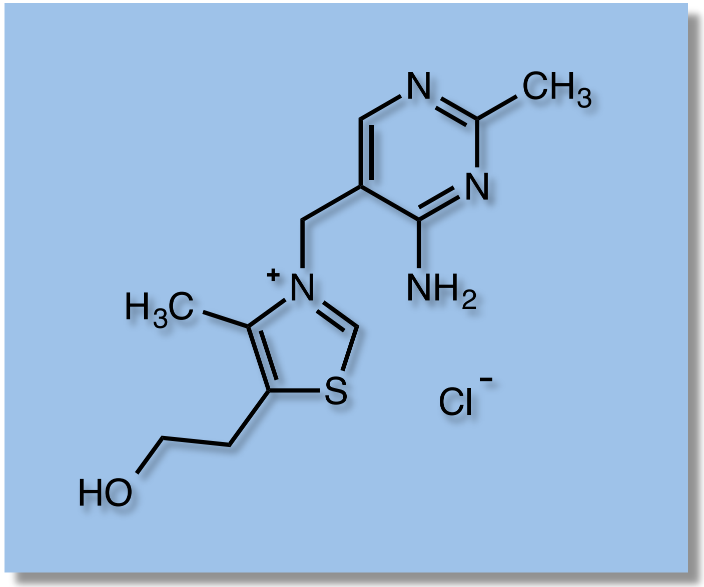
Asymmetric Organocatalysis with N-Heterocyclic Carbenes

History and Recent Developments



Adam Noble

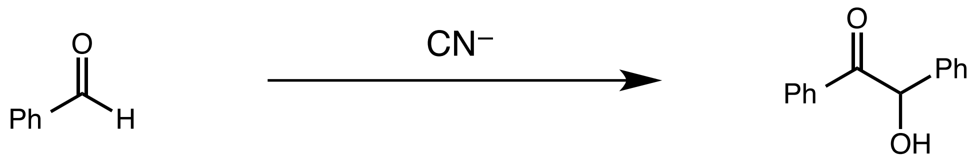
MacMillan Group Meeting

January 29th 2014

Early Developments

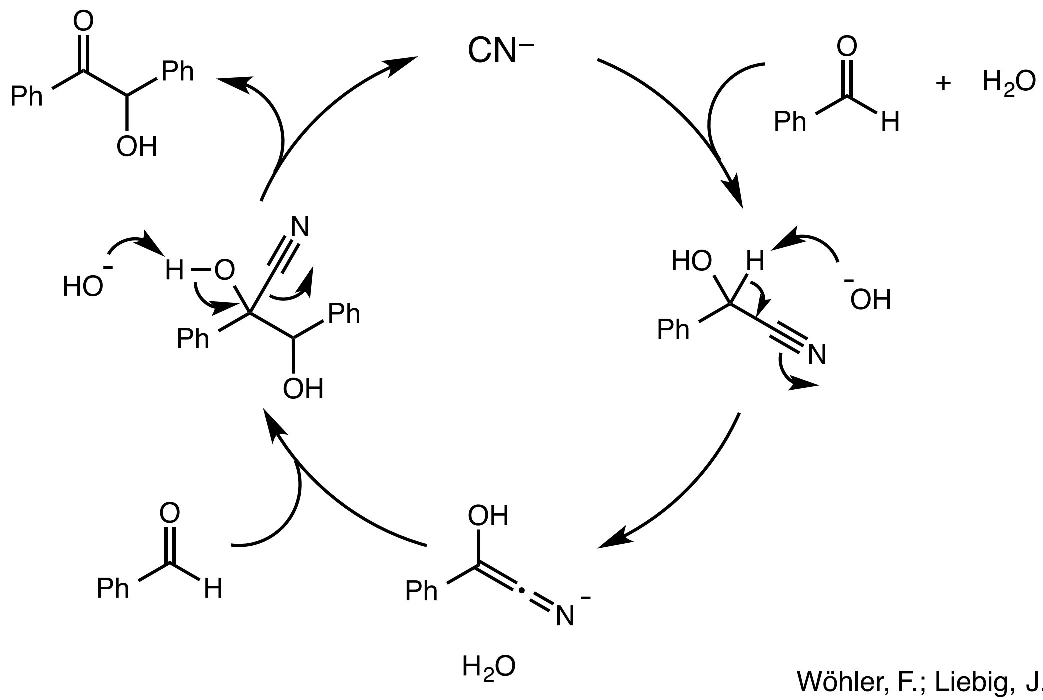
The Benzoin Condensation

■ 1832: First report of bezoin condensation by Wöhler and Liebig



benzoin

■ 1903: Mechanism proposed by Lapworth

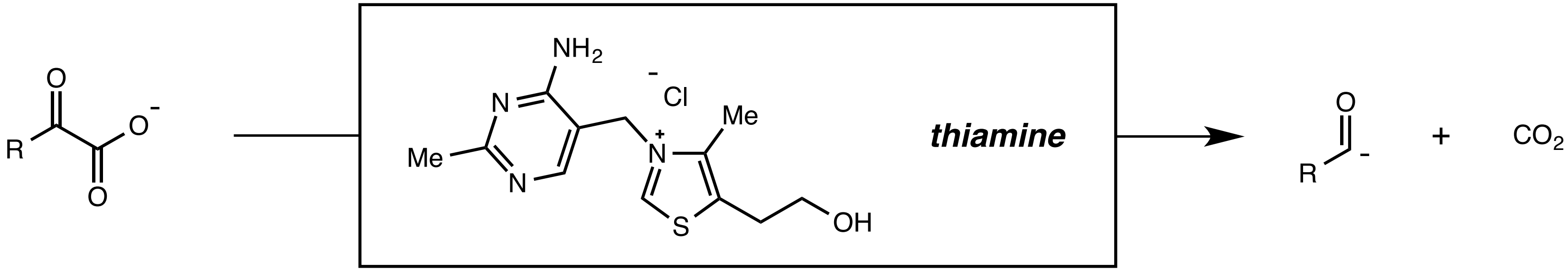


Wöhler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249.
Lapworth, A.; *J. Chem. Soc.* **1903**, *83*, 995.

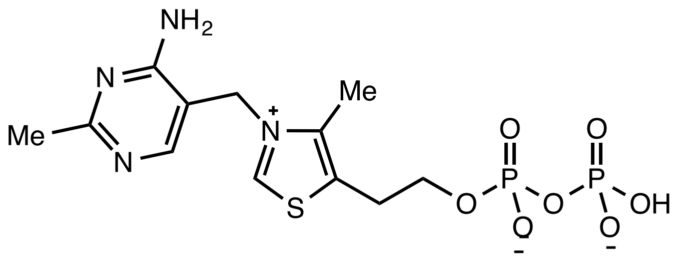
Thiamine (Vitamin B_1)

Enzymatic Acyl Anion Generation

- Thiamine is responsible for the genaration of acyl anion equivalents in a number of biochemical reactions



- Most commonly found as the co-enzyme thiamine diphosphate (TDP)



thiamine diphosphate (TDP)

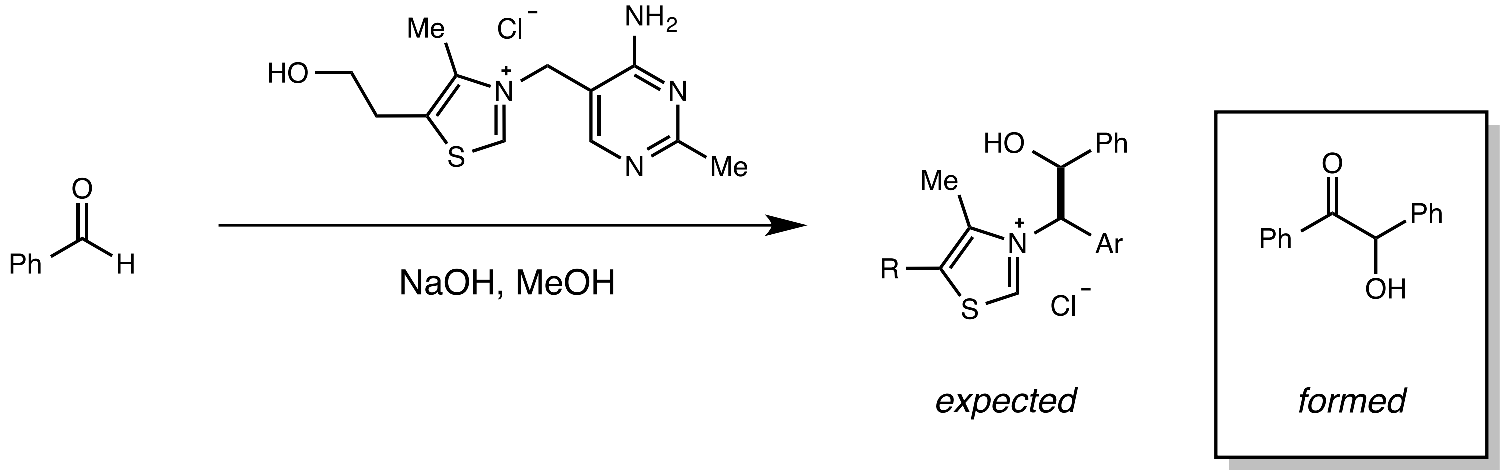
- Pyruvate decarboxylase
- Pyruvate oxidase
- Pyruvate dehydrogenase
- Transketolase

Kluger, R.; Tittmann, K. *Chem. Rev.* **2008**, *108*, 1797.

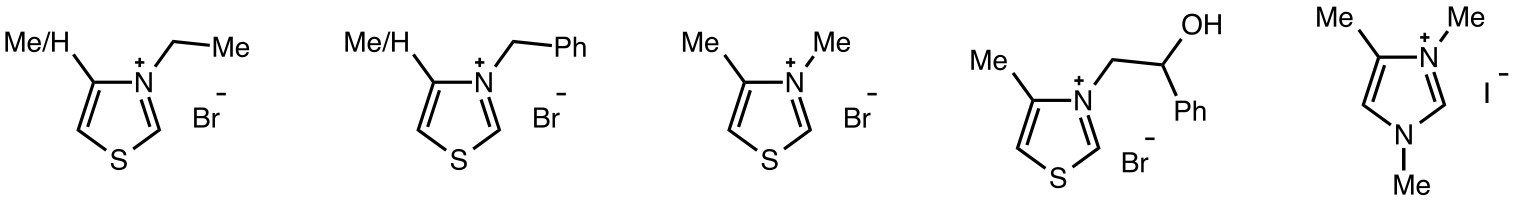
Early Developments

Thiamine-Catalyzed Benzoin Condensation

■ 1943: Ugai discovered that thiazolium salts could replace cyanide in benzoin condensations



A variety of other thiazolium compounds were also demonstrated to be effective catalysts

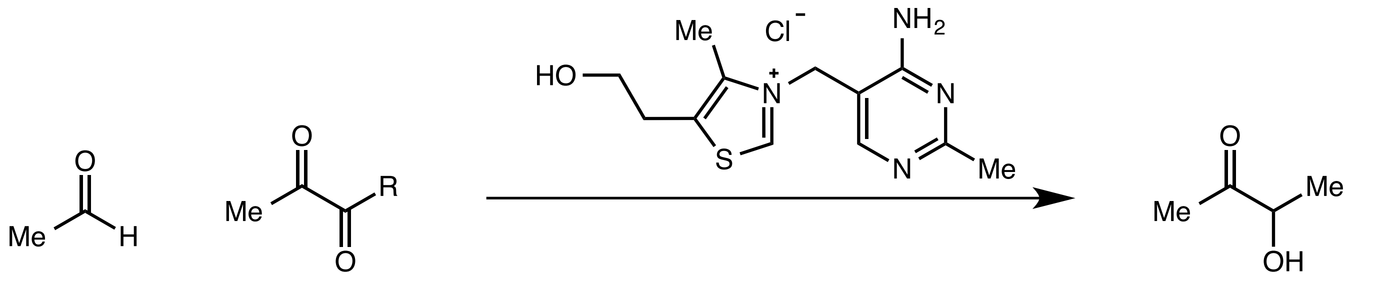


Ugai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.

Early Developments

Thiamine-Catalyzed Benzoin Condensation

- 1954: Mizuhara demonstrated that thiamine could catalyze a number of reactions that had also been observed in biological systems



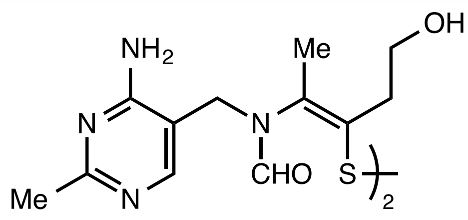
R = Me or OH

acyloin

+ AcOH (R = Me) or CO_2 (R = OH)

- Showed that the thiazolium moiety of thiamine was responsible for the catalytically activity

no reaction with:

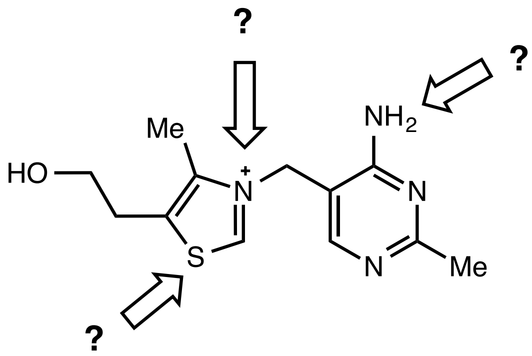


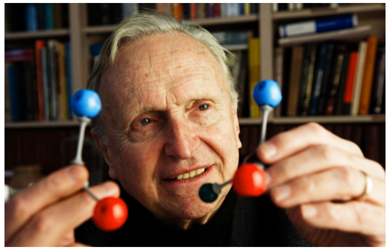
Mizuhara, S.; Handler, P. *J. Am. Chem. Soc.* **1954**, *76*, 571.

Early Developments

Mechanism of the Thiamine-Catalyzed Benzoin Condensation?

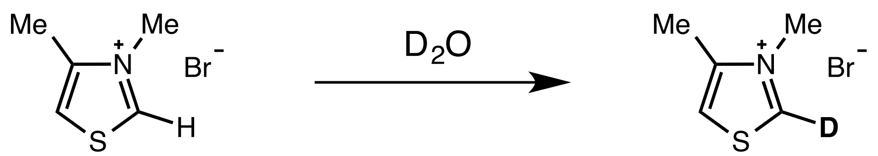
■ Reactions such as pyruvate decarboxylation and benzoin-type condensations catalyzed by thiamine (vitamin B_1) dependent enzymes were considered some of the most "mysterious" transformations

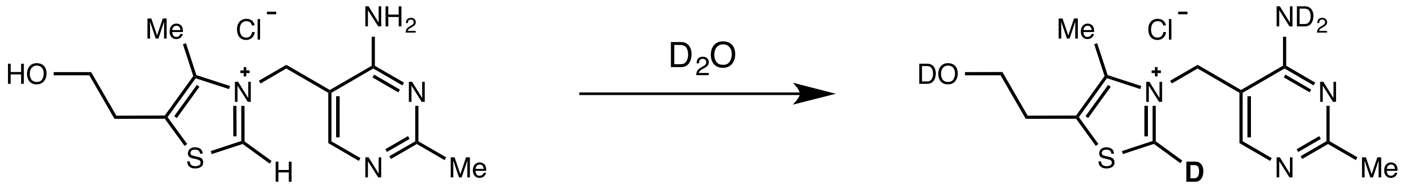




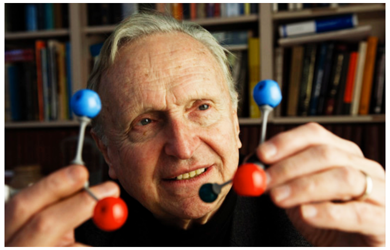
the origin of reactivity was unknown until the work of Breslow

■ 1958: Breslow demonstrated that the C-2 proton of thiazoliums exchanges rapidly with deuterium





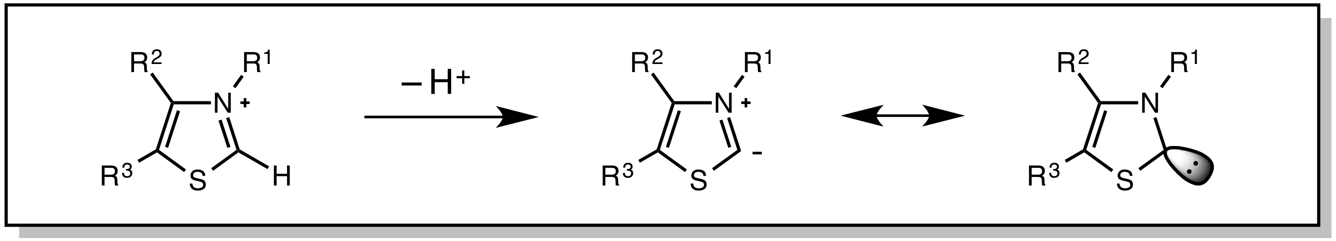
Breslow, R. *J. Am. Chem. Soc.*. **1958**, *80*, 3719.

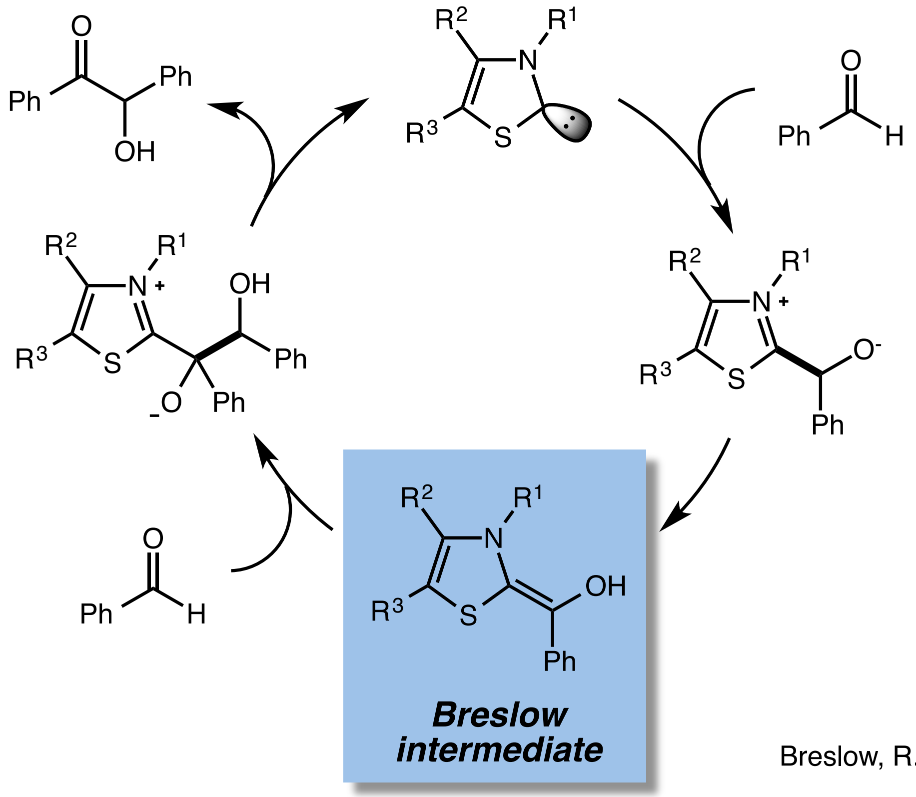


Early Developments

Breslows Proposed Mechanism

- 1958: Breslow proposed his mechanism for the thiazolium catalyzed benzoin condensation





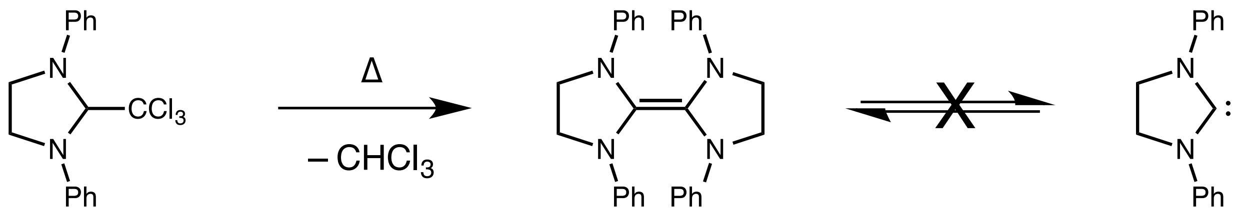
Breslow, R. *J. Am. Chem. Soc.*. **1958**, *80*, 3719.

From 'Laboratory Curiosities' to Catalysis Mainstays

Synthesis of Stable N-Heterocyclic Carbenes

- Since the mechanistic work by Breslow, NHCs were only considered as highly reactive intermediates.

- Their high reactivty made the isolation of such species seemingly impossible, with dimerization being a major reaction pathway.



