Exploring and Exploiting New Iminophosphorane Reactivity for Complex Molecule Synthesis

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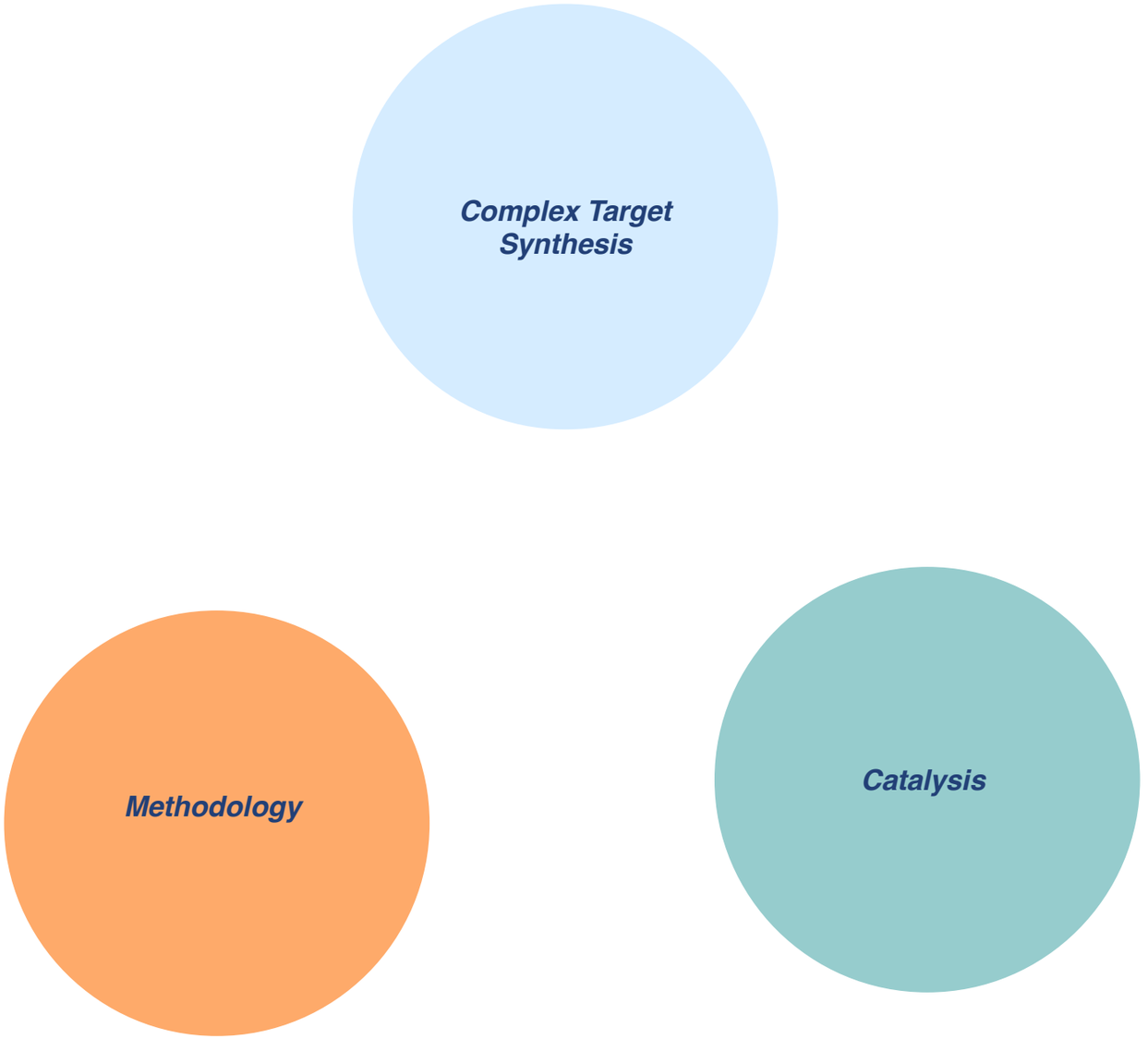
University of Oxford

IASOC 2026

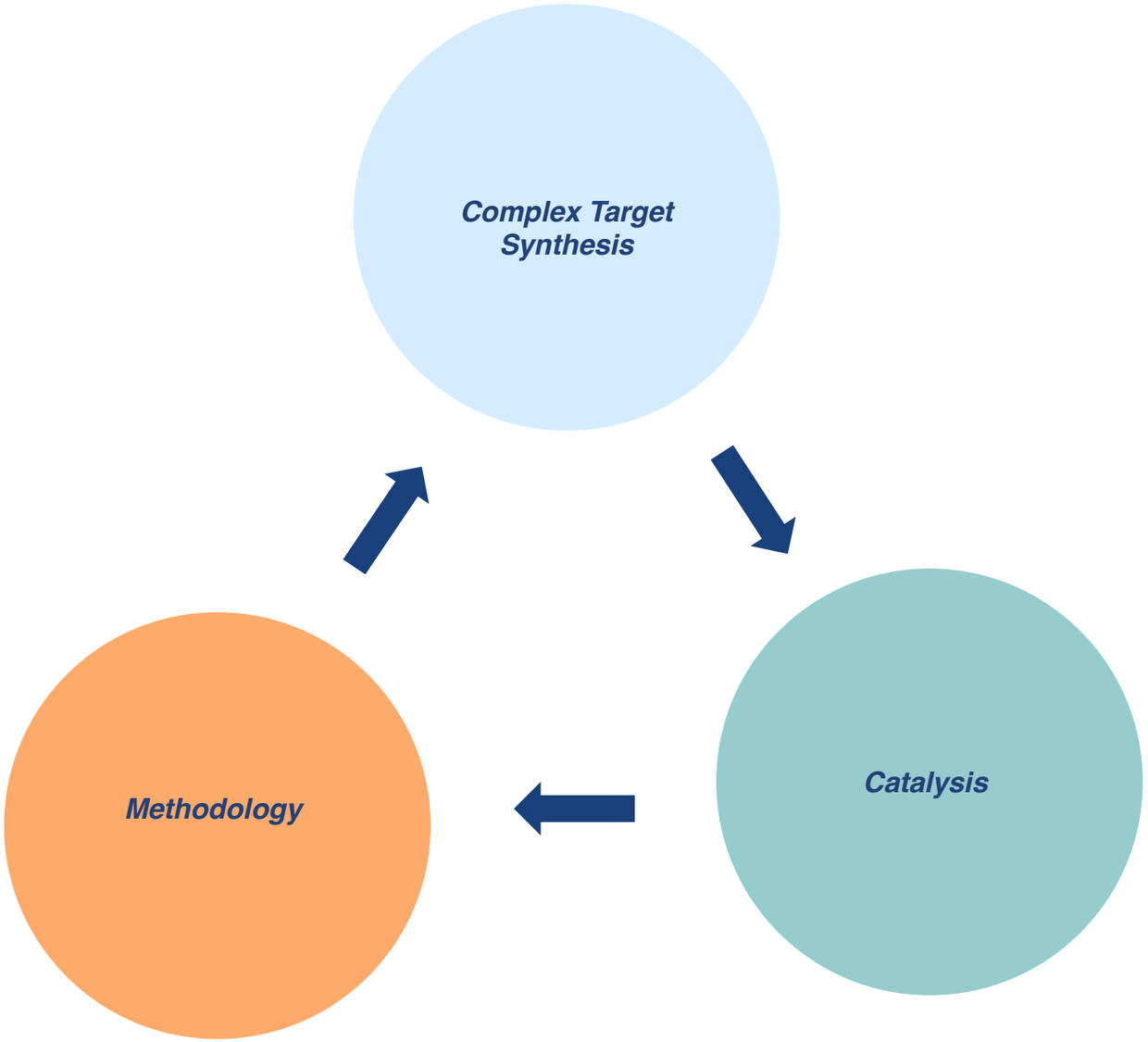
Ischia, Italy

17-21 September 2026

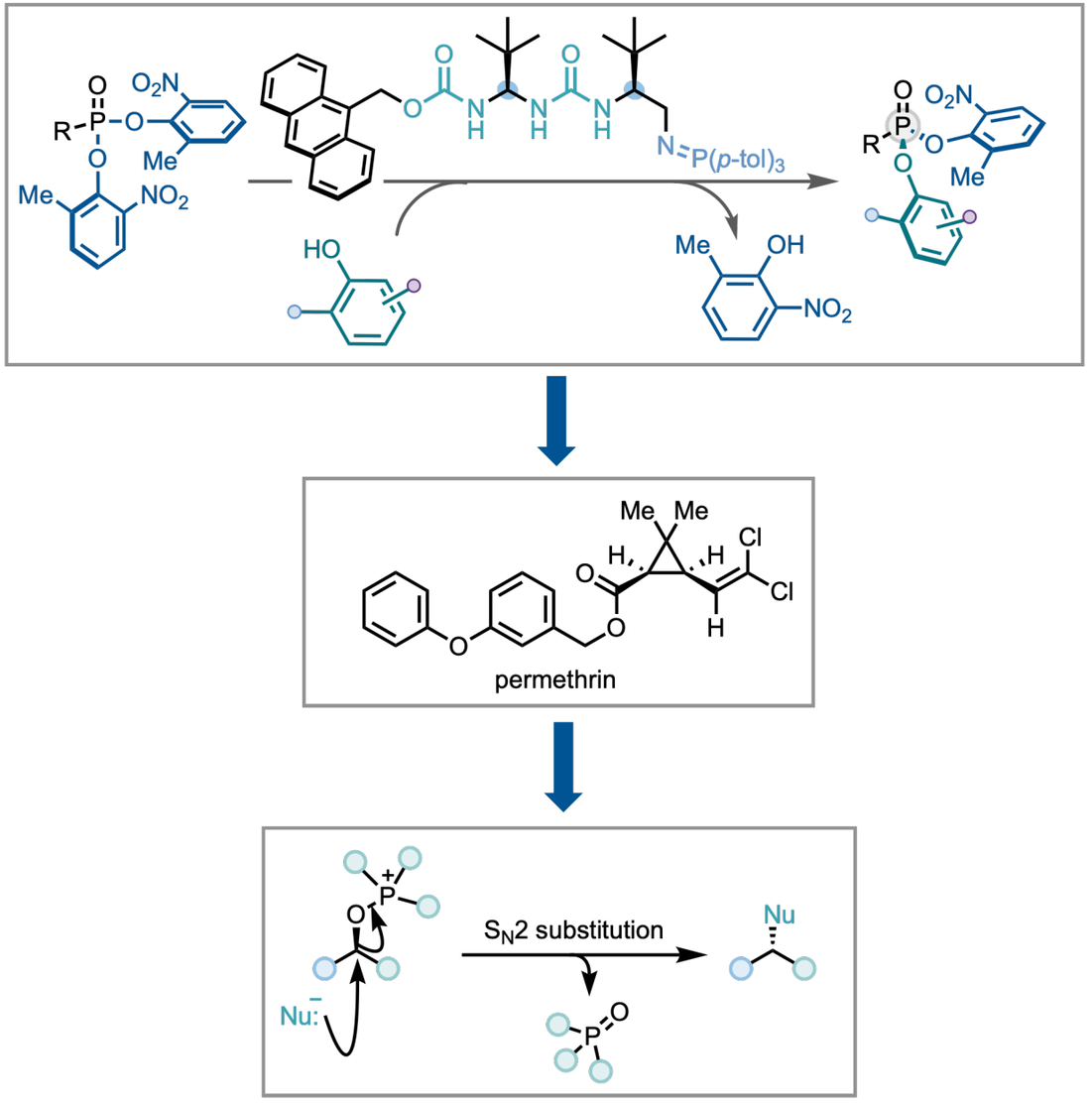
Dixon Group Research



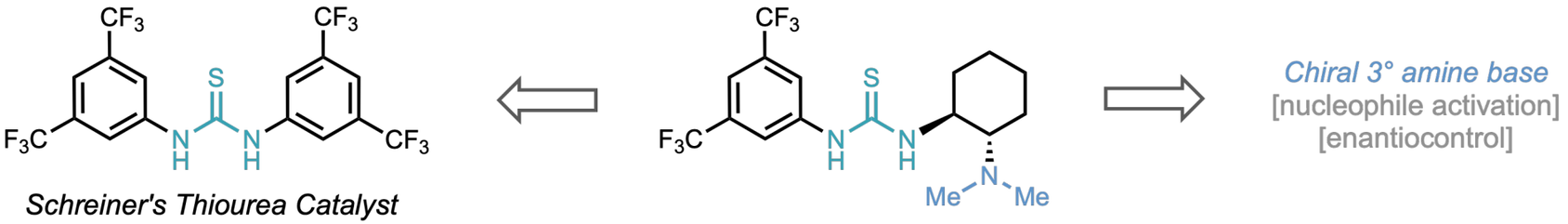
Dixon Group Research

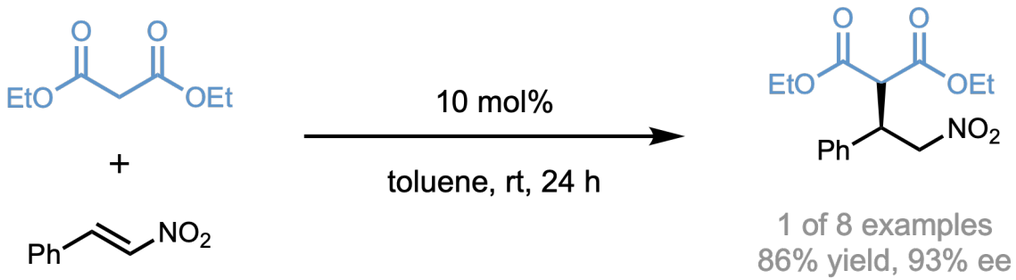


Lecture Overview



Introduction to Bifunctional Organocatalysis

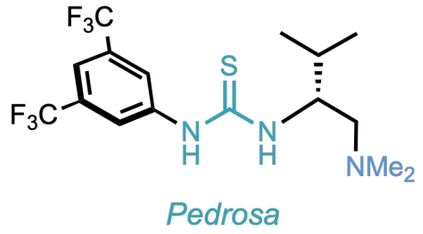




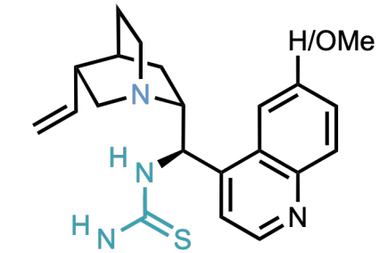
Reaction performs poorly if the two catalyst components are separate

Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673

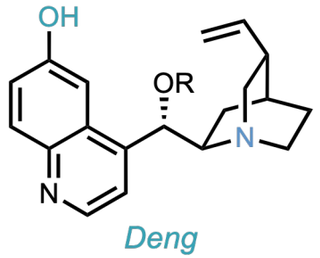
Other 3° Amine Bifunctional Organocatalysts



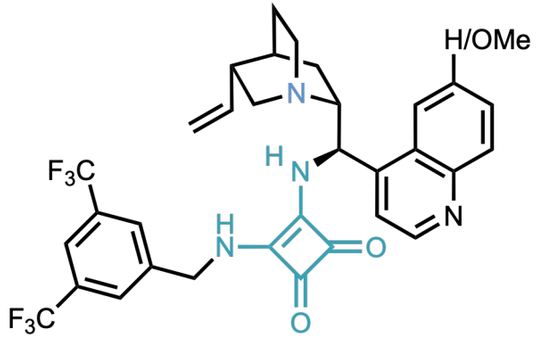
Pedrosa



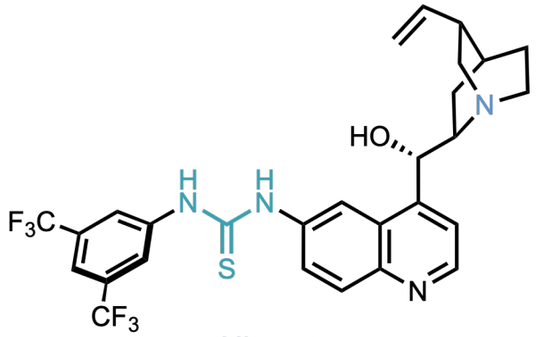
Chen, Connon, Dixon, Soós



Deng



Rawal



Hiemstra

✓ *Advantages*

tunable H-bond donor
[control/electrophile activation]

air stability / easy handling

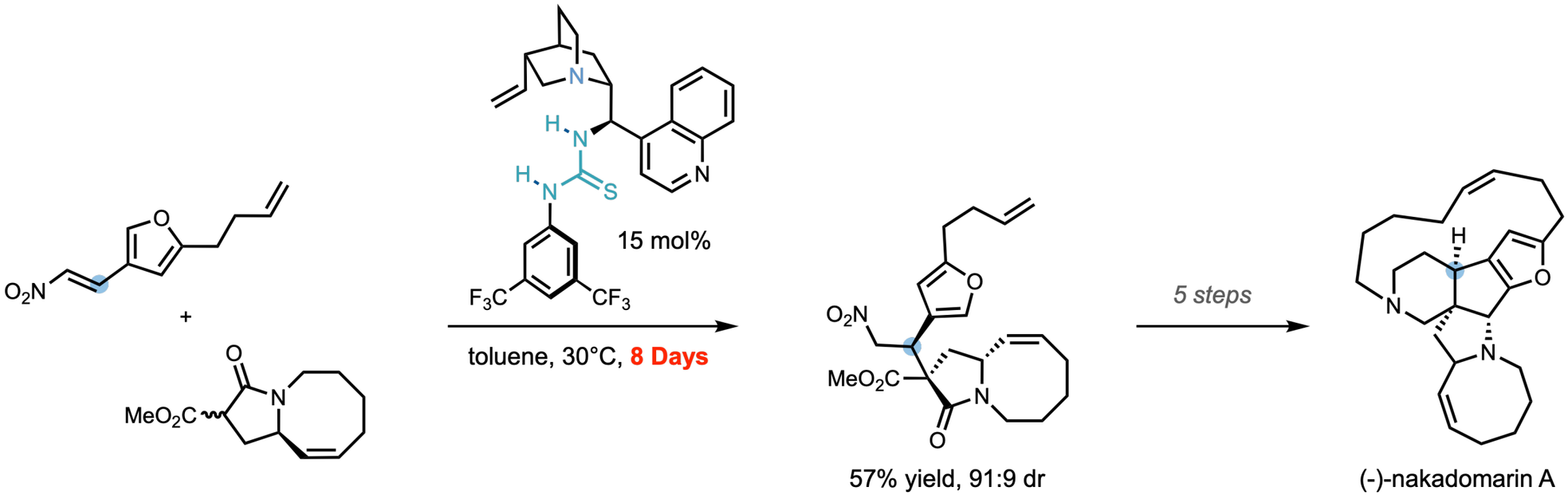
✗ *Limitations*

weak 3° amine base

[Only low pK_a pronucleophiles and reactive electrophiles accessible]

For a review on bifunctional 3° amine base catalysis see: Wang, J. *Catal. Sci. Technol.,* **2011**, *1*, 1298–1310.

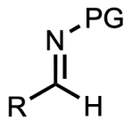
Nakadomarin A Total Synthesis



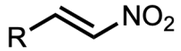
Dixon, D. J. *et al.*, *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633. Dixon, D. J. *et al. Tetrahedron Lett.* **2011**, *52*, 6094–6097.
Dixon, D. J. *et al. Chem. Commun.* **2011**, *47*, 10037–10039., Dixon, D. J. Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88-93.
Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *et al. Chem. Eur. J.* **2013**, *19*, 2726-2740.

Overcoming Limitations of Bifunctional 3° Amine Catalysts

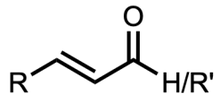
Strategy 1: Increase substrate electrophilicity



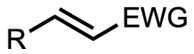
Imines derived from aldehydes



Reactive nitro-olefins

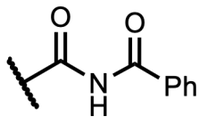


Enals enones

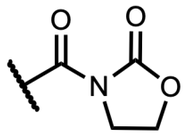


Activated esters

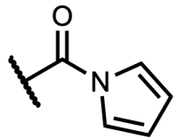
EWG =



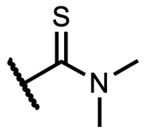
Imide



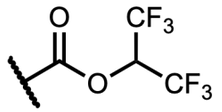
Oxazolidinone



N-Acyl pyrrole



Thioamide



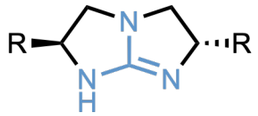
Fluorinated ester

- Non Ubiquitous
- Step Intensive
- Not always possible

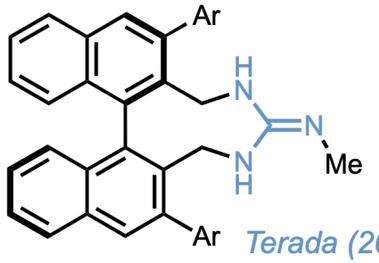
Overcoming Limitations of Bifunctional 3° Amine Catalysts

Strategy 2: Increase pK_{BH}+ of the Brønsted Base

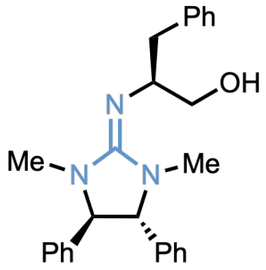
Guanidine Based



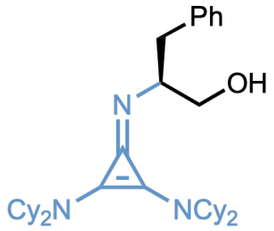
R = Ph: *Corey (1999)*
R = ^{t}Bu: *Tan (2007)*



Terada (2006)

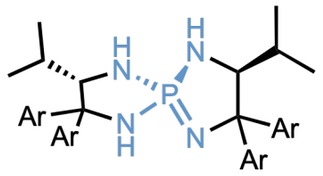


Ishikawa (2001)

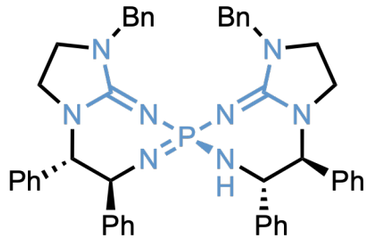


Lambert (2012)

Phosphazene Based



Ooi (2007)



Terada (2013)

✓ *Advantages*

superbasic moiety
[high pKa pronucleophiles accessible]

✗ *Limitations*

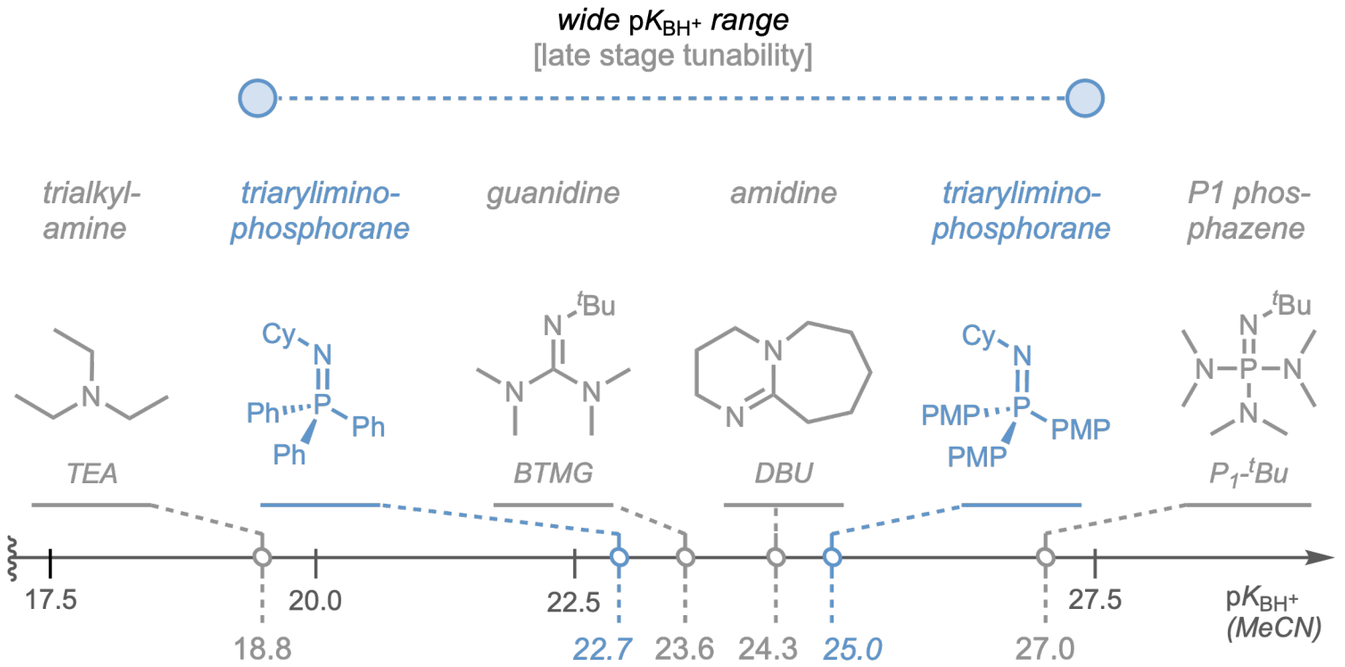
complex synthetic routes (in some cases)

tricky handling and storage (in some cases)

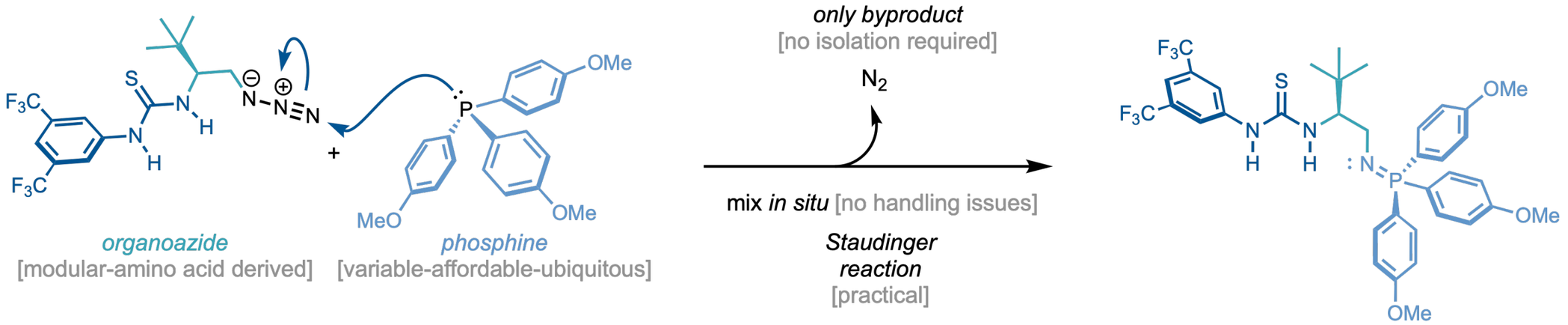
low modularity and tunability (course and fine)

For a recent review on superbase catalysis see: Zhou, J.; Tian, P. *Angew.Chem. Int.Ed.* **2020**, *59*, 8004–8014.

