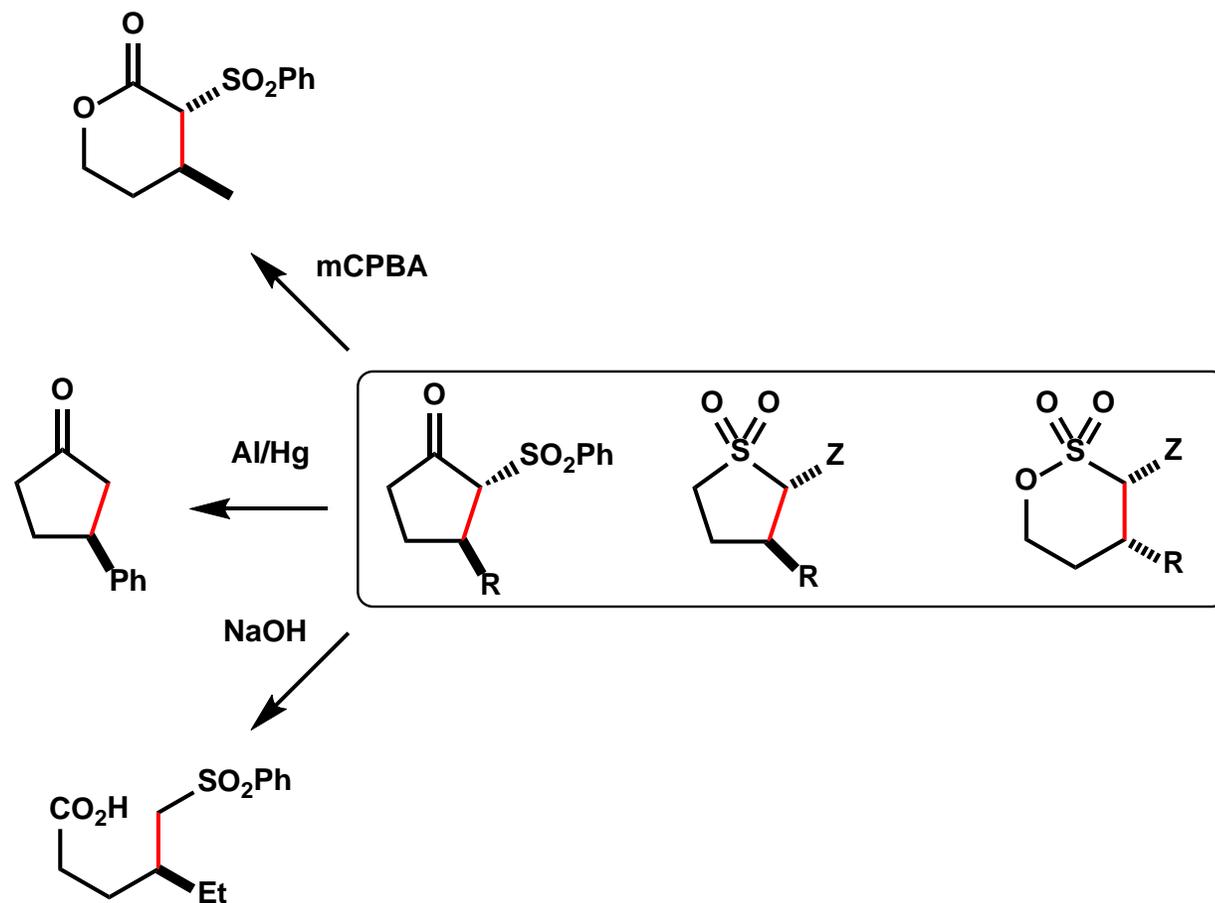
<sup>§</sup>School of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, Synthesis and Solid State Pharmaceutical Centre, University College Cork, Cork T12 K8AF, Ireland

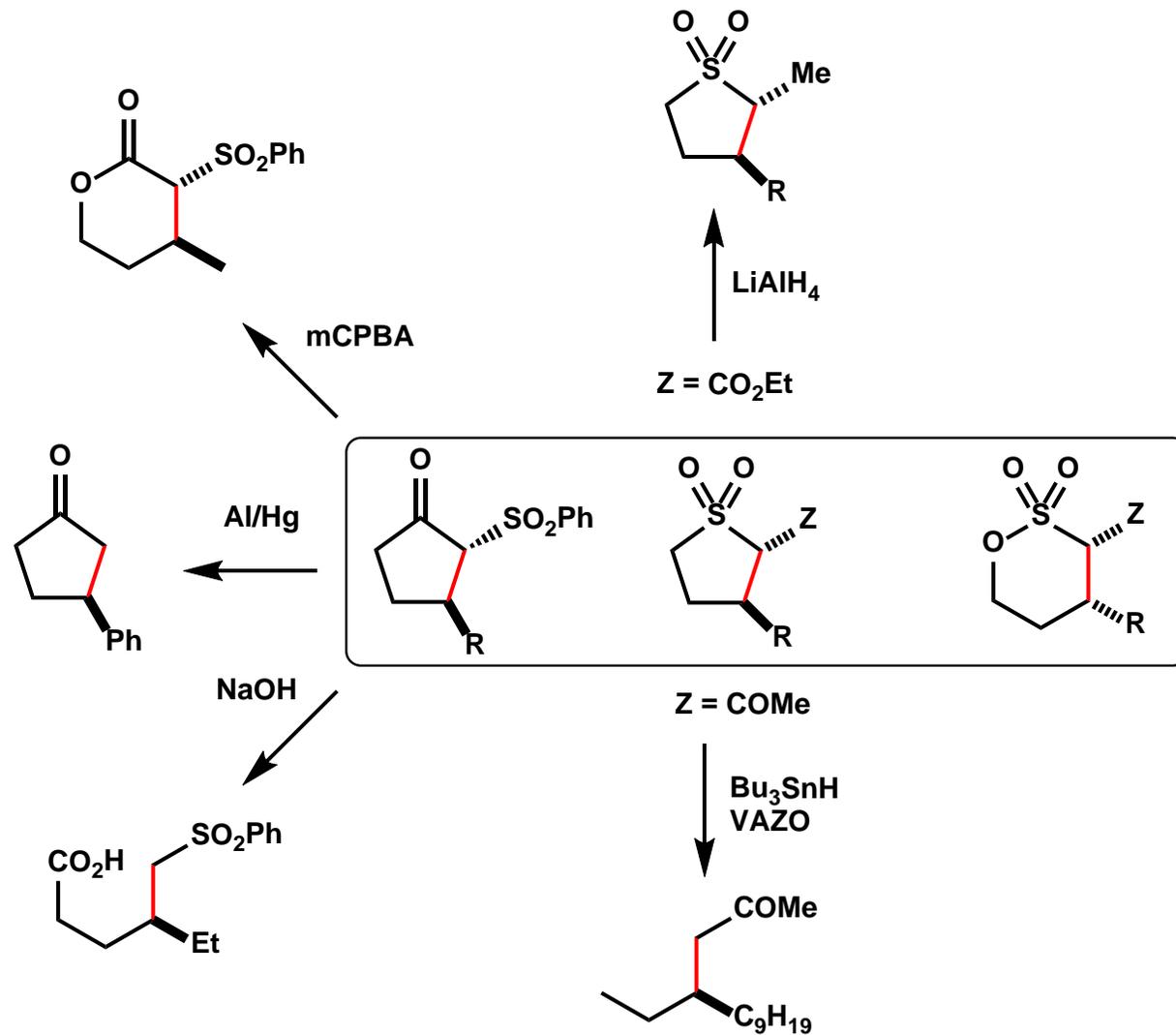
### Supporting Information

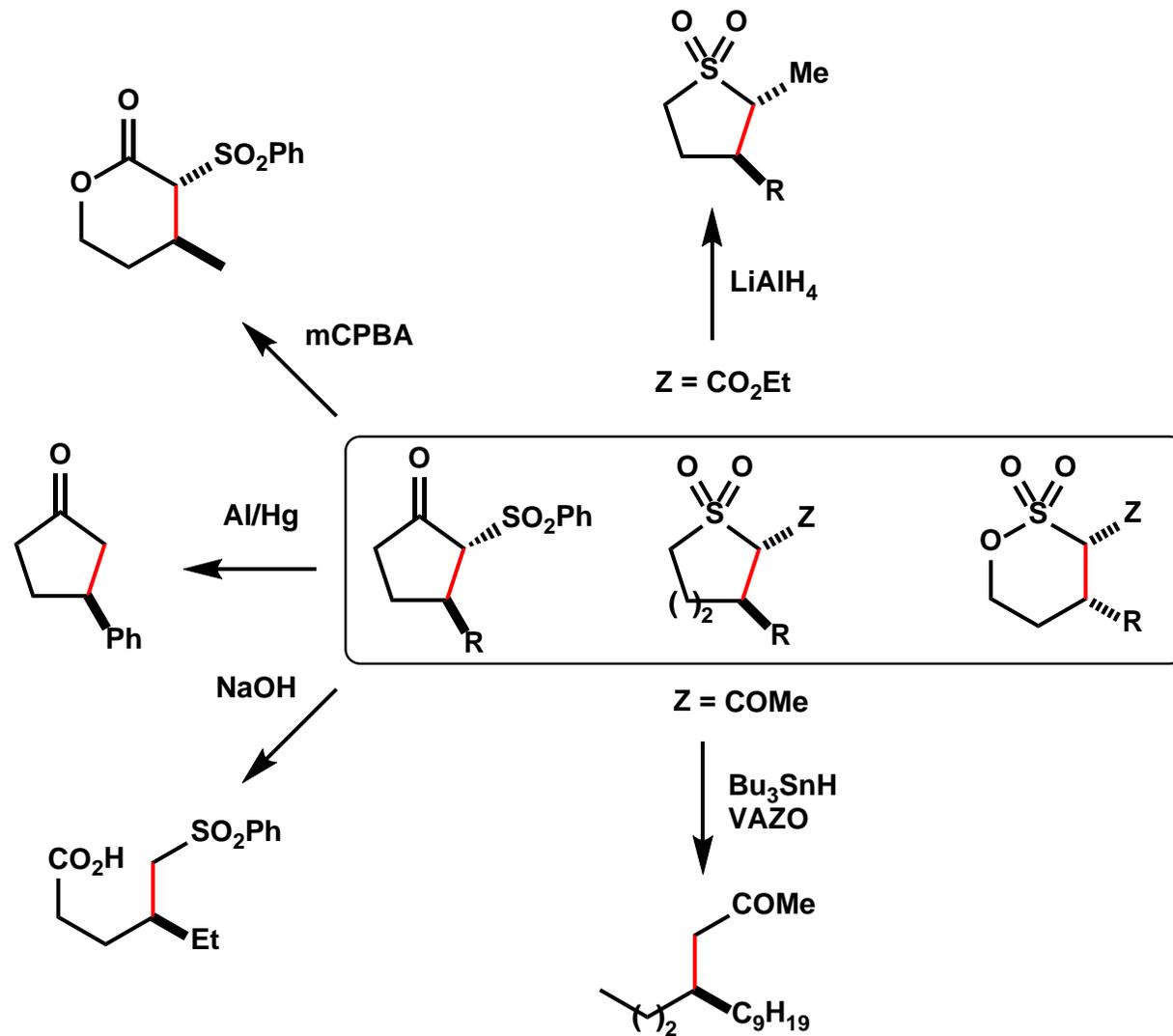
**ABSTRACT:** Effective desymmetrization in copper-catalyzed intramolecular C–H insertion reactions of  $\alpha$ -diazo- $\beta$ -oxosulfones in the formation of fused thiopyran dioxides is described for the first time. The use of a copper–bis(oxazoline)–NaBARF catalyst system leads to formation of the major thiopyran dioxide stereoisomer with up to 98:2 dr and up to 98% ee. The effect of varying the bis(oxazoline) ligand, copper salt, and site of C–H insertion on both diastereo- and enantioselectivities of these intramolecular C–H insertion reactions has been investigated. Similarly, desymmetrization in the formation of a fused cyclopentanone proceeds with up to 64% ee. These results represent the highest enantioselectivity reported to date in a copper-mediated desymmetrization through C–H insertion.

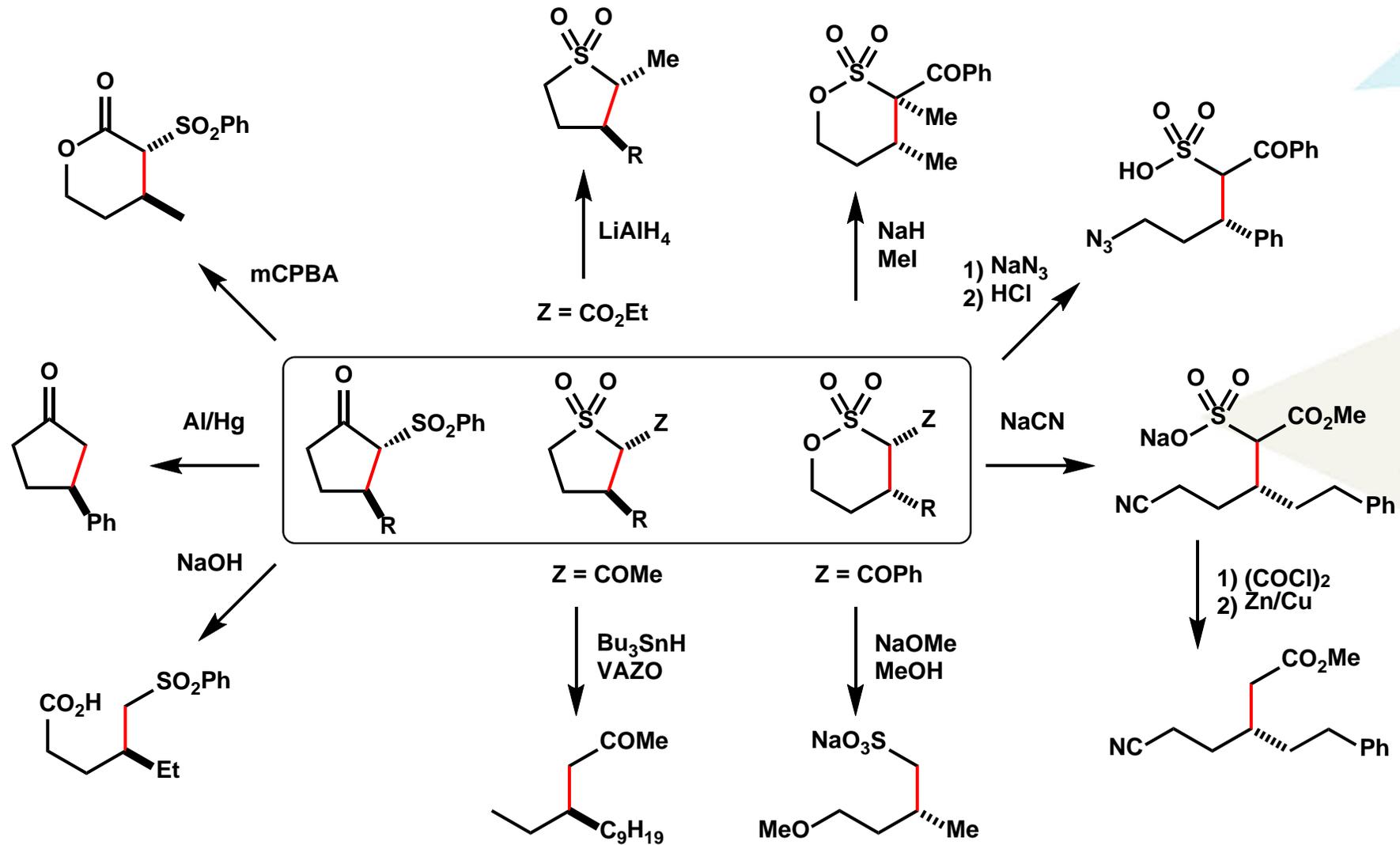




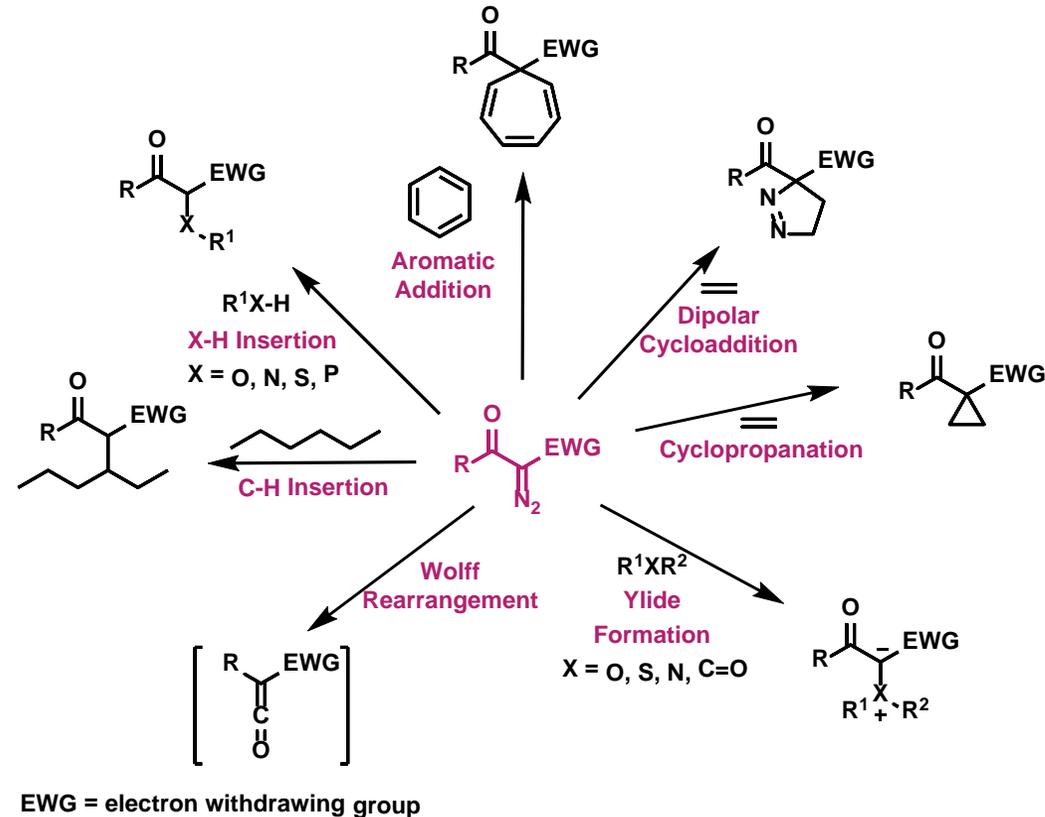








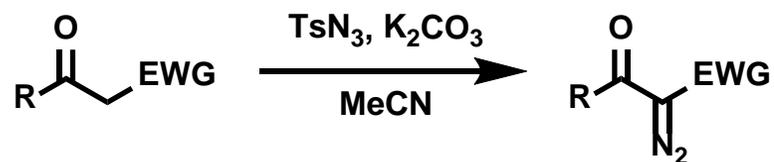
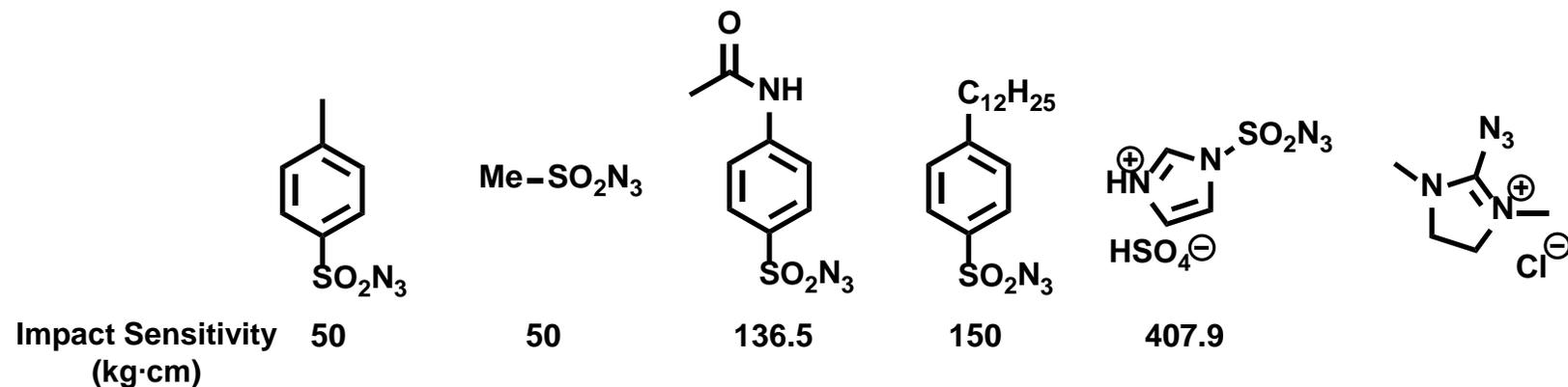
# $\alpha$ -Diazocarbonyl Compounds – *Versatile Synthetic Intermediates*



Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKerver, M. A. *Chem. Rev.*, **2015**, *115*, 9981.

