Organocatalysis with NHCs

Outline:
1. Introduction
2. Synthesis of Normal NHCs
3. General Reactivity
   - 3.1 Breslow intermediate
   - 3.2 Acyl Enolate
   - 3.3 Acyl Azolium
   - 3.4 Single Electron Transfer
   - 3.5 Miscellaneous Activation mode
4. Total Synthesis Examples with NHCs

Not included
- NHC as Metal Ligand
- NHC as C1 Synthon
- Brønsted Base Catalysts

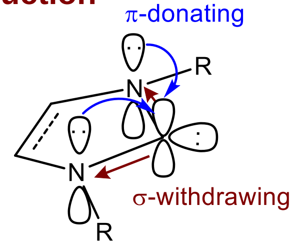
Relevant Reviews

Enders, D. et al. *Chem. Rev.* 2007, 107, 5606−5655.
https://doi.org/10.1021/cr068372z
César, V. et al. *Chem. Rev.* 2011, 111, 2705-2733.
https://doi.org/10.1021/cr100328e
Glorius, F. er al. *Nature*. 2014, 485−496.
https://doi.org/10.1038/nature13384
Rovis, T. et al. *Chem. Rev.* 2015, 115, 9307−9387.
https://doi.org/10.1021/acs.chemrev.5b00060
Chen, X. et al. *Chin. J. Chem.* 2020, 38, 1167−1202.
https://doi.org/10.1002/cjoc.202000107

Book

Buju, A. T., N-Heterocyclic Carbene in Organocatalysis. Wiley, 2018.

Introduction



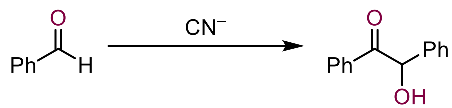
N-Substituted
- Prevent of dimerization
- Change the electronic property
- Asymmetric induction

Ring Size
- Change the Bent angle of carbene
- Cyclic structure favor singlet carbene

Heterocycle Back bone
- Aromaticity (nonessential) ~ 25 kcal/mol stabilization
- Change the electronic property

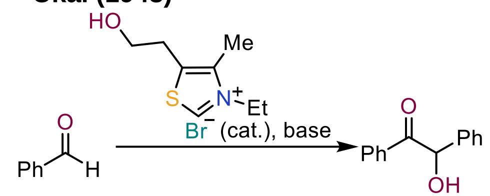
Glorius, F. er al. *Nature*. 2014, 485−496. https://doi.org/10.1038/nature13384

Wöhler, Liebig (1832)



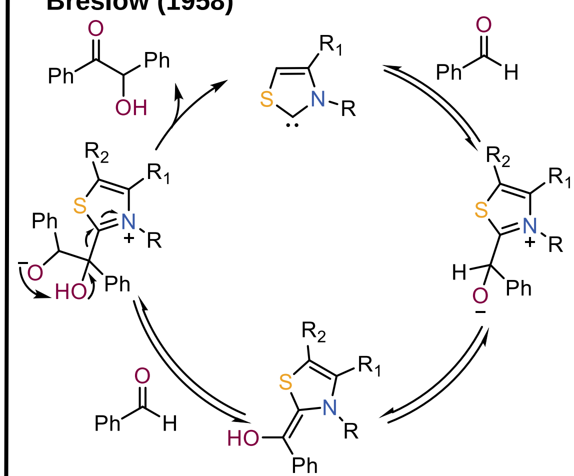
Wohler, F.; Liebig, J. *Ann. Der. Pharm.* 1832, 3, 249−287.

Ukai (1943)

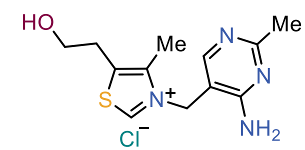


Ukai, T. et al. *I. J. Pharm. Soc. Jpn.* 1943, 63, 296−304

Breslow (1958)



Breslow intermediate



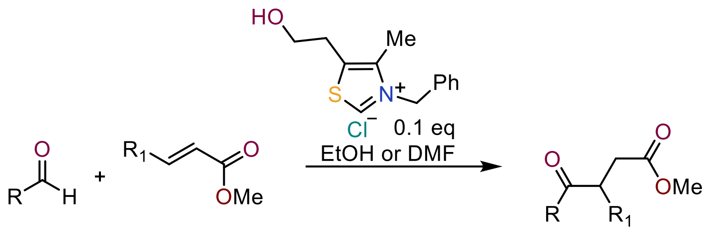
Thiamine Vit. B1

- Coenzyme of pyruvate decarboxylase
- Converting pyruvate to acetoin
- Catalyzing transketolase

Breslow, R. *J. Am. Chem. Soc.* 1958, 80, 3719−3726. (1958). https://doi.org/10.1021/ja01547a064

Organocatalysis with NHCs

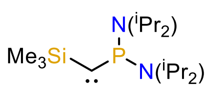
Stetter (1976)



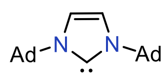
R, R_1=Alkyl, Ar

Stetter, H. et al. *Angew. Chem. Int. Ed.* 1973, 12, 81. https://doi.org/10.1002/anie.197300811

First Isolable Stabilized Carbene



Bertrand (1988)

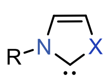


Arduengo (1991)

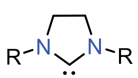
Bertrand, G. *J. Am. Chem. Soc.* 1988, 110, 6463−6466. https://doi.org/10.1021/ja00227a028

Arduengo III, A. J. *J. Am. Chem. Soc.* 1991, 113, 1, 361–363. https://doi.org/10.1021/ja00001a054

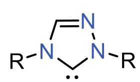
Common NHC Class



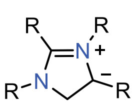
X=NR, Imidazolylidene
X=S, Thiazolylidene
X=O, Oxazolylidene



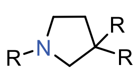
Imidazolinylidene



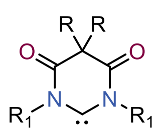
Triazolylidene



Abnormal imidazolylidene



Cyclic alkyl amino carbene (CACC)



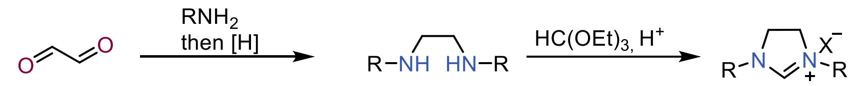
N,N'-diaminocarbene (DAC)

Glorius, F. er al. *Nature*. 2014, 485–496. https://doi.org/10.1038/nature13384

Synthesis of Normal NHCs

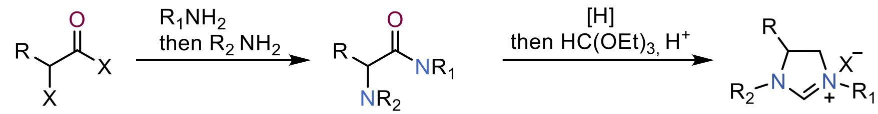
- **Imidazolinylidene**

symmetrical



Arduengo III, A. J. *Tetrahedron 1999, 55,14523.*. https://doi.org/10.1016/S0040-4020(99)00927-8

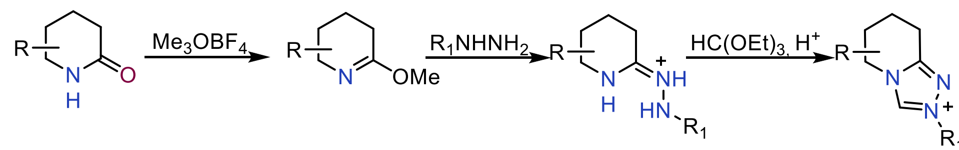
unsymmetrical



α-halogenoacyl core

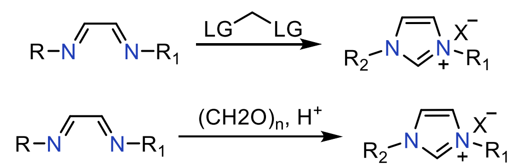
Kotschy, A. et al. *J. Org. Chem*. 2006, 71, 5969-597. https://doi.org/10.1021/jo060594+

- **Triazolium**



Leeper, F. J. et al. *J. Chem. Soc., Perkin Trans. 1*, 1998, 1891-1894 https://doi.org/10.1039/A803635G

- **Imidazolium**



common C1-synthons

CH_2I_2

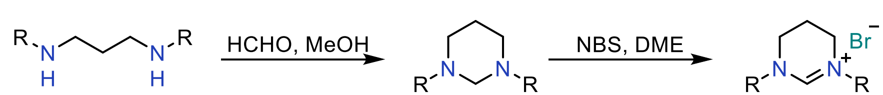
$[Ph_3As\text{-}CH_2\text{-}OTf]^+(TfO)^-$

$Cl\text{-}CH_2\text{-}OMe$

$tBuCO_2\text{-}CH_2\text{-}OTf$

César, V. et al. *Chem. Rev.* 2011, 111, 2705-2733. https://doi.org/10.1021/cr100328e

- **Tetrahydropyrimidinium**

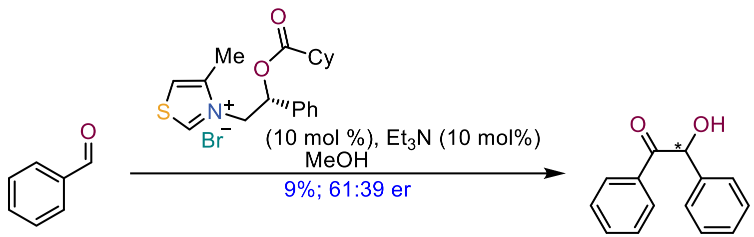


Buchmeiser, M. R. et al. *Macromol. Rapid Commun*. 2004, 25, 231–236. https://doi.org/10.1002/marc.200300173

General Reactivity

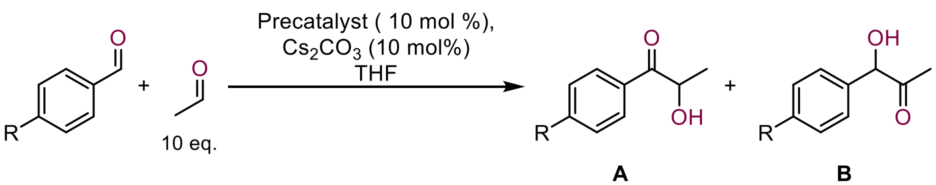
Breslow intermediate

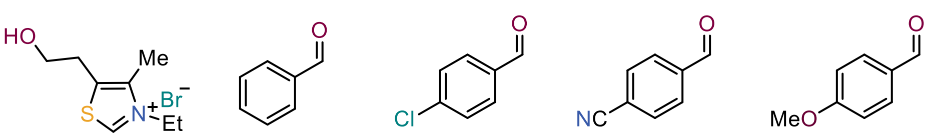
First Example of Asymmetric Benzoin Condensation



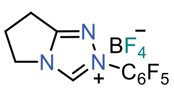
Sheehan, J. C. *J. Am. Chem. Soc.* 1966, 88, 15, 3666–3667. https://doi.org/10.1021/ja00967a049