Bifunctional Iminophosphoranes



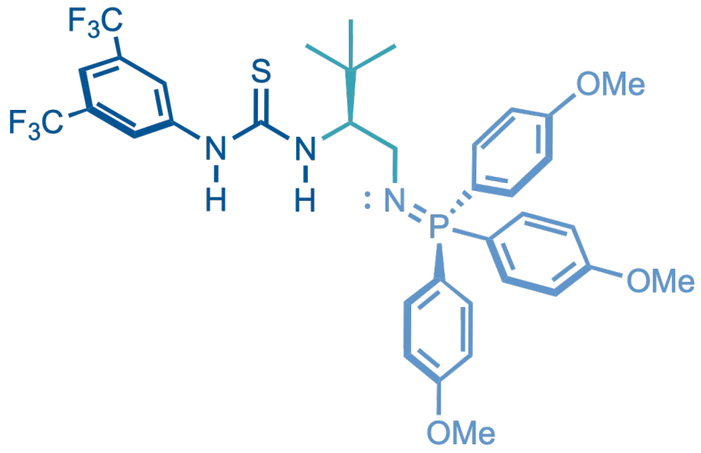
Bifunctional Iminophosphoranes



Bifunctional Iminophosphoranes

chiral backbone
[induction]

hydrogen bond donor
[reaction control]



iminophosphorane superbase
[access to high pK_a pronucleophiles]

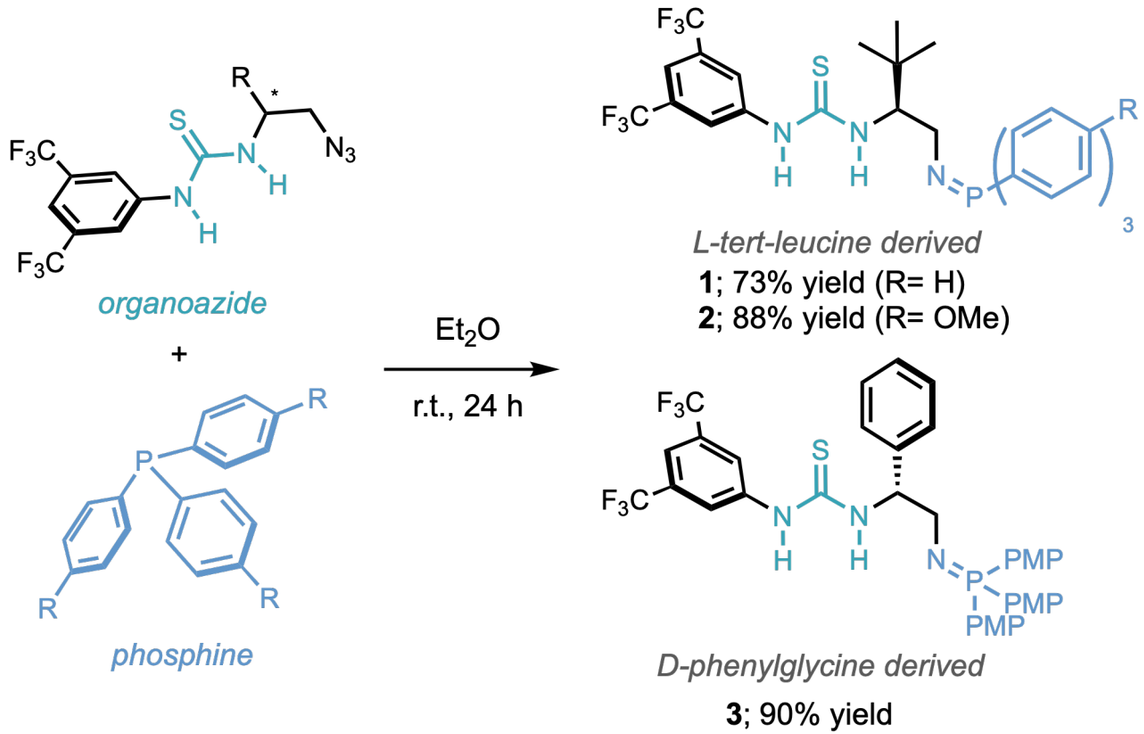
points of modularity

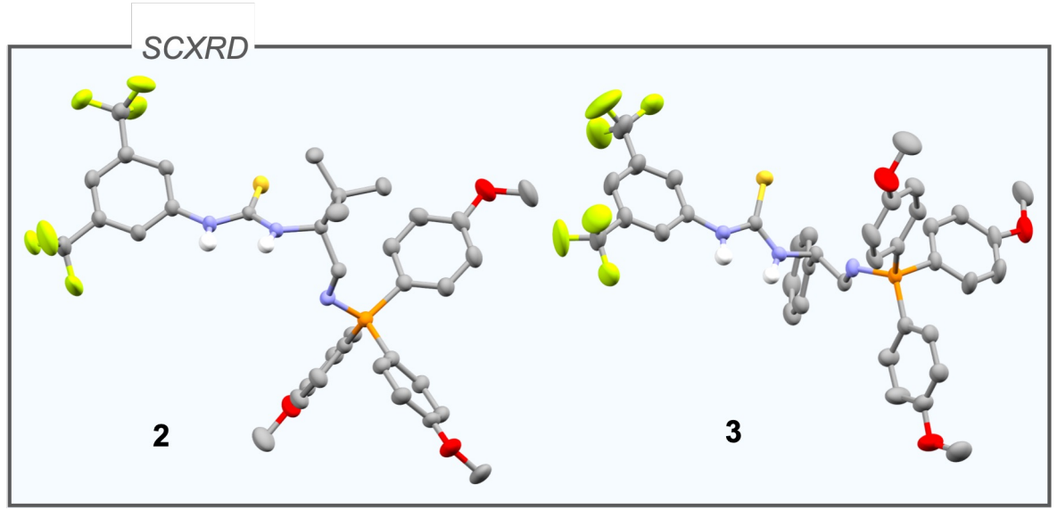


[bespoke catalyst design]

[air & moisture stable]

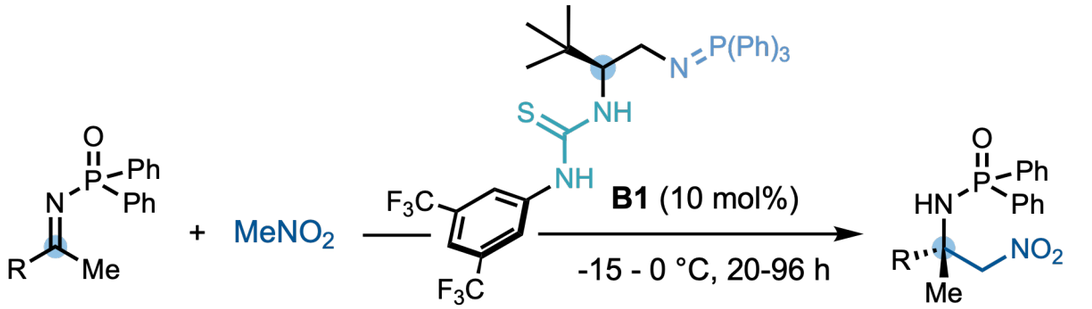
Bifunctional Iminophosphoranes





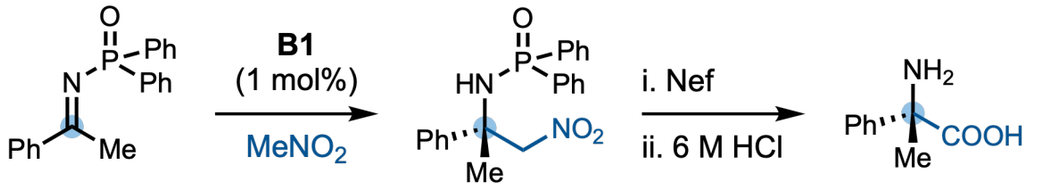
M. G. Núñez, A. J. M. Farley, D. J. Dixon, *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

Nitro-Mannich Reaction to Ketimines



17 examples
40-95% yield
up to 97.5:2.5 er

decagram scale nitro-Mannich



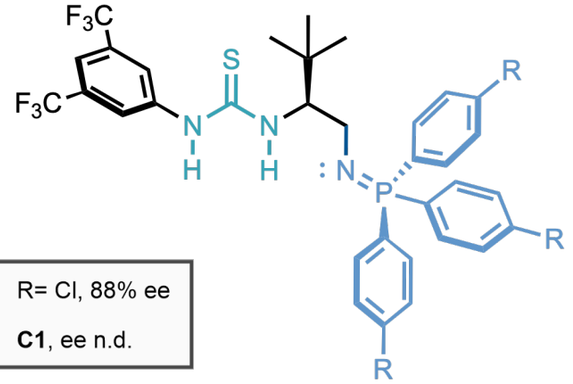
10.0 g

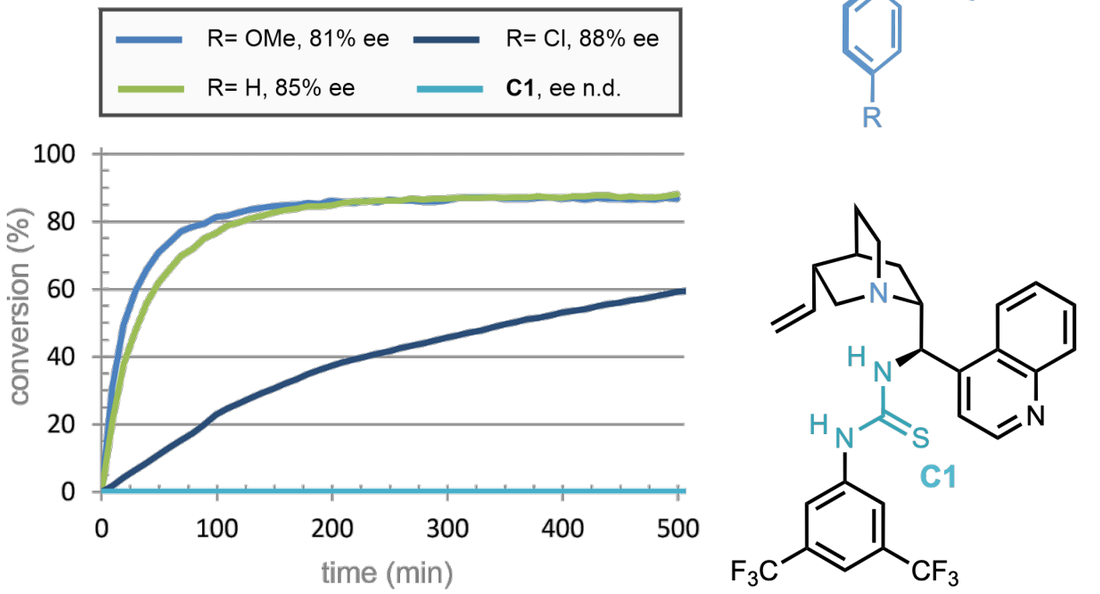
8.3 g, 63% yield,
>99:1 er
(after recrystallization)

α-quaternary amino acid
65% yield, >99:1 er

catalyst performance

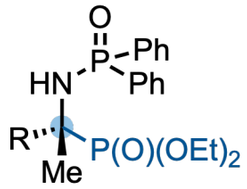
BIMP catalyst -vs- 3° amine catalyst



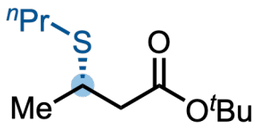


N. K. Pahadi, H. Ube, M. Terada, *Tetrahedron. Lett.* **2007**, *48*, 8700-8703.
M. G. Núñez, A. J. M. Farley, D. J. Dixon, *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

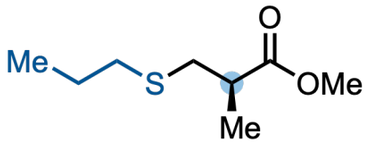
Bifunctional Iminophosphoranes



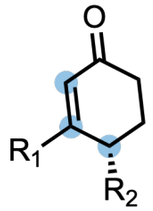
10 examples
78-99% yield
up to 85.5:14.5 er



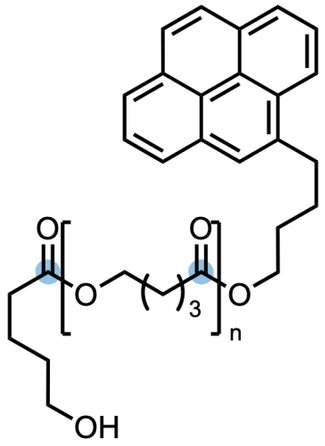
16 examples
68-99% yield
up to 97:3 er



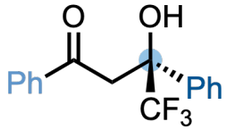
24 examples
36->99% yield
up to 98:2 er



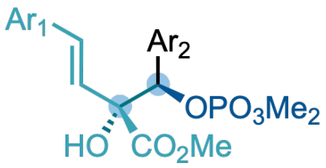
20 examples
50-99% yield
up to 99.5:0.5 er



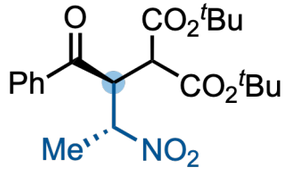
M_n (PDI) = 27500 g mol^{-1} (1.04)



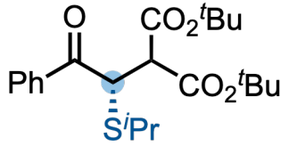
29 examples
60-98% yield
up to >99:1 er



18 examples
43-87% yield
up to 98.5:1.5 er
up to >20:1 dr

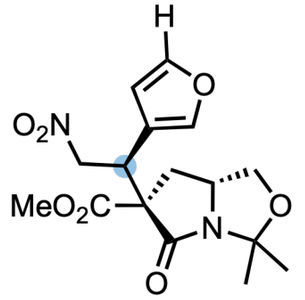


16 examples
78-96% yield
up to >99.5:0.5 er
>20:1 dr

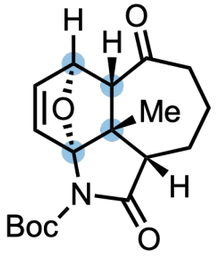


21 examples
86-98% yield
up to 98.5:1.5 er

[Jeffery Johnson, UNC]



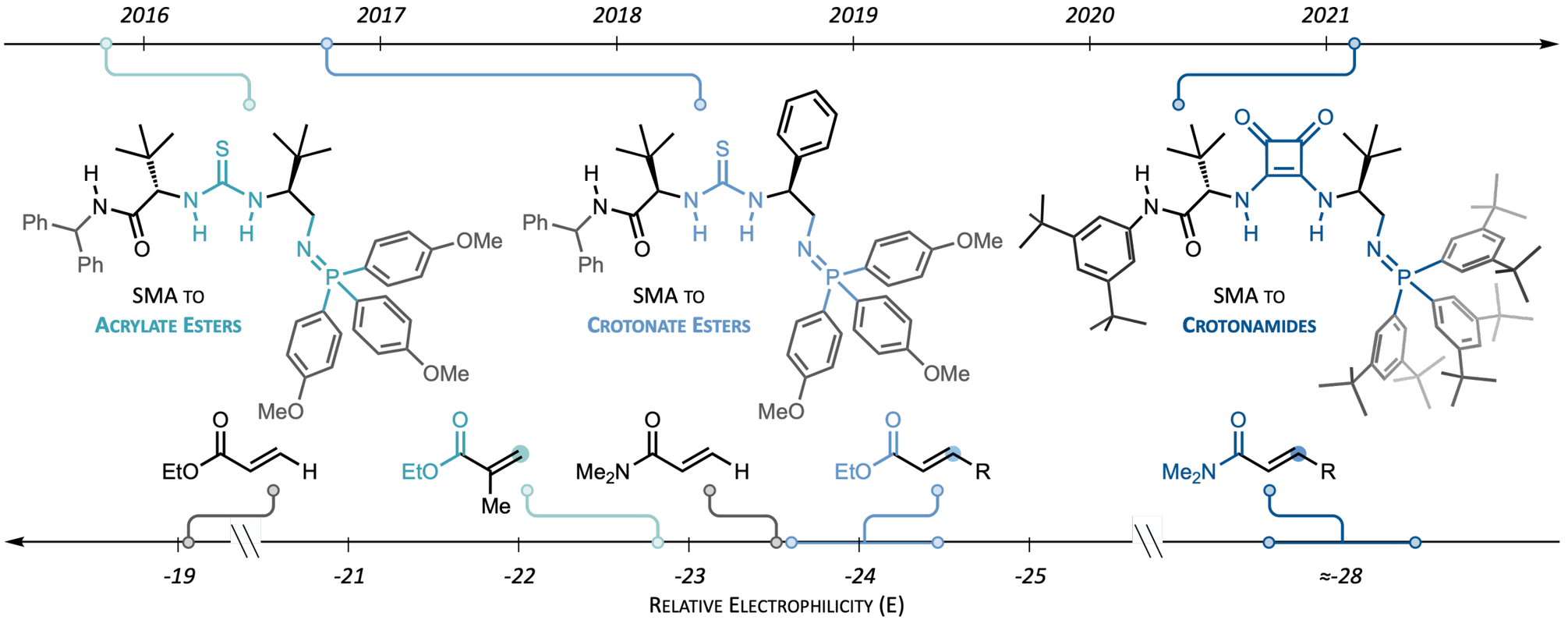
[Nakadomarin A]
3.5 hrs vs 8 days



[Himalensine A]
IMDAF cascade

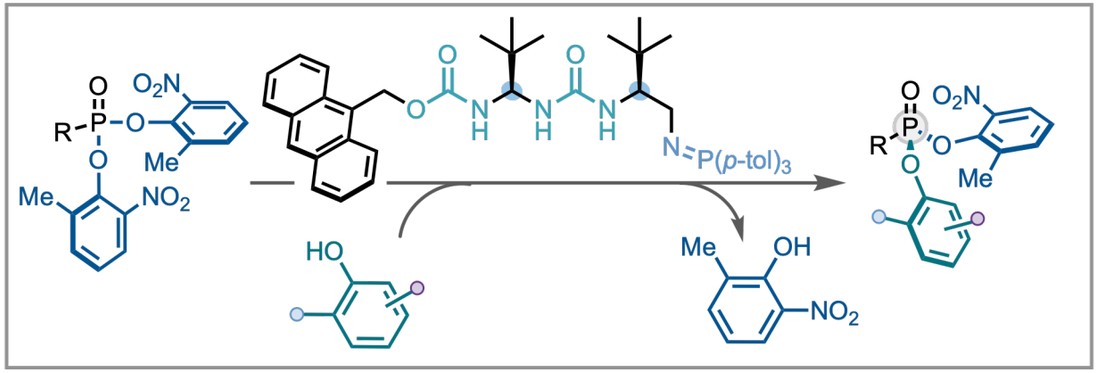
M. Formica, D. Rozsar, G. Su, A. J. M. Farley and D. J. Dixon *Acc. Chem Res.* **2020**, 53, 2235–2247.

Metal-Free Conjugate Addition to Unactivated α,β-Unsaturated Systems

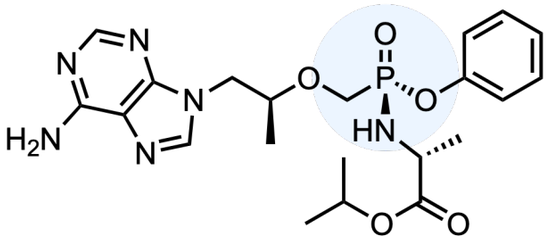


Allgäuer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2017**, *139*, 13318–13329.
Farley, A. J. M; Sandford, C.; Dixon D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992–15995.
Yang, J.; Farley, A. J. M.; Dixon, D. J. *Chem. Sci.* **2017**, *8*, 606–210.
Rozsar, D.; Formica, M.; Yamazaki, K.; Hamlin, T. A.; Dixon, D. J. *J. Am. Chem. Soc.* **2022**, *144,* 1006–1015.

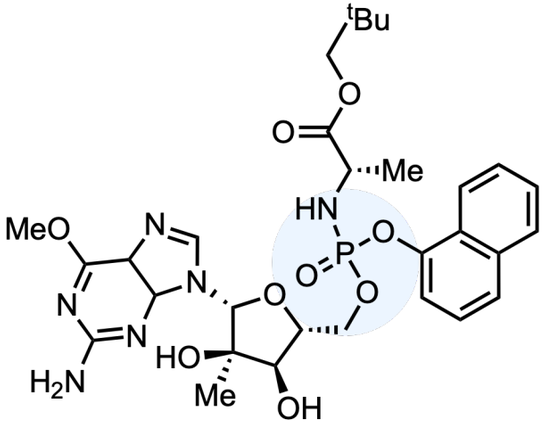
Lecture Overview



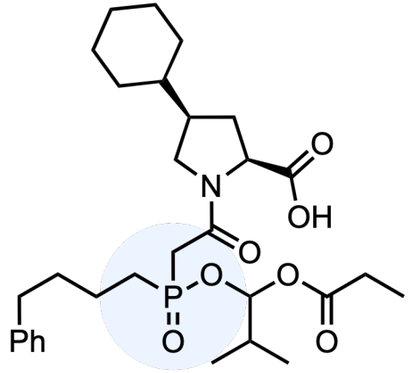
Why Chiral P(V)?



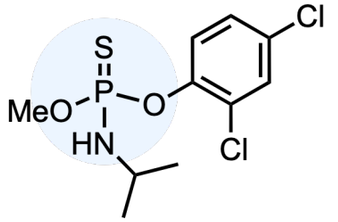
Tenofovir alafenamide
Gilead
HIV and Hepatitis B



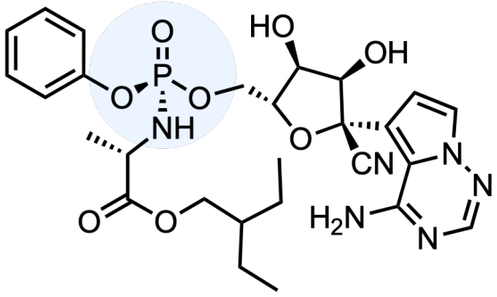
BMS-986094
BMS
Hepatitis C



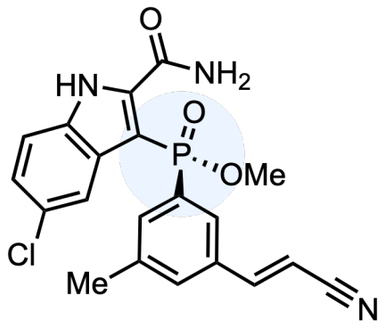
Fosinopril
BMS
Hypertension and heart faliure



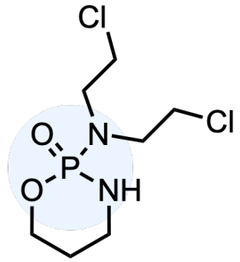
Zytron (DMPA)
Dow Chemical Company
Herbicide



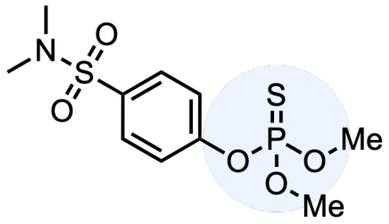
Remdesivir
Gilead
Ebola & SARS-CoV-2



Fosdevirine (discontinued)
GSK/ViiV Healthcare
HIV-AIDS

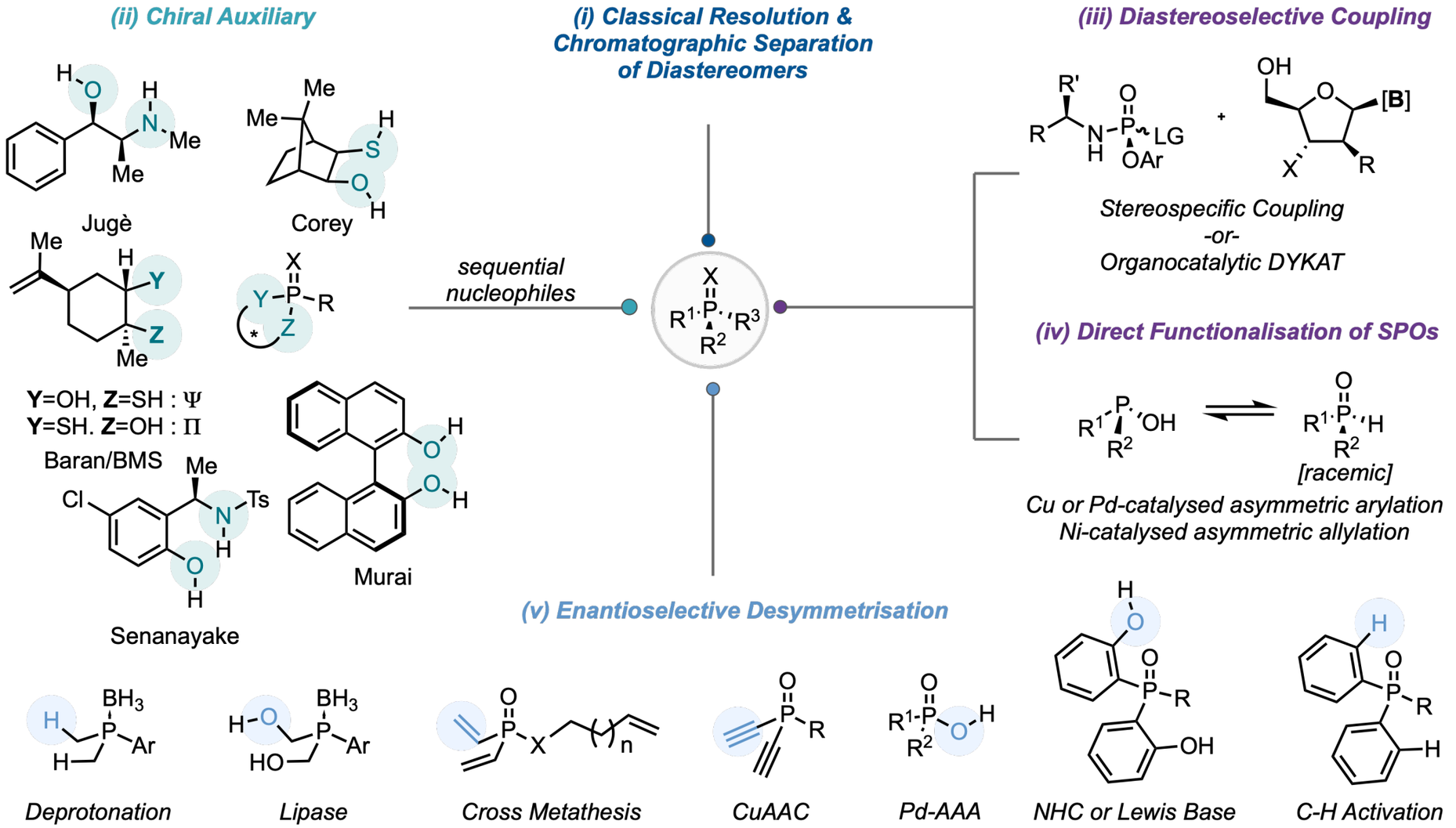


Cyclophosphamide
Chemotherapy
WHO List of Essential Medicines
Numerous analogues in clinical trials



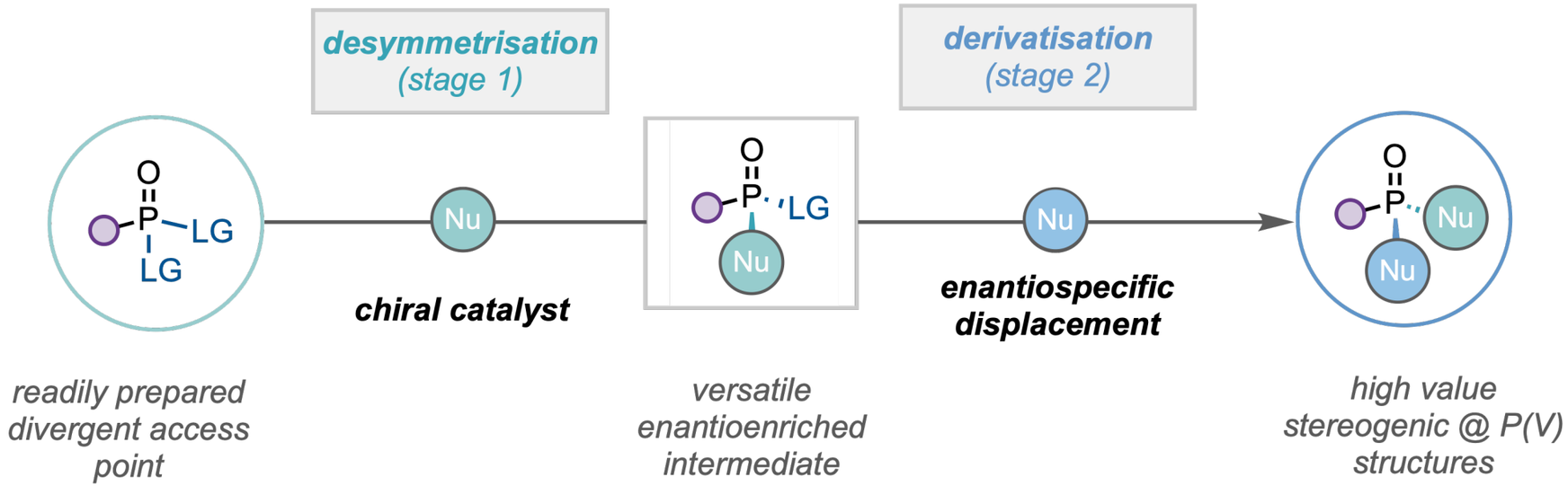
Famphur
grub infestations in cattle

Approaches to P(V) Synthesis



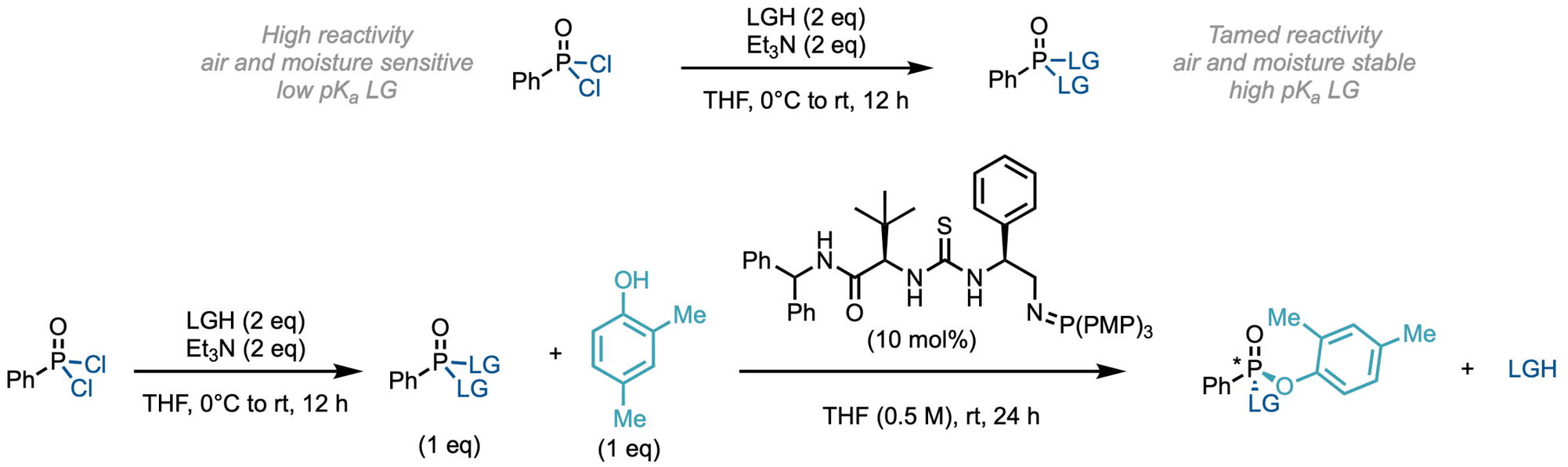
1) Amblard, F. et al. *Chem. Rev*. **2014**, *114*, 9154–9218. 2) DiRocco, D. A. et al. *Science* **2017**, *356*, 426–430. 3) Knouse, K. W. et al. *Science* **2018**, *361*, 1234–1238. 4) Sun, Y.; et al. *Chem. Sci*. **2018**, *9*, 2981–2985. 5) Jang, H. et al. *Nat. Chem.* **2017**, *9*, 1269–1275. 6) Del Águila-Sánchez, M. A. et al. Dalt. Trans. **2016**, *45*, 2008–2022. 7) Jang, Y.-S.; et al. *Angew. Chemie Int. Ed*. **2018**, *57*, 12901–12905. 9) Yang, G. et al. *Chem. Sci*. **2019**, *10*, 4322–4327. 10) Beaud, R. et al. *J. Am. Chem. Soc.* **2016**, *138*, 13183–13186.

A New 2 Stage Strategy?

