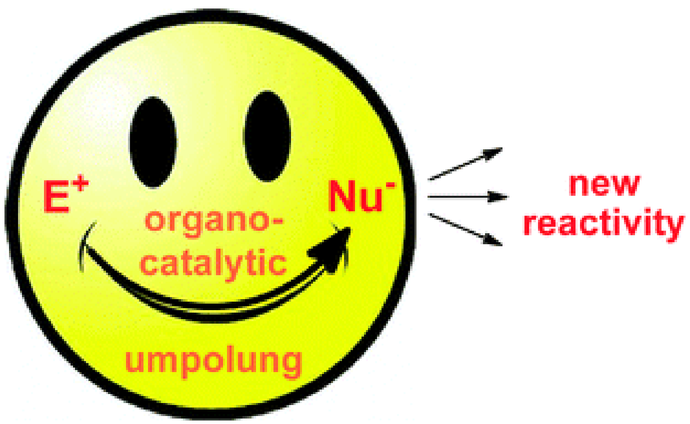
Organocatalytic Umpolung via N-Heterocyclic Carbenes



Qinghe Liu

Hu Group Meeting
August 20th 2015

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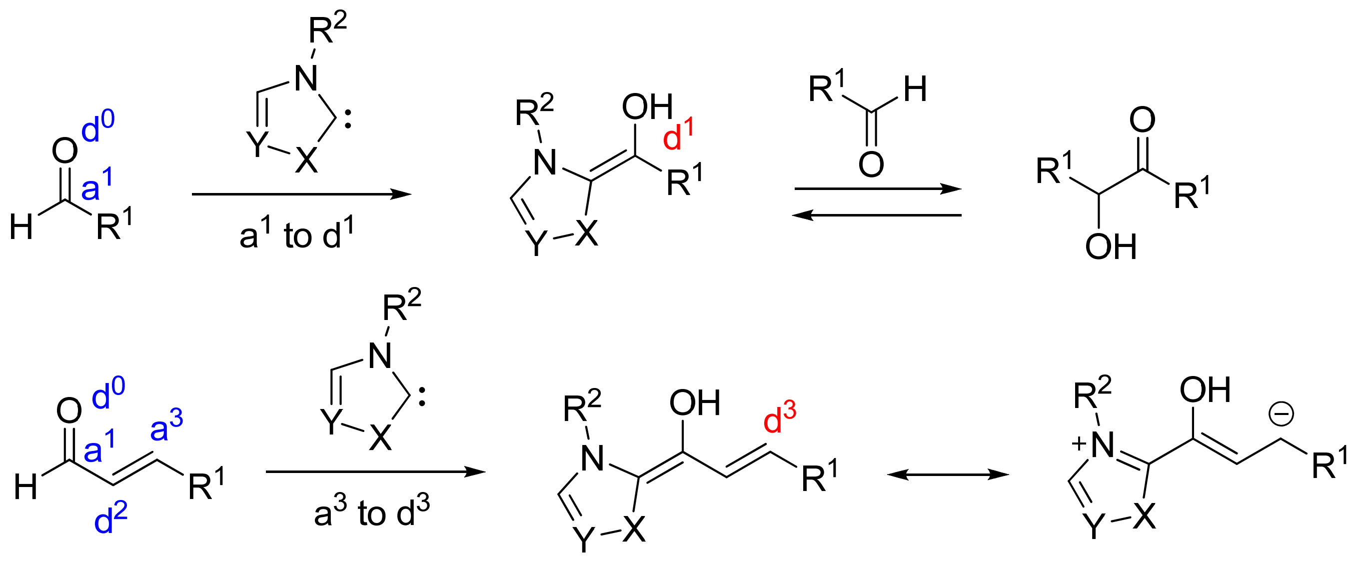

■ Part 2: *N*-Heterocyclic carbene-catalyzed umpolung: classical umpolung, conjugated umpolung, and umpolung of Michael acceptors

■ Part 3: Conclusion and outlook

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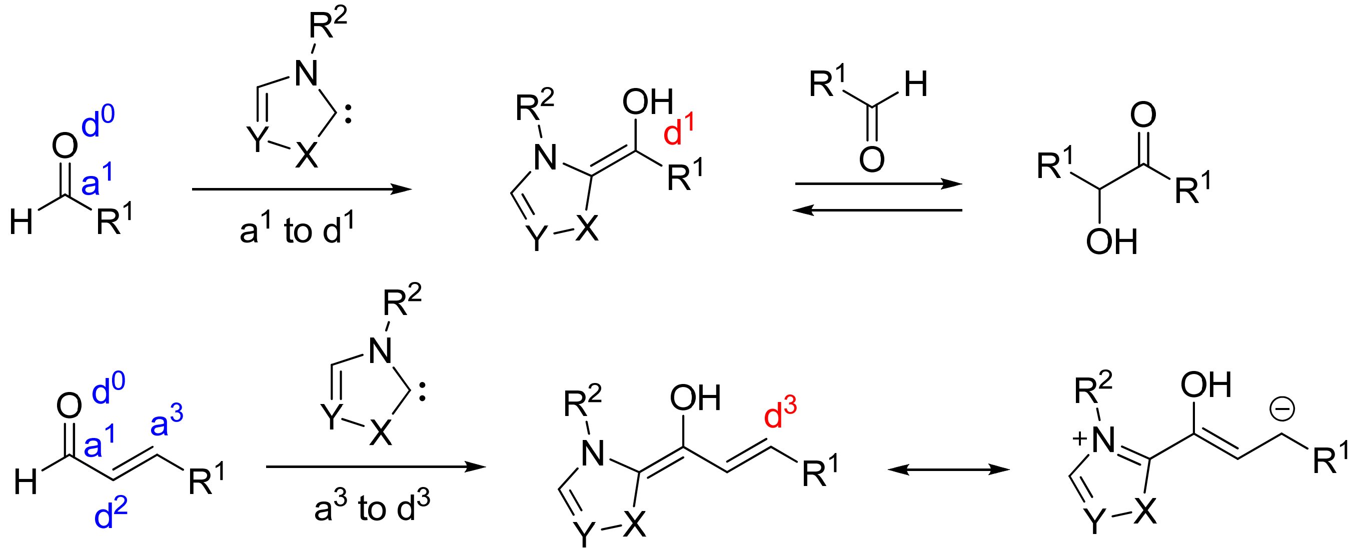


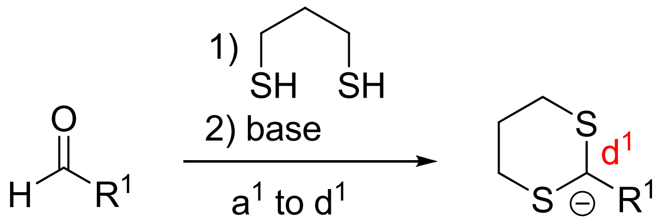
■ Part 2: *N*-Heterocyclic carbene-catalyzed umpolung: classical umpolung, conjugated umpolung, and umpolung of michael acceptors

■ Part 3: Conclusion and outlook

Introduction

G. Wittig

D. Seebach



Use of dithianes to access acyl anion synthetic equivalents.

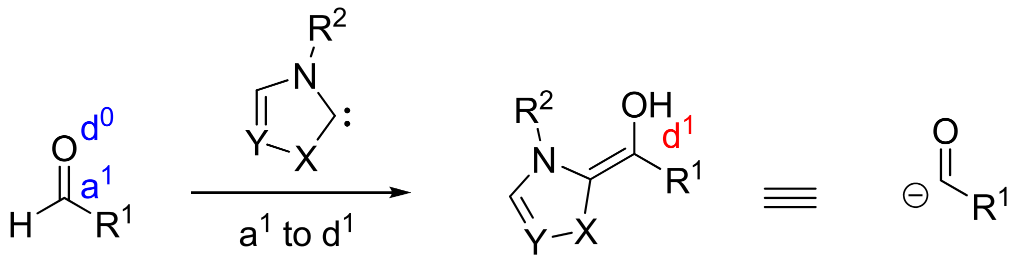
■ Introduced to chemistry by wittig in 1951, the word umpolung was then popularized by seebach, who described with it the use of dithianes to access acyl anion synthetic equivalents. And now the term umpolung refers to a powerful strategy in organic synthesis that consists of the inversion of the innate reactivity of a functional group.

(a) Wittig, G. et al. *Chem. Ber*. **1951**, *84*, 627. (b) Seebach, D. *Angew. Chem. Int. Ed*. **1965**, *4*, 1075. (c) Seebach, D. *Angew. Chem. Int. Ed*. **1965**, *4*, 1077.