Different Catalyst Override Innate Reactivity





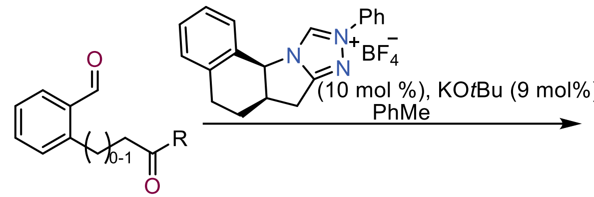
	(Ph)	(4-Cl)	(4-CN)	(4-OMe)
% Yield	87	88	90	45
A:B	93:7	95:5	98:2	92:8

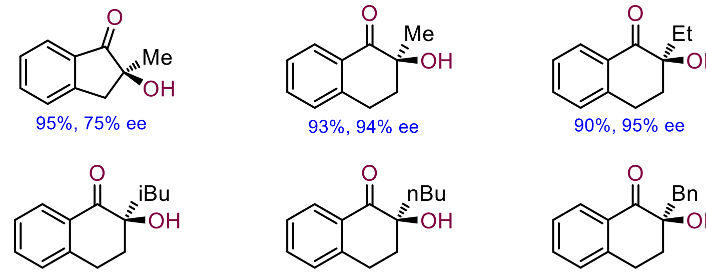


	(Ph)	(4-Cl)	(4-CN)	(4-OMe)
% Yield	90	95	90	53
A:B	13:87	14:86	28:72	11:89

Yang, J.W.. Et al. *Org. Lett.* 2011, 13, 880 –883. https://doi.org/10.1021/ol102937w

Intramolecular Benzoin Condensation



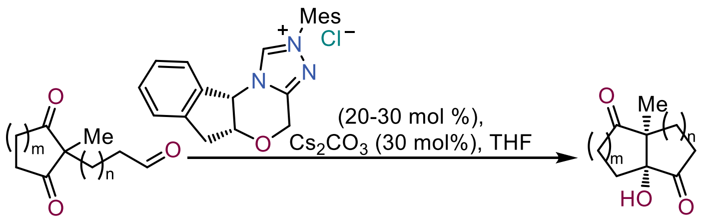


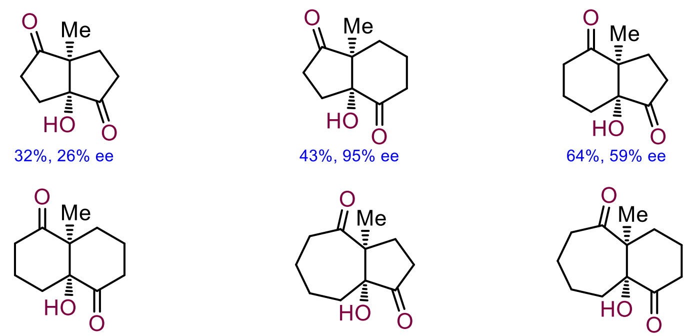
95%, 75% ee; 93%, 94% ee; 90%, 95% ee

91%, 98% ee; 85%, 98% ee; 43%, 93% ee

Enders, D. et al. *Angew. Chem. Int. Ed.* 2006, 45, 1463 –1467. https://doi.org/10.1002/anie.200503885

Desymmertrization of 1,3-Diketone by Benzoin condensation



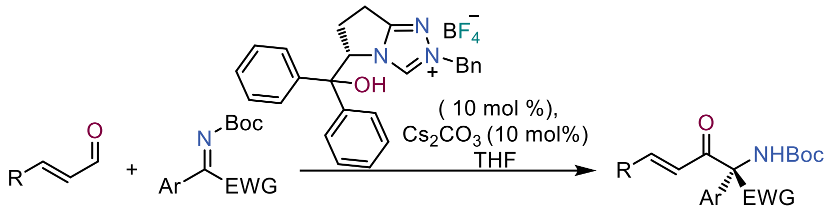


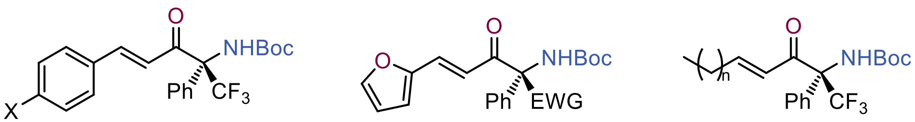
32%, 26% ee; 43%, 95% ee; 64%, 59% ee

67%, 99% ee; 83%, 69% ee; 47%, 84% ee

Ema. T. et al. *Org. Lett.* 2009, 11, 4866 –4869. https://doi.org/10.1021/ol9019293

Aza-Benzoin Condensation



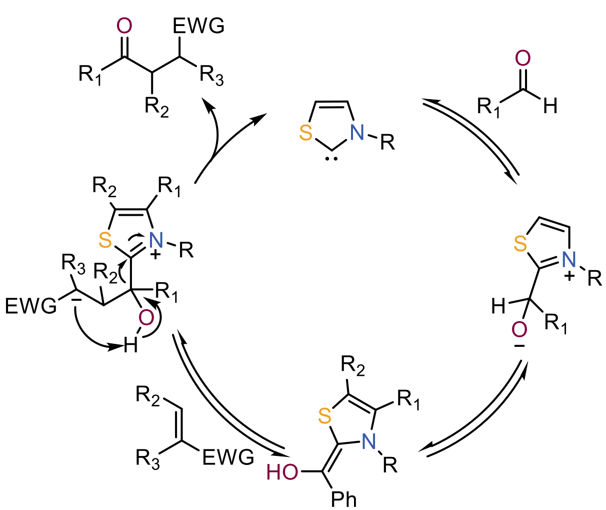


X = Cl	60%, 92% ee	EWG = CF_3	68%, 90% ee	n = 4	51%, 90% ee
X = Me	70%, 90% ee	EWG = CO_2Me	69%, 88% ee	n = 5	43%, 87% ee
X = MeO	89%, 92% ee			n = 6	56%, 90% ee

Ye, S. et al. *Angew. Chem. Int. Ed.* 2013, 52, 5803 –5806. https://doi.org/10.1002/anie.201301304

Stetter reaction

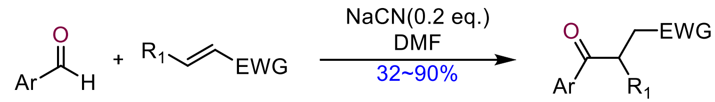
Mechanism



Breslow intermediate

Rovis, T. et al. *Org. Lett.* 2011, 13, 7, 1742–1745. https://doi.org/10.1021/ol200256a

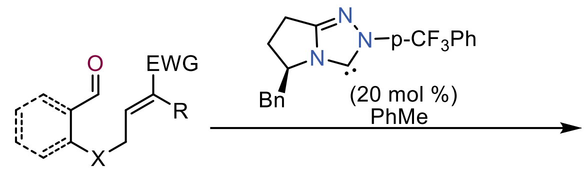
First Report of Stetter Reaction



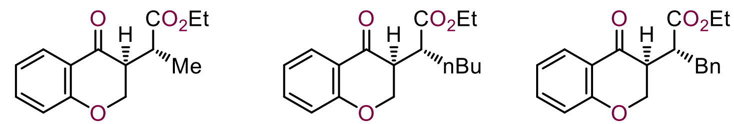
R = Alkyl, Ar
R_1 = CN or CO_2Et

Stetter, H. et al. *Angew. Chem. Int. Ed.* 1973, 12, 81. https://doi.org/10.1002/anie.197300811

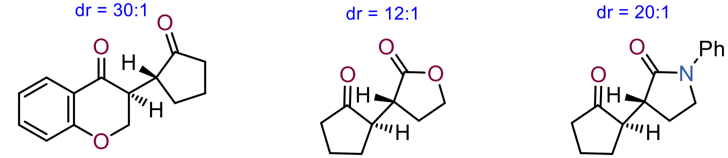
Intramolecular Stetter Reaction



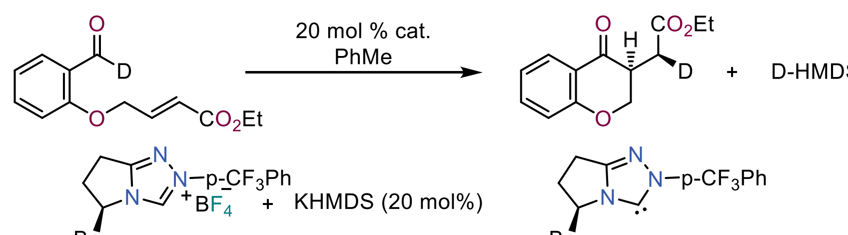
X = O, CH_2



94%, 95% ee dr = 30:1	53%, 94% ee dr = 12:1	80%, 84% ee dr = 20:1



80%, 95% ee dr = 18:1	94%, 99% ee dr = 50:1	80%, 88% ee dr = 15:1



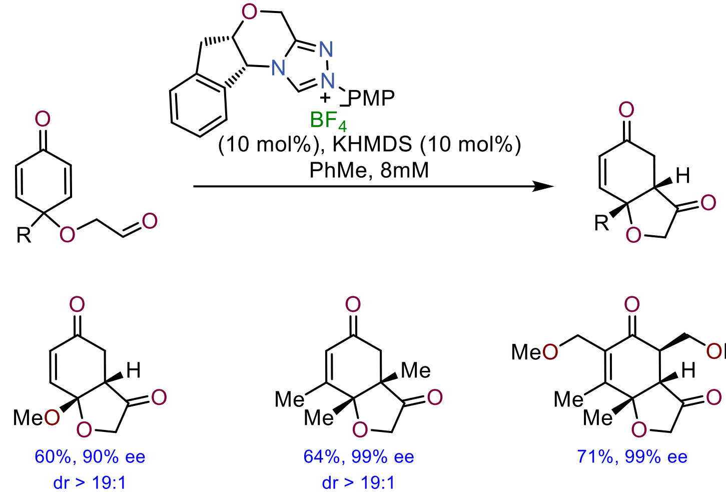
dr = 3:1 (α-D)

dr = 9:1 (α-D)

Rovis, T. et al. *J. Am. Chem. Soc.* 2005, 127, 17, 6284–6289. https://doi.org/10.1021/ja0425132

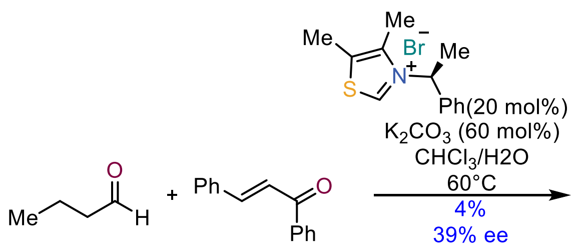
Organocatalysis with NHCs

Desymmertization by Stetter Reaction

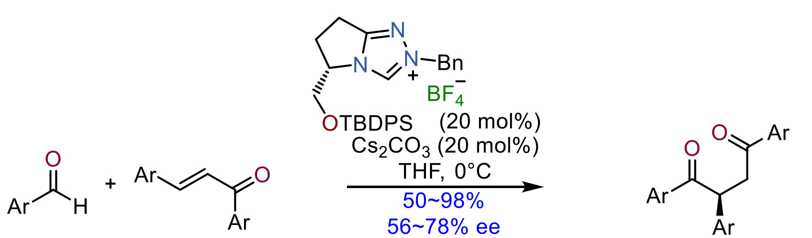


Rovis, T. et al. *J. Am. Chem. Soc.* 2006, 128, 8, 2552–2553. https://doi.org/10.1021/ja058337u

Intermolecular Stetter reaction

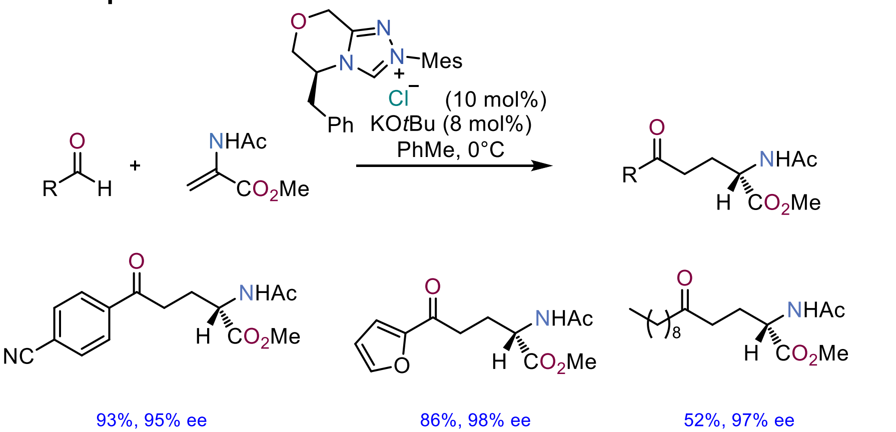


Enders, D. (1993). Stereoselective Synthesis, 63–90. Heidelberg,Germany: Springer-Verlag.