# Regitz Diazo Transfer

Diazo Transfer Reagents:



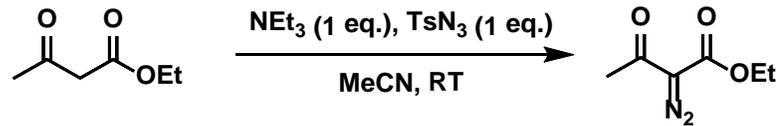
Heydt, H.; Regitz, M.; Mapp, A. K.; Chen, B. *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, Chichester, UK, **2008**.

Bollinger, F. W.; Tuma, L. D. *Synlett*, **1996**, 407.

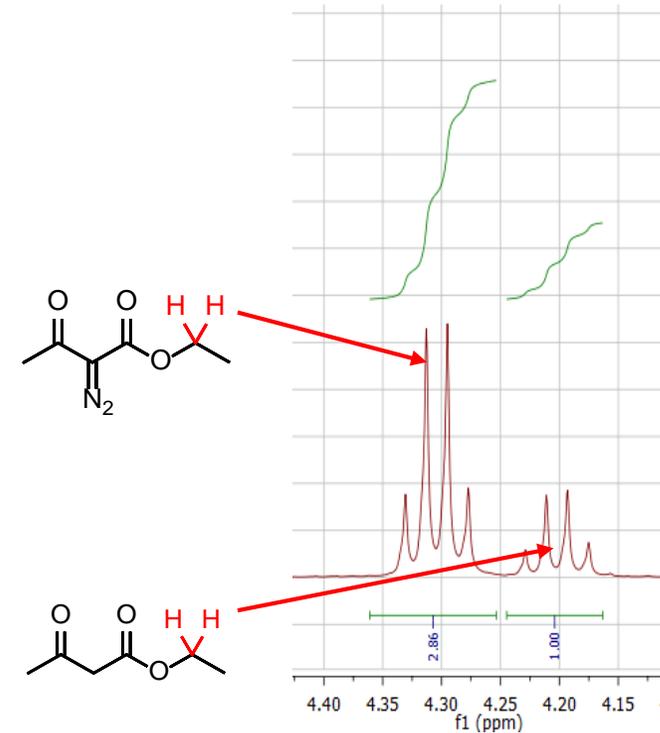
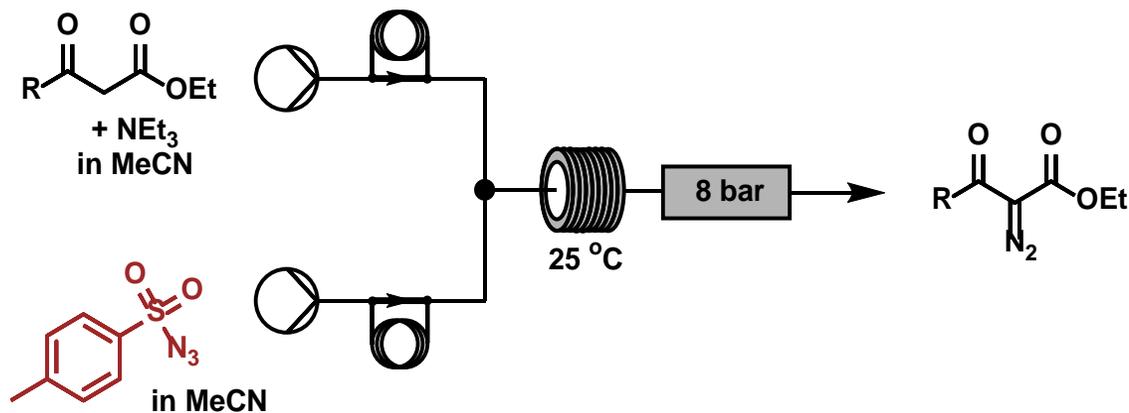
Fischer, N.; Goddard-Borger, E. D.; Greiner, R.; Klapötke, T. M.; Skelton, B. W.; Stierstorfer, J. *J. Org. Chem.*, **2012**, *77*, 1760.

Kitamura, M.; Tashiro, N.; Miyagawa, S.; Okauchi, T. *Synthesis* **2011**, *7*, 1037.

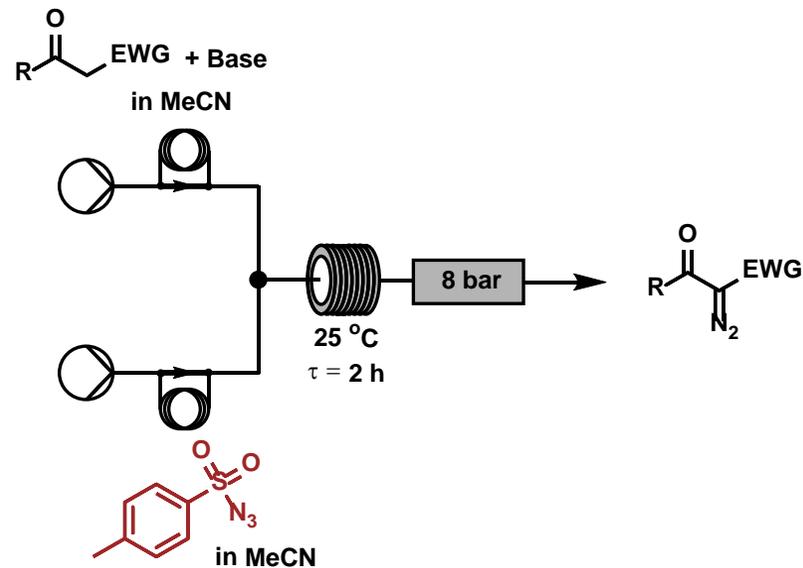
# Comparisons of Batch and Flow Diazo Transfer



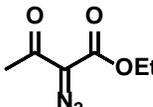
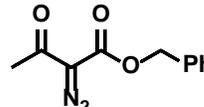
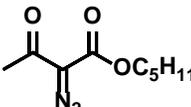
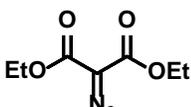
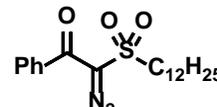
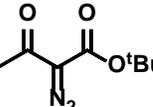
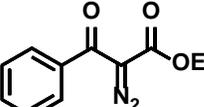
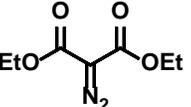
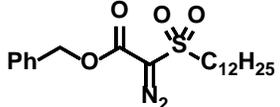
Entry No.	Conditions	Time	% Conversion
1	Batch	140 mins	97
2	Batch	25 mins	52
3	Flow	25 mins	57
4	Batch	50 mins	88
5	Flow	50 mins	84



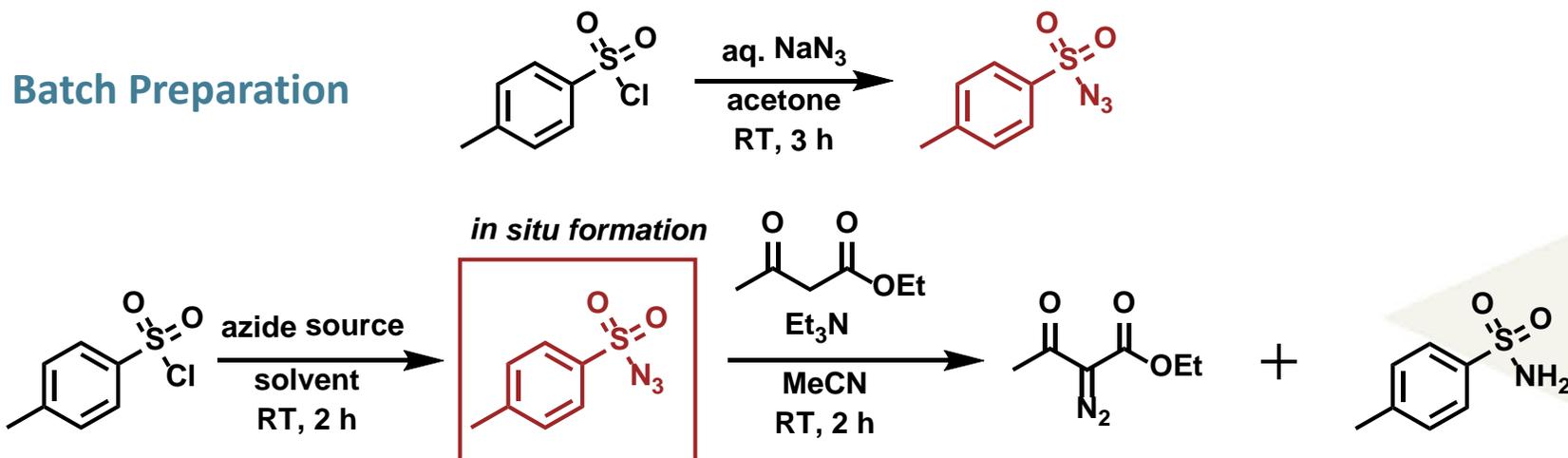
# Continuous Diazo Transfer Reaction- 1<sup>st</sup> Generation Process



Conversion by <sup>1</sup>H NMR  
Isolated Yield

Base = Et <sub>3</sub> N			Base = DBU	
				
100%	100%	95%	100%	100%
54%	61%	84%	53%	50%
				
80%	100%	20%	100%	
46%	61%		65%	

# *In Situ* Tosyl Azide Generation – 2<sup>nd</sup> Generation Process



$(\text{Bu}_4\text{N})\text{N}_3$   
in MeCN

**Desired  
product not  
observed**

$\text{NaN}_3$   
in  $\text{H}_2\text{O}/\text{MeCN}$

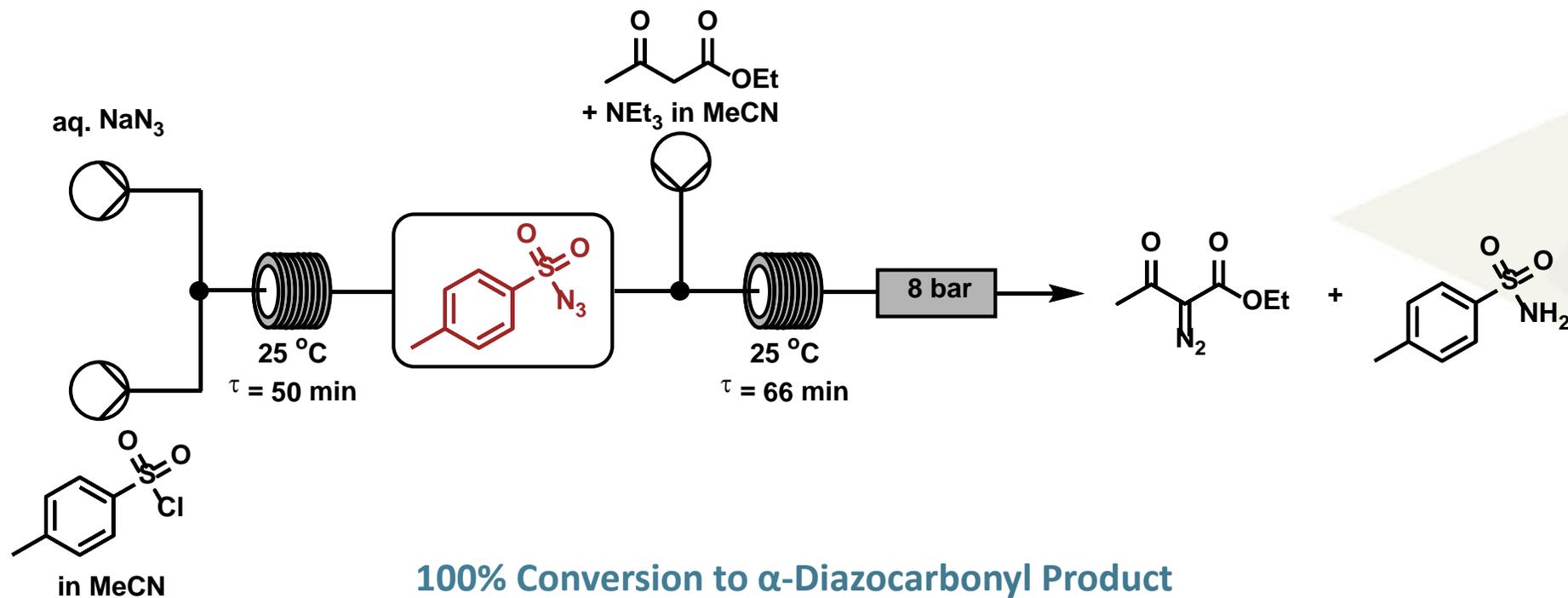
**100%  
conversion**

- Demonstrated in NMP by Monbaliu and co-workers.

Curphey, T. J. *J. Org. Prep. Proced. Int.*, **1981**, *13*, 112.

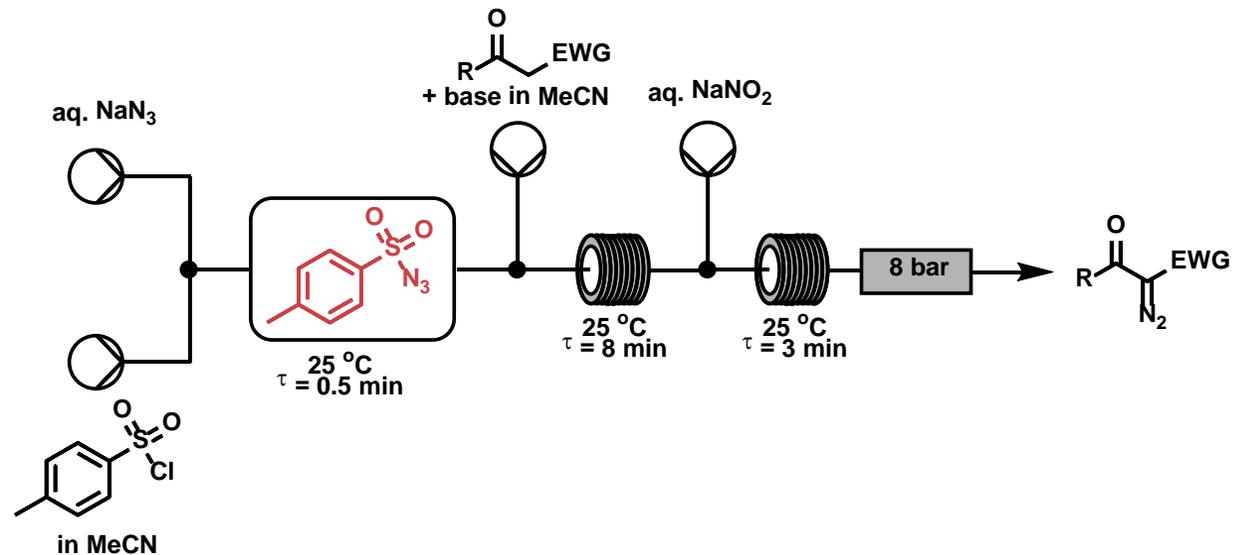
Gérardy, R.; Winter, M; Vizzab A.; Monbaliu, J.-C. M. *React. Chem. Eng.* **2017**, *2*, 149-158.

# 2<sup>nd</sup> Generation Process – Telescoped Generation & Use of Tosyl Azide

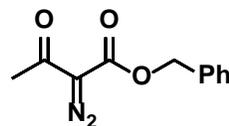


Deadman, B. J.; O'Mahony, R. M.; Lynch, D.; Crowley, D. C.; Collins, S. G.; Maguire, A. R.  
*Org. Biomol. Chem.*, **2016**, *14*, 3423.