Introduction

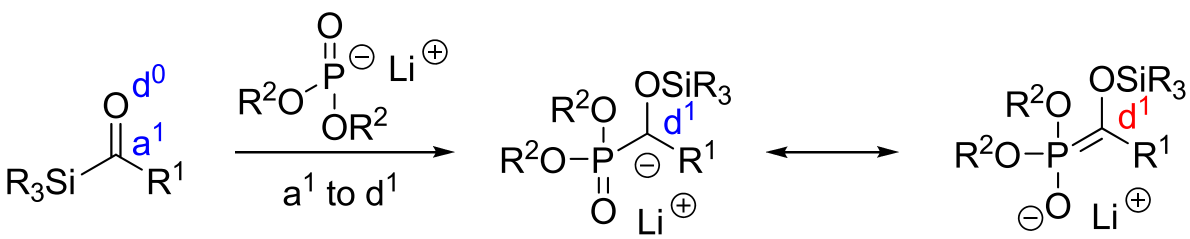
■ The presence of lone pairs on heteroatoms, such as nitrogen and oxygen, offers them the possibility of donating electron. As a result, the atoms of the skeleton of the molecule are defined as being donor (d^{2n}) and acceptor (a^{2n+1}) positions. Any process to change this normal reactivity falls under the definition of reactivity umpolung. Several modes of organocatalyzed umpolung are showed as follows.

a)



N-Heterocyclic carbene-catalyzed umpolung

b)



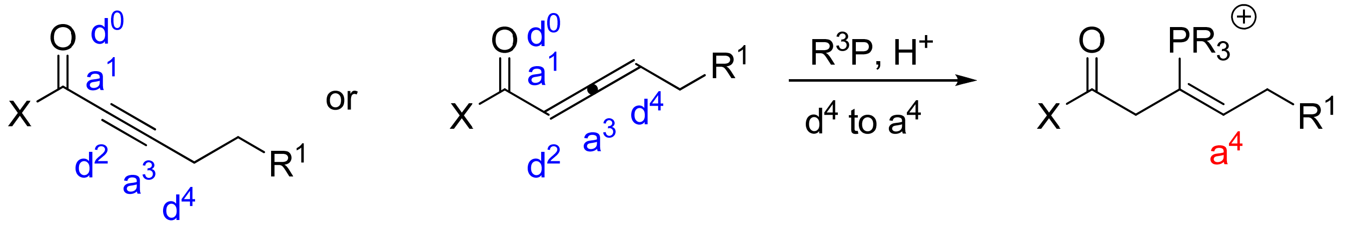
Metallophosphite-catalyzed umpolung

Glorius, F. et al. *Chem. Soc. Rev.* **2012**, *41*, 3511.

Introduction

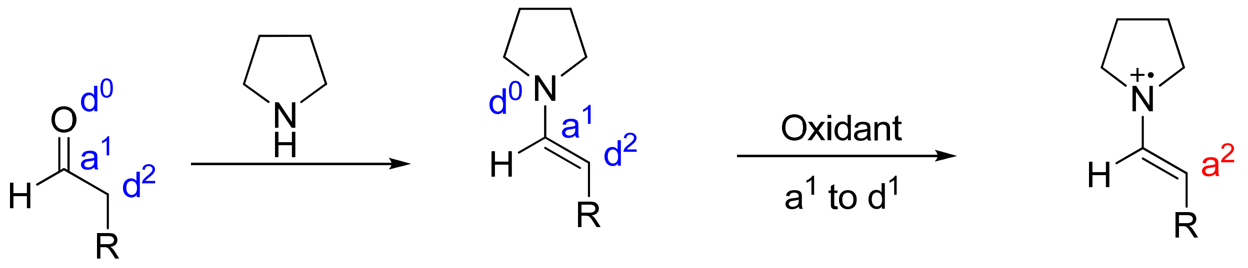
■ Indeed, the presence of lone pairs on heteroatoms, such as nitrogen and oxygen, offers them the possibility of donating electron. As a result, the atoms of the skeleton of the molecule are defined as being donor (d^{2n}) and acceptor (a^{2n+1}) positions. Any process to change this normal reactivity falls under the definition of reactivity umpolung. So a variety of organocatalysed umpolung are showed as follows.

c)



Phosphine-catalyzed umpolung

d)



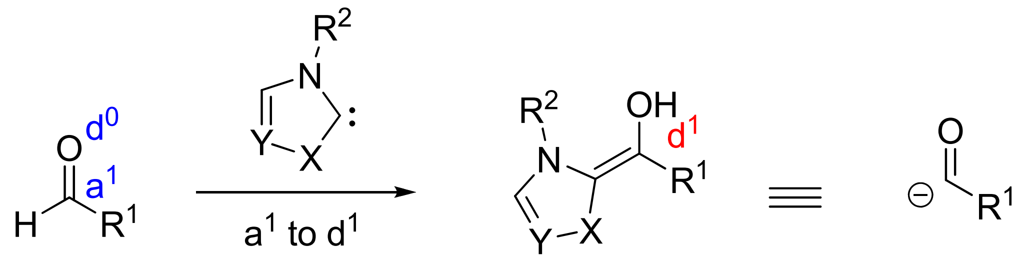
Secondary amine-catalyzed umpolung

Glorius, F. et al. *Chem. Soc. Rev.* **2012**, *41*, 3511.

Introduction

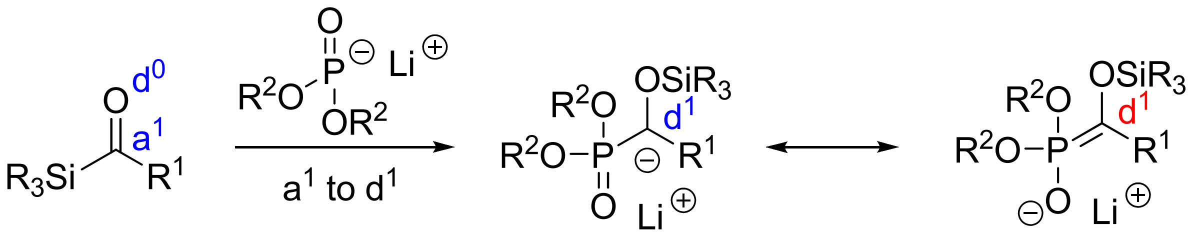
■ Indeed, the presence of lone pairs on heteroatoms, such as nitrogen and oxygen, offers them the possibility of donating electron. As a result, the atoms of the skeleton of the molecule are defined as being donor (d^{2n}) and acceptor (a^{2n+1}) positions. Any process to change this normal reactivity falls under the definition of reactivity umpolung. So a variety of organocatalysed umpolung are showed as follows.

a)



N-Heterocyclic carbene-catalyzed umpolung

b)



