Bibliography :
Organocatalytic Formation of Quaternary Stereocenters

Alexandra, 04/03/10

Introduction:

Synthesis of Quaternary Stereocenters : one of the most challenging tasks in organic synthesis

Steric encumbrance ➔ Relatively harsh conditions

Limited combinations of nucleophiles and electrophiles

New organocatalyzed reactions ➔ Excellent control of stereoselectivity

Mild reaction conditions

Simple organic molecules

Avoid the use of transition metals

Bella M.; Gasperi T. *Synthesis* 2009, *10*, 1583-1614

General Considerations and limitations:

Limitations in its substrate scope for every chemical reaction

Reactions forming quaternary carbon stereocenters presents additional limitations :

Reactions conditions quite unusual (high temperatures and concentration, long time reaction)

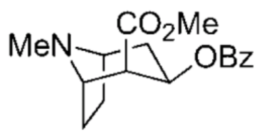
➡ affected enantioselection

Strong limitations in the « partners combination »

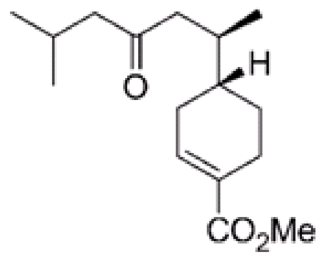
➡ loss of stereocontrol

➡ major issue with organocatalyzed reactions

Despite all these limitations, organocatalytic formation of quaternary stereocenters is a powerful tool.



(+)-cocaine



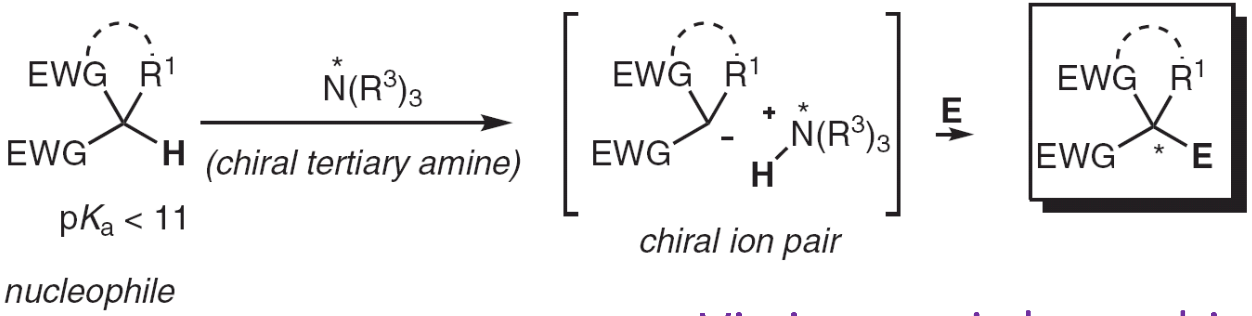
(+)-juvabione

Marcia de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* ***2007, 2575.***

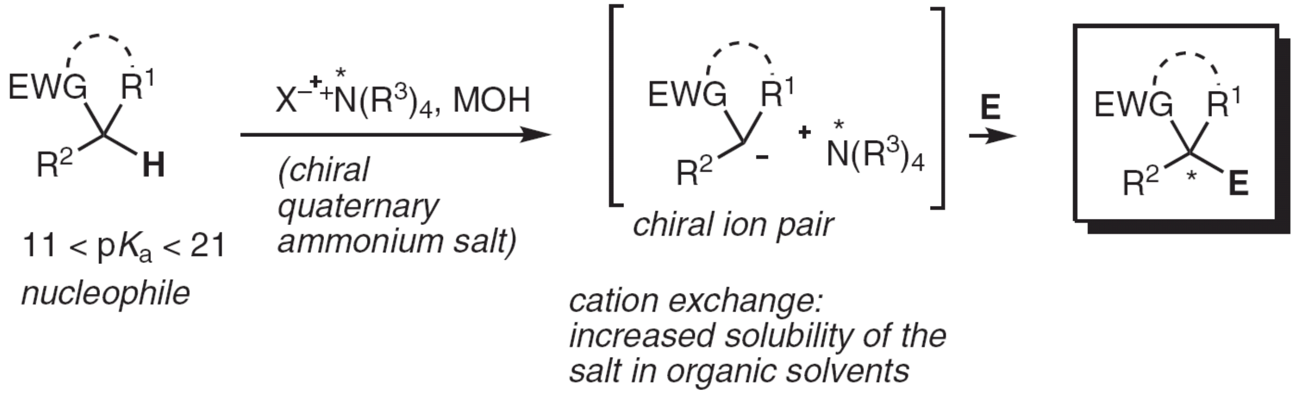
Mechanistic Considerations :