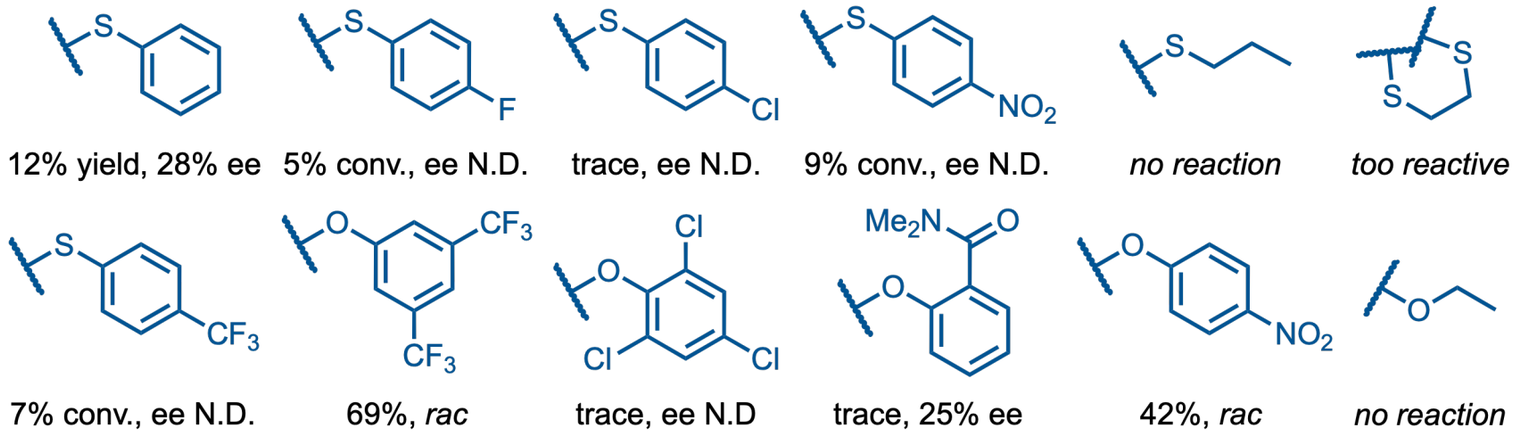


Formica, M.; Rogova, T; Shi, H.; Sahara, N.; Ferko, B.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Yamazaki, K.; Dixon, D. J. *Nat. Chem.* **2023**, *15*, 714-721
See also: Forbes, K. C.; Jacobsen, E. N. *Science* **2022**, *376*, 1230-1236

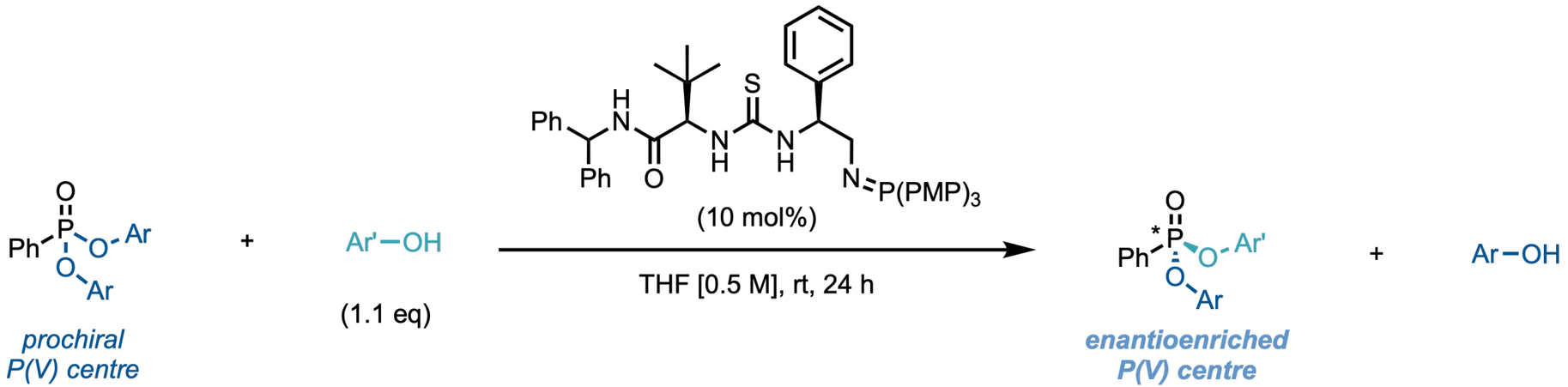
Leaving Group Optimization

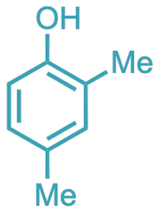
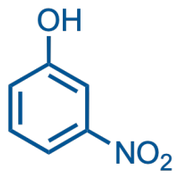
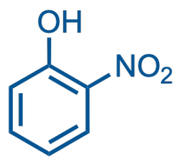


Potential LGs assessed

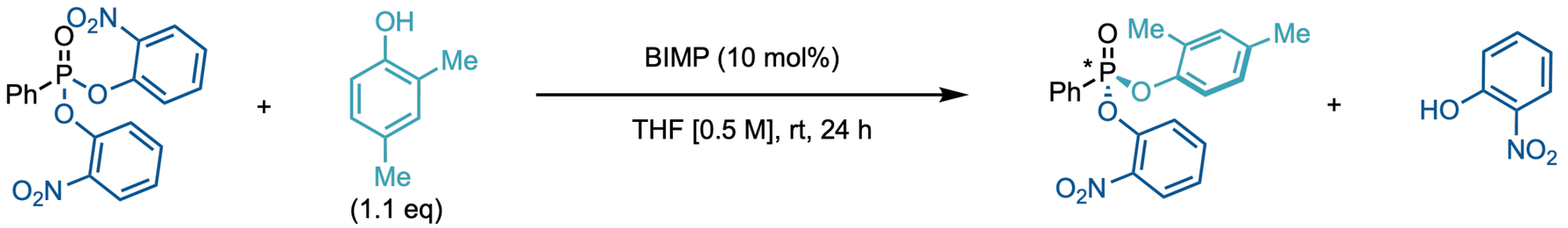


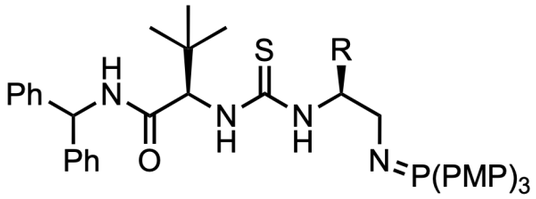
Leaving Group Optimization



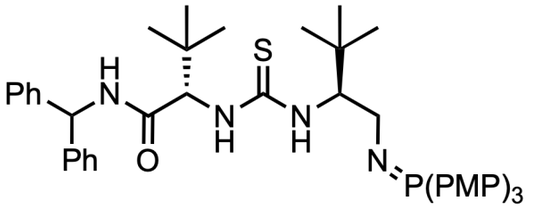
Ar'–OH	Ar–OH		
			
model nucleophile	42% yield *rac*	60% yield 17% ee	65% yield 26% ee

Selected Catalyst Evaluation

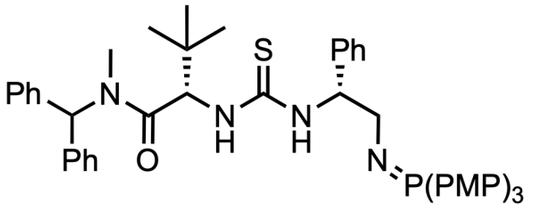




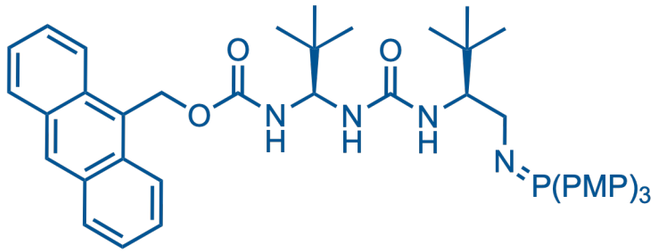
R= Ph 60% yield, 26% ee
R=1-nap 57% yield, 31% ee
R= ^{t}Bu 35% yield, 24% ee



22% yield, rac

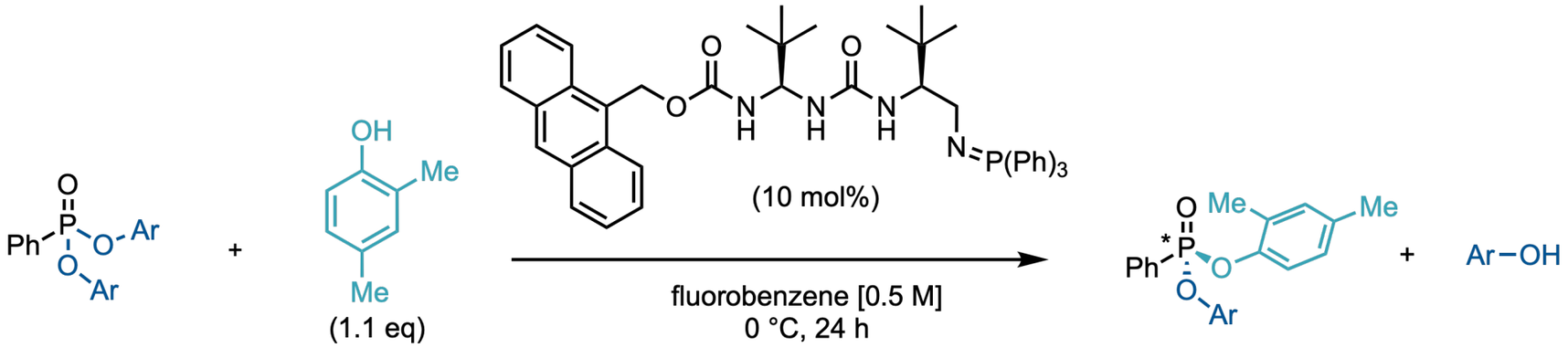


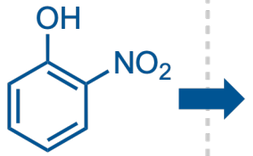
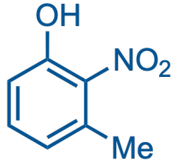
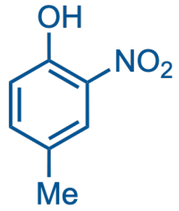
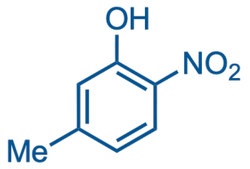
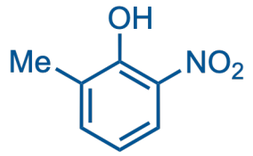
52% yield, -27% ee



58% yield, 52% ee

Leaving Group Fine Tuning



Initial conditions	Ar–OH				*Final conditions*
					*BIMP (15 mol%)* *rt, 0.25 M* *P(p-tol)$_3$ instead of PPh$_3$*
41% yield 87% ee	5% yield 50% ee	61% yield 89% ee	34% yield 67% ee	10% yield 94% ee	***84% yield*** ***91% ee***

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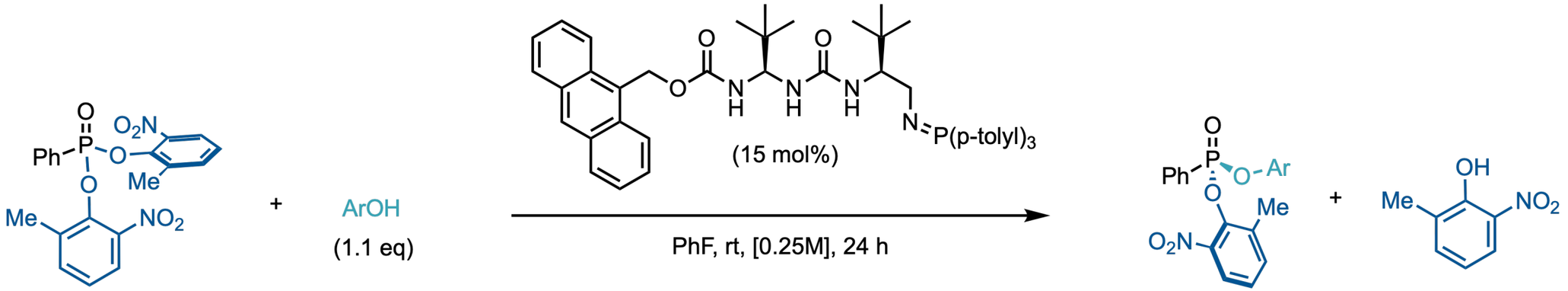
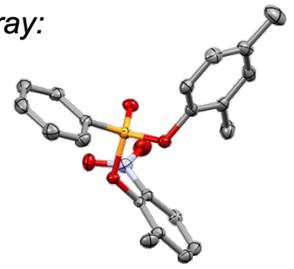
Desymmetrisation: Phenol Scope

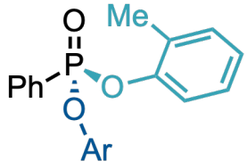


Phenol Variation

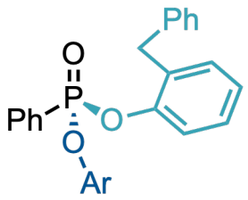
0.1 mmol: 82% yield, 91% ee
3 mmol: 88% yield, 92% ee

X-ray:

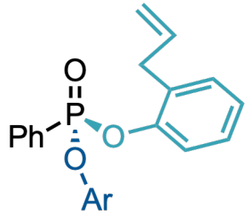




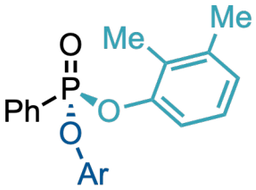
82% yield, 82% ee



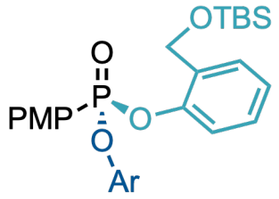
80% yield, 88% ee



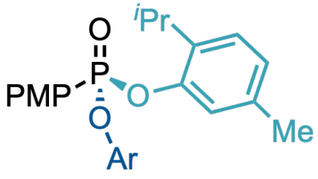
71% yield, 90% ee



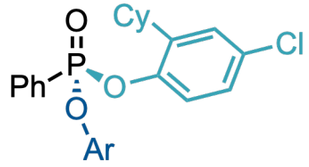
93% yield, 88% ee



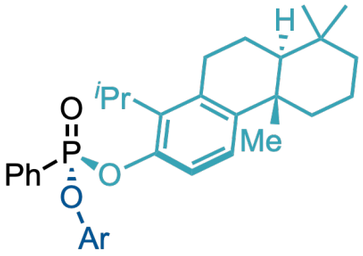
98% yield, 91% ee



64% yield, 96% ee



61% yield, 75% ee



63% yield, 97:3 dr
from totarol

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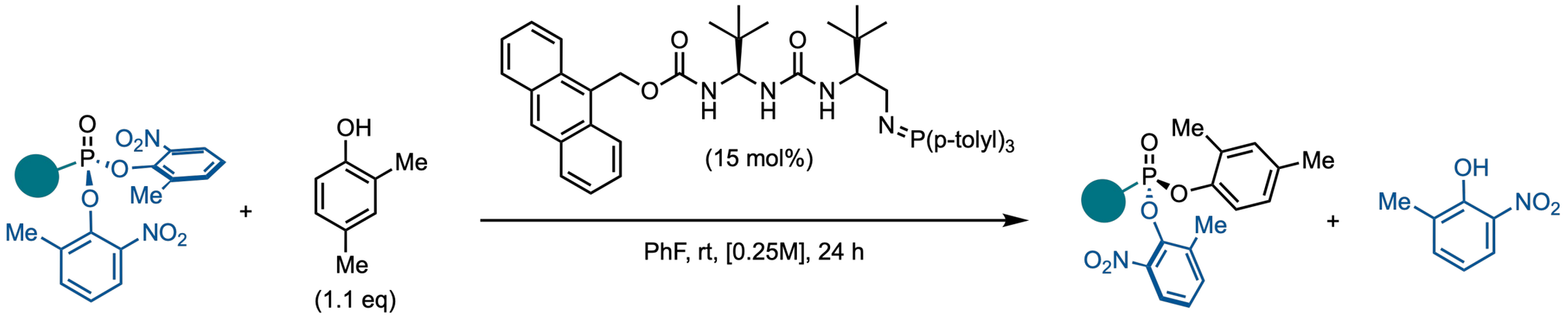
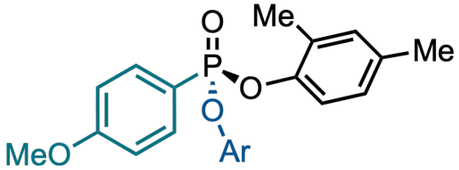
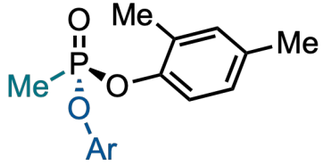
Desymmetrisation: Backbone Scope



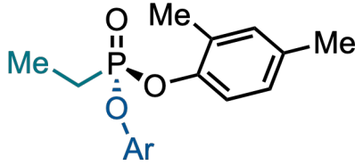
Backbone Variation



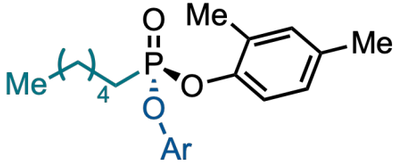
69% yield, 97% ee



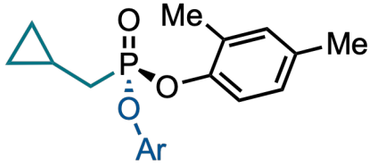
71% yield, 84% ee



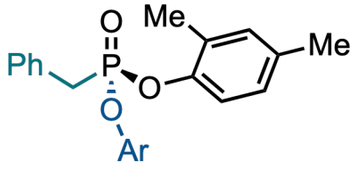
63% yield, 93% ee



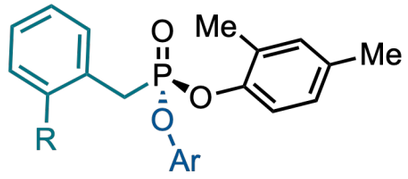
60% yield, 94% ee



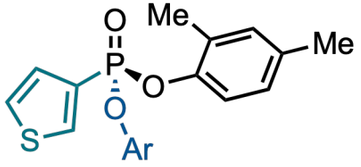
46% yield, 88% ee



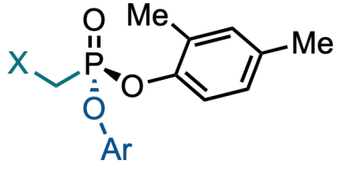
73% yield, 78% ee



R=Me: 42% yield, 86% ee
R= CF_3: 43% yield, 78% ee



75% yield, 92% ee



X= SMe: 77% yield, 92% ee
X= OBn:72% yield, 83% ee

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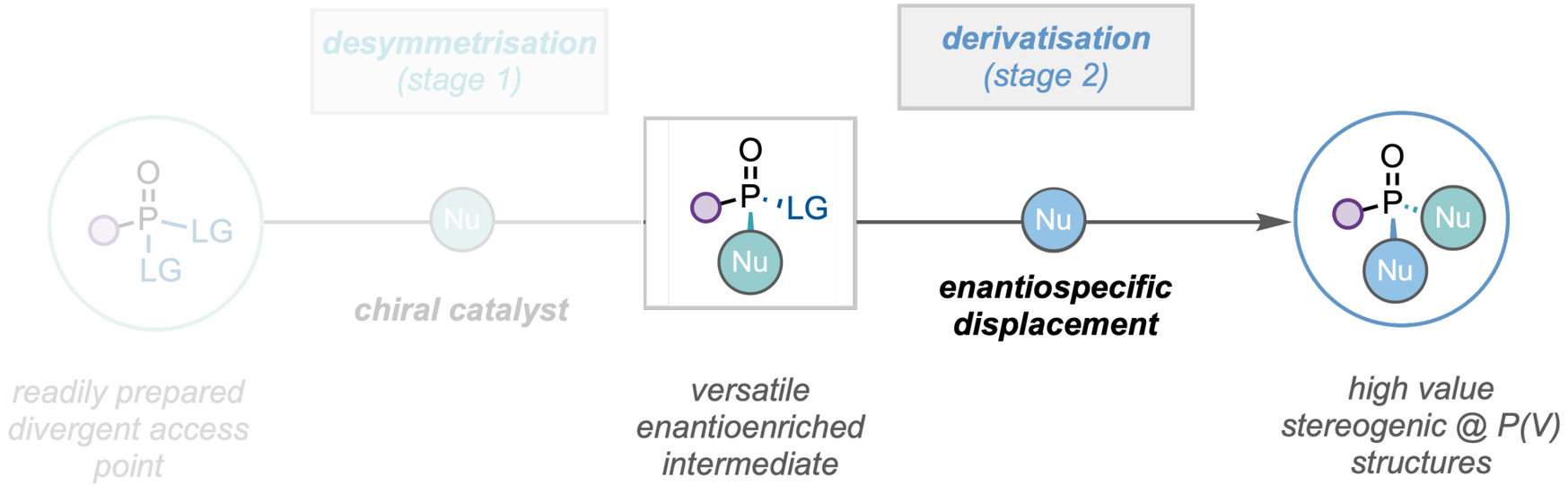
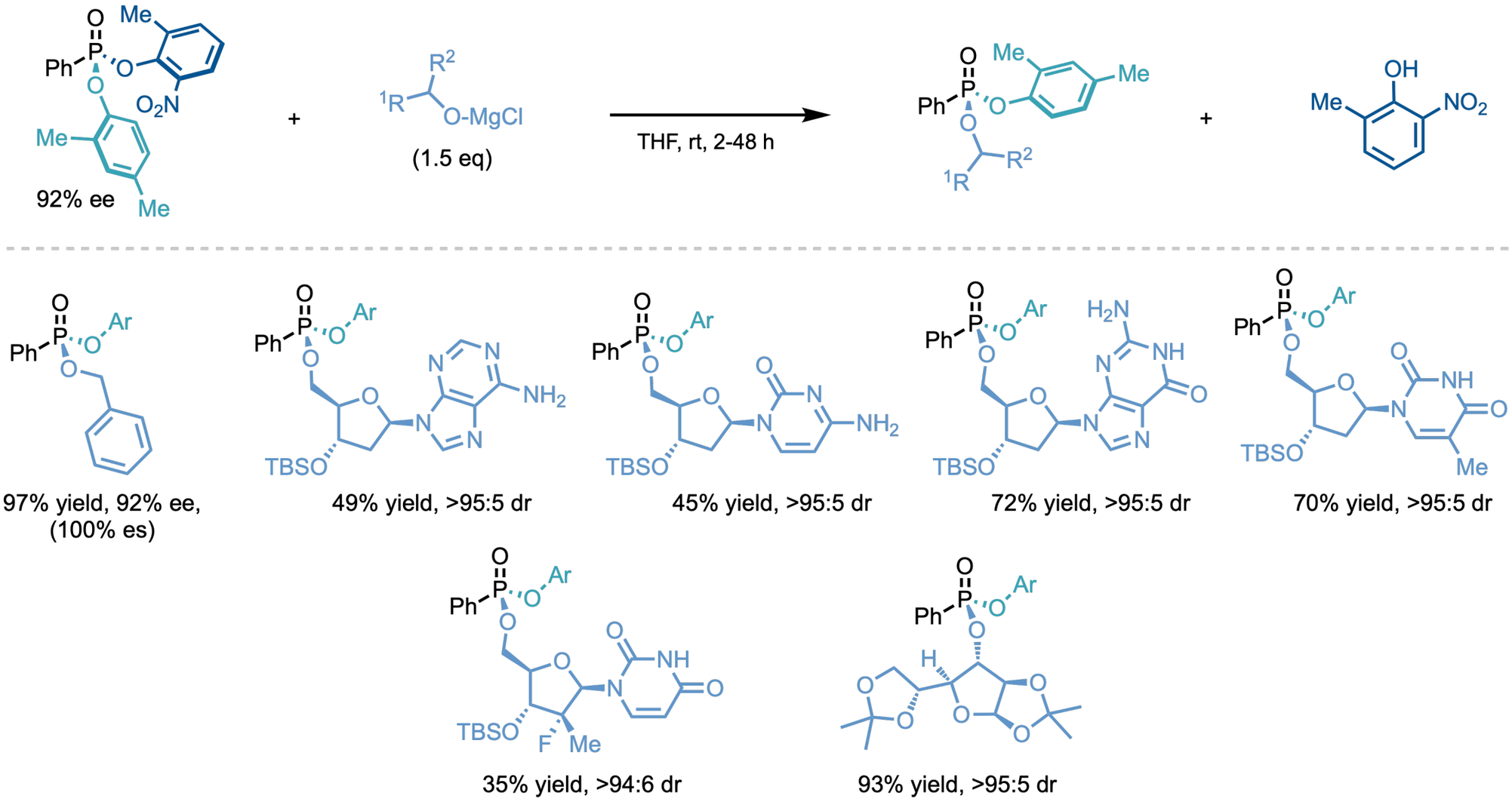
Stage 2 – Derivatisation Strategy



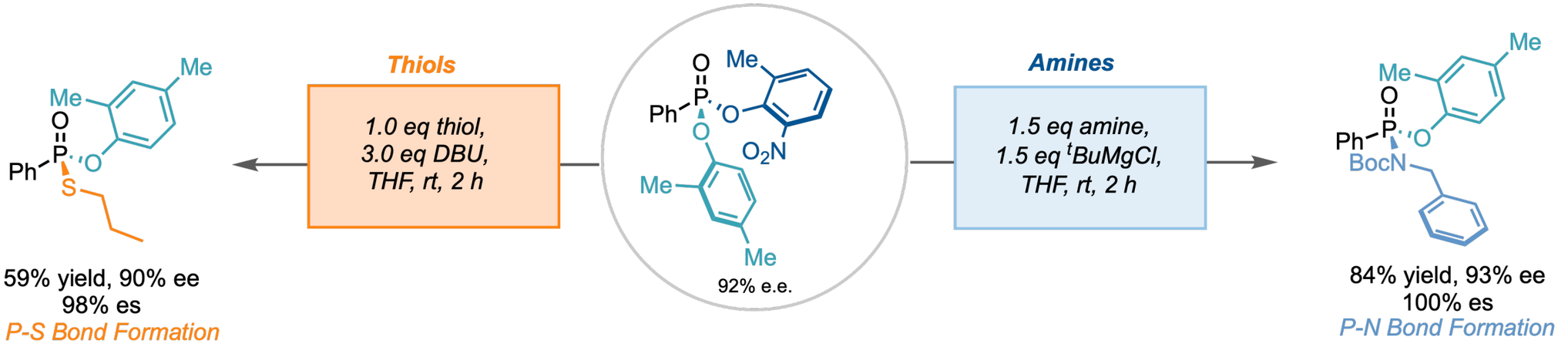
Formica, M.; Rogova, T; Shi, H.; Sahara, N.; Ferko, B.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Yamazaki, K.; Dixon, D. J. *Nat. Chem.* **2023**, *15*, 714-721

Derivatisation: P-O Bond Formation

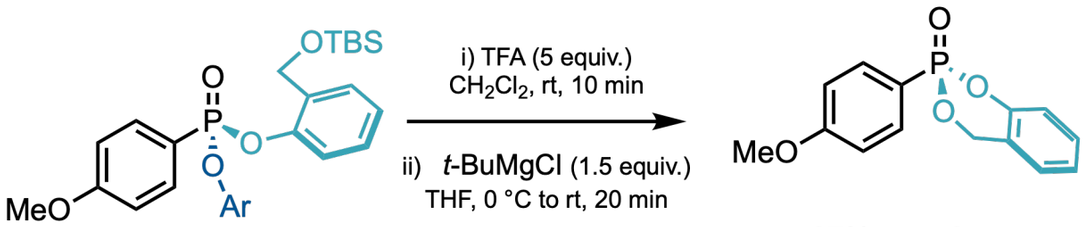


Formica, M.; Rogova, T; Shi, H.; Sahara, N.; Ferko, B.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Yamazaki, K.; Dixon, D. J. *Nat. Chem.* **2023**, *15*, 714-721

Derivatisation: P-X Bond Formation

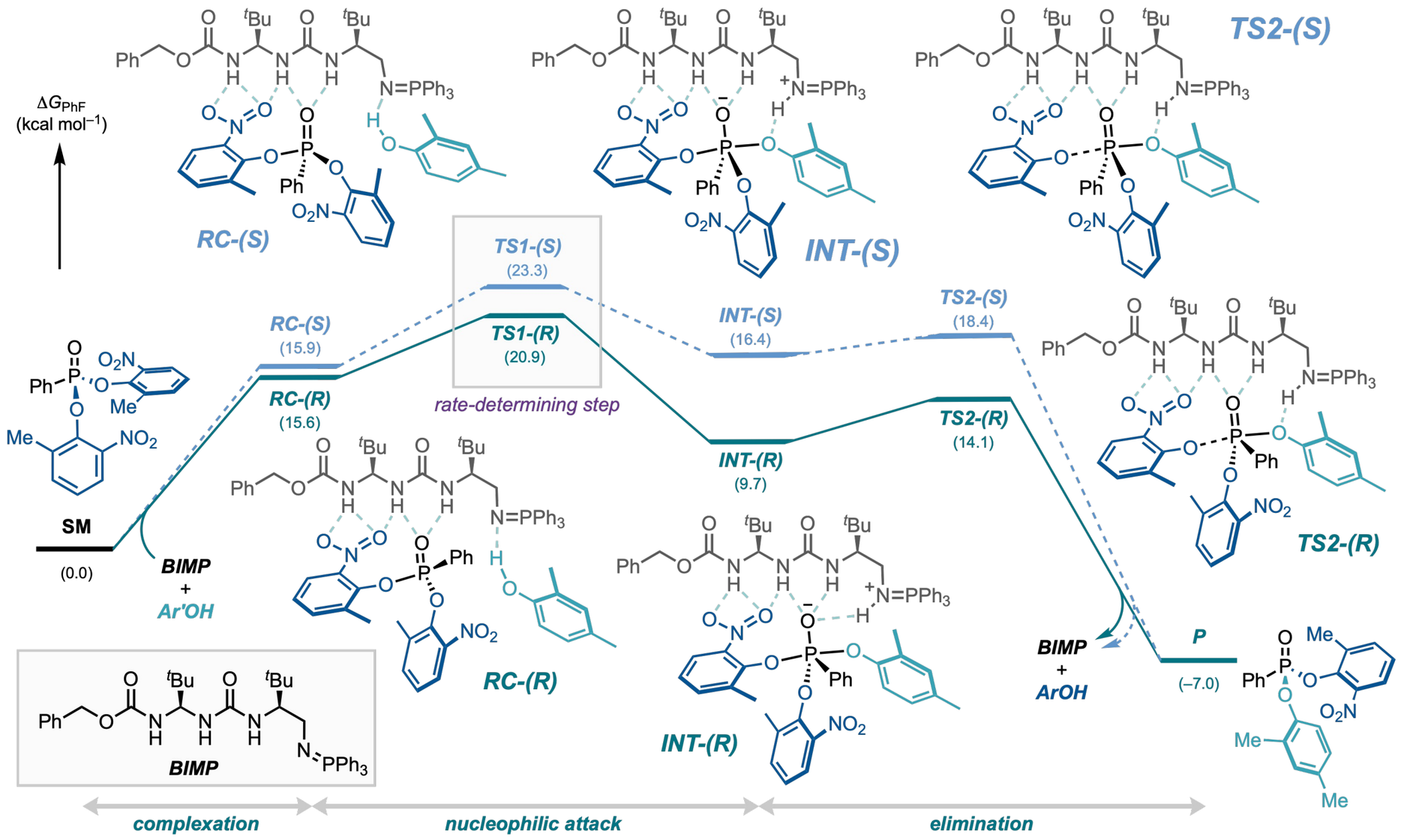


Acces to CycloSal Derivative



Formica, M.; Rogova, T; Shi, H.; Sahara, N.; Ferko, B.; Farley, A. J. M.; Christensen, K. E.; Duarte, F.; Yamazaki, K.; Dixon, D. J. *Nat. Chem.* **2023**, *15*, 714-721