- This was the case until 1968, when seminal work by the groups of Wanzlick and Öfele demonstrated that NHCs could be isolated in their metal-ligated forms

Hans-Werner Wanzlick

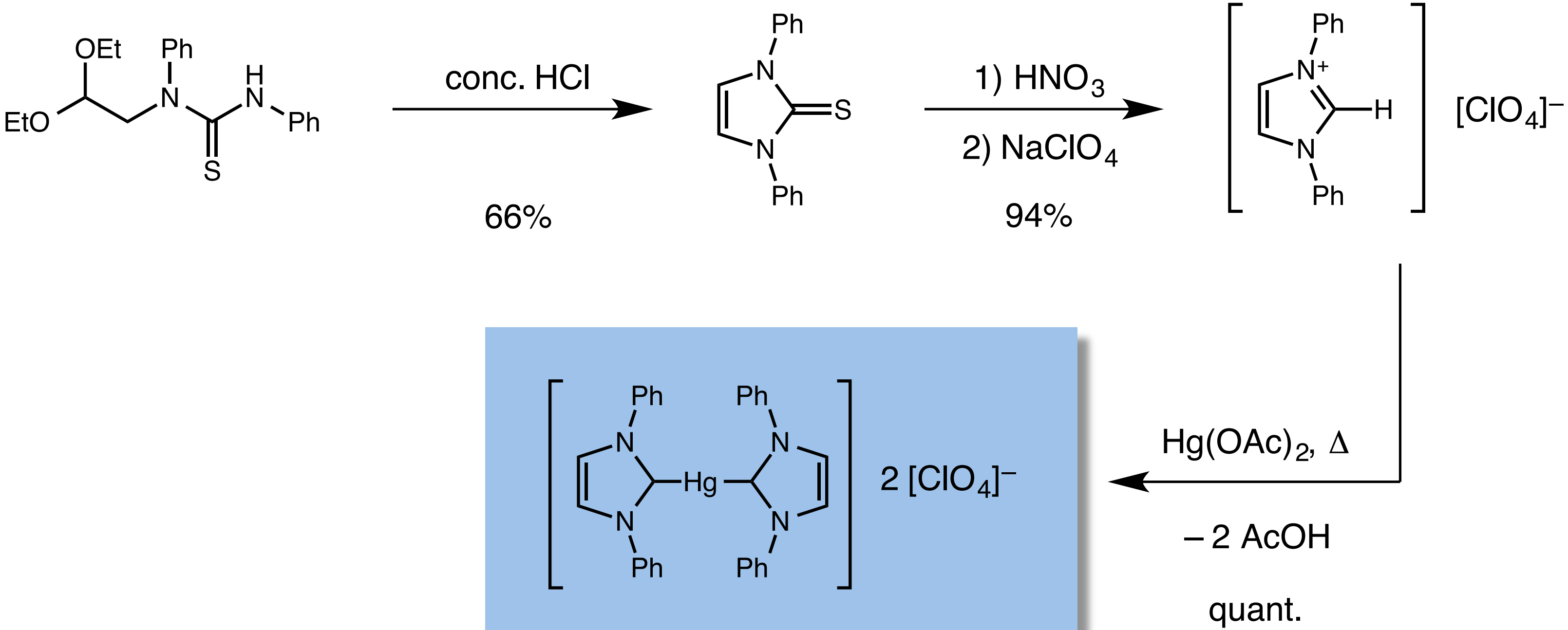
Karl Öfele

Wanzlick, H.-W. *Angew. Chem. Int. Ed.* **1962**, *1*, 75.
Rovis, T, Nolan, S. P. *Synlett* **2013**, 1188.

Wanzlick and Öfele

1968: First isolation of ligated NHCs

■ Wanzlick *et al* isolated a mercury complexed NHC



■ Isolated as colourless plates

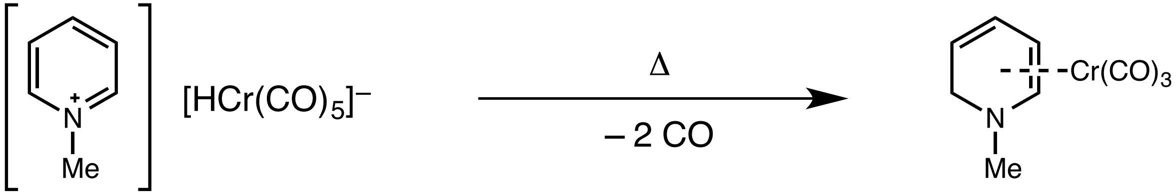
■ Structure confirmed by ^{1}H NMR

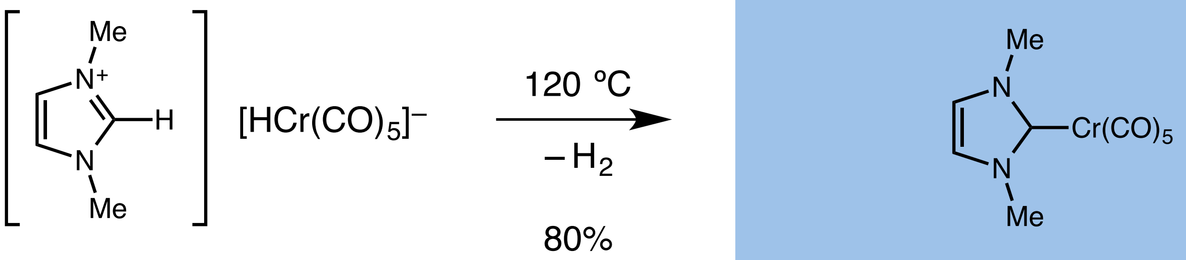
Wanzlick, H.-W.; Schönherr, H.-J. *Angew. Che. Int. Ed.* **1968**, *7*, 141.

Wanzlick and Öfele

1968: First isolation of ligated NHCs

- Öfele isolated a chromium NHC complex while trying to generate dehydro-complexes from heterocyclic salts





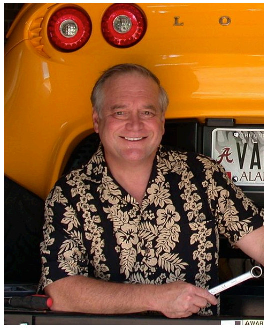
- Light yellow crystalline solid
- Structure confirmed by ^{1}H NMR

- Despite these advances, the field remained relatively inactive for 23 years until a breakthrough discovery by the group of Arduengo

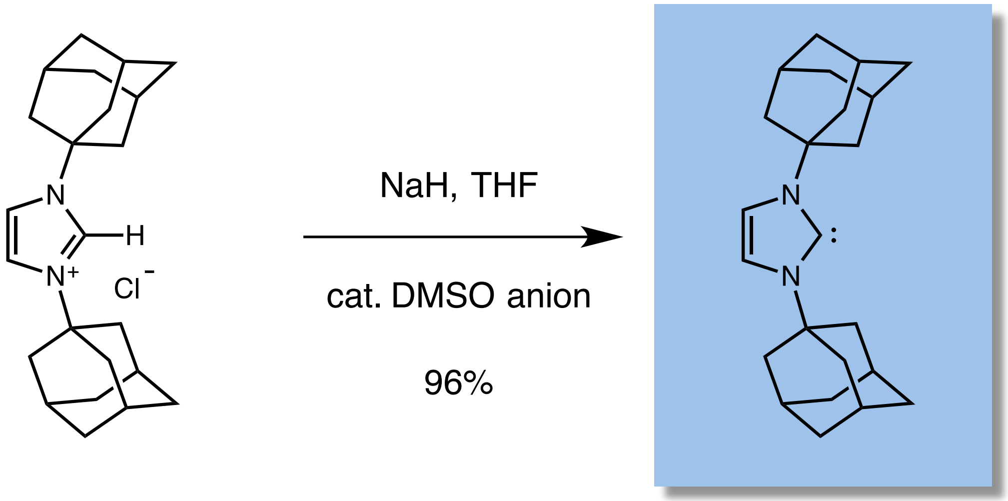
Öfele, K. *J. Organomet. Chem.* **1968**, *12*, 42.

Arduengo

1991: First isolation of a stable crystalline NHC



- Isolated the free carbene by deprotonation of a bis-adamantyl imidazolium chloride



- The structure was unequivocally established by single-crystal X-ray analysis
- Thermally stable in the absense of oxygen and moisture

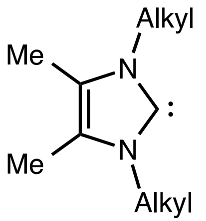
- The synthesis of isolable NHCs was instrumental in causing the explosion in interest in *stable carbene chemistry*

Arduengo, III, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

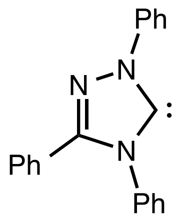
Isolable NHCs

Explosion in the Number of Reported Isolations

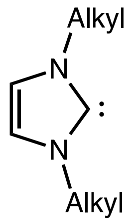
- After the first report from Arduengo in 1991, many other groups reported successful syntheses of a variety of new NHCs



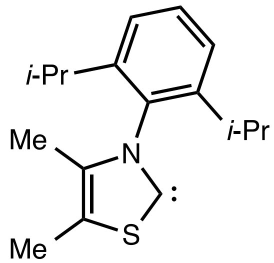
Arduengo et al
1992



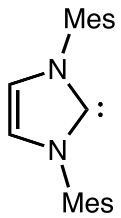
Enders et al
1995
(first commercially available carbene)



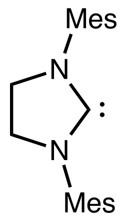
Herrmann et al
1996



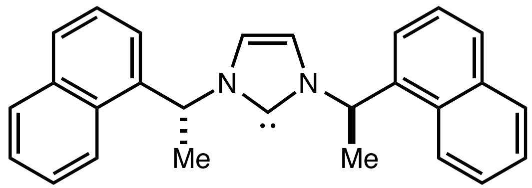
Arduengo et al
1997



Arduengo et al
1992



Arduengo et al
1995



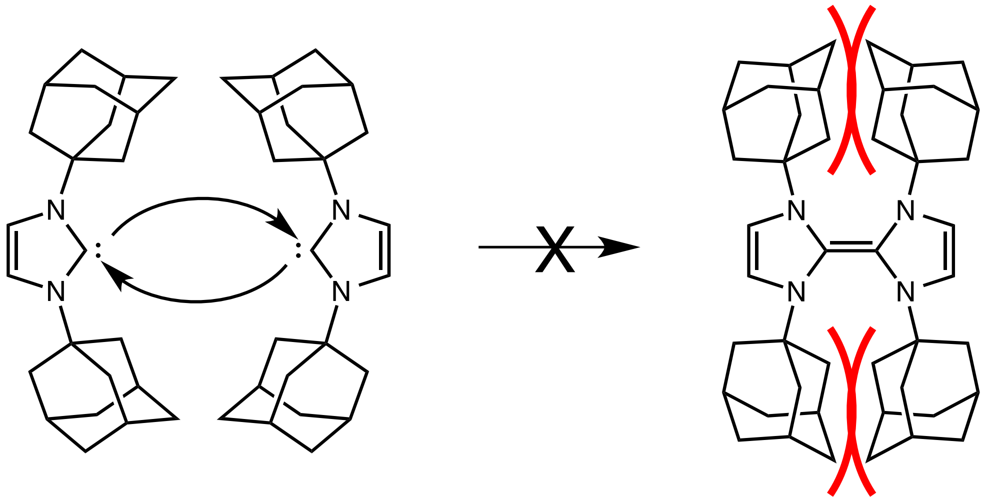
Herrmann et al
1996

Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

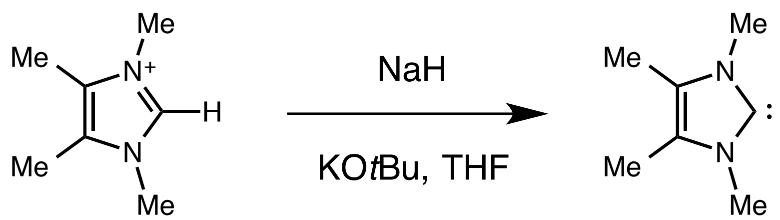
Isolable NHCs

Stability

- Original reports suggested that isolation was due to sterics preventing dimerization



- The isolation of the carbene from 1,3,4,5-tetramethylimidazolium chloride suggested that electronic factors may have greater impact on the stability of carbenes than sterics.

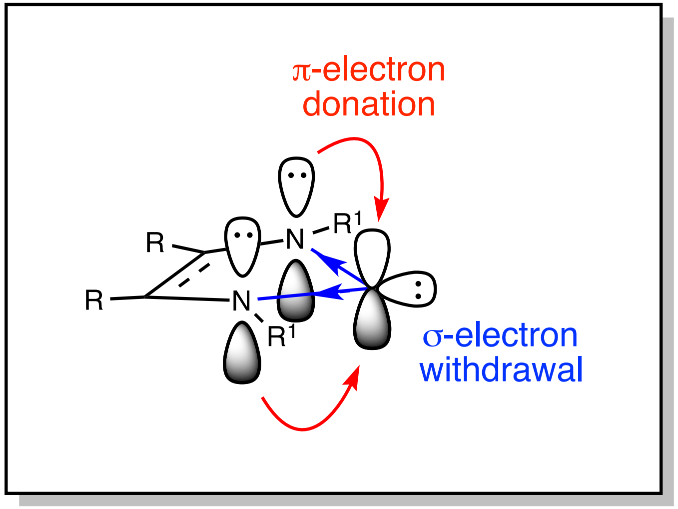


Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

Isolable NHCs

Stability

- Electronic factors operating in both the π and σ frameworks result in a "push-pull" synergistic effect to stabilize the carbene.



- π donation into the carbene from the out-of-plane π orbital stabilizes electrophilic reactivity

- σ withdrawal by electronegative atoms stabilizes nucleophilic reactivity

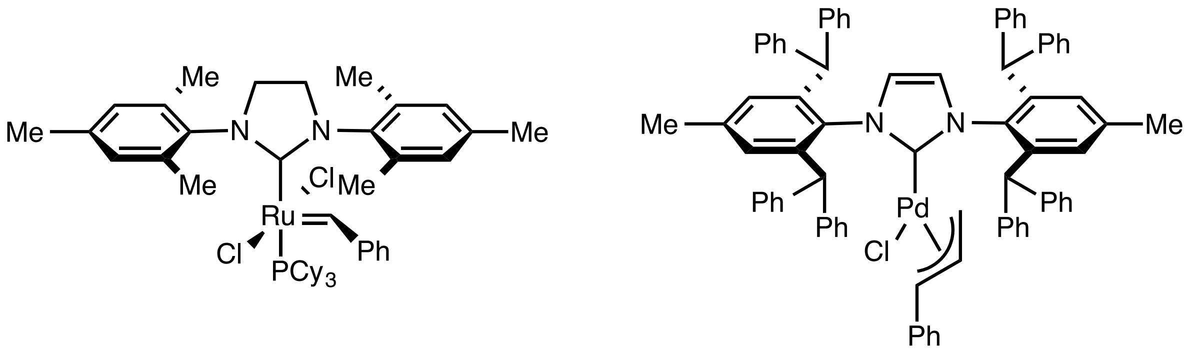
- The combined effect is to increase the singlet-triplet gap and stabilize the singlet-state carbene over the more reactive triplet-state carbene

Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Act.* **2009**, *42*, 55.
Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

Isolable NHCs

Reactivity: Why are they so useful?

- NHCs are exceptionally good σ donors so form strong metal–carbon bonds:
- Compared to phosphines, NHCs form complexes that:
  - are more straightforward to prepare (due to *in situ* NHC formation)
  - show greater air and thermal stability
  - often have catalytic activities 100 to 1000 times greater



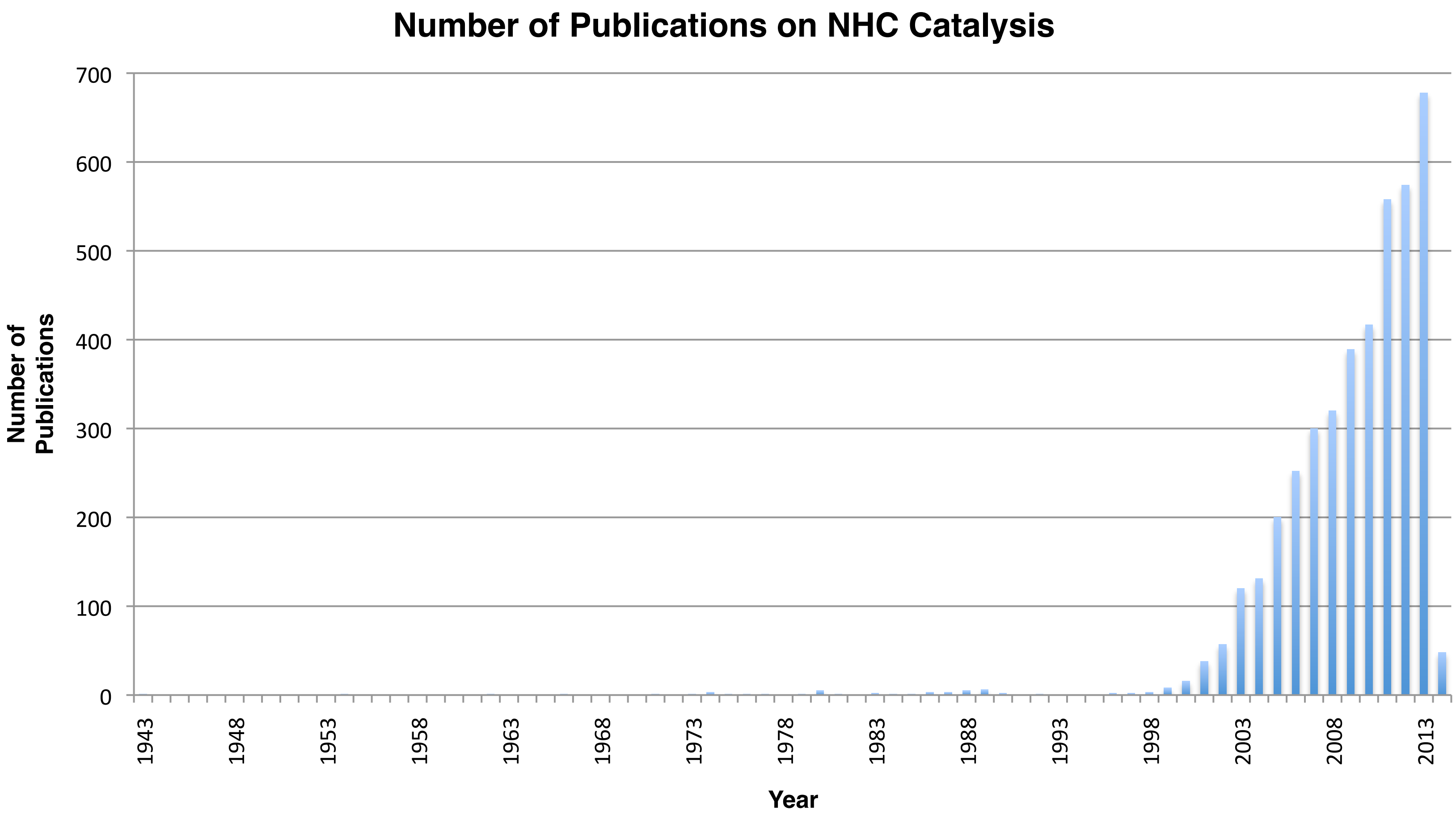
- Singlet carbenes of NHCs are distinct Lewis bases that show both σ basicity and π acidity:
  - Allows for the generation of a second nucleophile during a reaction (e.g. Breslow intermediate)
  - This unique "doubly" nucleophilic aspect allows NHCs to react as powerful organocatalysts

Rovis, T, Nolan, S. P. *Synlett* **2013**, 1188.
Arnold, P. L.; Pearson, S. *Coord. Chem. Rev.* **2007**, *251*, 596.
Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Act.* **2009**, *42*, 55.

Isolable NHCs

Reactivity: Why are they so useful?

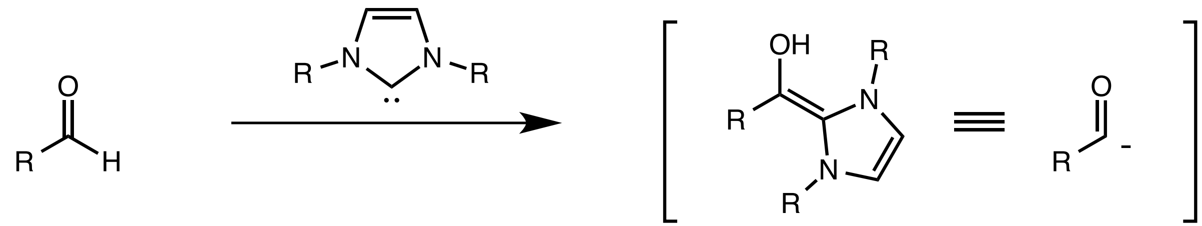
- These factors have resulted in a huge increase in interest in NHCs over the past 70 years



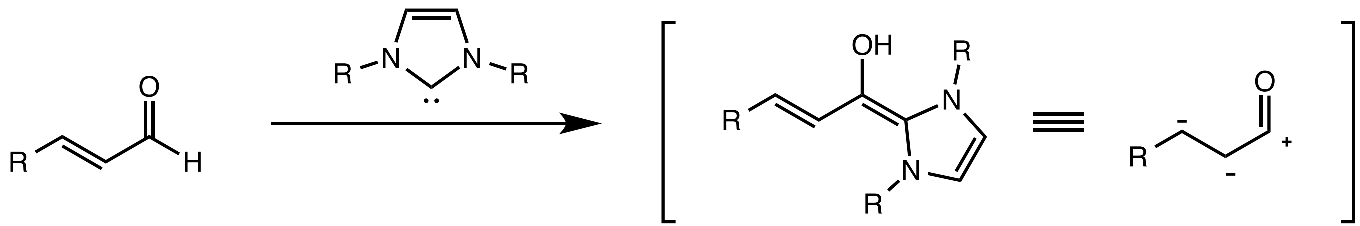
N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