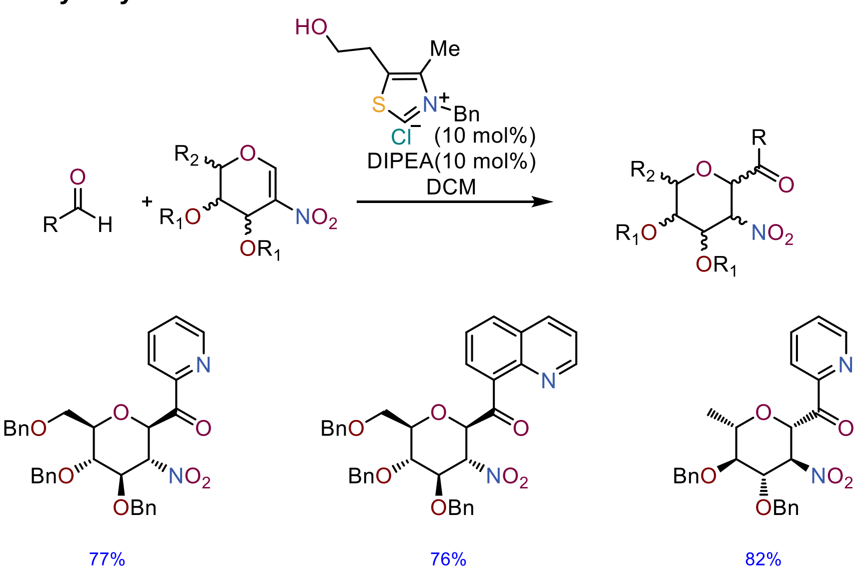
Enders, D. et al. *Chem.Commun.,* 2008, 3989–3991. https://doi.org/10.1039/B809913H

Enantiopure α Amino Acid



Glorius, F. et al. *Angew. Chem. Int. Ed*. 2011, 50, 1410 –1414. https://doi.org/10.1002/anie.201006548

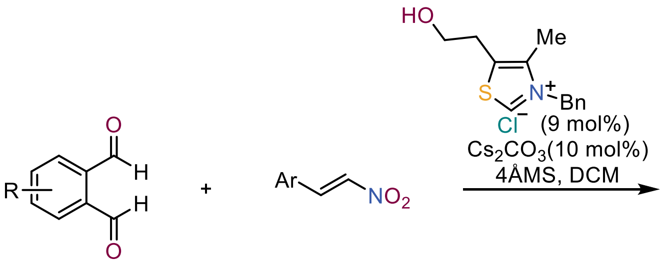
C-Glycosylation



Liu, X. W. et al. *Org. Lett.* 2012, 14, 1, 174–177. https://doi.org/10.1021/ol202959y

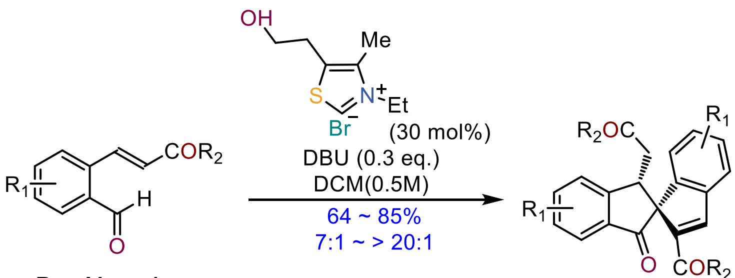
Organocatalysis with NHCs

Tandem Reaction



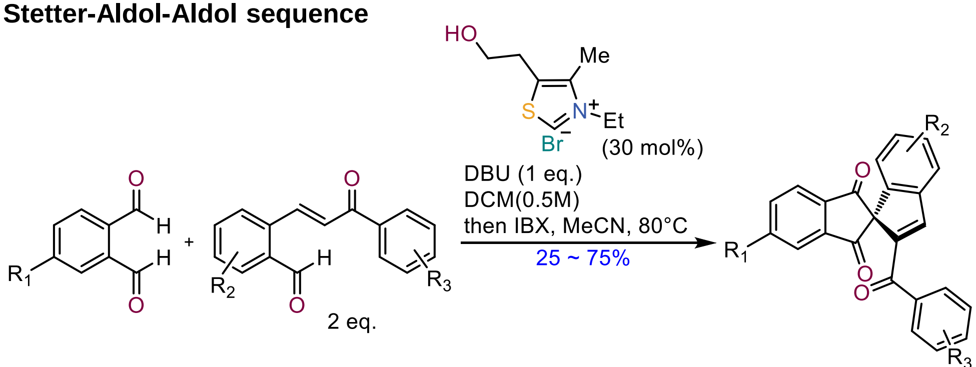
Maiti, D. K. et al. *J. Org. Chem.* 2019, 84, 1, 42–52. https://doi.org/10.1021/acs.joc.8b01503

Stetter-Aldol-Michael sequence



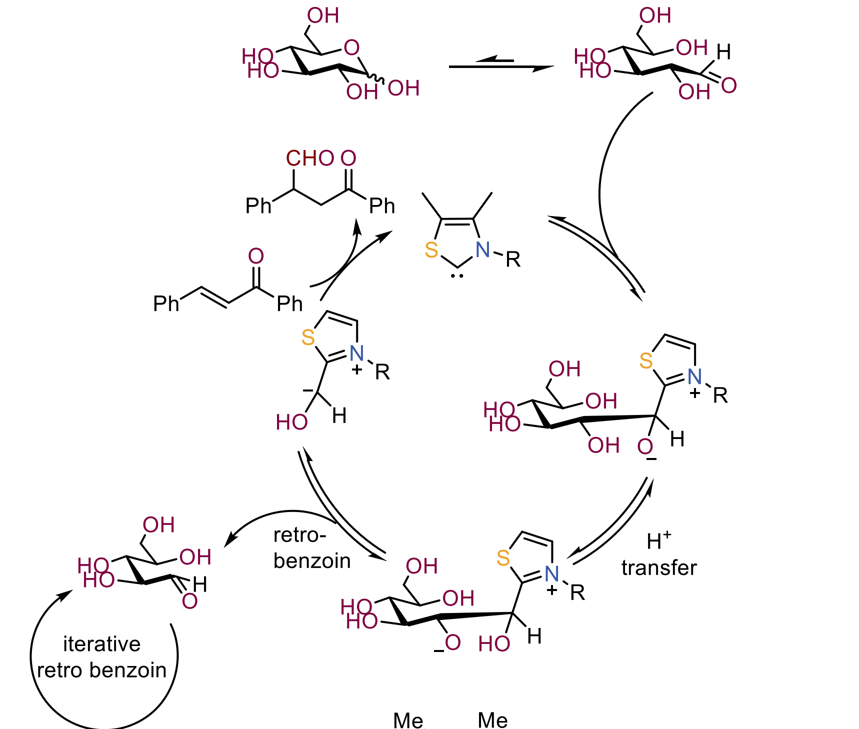
R_2 = Me or Ar

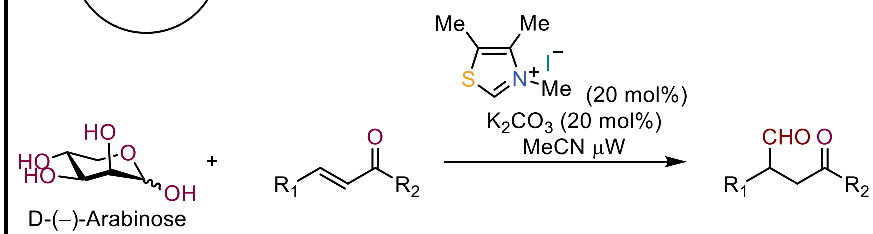
Stetter-Aldol-Aldol sequence

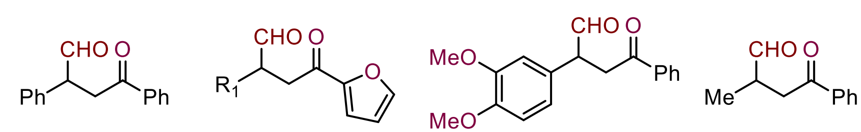


Gravel, M. Et al. Org. Lett. 2010, 12, 24, 5772–5775. https://doi.org/10.1021/ol102685u

Monosaccharide as Formaldehyde Equivalent



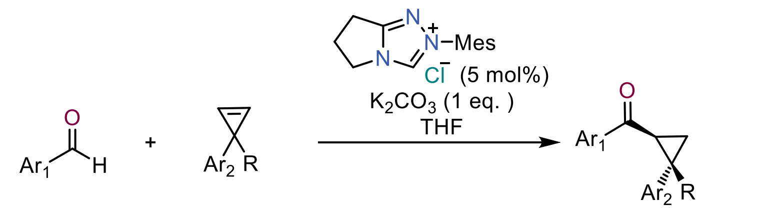


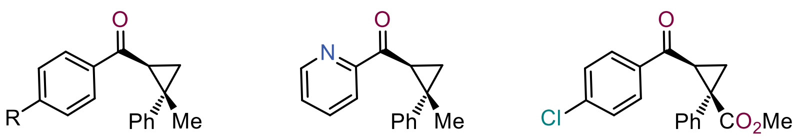


81% | 81% | 86% | 43%

Chi, Y. R. et al. *J. Am. Chem. Soc.* 2013, 135, 22, 8113–8116 https://doi.org/10.1021/ja401511r

Hydroacylation

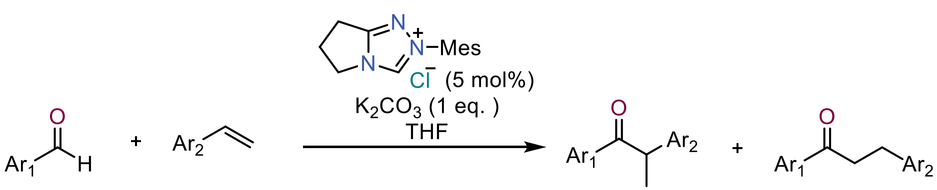


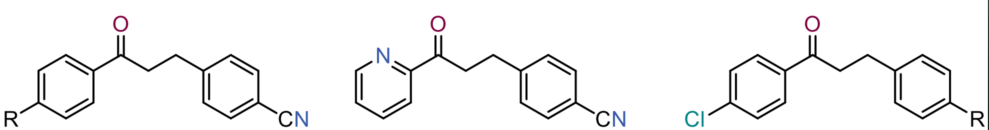


R = Br	96%, dr>20:1	72%, dr>20:1	52%, dr>1.6:1
R = CF_3	78%, dr=11:1		
R= OMe	44%, dr>20:1		