Metallophosphite-catalyzed umpolung

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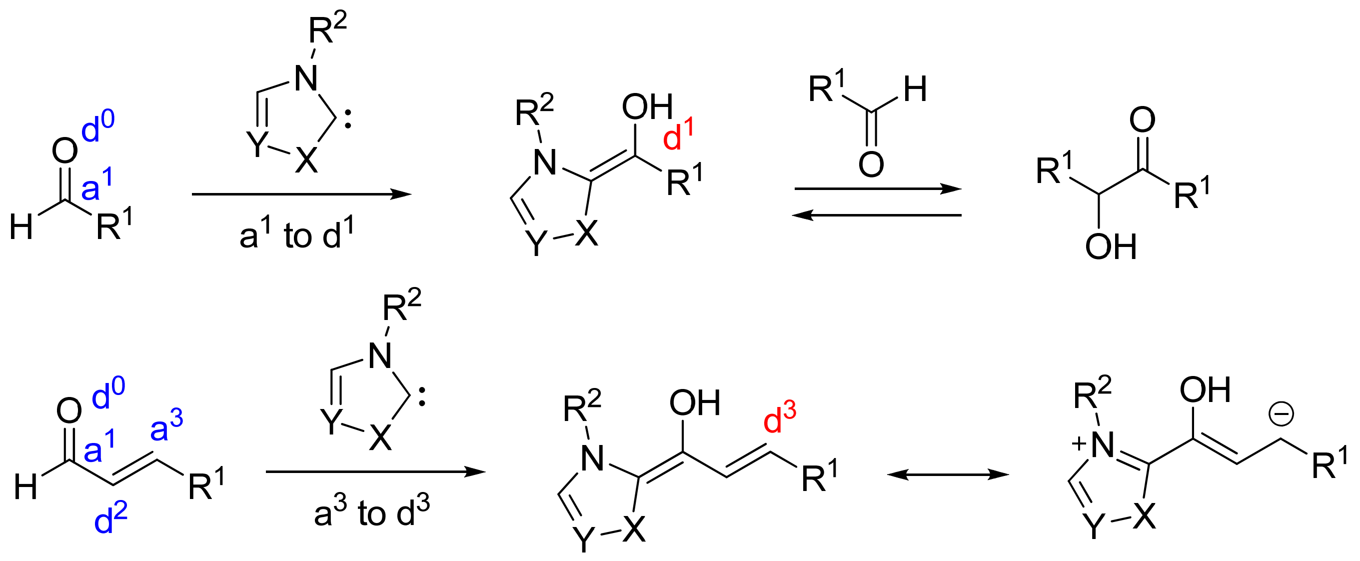
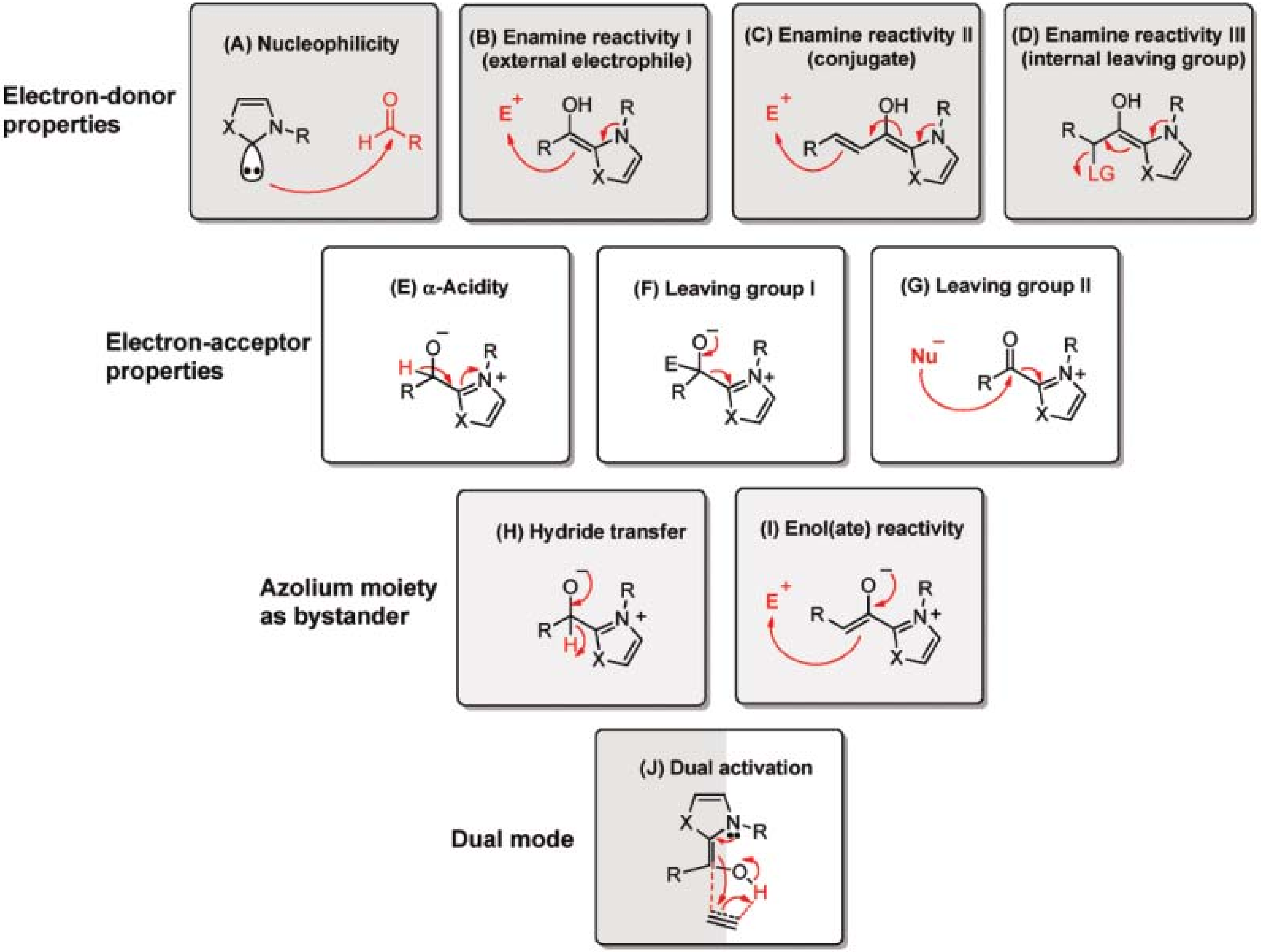


■ Part 2: *N*-Heterocyclic carbene-catalyzed umpolung: classical umpolung, conjugated umpolung, and umpolung of Michael acceptors

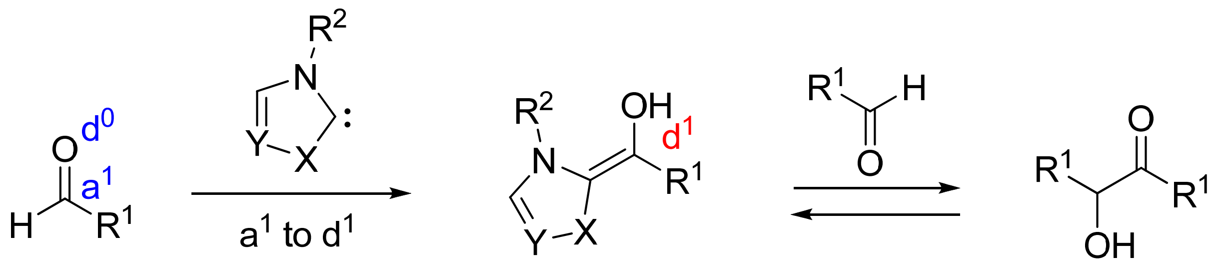
■ Part 3: Conclusion and outlook

Modes of action in NHC-organocatalysis



Glorius, F. *Acc. Chem. Res*. **2011**, *44*, 1182.

Major advantages



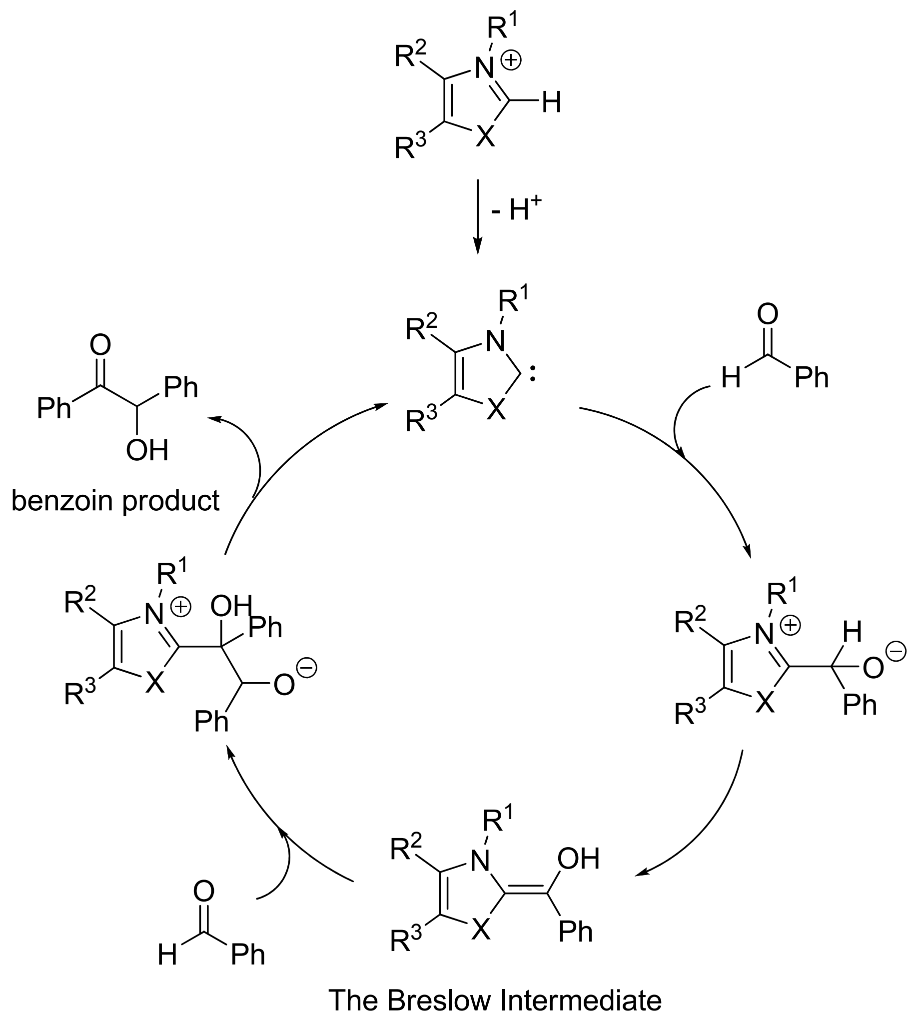
■ A lower toxicity.