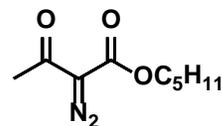
# Substrate Scope - 2<sup>nd</sup> Generation Process



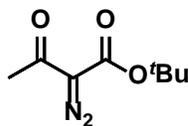
Conversion by <sup>1</sup>H NMR



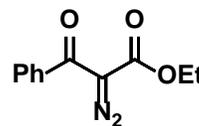
80%



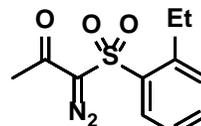
91%



80%

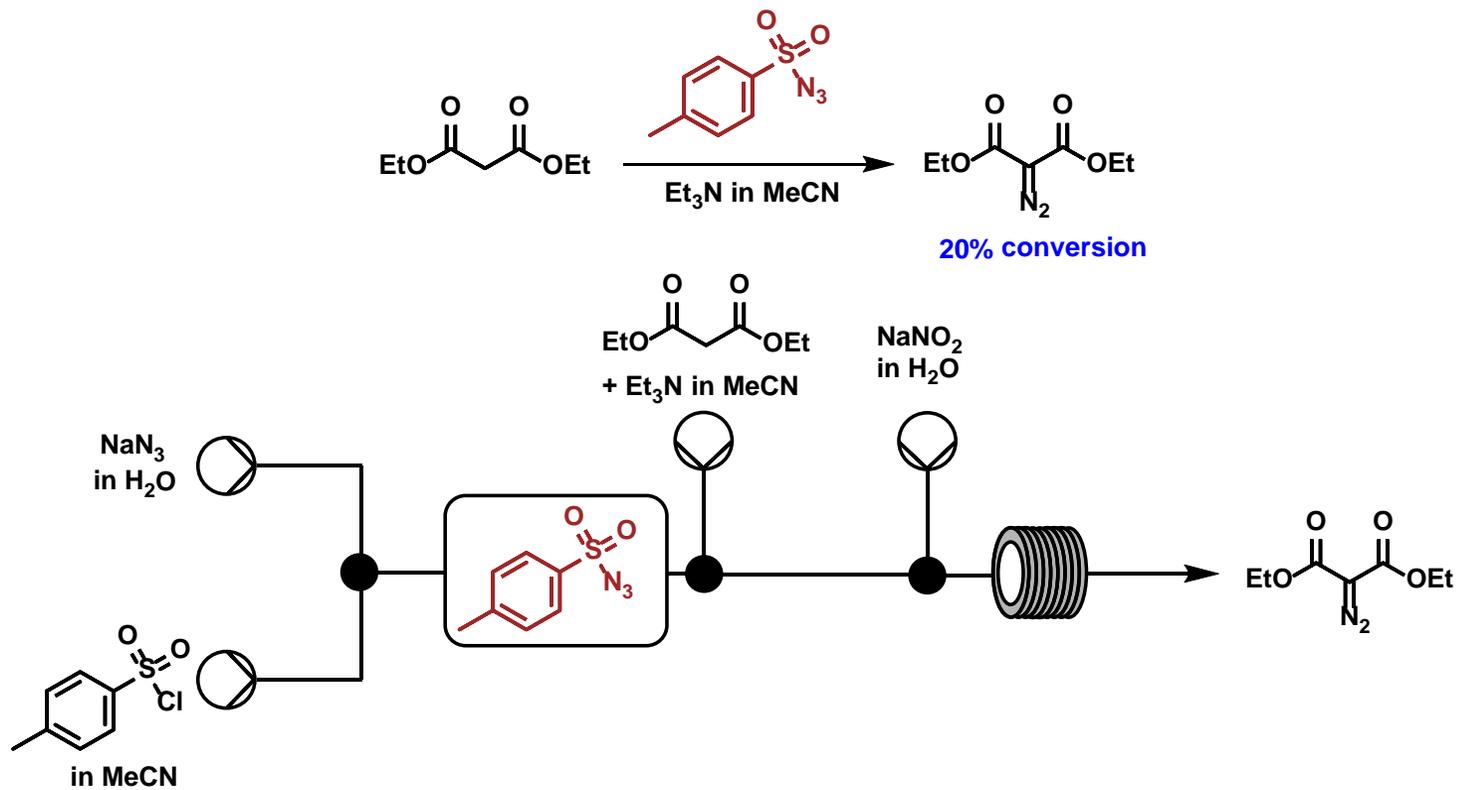


63%



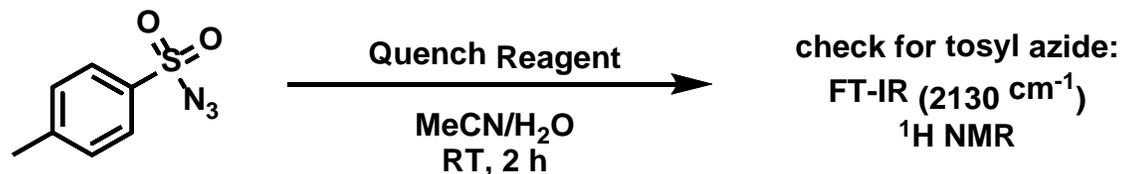
87%

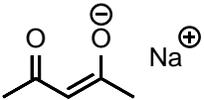
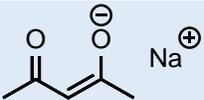
# Diazo Transfer to Diethyl Malonate



- Diazo transfer to diethyl malonate using  $\text{Et}_3\text{N}$  poorly efficient (20%)
- $\text{NaNO}_2$  used to quench free azide
- Residual tosyl azide?

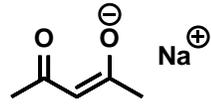
# Design of Sulfonyl Azide Quench



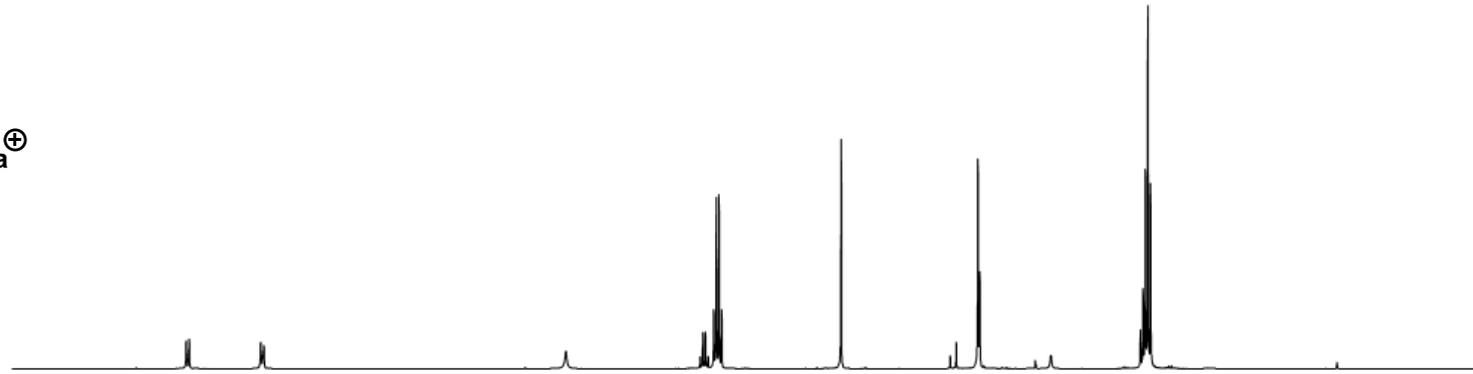
Entry	Quench	Time (min)	Result
1	-	120	tosyl azide remaining
2	$\text{NaNO}_2$	120	tosyl azide remaining
3	$\text{NaNO}_2/\text{H}_2\text{SO}_4$	120	tosyl azide remaining
4		120	100% tosyl azide consumed
5		2	100% tosyl azide consumed

Deadman, B. J.; O'Mahony, R. M.; Lynch, D.; Crowley, D. C.; Collins, S. G.; Maguire, A. R. *Org. Biomol. Chem.*, **2016**, *14*, 3423.