DFT Studies: Reaction Potential Energy Surface

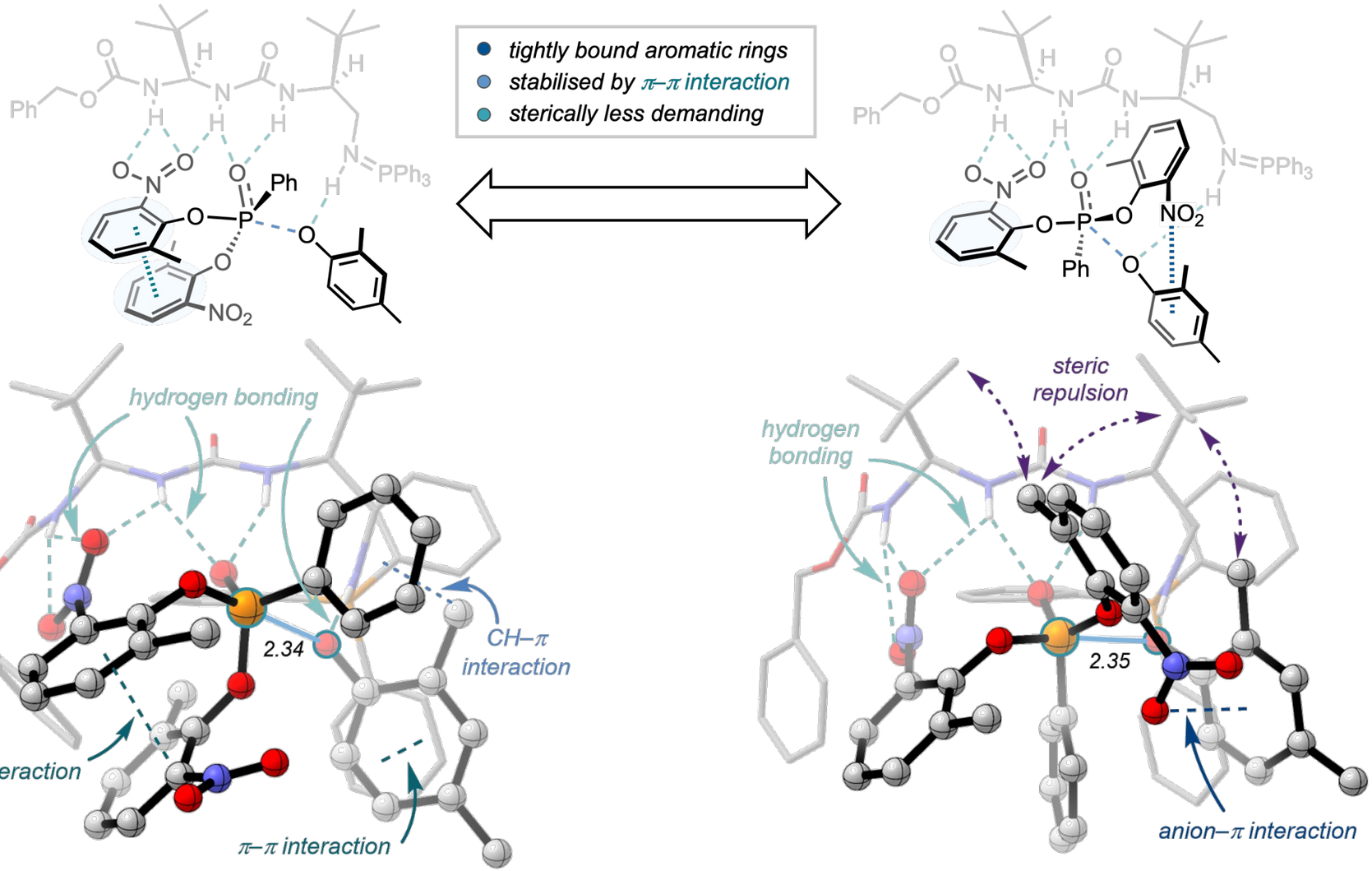


Computed at the SMD(fluorobenzene)/M06-2X/def2TZVP//SMD(fluorobenzene)/M06-2X/def2SVP level of theory *(by Ken Yamazaki)*

Enantioselectivity-Determining Nucleophilic TS Structures

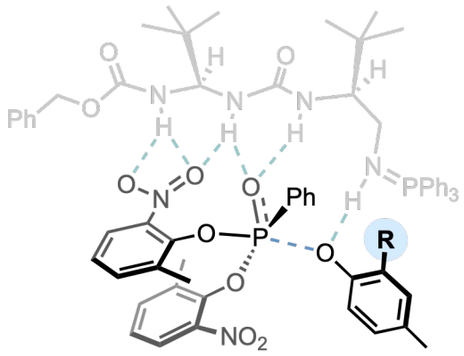
TS1-(*R*) (favoured)

TS1-(*S*)

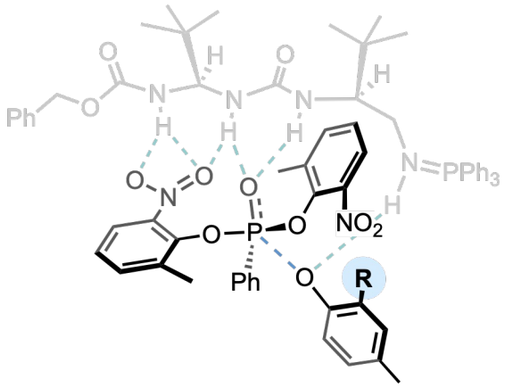


Computed at the SMD(fluorobenzene)/M06-2X/def2TZVP//SMD(fluorobenzene)/M06-2X/def2SVP level of theory *(by Ken Yamazaki)*

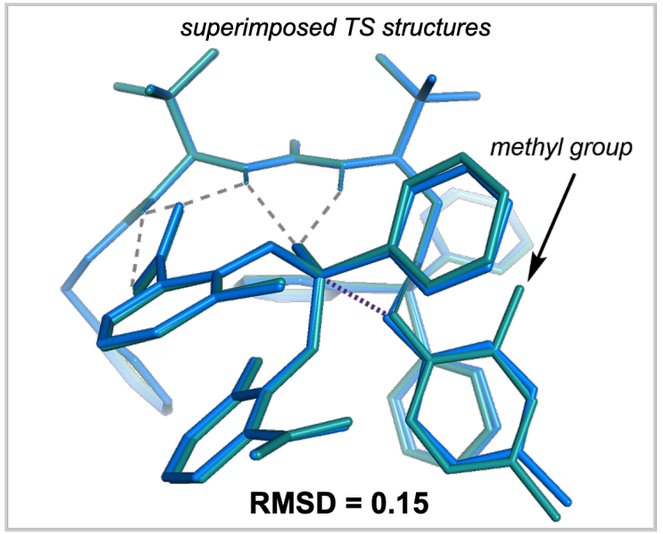
Origin of Ortho-Substituent Effect in P(V) Desymmetrisation

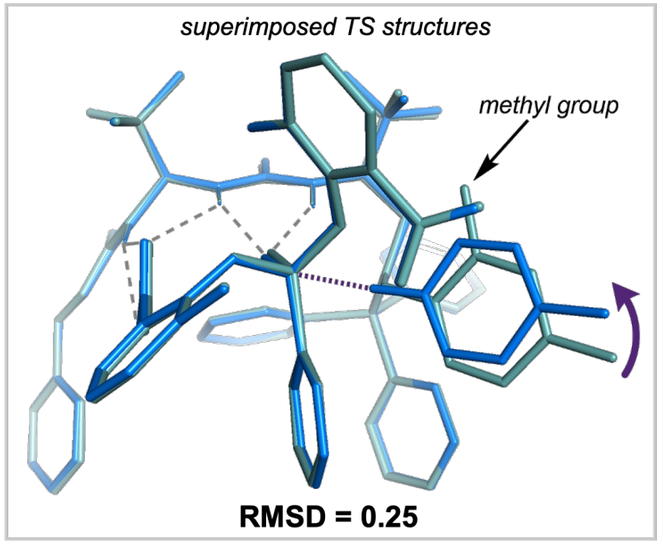


TS1-(*R*)-Me (R = Me)
TS1-(*R*)-H (R = H)



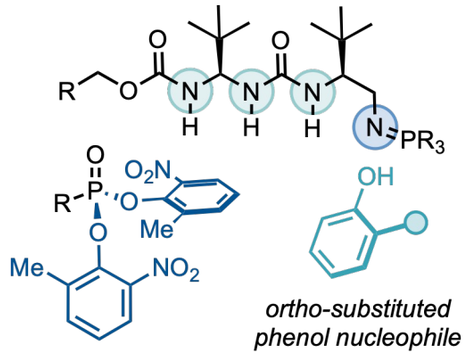
TS1-(*S*)-Me (R = Me)
TS1-(*S*)-H (R = H)





R = Me (green) or H (blue)

1st generation desymmetrization



ortho-substituted phenol nucleophile

DFT calculation

TS1-(*R*)-Me *v.s.* **TS1-(*S*)-Me**
$\Delta\Delta G^{\ddagger}$ = 2.4 kcal mol^{-1}

removal of ortho-Me group

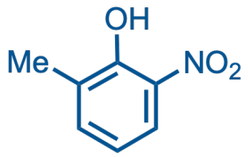
TS1-(*R*)-H *v.s.* **TS1-(*S*)-H**
$\Delta\Delta G^{\ddagger}$ = 0.9 kcal mol^{-1}

strain relief in the absence of ortho substituent

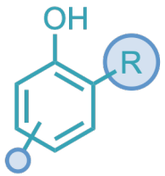
- *ortho-substituent required for high e.r.*
- *negligible geometry change in **TS1-(R)***
- *The absence of ortho-Me group stabilizes TS1-(S)-H due to strain relief*

Computed at the SMD(fluorobenzene)/M06-2X/def2TZVP//SMD(fluorobenzene)/M06-2X/def2SVP level of theory *(by Ken Yamazaki)*

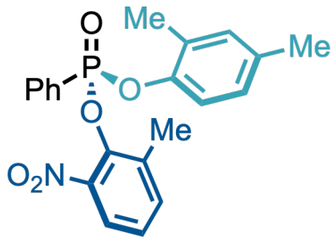
Limitations



Low pKa phenol LG deactivates catalyst [15 mol% required] and has a relatively high cost [$9/g]



Limited scope of phenol nucleophiles in desymmetrisation step [ortho substituent required for high ee]



Stage 2 only compatible with O,S and N nucleophiles [no C-centred and ArOH nucleophiles]

Overcoming Limitations - 2nd Generation



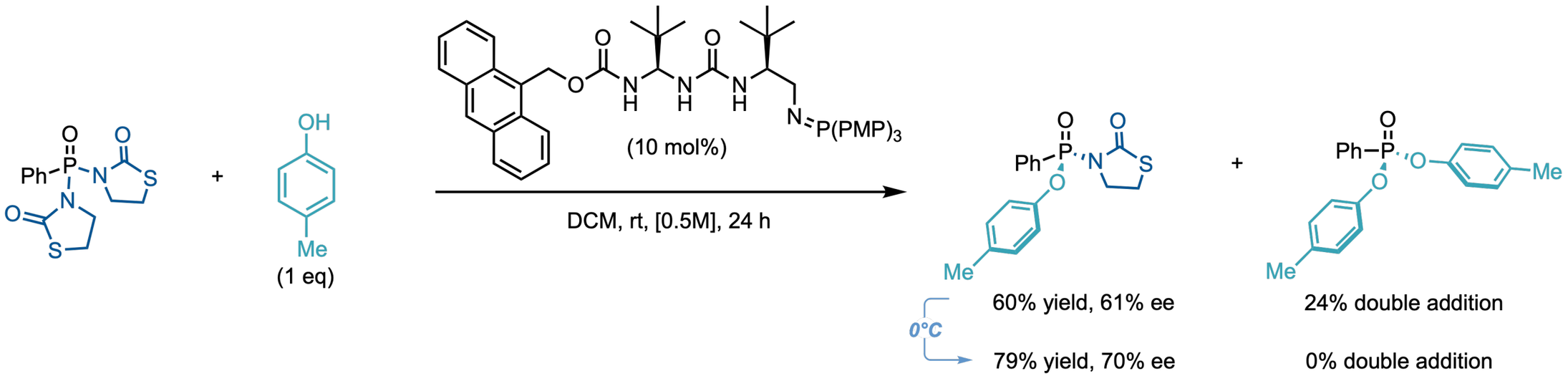
pK_a = ~12 (DMSO) pK_a = ~ 20 (DMSO)

[proximal Lewis basic site maintained]



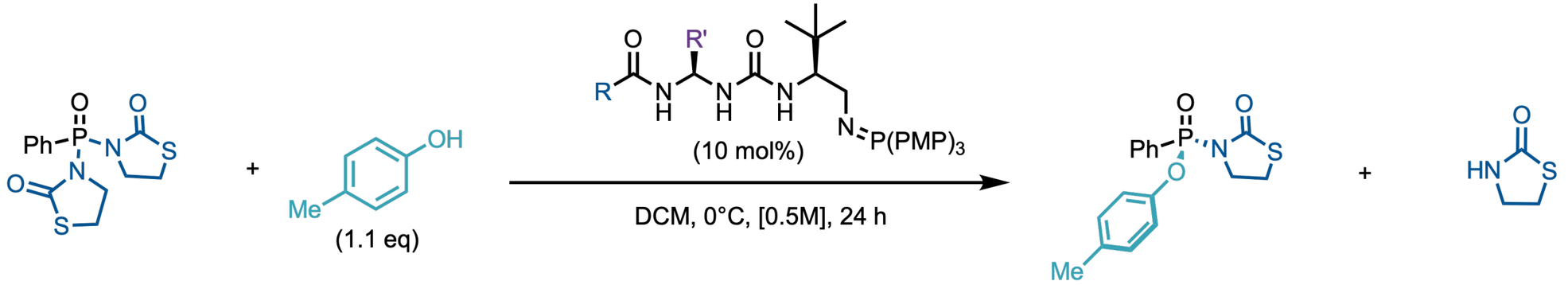
[catalyst re-opimisation]

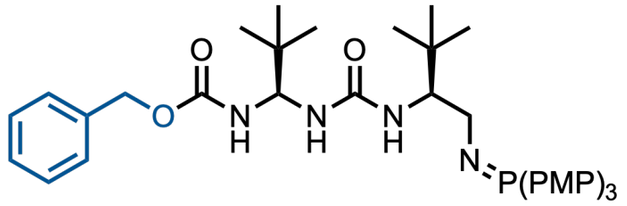
Leaving Group Fine Tuning



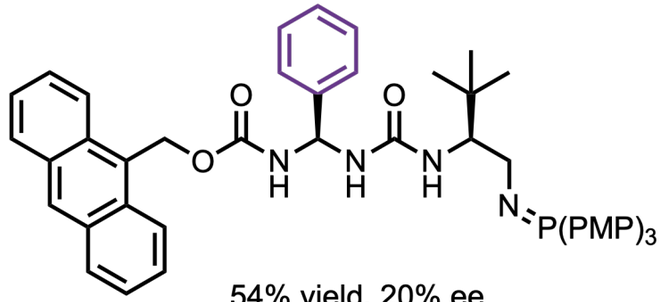
M. Formica, B. Ferko, T. Marsh, T. J. Davidson, K. Yamazaki, D. J. Dixon, *Angew. Chemie. Int Ed.* **2024**, *63*, e202400673

Catalyst Fine Tuning

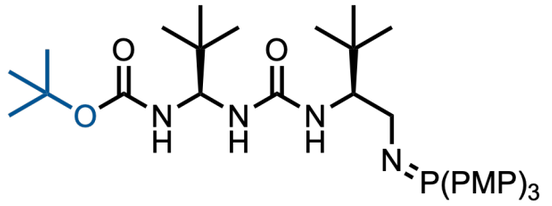




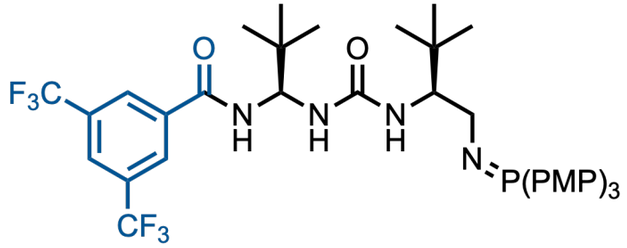
17% yield, 41% ee



54% yield, 20% ee



99% yield, 77% ee



99% yield, 83% ee

Final conditions

EtOAc
0 °C, [0.0625M]

99% yield, 98% ee

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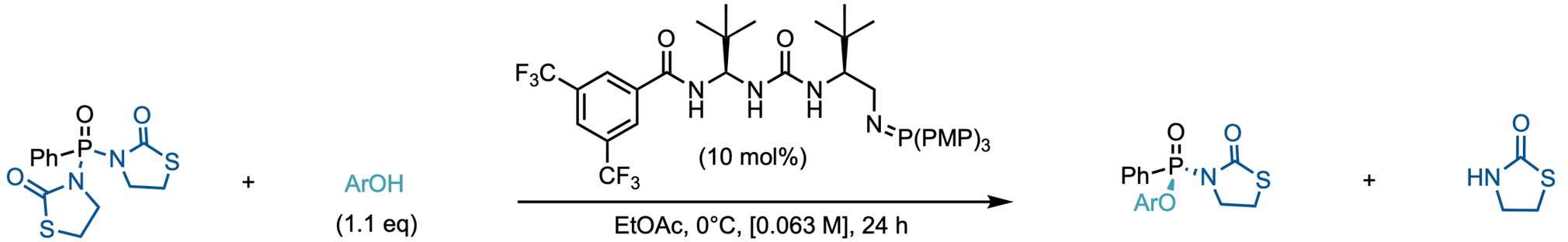
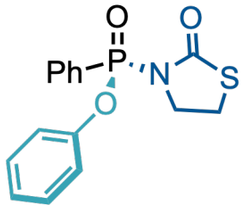
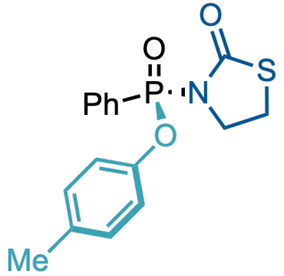
Desymmetrisation Phenol Scope



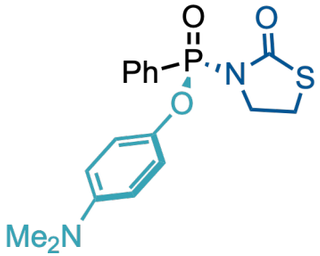
Phenol Variation



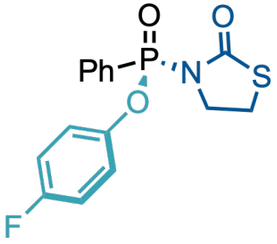
75% yield, 98% ee
[57% yield, 6% ee with Gen 1 system]



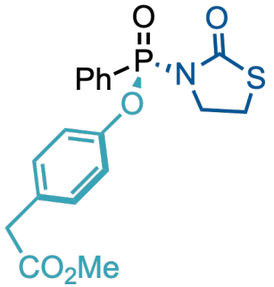
99% yield, 98% ee



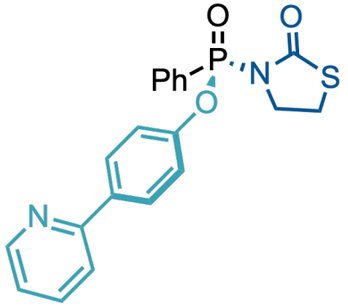
88% yield, 84% ee



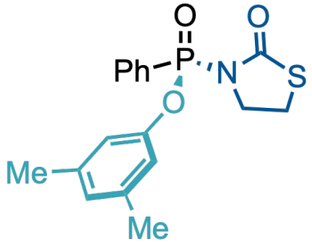
48% yield, 86% ee
(2 eq. of phenol, 48 h)



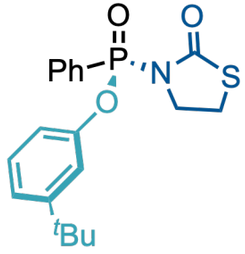
74% yield, 95% ee



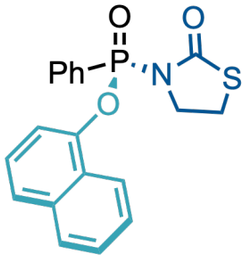
53% yield, 84% ee



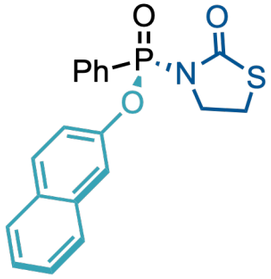
98% yield, 96% ee



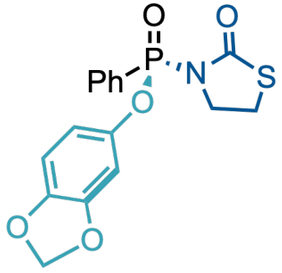
76% yield, 92% ee
[47% yield, 19% ee with Gen 1 system]



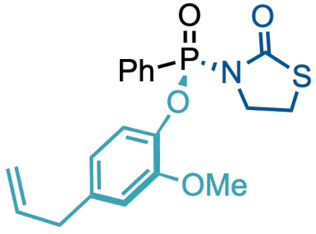
95% yield, 76% ee



64% yield, 96% ee
[<10% conv. with Gen 1 system]



66% yield, 92% ee
[from sesamol]



84% yield, 90% ee
[from eugenol]

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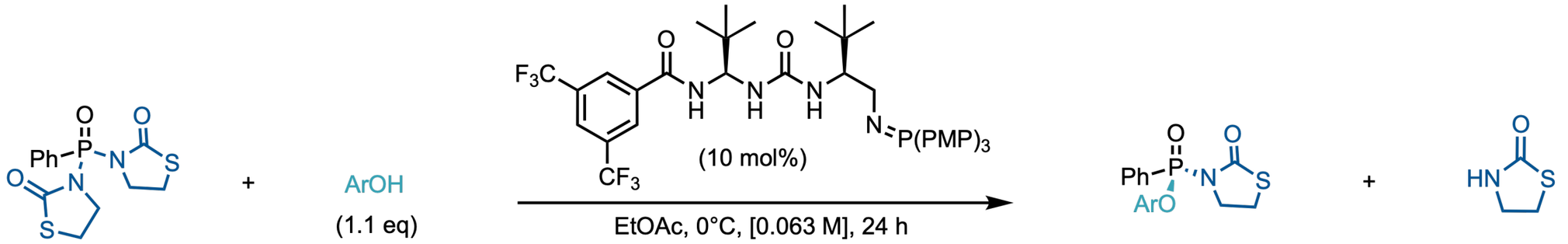
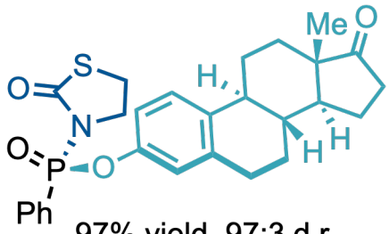
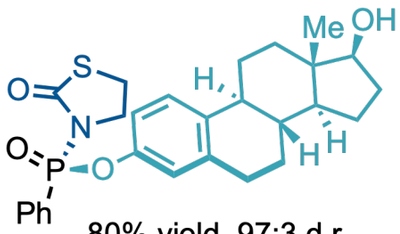
Desymmetrisation Phenol Scope



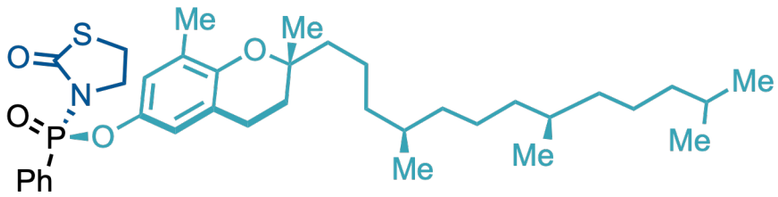
Phenol Variation



97% yield, 97:3 d.r.
[from estrone]



80% yield, 97:3 d.r.
[from estradiol]



98% yield, 94:6 d.r.
[from δ-tocopherol]

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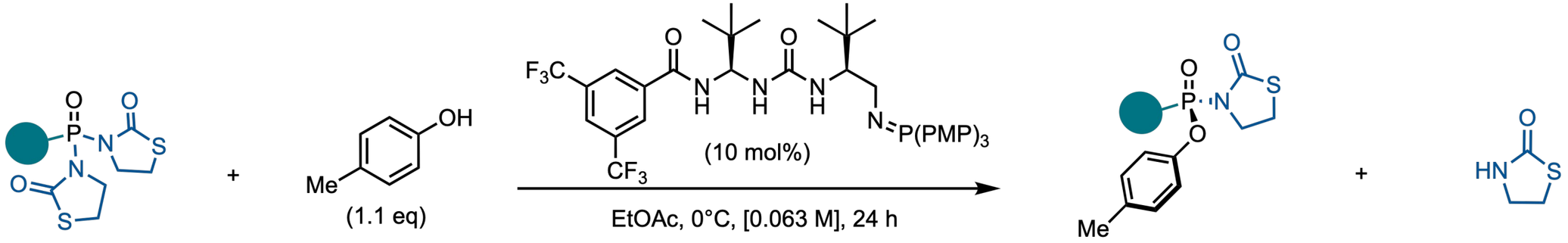
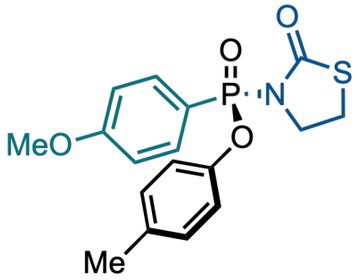
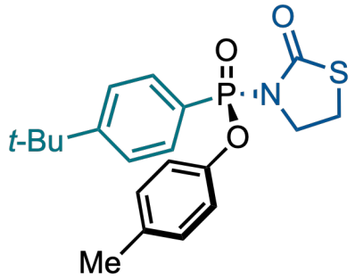
Desymmetrisation Backbone Scope



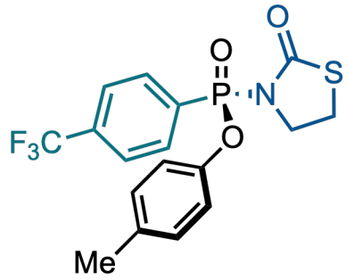
Backbone Variation



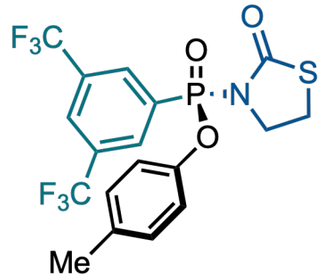
73% yield, 92% ee



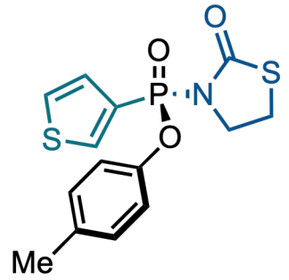
77% yield, 96% ee



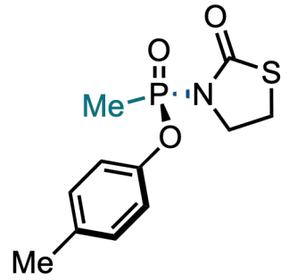
63% yield, 90% ee



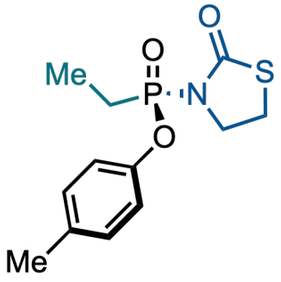
69% yield, 72% ee
(–20 ˚C, 72 h)



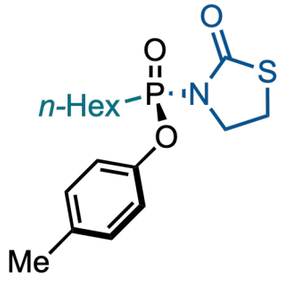
90% yield, 90% ee



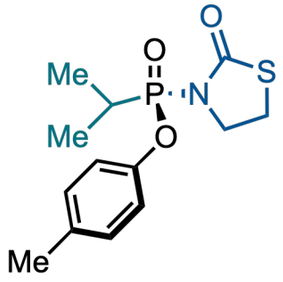
97% yield, 80% ee



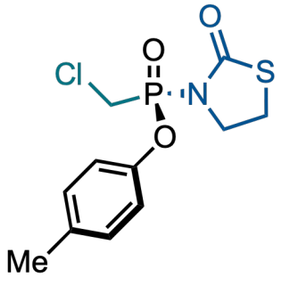
95% yield, 86% ee



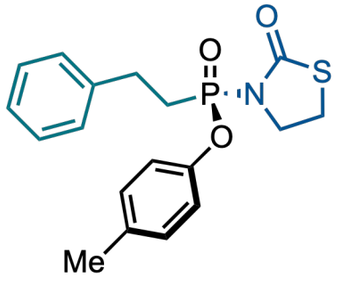
88% yield, 84% ee



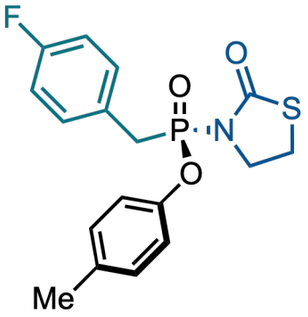
79% yield, 88% ee



46% yield, 78% ee



69% yield, 88% ee



65% yield, 82% ee

[7% yield, 77:23 e.r. with Gen 1 system]