■ The possibility to tune the reactivity of the catalyst by modifying its structure.

■ The opportunity to control the stereochemistry of the newly formed stereocenter by designing chiral NHCs.

Glorius, F. *Acc. Chem. Res*. **2011**, *44*, 1182.

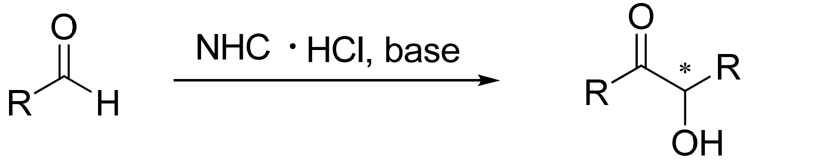
■ In 1943, Ukai and co-workers showed that a catalytic amount of thiazolium salts could achieve the benzoin reaction. Breslow made a mechanistic proposal for this transformation in 1958, which has since then provided the guideline for most developments in NHC-catalyzed reactions.

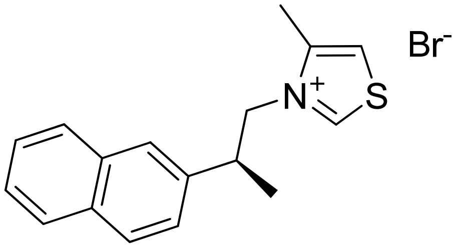


(a) Ukai, T. et al. *J. Pharm. Soc. Jpn*, **1943**, 63, 296. (b) Breslow, R. *J. Am. Chem. Soc*. **1958**, 80, 3719.

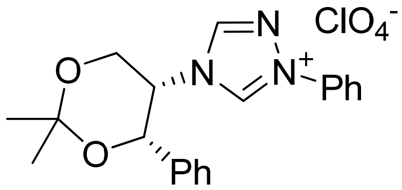
Classical umpolung

■ Selected enantioselective benzoin condensation:

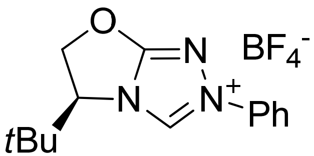




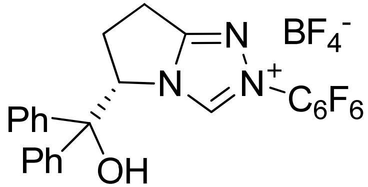
Sheehan et al.
up to 52% ee



Enders et al.
up to 86% ee



Enders et al.
up to 95% ee



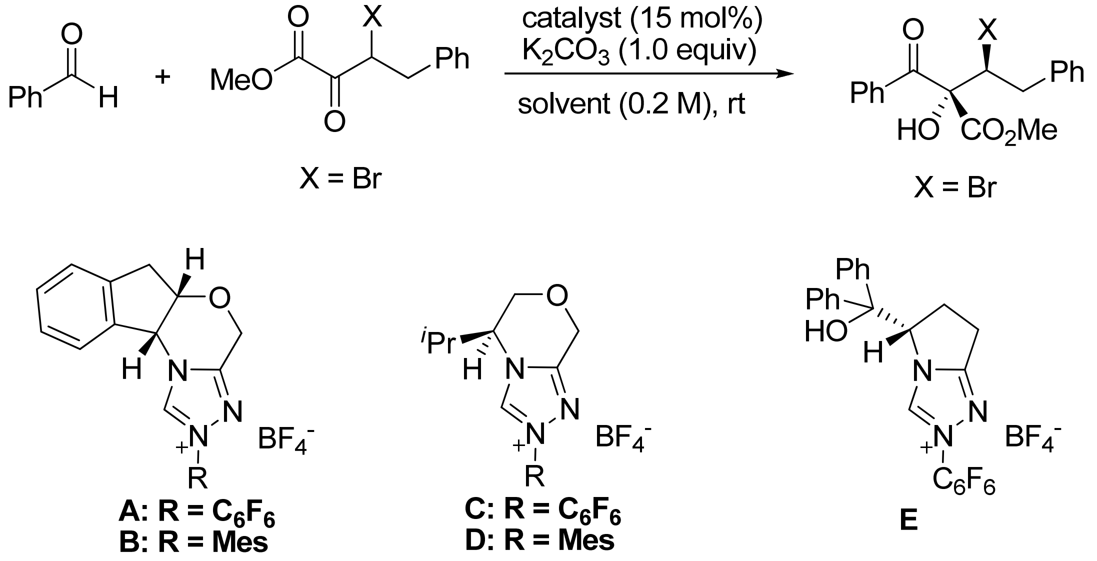
Zeitler et al.
up to >99% ee

Milestones on the way to NHC-catalyzed enantioselective benzoin condensation.

(a) Sheehan, J. C. et al. *J. Am. Chem. Soc*. 1**966**, *88,* 3666. (b) Enders, D. et al. *Helv. Chim. Acta*. **1996,** *79*, 1217. (c) Enders D. et al. *Angew. Chem. Int. Ed*. **2002**, *41*, 1743. (d) Connon, S. J. et al. *J. Org. Chem*. **2009**, *74*, 9214.

Classical umpolung

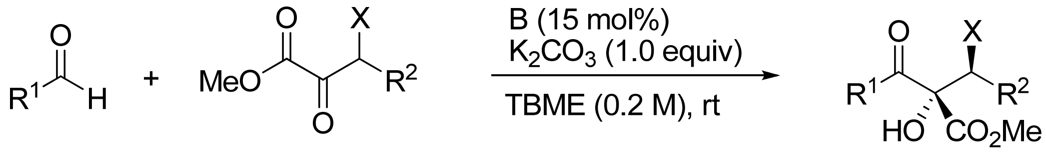
■ Selected enantioselective benzoin condensation: dynamic kinetic asymetric cross-benzoin addition of β-stereogenic α-keto esters