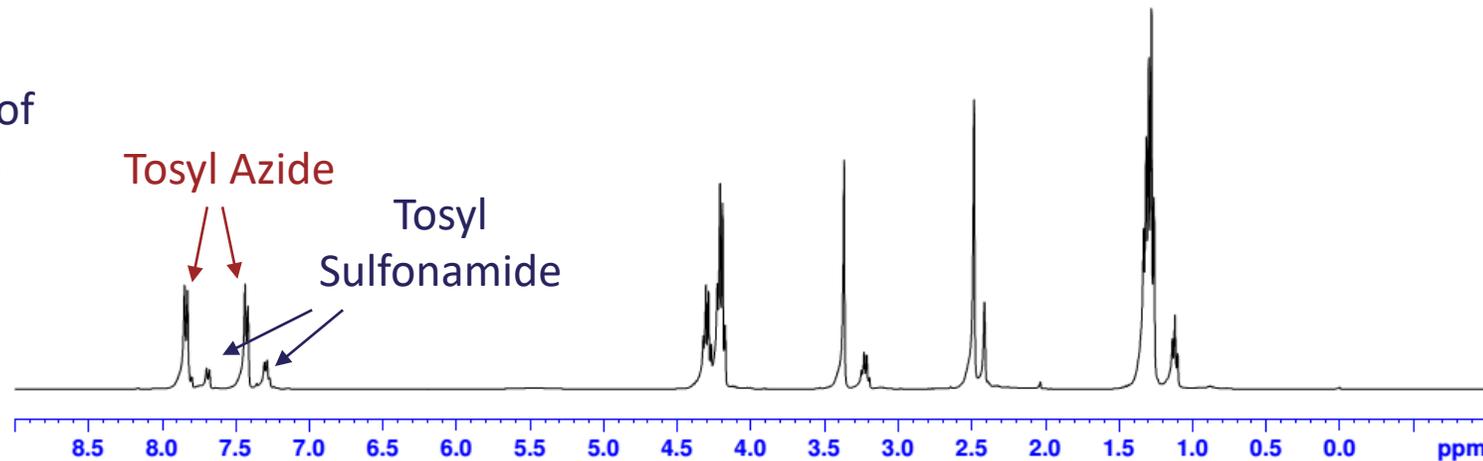
# Design of Sulfonyl Azide Quench



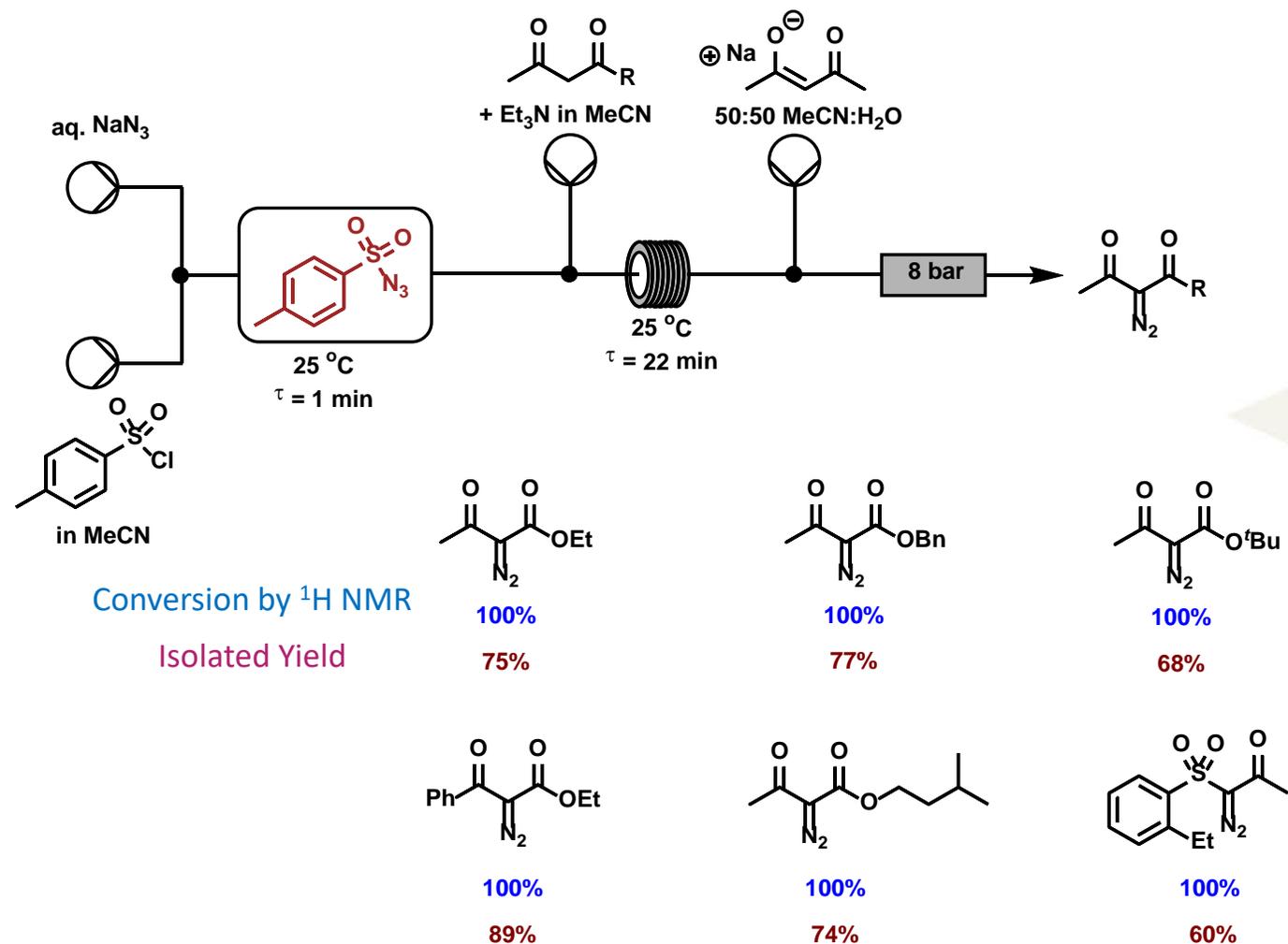
quench



absence of  
quench

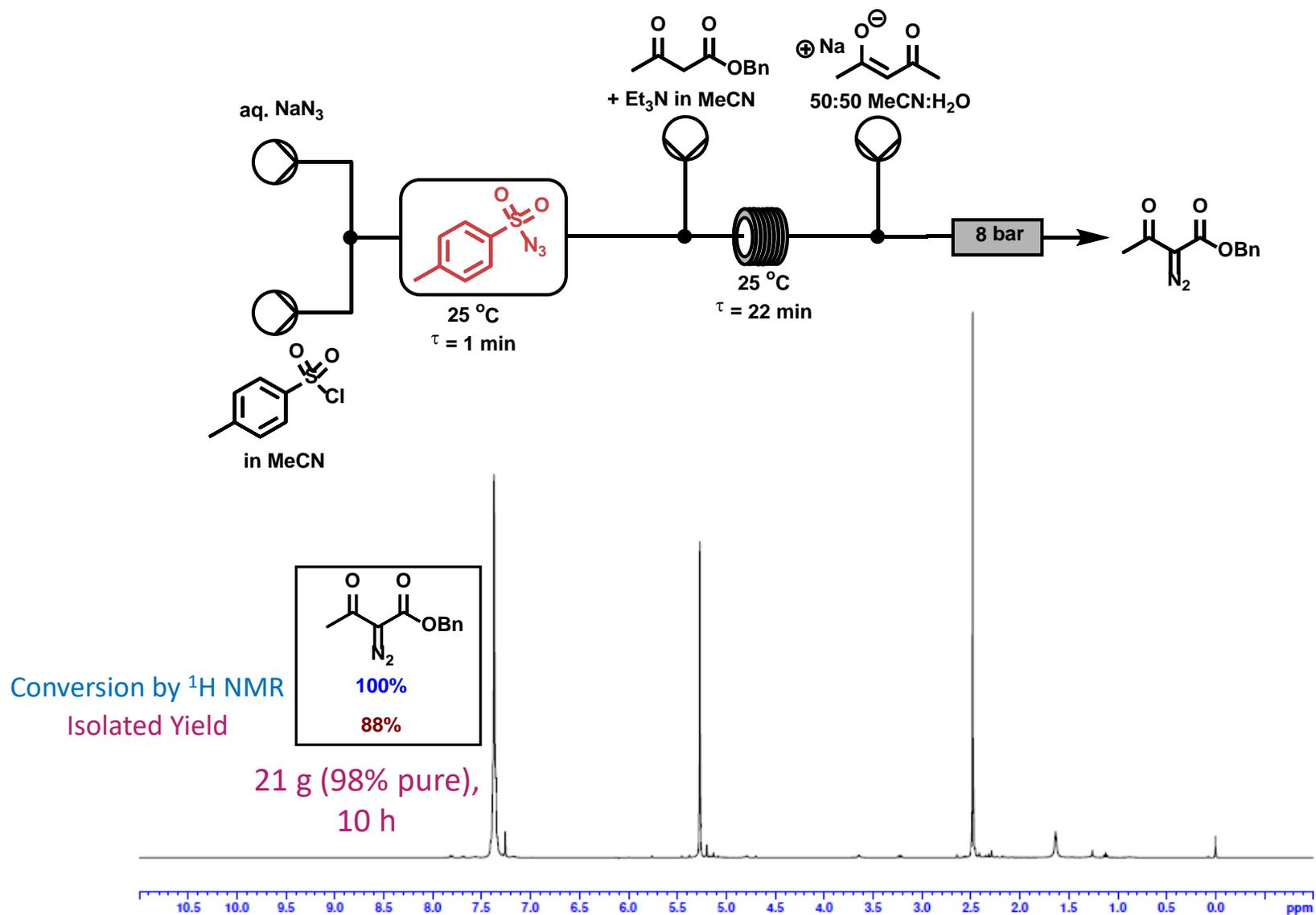


# Telescoped Generation & Use of Tosyl Azide

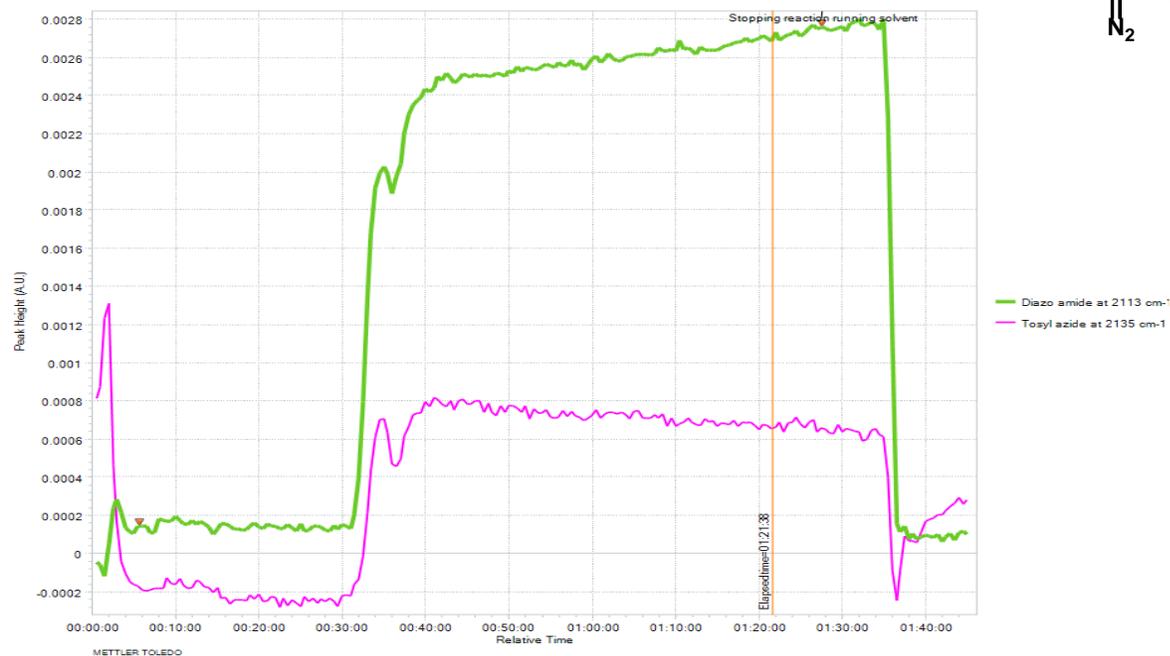
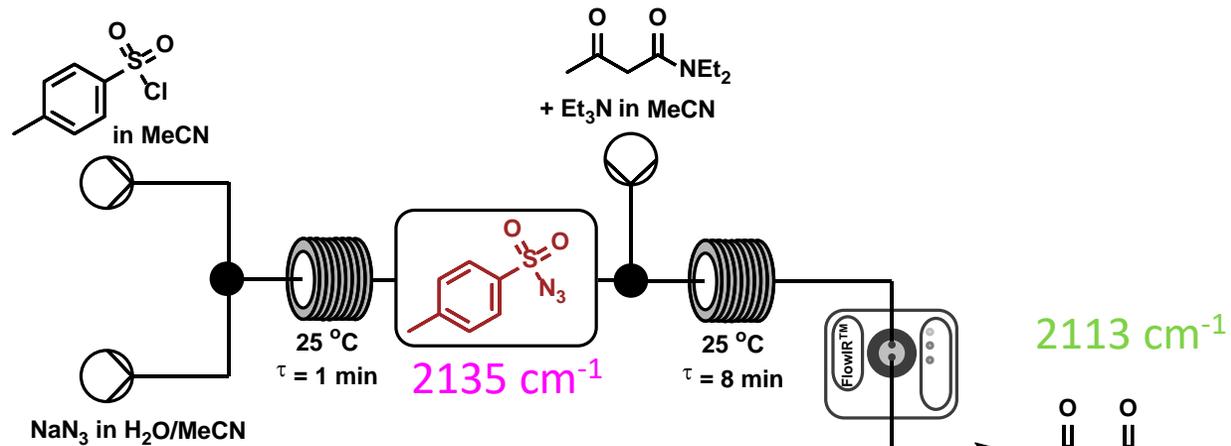


Deadman, B. J.; O'Mahony, R. M.; Lynch, D.; Crowley, D. C.; Collins, S. G.; Maguire, A. R. *Org. Biomol. Chem.*, **2016**, *14*, 3423.

# Telescoped Generation & Use of Tosyl Azide



# In-Line IR Spectroscopy



# Diazo Transfer – Summary

## Safety

- Isolation and handling of sulfonyl azide reagent avoided
- Mild reaction conditions – room temperature
- Rapid formation of tosyl azide *in situ*
- Sacrificial quench system developed – by products safely destroyed

## Efficiency

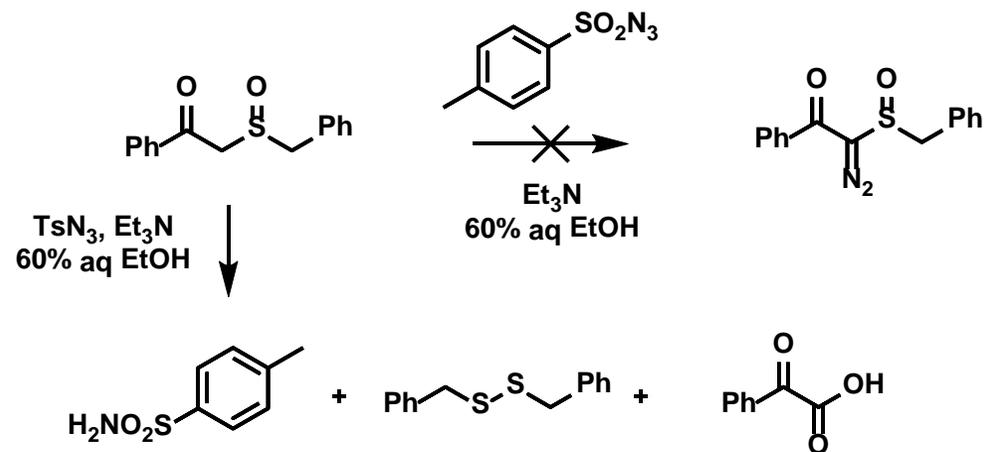
- Complete diazo transfer in under 22 min
- Applicable to a range of substrates
- Scale-up (>20 g) successfully executed in 10 h

## Control & Ability to Monitor

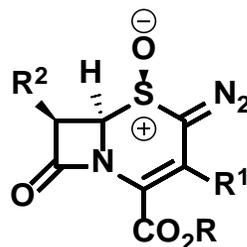
- In-line IR spectroscopy enables monitoring of tosyl azide – reaction control

# $\alpha$ -Diazosulfoxides

- First report of diazo transfer to  $\beta$ -keto sulfoxides was by Hodson and Holt



- First isolated and characterized  $\alpha$ -diazosulfoxide was a cephalosporin derivative



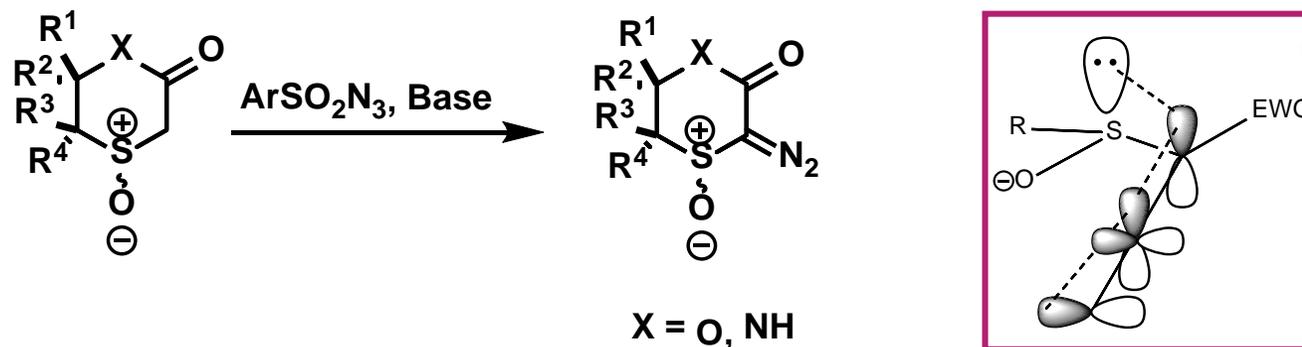
D. Hodson and G. Holt, *J. Chem. Soc. (C)*, **1968**, 1602.

D. H. Bremner and M. M. Campbell, *J. Chem. Soc., Chem. Commun.*, **1976**, 538.

Ebbinghaus, C. F.; Morrissey P.; Rosati, R. L. *J. Org. Chem.*, **1979**, *44*, 2298.

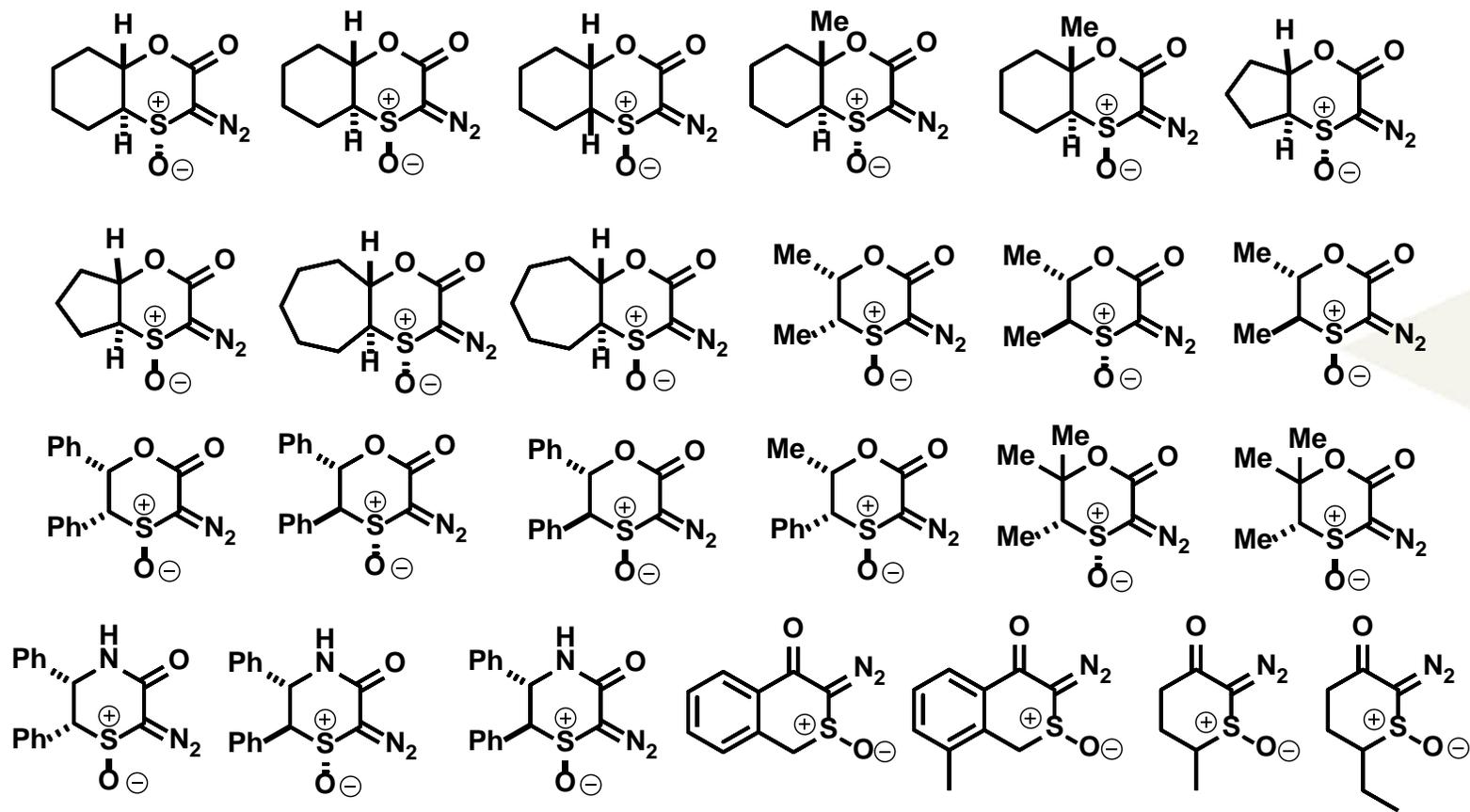
# Stability of $\alpha$ -Diazosulfoxides

- Rigid bicyclic system providing reduced conformational mobility



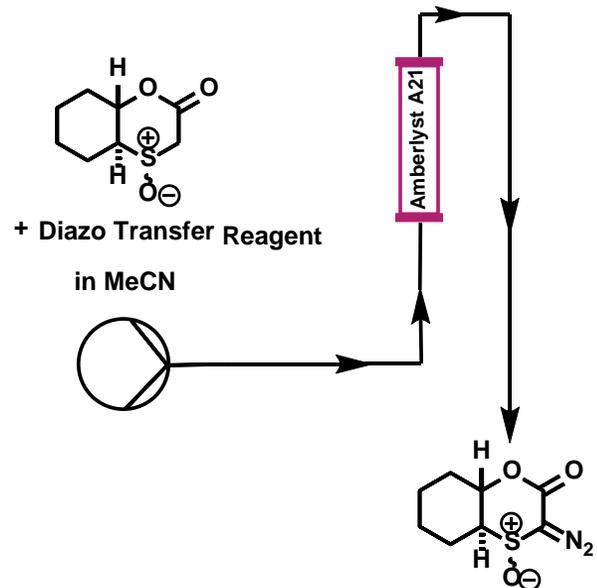
Maguire, A. R.; Kelleher, P. G.; Ferguson, G.; Gallagher, J. F. *Tetrahedron Lett.* **1998**, *39*, 2819.  
Sander, W.; Strehl, A.; Maguire, A. R.; Collins, S.; Kelleher, P. G. *Eur. J. Org. Chem.* **2000**, 3329.  
O'Sullivan, O. C. M.; Collins, S. G.; Maguire, A. R.; Böhm, M.; Sander, W. *Eur. J. Org. Chem.* **2006**, 2918.  
O'Sullivan, O.; Collins, S.; Maguire, A. *Synlett* **2008**, 659.  
Collins, S. G.; O'Sullivan, O. C. M.; Kelleher, P. G.; Maguire, A.R. *Org. Biomol. Chem.* **2013**, *11*, 1706.

# Synthesis of Stable $\alpha$ -Diazosulfoxides



Collins, S. G.; O'Sullivan, O. C. M.; Kelleher, P. G.; Maguire, A. R. *Org. Biomol. Chem.* **2013**, *11*, 1706.  
Buckley, N. M., *PhD. Thesis, National University Ireland Cork*, 2013.

# Batch vs. Continuous Flow



Flow Crude product  
vs. Batch Crude product

- Optimised conditions (5 eq. Amberlyst A21, 9 min res. time) applied.

Product	Conversion in Flow (%) <sup>*</sup>	Yield in Flow (%)	Yield in Batch (%)
	86	76	39
	96	88	28
	100	86	35
	98	86	33

<sup>\*</sup>Determined by <sup>1</sup>H NMR analysis

McCaw, P. G.; Deadman, B. J.; Maguire, A. R.\*; Collins, S. G.\* *J. Flow. Chem.*, **2016**, 6, 226;

McCaw, P. G.; Buckley, N. M.; Eccles, K. S.; Lawrence, S. E.; Maguire, A. R.\*; Collins, S. G.\* *J. Org. Chem.*, **2017**, 82, 7, 3666.

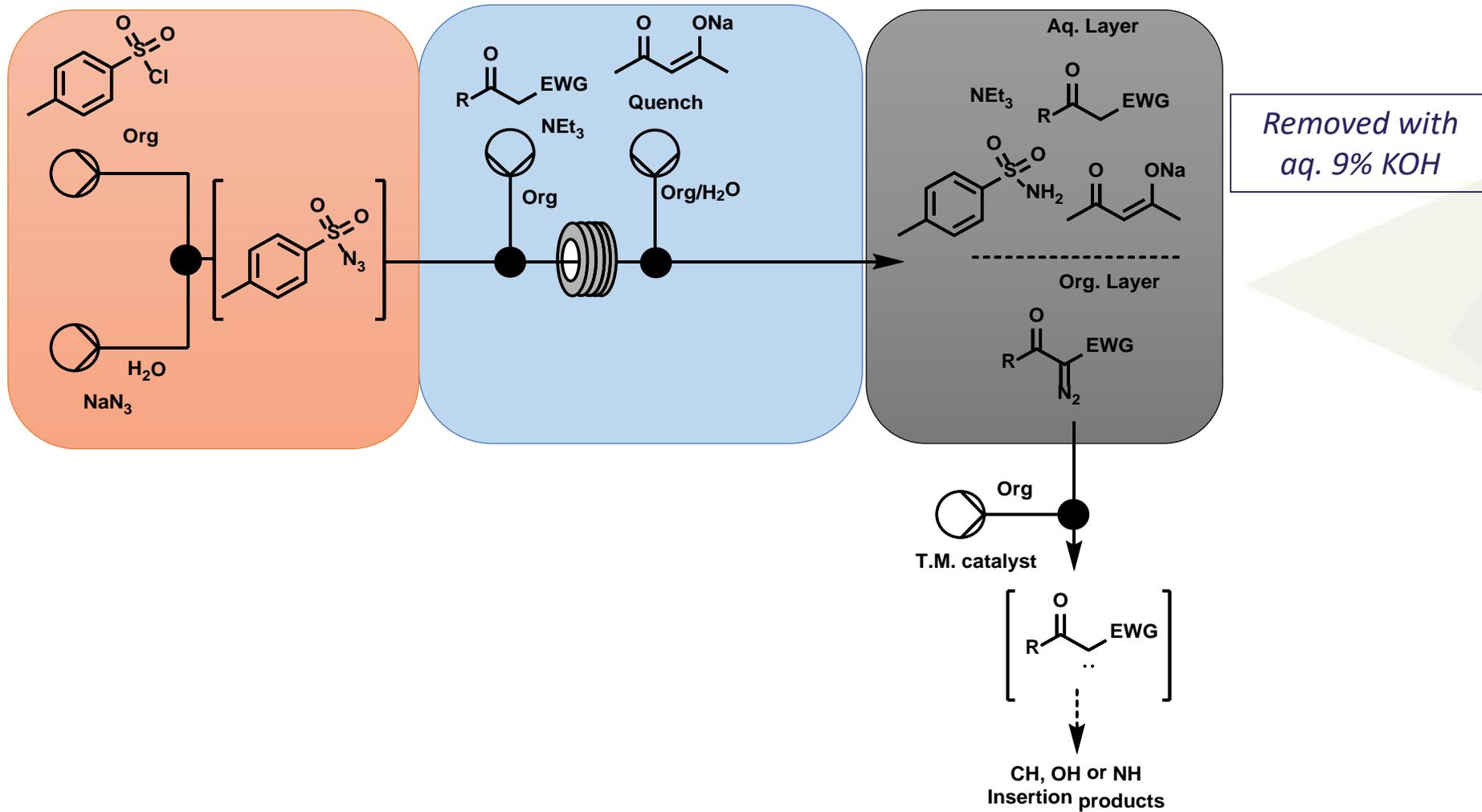
(Highlighted in *Org. Process Res. Dev.* 2017, 21, 469)