Glorius, F. et al. *J. Am. Chem. Soc.* 2011, 133, 21, 8130–8133. https://doi.org/10.1021/ja202594g

Hydroacylation

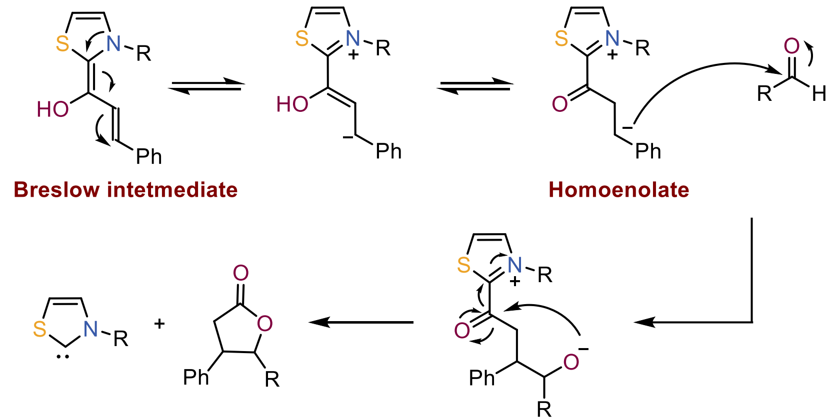




R = Me	47%	97%, l:b=2.7:1	R = CO_2Me	84%, l:b=3.9:1
R = Br	73%, l:b=6:1		R = CF_3	52%, l:b=1.1:1
R= Cl	89%, l:b=5:1		R= t-Bu	39%, l:b=1:20
			R= O-*t*-Bu	20%, l:b=1:20

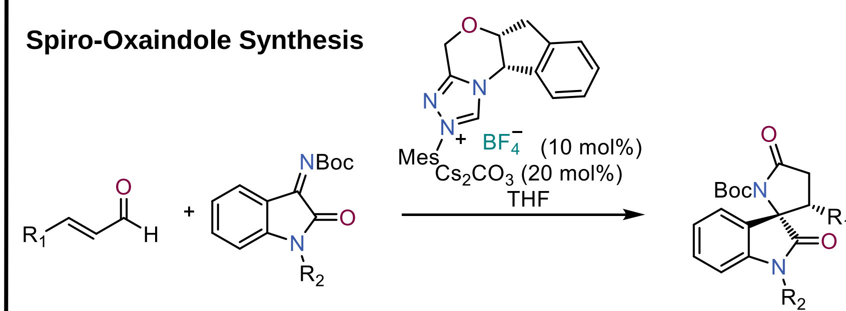
Glorius, F. et al. *Angew. Chem. 2013, 125, 2645 –2649.* https://doi.org/10.1002/ange.201209291

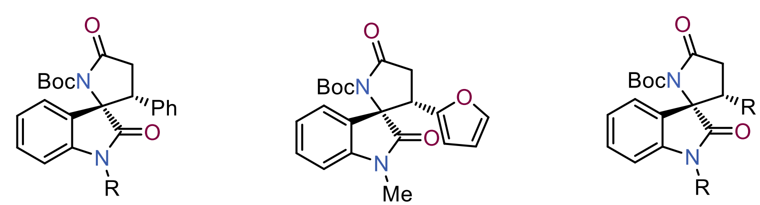
Homoenolate



Glorius, F. et al. Angew. Chem. Int. Ed. 2004, 43, 6205 –6208 https://doi.org/10.1002/anie.200461572
Bode, J. W. et al. *J. Am. Chem. Soc.* 2004, 126, 44, 14370–14371. https://doi.org/10.1021/ja044714b

Spiro-Oxaindole Synthesis



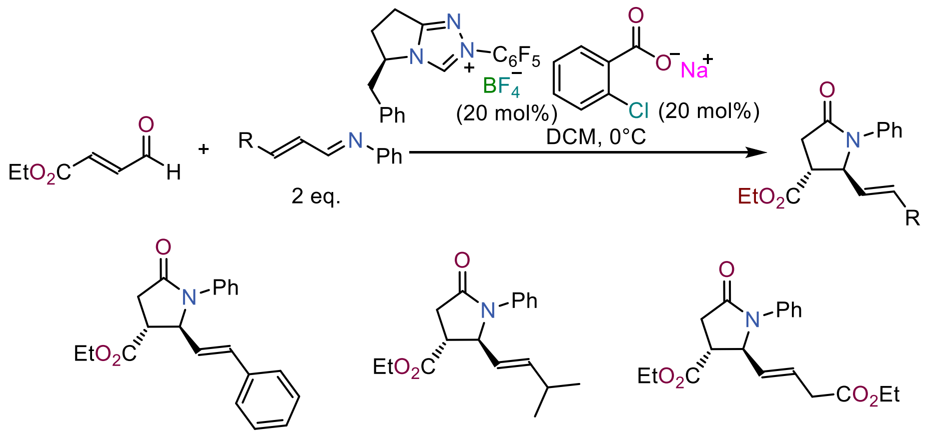


R = H	64%, dr=17:1, 99% ee	80%, dr>20:1	R = Me	64%, dr=4:1, 94% ee
R = Me	83%, dr>20:1, 99% ee	94% ee	R = n-Pr	58%, dr=5:1, 99% ee
R= OMe	78%, dr=18:1, 99% ee			

Chi, Y. R. et al. Org. Lett. 2012, 14, 21, 5412–5415. https://doi.org/10.1021/ol302475g

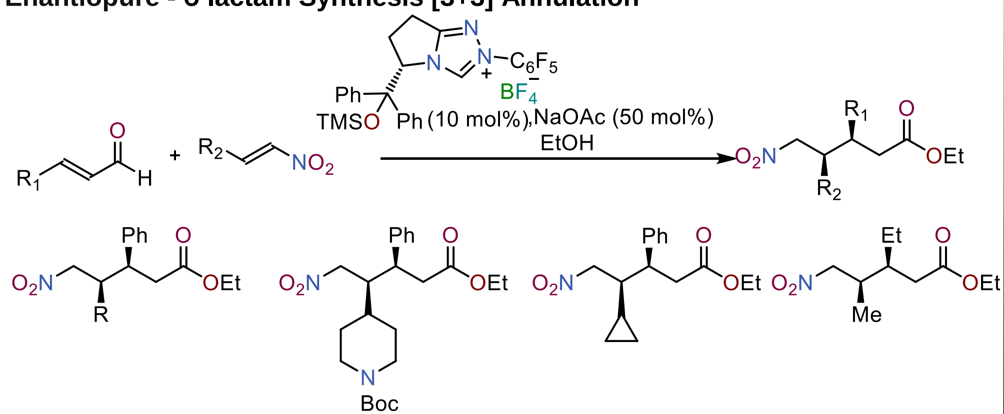
Organocatalysis with NHCs

Enantiopure γ- lactam Synthesis [3+2] Annulation



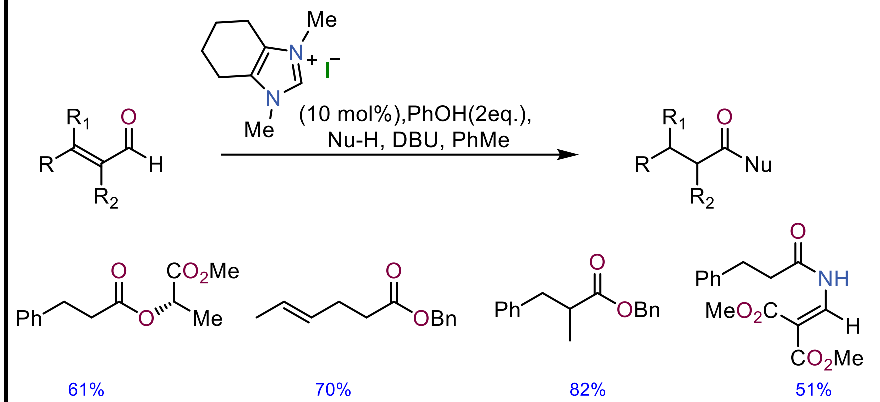
Rovis, T. et al. *J. Am. Chem. Soc.* 2011, 133, 32, 12466–12469. https://doi.org/10.1021/ja205714g

Enantiopure - δ lactam Synthesis [3+3] Annulation



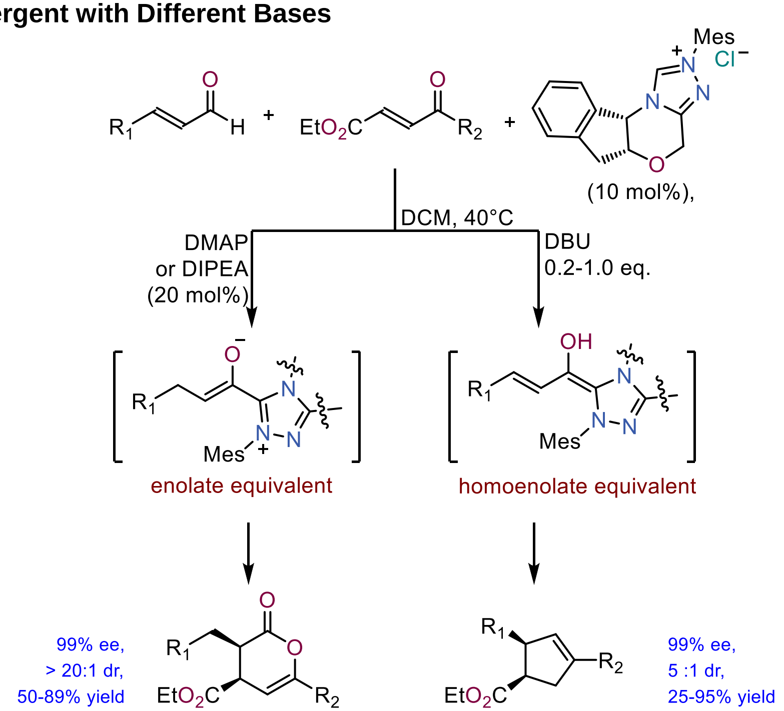
Rovis, T. et al. *J. Am. Chem. Soc.* 2013, 135, 23, 8504–8507. https://doi.org/10.1021/ja403847e