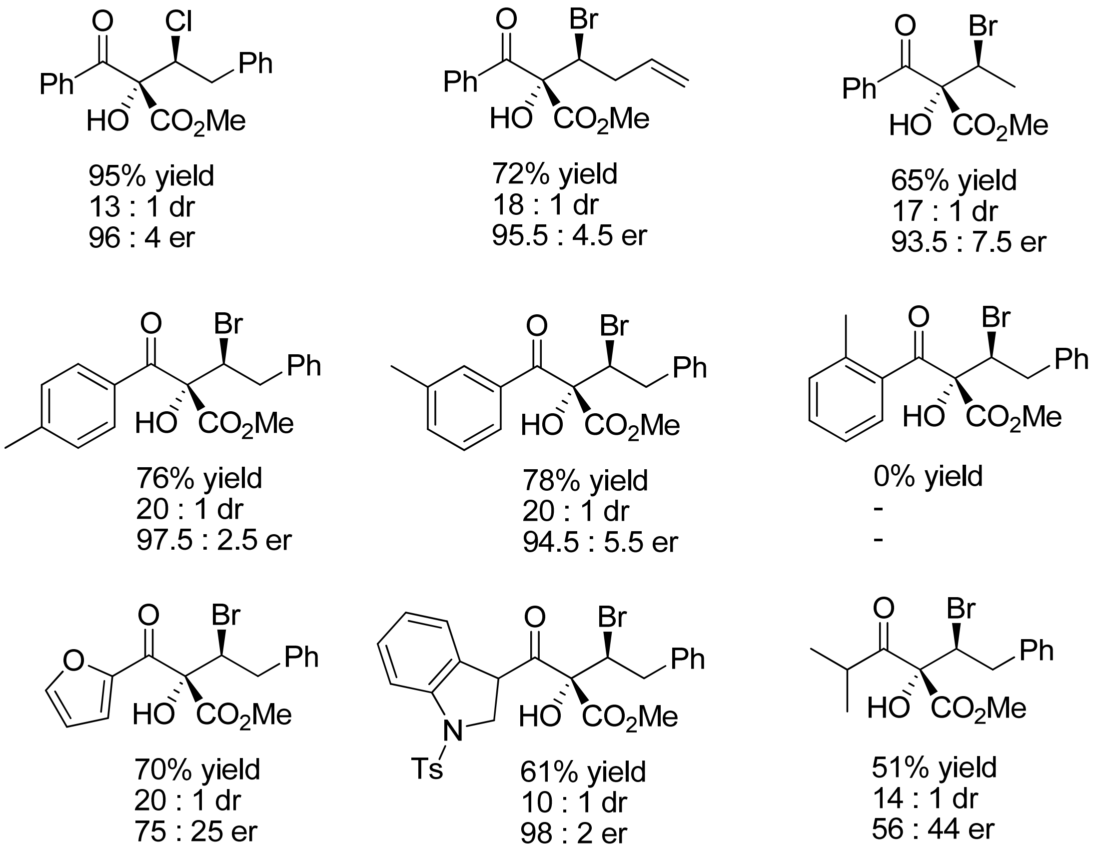


entry	catalyst	solvent	conv. (%)	dr	er
1	A	THF	<5	-	-
2	B	THF	>95	>20 : 1	96 : 4
3	C	THF	<5	-	-
4	D	THF	30	-	-
5	E	THF	<5	-	-
6	B	TBME	100	>20 : 1	96 : 4

Johnson, J.S.et al. *J. Am. Chem. Soc.* **2014**, *136*, 14698.

Classical umpolung





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Classical umpolung

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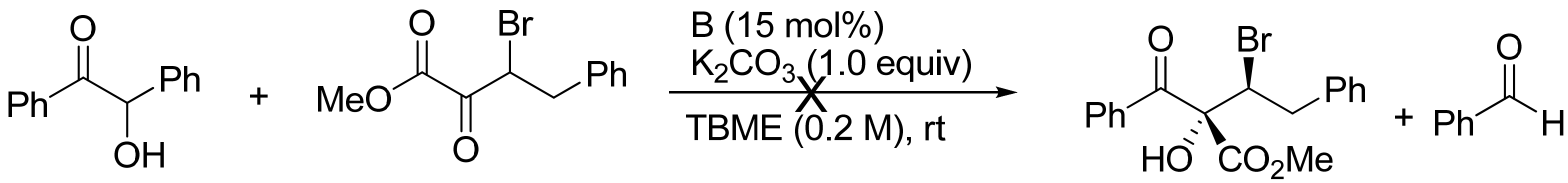
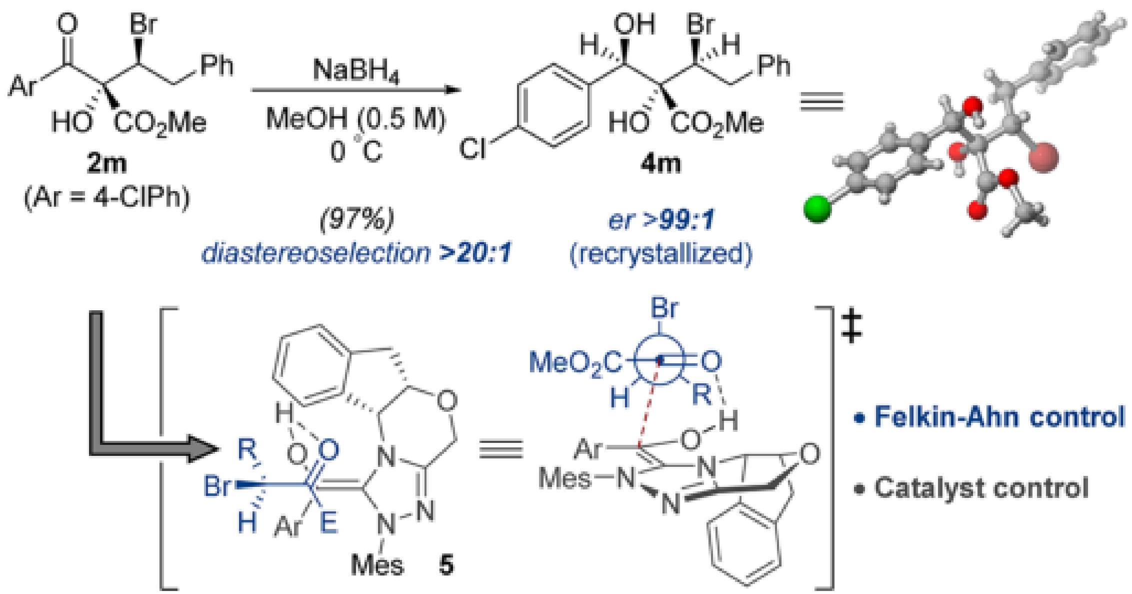
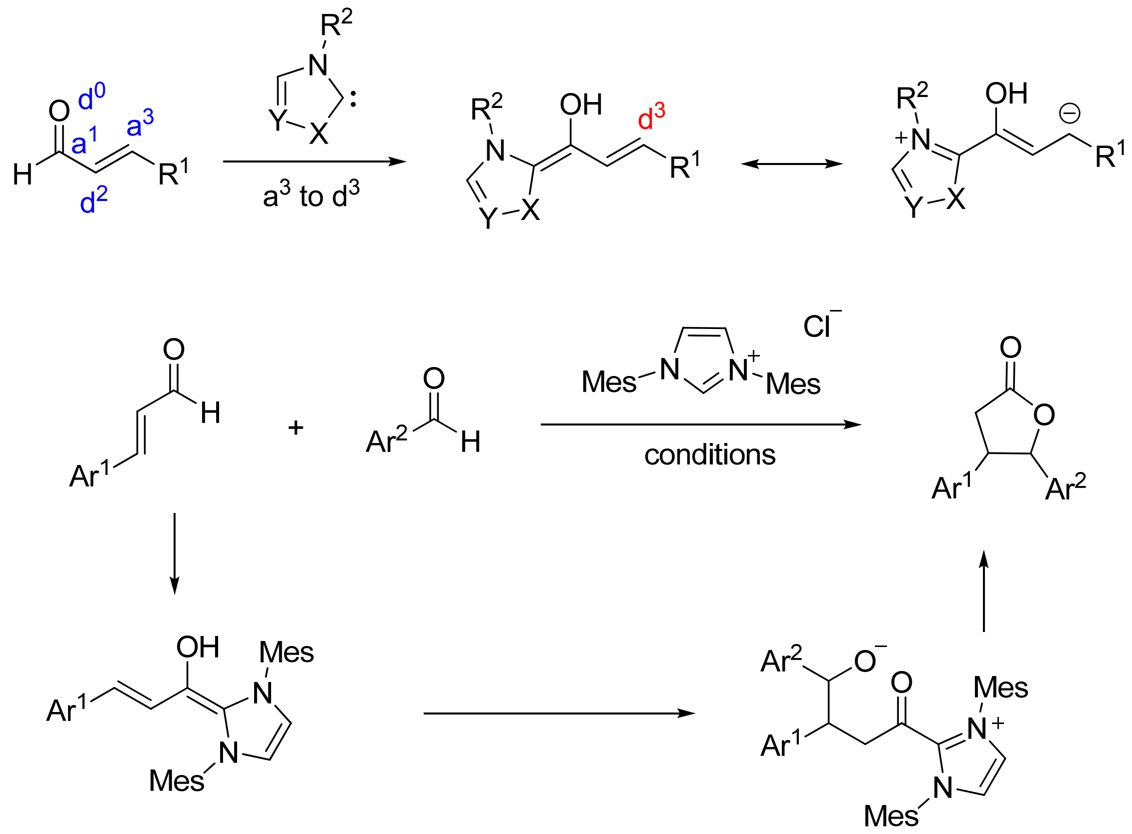




Johnson, J.S.et al. *J. Am. Chem. Soc*. **2014**, *136*, 14698.