# $\alpha$ -Diazosulfoxides – Summary

- Use of continuous flow with a solid supported base significantly enhances yields of diazo transfer
- Typically a two-fold increase in yield of desired product compared with traditional batch methods:  
~30%  $\rightarrow$  ~80%
- Readily applicable to a range of  $\alpha$ -diazo sulfoxides
  - *e.g.* ketones, lactones, lactams

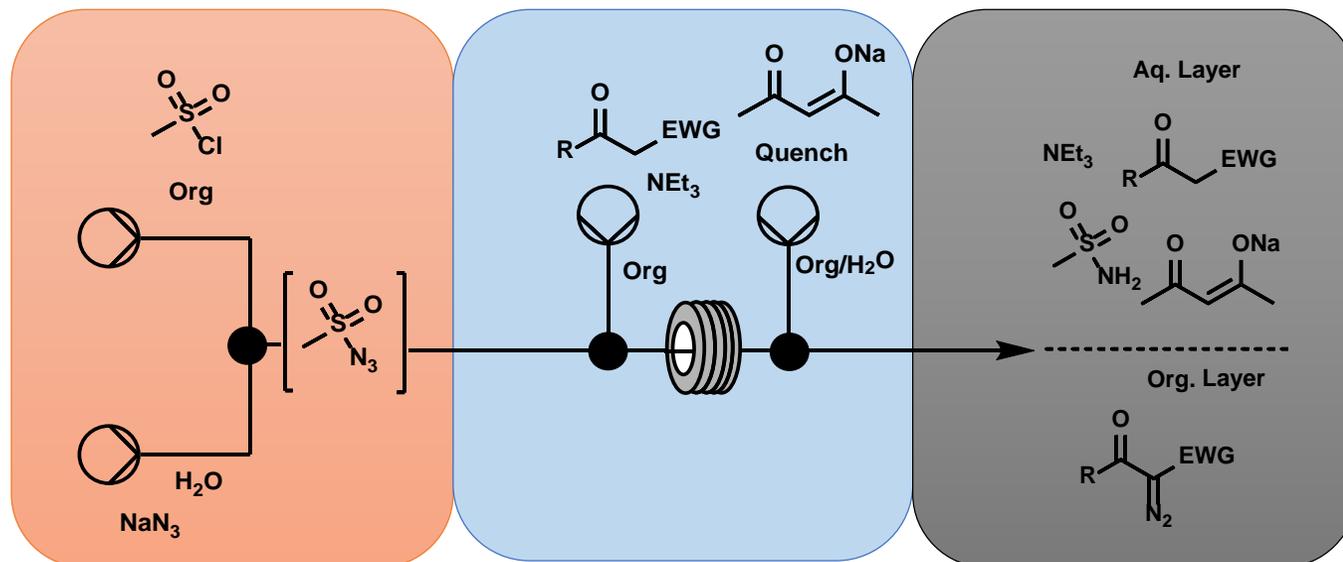
# Telescoped Reactions

Tosyl Azide:



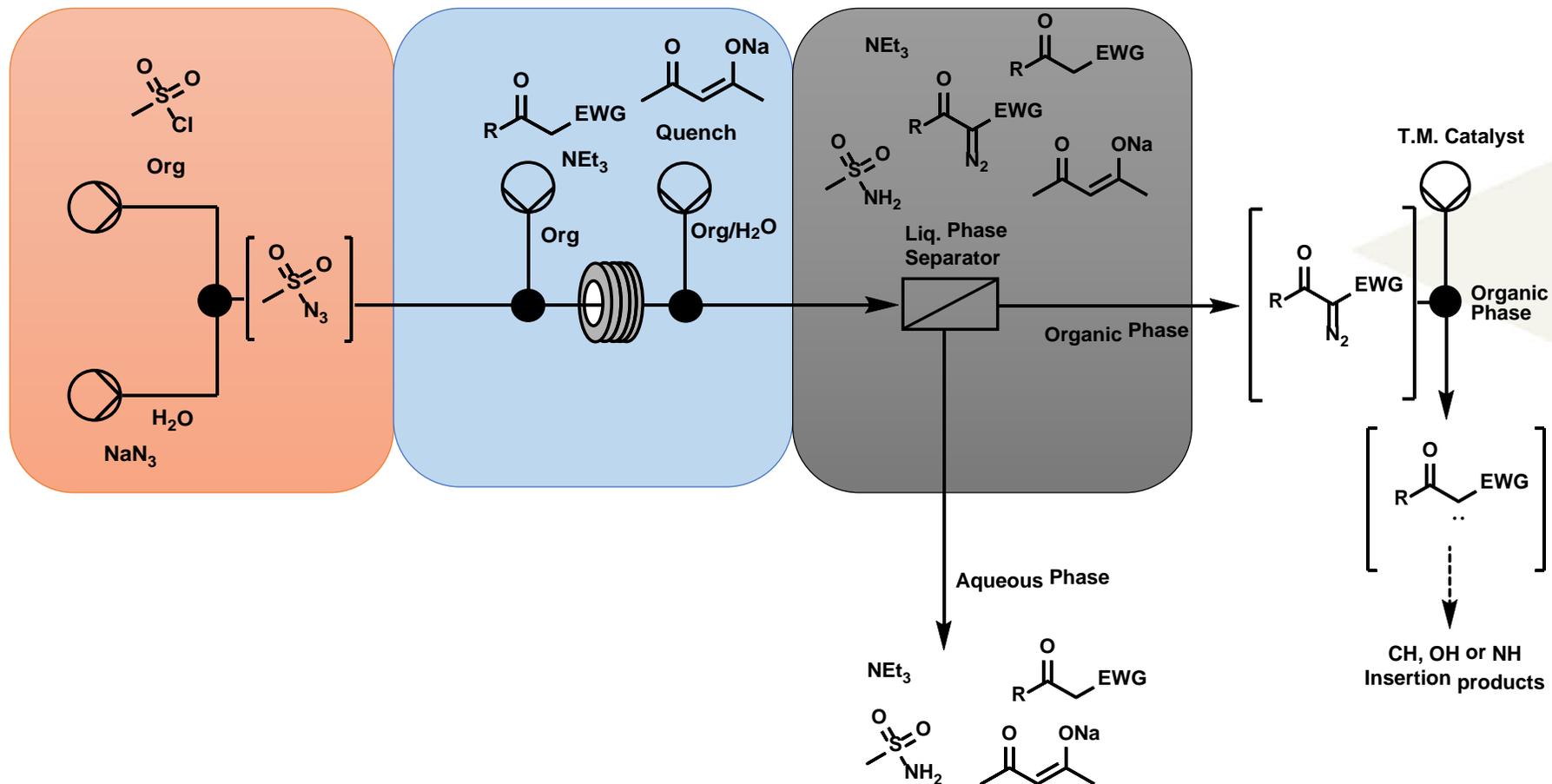
# Telescoped Reactions

Mesyl Azide:

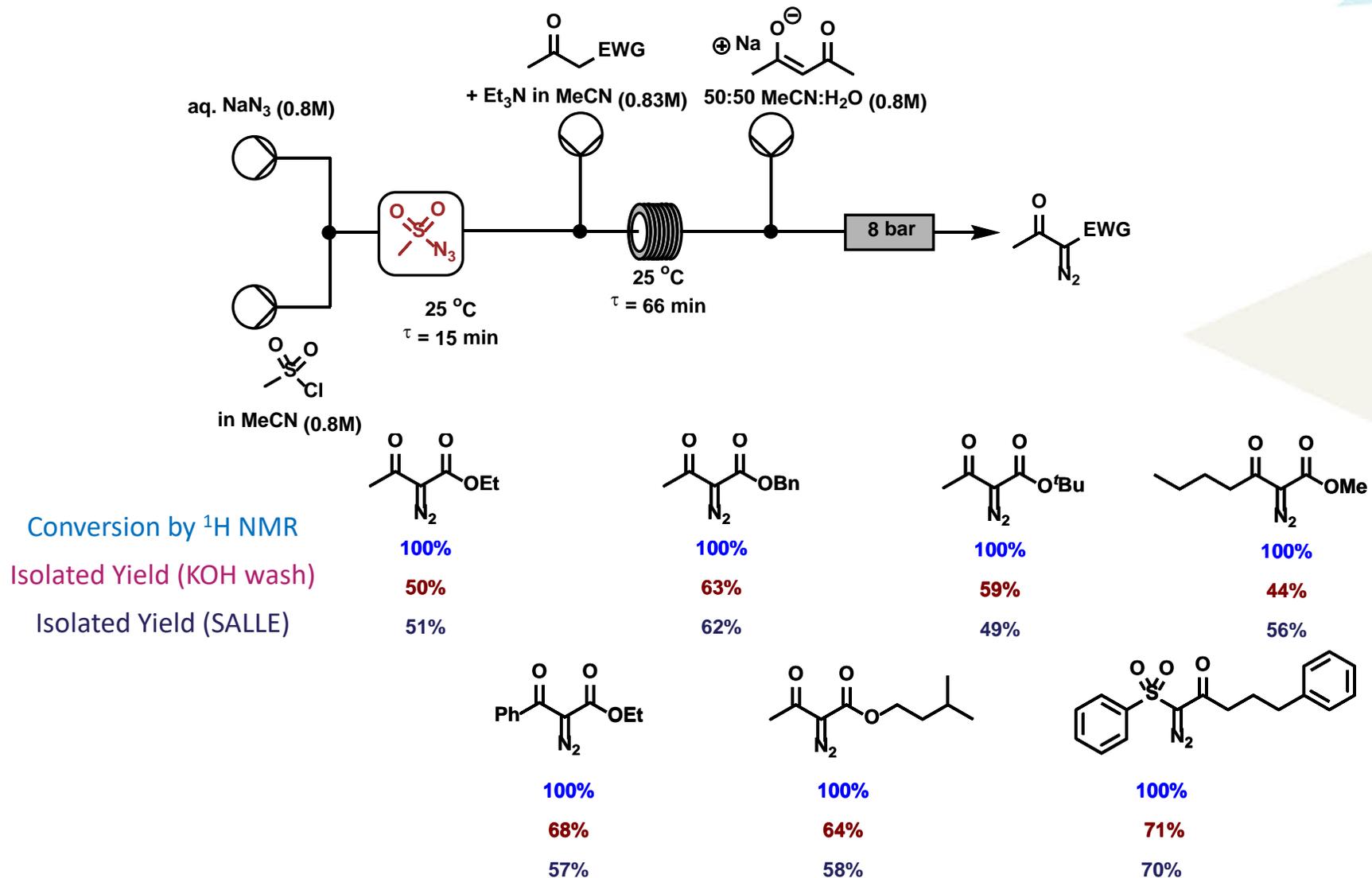


# Telescoped Reactions

Mesyl Azide:

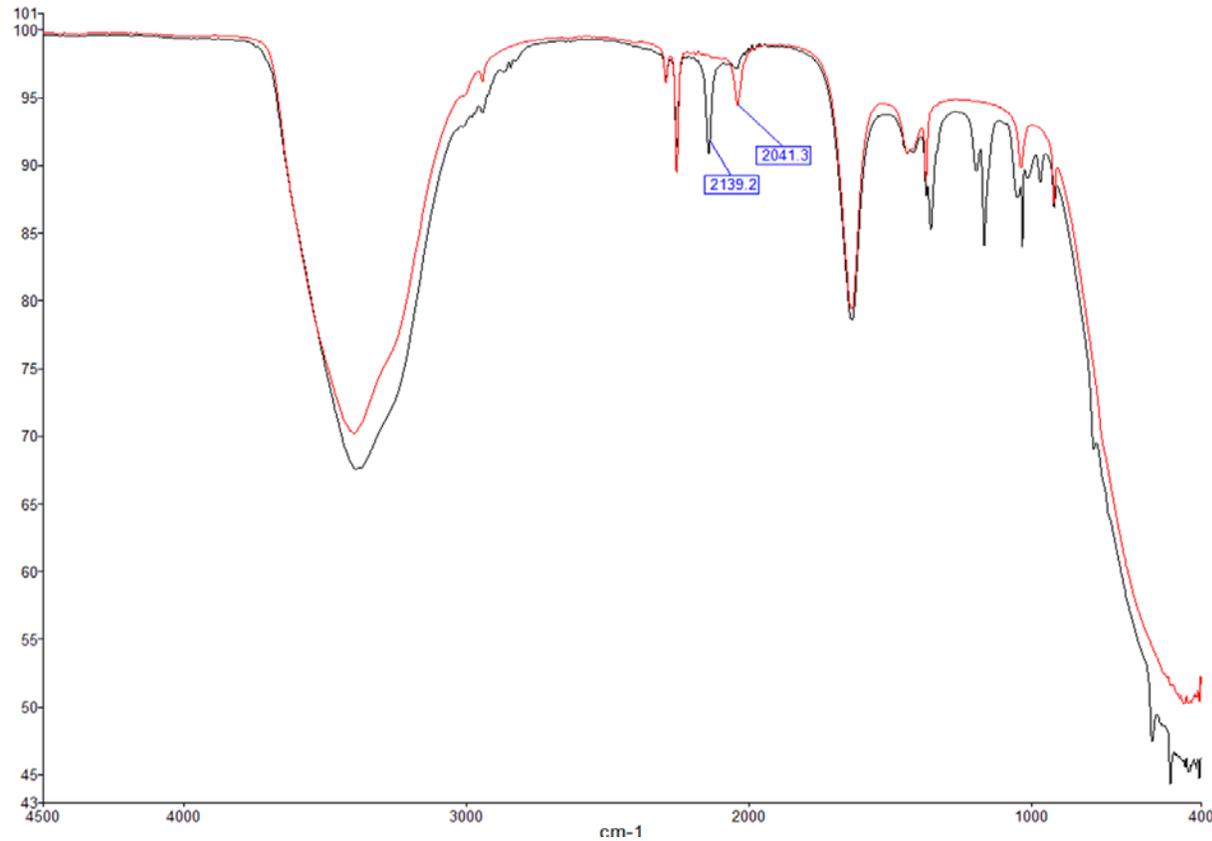


# Telescoped Generation & Use of Mesityl Azide



# IR Spectroscopy

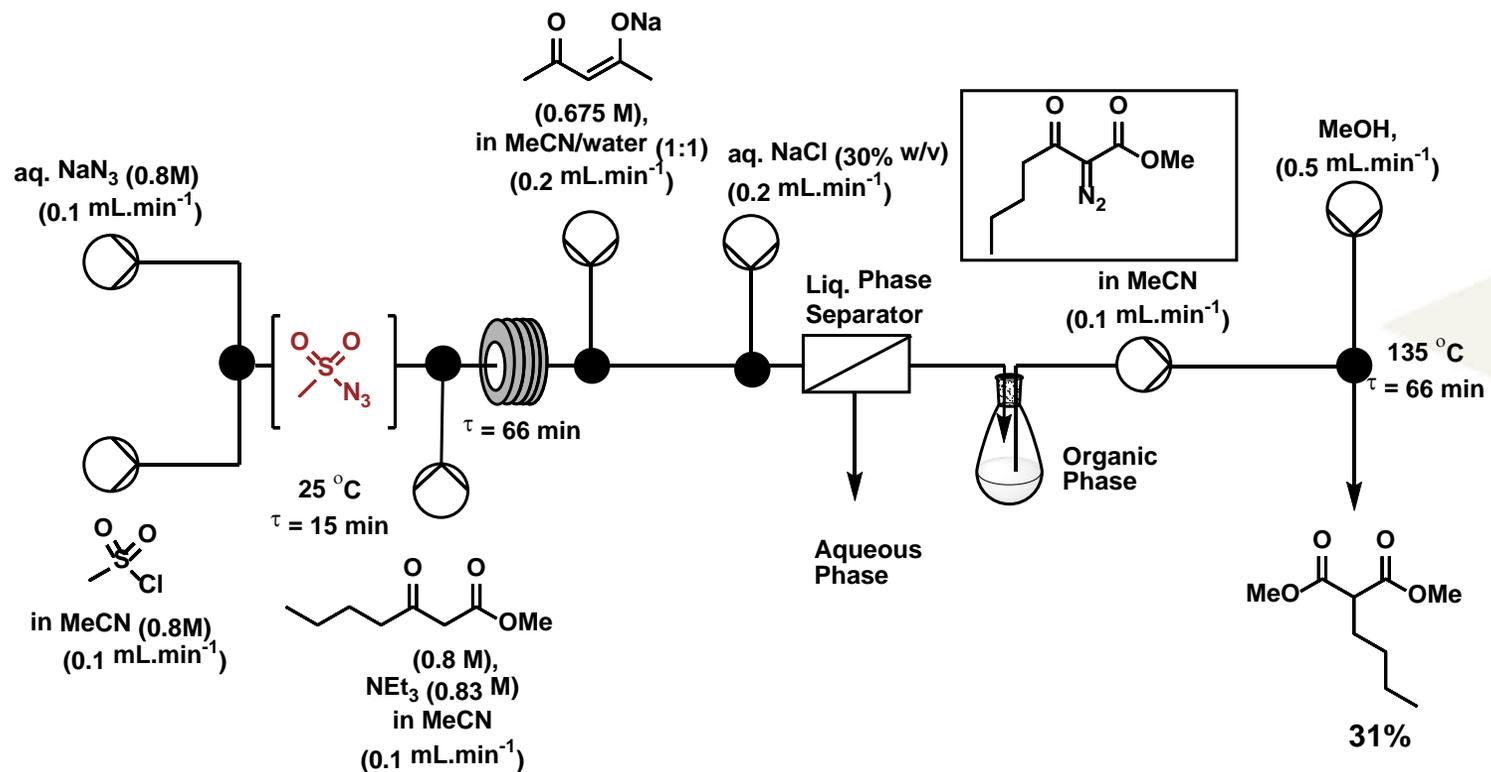
- $\text{MsN}_3$  generation at 12 min reaction time.