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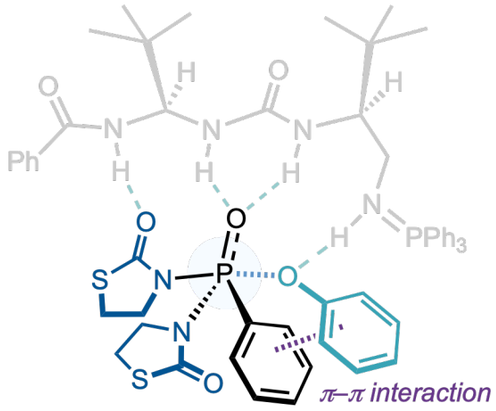
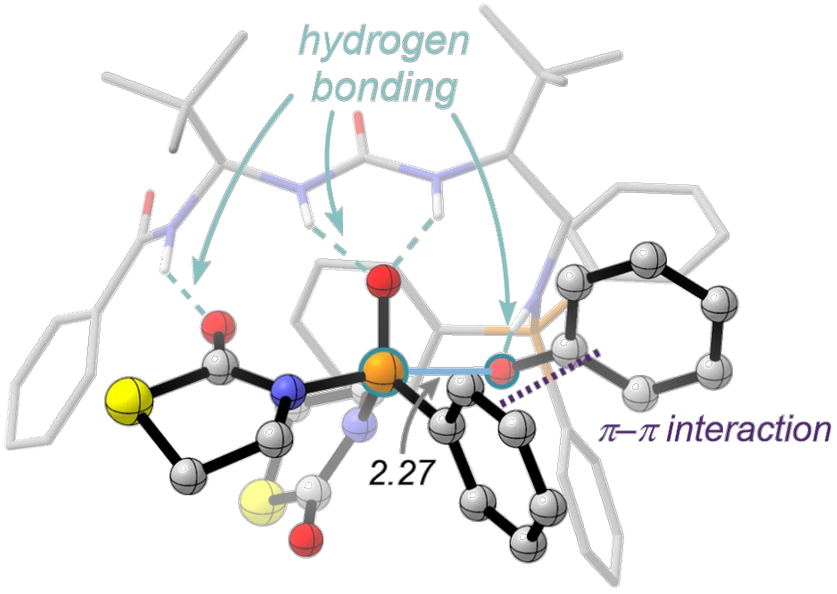
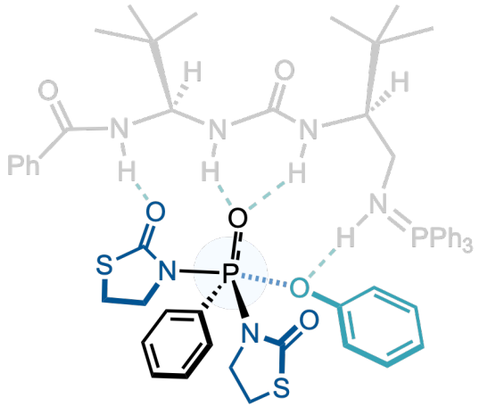
Enantioselectivity-Determining Nucleophilic TS Structures

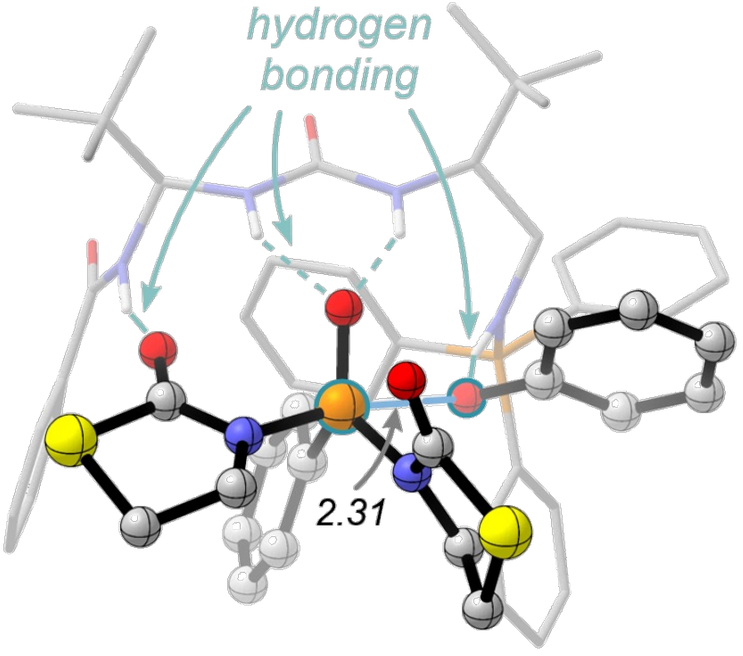
TS2-(R) (favored)
$\Delta\Delta G^{\ddagger}$ = 0.0 kcal mol^{-1}





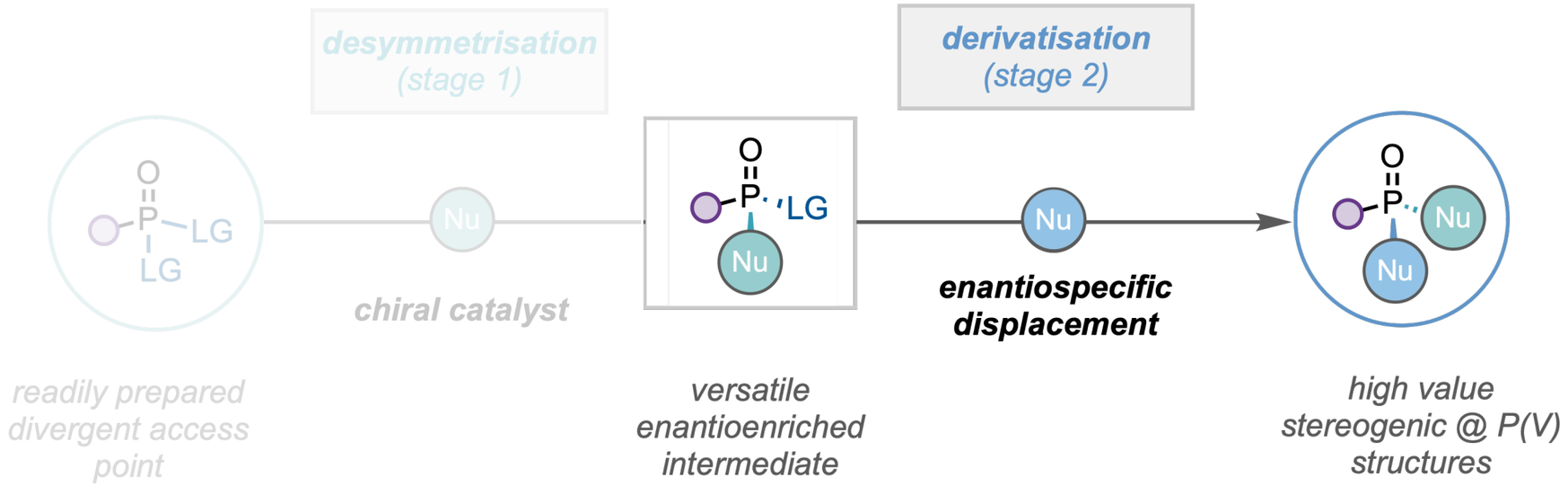
TS2-(S)
$\Delta\Delta G^{\ddagger}$ = 3.3 kcal mol^{-1}





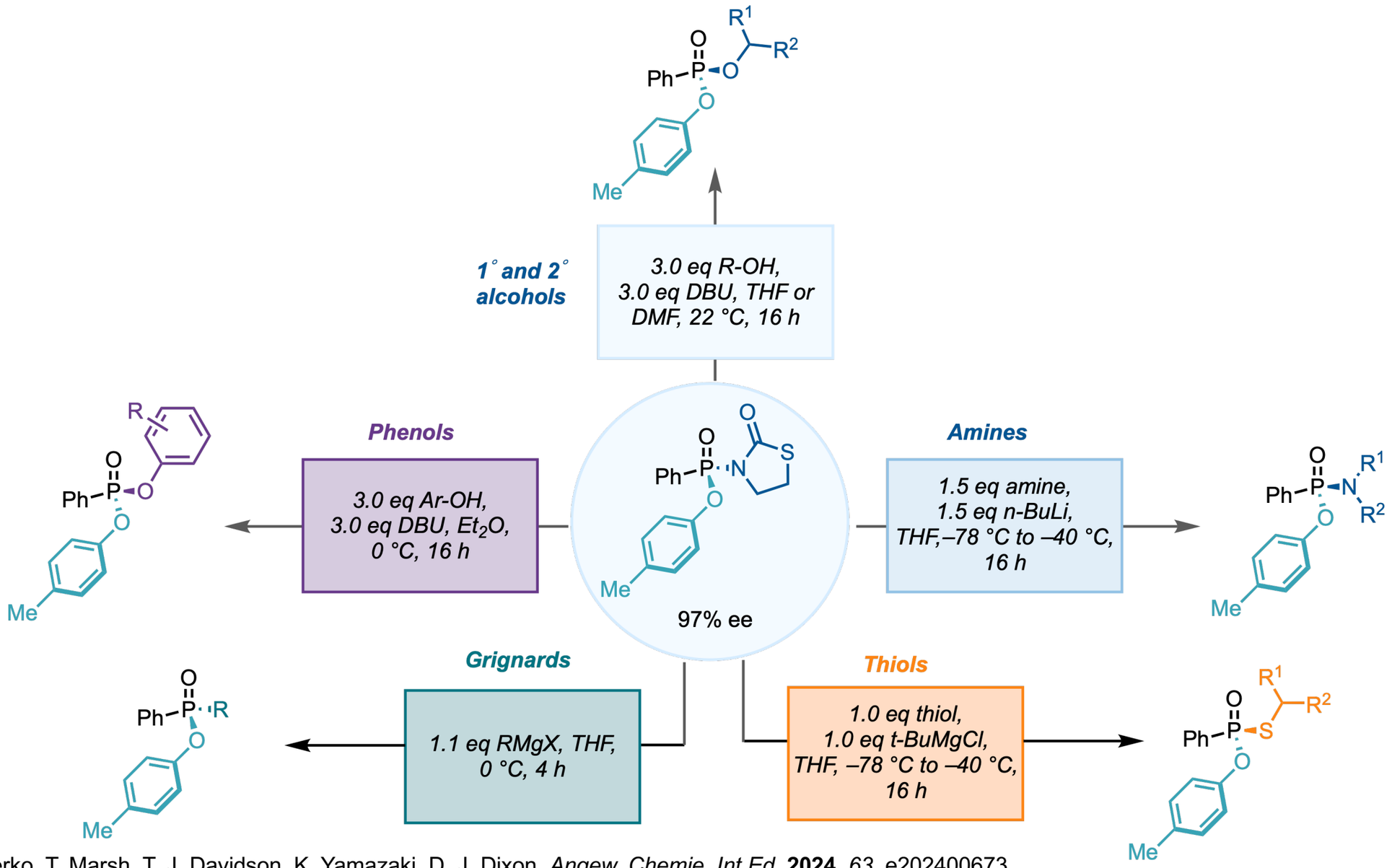
Computed at the SMD(fluorobenzene)/M06-2X/def2TZVP//SMD(fluorobenzene)/M06-2X/def2SVP level of theory *(by Ken Yamazaki)*

Stage 2 – Derivatisation Strategy



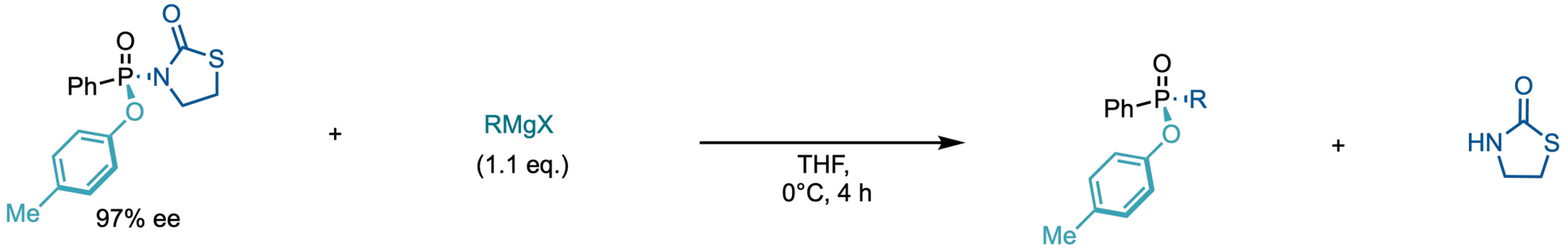
M. Formica, B. Ferko, T. Marsh, T. J. Davidson, K. Yamazaki, D. J. Dixon, *Angew. Chemie. Int Ed.* **2024**, *63*, e202400673

Derivatisation: Overview

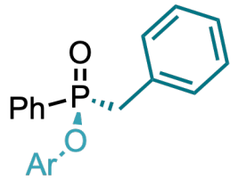


M. Formica, B. Ferko, T. Marsh, T. J. Davidson, K. Yamazaki, D. J. Dixon, *Angew. Chemie. Int Ed.* **2024**, *63*, e202400673

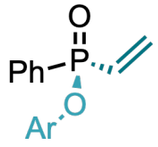
Derivatisation: P-C Bond Formation



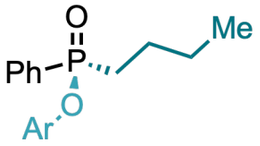
Grignard Variation



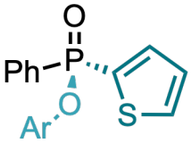
56% yield, 96% ee,
99% es



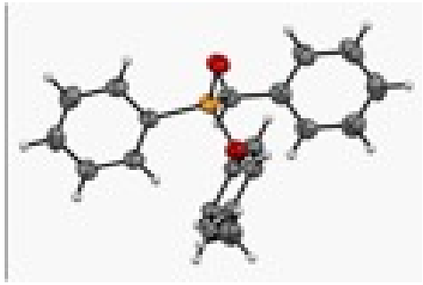
43% yield, 94% ee,
97% es



53% yield, 92% ee,
95% es (0.5 mmol scale)



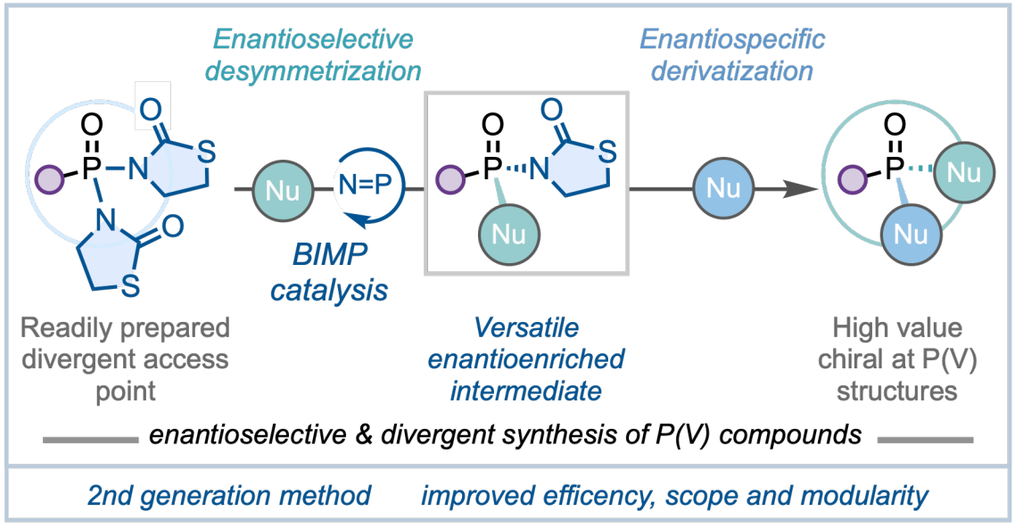
71% yield, 88% ee,
91% es

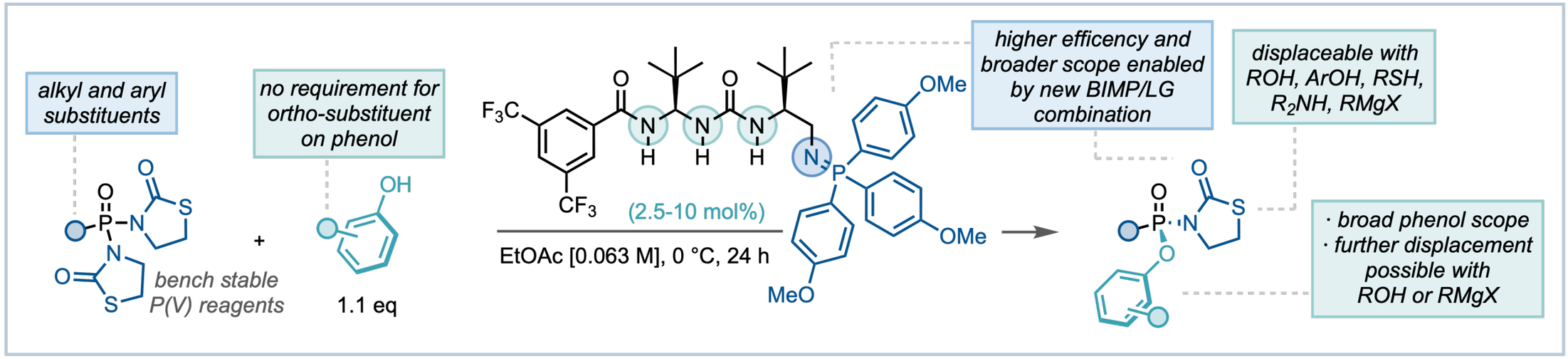


X-ray confirmed retention at P(V)

M. Formica, B. Ferko, T. Marsh, T. J. Davidson, K. Yamazaki, D. J. Dixon, *Angew. Chemie. Int Ed.* **2024**, *63*, e202400673

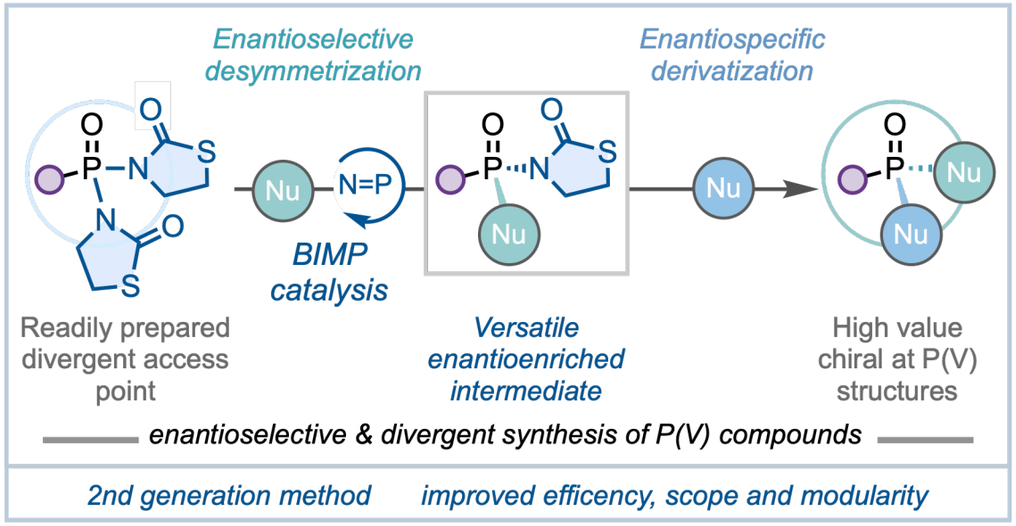
Summary





M. Formica, B. Ferko, T. Marsh, T. J. Davidson, K. Yamazaki, D. J. Dixon, *Angew. Chemie. Int Ed.* **2024**, *63*, e202400673

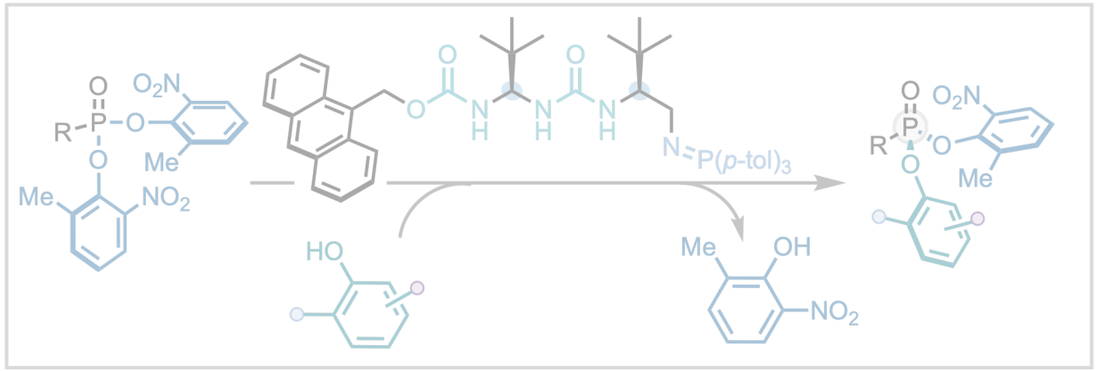
Summary

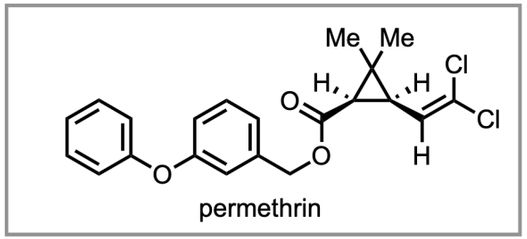


For recent and related desymmetrisation @ P papers, see:

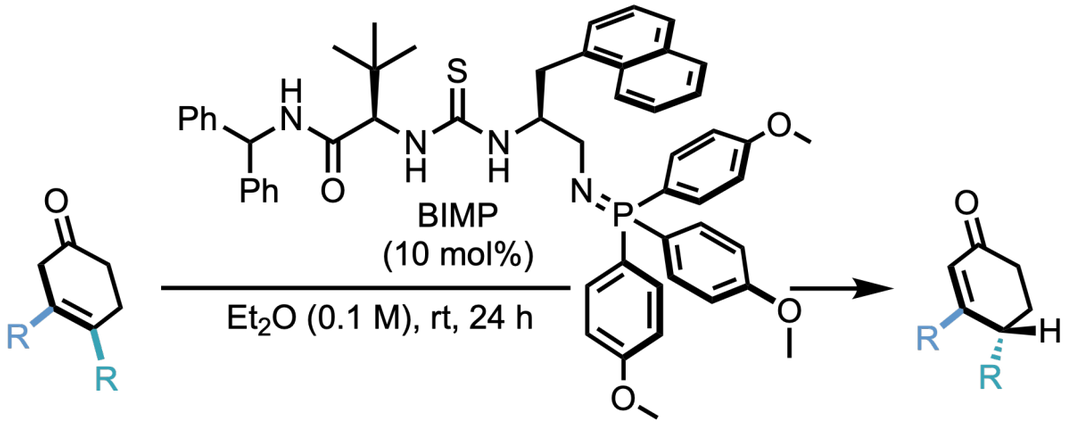
1) X. -K. Nie, S. -Q. Zhang, X. -Y. Wang, W. -T. Yang, X. Zhang, S. -J. Chen, X. Cui, Z.Tang, G. -X. Li, JACS, **2025**, *147*, 11010-11018
2) G. -L. Zheng, Y. Zhang, J. -M. Zhang, L. Chen, X. -S. Xue, Z. -T. He, *JACS*, **2025**, *147*, 13566-13576
3) B. S. Daniels, B. G. Blackburn, S. J. Scriber, V. M. Dong, *JACS*, **2025**, *147*, 21339-21346
4) Y. Wang, K. Chen, F. Che, S. Zhao, P. Feng, Q. Zhao, D. Wei, X. Wu, Y. R. Chi, *Chem*, **2025**, *11*, 102586-102597
5) H. -Q. Yao, Y. -M. Cai, T. Xie, J. -Y. Lv, S. -S. Fang, M. -H. Li, M. Shang, *ACIE*, **2025**, e202509807

Lecture Overview





BIMP Catalysed Enantioselective Prototropism in Cyclohexenes

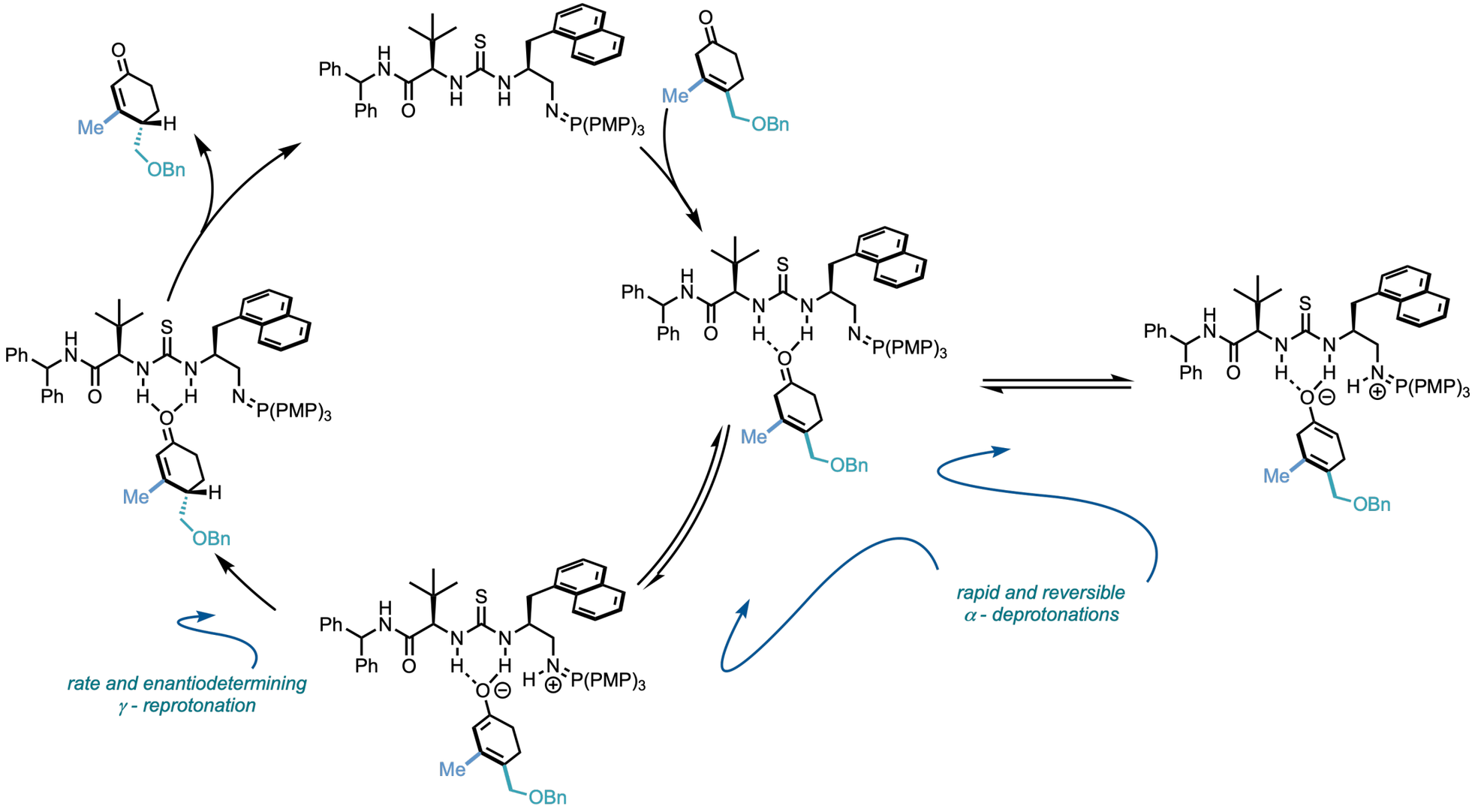


up to 99% yield
up to 99% ee

- *20 examples*
- *high functional group tolerance*
- *key building block of (-)-reserpine*
- *deuterium labelling investigations*
- *computational study*

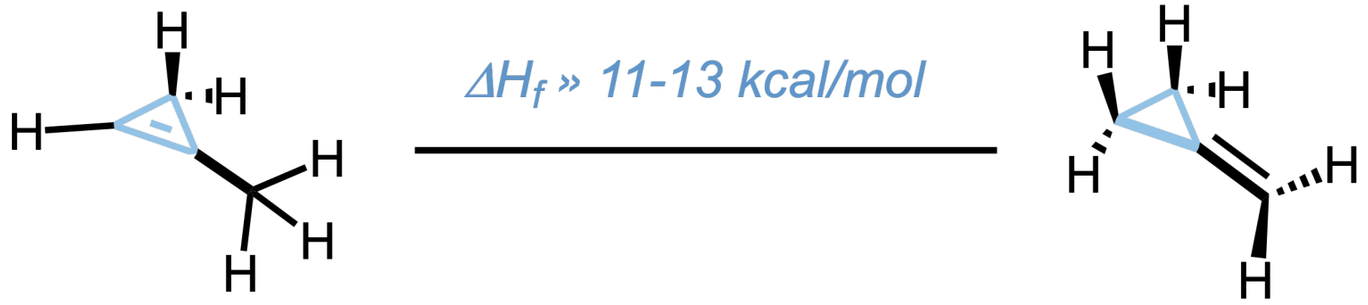
Dixon *et al. Angew. Chem. Int. Ed.* **2020**, *59,* 17417–17422.