Activation of the nucleophile

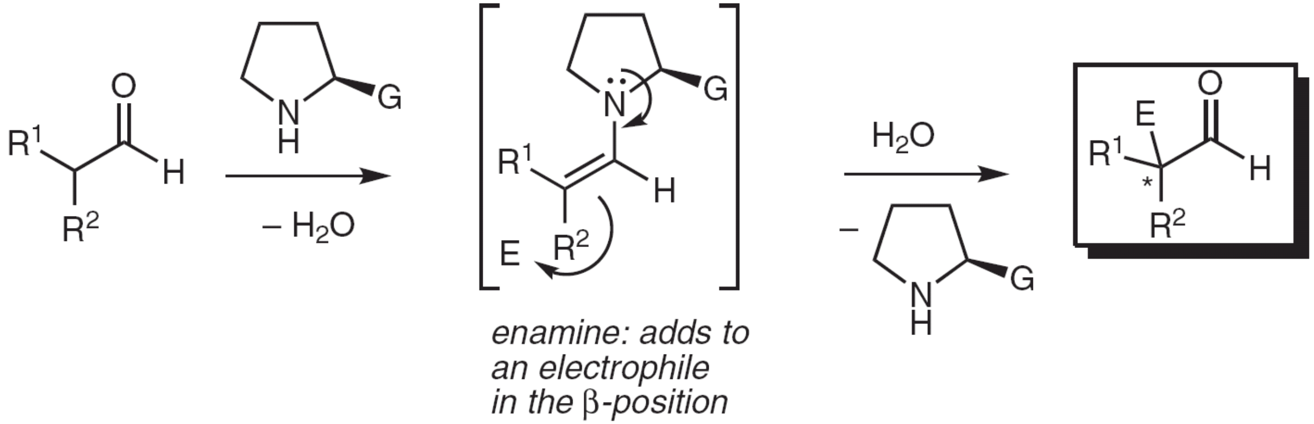
Via tertiary amine



Via inorganic base-chiral quaternary ammonium salt

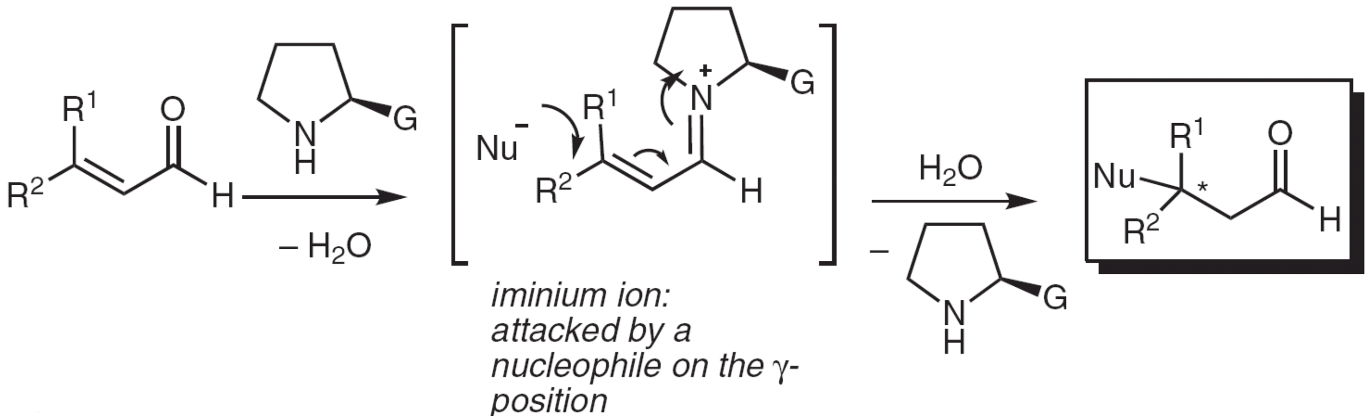


Via enamine

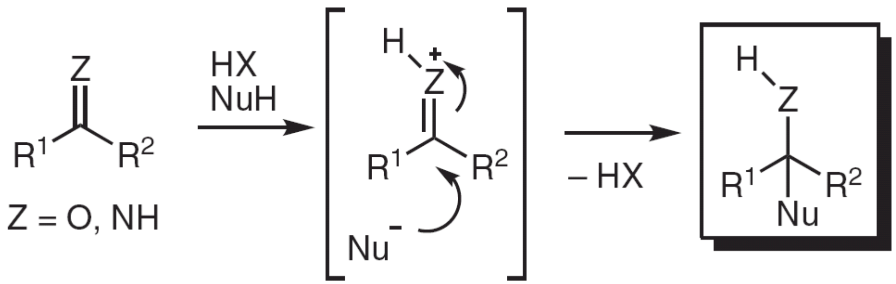


Activation of the electrophile

Via iminium ion



Via Brønsted acid

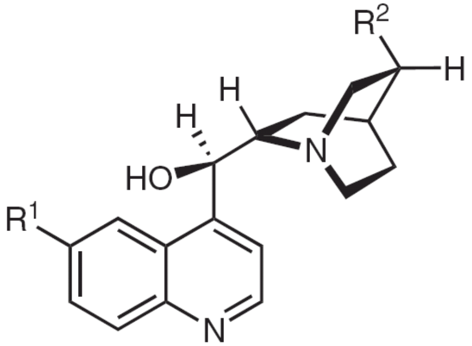


Via hererocyclic carbenes : Umpolung concept

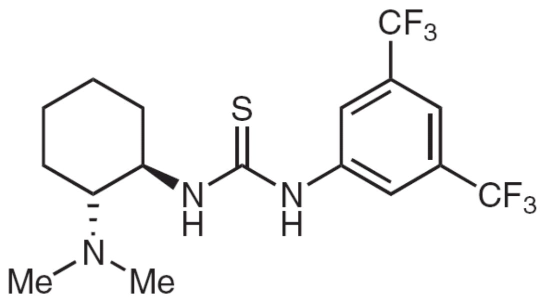
Via mixed activation: use of catalysts combinations