β Protonation



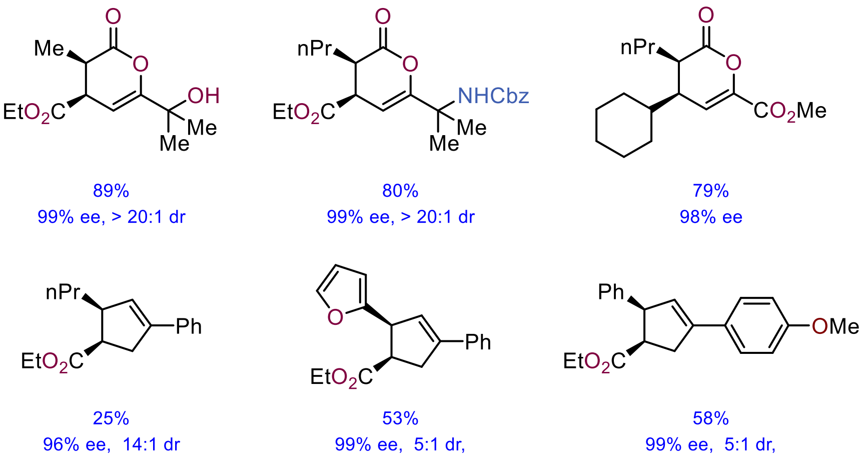
Scheidt, K. A. et al. *Org. Lett.* 2005, 7, 5, 905–908 https://doi.org/10.1021/ol050100f

Divergent with Different Bases



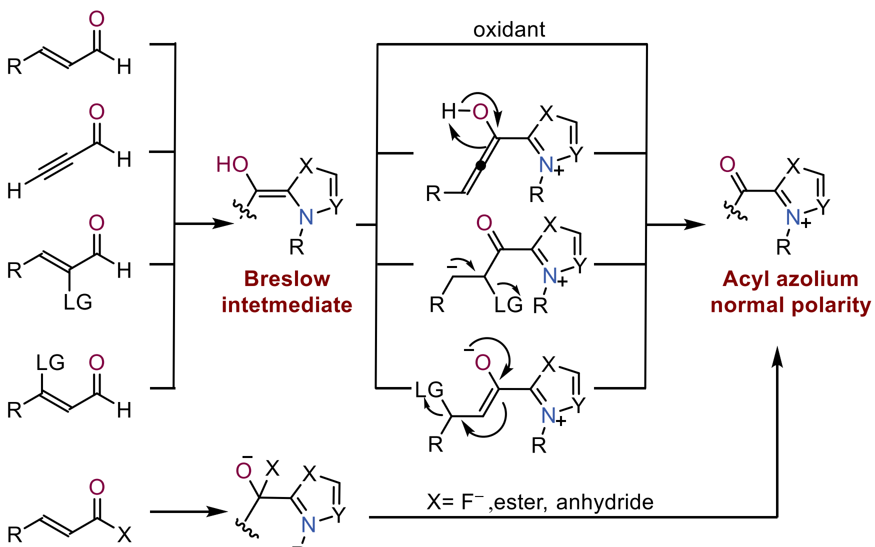
Bode, J. W. et al. *PNAS* 107 (48) 20661-20665. https://doi.org/10.1073/pnas.1007469107

Organocatalysis with NHCs



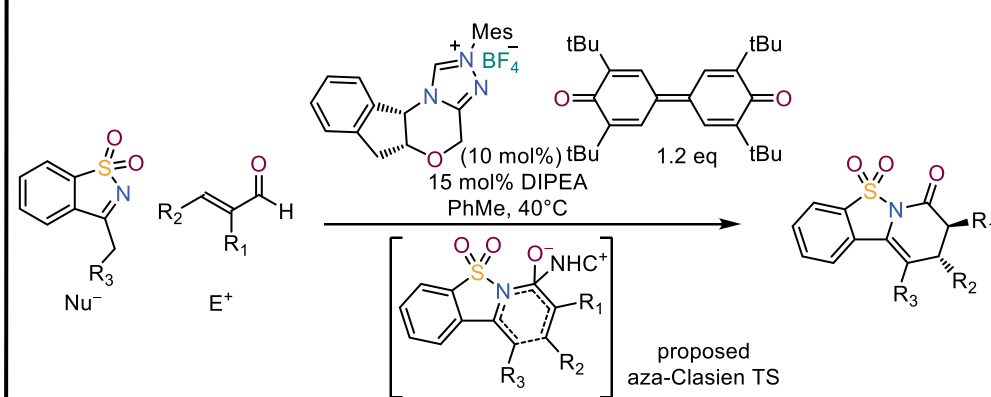
Bode, J. W. et al. *PNAS* 107 (48) 20661-20665. https://doi.org/10.1073/pnas.1007469107

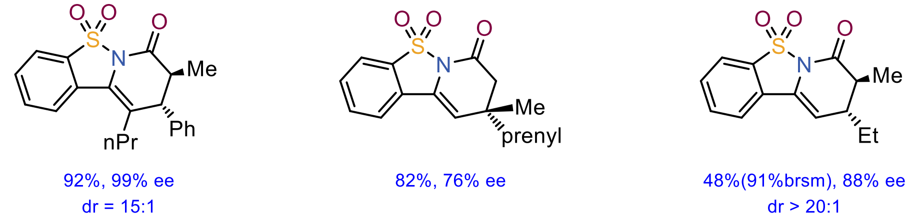
Acyl Azolium



Buju, A. T., N-Heterocyclic Carbene in Organocatalysis. Wiley, 2018

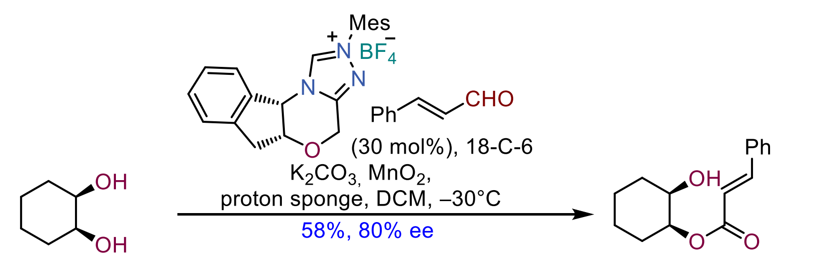
Aza-Clasien





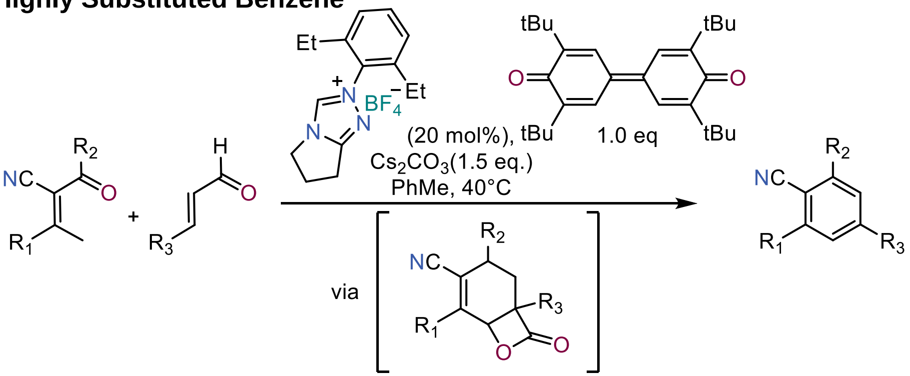
Bode, J. W. et al. *Angew. Chem. Int. Ed. 2012, 51, 9433 –9436* .https://doi.org/10.1002/anie.201204145

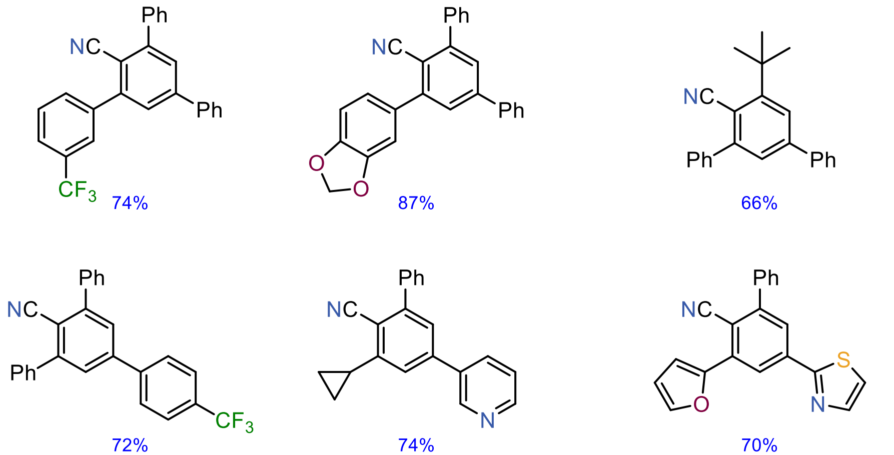
Desymmetrization of 1,2-diol



Scheidt, K. A. et al *Org. Lett.* 2007, 9, 2, 371–374. https://doi.org/10.1021/ol062940f

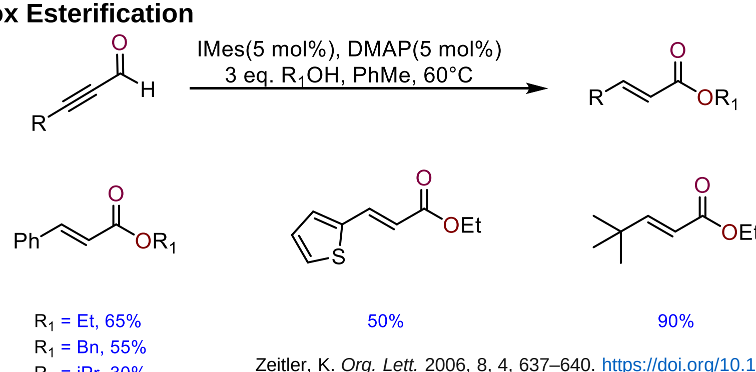
Highly Substituted Benzene





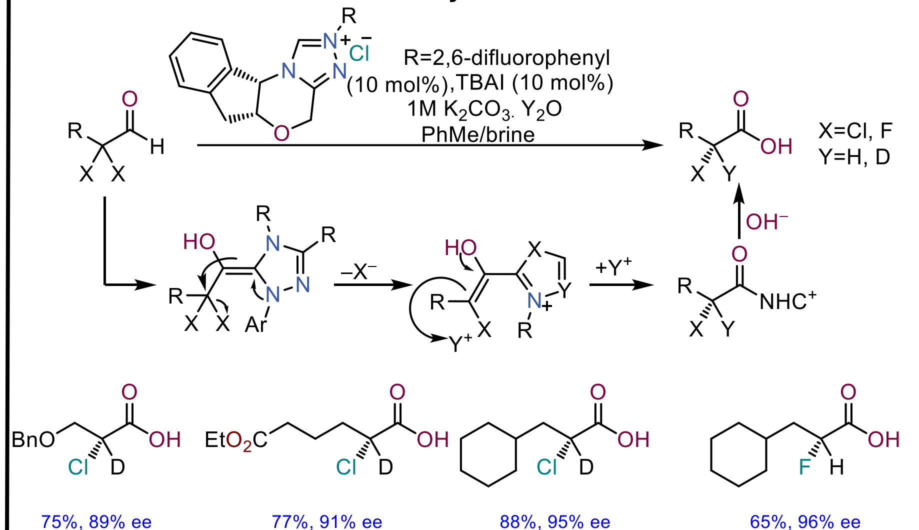
Wang, J. et al. *Org. Lett.* 2016, 18, 9, 2212–2215. https://doi.org/10.1021/acs.orglett.6b00844