BIMP Catalysed Enantioselective Prototropism in Cyclohexenes



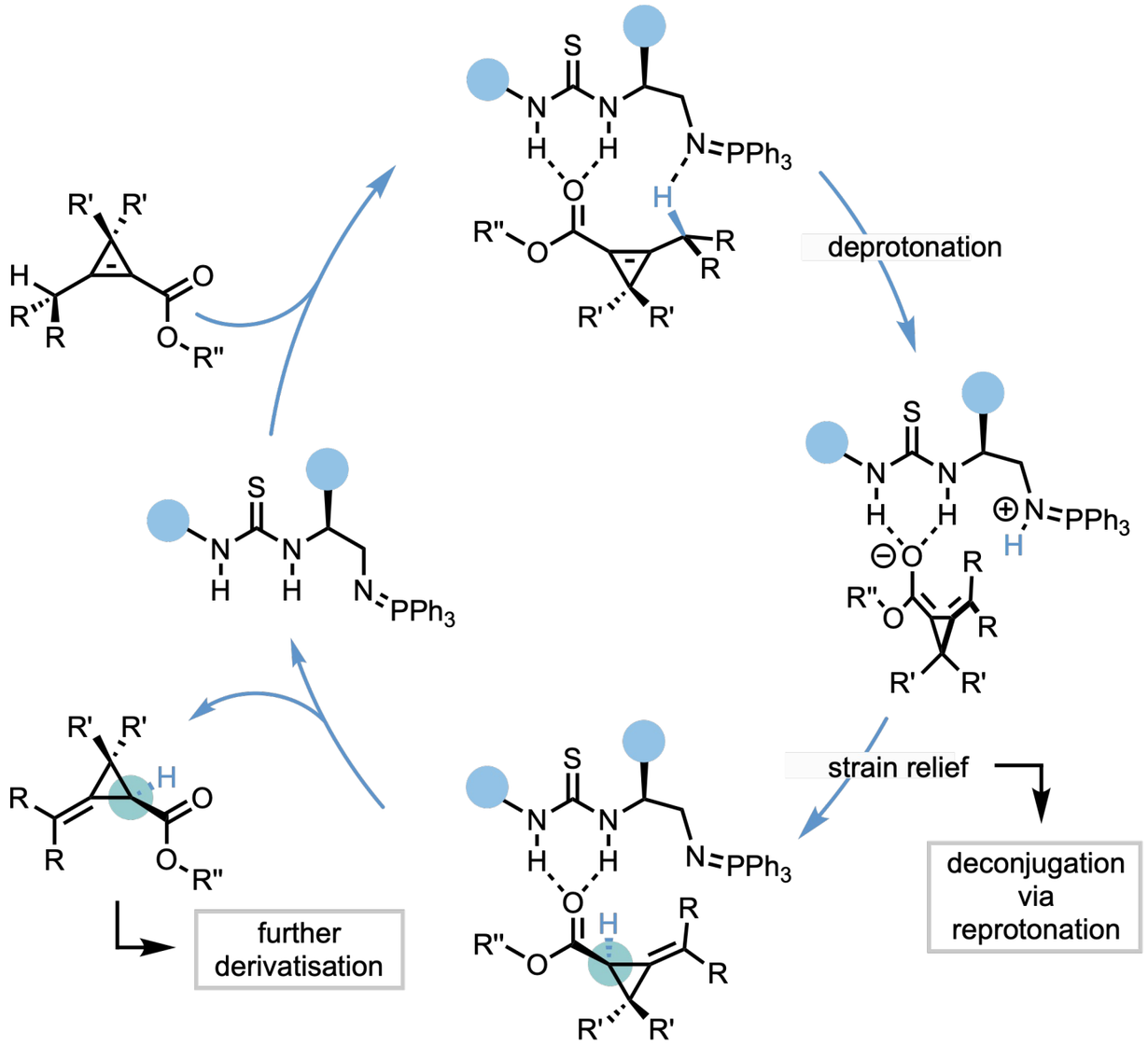
Dixon *et al. Angew. Chem. Int. Ed.* **2020**, *59,* 17417–17422.

BIMP Catalysed Enantioselective Prototropism in Cyclopropenes

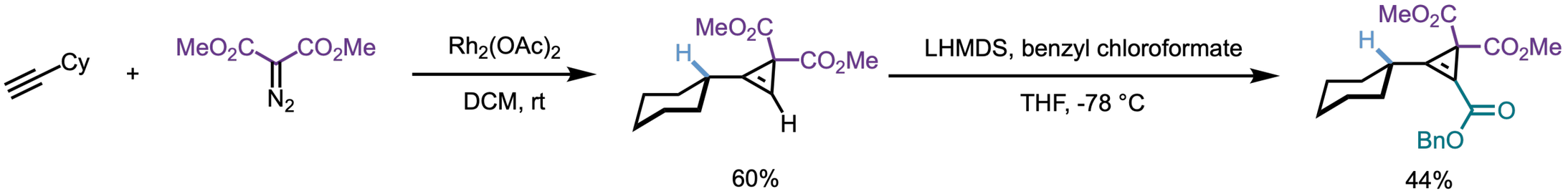


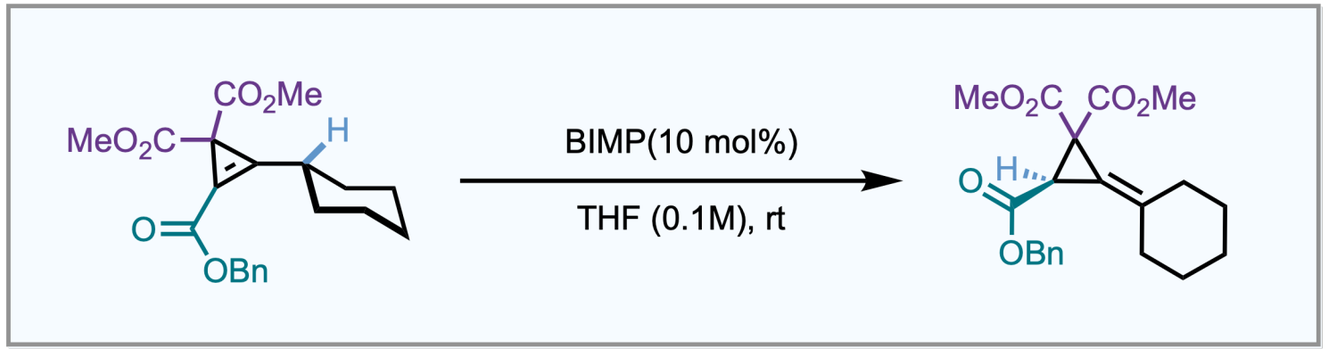
Borden *et al. J. Am. Chem. Soc.* **1997**, *119*, 5933

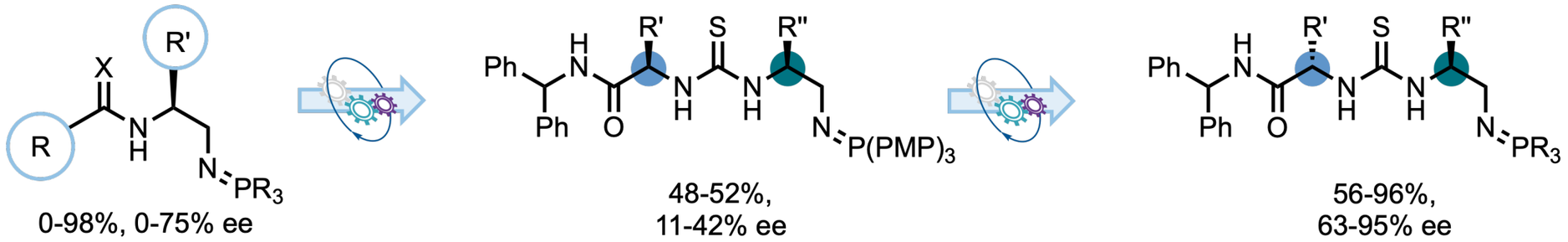
BIMP Catalysed Enantioselective Prototropism in Cyclopropenes



Substrate Synthesis and Catalyst Screening

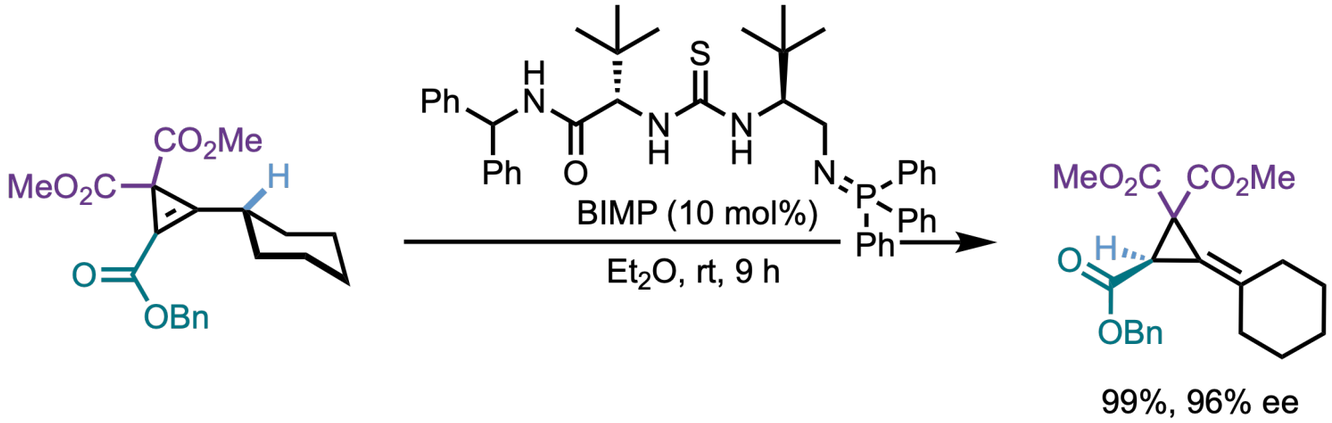




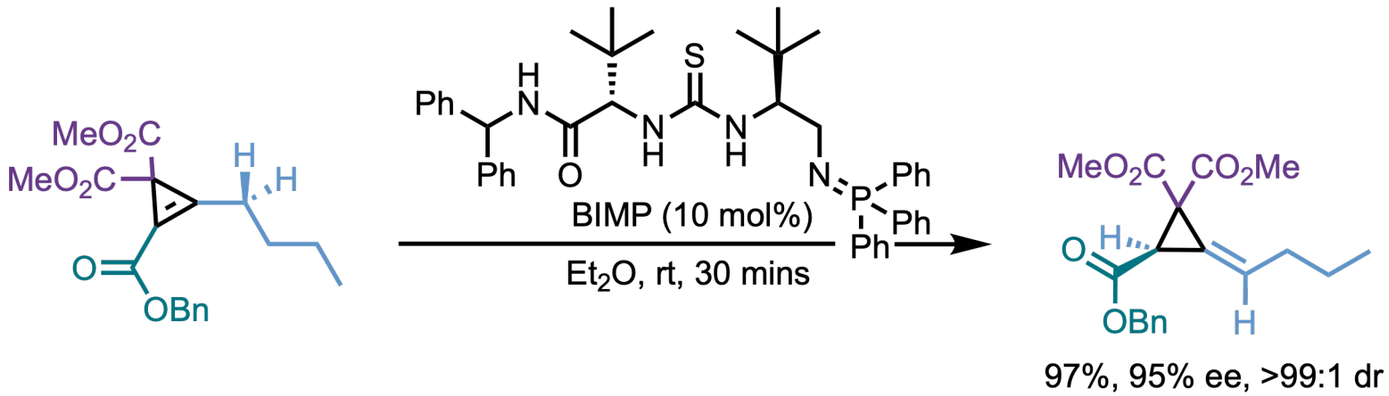


J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

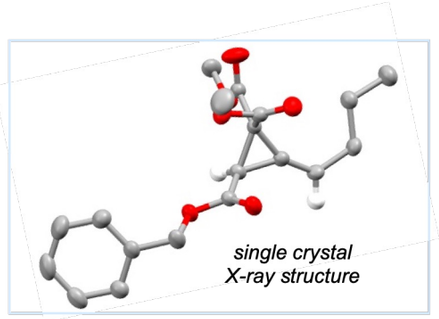
Optimised Conditions



99%, 96% ee

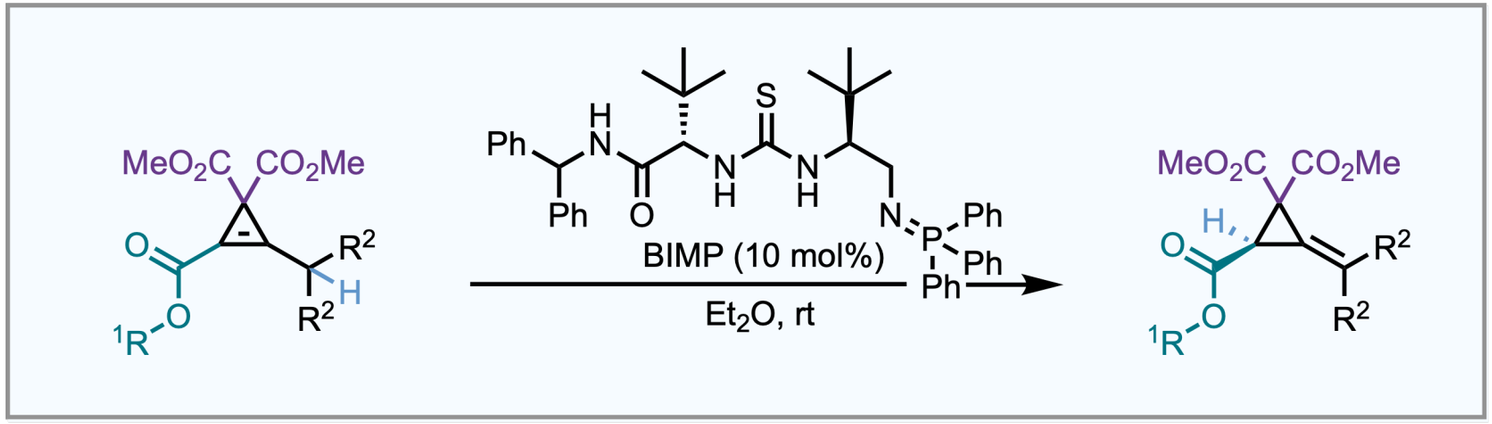


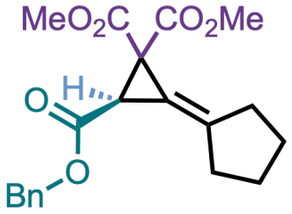
97%, 95% ee, >99:1 dr



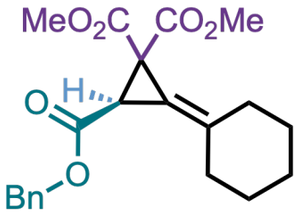
J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Scope of (Hetero)cycloalkyl Containing Substrates

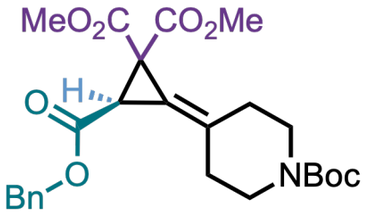




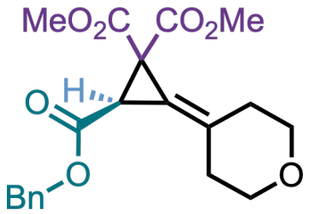
96%, 94% ee, (5 h)



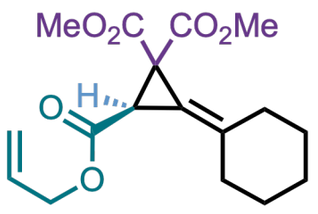
99%, 97% ee, (4 h)



85%, 95% ee, (1 h)



73%, 96% ee, (1 h)



75%, 97% ee, (9 h)

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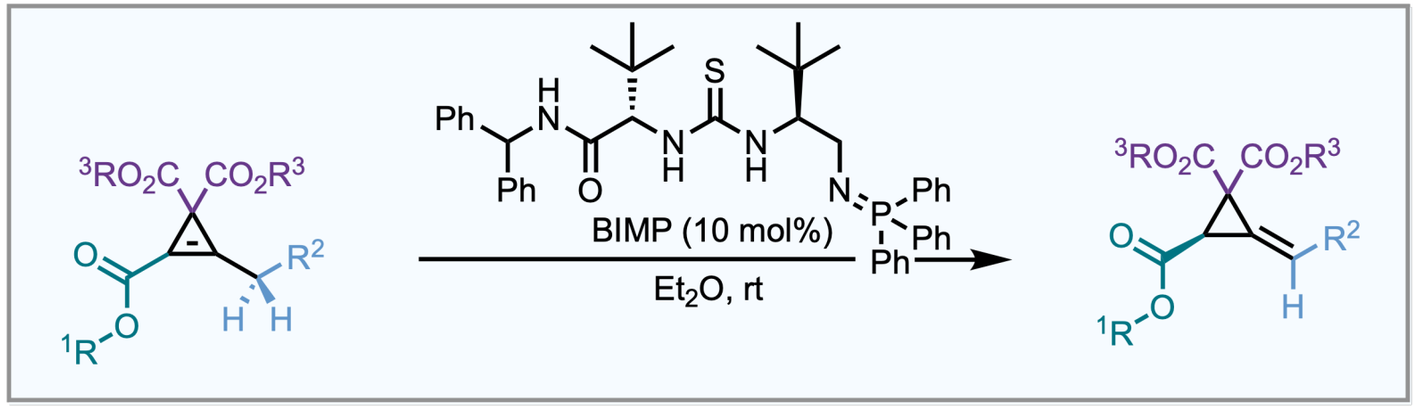
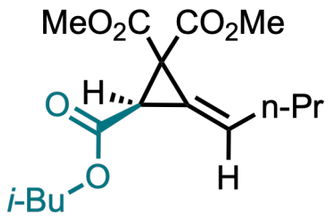
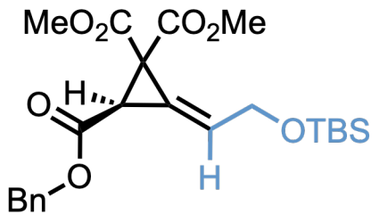
Scope of Ester Substrates

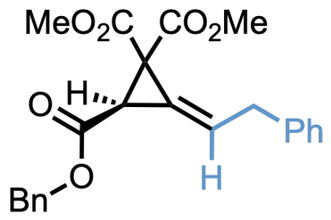




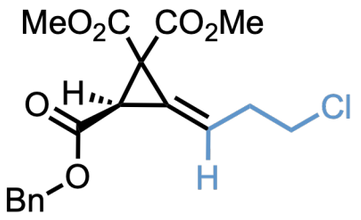
96%, >20:1 dr
94% ee, (3 h)



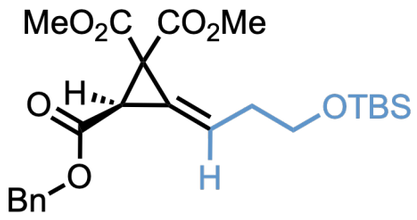
74%, 89:11 dr
86% ee, (1 h)



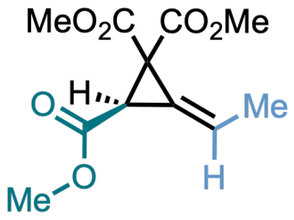
85%, >20:1 dr
92% ee, (1 h)



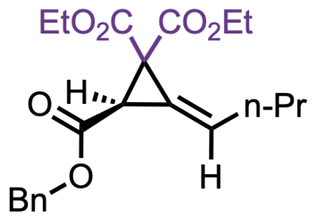
79%, >20:1 dr
94% ee, (1 h, -78 C)



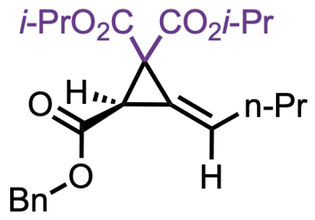
96%, >20:1 dr
92% ee, (1 h)



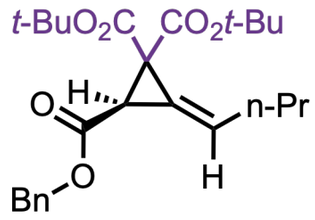
99%, >20:1 dr
90% ee (0.5 h)



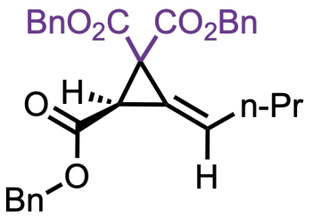
96%, >20:1 dr
92% ee (1 h)



99%, >20:1 dr
90% ee (1 h)



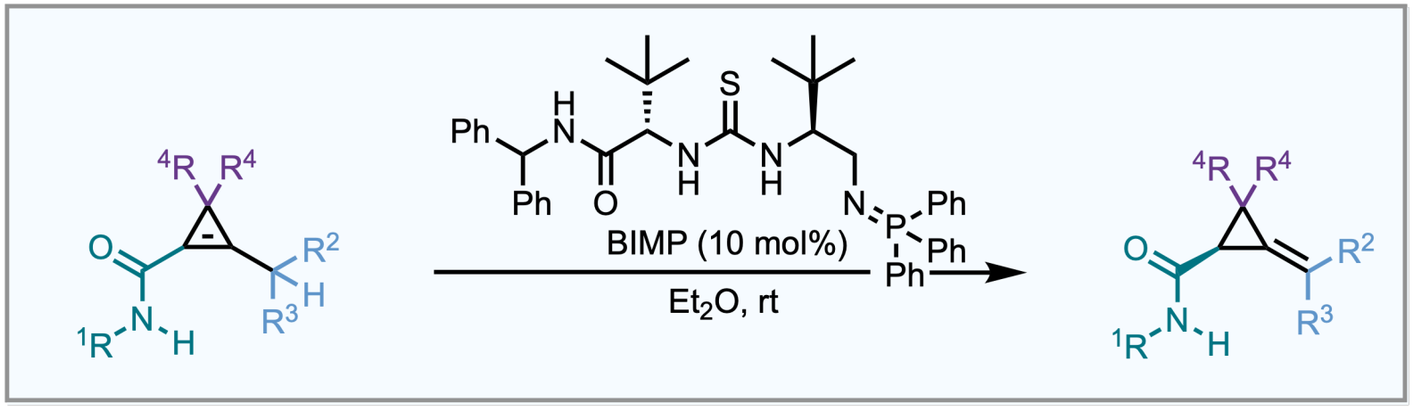
91%, >20:1 dr
91% ee (12 h)

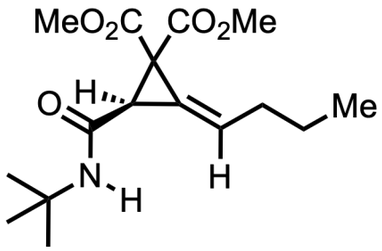


91%, >20:1 dr
92% ee, (1 h)

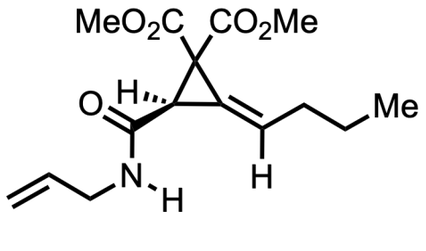
J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Scope of Amide Substrates

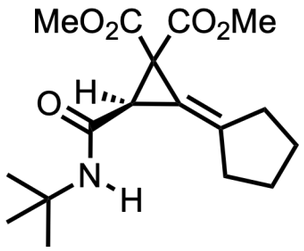




>99%, >20:1 d.r.
98% ee, (0.75 h)

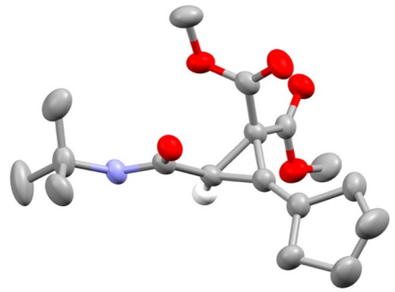


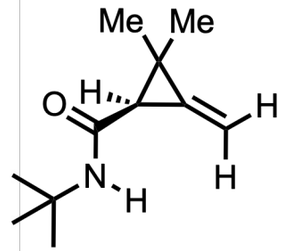
73%, >20:1 d.r.
97% ee, (2 h)



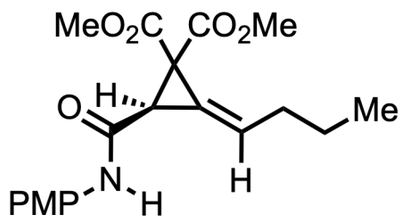
93%, 99% ee (25 h)

≡



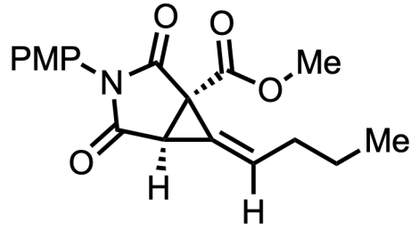


78%, 99% ee
(24 h)



>99%, >20:1 d.r.
94% ee, (1.75 h)

prolonged reaction time



61%, >20:1 d.r.
97% ee, (24 h)

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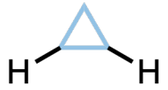
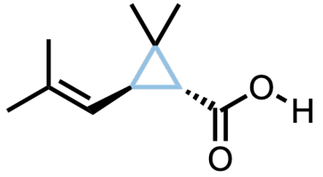
Application in Crop Protection Agent Synthesis

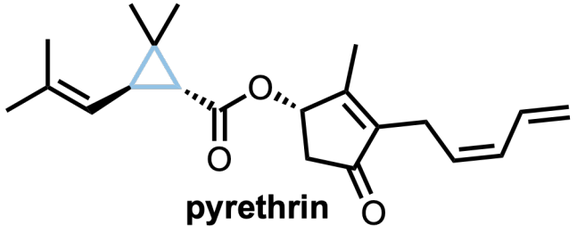


20 of the 150 most recent crop protection active ingredients



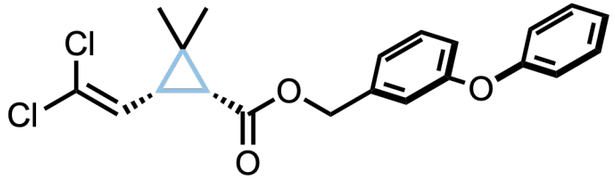
chrysanthemic acid

12 of which are structurally similar to chrysanthemic acid



pyrethrin

some are naturally occuring and extracted from chrysanthemums

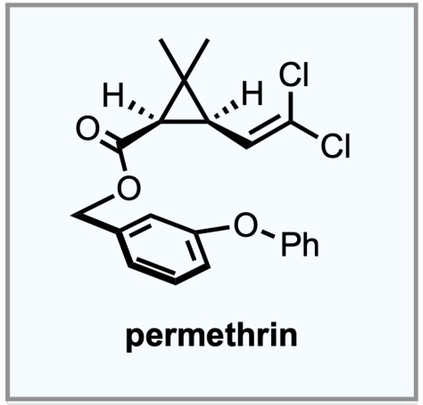


permethrin

some synthetic variants are not derived from chrysanthemic acid

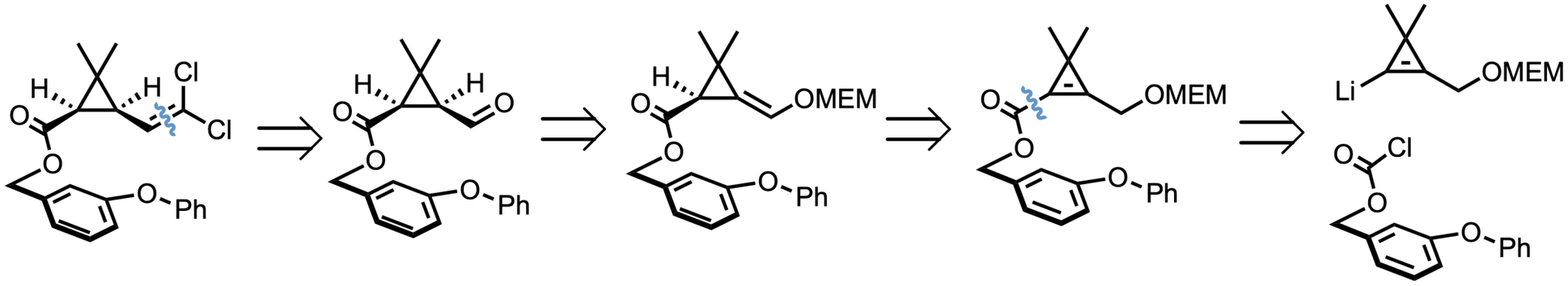
J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Application in Crop Protection Agent Synthesis



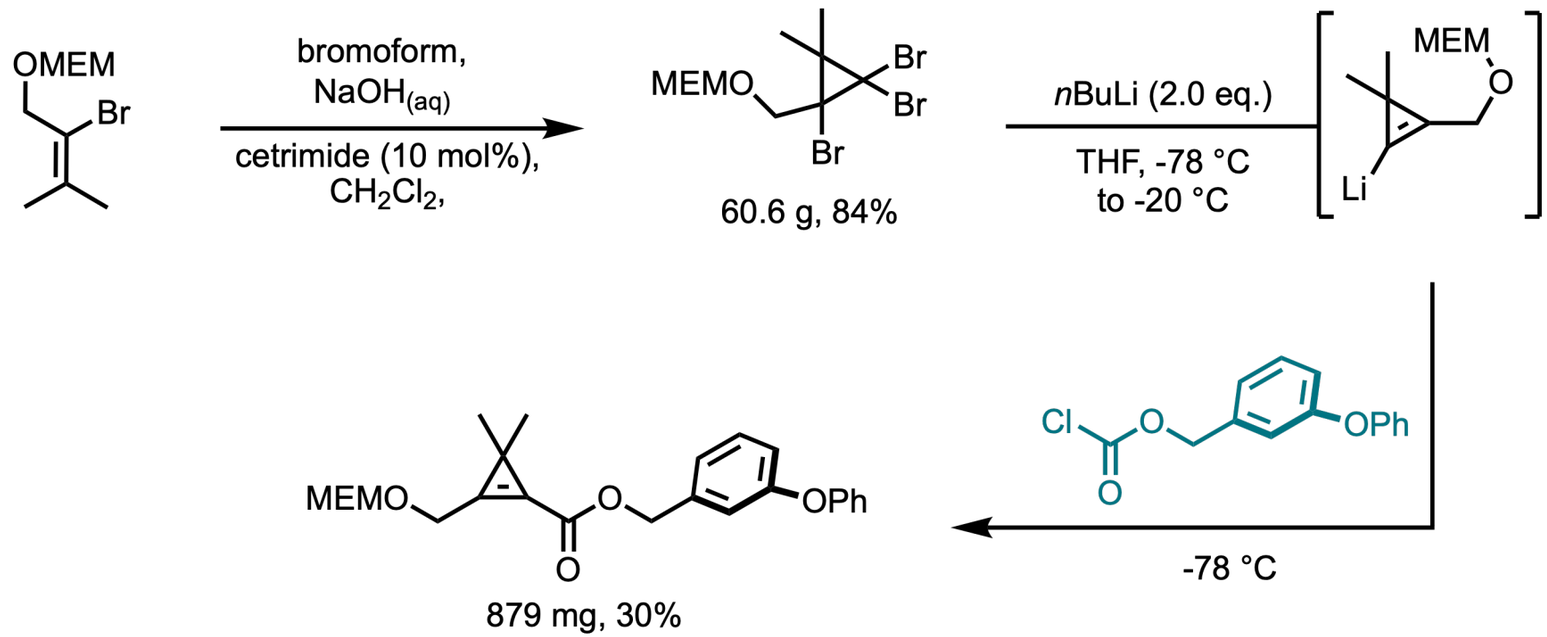
permethrin

- insecticide: mosquitos, fleas, head lice and scabies
- few catalytic enantioselective methods to synthesise pyrethroids