Addition to Carbon-Carbon Multiple Bonds:

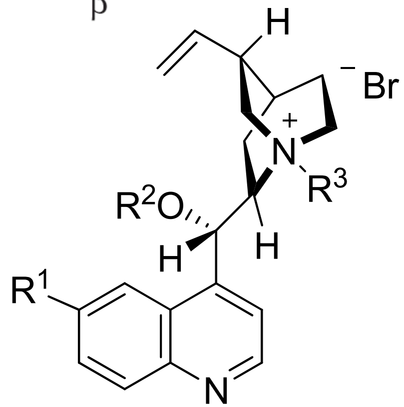
« Classic » conjugate addition : Formation of a Single Stereocenter or Multiple Stereocenters



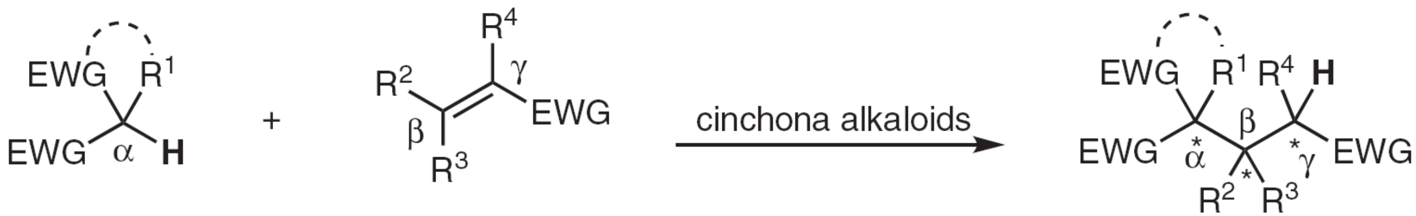
2 : Tertiary amines cinchona alkaloids



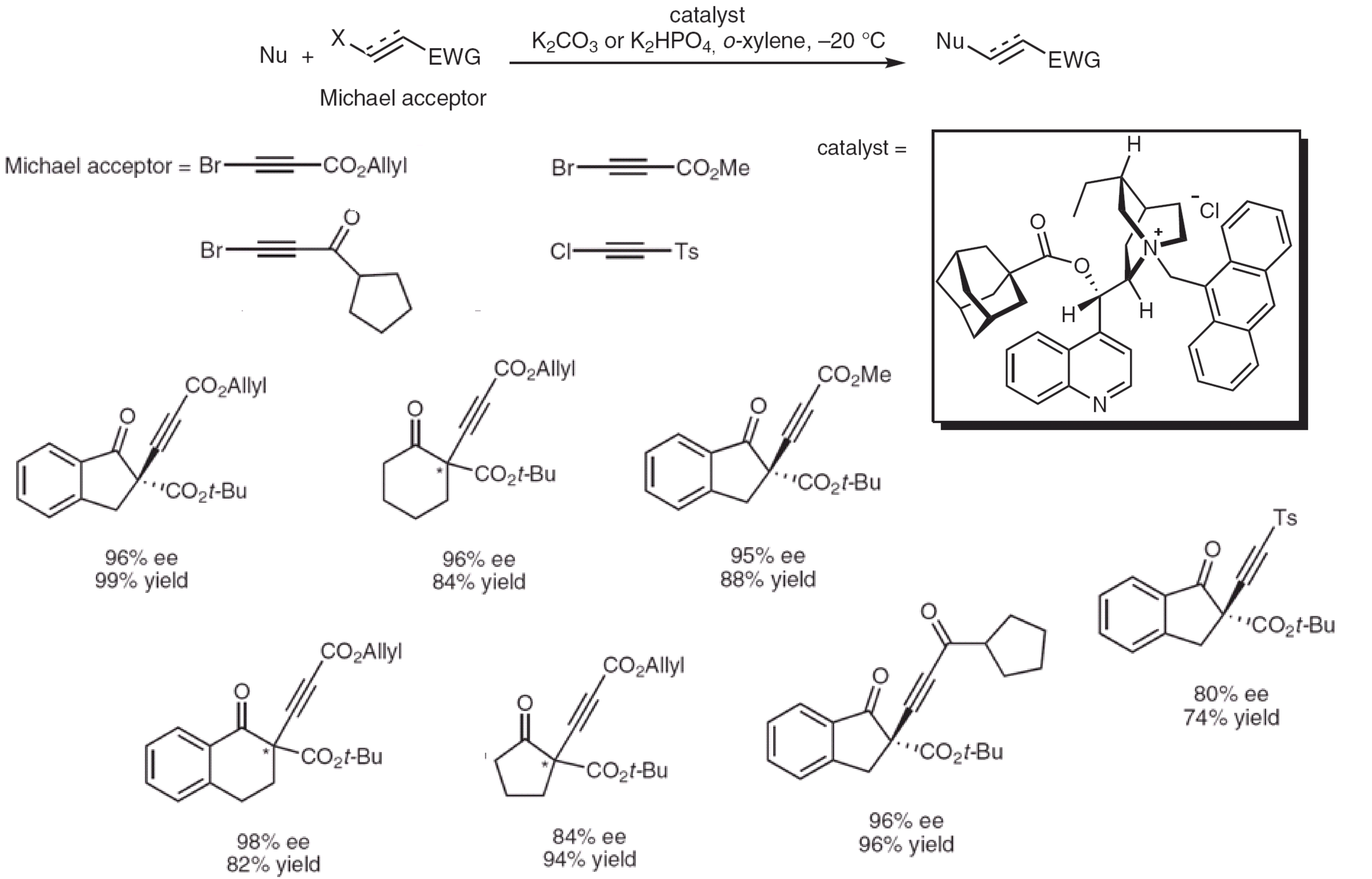
4 : Chiral thioureas