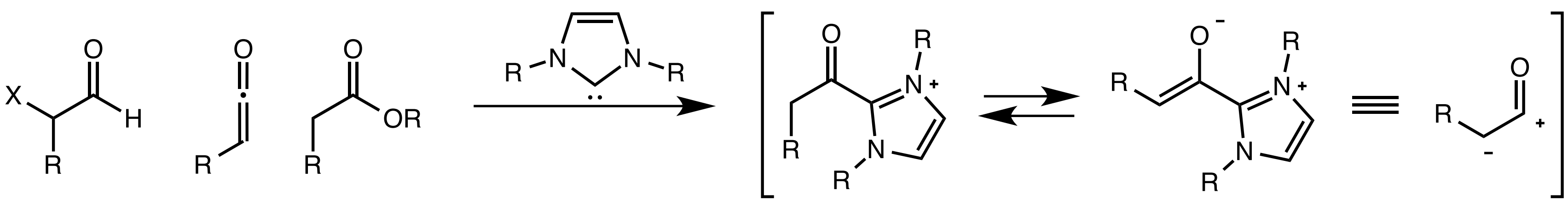
Acyl Anions



Homoenolates



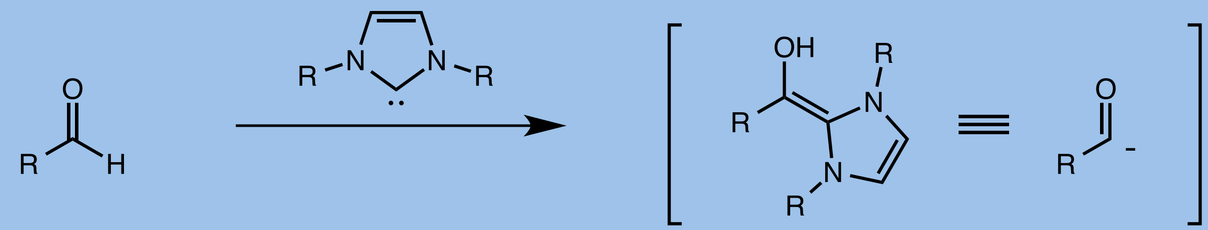
Azolium Enolates / Acyl Azoliums



N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

Acyl Anions

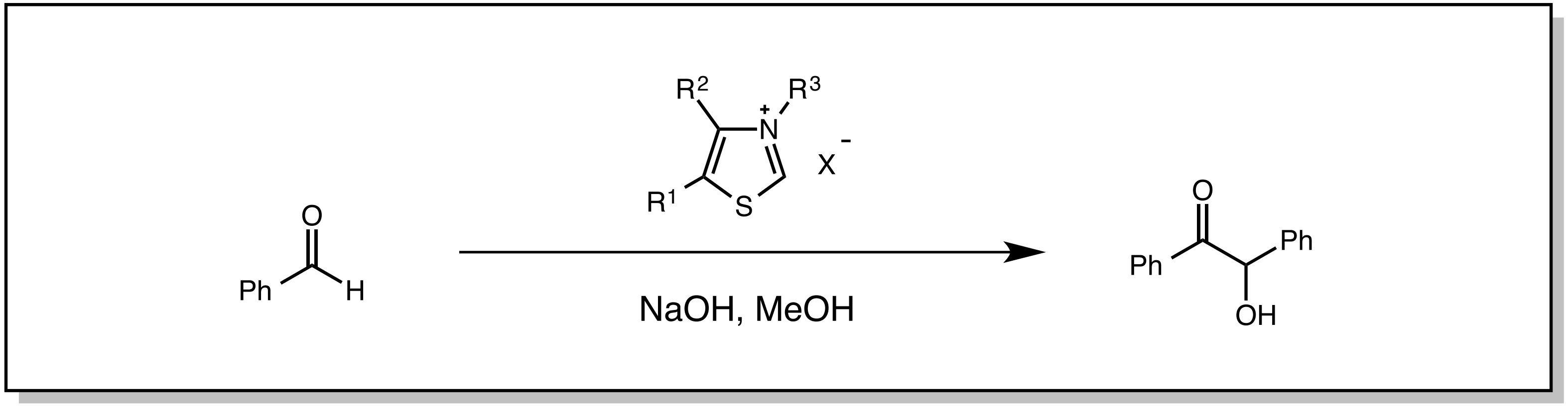


- Benzoin Condensations
- Stetter Reactions
- Hydroacylations

The Use of NHCs for the Generation of Acyl Anion Equivalents

Early Developments

■ 1943: Ugai discovered the thiazolium-catalyzed benzoin condensation

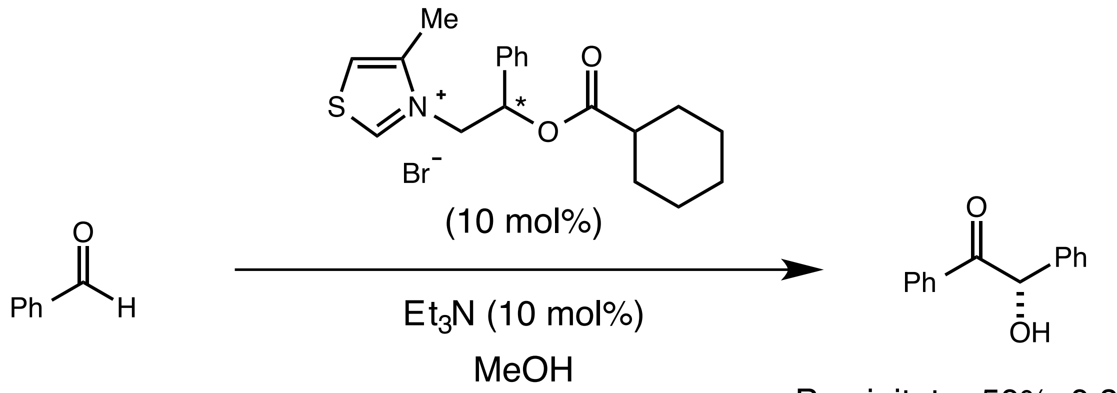


Ugai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.

The Use of NHCs for the Generation of Acyl Anion Equivalents

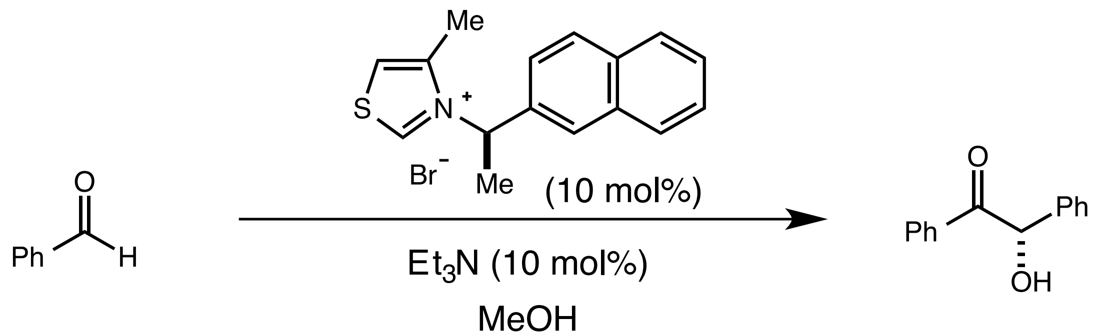
The First Asymmetric Examples

- 1966: Sheehan described the first asymmetric benzoin condensations catalyzed by chiral thiazolium salts



Precipitate: 50%, 0.8% ee
Filtrate: 9% yield, 22% ee

- 1974: Sheehan reported slight improvements to enantioselectivity but still low yield



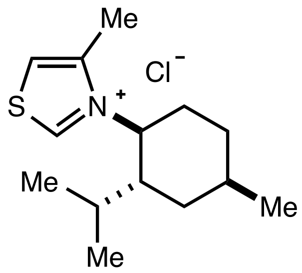
6% yield, 52% ee

Sheehan, J. C.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666.
Sheehan, J. C.; Hara, T. *J. Org. Chem* **1974**, *39*, 1196.

The Use of NHCs for the Generation of Acyl Anion Equivalents

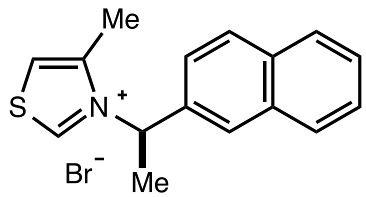
The First Asymmetric Examples

■ Following the work of Sheehan, a number of other groups reported the use of similar NHCs to catalyze benzoin condensations



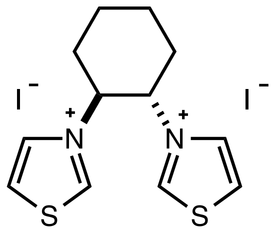
20%, 35% ee

Takagi et al, 1980



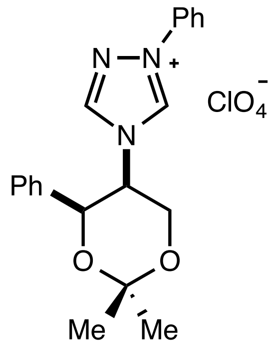
47-57%, 20-30% ee

Zhao et al, 1988



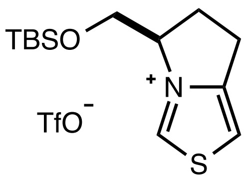
21%, 26% ee

López-Calahora et al, 1993



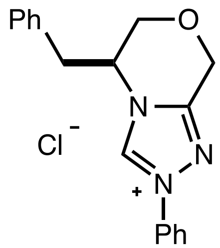
66%, 75% ee

Enders et al, 1996



50%, 21% ee

Leeper et al, 1997



45%, 80% ee

Leeper et al, 1998

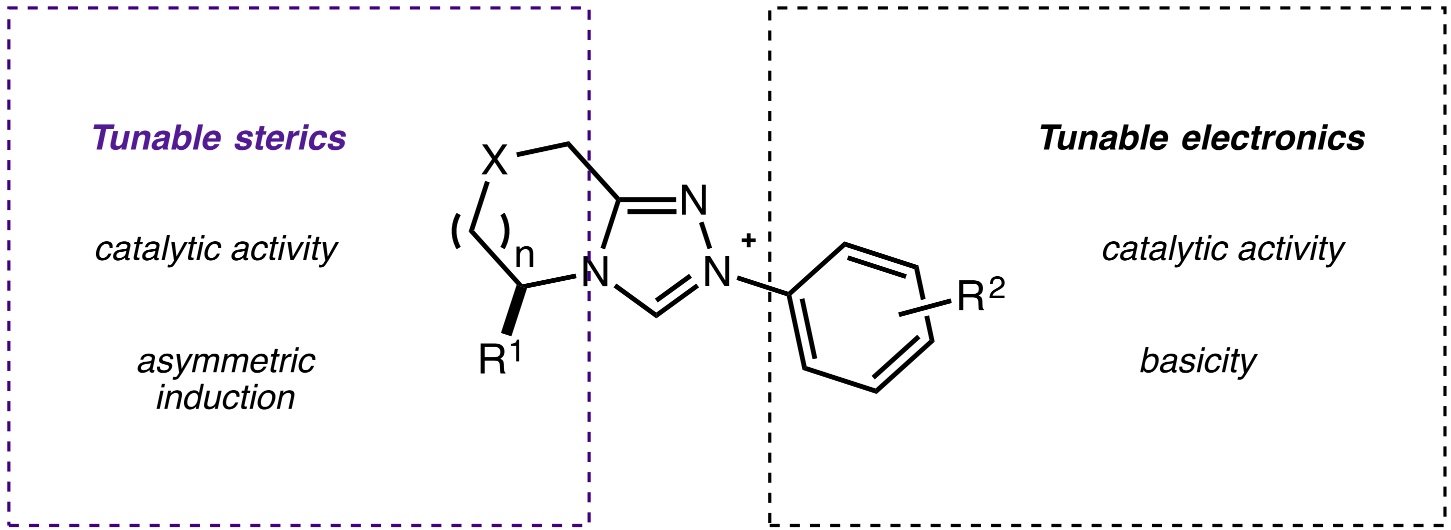
Bicyclic triazoliums are key!

Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

The Use of NHCs for the Generation of Acyl Anion Equivalents

The First Asymmetric Examples

■ The initial development of *N*-aryl-bicyclic triazoliums led the way to improved catalyst efficiency

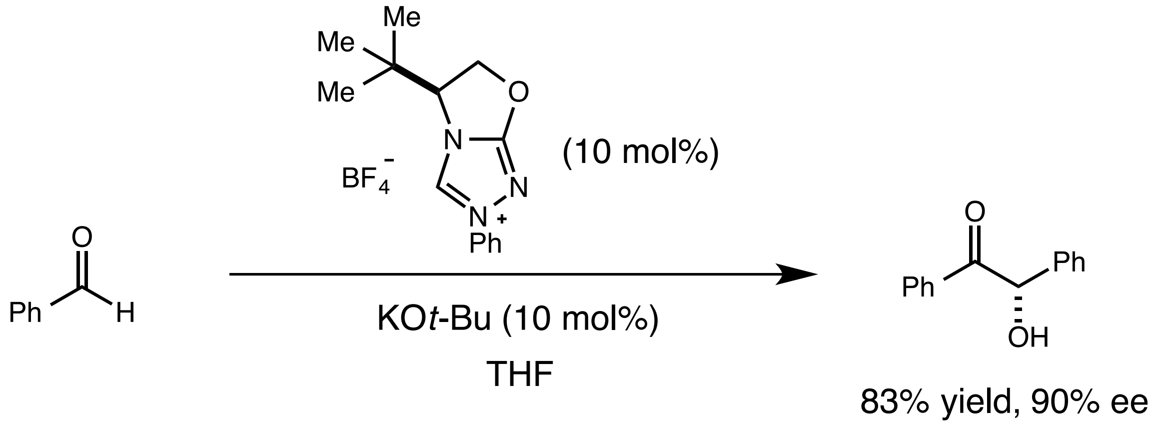


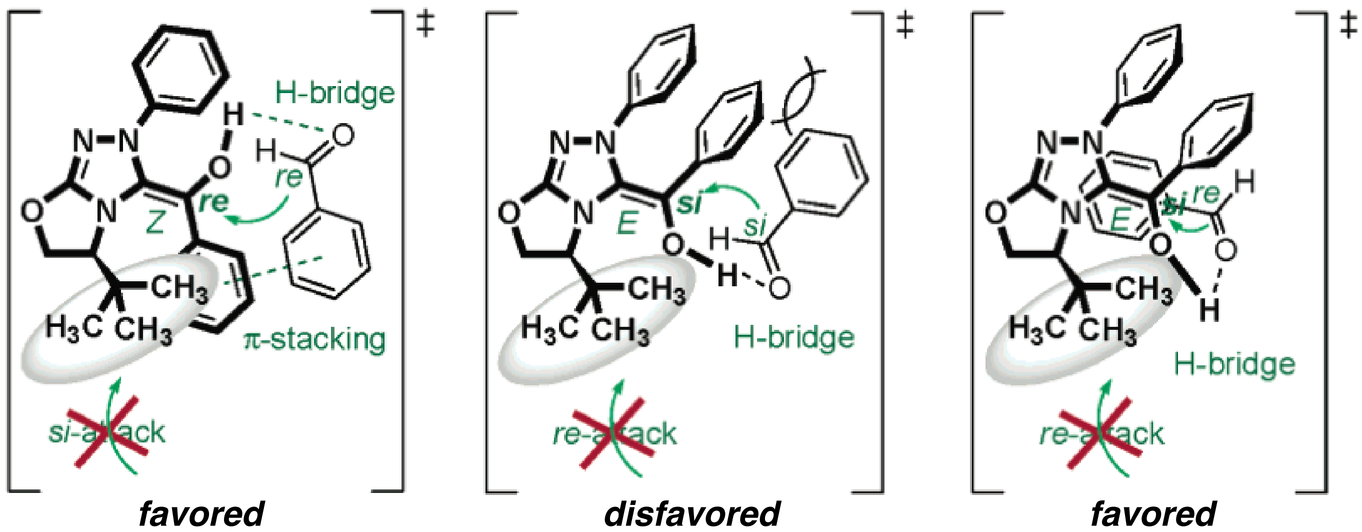
Rovisr, T. *Chem. Lett.* **2008**, *37*, 534.

The Use of NHCs for the Generation of Acyl Anion Equivalents

Bicyclic Triazolium Salts Give High Enantioselectivities

■ Modification of Leepers bicyclic triazoliums allowed Enders to develop a highly efficient NHC catalysts



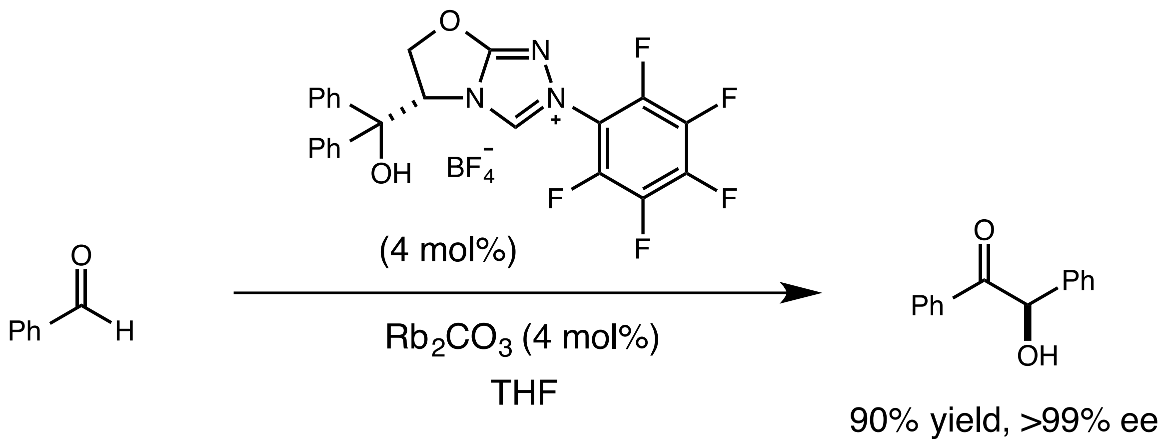


Dudding, T.; Houk, K. N. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5770.
Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.

The Use of NHCs for the Generation of Acyl Anion Equivalents

Bicyclic Triazolium Salts Give High Enantioselectivities

■ Connon *et al* demonstrated the NHCs bearing alcohol directing groups can give exceptional levels of enantioinduction

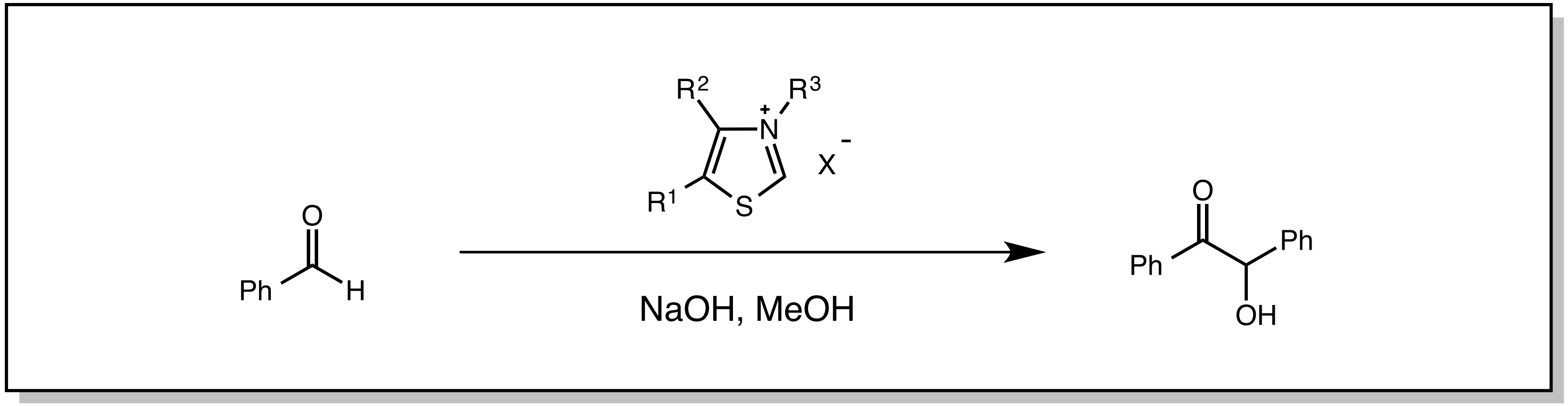


Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214.

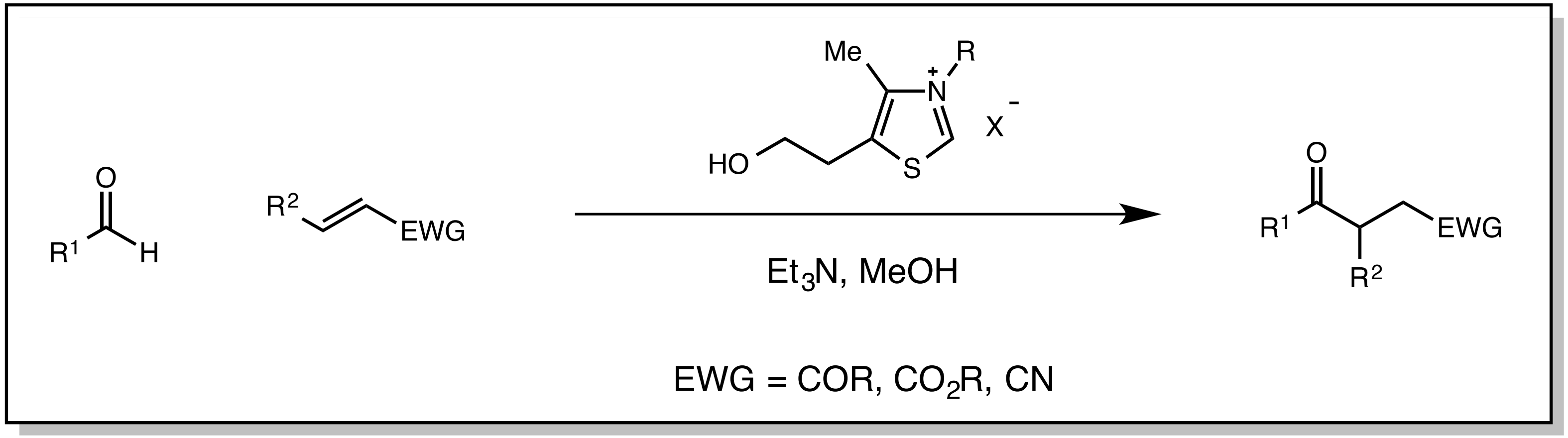
The Use of NHCs for the Generation of Acyl Anion Equivalents

Early Developments

■ 1943: Ugai discovered the thiazolium-catalyzed benzoin condensation



■ 1974: Stetter reported the 1,4-addition variant = ***The Stetter Reaction***



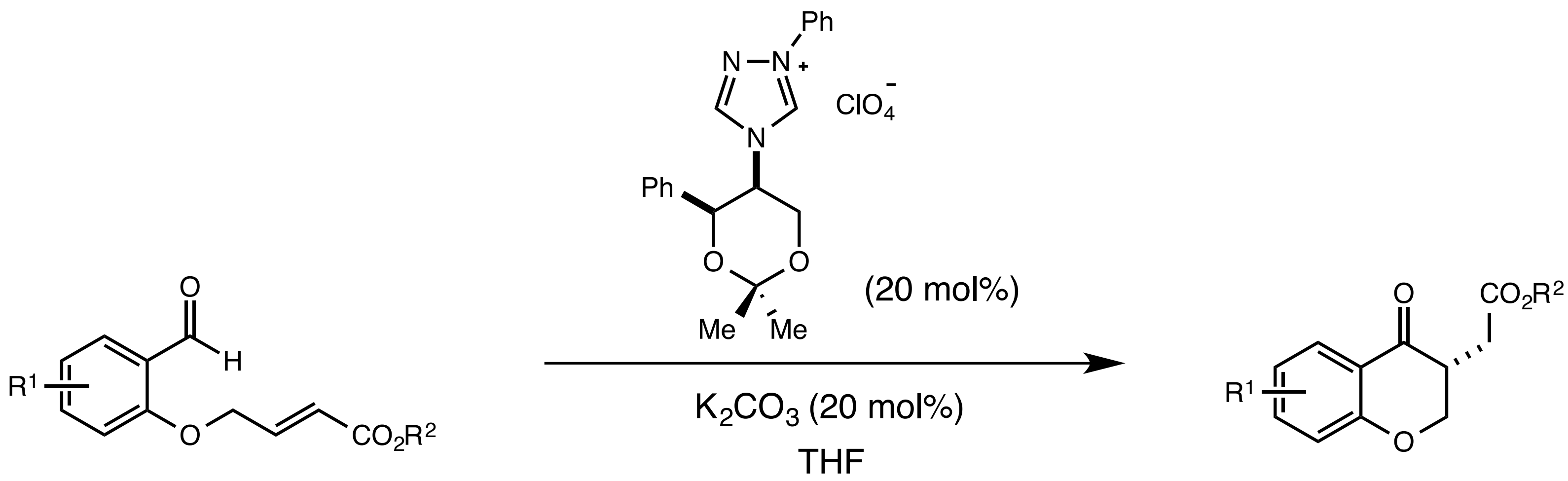
Ugai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.