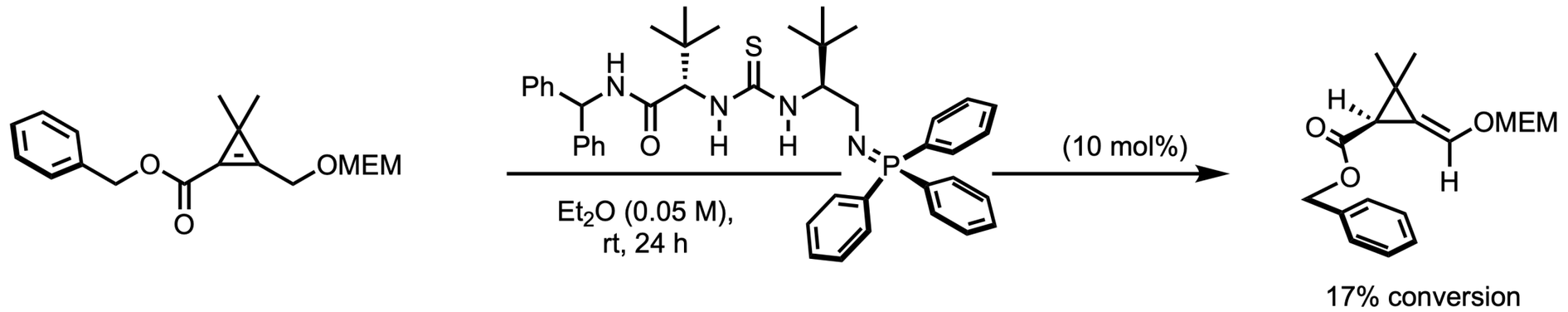
J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Permethrin Substrate Synthesis



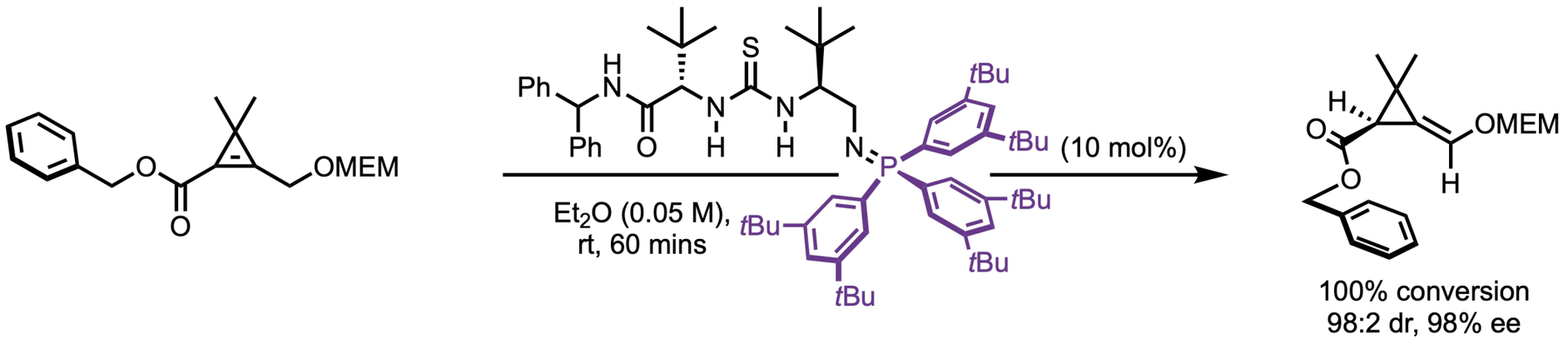
J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Key BIMP Catalysed Enantioselective Prototropic Reaction



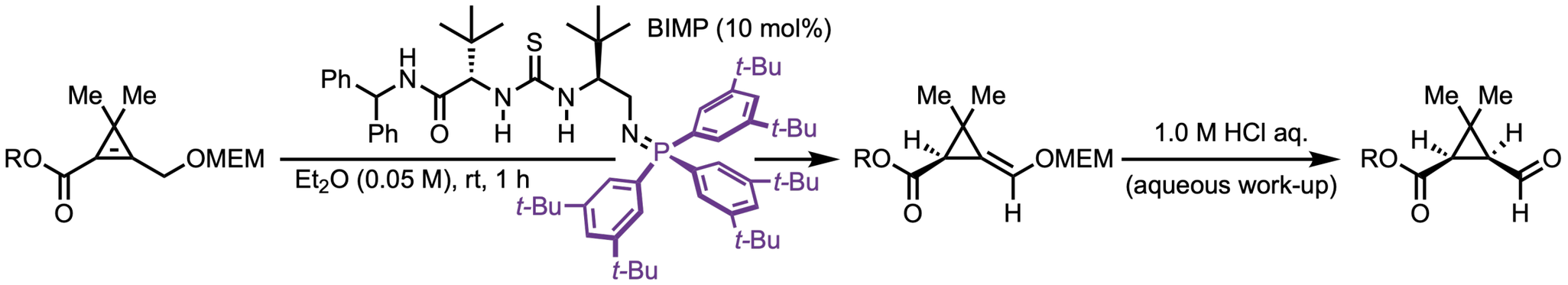
J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

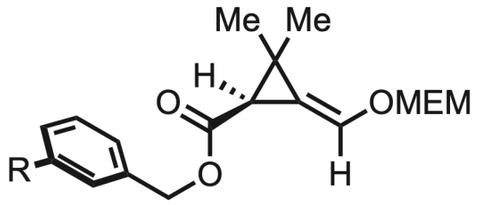
Key BIMP Catalysed Enantioselective Prototropic Reaction



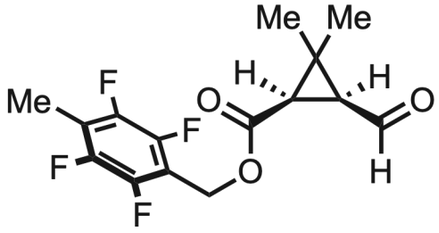
J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Accessing Insecticide Cores

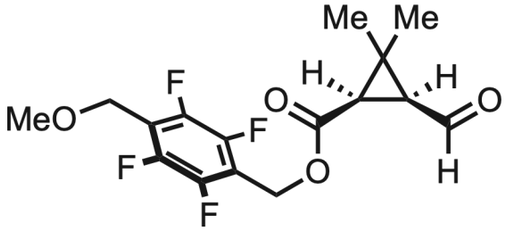




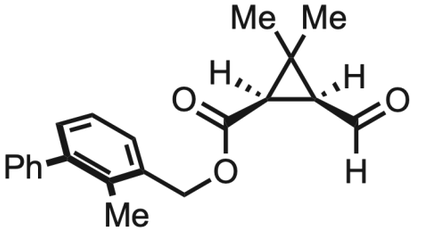
R = H, 90%, >20:1 d.r., 98% ee
R = OPh, 88%, >20:1 d.r., 98% ee



75%, >20:1 d.r., 98% ee
kappa-tefluthrin core



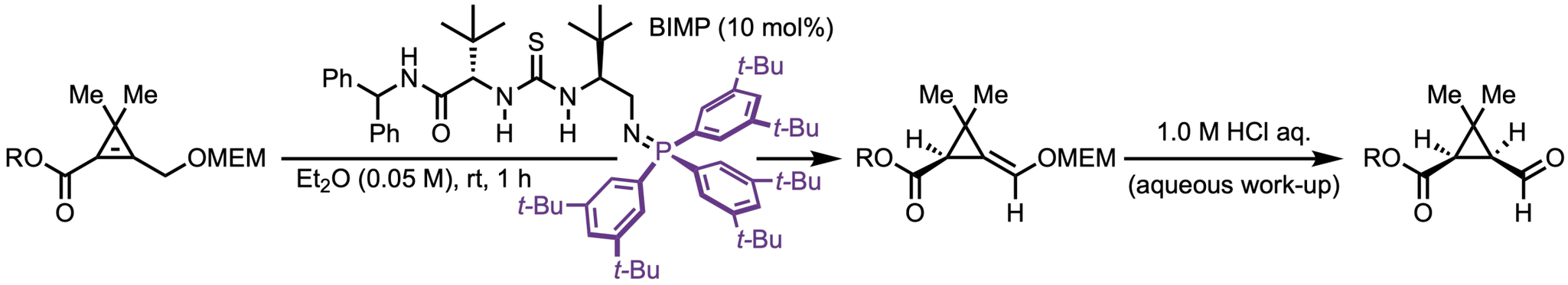
76%, >20:1 d.r., 97% ee
dimefluthrin core

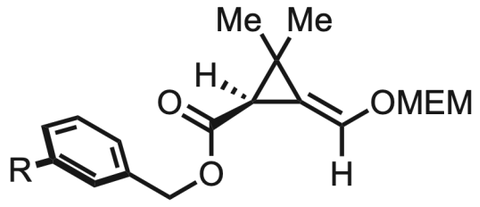


74%, >20:1 d.r., 98% ee
kappa-bifenthrin core

J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Total Synthesis of (1R, 3R)-cis-Permethrin

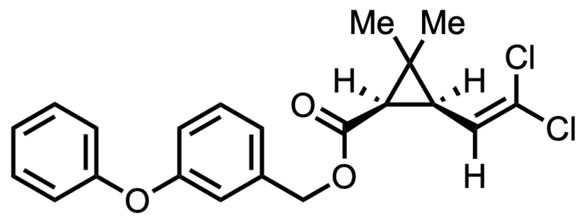




R = H, 90%, >20:1 d.r., 98% ee
R = OPh, 88%, >20:1 d.r., 98% ee

1.0 M HCl aq.
(work-up)

PPh_3
CCl_4, CH_2Cl_2,
0 °C to rt

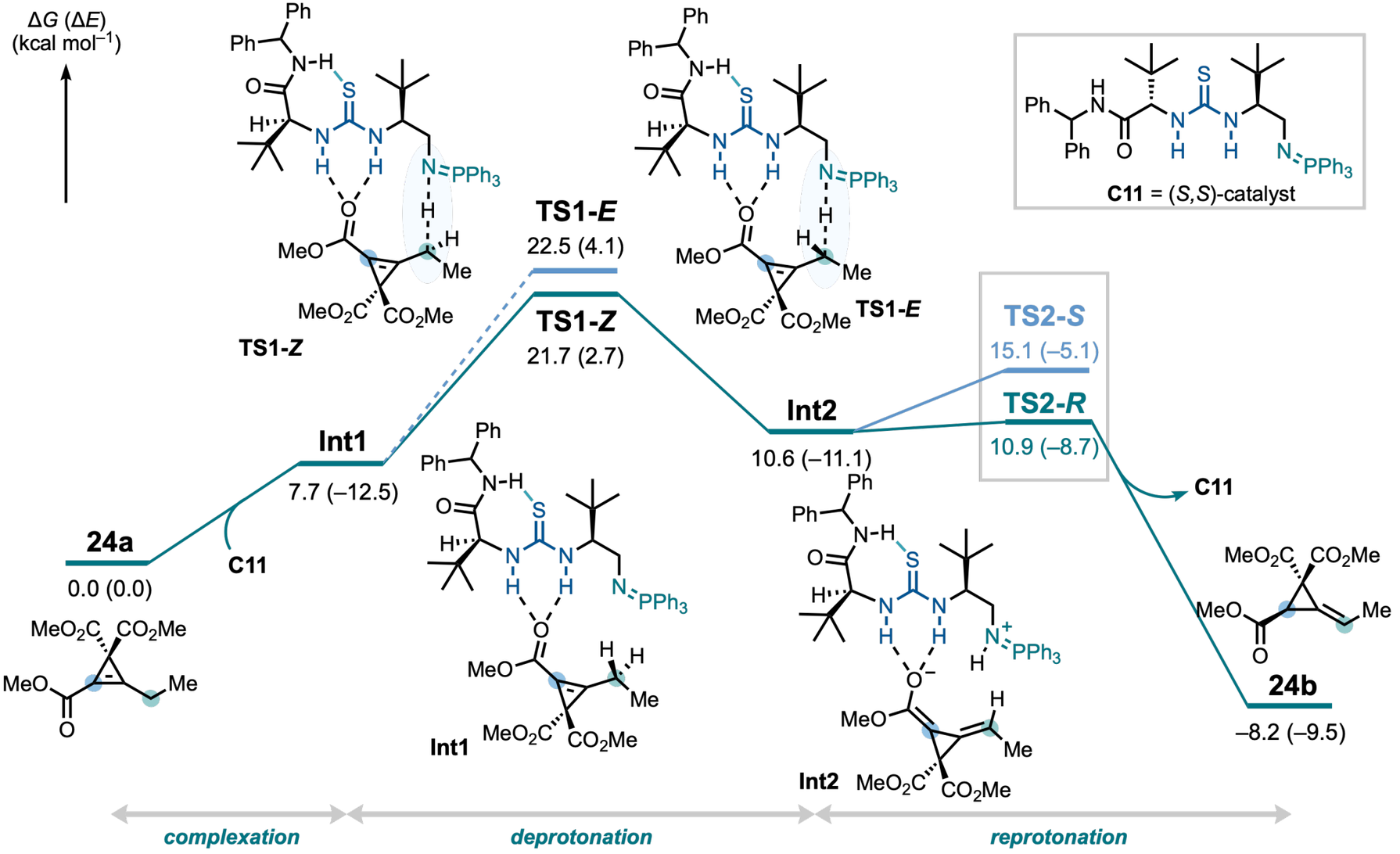


(1*R*,3*R*)-*cis*-permethrin
31%, >20:1 d.r., 98% ee
(over two steps)

J. C. Golec, D.-H. Tan, K. Yamazaki, E. H. Tiekink, K. E. Christensen, T. A. Hamlin, D. J. Dixon *Nature* **2025**, *645*, 932-938

Energy Profile and Origins of Stereocontrol

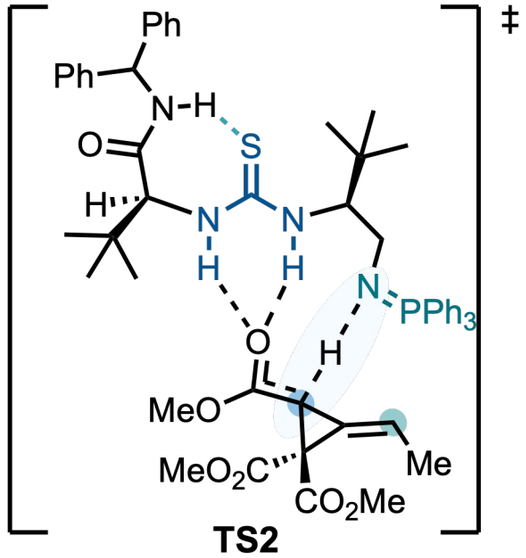
A - *Potential energy surface diagram*



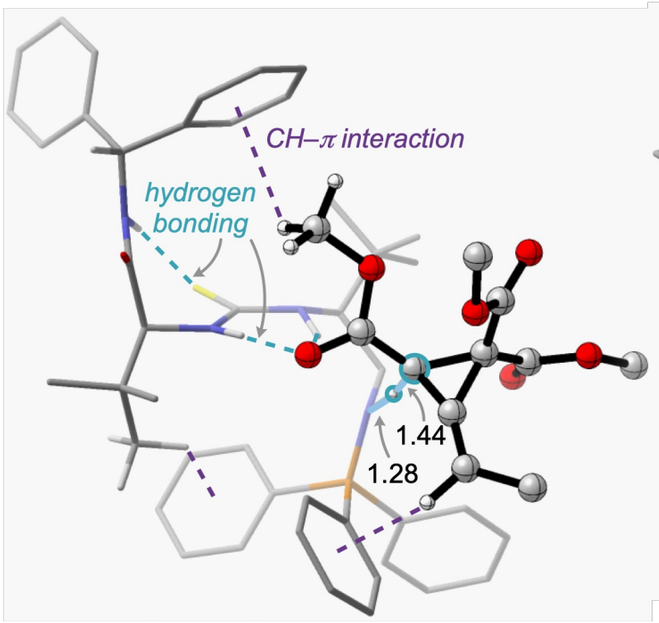
Dixon and Hamlin *et al. Nature* **2025**, *645*, 932-938.
All computational work carried out by Ken Yamazaki, Eveline Tiekink and Trevor Hamlin

Energy Profile and Origins of Stereocontrol

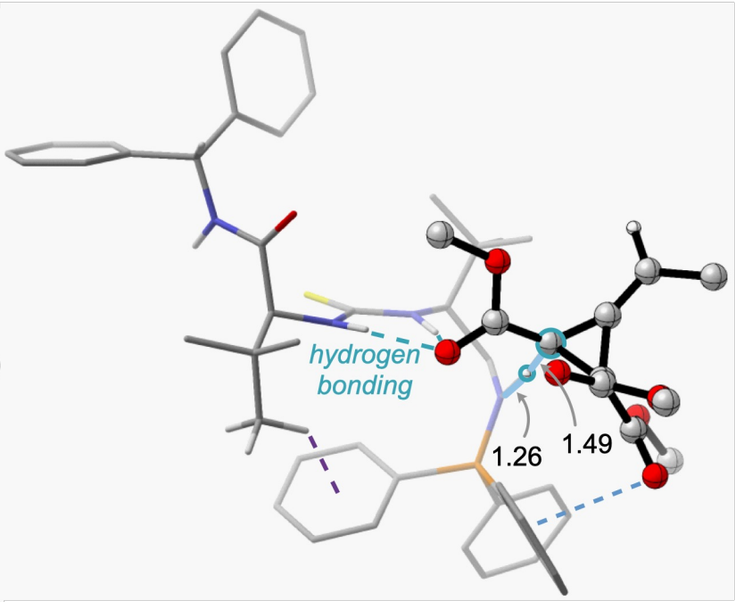
B - *Transition state structures for reprotonation*



TS2



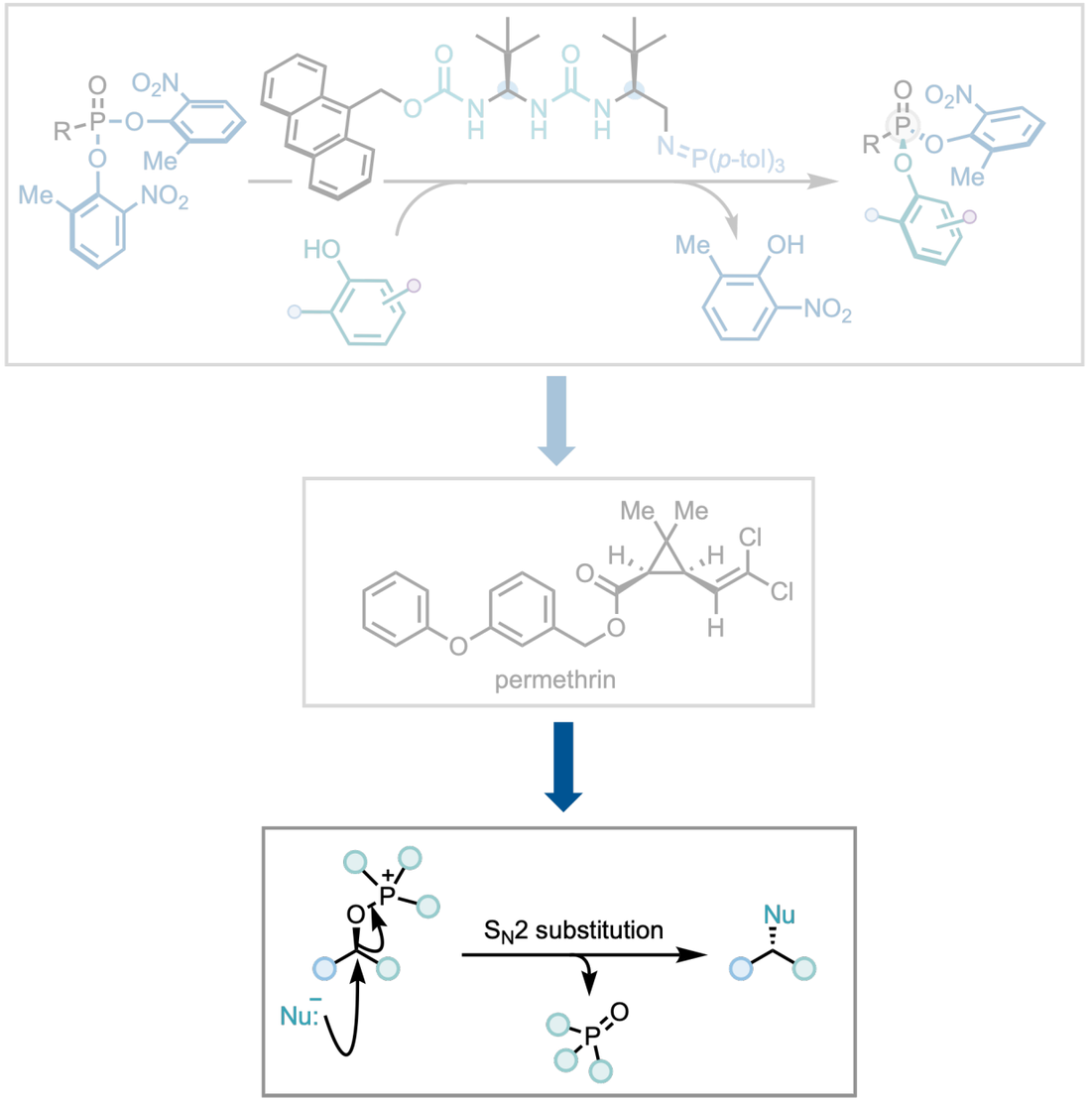
TS2-*R* *(favoured)*



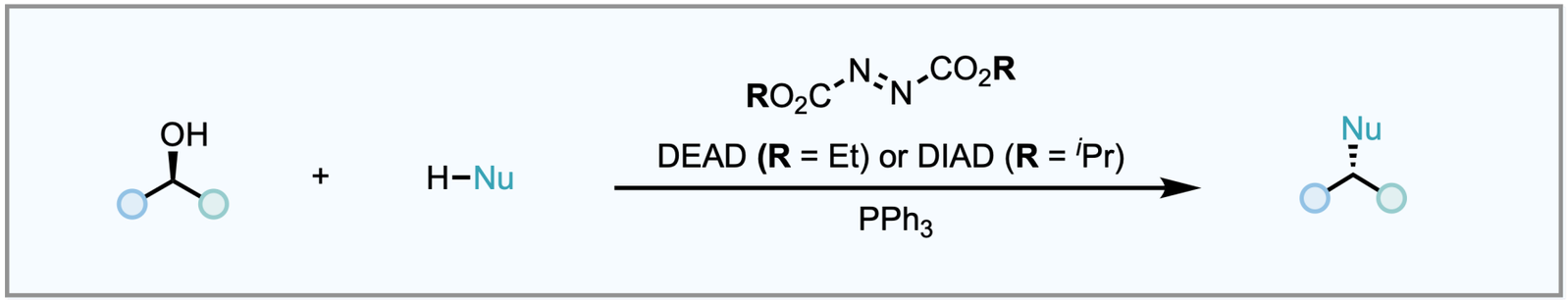
TS2-*S* *(disfavoured)*

Dixon and Hamlin *et al. Nature* **2025**, *645*, 932-938.
All computational work carried out by Ken Yamazaki, Eveline Tiekink and Trevor Hamlin

Lecture Overview

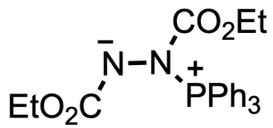


The Mitsunobu Reaction



Limitations

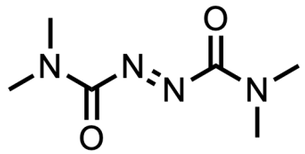
- DEAD is shock-sensitive and poses an explosive hazard and DIAD is thermally unstable
- Stoichiometric quantities of the reduced hydrazide and triphenyl phosphine oxide present purification challenges
- *p*K_a range of suitable pronucleophiles is limited by the basicity of the Morrison-Brunn-Huisgen intermediate



Tsunoda, T., Itô, S. Development of New Mitsunobu Reagents. *Journal of Synthetic Organic Chemistry, Japan* **55**, 631–641 (1997), Beddoe, R. H. *et al.* Redox-neutral organocatalytic Mitsunobu reactions. *Science* **365**, 910–914 (2019), Szigeti, M., Dobi, Z. & Soós, T. The Goldilocks Principle in Phase Labeling. Minimalist and Orthogonal Phase Tagging for Chromatography-Free Mitsunobu Reaction. *J Org Chem* **83**, 2869–2874 (2018)

Key Advances to The Mitsunobu Reaction

diazodicarboxamides



TMAD

Tsunoda reagents



(CMMP)

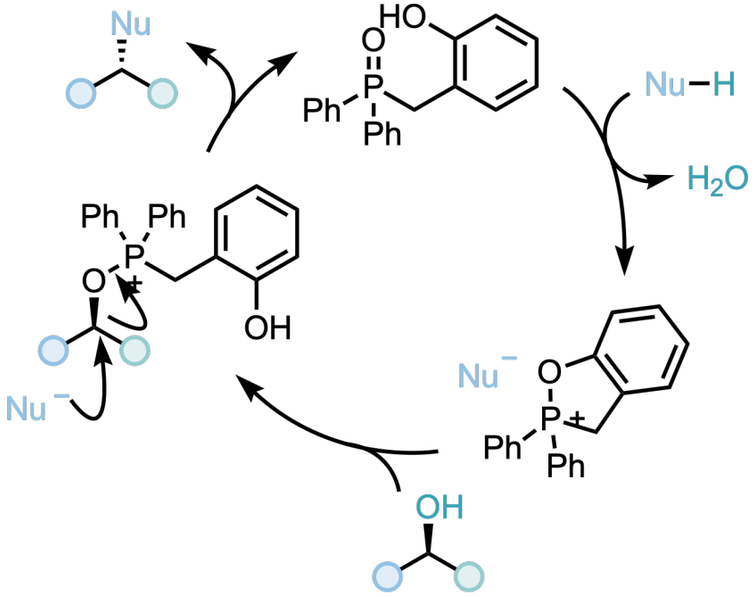
(cyanomethylene)trimethylphosphorane



(CMBP)

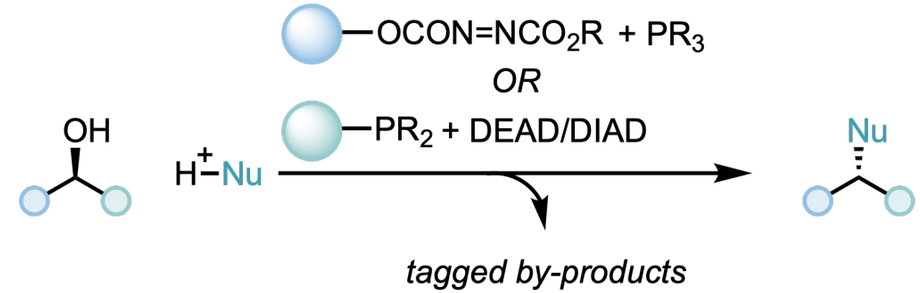
(cyanomethylene)tributylphosphorane

Catalytic Mitsunobu protocol

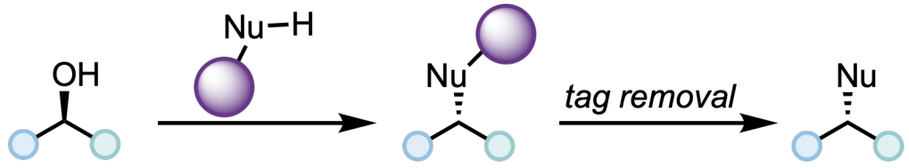


Purification strategies

Reagent-tagging

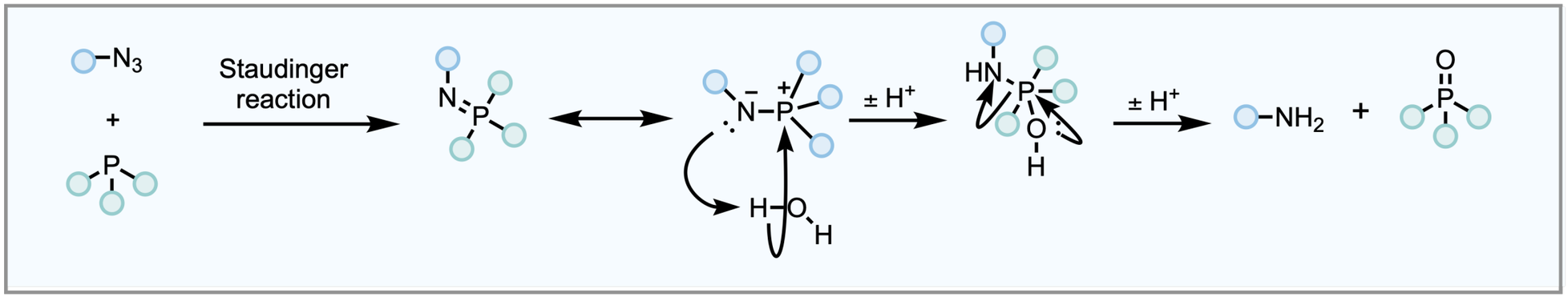


Substrate-tagging



Tsunoda, T., Itô, S. Development of New Mitsunobu Reagents. *Journal of Synthetic Organic Chemistry, Japan* **55**, 631–641 (1997), Beddoe, R. H. *et al.* Redox-neutral organocatalytic Mitsunobu reactions. *Science* **365**, 910–914 (2019), Szigeti, M., Dobi, Z. & Soós, T. The Goldilocks Principle in Phase Labeling. Minimalist and Orthogonal Phase Tagging for Chromatography-Free Mitsunobu Reaction. *J Org Chem* **83**, 2869–2874 (2018)

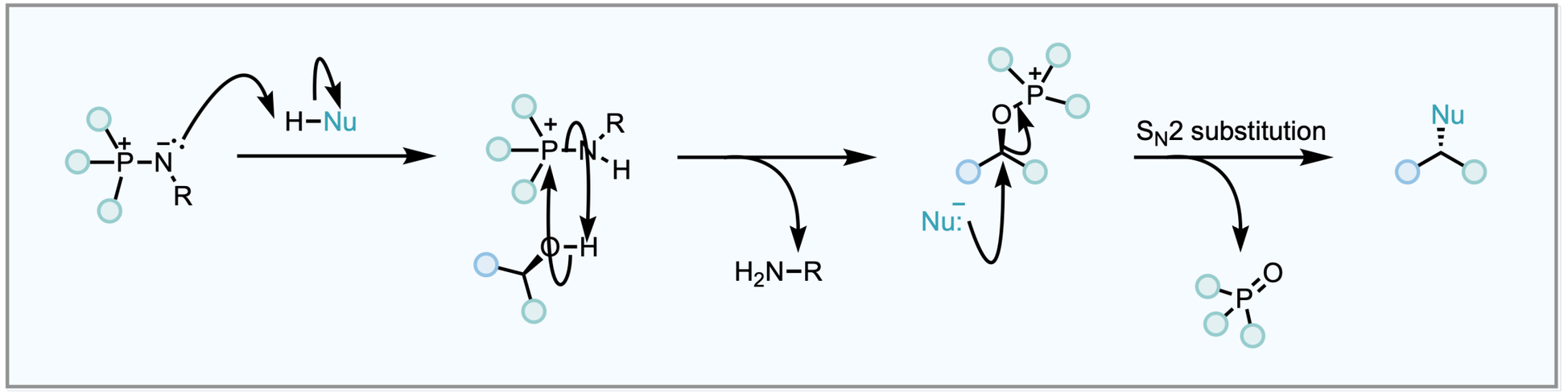
Reaction Inspiration – Iminophosphorane Hydrolysis



- Can iminophosphoranes be used as “all-in-one” reagents in the Mitsunobu reaction?