3 : Quaternary ammonium salts cinchona alkaloids



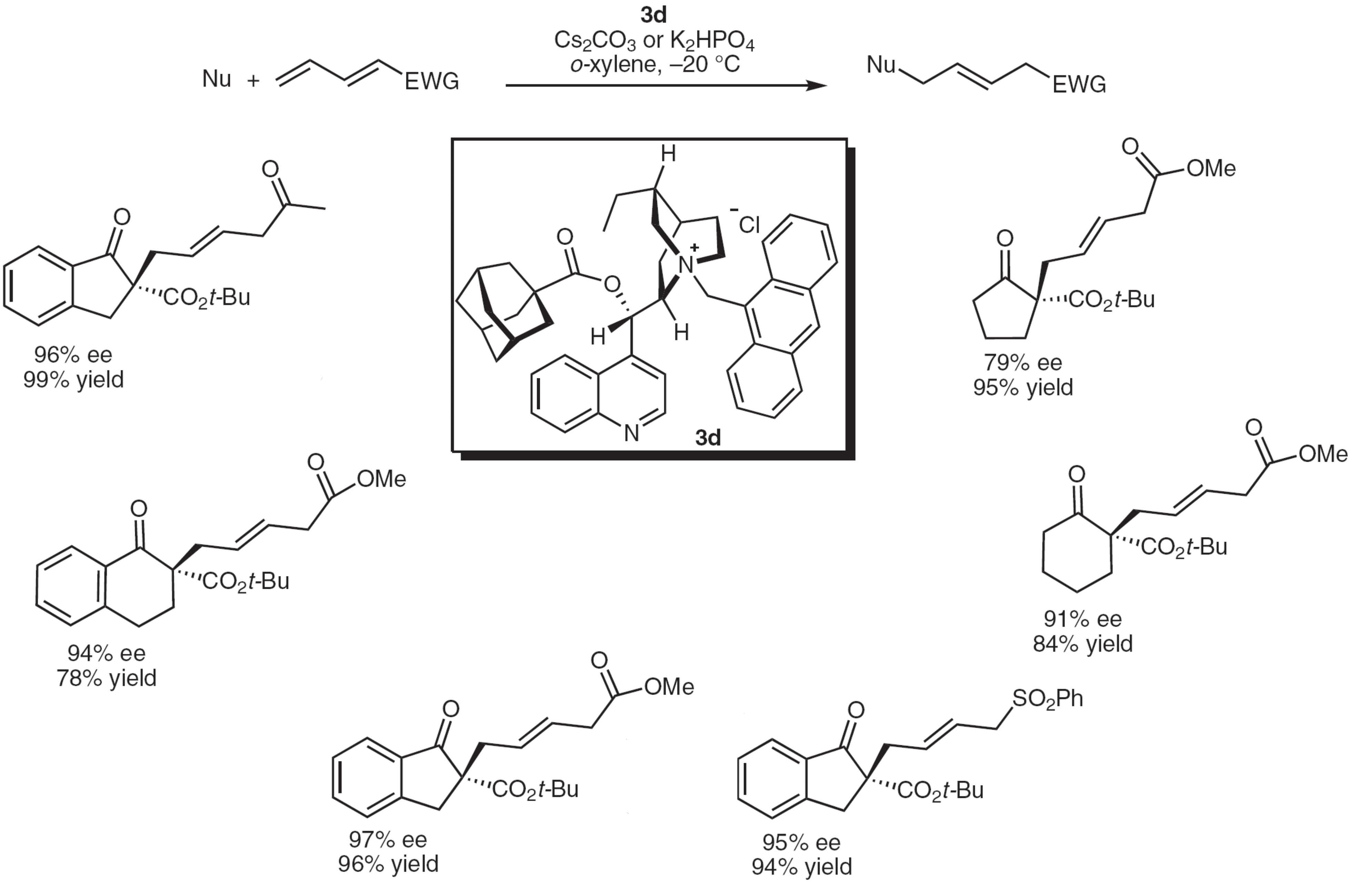
Addition-Elimination Conjugate Addition



Poulsen, T. B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007, 129, 441.**

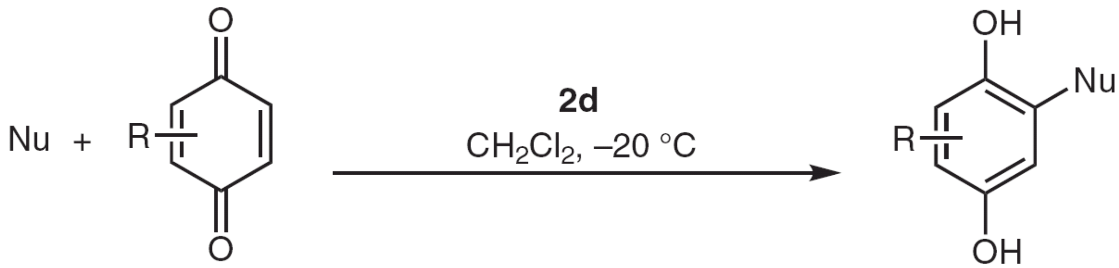
Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006, 45, 6551.**