Stetter, H.; Kuhlmann, H. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 539.

The Use of NHCs for the Generation of Acyl Anion Equivalents

Intramolecular Stetter Reactions

■ In 1996 Enders *et al.* reported the first asymmetric Stetter Reaction



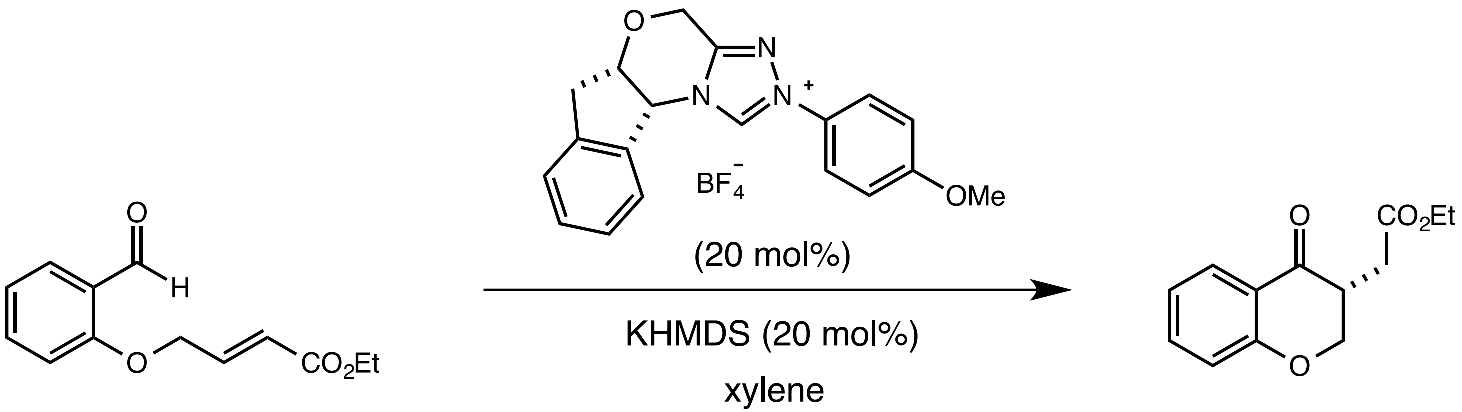
22-73% yield, 41-74% ee

Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Act.* **1996**, *79*, 1899.

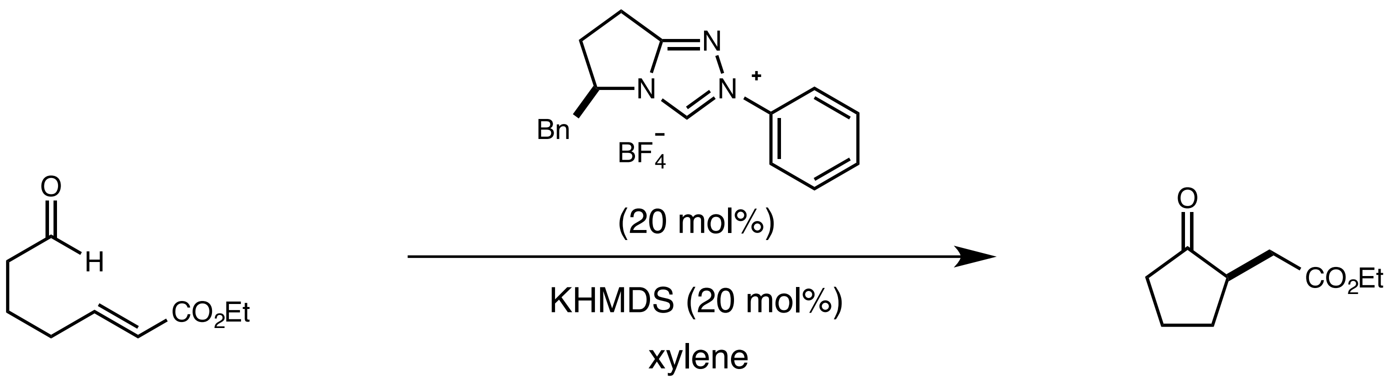
The Use of NHCs for the Generation of Acyl Anion Equivalents

Intramolecular Stetter Reactions

■ Following the original report by Enders, Rovis *et al.* developed the first highly enantioselective intramolecular Stetter reactions



94% yield, 94% ee



81% yield, 95% ee

Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

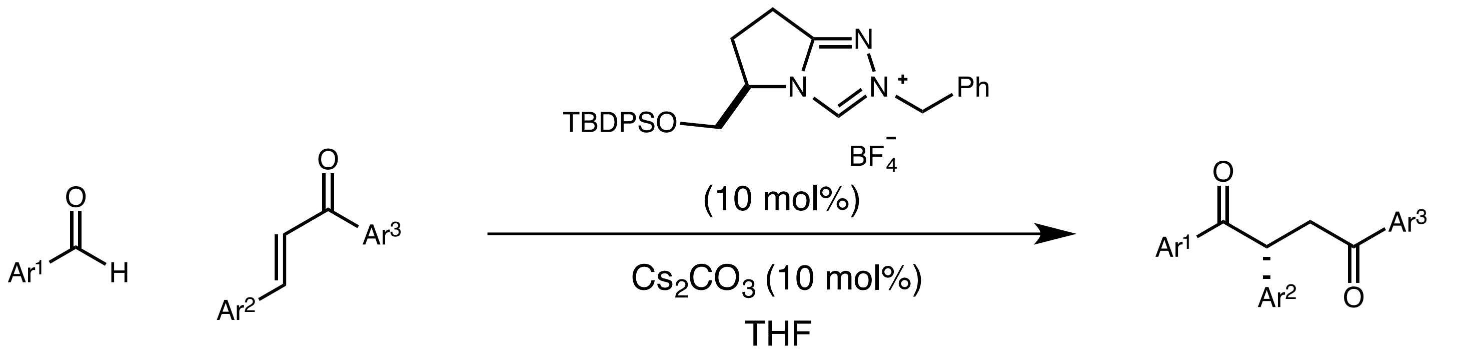
The Use of NHCs for the Generation of Acyl Anion Equivalents

Intermolecular Stetter Reactions

- Development of asymmetric intermolecular Stetter reactions still remains a formidable challenge

- This is due to the diminished reactivity of Michael acceptors containing a β-substituent

- Enders *et al.* developed a high yielding protocol taking advantage of the higher reactivity of chalcones, although the enantioselectivities were only moderate



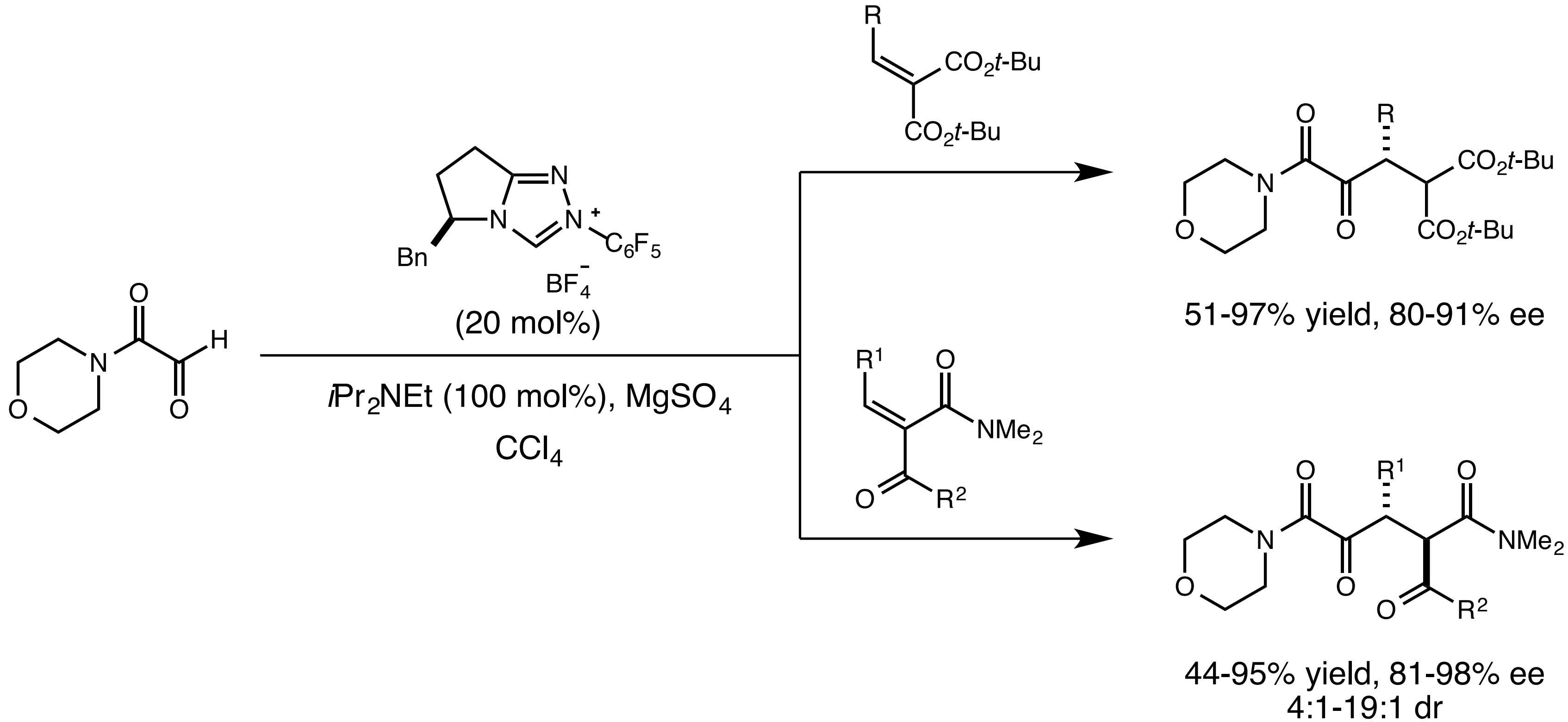
49-98% yield, 58-78% ee

Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989.

The Use of NHCs for the Generation of Acyl Anion Equivalents

Intermolecular Stetter Reactions

- In the same year Rovis *et al.* reported a highly enantioselective intermolecular Stetter reaction of glyoxamides a number of Michael acceptors



- A limitation was the need for highly activated alkylidene dicarbonyls

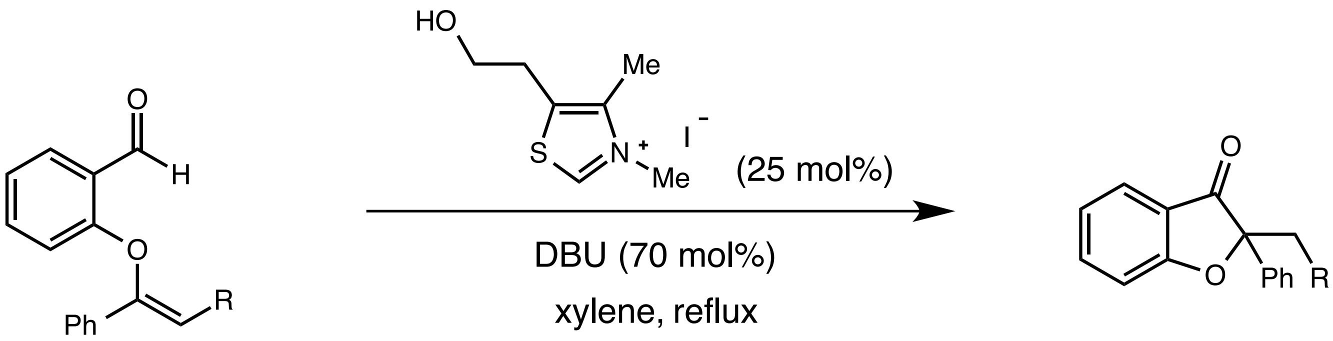
A general strategy for asymmetric intermolecular Stetter reactions has not yet been developed!

Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856.
Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066.

The Use of NHCs for the Generation of Acyl Anion Equivalents

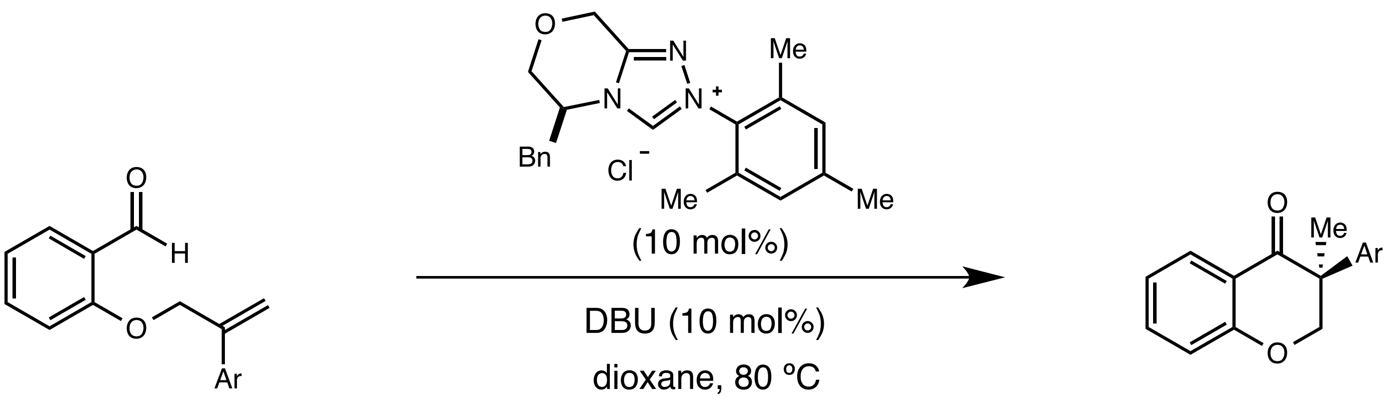
Hydroacylation of Unactivated Double Bonds

- In 2008, She *et al.* reported the intramolecular hydroacylation of enol ethers



66-99%

- In 2011, Glorius *et al.* reported a highly asymmetric variant



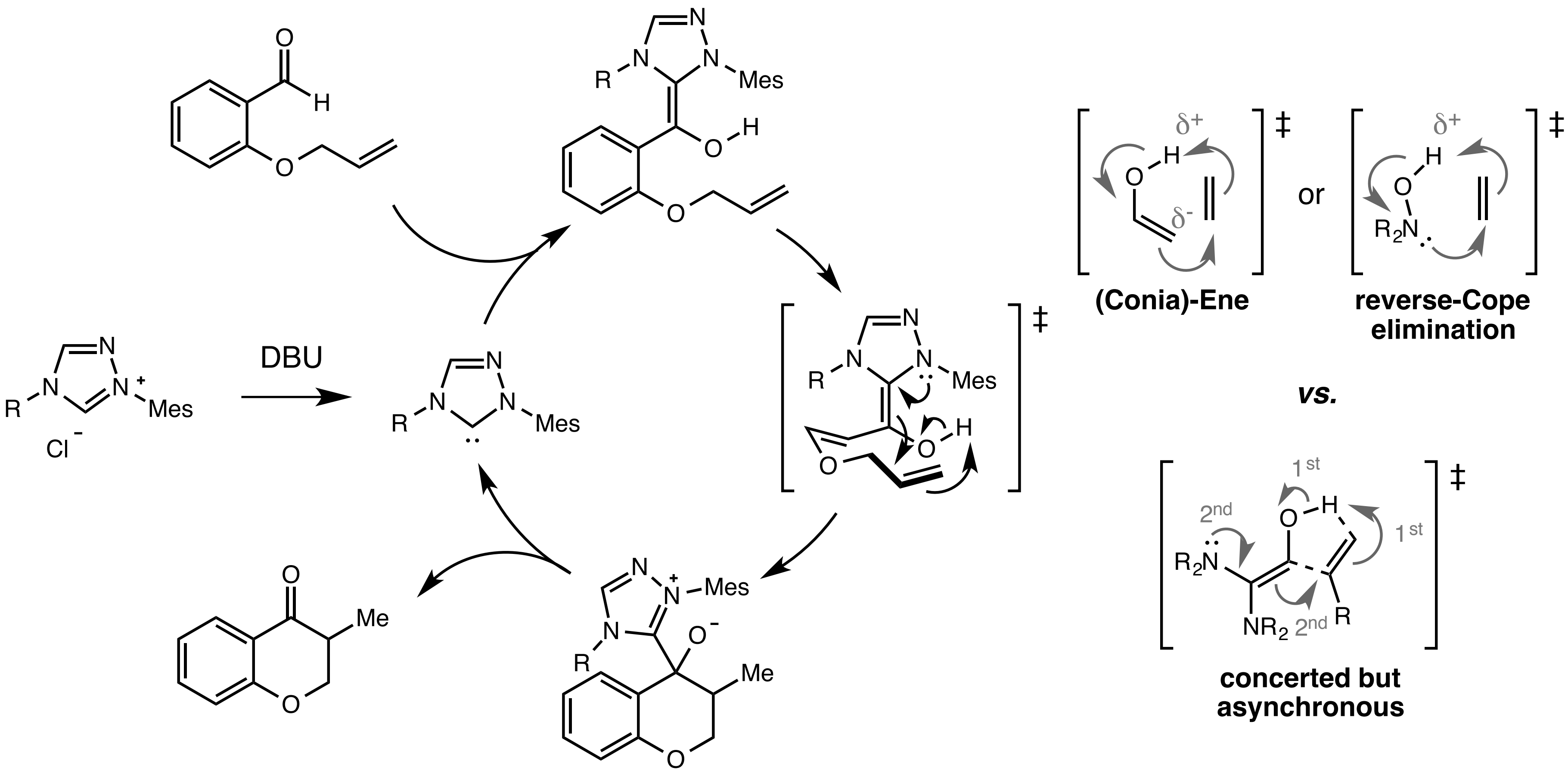
28-99% yield, 96-99% ee

Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.
He, J.; Tang, S.; Liu, J.; Su, Y.; Pan, X.; She, X. *Tetrahedron* **2008**, *64*, 8797.

The Use of NHCs for the Generation of Acyl Anion Equivalents

Hydroacylation of Unactivated Double Bonds

- The mechanism was investigated by Glorius and Grimme and found to likely proceed via a concerted but highly asynchronous transition state.

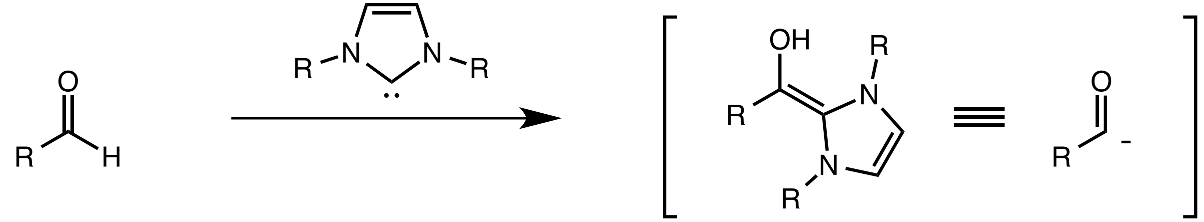


Hirano, K.; Biju, A. T.; Piel, K.; Grimme, S.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190.
Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.