$\text{NaN}_3 - 2041 \text{cm}^{-1}$

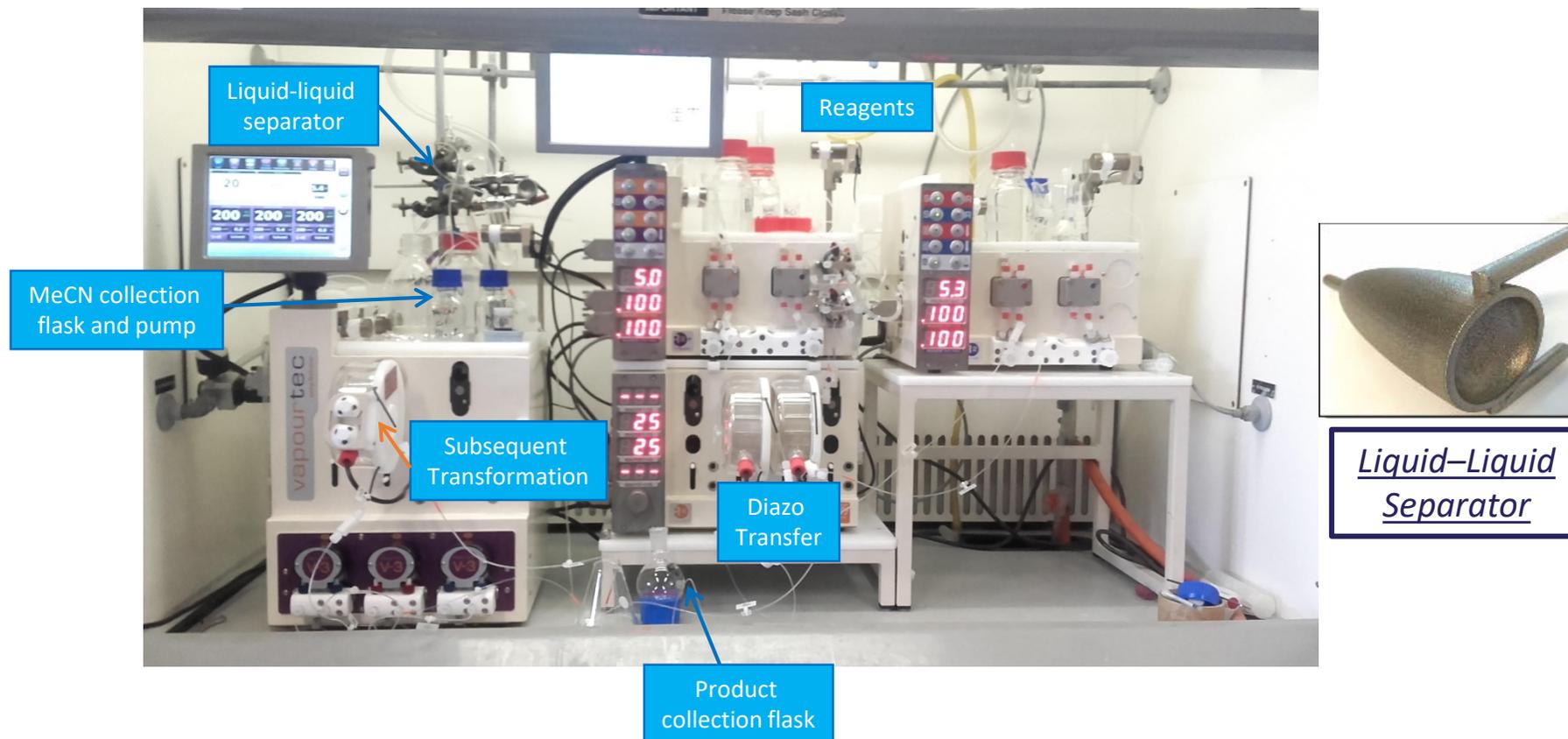
$\text{MsN}_3 - 2139 \text{cm}^{-1}$

# Telescoped Generation & Use of Mesityl Azide



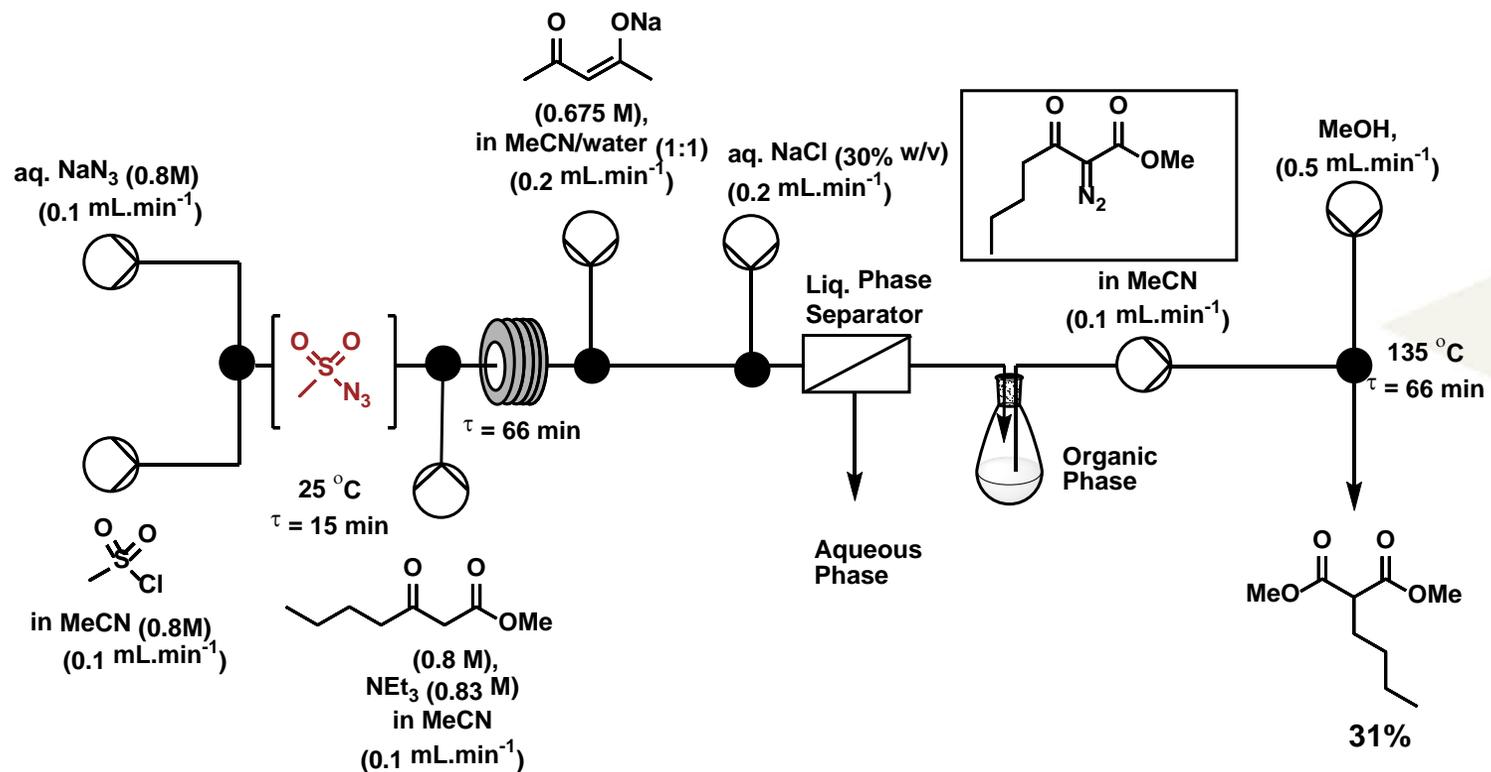
O'Mahony, R. M.; Lynch, D.; Hayes, H. L. D.; Ní Thuma, E.; Donnellan, P.; Jones, R. C.; Glennon, B.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.*, **2017**, 6533.

# Telescoped Generation & Use of Mesityl Azide



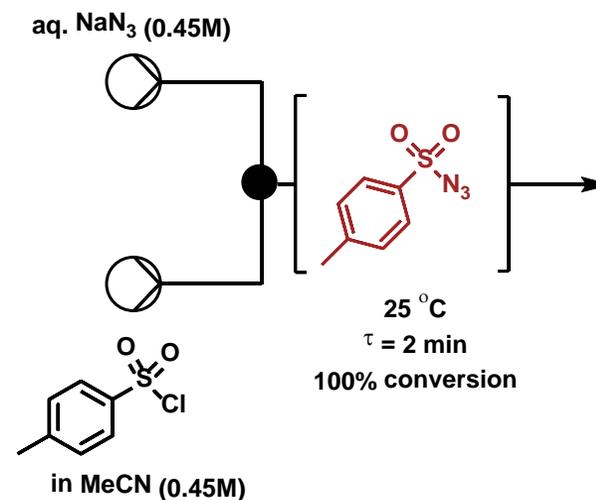
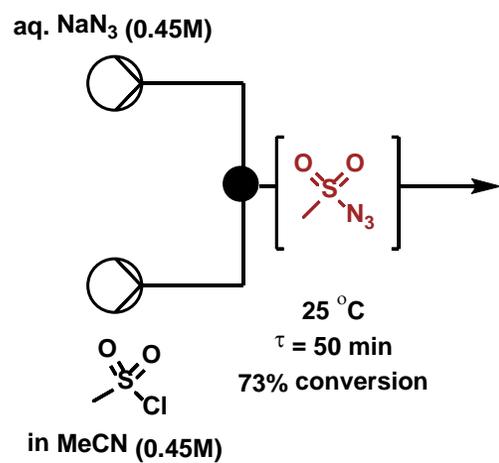
O'Mahony, R. M.; Lynch, D.; Hayes, H. L. D.; Ní Thuma, E.; Donnellan, P.; Jones, R. C.; Glennon, B.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.*, **2017**, 6533.

# Telescoped Generation & Use of Mesityl Azide



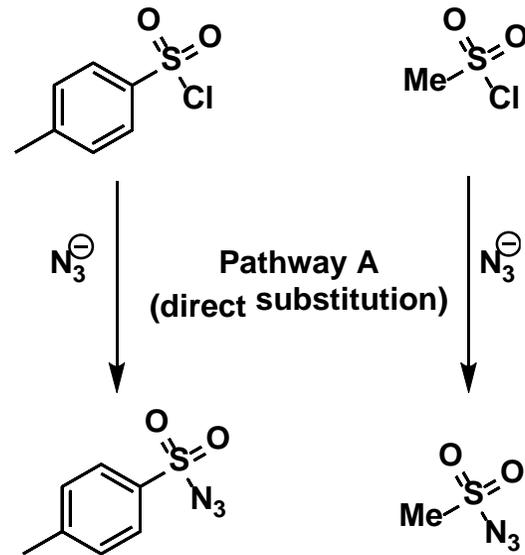
O'Mahony, R. M.; Lynch, D.; Hayes, H. L. D.; Ní Thuma, E.; Donnellan, P.; Jones, R. C.; Glennon, B.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.*, **2017**, 6533.

# *In Situ* Generation of Mesyl Azide



O'Mahony, R. M.; Lynch, D.; Hayes, H. L. D.; Ní Thuma, E.; Donnellan, P.; Jones, R. C.; Glennon, B.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.*, **2017**, 6533.

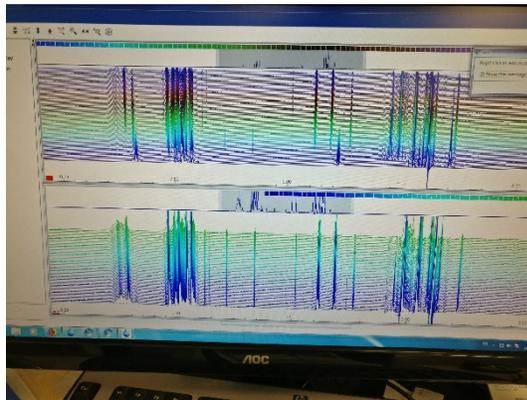
# *In Situ* Generation of Mesyl Azide



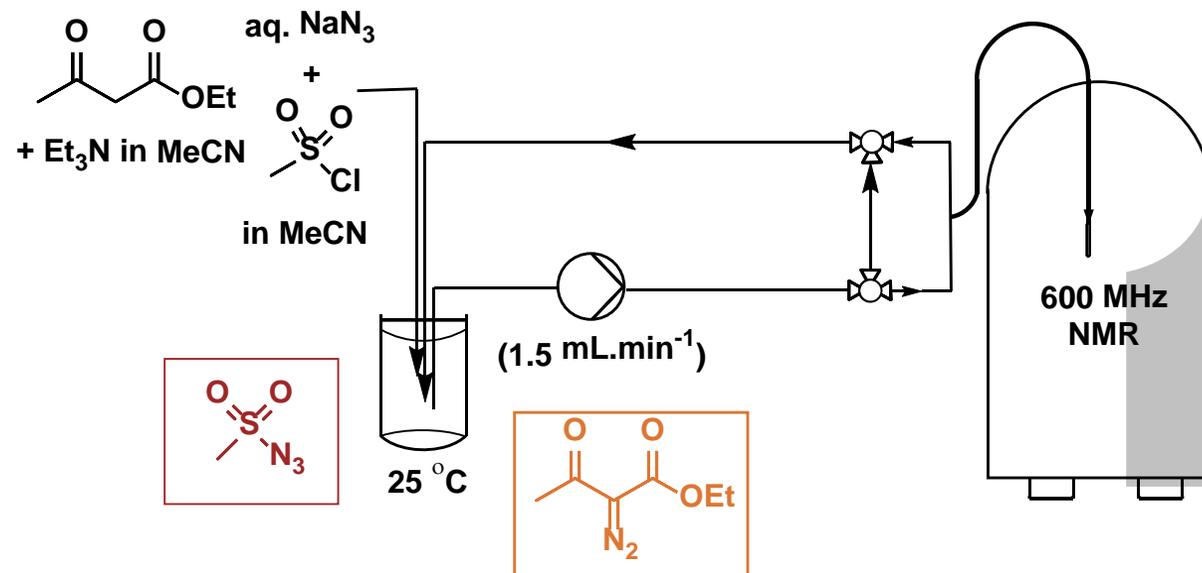
# ProSpect

## Process Flow Spectroscopy Suite:

- Instrumentation for process analysis:
  - **FlowNMR**, Bruker *InsightMR* flow tube and 600 MHz broadband cryoprobe
  - **ReactIR**, Mettler–Toledo *ReactIR 15* (batch) and *FlowIR* (continuous)
  - **UPLC–MS**, Agilent *1290 LC-QToF* system
  - **ReactUV**, Perkin–Elmer *Lambda 265* spectrophotometer
  - **Reaction Autosampling**, Gilson *GX-241 liquid handler*
  - **Continuous Processing**, Vapourtec *R-series*, configurable for cryogenic conditions ( $-70\text{ }^{\circ}\text{C}$ ) and photochemical reactions