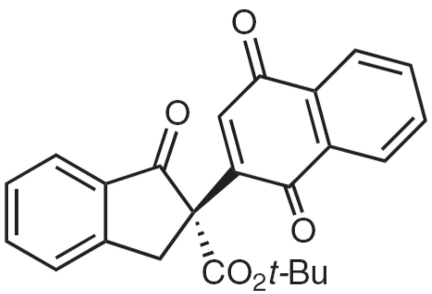
1,6-Conjugate Addition



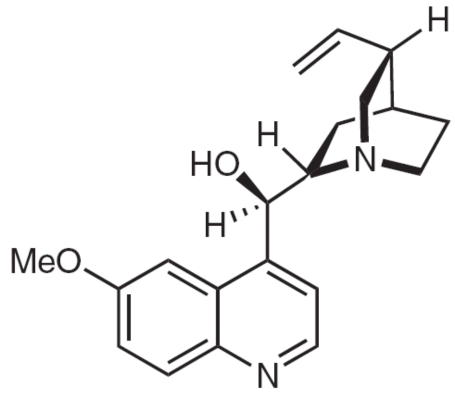
Bernardi, L.; Cantarero, J. L.; Niess, B.; Jørgensen, K. A. *J. Am. Chem. Soc.* ***2007, 129, 5772.***