Redox Esterification



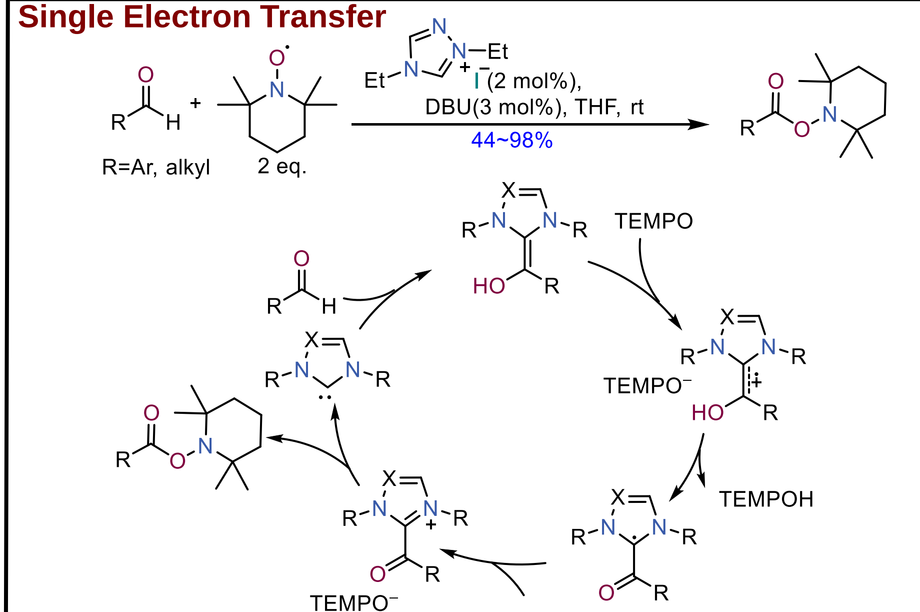
Zeitler, K. *Org. Lett.* 2006, 8, 4, 637–640. https://doi.org/10.1021/ol052826h

Enantioselective α-chloro Carboxylic Acid



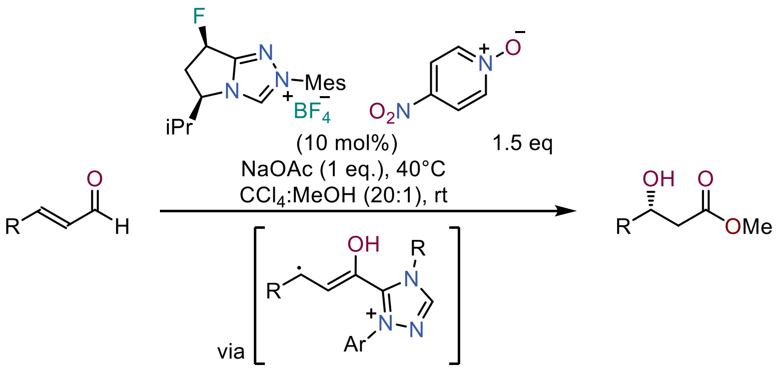
Rovis, T. et al. *J. Am. Chem. Soc.* 2010, 132, 9, 2860–2861. https://doi.org/10.1021/ja910281s

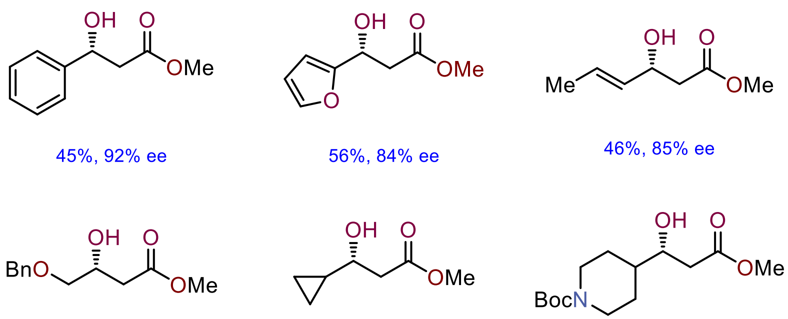
Single Electron Transfer



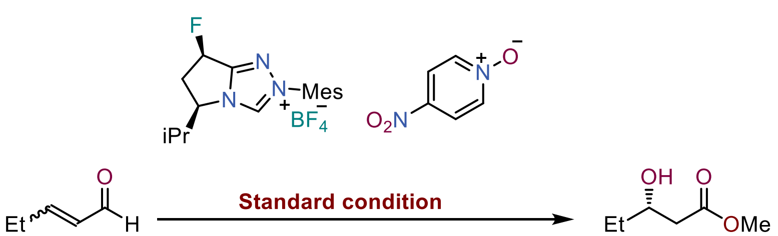
Studer, A. et al. *Angew. Chem. Int. Ed.* 2008, 47, 8727 –8730. https://doi.org/10.1002/anie.200802735

Enantioselective β-oxidation





45%, 92% ee	56%, 84% ee	46%, 85% ee
71%, 81% ee	61%, 80% ee	74%, 84% ee

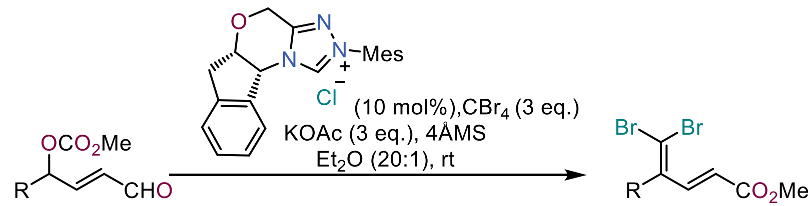


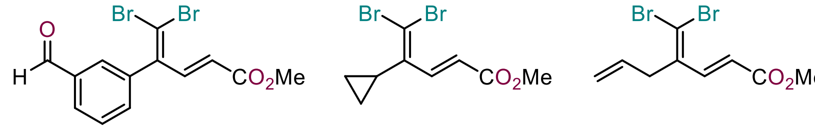
trans (>20:1)
cis (1:3)

	from trans	from cis
23 °C	65%, 86% ee	62%, –32% ee
65 °C	54%, 74% ee	53%, 33% ee

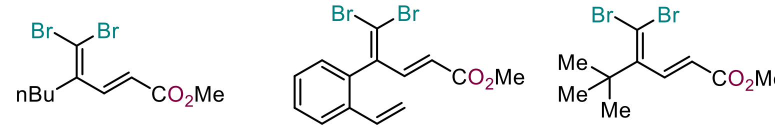
Rovis, T. et al. *J. Am. Chem. Soc.* 2014, 136, 42, 14674–14677. https://doi.org/10.1021/ja5080739

Dibromomethylenation



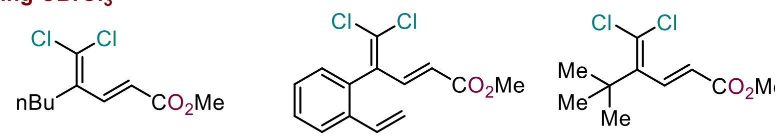


60%	75%	85%

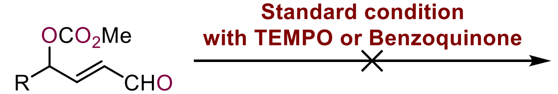


64%	75%	62%

If using $CBrCl_3$

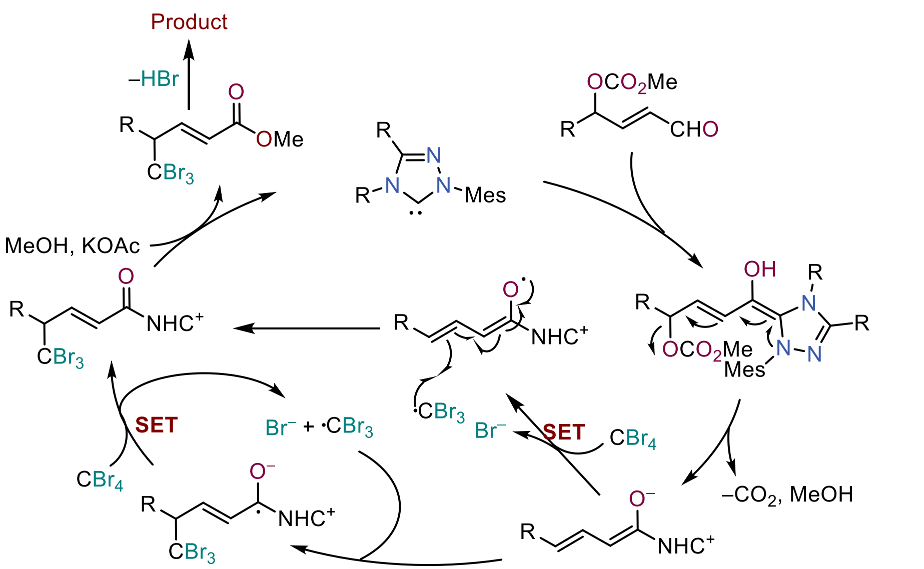


79%	84%	65%



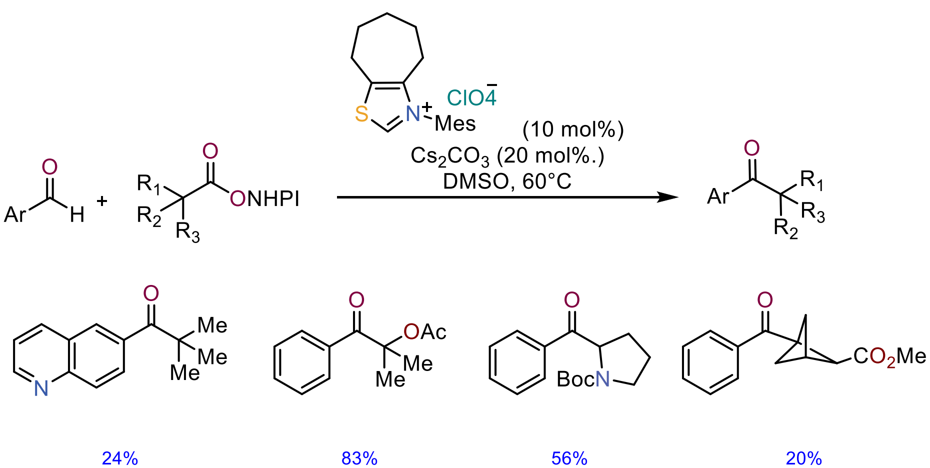
Sun, J. et al. *Angew. Chem. Int. Ed. 2016, 55, 15783 – 15786* https://doi.org/10.1002/anie.201608371

Organocatalysis with NHCs



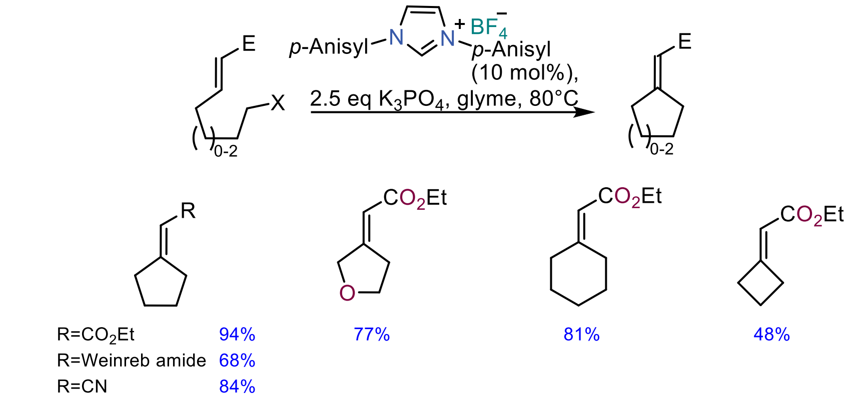
Sun, J. et al. *Angew. Chem. Int. Ed. 2016, 55, 15783 – 15786* https://doi.org/10.1002/anie.201608371