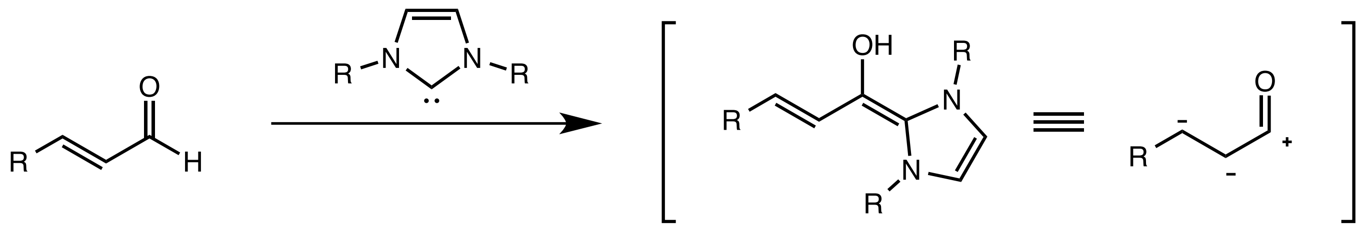
N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

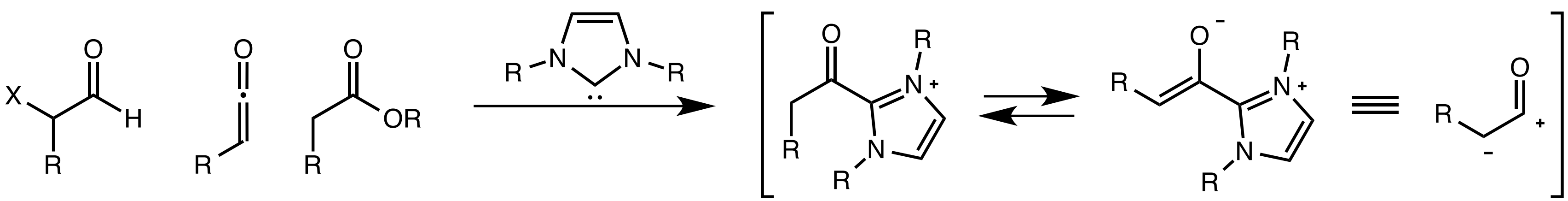
Acyl Anions



Homoenolates



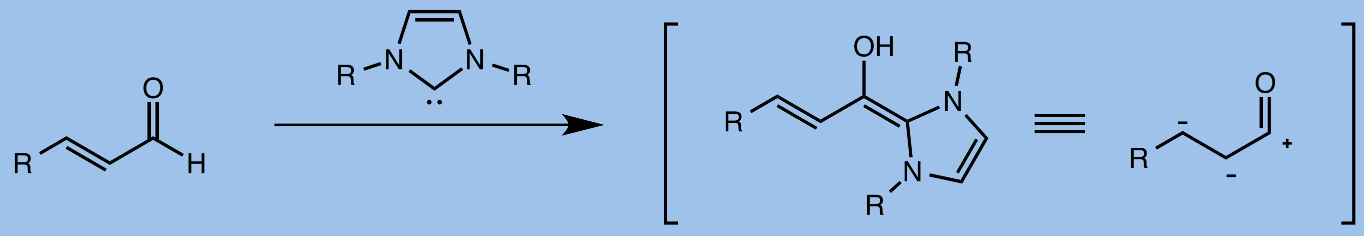
Azolium Enolates / Acyl Azoliums



N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

Homoenolates



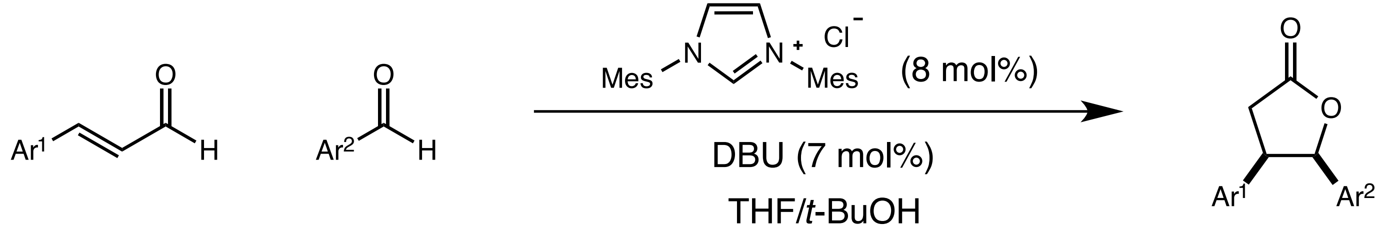
- Cyclopentene Synthesis
- Spiroannulations
- Lactam/Lactone Synthesis
- Conversion of Enals to Saturated Esters

The Use of NHCs for the Generation of Homoenolates

The First Examples

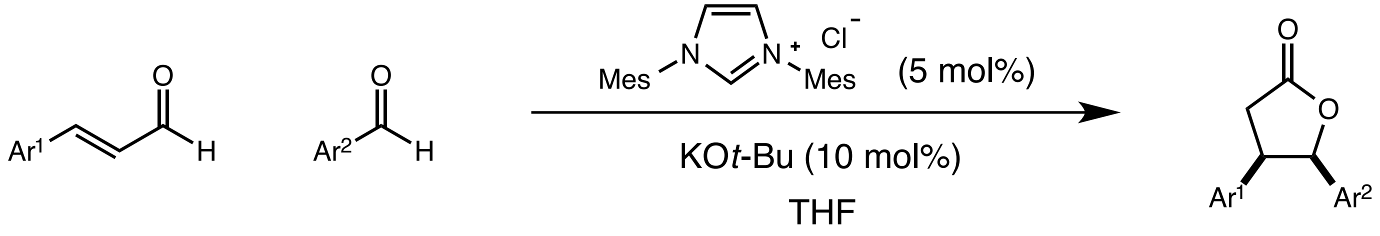
■ In 2004, the groups of Bode and Glorius reported the use of NHC-catalyzed homoenolate formation for the synthesis of γ-butyrolactones

Bode:



41-87%, 3:1-7:1 *cis*:*trans*

Glorius:



33-70%, up to 4:1 *cis*:*trans*

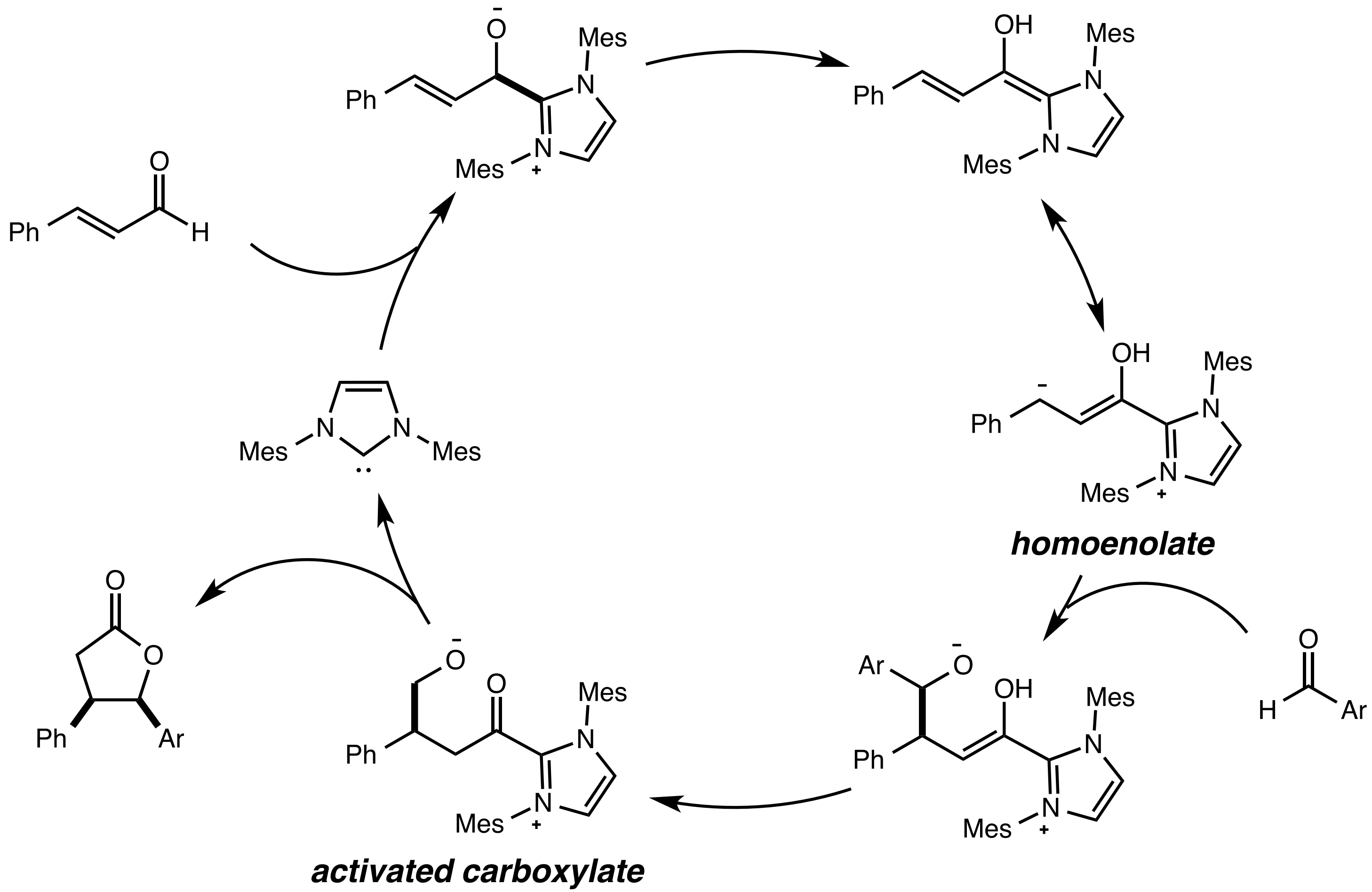
Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *116*, 6331.

Sohn, S. S.; Rosen, E. L.; Bode, J. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

The Use of NHCs for the Generation of Homoenolates

The First Examples

■ Proposed mechanism for the NHC-catalyzed formation γ-butyrolactones

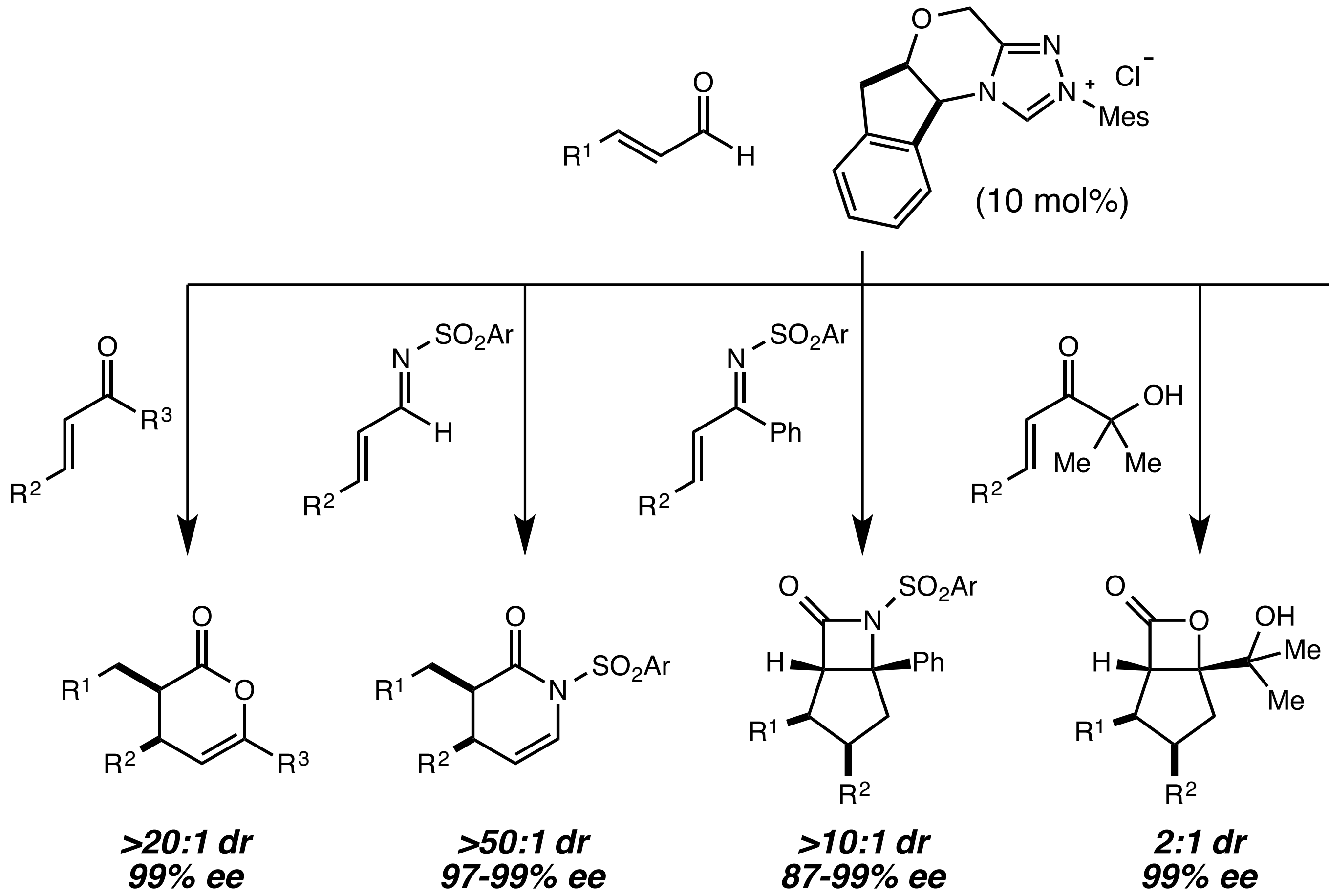


Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *116*, 6331.
Sohn, S. S.; Rosen, E. L.; Bode, J. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

The Use of NHCs for the Generation of Homoenolates

Many Asymmetric Examples Followed

■ Bode *et al.* demonstrated a variety of highly enantioselective transformations of homoenolates



He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418.
Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677.
He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.
Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.
Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Nat. Acad. Sci.* **2010**, *107*, 20661.

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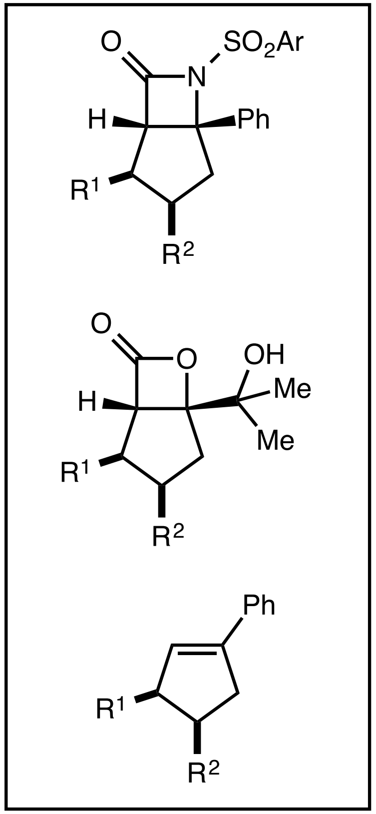
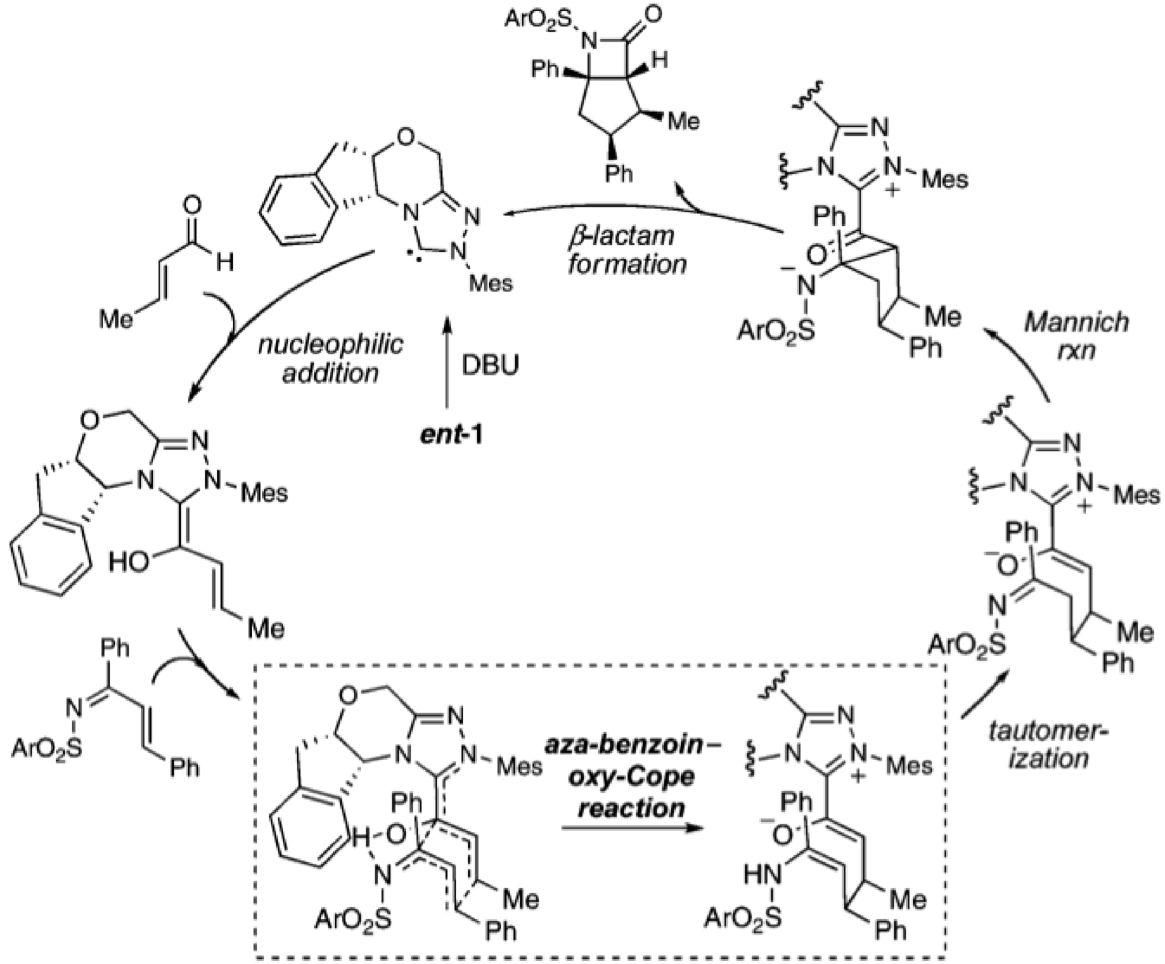


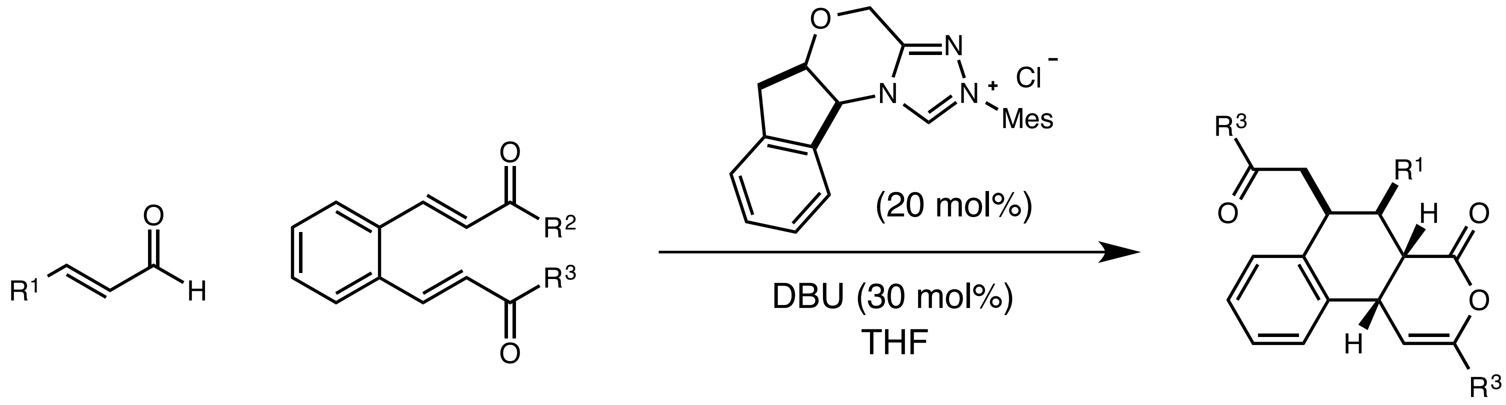


He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418.
Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677.
Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.

The Use of NHCs for the Generation of Homoenolates

Many Asymmetric Examples Followed

■ Recently, Chi *et al.* demonstrated a homoenolate coupling with benzodi(enone)s for the synthesis of complex tricyclic structures



53-84% yield
96-99% ee
10-20:1 dr

Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 1910.

The Use of NHCs for the Generation of Homoenolates

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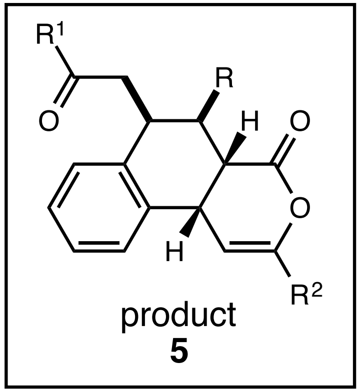