Conjugate Addition-Aromatization

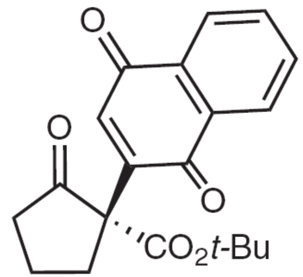




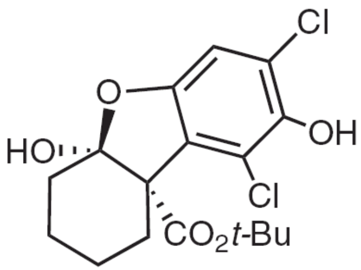
94% ee
76% yield



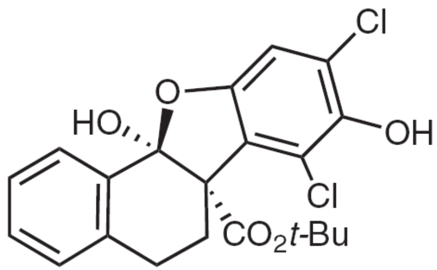
2d



96% ee
59% yield



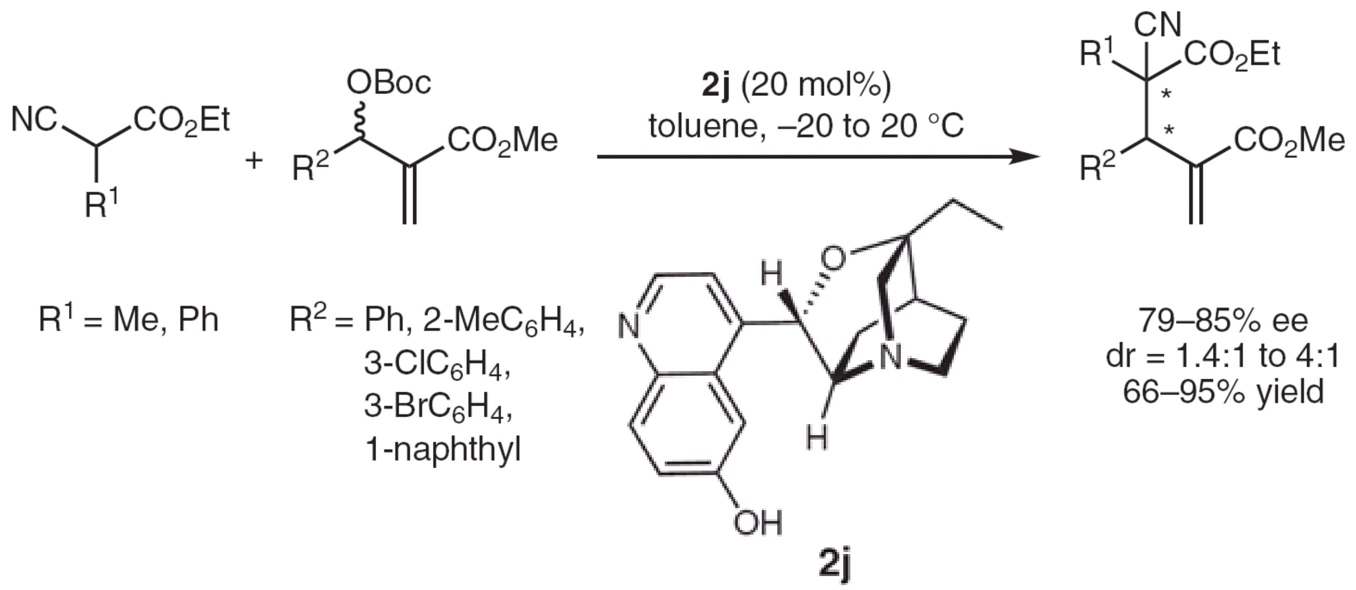
90% ee
66% yield



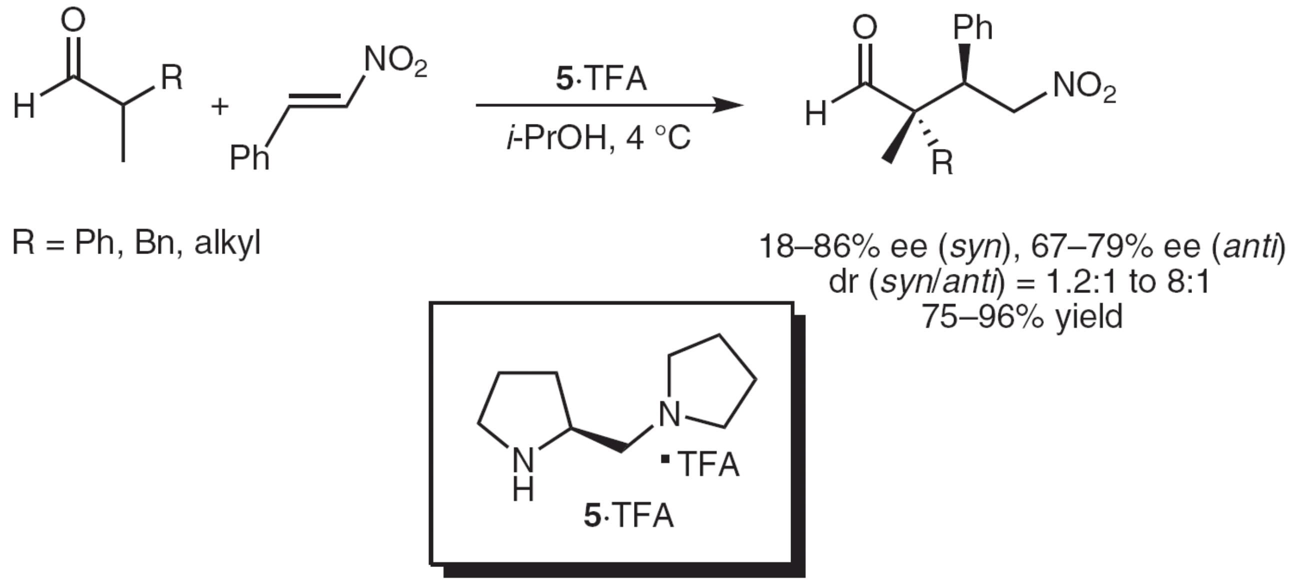
94% ee
88% yield

(a) Aléman, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* ***2007, 46, 5520.***
(b) Aléman, J.; Richter, B.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* ***2007, 46, 5515.***

Miscellaneous Conjugate Addition



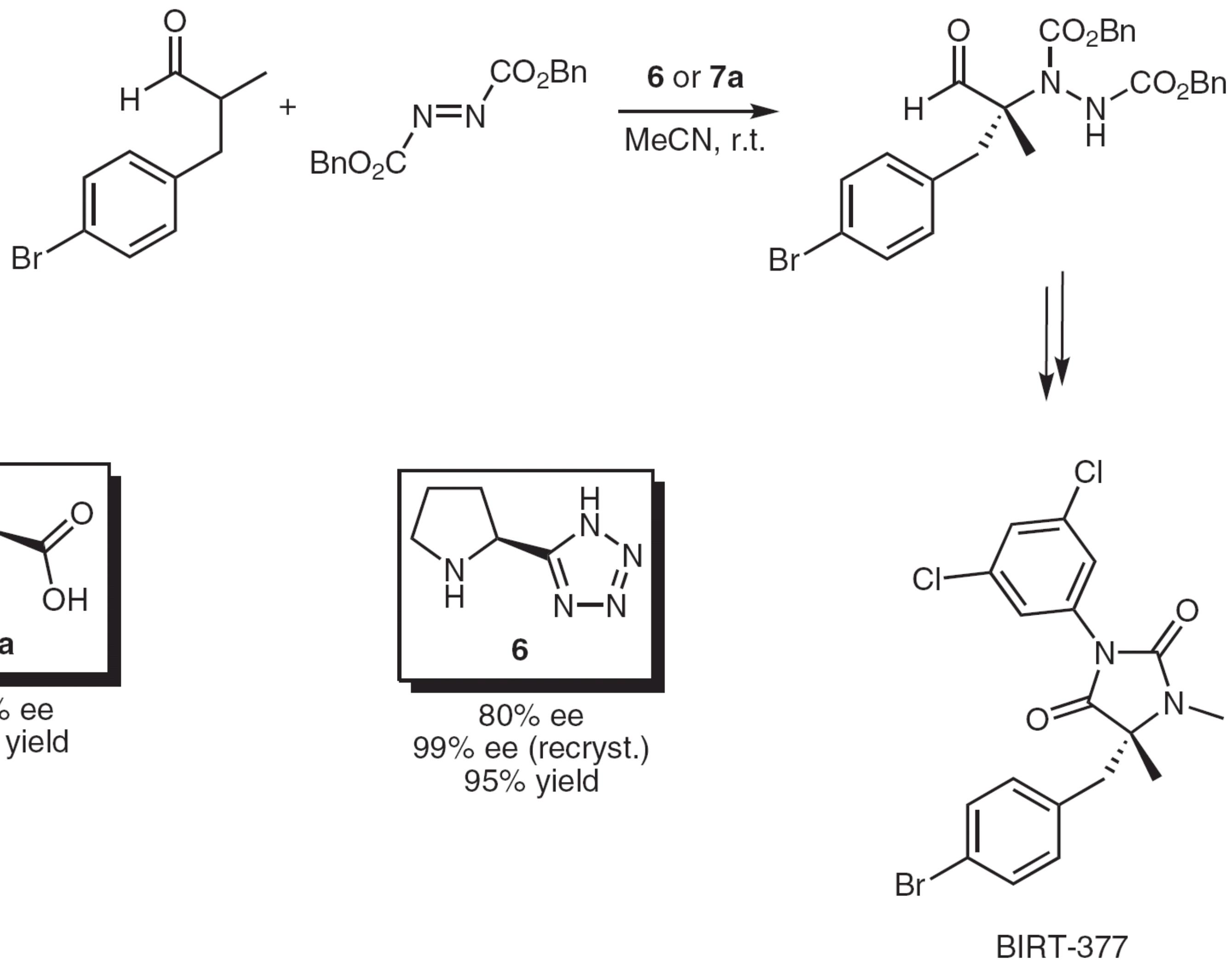
Conjugate Addition via Enamine Catalysis