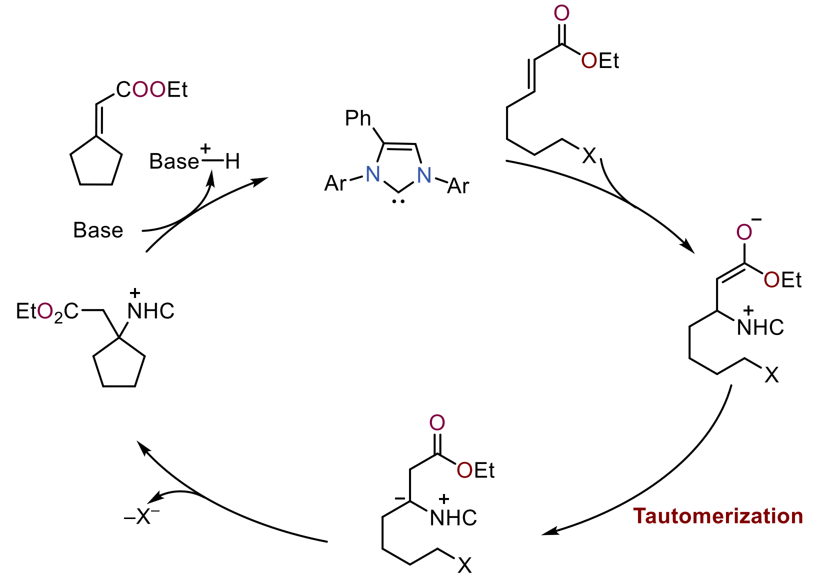
SET with Redox-Active Ester



Ohmiya, H. et al. *J. Am. Chem. Soc.* 2019, 141, 9, 3854–3858. https://doi.org/10.1021/jacs.9b00880

Umpolung MBH reaction

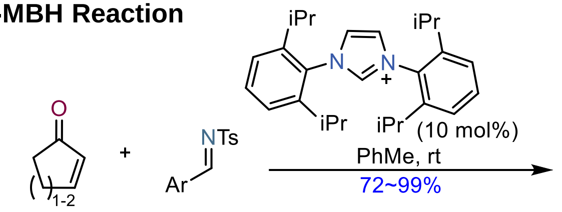




Fu, G. C. et al. *J. Am. Chem. Soc.* 2006, 128, 5, 1472–1473. https://doi.org/10.1021/ja058222q

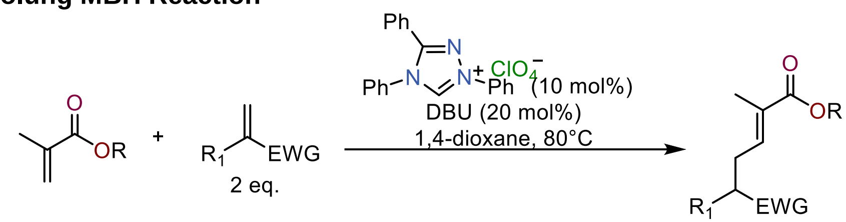
Organocatalysis with NHCs

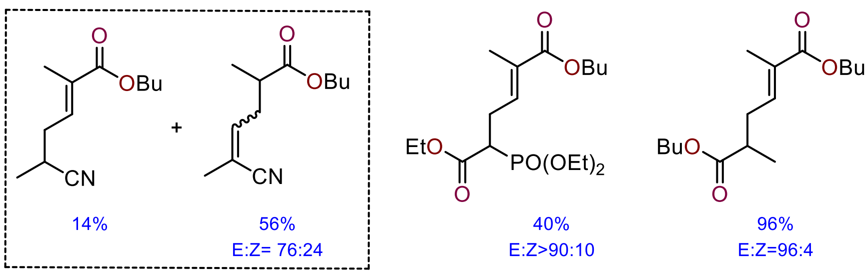
Aza-MBH Reaction

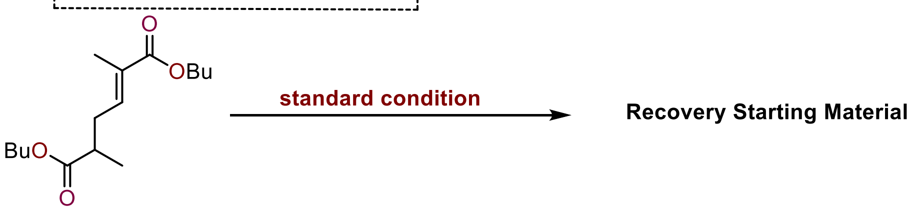


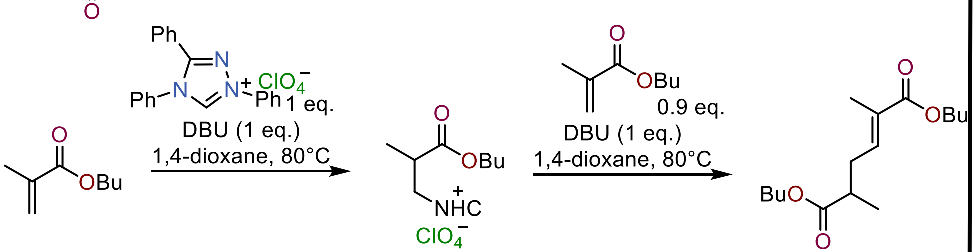
Ye, S. et al. *J. Org. Chem.* 2007, 72, 19, 7466–7468. https://doi.org/10.1021/jo071247i

Umpolung MBH Reaction



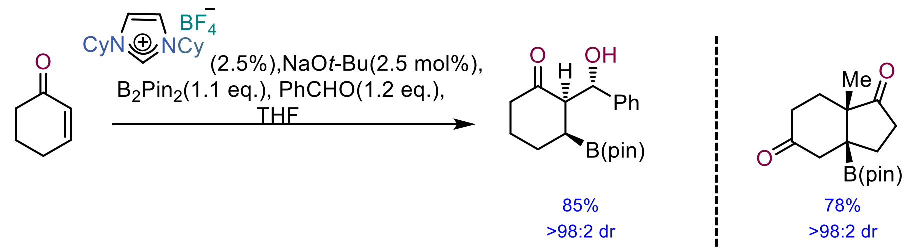




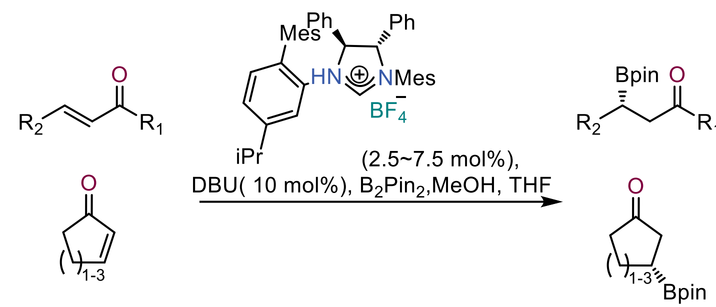


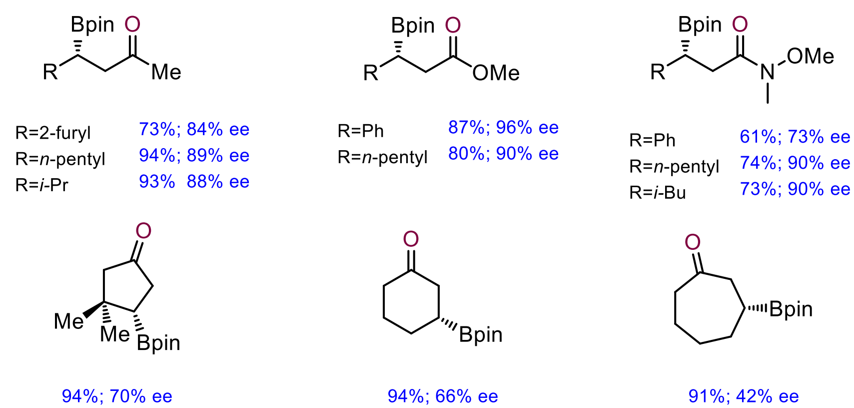
Glorius, F. et al. *Angew. Chem. Int. Ed.* 2011, 50, 8412 –8415. https://doi.org/10.1002/anie.201103555

Activation of Diboron



Hoveyda, A. H. et al. *J. Am. Chem. Soc.* 2009, 131, 21, 7253–7255. https://doi.org/10.1021/ja902889s

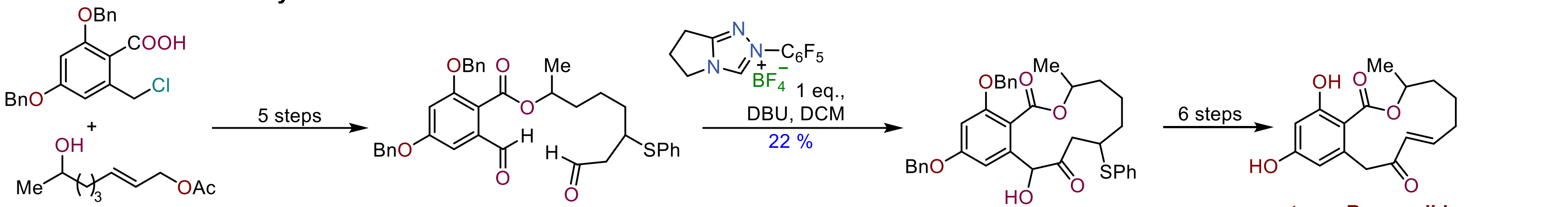




Hoveyda, A. H. et al. *J. Am. Chem. Soc.* 2015, 137, 33, 10585–10602. https://doi.org/10.1021/jacs.5b06745.