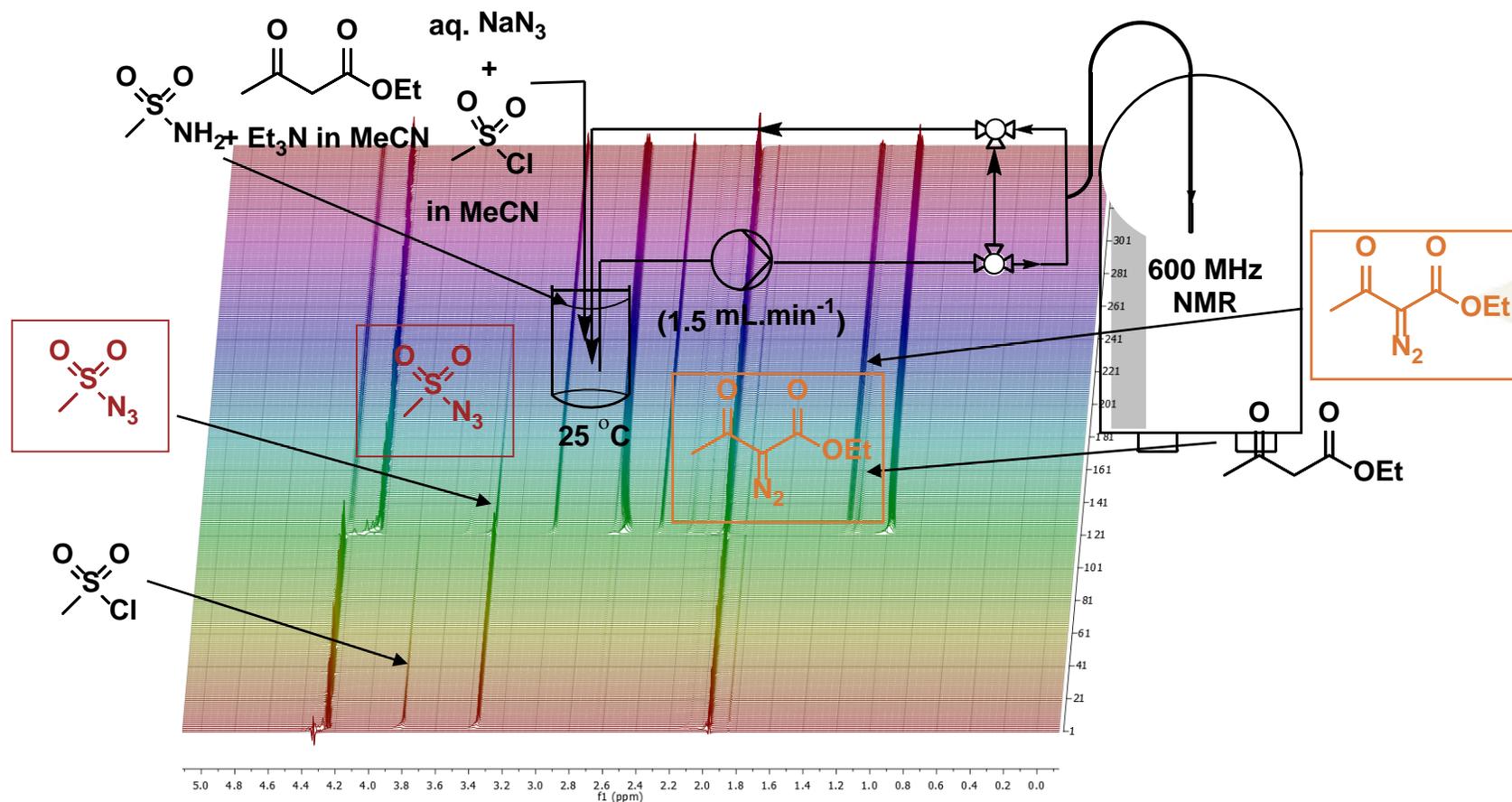


# Mesyl Azide



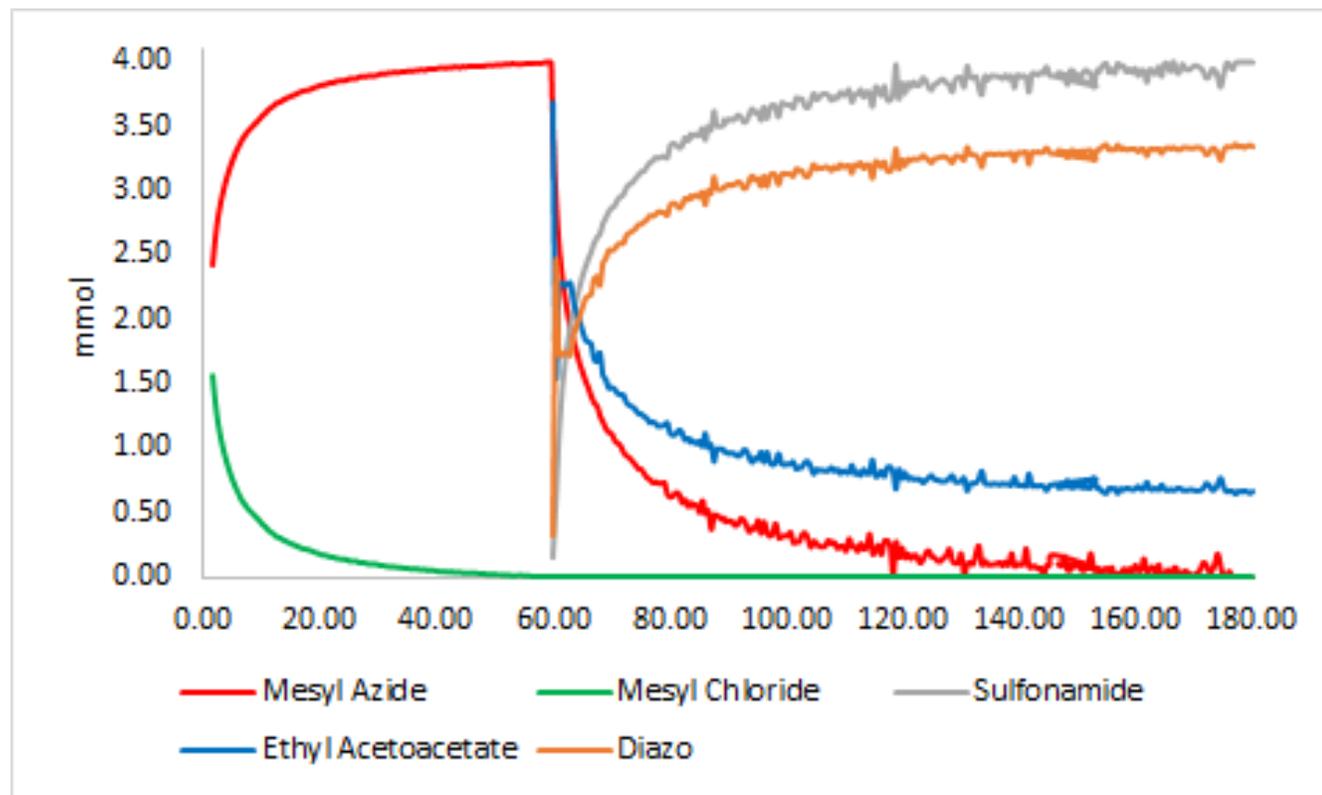
Lynch, D.; O'Mahony, R. M.; McCarthy, D. G.; Bateman, L. M.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.* **2019**, 3574.

# Mesyl Azide



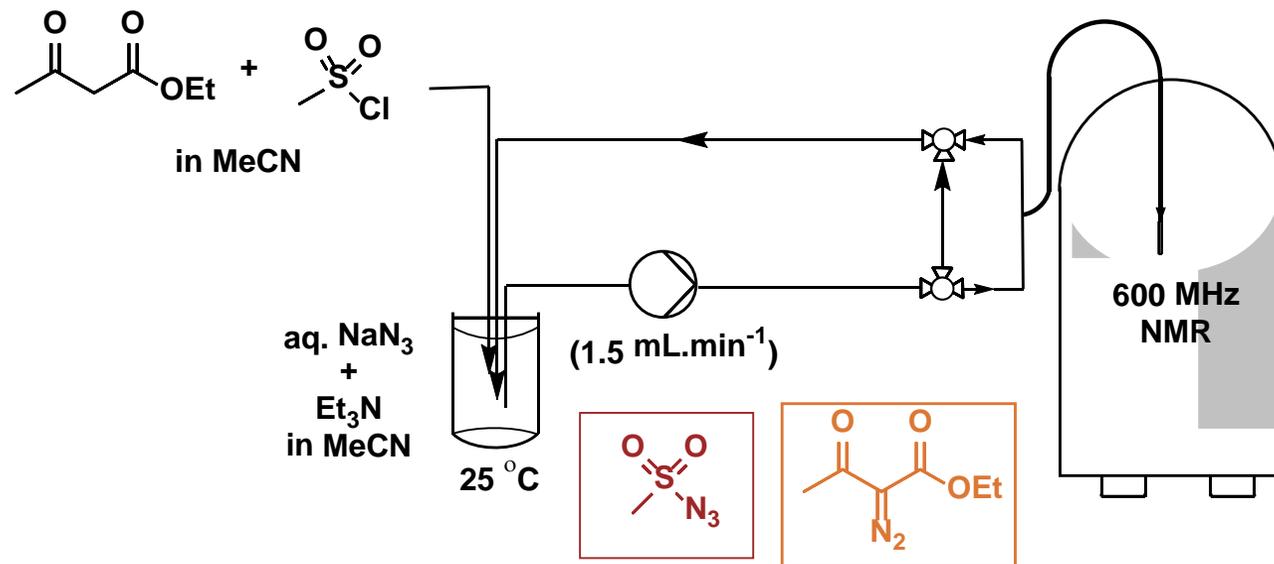
Lynch, D.; O'Mahony, R. M.; McCarthy, D. G.; Bateman, L. M.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.* **2019**, 3574.

# Mesyl Azide



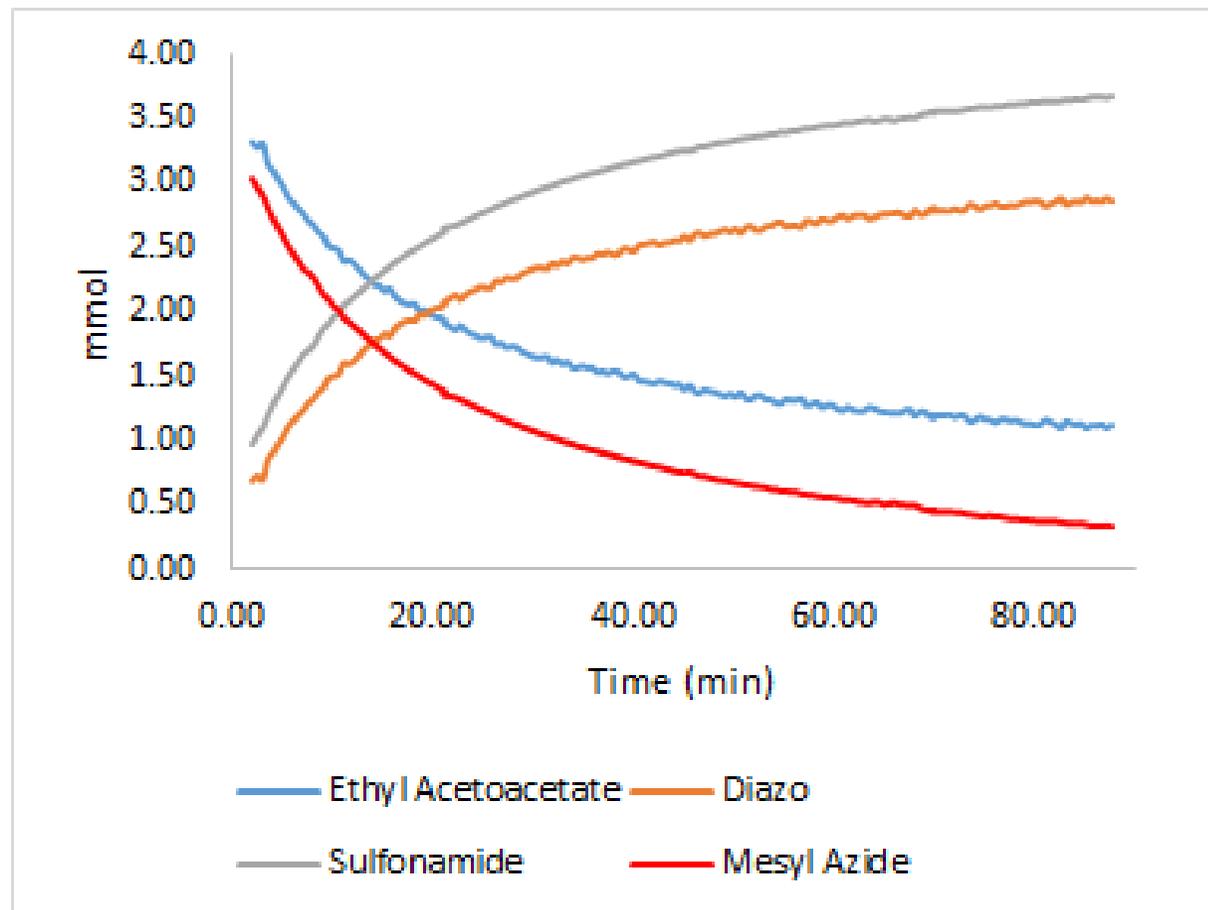
Lynch, D.; O'Mahony, R. M.; McCarthy, D. G.; Bateman, L. M.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.* **2019**, 3574.

# Mesyl Azide



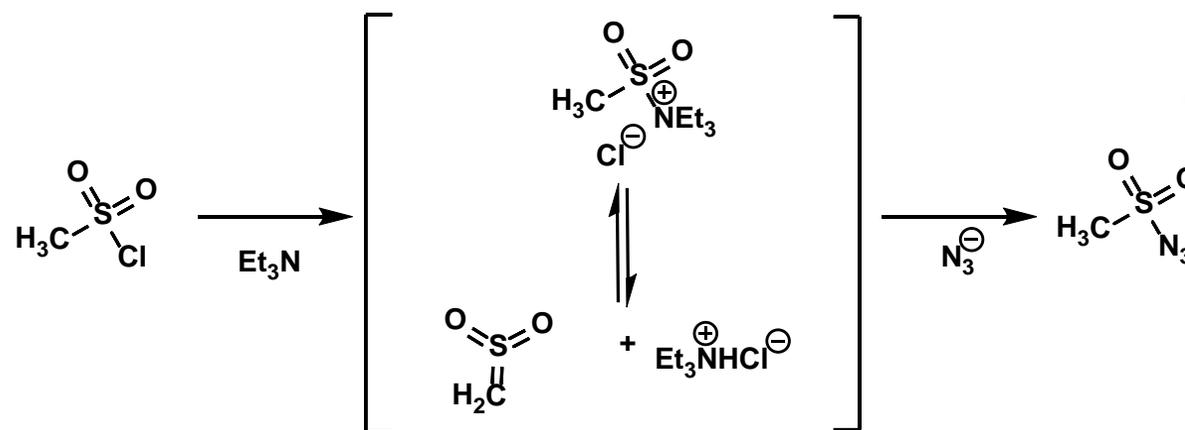
Lynch, D.; O'Mahony, R. M.; McCarthy, D. G.; Bateman, L. M.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.* **2019**, 3574.

# Mesyl Azide



Lynch, D.; O'Mahony, R. M.; McCarthy, D. G.; Bateman, L. M.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.* **2019**, 3574.

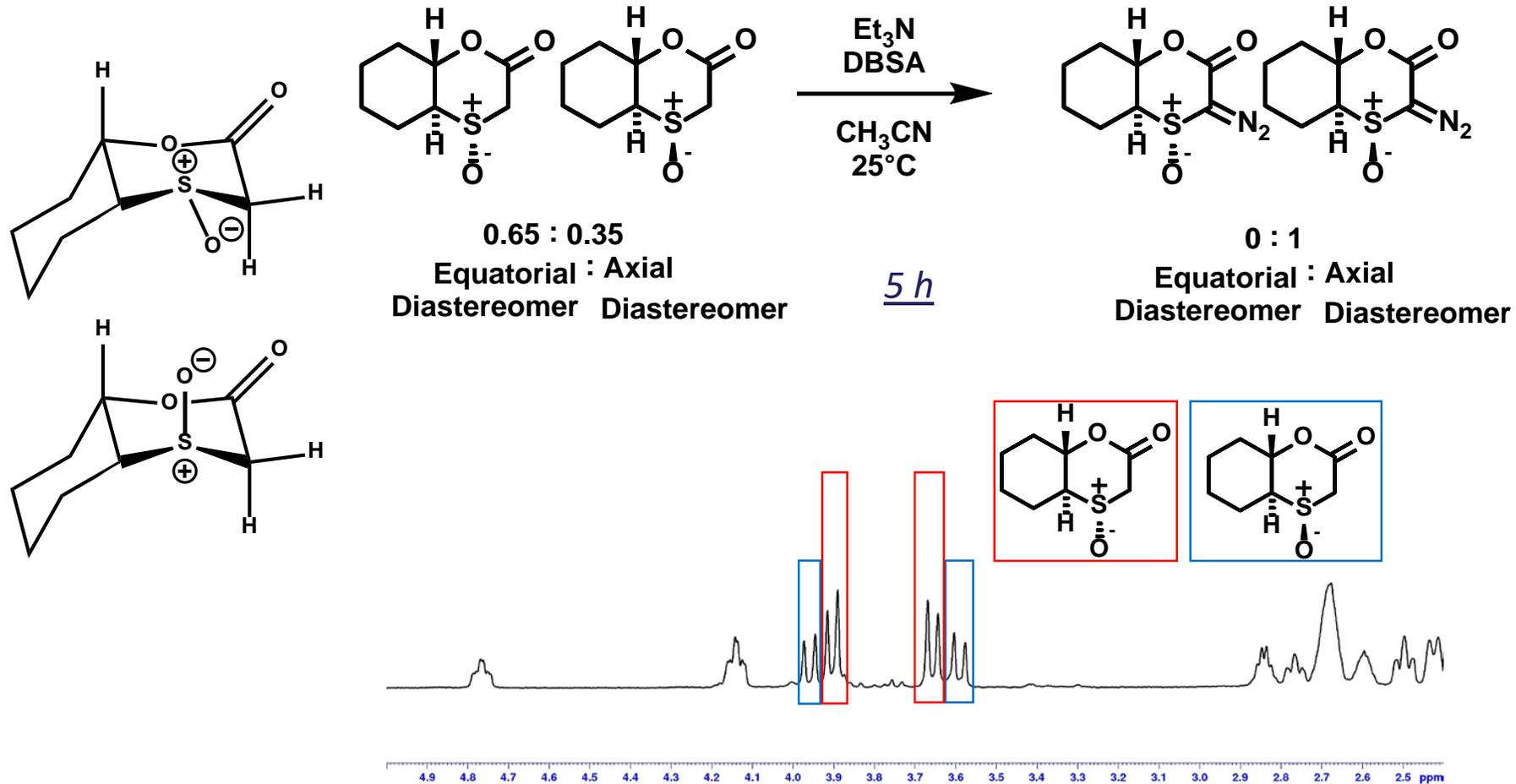
# Mesyl Azide



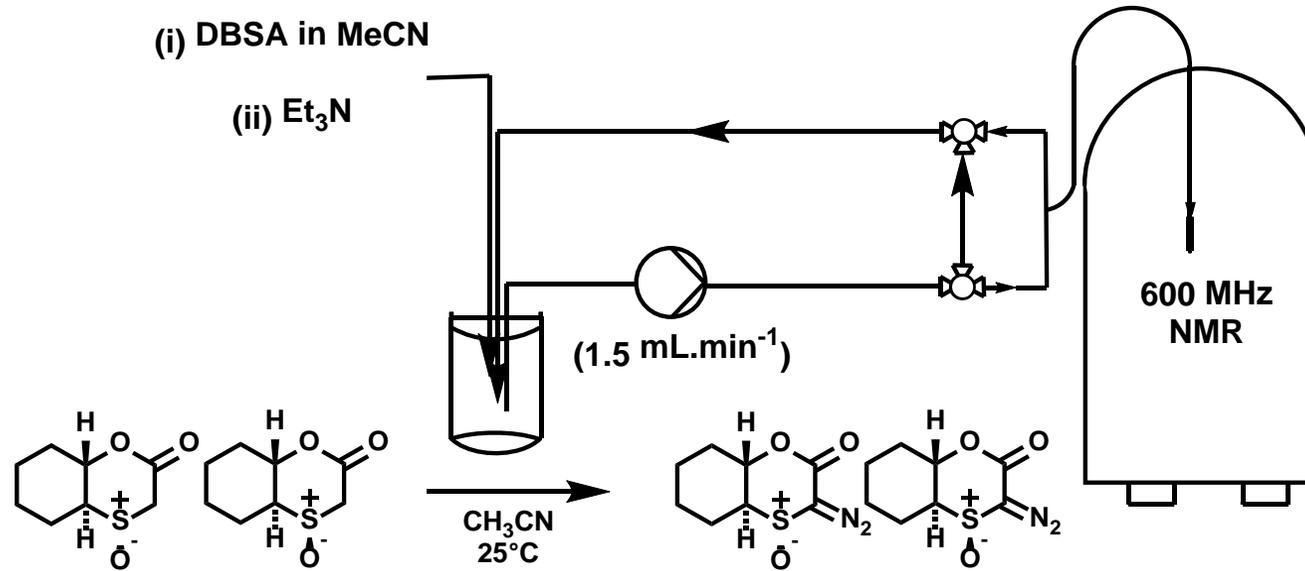
Lynch, D.; O'Mahony, R. M.; McCarthy, D. G.; Bateman, L. M.; Collins S. G.; Maguire, A. R. *Eur. J. Org. Chem.* **2019**, 3574.