Conjugated umpolung

■ Selected conjugated umpolung: formation of γ-butyrolactones

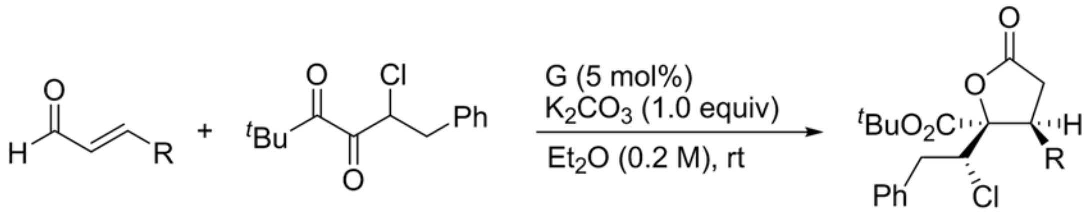


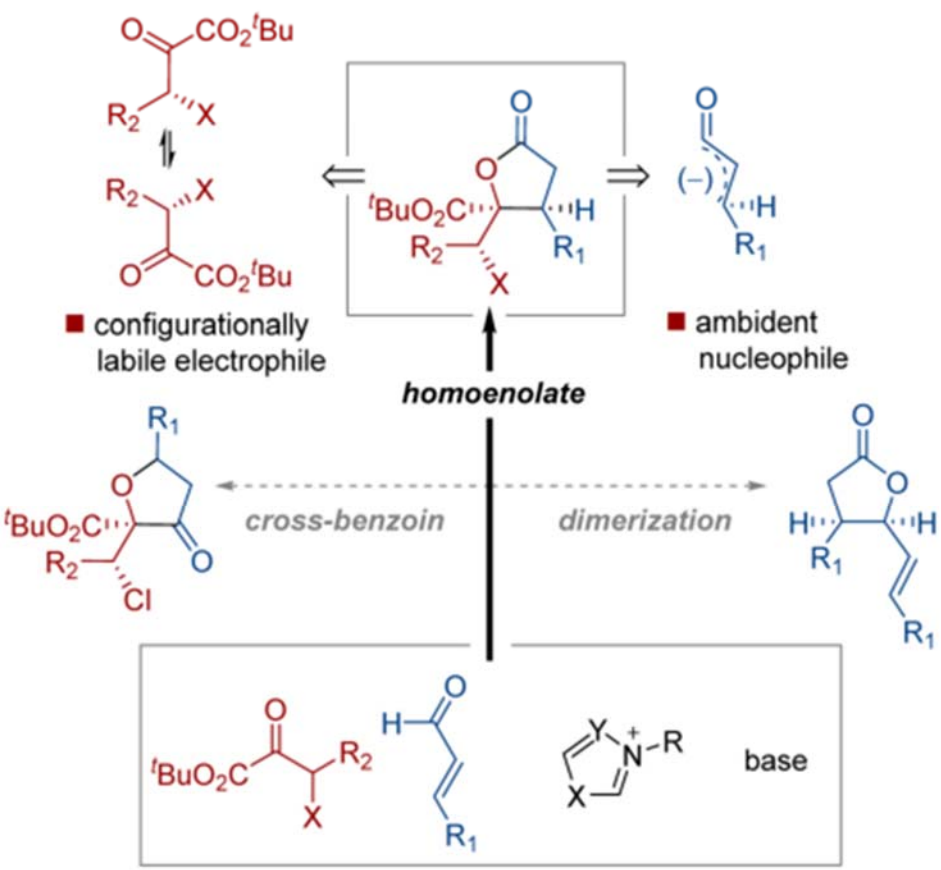
Bode et al.: IMes HCl (8 mol%), DBU, THF/^{t}BuOH
Glorius et al.: IMes HCl (5 mol%), ^{t}BuOK, THF

(a) Bode et al. *J. Am. Chem. Soc*. **2004**, *126*, 14370; (b) Glorius et al. *Angew. Chem. Int. Ed*. **2004**, *43*, 6205.

Conjugated umpolung

■ Selected conjugated umpolung: (3 + 2)-annulation

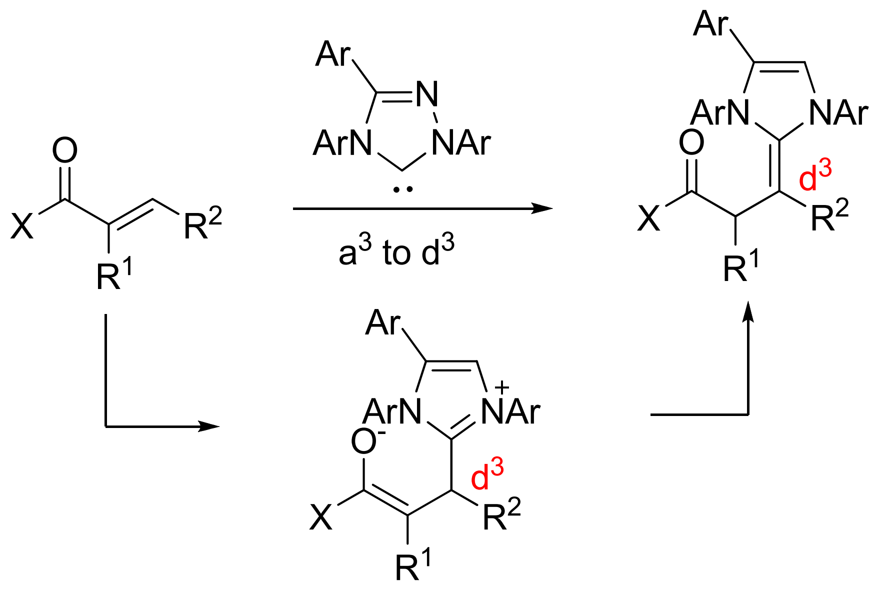




Johnson, J.S.et al. *J. Am. Chem. Soc*. **2015**, *137*, 122.

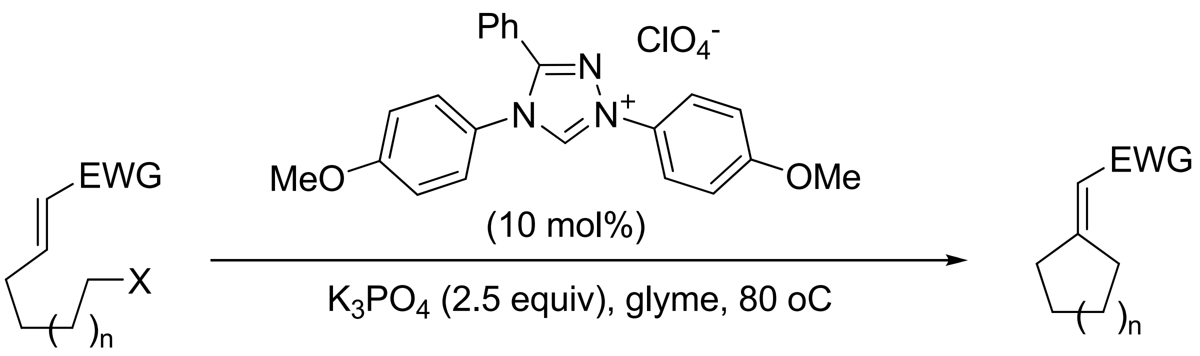
Umpolung of Michael acceptors

- Umpolung of Michael acceptors:

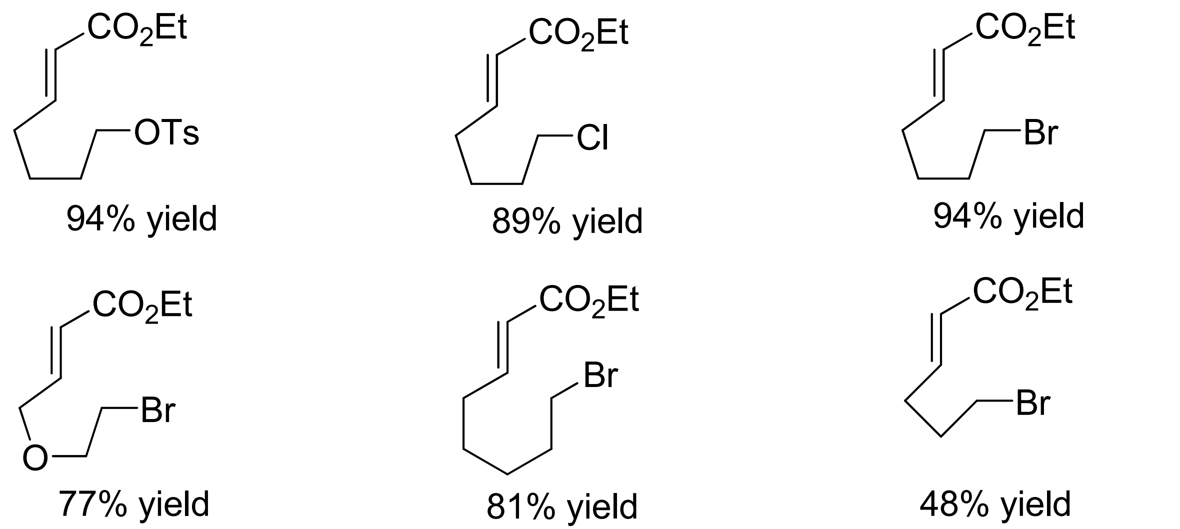


Umpolung of Michael acceptors

■ Selected umpolung of Michael acceptors (intramolecular):