Total synthesis examples with NHCs

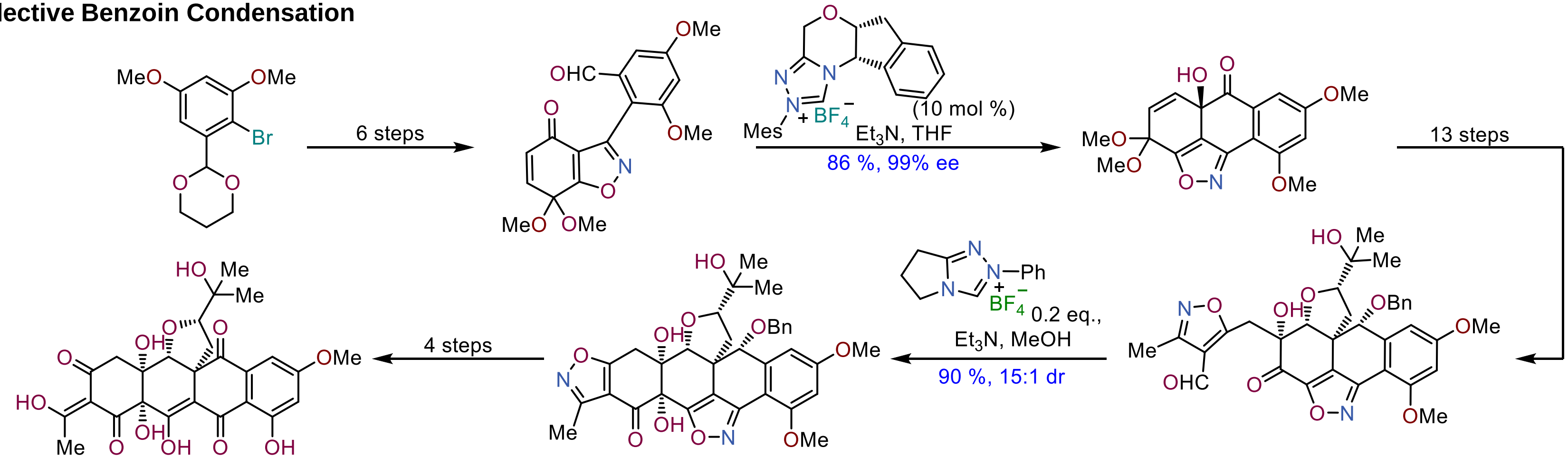
Benzoin Condensation - Macrocyclization



trans-Resorcylide

Miller, S. J. et al *J. Org. Chem.* 2007, 72, 14, 5260–5269. https://doi.org/10.1021/jo070676d

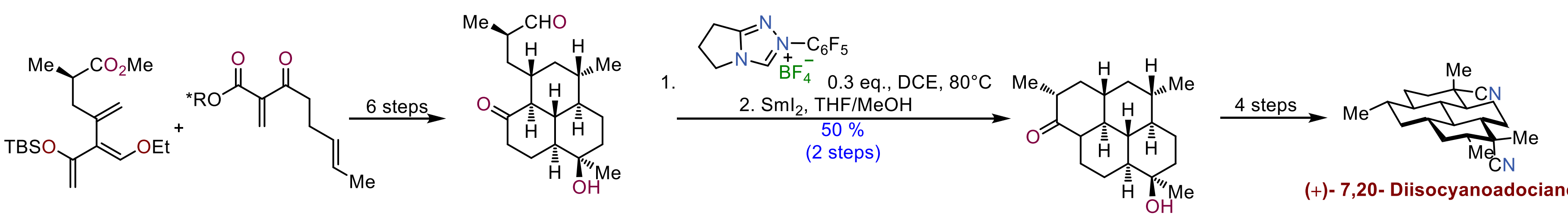
Enantioselective Benzoin Condensation



(–)- Seragakinone A

Suzuki, K. et al. *Angew. Chem. Int. Ed.* 2011, 50, 2297 –2301 https://doi.org/10.1002/anie.201006528

Benzoin Condensation Keto-Aldehyde

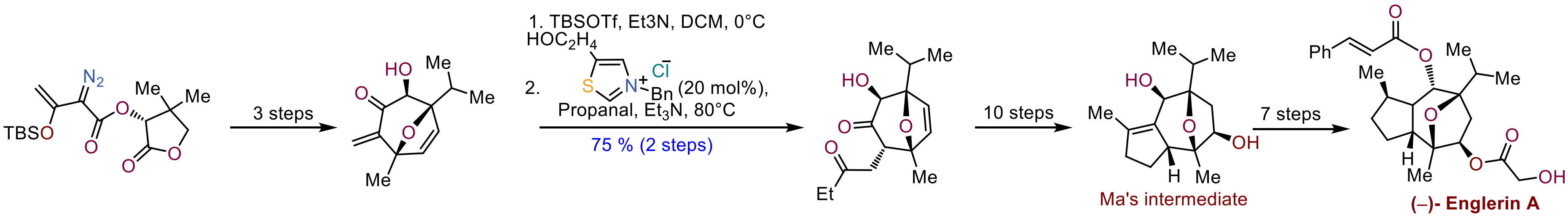


(+)- 7,20- Diisocyanoadociane

Shenvi, R. et al. *J. Am. Chem. Soc.* 2016, 138, 23, 7268–7271. https://doi.org/10.1021/jacs.6b03899.

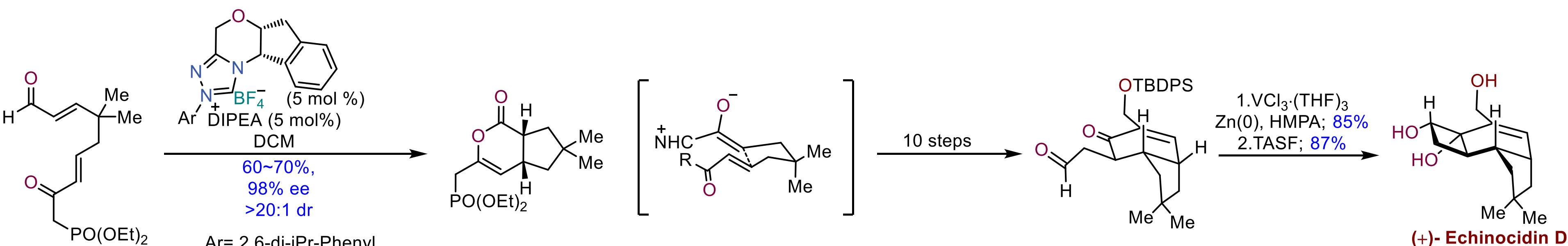
Organocatalysis with NHCs

Stetter reaction



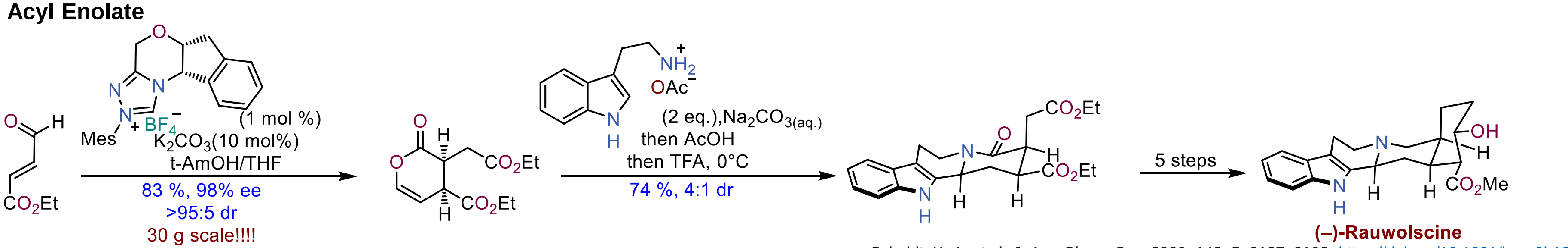
Theodorakis, E. A. et al. *Org. Lett.* 2010, 12, 16, 3708–3711. https://doi.org/10.1021/ol1015652
Ma, D. et al. *Angew. Chem. Int. Ed.* 2010, 49, 3513 –3516 https://doi.org/10.1002/anie.201000888

Acyl Enolate



Scheidt, K. A. et al. *Angew. Chem. Int. Ed.* 2017, 56, 9864 –9867. https://doi.org/10.1002/anie.201705308

Acyl Enolate



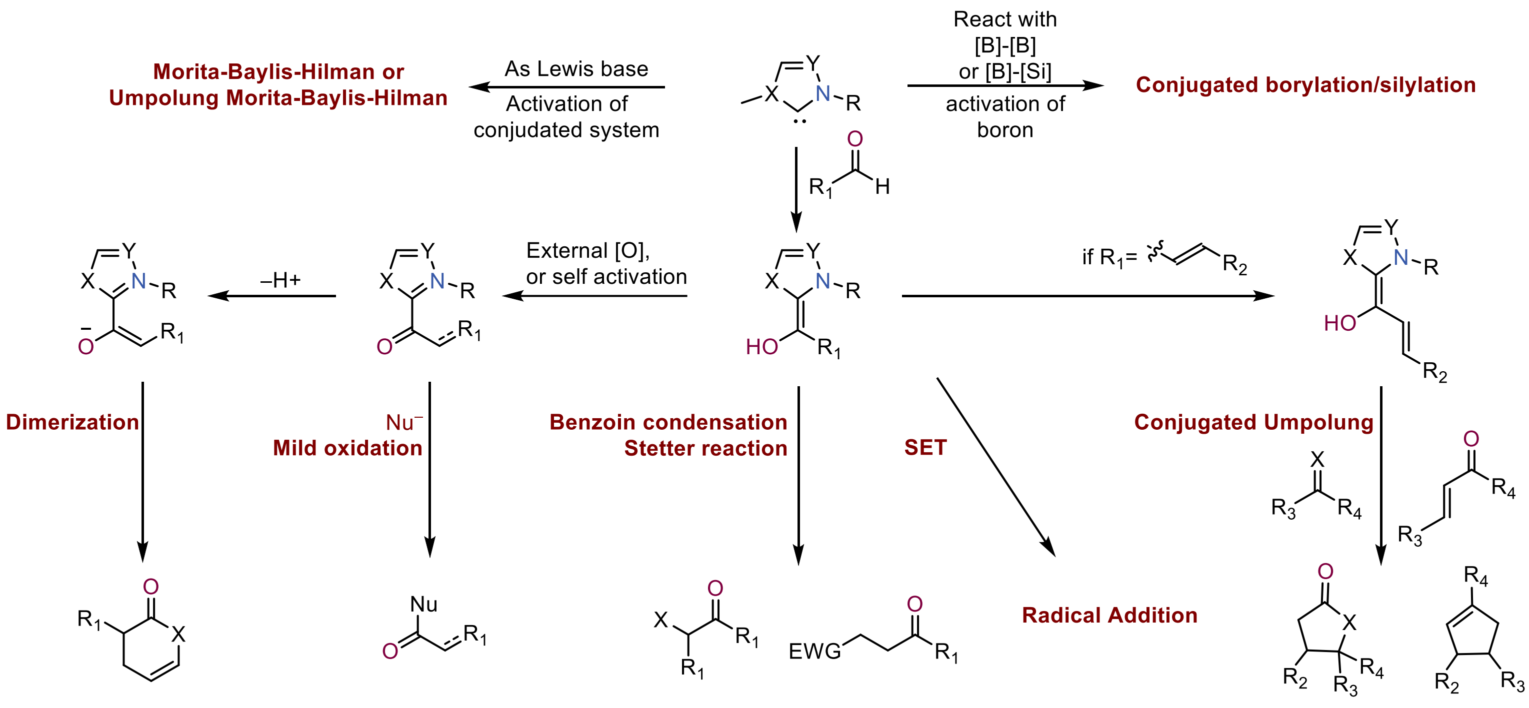
Scheidt, K. A. et al. *J. Am. Chem. Soc.* 2020, 142, 5, 2187–2192. https://doi.org/10.1021/jacs.9b12319

Other Remarkable Total Synthesis with NHCs

- Kinamycin C, F, J (Nicolaou, 2007) (benzoin condensation with complex skeleton)
- Bryostatin 7 (Krische, 2011) (late-stage redox esterification)

Nicolaou, K. C. Et al. *J. Am. Chem. Soc.* 2007, 129, 34, 10356–10357. https://doi.org/10.1021/ja074297d
Krische, M. J. et al. *J. Am. Chem. Soc.* 2011, 133, 35, 13876–13879. https://doi.org/10.1021/ja205673e

Reactivity Map of NHC



Glorius, F. er al. *Nature*. 2014, 485−496. https://doi.org/10.1038/nature13384

Advantage
- Versatile activation mode
- Fastly access complex skeleton
- Enable asymmetric synthesis

Disadvantage
- Tailored substrate required
- No generation condition (reactivity depends on substrate, counter ion, stereoelectronic property of NHC
- Activated substrates mostly (conjugated system)