M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

Staudinger meets Mitsunobu – A New Hope

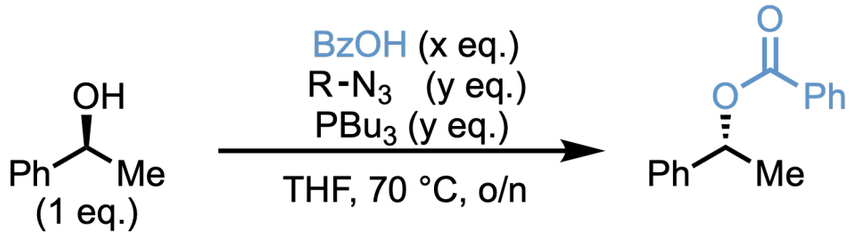


- Can iminophosphoranes be used as “all-in-one” reagents in the Mitsunobu reaction?
- Iminophosphoranes are known superbases (BIMP catalysis!)
- Mechanistic similarities between iminophosphorane hydrolysis and the Mitsunobu reaction

M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

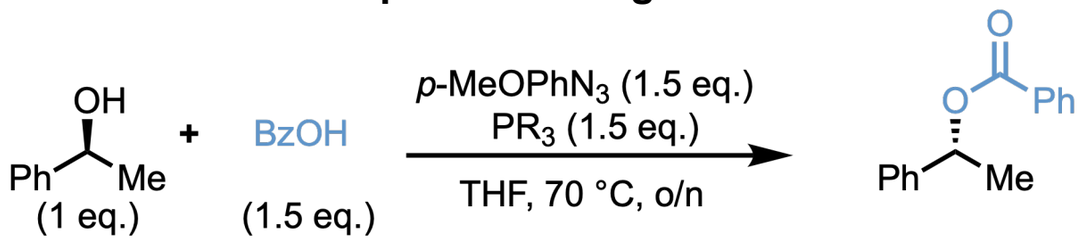
New Reaction Discovery

Azide investigation

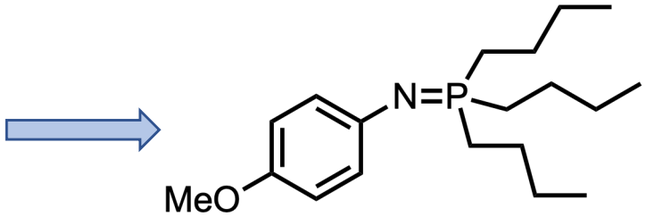


Entry	R	X	Y	Yield (%)
1	$SiMe_3$	0.5	1	0
2	*c*-Hex	0.5	1	0
3	adamantyl	0.5	1	0
4	Bn	2	2	52
5	*p*-NO_2Ph	0.5	1	18
6	Ph	0.5	1	64
7	*p*-MeOPh	0.5	1	74
8	*p*-MeOPh	2	2	88

Phosphine investigation



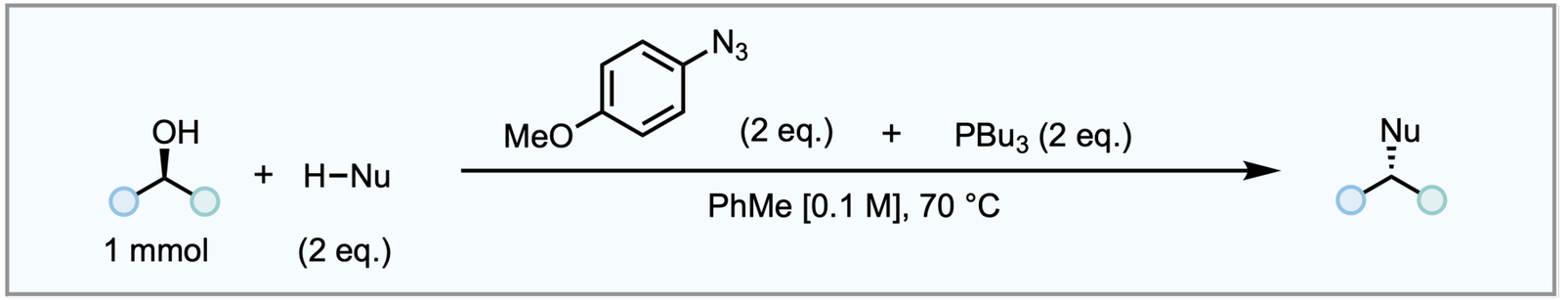
Entry	R	Yield (%)
1	*p*-ClPh	3
2	Ph	1
3	*p*-MeOPh	0
4	*c*-Hex	20
5	Bu	88



optimal iminophosphorane

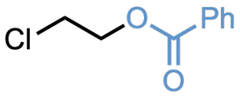
M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

Scope of Oxygen and Nitrogen Pronucleophiles

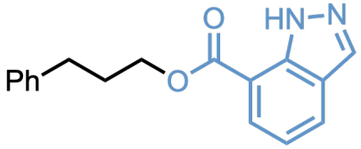




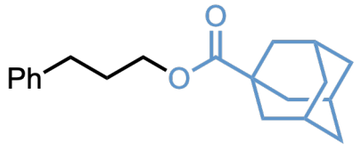
72%



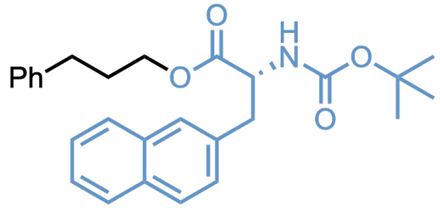
83%



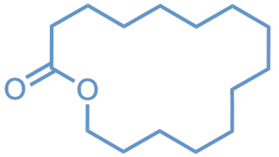
81%



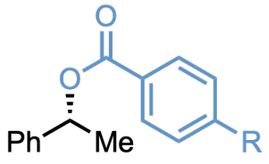
89% (10 mmol scale)



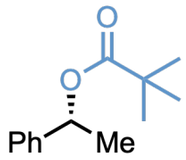
83% (20 mmol scale)



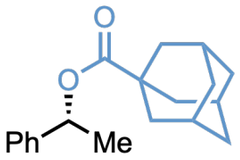
44%



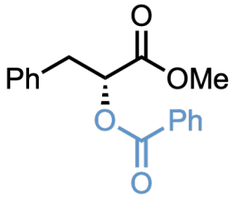
R = OMe, **79%**, >99% ee
= H, **78%**, >99% ee
= NO_2, **80%**, >99% ee



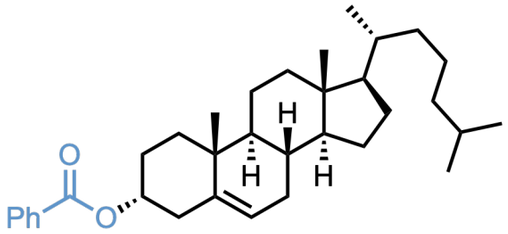
82%, >99% ee



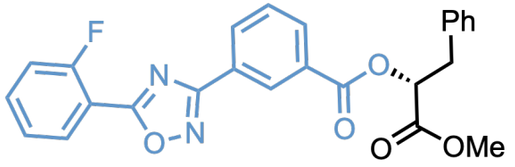
60%, >99% ee



94%, 99% ee



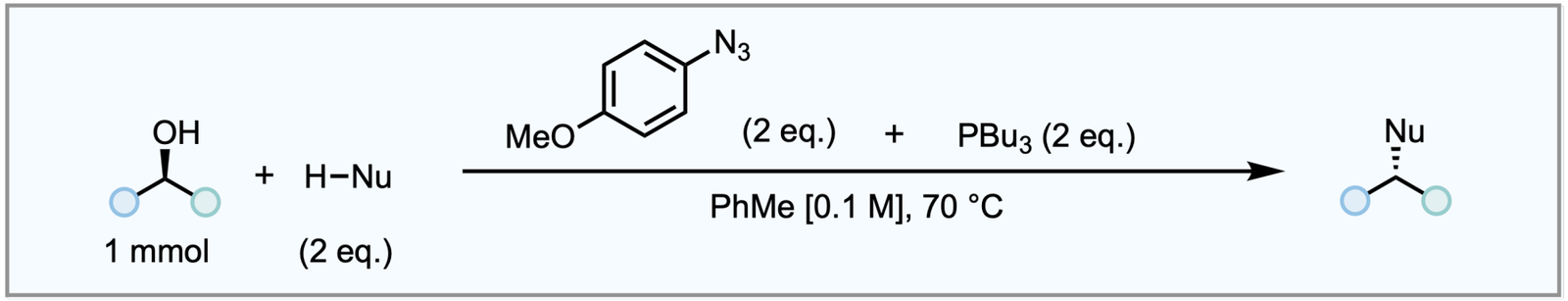
58%, >20:1 dr
from cholesterol

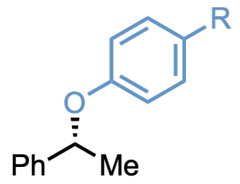


89%, >99% ee
from ataluren

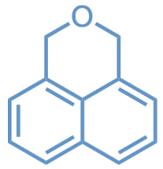
M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

Scope of Oxygen and Nitrogen Pronucleophiles





R = OMe, **85%**, >99% ee
= NO_2, **52%**, 92% ee



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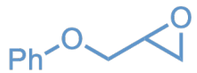

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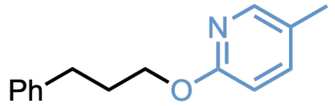

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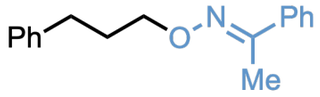

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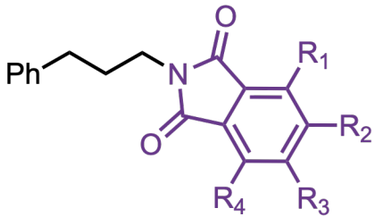
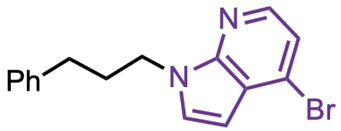


R_1, R_2, R_3, R_4 = H, **67%**
R_1, R_2, R_3, R_4 = Cl, **76%**
R_1, R_2, R_4 = H, R_3 = NO_2, **84%**



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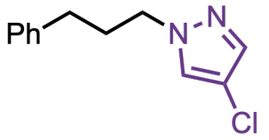
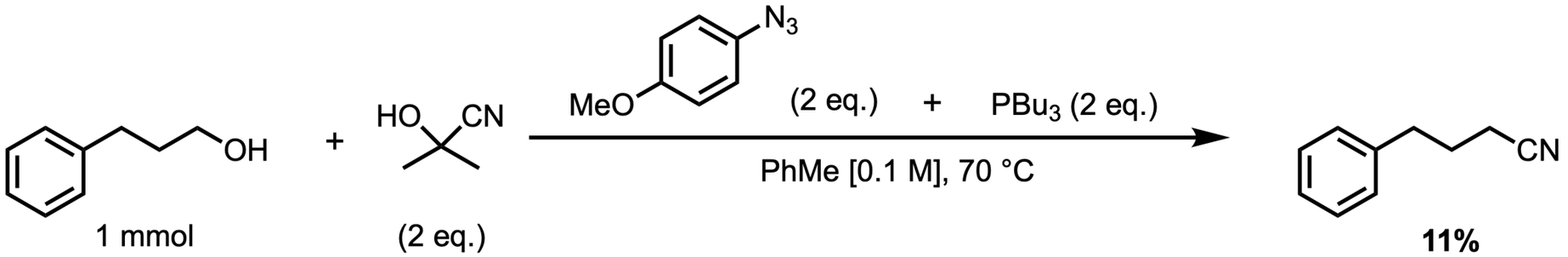


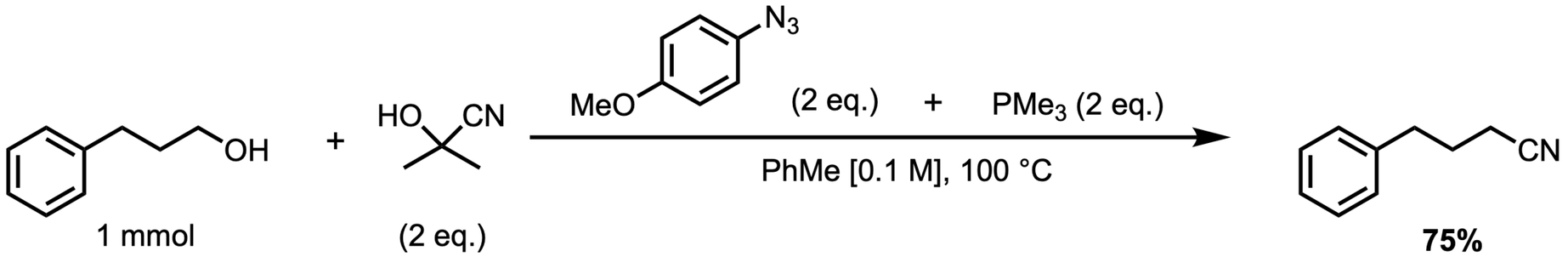
62%

M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

Reoptimisation for Carbon Pronucleophiles



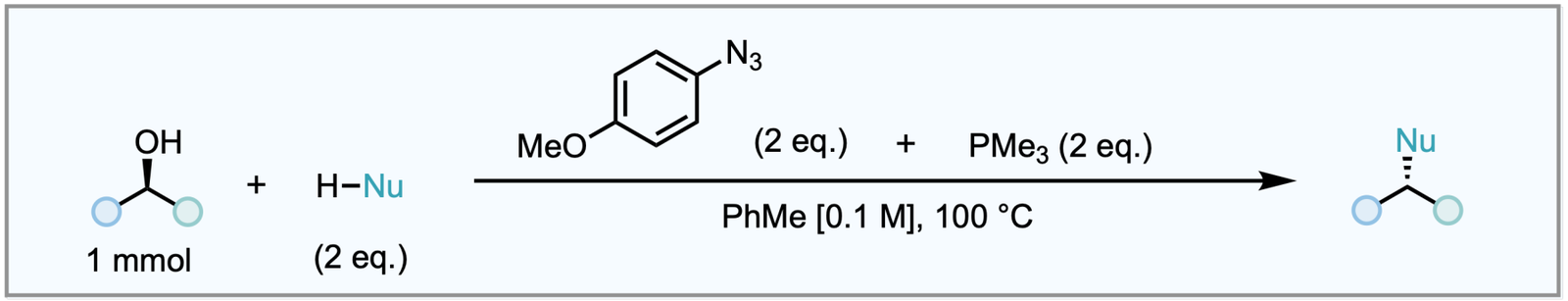


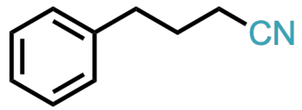


- **Substitution of PBu_3 for PMe_3 and raising the temperature enabled C-C bond formation**

M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

Scope of Carbon Pronucleophiles





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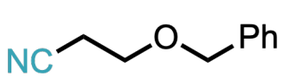

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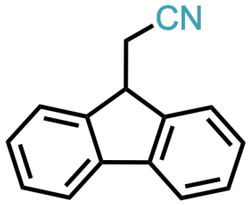

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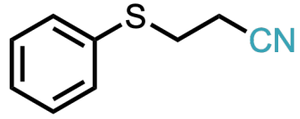

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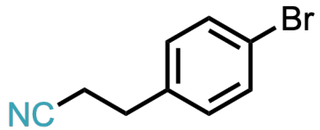

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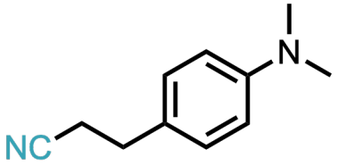

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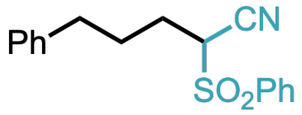

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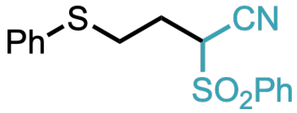

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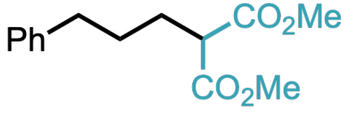

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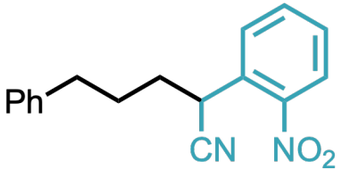

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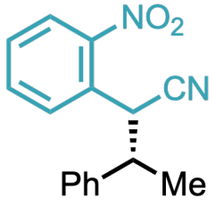
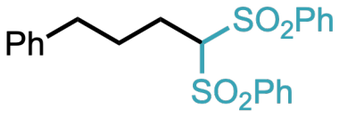


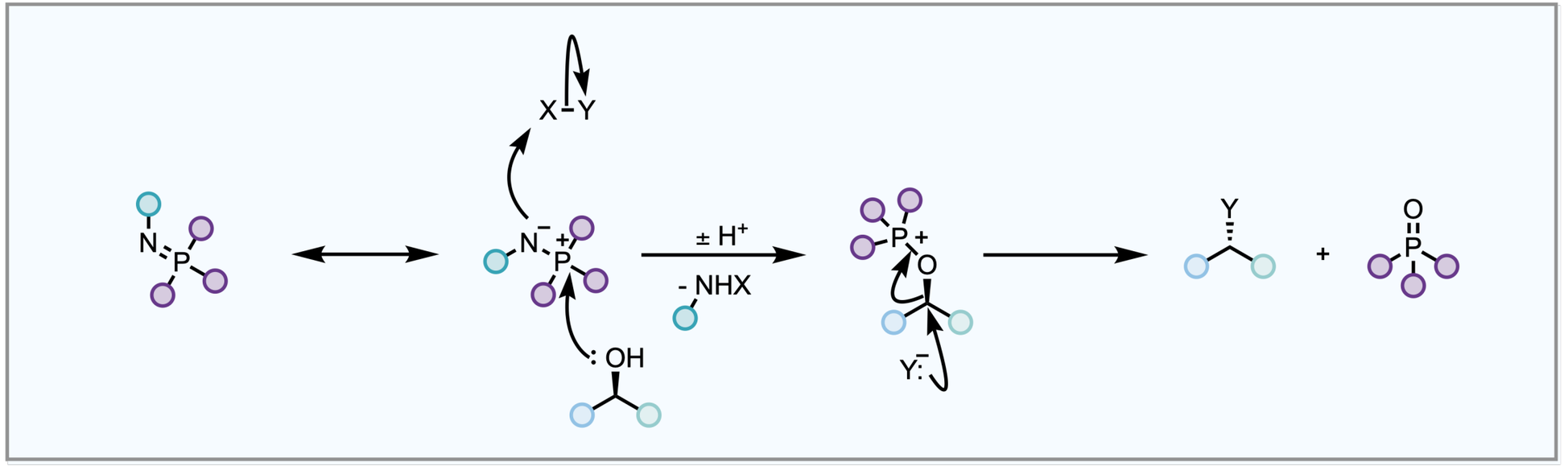
78% 1:1 dr
86% ee : 89% ee



52%

M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

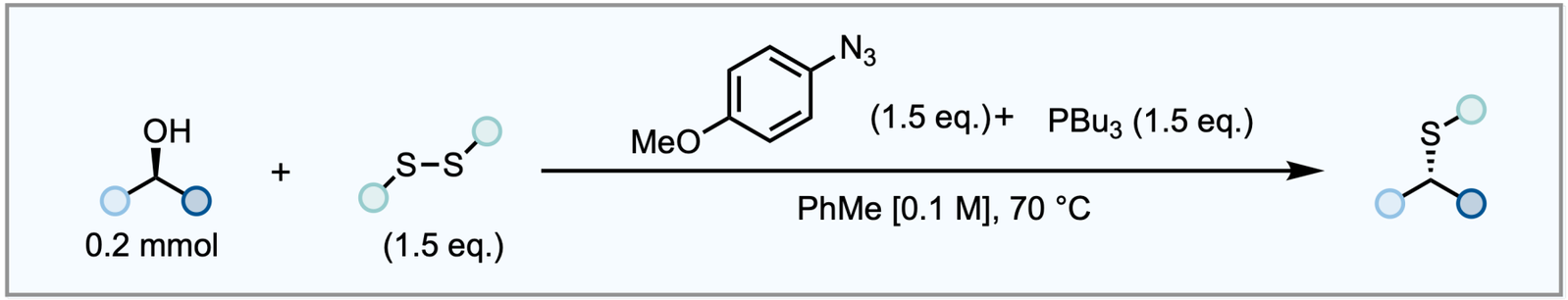
Alternative Pronucleophile Activation Mode?

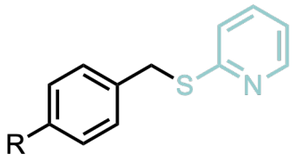


- **Exploit iminophosphorane nucleophilicity for C-Y bond formation**

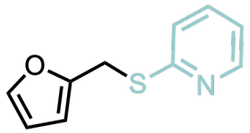
M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

Scope of Disulfide Pronucleophiles





R = F, **57%**
= H, **94%**
= MeO, **51%**



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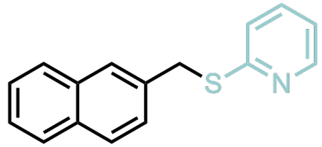

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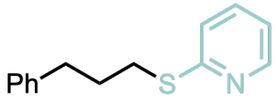

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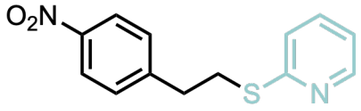

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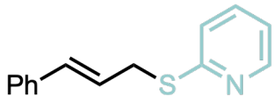

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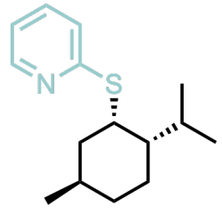
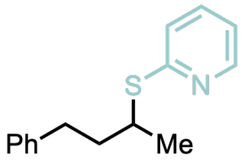
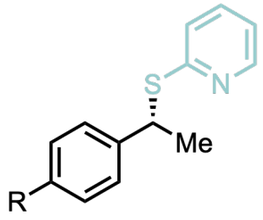


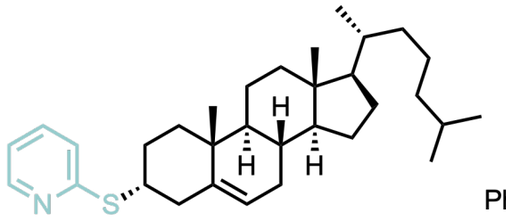
92%, >20:1 dr
from L-menthol



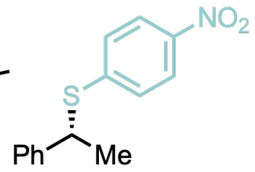
73%



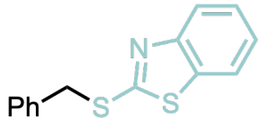
R = H, **73%**, >99% ee
= NO_2 (*rac SM*), **31%**



92%, >20:1 dr
from cholesterol



60%, >99% ee



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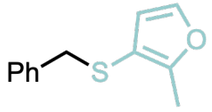

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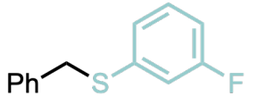

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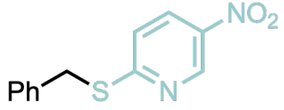

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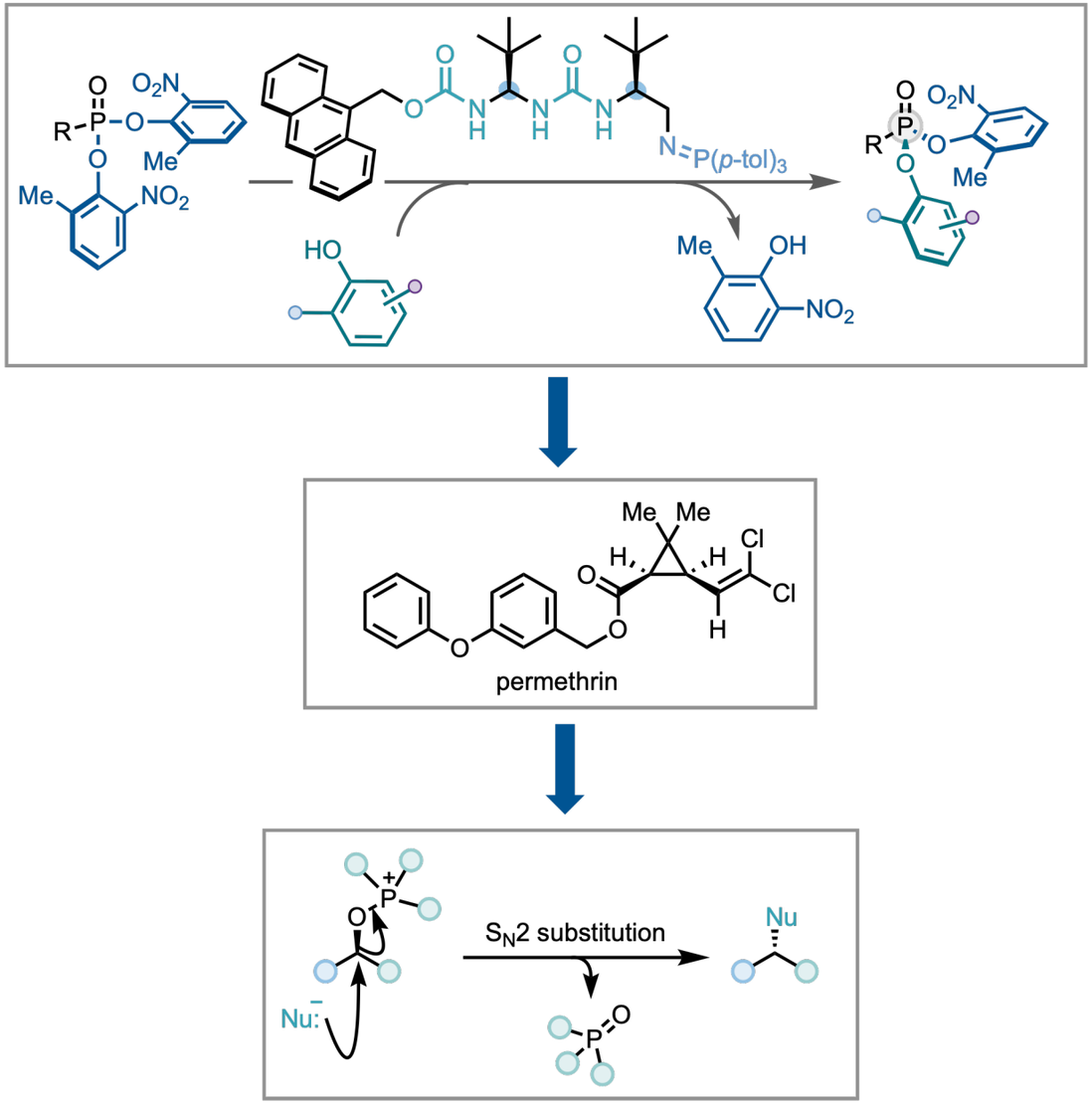
M. Tregear, S. Yamamura, D. J. Dixon, https://doi.org/10.26434/chemrxiv.15006188/v1, and in press

Lecture Overview



Dixon Group Past and Present

BIMP Catalysis
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Connor Thomson
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Naoto Sahara
Yao Shi
Timothy Davidson
Thomas Marsh

Cyclopropenes
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Dong-Hang Tan

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Shisato Yamamura
Arianna Montoli

DFT
Trevor Hamlin
Ken Yamazaki
Eveline Tiekink

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