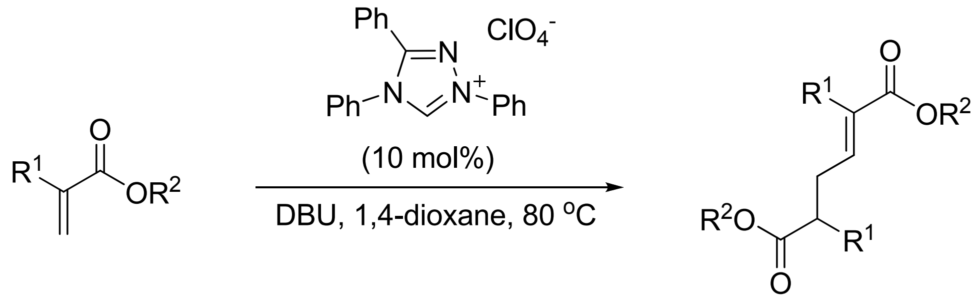
selected examples (starting materials):



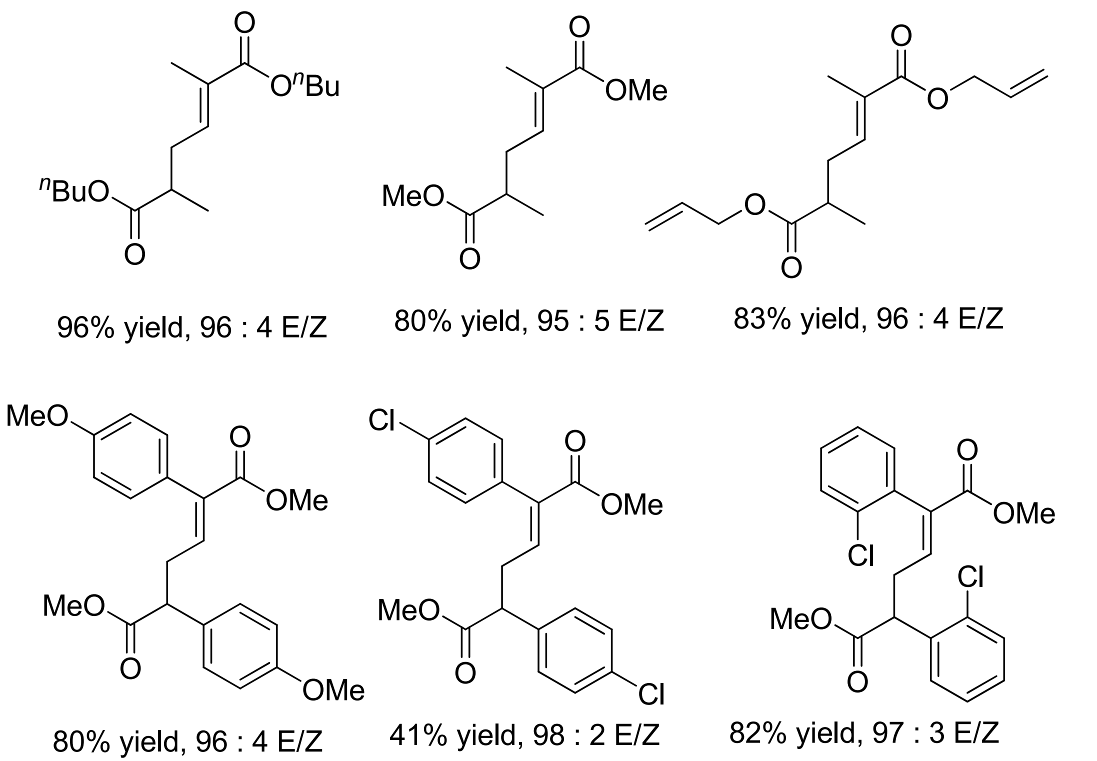
Fu, G.C. et al. *J. Am. Chem. Soc*. **2006**, *128*, 1472.

Umpolung of Michael acceptors

■ Selected umpolung of Michael acceptors (intermolecular):



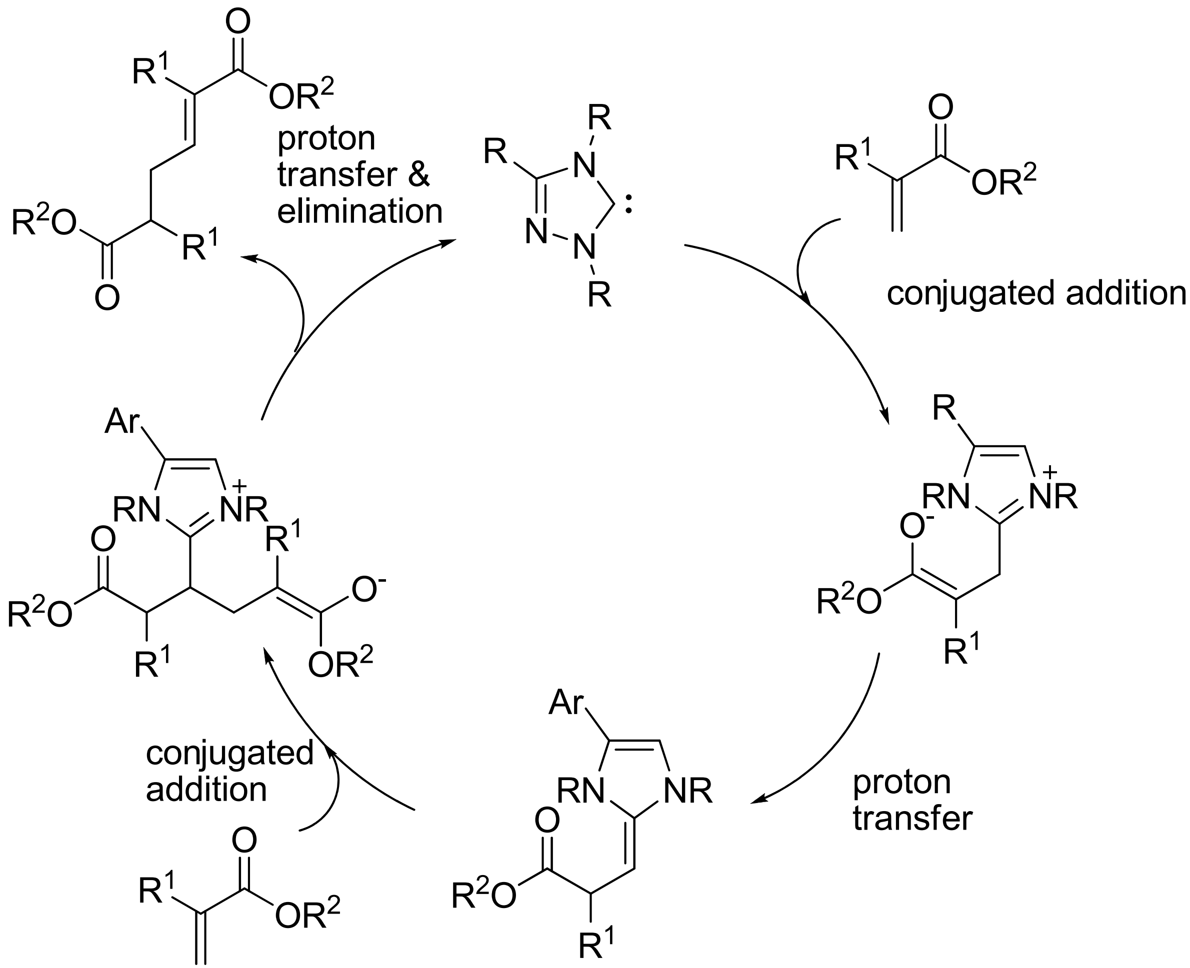
selected examples:



Glorius, F. et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 8412.