van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maareseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2007, *349*, 281.**
Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. III *Org. Lett.* ***2004*, *6*, 2527.**

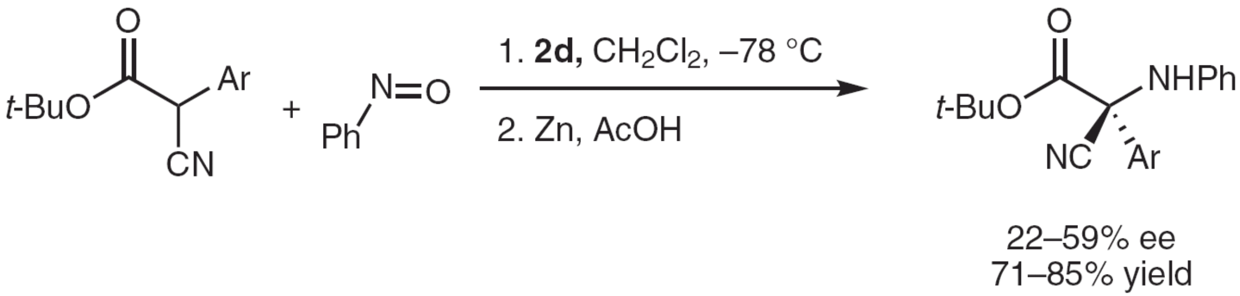
Addition to N-X Double Bonds:

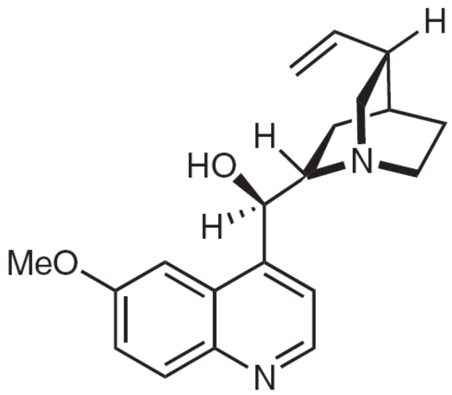
Addition to Nitrogen-Nitrogen Double Bonds



Chowdari, N. S.; Barbas, C. F. III *Org. Lett.* ***2005, 7, 867.***

Addition to Nitrogen-Oxygen Double Bonds



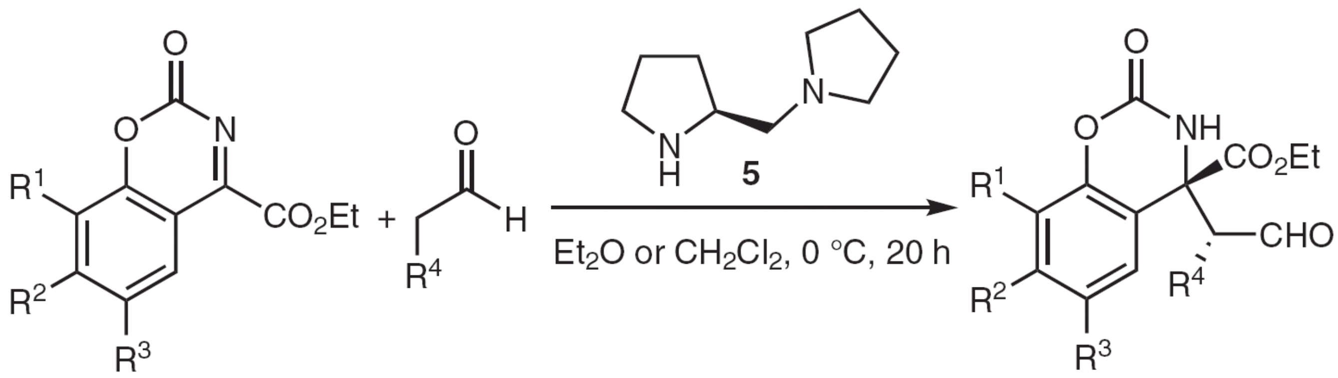


2d

Lopez-Cantarero, J.; Cid, M. B.; Poulsen, T. B.; Bella, M.; Ruano, J. L. G.; Jørgensen, K. A. *J. Org. Chem.* ***2007, 72,*** 7062.