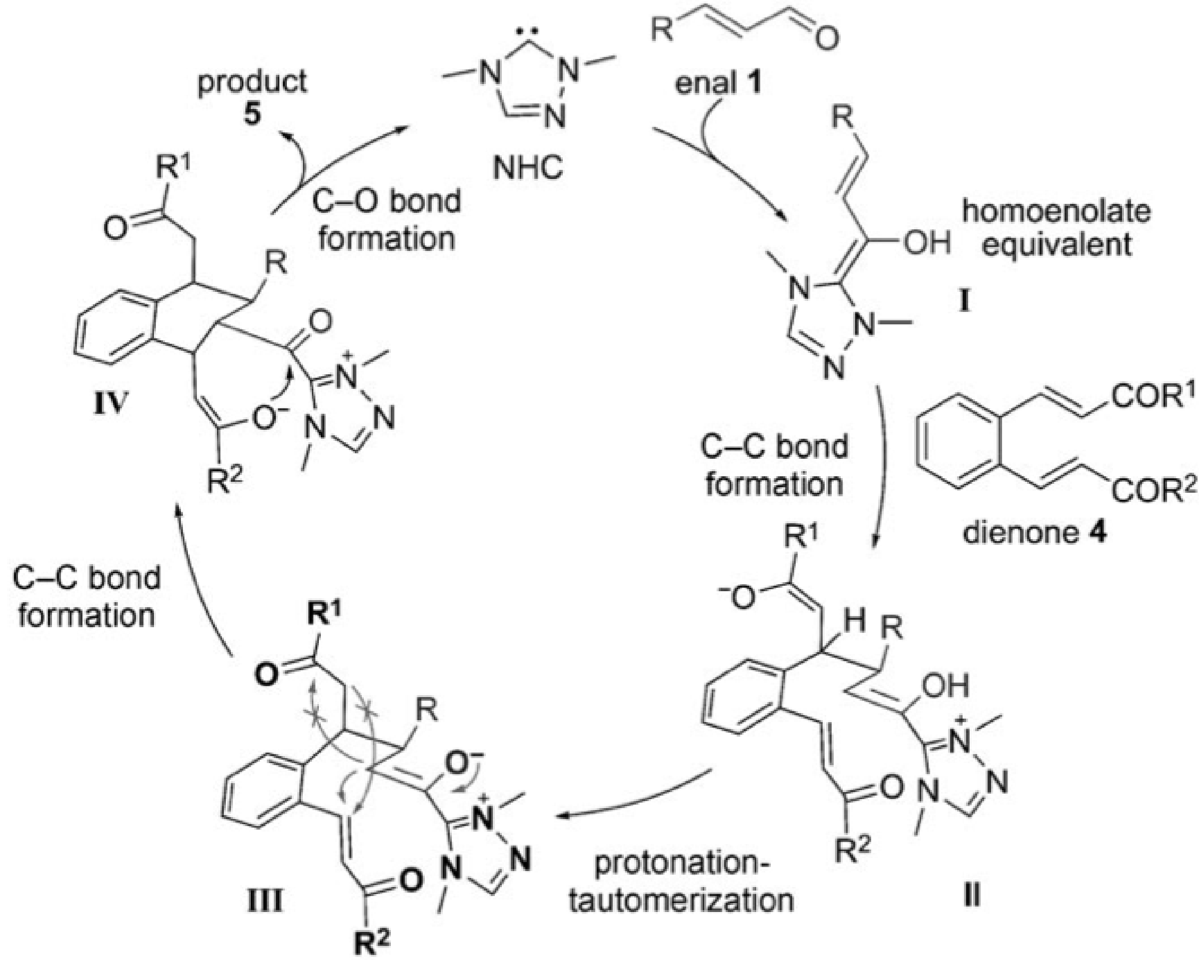

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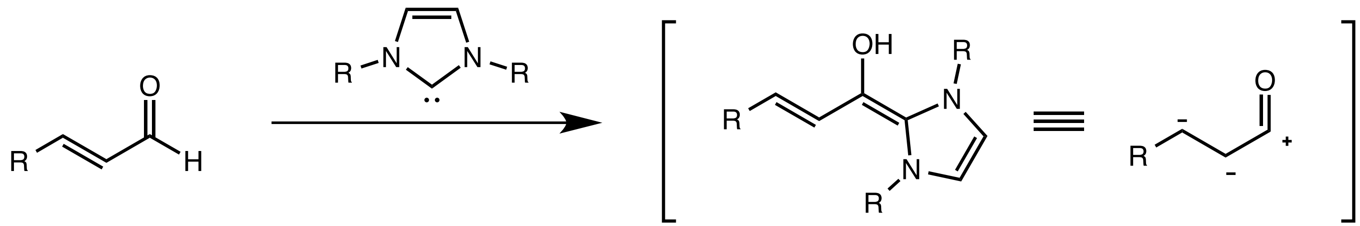
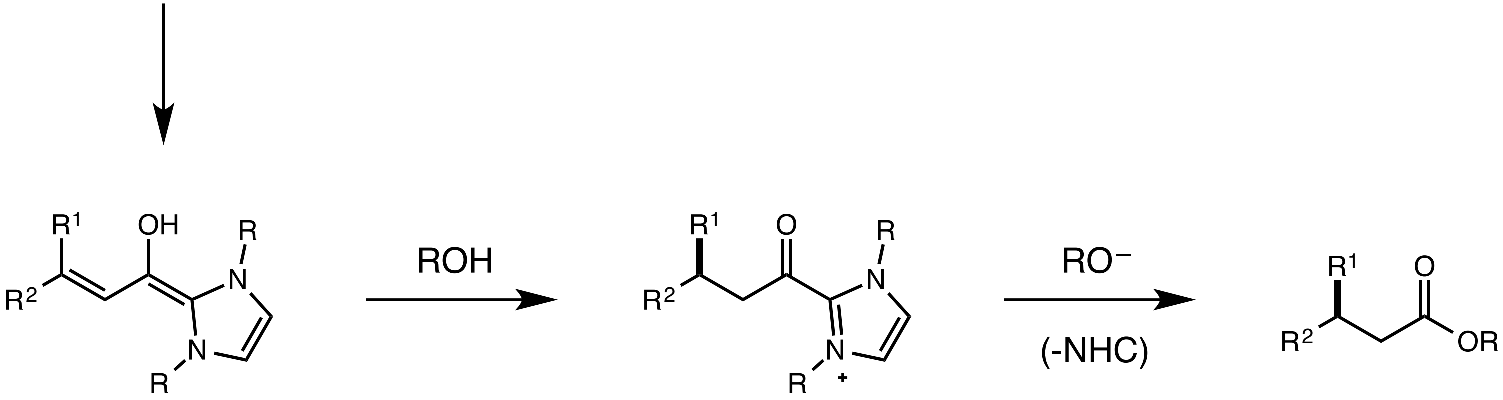
N-Heterocyclic Carbenes As Enantioselective Organocatalysts

Alternative Applications of Homoenolates

Homoenolates



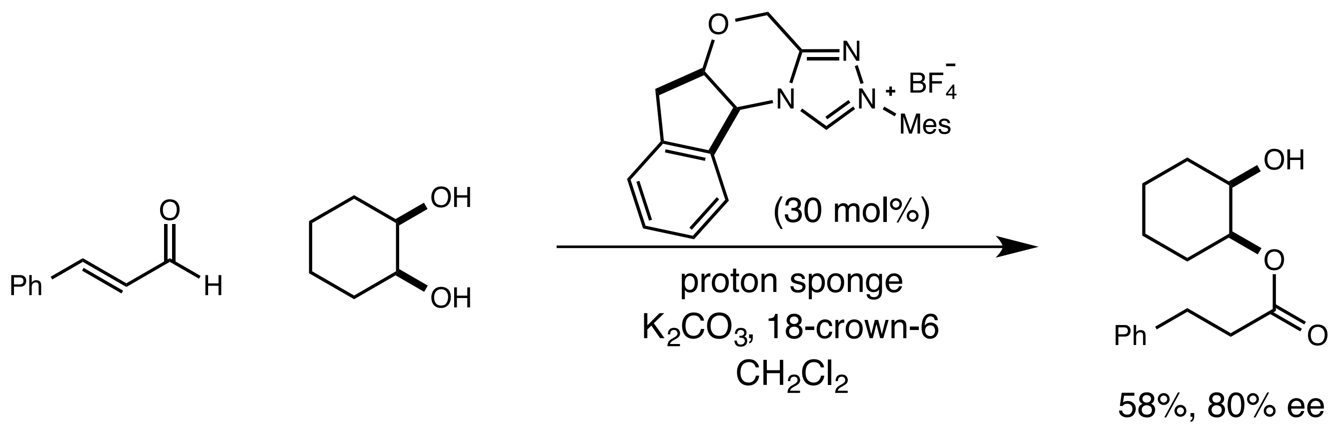


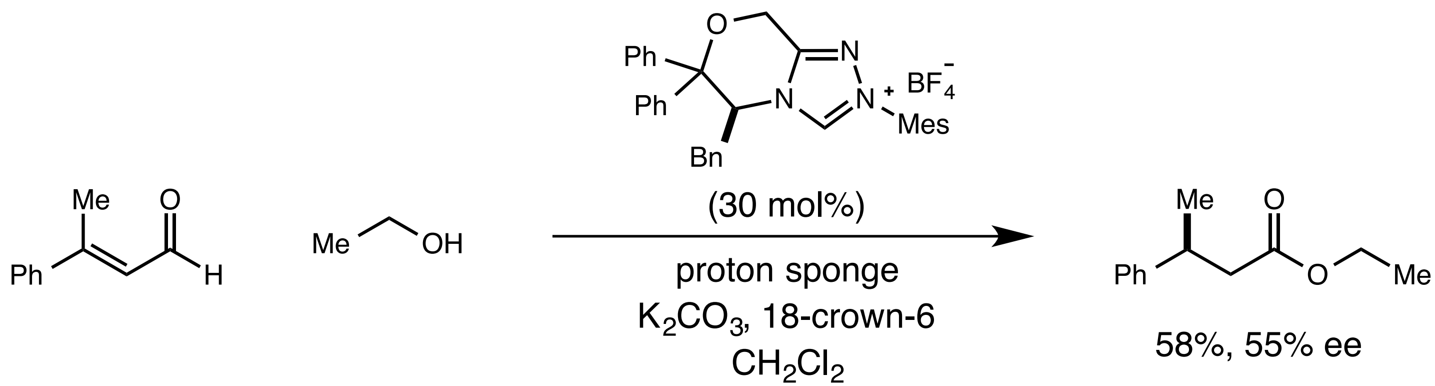
"Redox Relay"

The Use of NHCs for the Generation of Homoenolates

Alternative Applications of Homoenolates

■ Using this ester formation reaction they could perform desymmetrizations of *meso* diols and enantioselective protonations of β,β-disubstituted enals



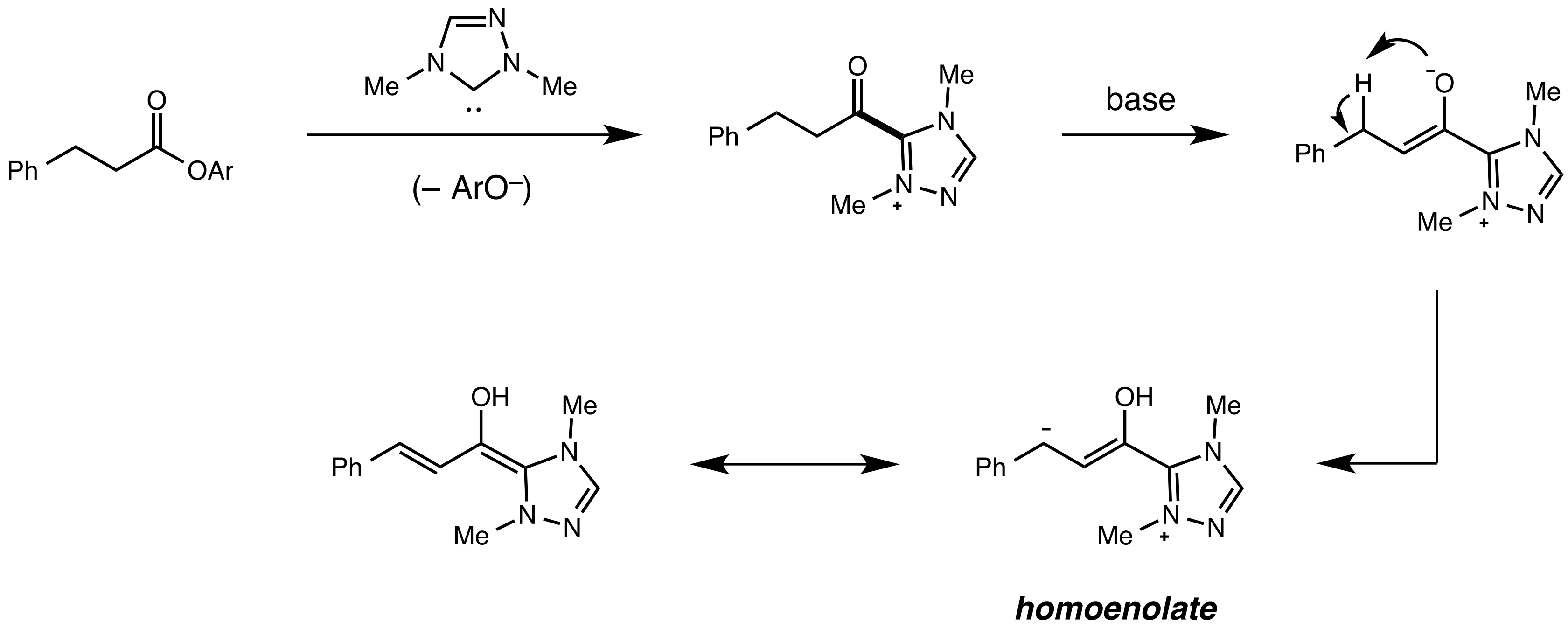


Maki, B.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371.
Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905.

The Use of NHCs for the Generation of Homoenolates

Alternative Applications of Homoenolates

■ The group of Chi has reported the reversed process for the generation of homoenolates from saturated esters, allowing for direct β-substitution.



Fu, Z.; Xu, X.; Zhu, X.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835.

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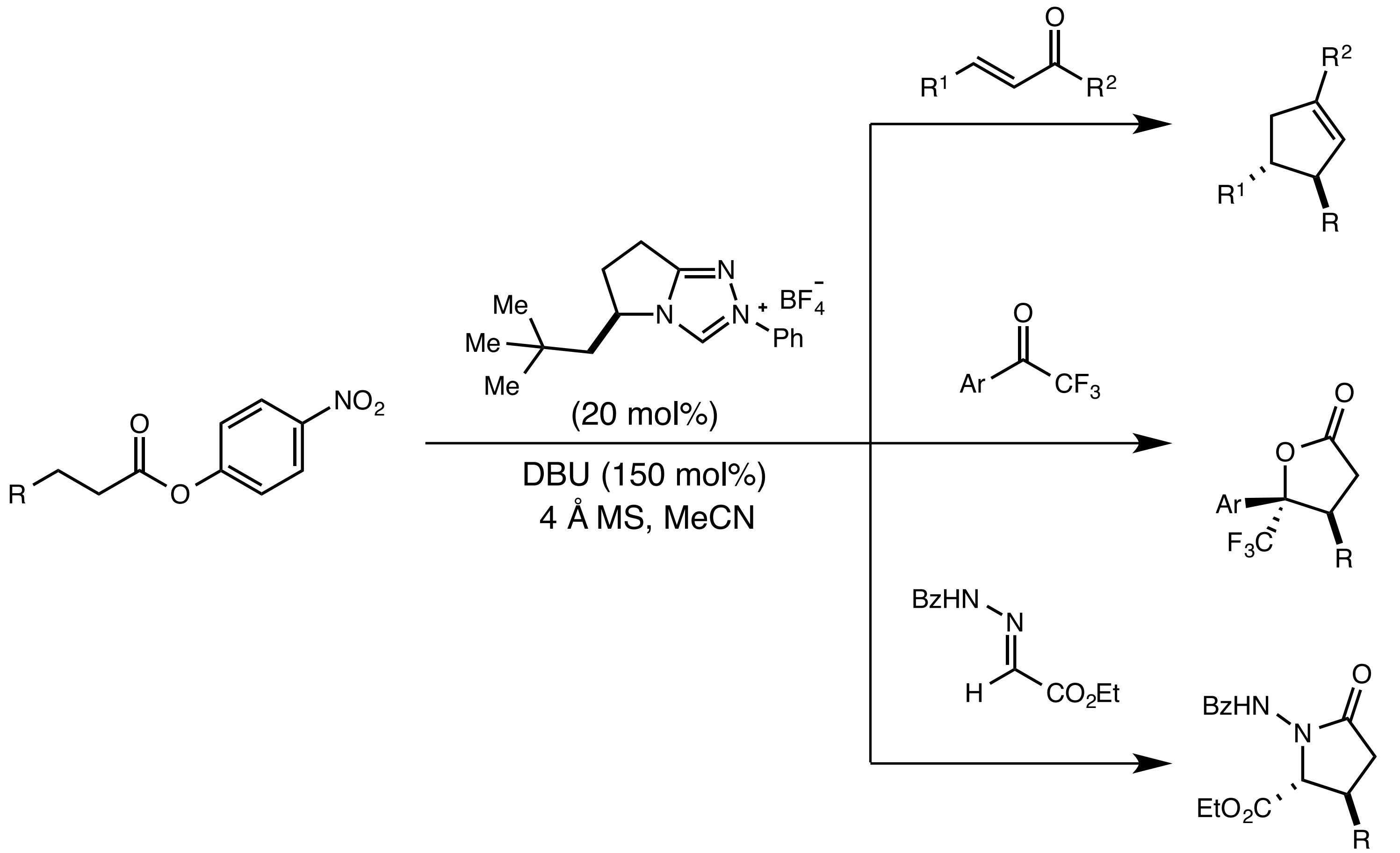


up to 81% yield
94% ee, 20:1 dr

up to 61% yield
88% ee, 2:1 dr

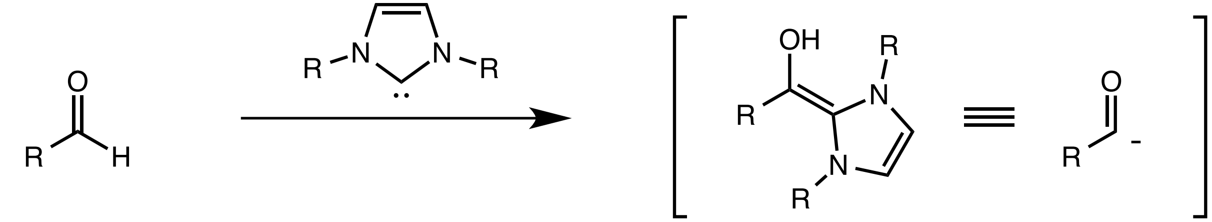
up to 76% yield
94% ee, 7:1 dr

Fu, Z.; Xu, X.; Zhu, X.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835.

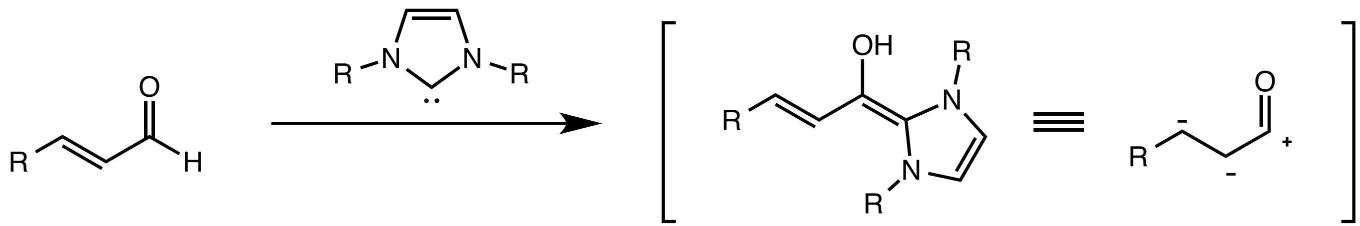
N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

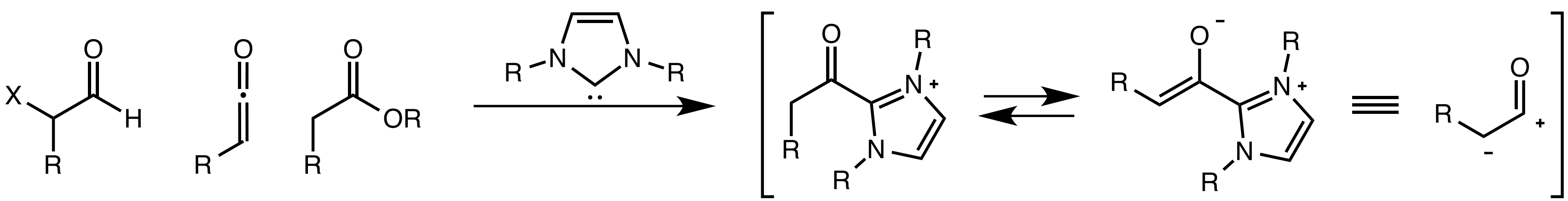
Acyl Anions



Homoenolates



Azolium Enolates / Acyl Azoliums



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Modes of Reactivity

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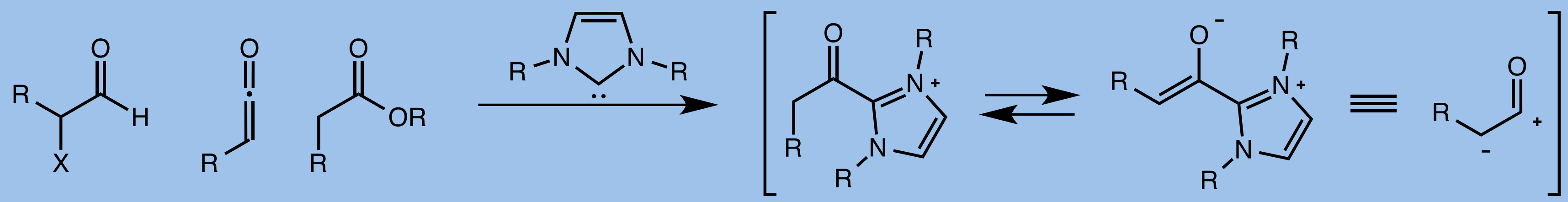
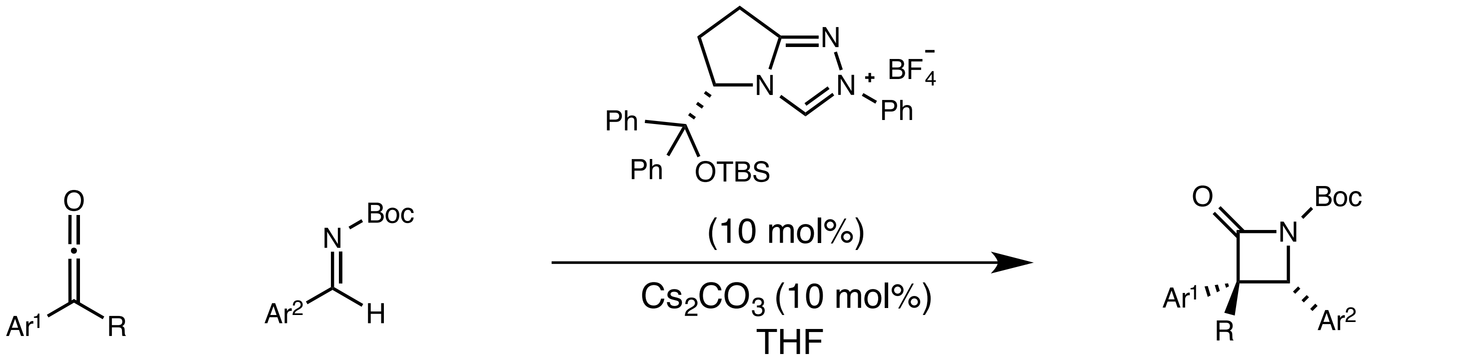


- [2+2] Cycloadditions
- [4+2] Cycloadditions
- [3+2] cycloadditions
- Enolate Chemistry

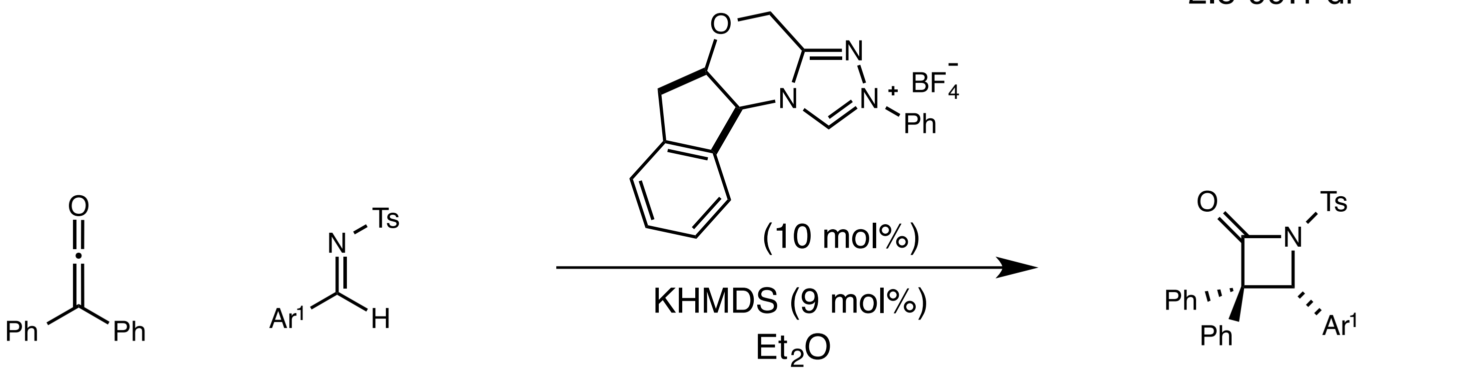
The Use of NHCs for the Generation of Azolium Enolates

The First Examples

■ The groups of Ye and Smith independently developed formal [2+2] cycloadditions promoted by the addition of NHCs to ketenes



53-78% yield, 91-99% ee
2.5-99:1 dr



79-96% yield, up to 75% ee
(>99% ee after recryst.)

Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S.; *Org. Lett.* **2008**, *10*, 277.
Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. C. *Org. Biomol. Chem.* **2008**, *6*, 1108.

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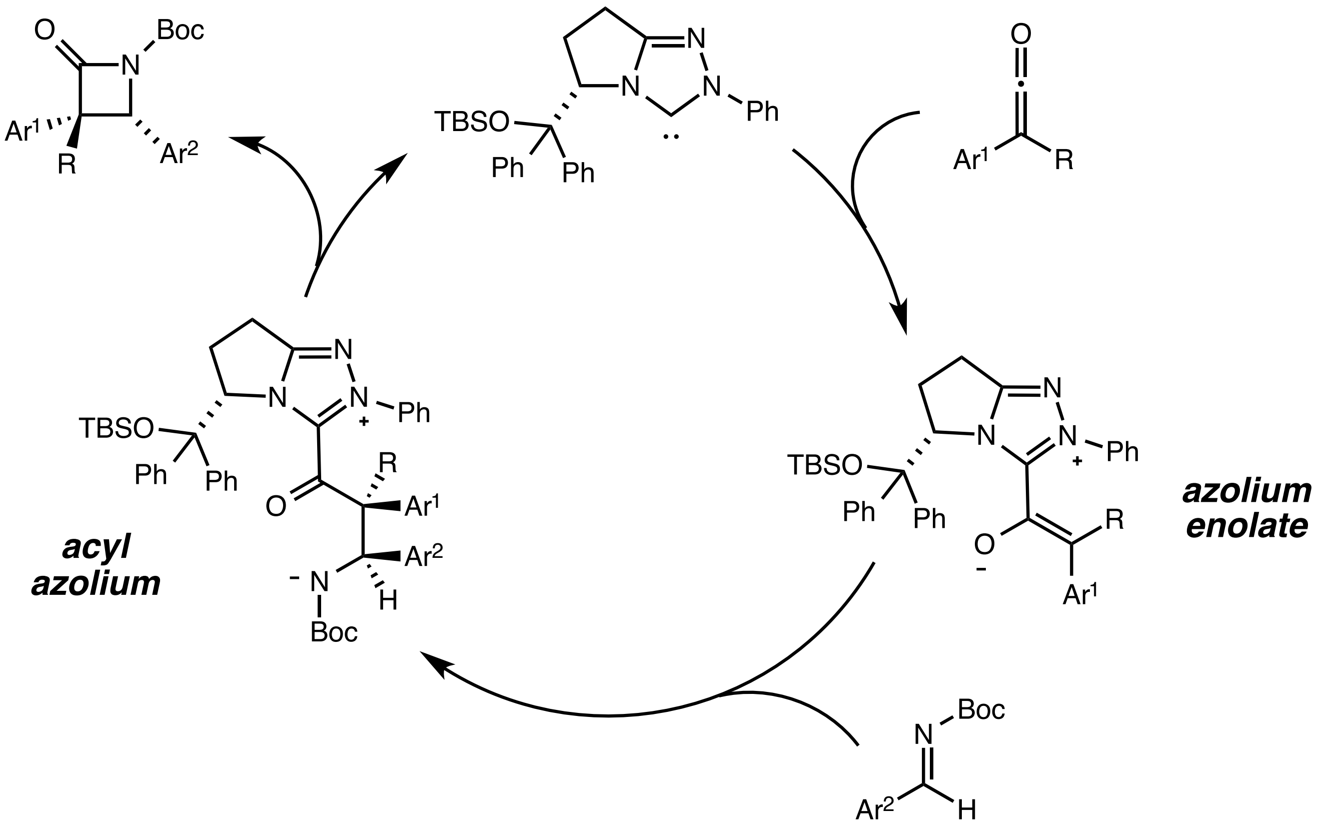

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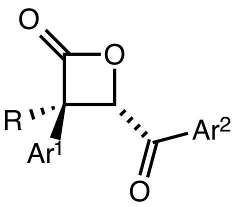
Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. C. *Org. Biomol. Chem.* **2008**, *6*, 1108.

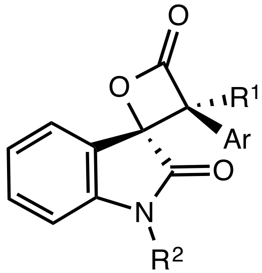
The Use of NHCs for the Generation of Azolium Enolates

Expanding the Scope of [2+2] Cycloadditions

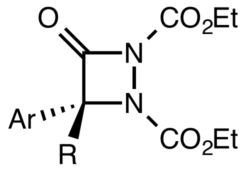
- Since 2008, Ye *et al.* have reported numerous other enantioselective [2+2] cycloadditions



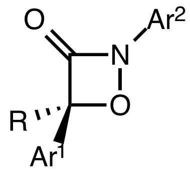
2008



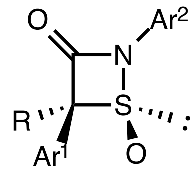
2010



2010



2011



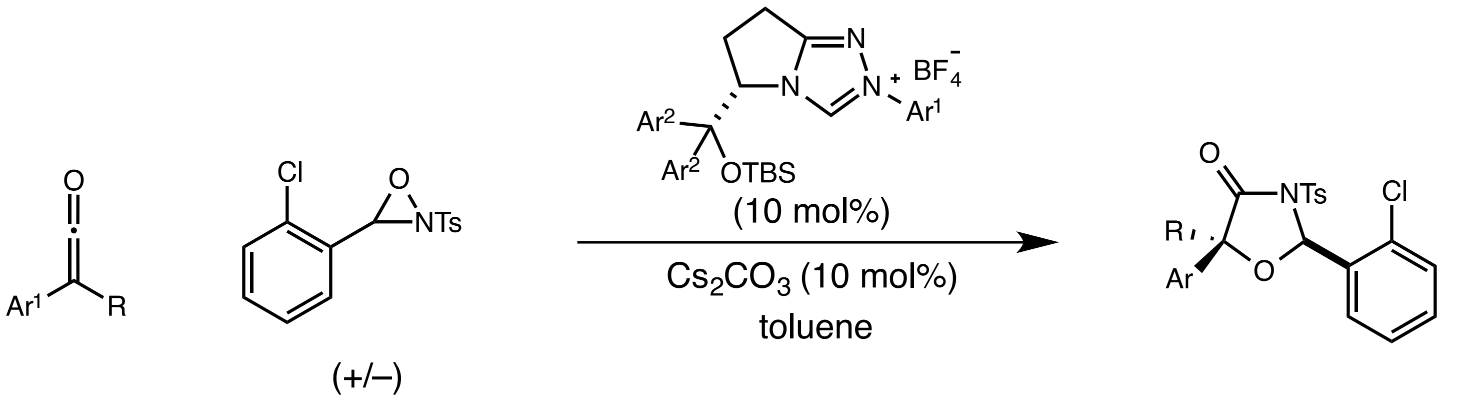
2011

Chen, X.-Y.; Ye, S. *Synlett* **2013**, 1614.
Douglas, J.; Churchill, G.; Smith, A. C. *Synthesis* **2012**, *44*, 2295.

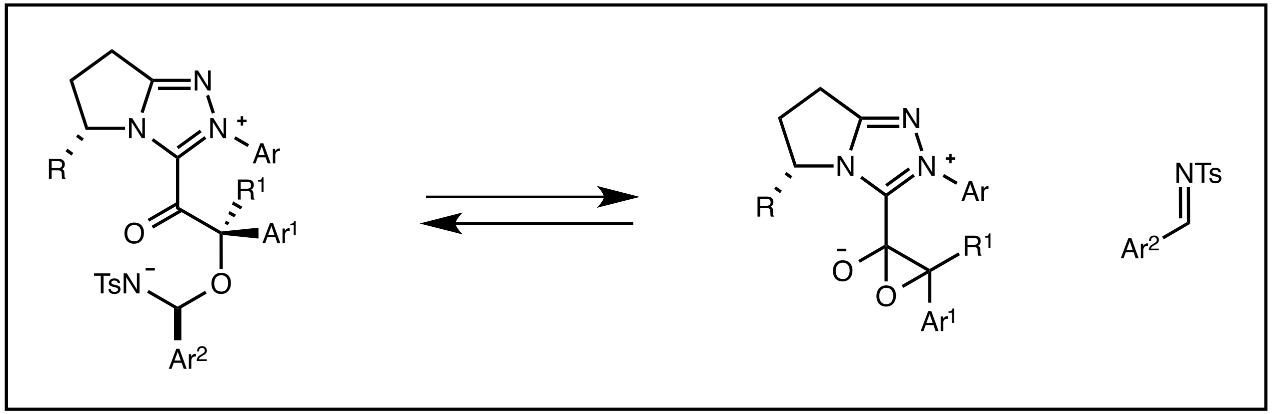
The Use of NHCs for the Generation of Azolium Enolates

[3+2] Cycloadditions

- The same group also reported an analogous [3+2] cycloaddition using oxaziridines



up to 78% yield, up to 95% ee
8-15:1 dr

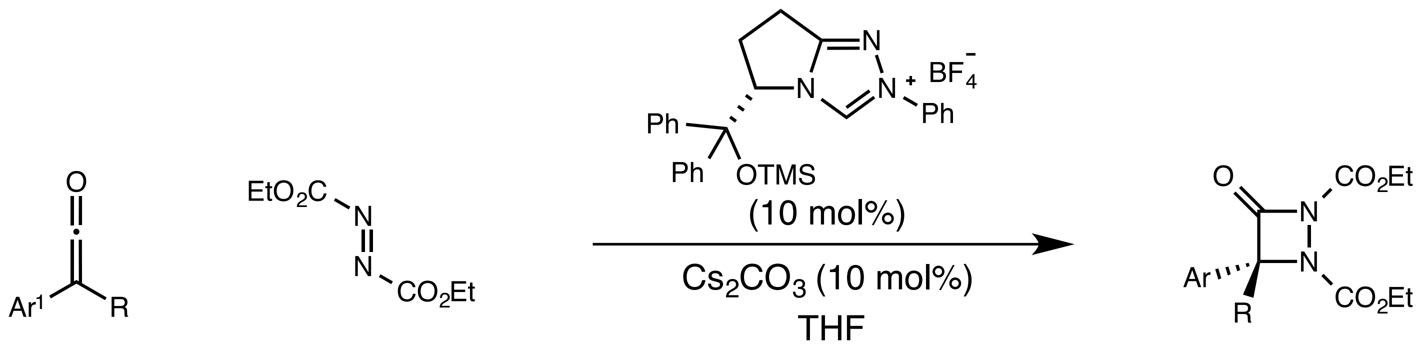


Chen, X.-Y.; Ye, S. *Synlett* **2013**, 1614.
Douglas, J.; Churchill, G.; Smith, A. C. *Synthesis* **2012**, *44*, 2295.

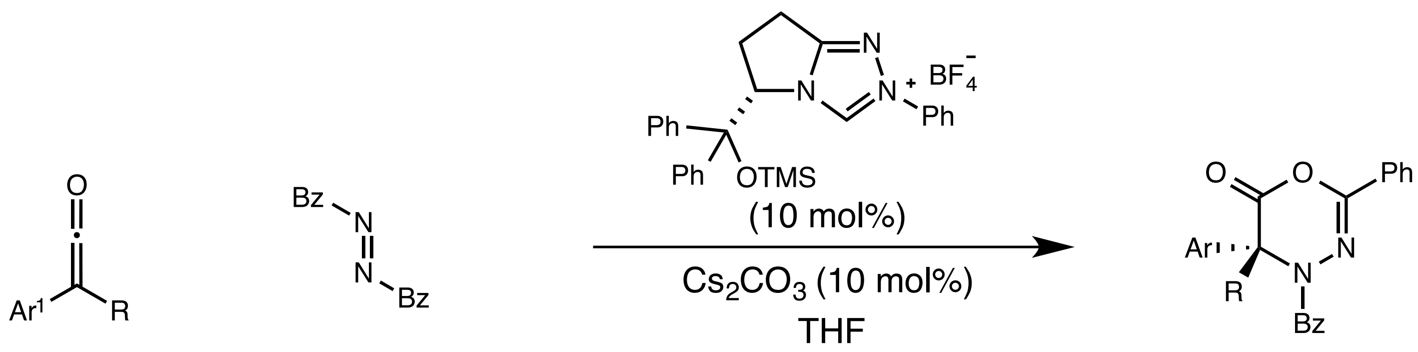
The Use of NHCs for the Generation of Azolium Enolates

[4+2] Cycloadditions

- Ye *et al.* also demonstrated a number [4+2] cycloaddition reactions



52-95% yield, 33-91% ee



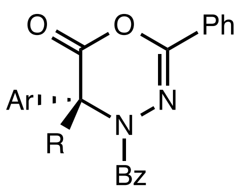
52-95% yield, 33-91% ee

Chen, X.-Y.; Ye, S. *Synlett* **2013**, 1614.
Douglas, J.; Churchill, G.; Smith, A. C. *Synthesis* **2012**, *44*, 2295.

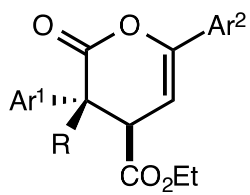
The Use of NHCs for the Generation of Azolium Enolates

[4+2] Cycloadditions

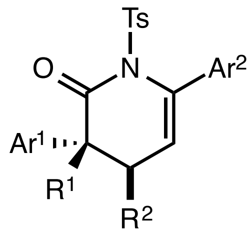
- Ye *et al.* reported the use of a variety of other 'dienes' in [4+2] cycloaddition reactions



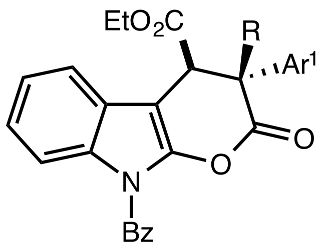
50-92% yield
>90% ee



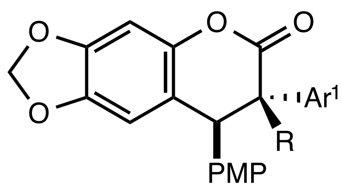
>80% yield
57-93% ee
>15:1 dr



>80% yield
83-93% ee
>10:1 dr



88-99% yield
69-90% ee
3-10:1 dr



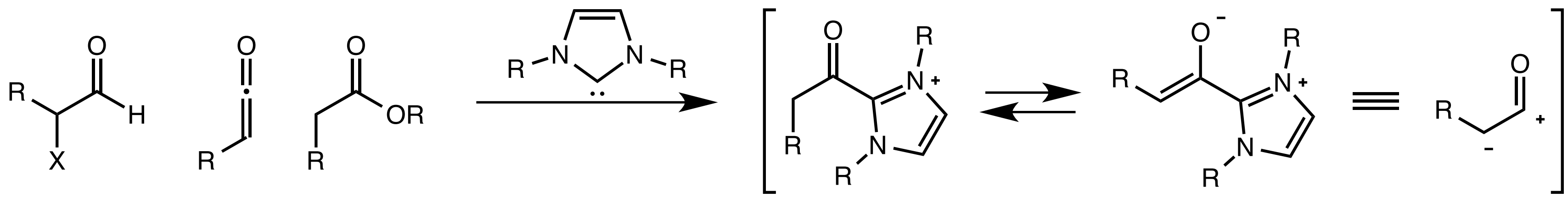
30-96% yield
51-99% ee
2-9:1 dr

Chen, X.-Y.; Ye, S. *Synlett* **2013**, 1614.
Douglas, J.; Churchill, G.; Smith, A. C. *Synthesis* **2012**, *44*, 2295.

N-Heterocyclic Carbenes As Enantioselective Organocatalysts

Modes of Reactivity

Azolium Enolates / Acyl Azoliums

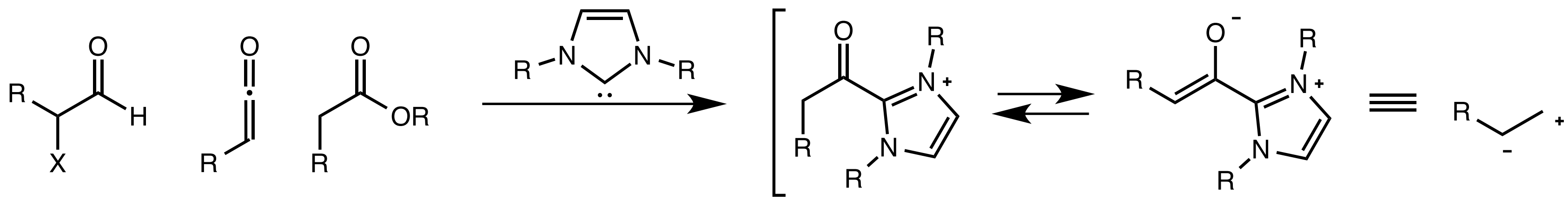


- [2+2] Cycloadditions
- [4+2] Cycloadditions
- [3+2] cycloadditions
- Enolate Chemistry

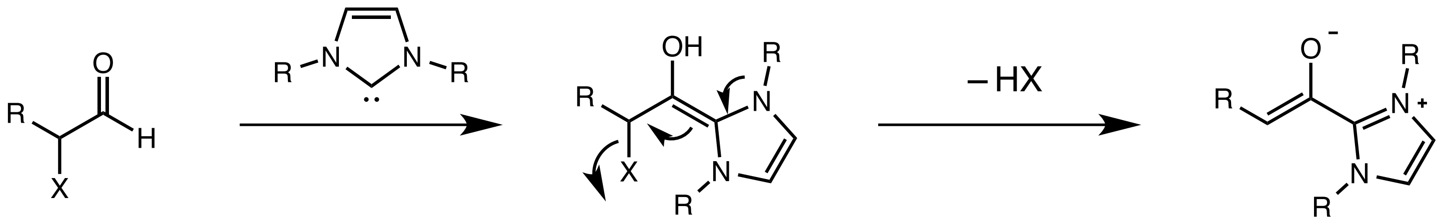
N-Heterocyclic Carbenes As Enantioselective Organocatalysts

Modes of Reactivity

Azolium Enolates / Acyl Azoliums



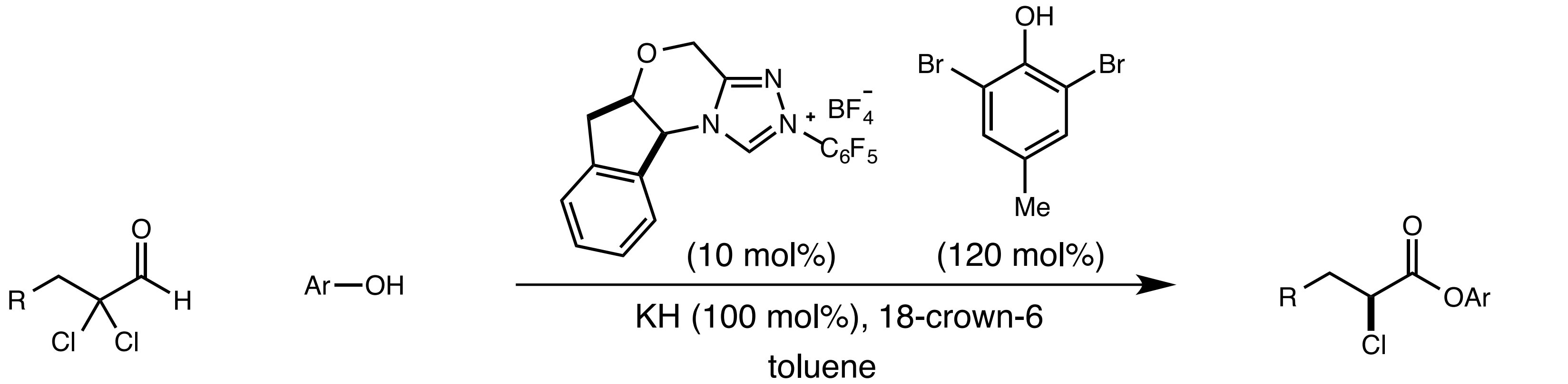
■ Enolate chemistry of α-functionalized aldehydes



The Use of NHCs for the Generation of Azolium Enolates

Utilizing α Functionalized Aldehydes

■ In 2005, Rovis *et al.* devloped a synthesis of α-chloro esters utilizing an enantioselective protonation of an *in situ* generated α-chloro enolate



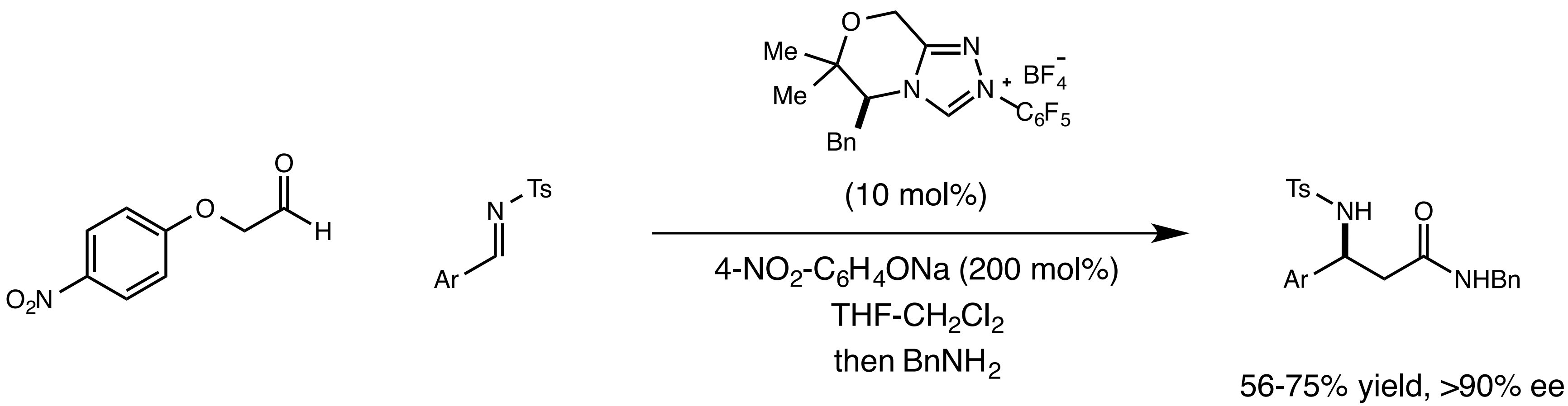
65-79% yield, 84-93% ee

Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *128*, 2860.