# Diazo Transfer – $\alpha$ -Diazosulfoxides

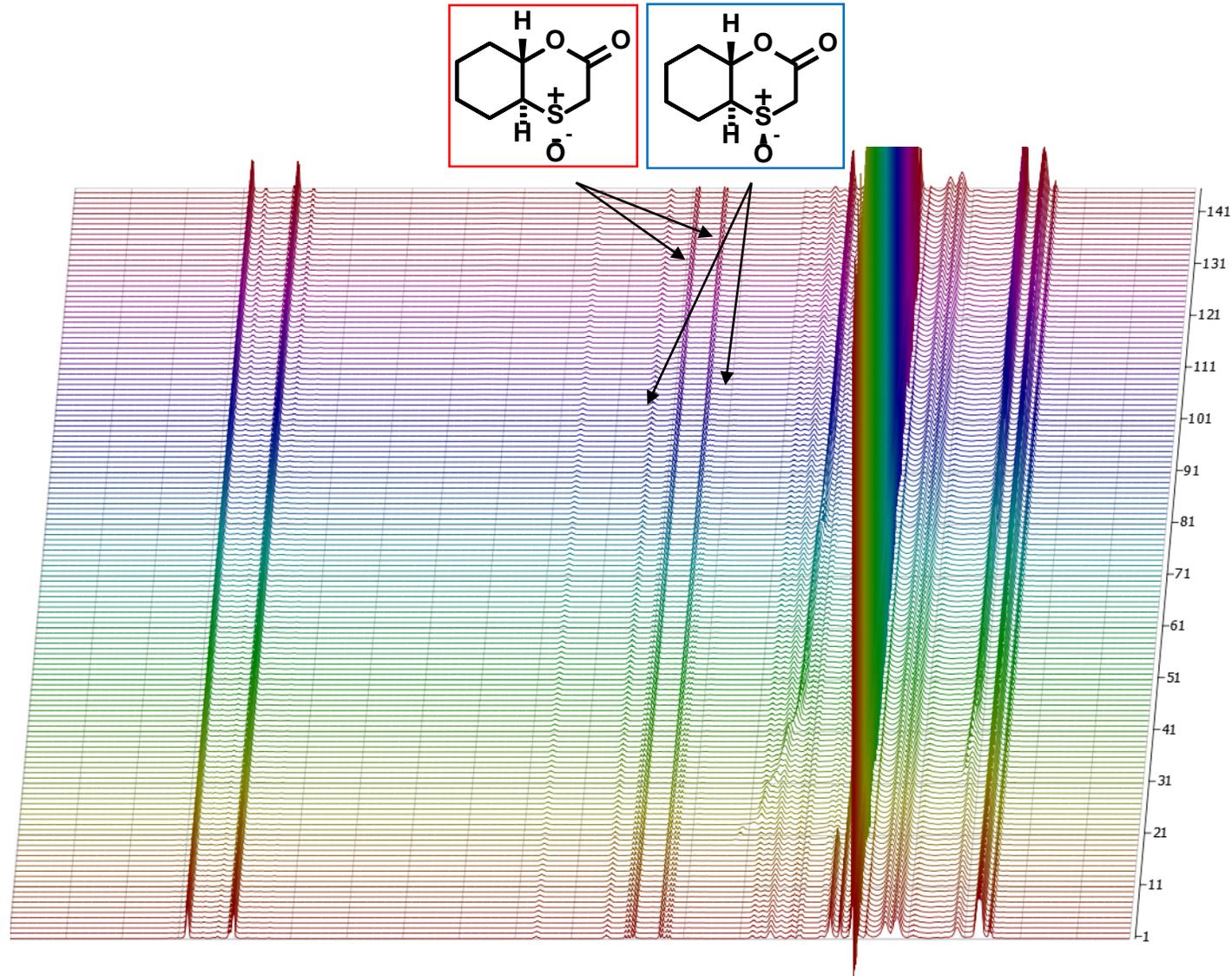
- Diastereoselective diazo transfer observed:



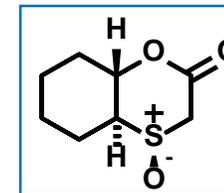
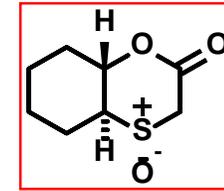
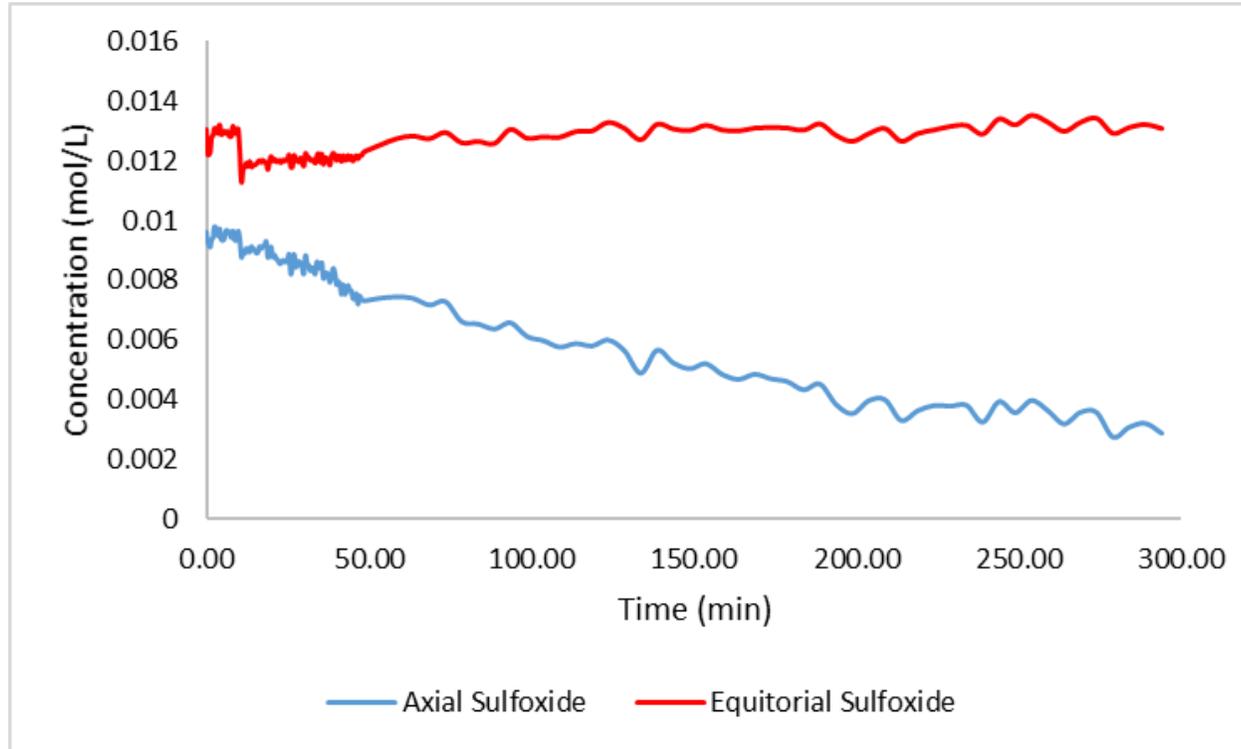
# Diazo Transfer – $\alpha$ -Diazosulfoxides



# Diazo Transfer – $\alpha$ -Diazosulfoxides

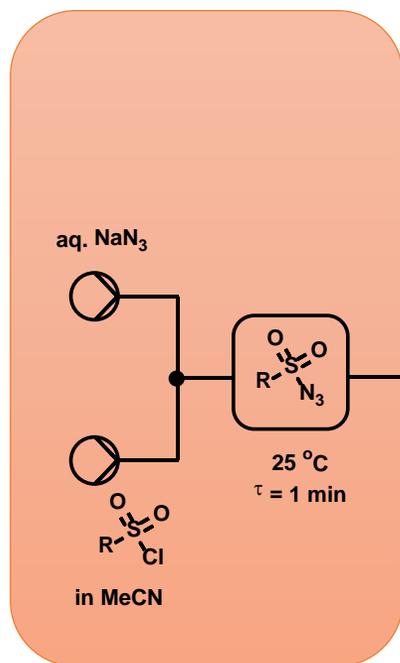


# Diazo Transfer – $\alpha$ -Diazosulfoxides

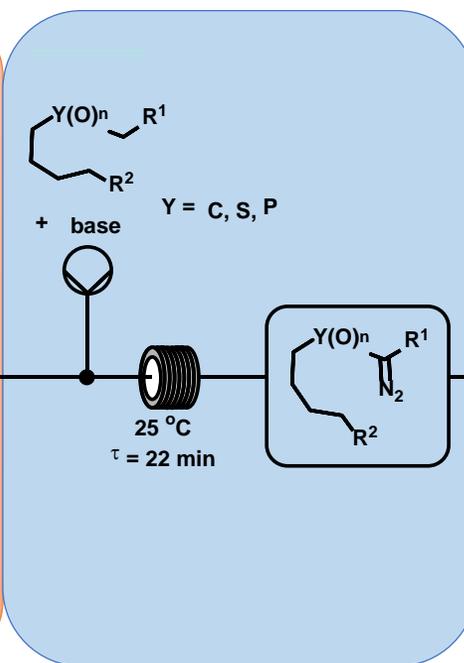


# Telescoped Transition Metal Catalysed Processes

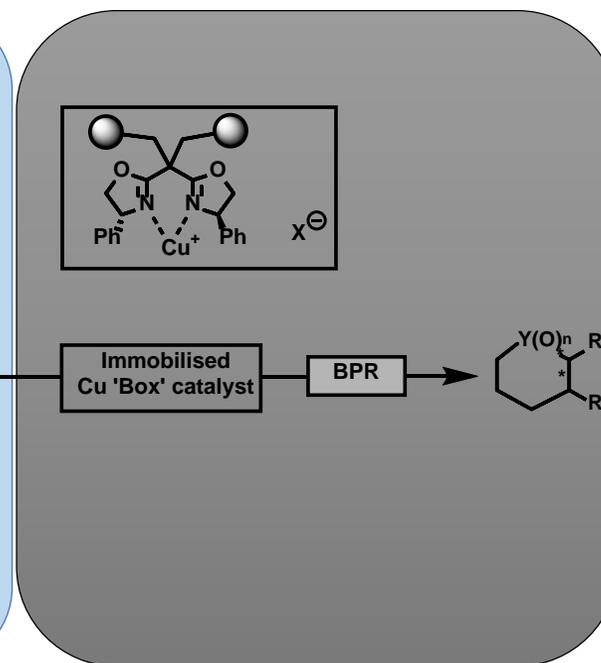
Sulfonyl azide  
Formation



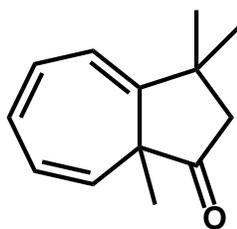
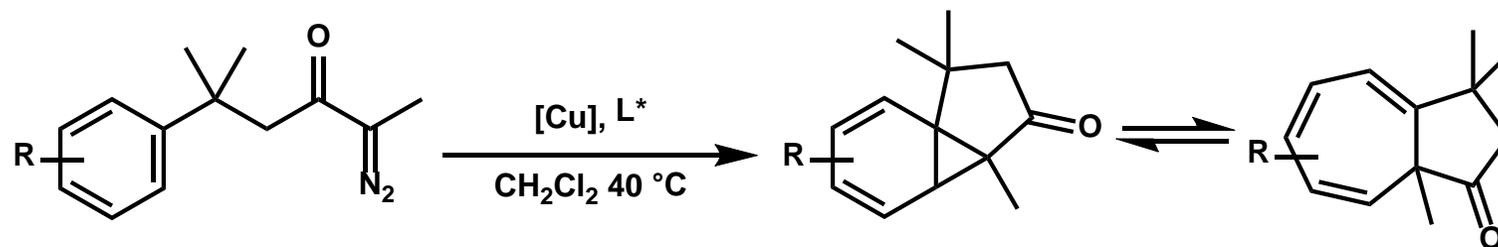
Diazo Transfer



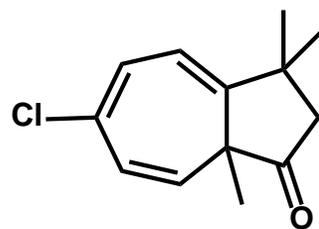
Enantioselective  
C-H Insertion



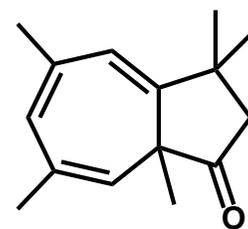
# Intramolecular Buchner Reaction



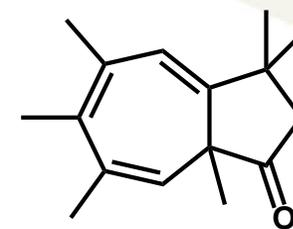
78%ee



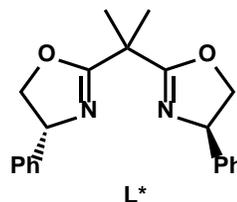
78%ee



92%ee

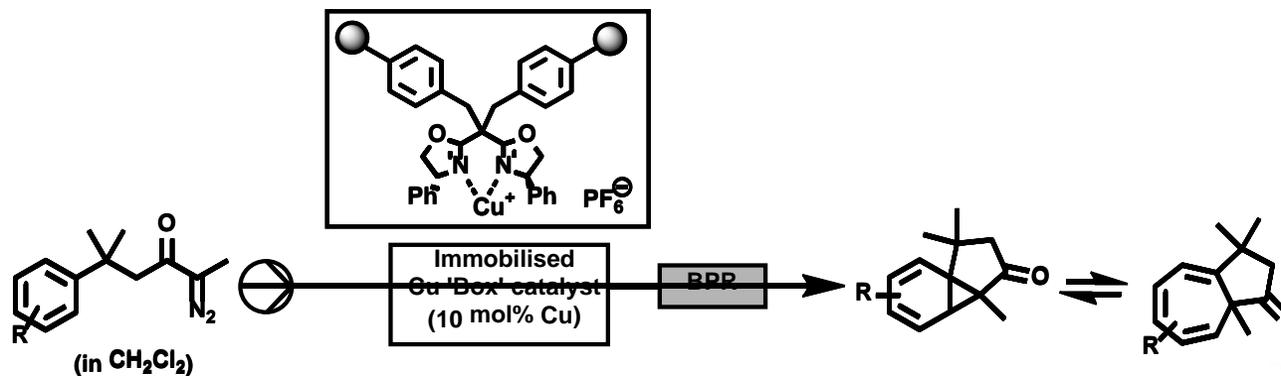


95%ee  
room temp.



Slattery, C. N.; Clarke, L-A.; O'Neill, S.; Ring, A.; Ford, A.; Maguire, A. R. *Synlett* **2012**, 23, 765-767.

# Copper-catalysed Enantioselective Aromatic addition *in Continuous Flow*



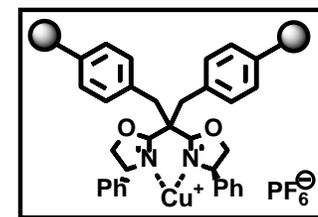
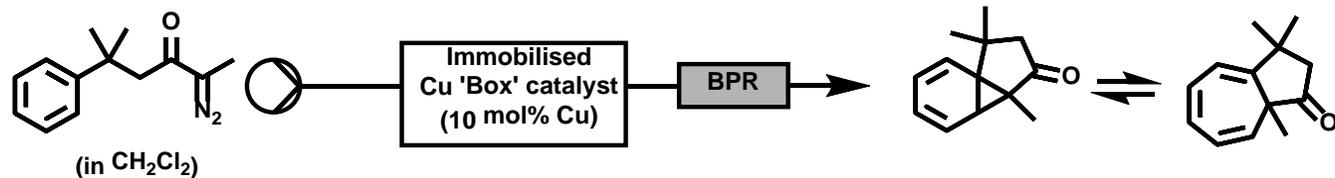
Homogeneous  
Batch

Entry	R	Flow Rate (mL min <sup>-1</sup> )	Temperature (°C)	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	H	1.00	45	74	78
2	4-Cl	1.00	45	63	62
3 <sup>c</sup>	4-F	1.00	45	74	56
4	3,4,5-Me	0.75	22	-	95

<sup>a</sup>Isolated after chromatography. Determined by chiral shift <sup>1</sup>H NMR experiment using (+)-Eu(hfc)<sub>3</sub>. <sup>c</sup>IPB catalyst formed using Cu(OTf)<sub>2</sub> as copper source.

Crowley, D. C.; Lynch, D.; Maguire, A.R. *J. Org. Chem.* **2018**, *83*, 3794.

# Catalyst Reusability



Cu 'Box' catalyst

Entry	Flow Rate (mL min <sup>-1</sup> )	Temperature (°C)	Yield (%) <sup>a</sup>	Efficiency (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	(Batch)	45	53	80	62
2	(Batch)	45	85	81	64
3	0.175	45	62	78	61
4	0.200	45	50	73	64
5	0.250	45	55	75	62
6	0.300	45	60	78	61
7	0.300	45	65	78	60
8	0.300	45	41	76	55

<sup>a</sup>Isolated after chromatography. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis. <sup>c</sup>Determined by chiral shift <sup>1</sup>H NMR experiment using (+)-Eu(hfc)<sub>3</sub>.

Crowley, D. C.; Lynch, D.; Maguire, A.R. *J. Org. Chem.* **2018**, *83*, 3794.

# IUPAC 100<sup>th</sup> Anniversary

NEWS

## Iupac names 10 chemistry innovations that will change the world



BY KATRINA KRÄMER | 3 APRIL 2019



- 1 Nanopesticides
- 2 Enantioselective organocatalysis
- 3 Solid-state batteries
- 4 Flow chemistry
- 5 Mechanochemistry and reactive extrusion
- 6 MOFs
- 7 Directed enzyme evolution
- 8 Turning polymers back into monomers
- 9 Reversible deactivation radical polymerisation (RDRP)
- 10 3D bioprinting

<https://www.chemistryworld.com/news/iupac-names-10-chemistry-innovations-that-will-change-the-world/3010335.article>

# Acknowledgements

Dr Stuart Collins  
Dr Humphrey Moynihan



Rosella O'Mahony  
Ben Deadman  
Dan Crowley



Patrick McCaw  
Eilís Ní Thuama



Olga Dennehy  
Valerie Cacheux  
Marie Kissane



Catherine Slattery  
Chris Flynn  
Leslie Ann Clarke  
Aoife Ring  
Amy Shiely

Dr Alan Ford  
Dr Simon Lawrence  
Dr Lorraine Bateman  
Dr Dan McCarthy

Prof. Brian Glennon, UCD  
Dr Philip Donnellan  
Dr Roderick Jones