Umpolung of Michael acceptors

■ Selected umpolung of Michael acceptors :



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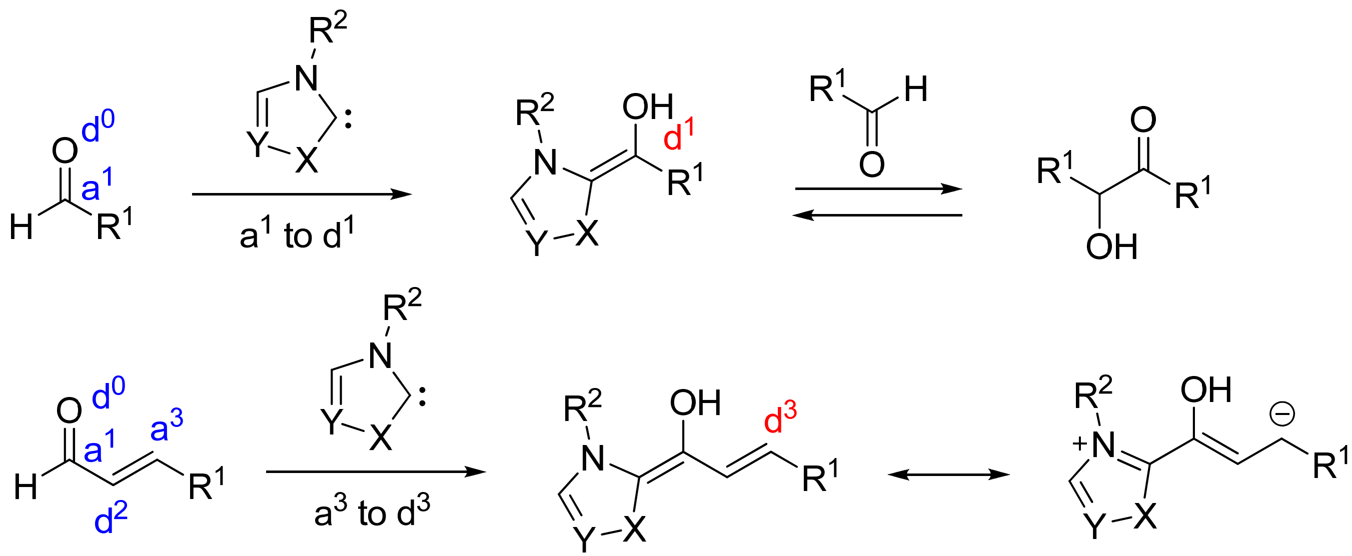

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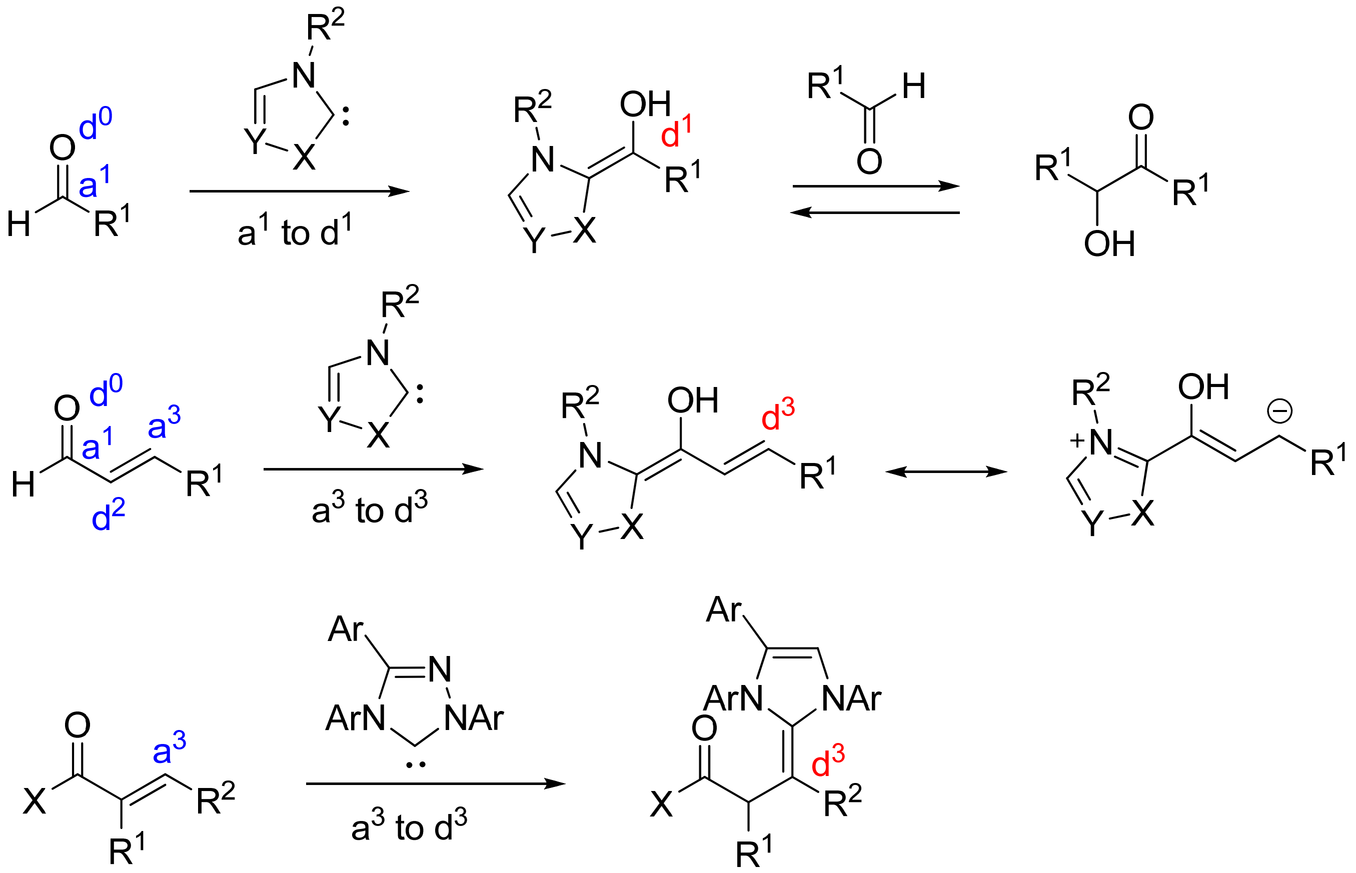
■ Part 3: Conclusion and outlook

Summary and Outlook



■ This report consists of the above three modes of umpolung catalyzed by NHCs: classical umpolung, conjugated umpolung, and umpolung of Michael acceptors.

■ Although a large variety of reactions have been reported, the mechanism of these reactions need to be explored deeply, especially those reactions employing more sophisticated NHCs.

Reference

(1) Wittig, G. et al*. Chem. Ber*. **1951***, 84*, 627.
(2) Seebach, D. *Angew. Chem. Int. Ed*. **1965**, *4*, 1075.
(3) Seebach, D. *Angew. Chem. Int. Ed*. **1965**, *4*, 1077.
(4) Glorius, F. et al. *Chem. Soc. Rev.* **2012**, *41*, 3511.
(5) Glorius, F. *Acc. Chem. Res*. **2011**, *44*, 1182.
(6) Ukai, T. et al. *J. Pharm. Soc. Jpn*, **1943**, 63, 296.
(7) Breslow, R. *J. Am. Chem. Soc*. **1958**, 80, 3719.
(8) Sheehan, J. C. et al. *J. Am. Chem. Soc*. 1**966**, *88,* 3666.
(9) Enders, D. et al. *Helv. Chim. Acta*. **1996,** *79*, 1217.
(10) Enders D. et al. *Angew. Chem. Int. Ed*. **2002**, *41*, 1743.
(11) Connon, S. J. et al. *J. Org. Chem*. **2009**, *74*, 9214.
(12)Johnson, J.S.et al. *J. Am. Chem. Soc*. **2014**, *136*, 14698.
(13) Bode et al. *J. Am. Chem. Soc*. **2004**, *126*, 14370.
(14) Glorius et al. *Angew. Chem. Int. Ed*. **2004**, *43*, 6205.
(15) Johnson, J.S.et al. *J. Am. Chem. Soc*. **2015**, *137*, 122.
(16) Fu, G.C. et al. *J. Am. Chem. Soc*. **2006**, *128*, 1472.
(17) Glorius, F. et al. Angew. Chem., Int. Ed. **2011**, *50*, 8412.

Thanks for your attention!