The Use of NHCs for the Generation of Azolium Enolates

Utilizing α Functionalized Aldehydes

■ In 2009, Scheidt *et al.* demonstrated that α-aryloxyacetaldehyde to be competent enolate equivalents in Mannich reactions, giving β-amino amide derivatives

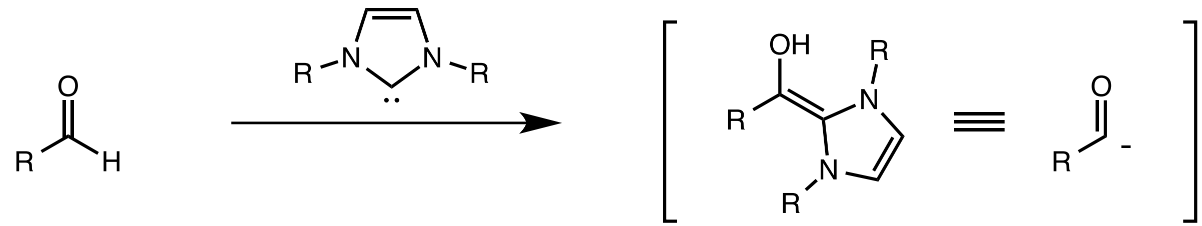


Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028.

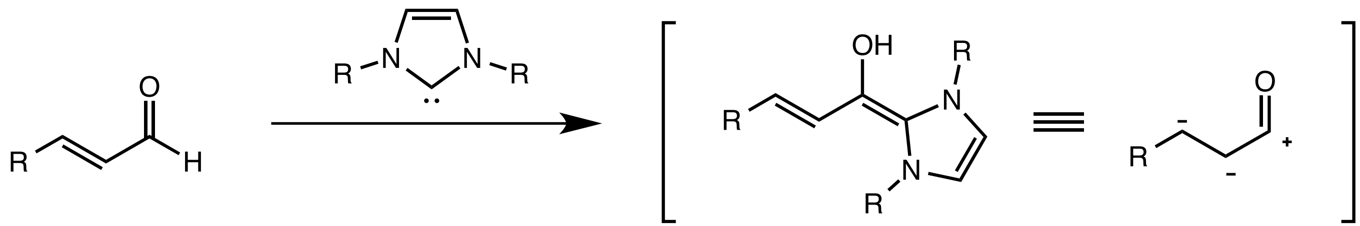
N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

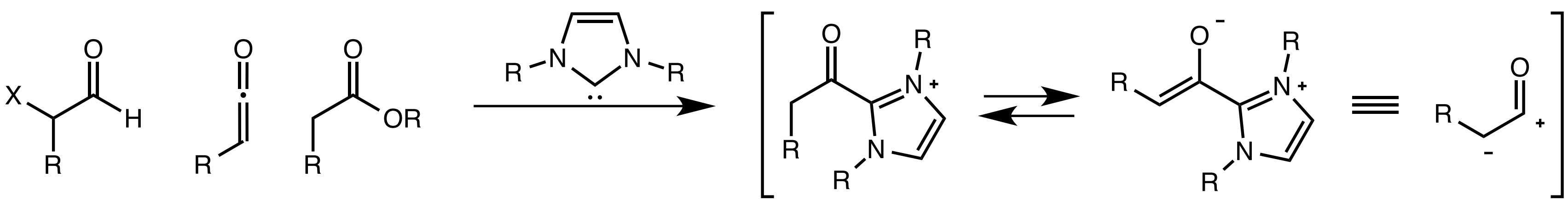
Acyl Anions



Homoenolates



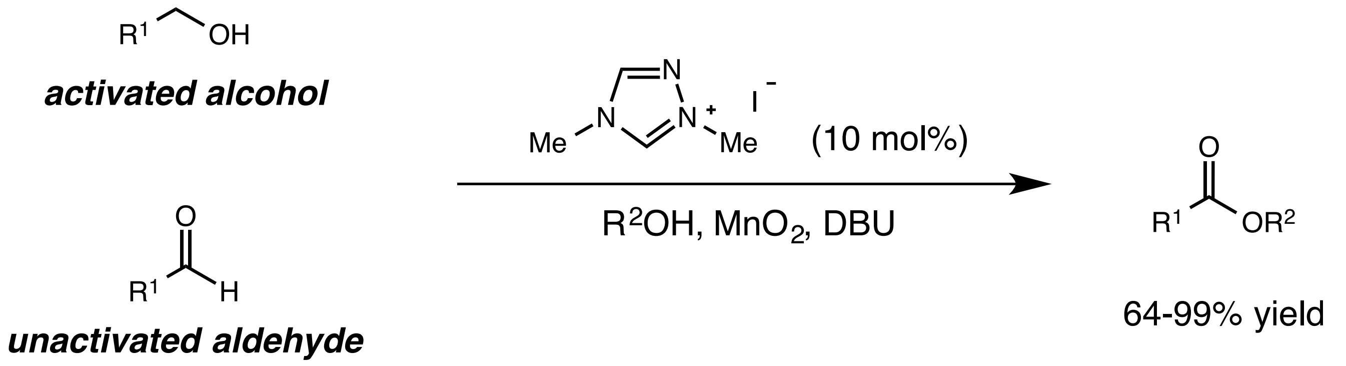
Azolium Enolates / Acyl Azoliums

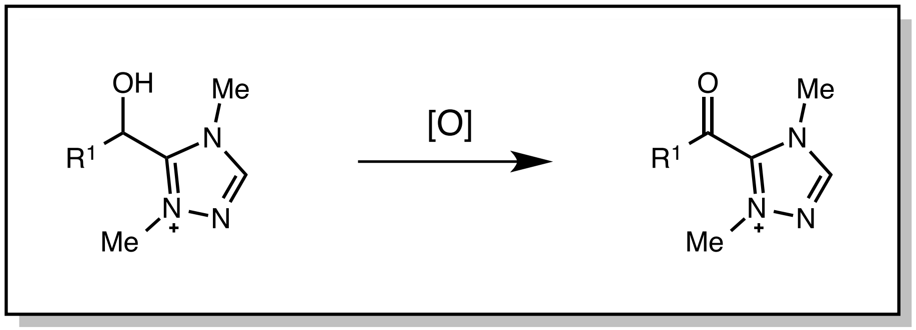


Oxidative NHC Catalysis

Oxidative Functionalization of Aldehydes

- In 2007 and 2008, Scheidt *et al.* demonstrated NHCs could catalyze the MnO_2-promoted oxidation of benzylic and vinylic alcohols to esters, and unactivated aldehydes to esters



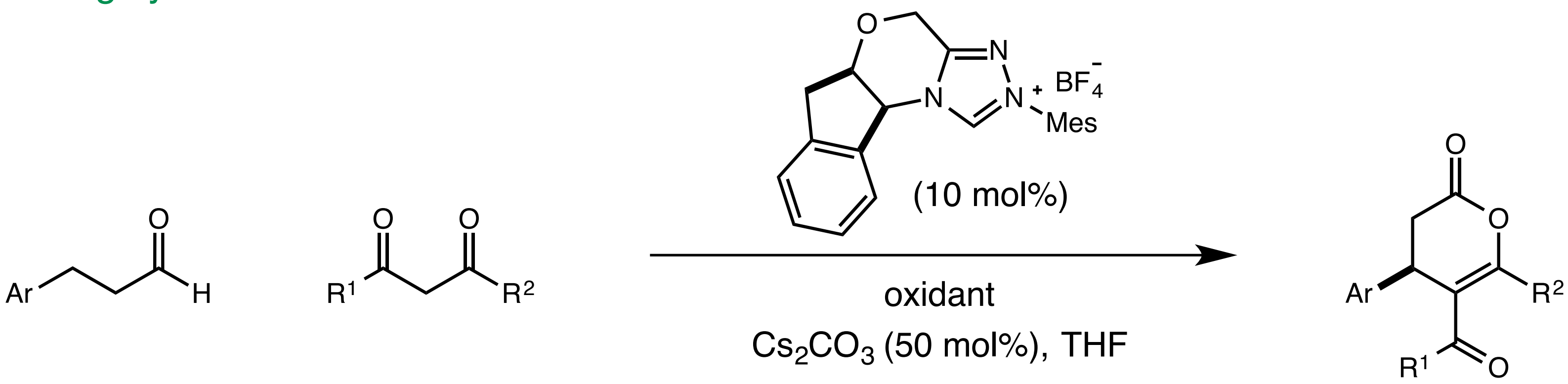


Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371.
Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331.

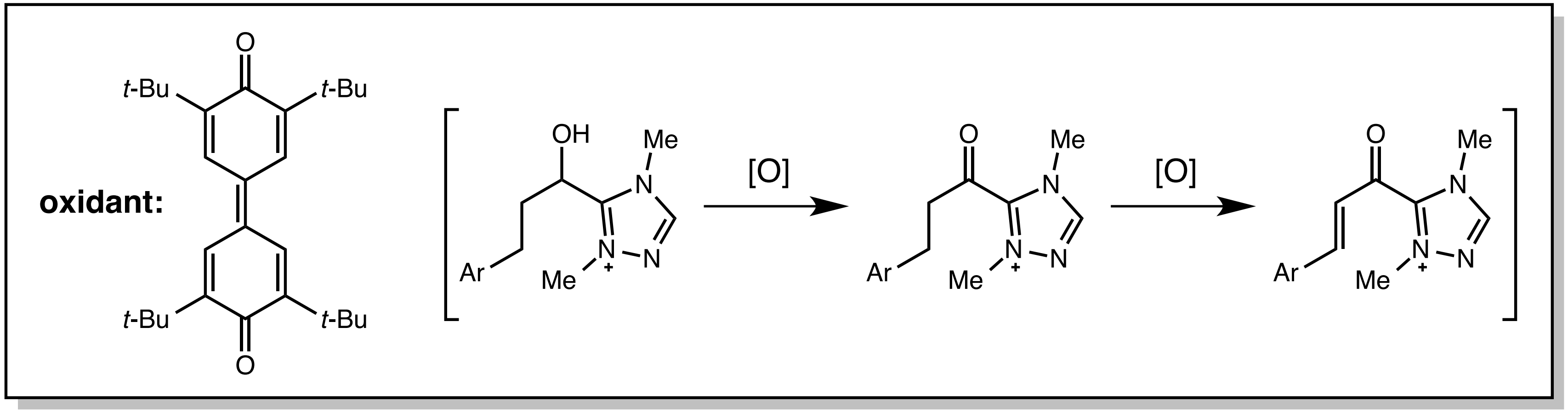
Oxidative NHC Catalysis

Oxidative Functionalization of Aldehydes

- Since these reports, Chi *et al.* have demonstrated the use of oxidative NHC catalysis in a variety of highly enantioselective reactions



53-98% yield, 70-94% ee



Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8588.

Oxidative NHC Catalysis

Oxidative Functionalization of Aldehydes

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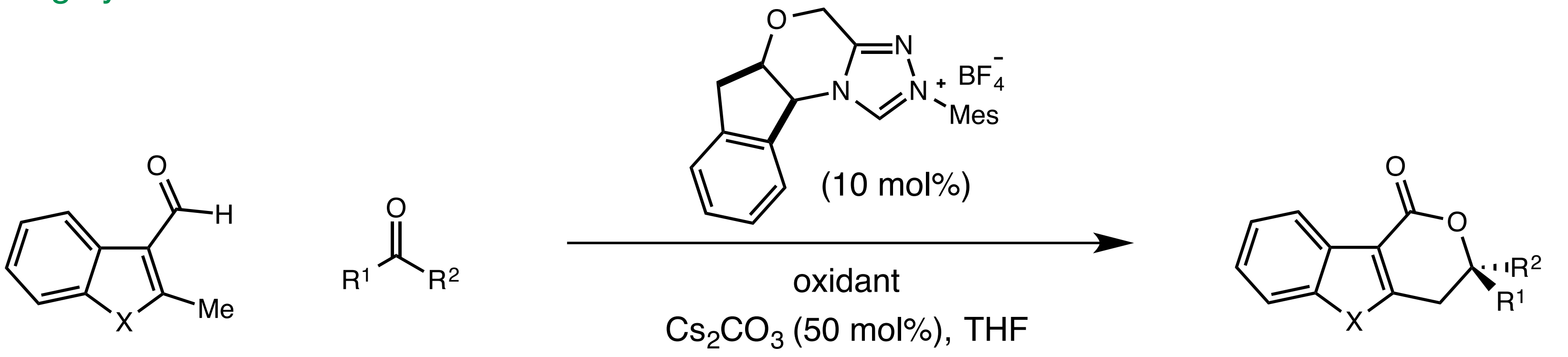
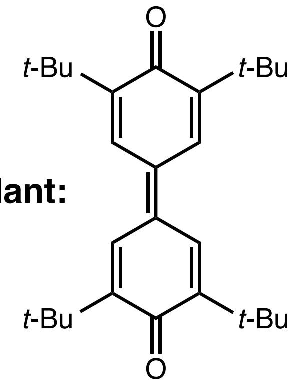
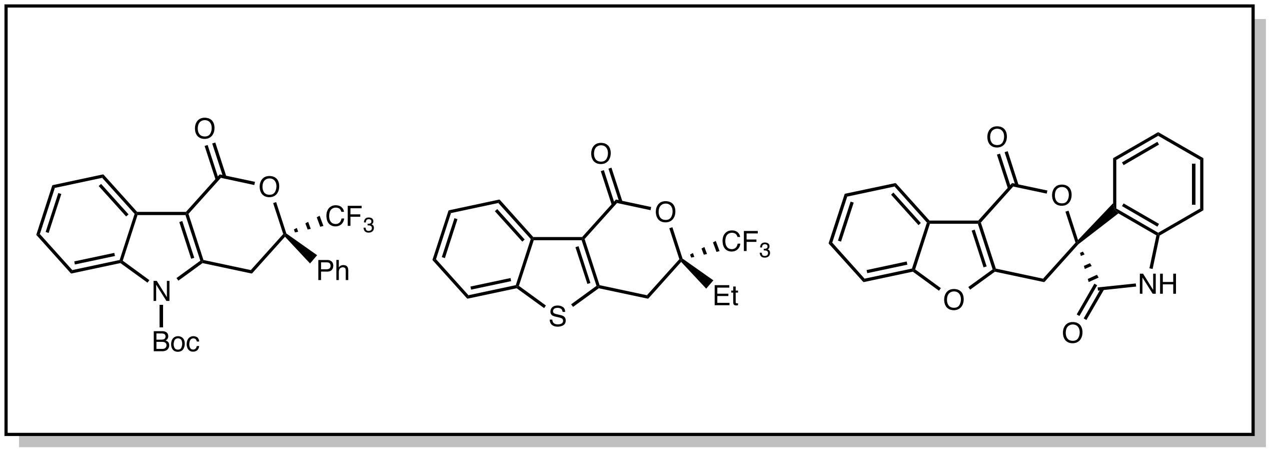


61-89% yield, 84-99% ee

oxidant:





Chen, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 11134.

Oxidative NHC Catalysis

Oxidative Functionalization of Aldehydes

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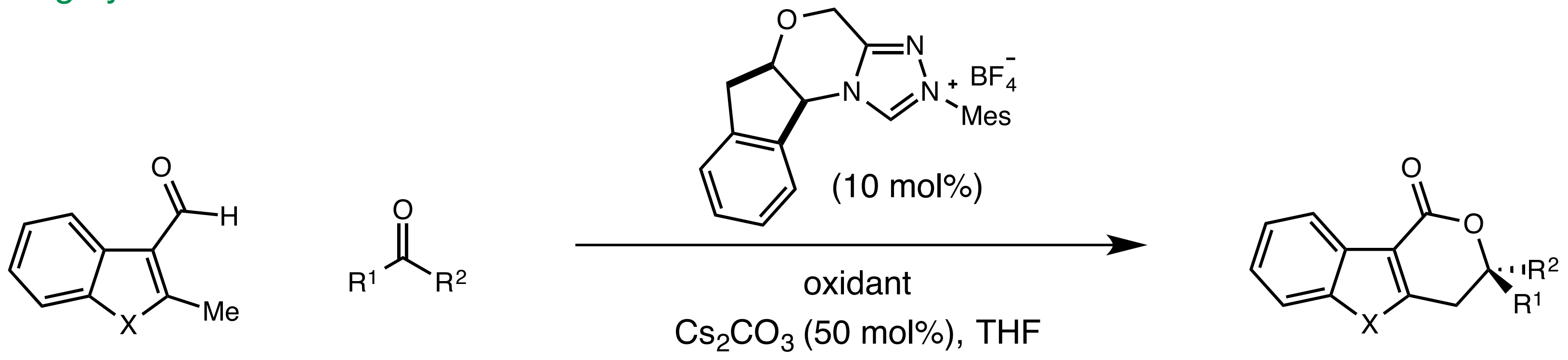
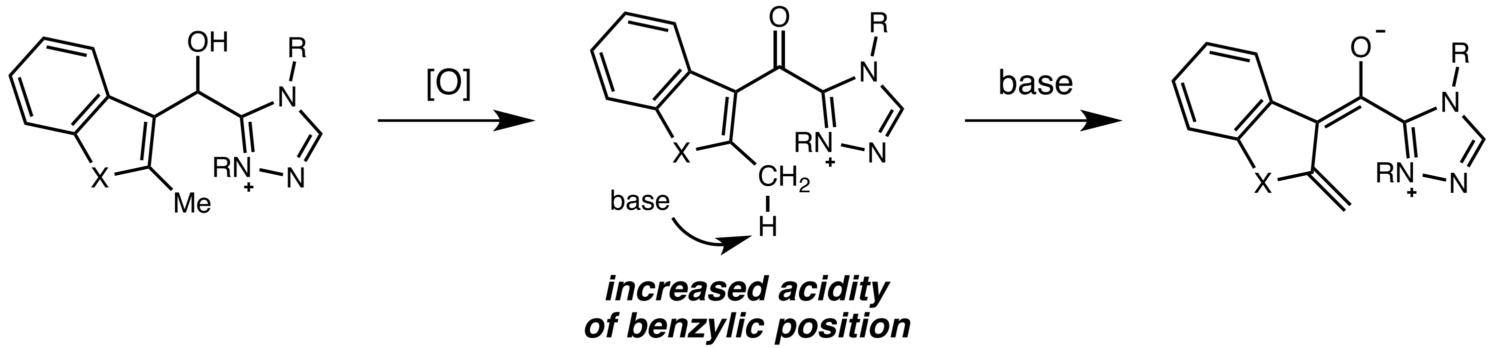


61-89% yield, 84-99% ee

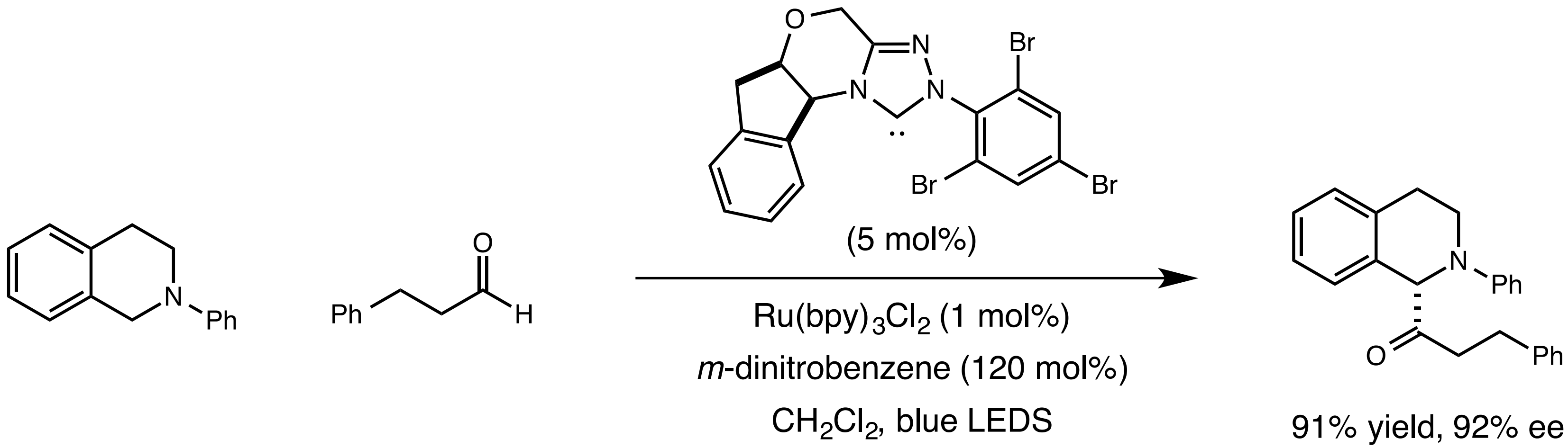


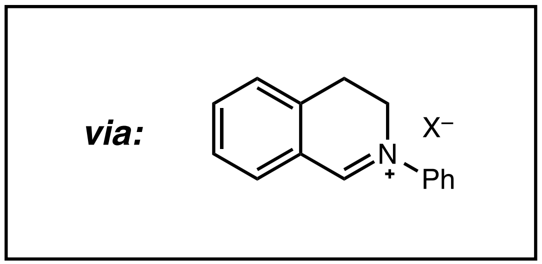
Chen, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 11134.

Oxidative NHC Catalysis

An Enantioselective Oxidative Aza-Acyloin Reaction

- In 2012, Rovis *et al.* reported the merger of photoredox and NHC catalysis for the enantioselective α-acyaltion of tertiary amines





DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094.