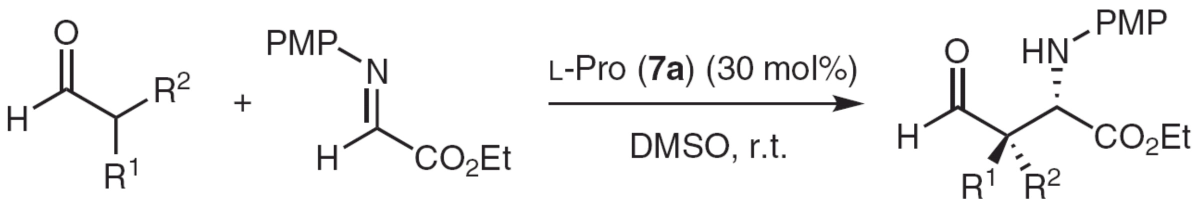
Addition to Carbon-Nitrogen Double Bonds

Mannich Reaction



R^1, R^2 = H, OMe, -$(CH_2)_4$-
R^3 = H, Me, OMe, F
R^4 = H, Me, *i*-Pr, Allyl

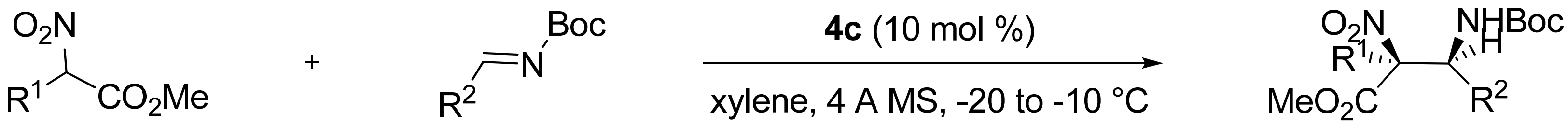
83–98% ee
dr = 4:1 to 20:1
72–99% yield



R^1 = Me
R^2 = Ph, thienyl,
4-MeC_6H_4,
4-(*i*-Pr)$C_6H_4CH_2$

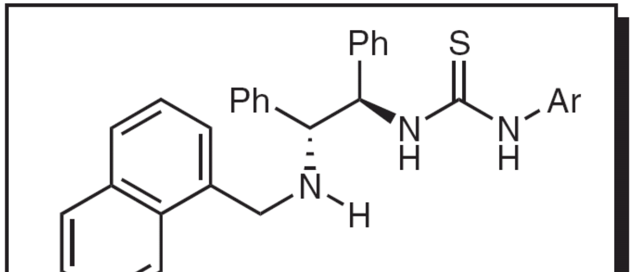
syn/*anti* 60:40 to 96:4
86–99% ee (*syn*)
5–64% ee (*anti*)
66–99% yield

Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* ***2004, 43, 4476.***
Chowdary, N. S.; Suri, T. J.; Barbas, C. F. III *Org. Lett.* **2004, *6, 2507.***

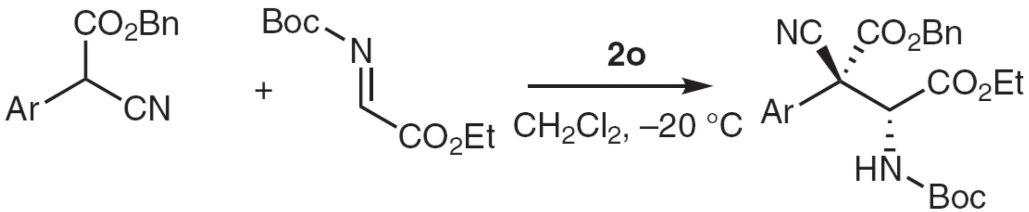


R^1 = Me, Bn, Ph, *i*-Pr
R^2 = Ph, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-MeC_6H_4, 2-thienyl, 3-Mec_6H_4, 2-furyl

91-96 % ee
dr = 3.8:1 to 17.2 : 1
38-86 % yield

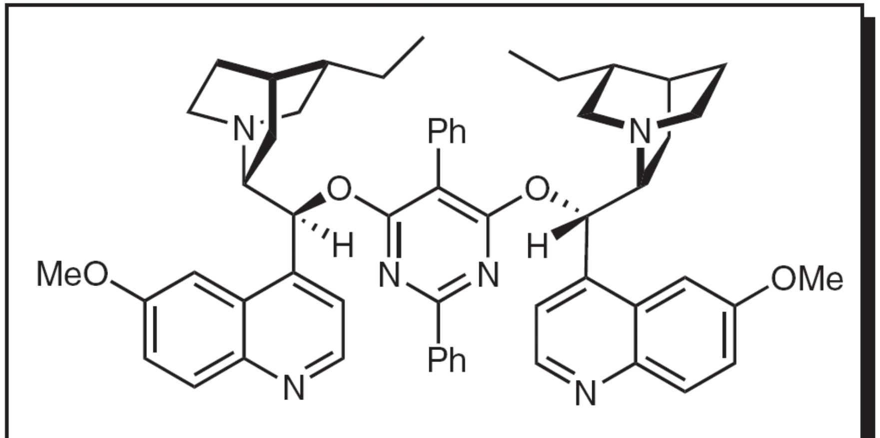


4c



Ar = Ph, 2-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl

91–97% ee
dr = 80:20 to 88:12
95–99% yield



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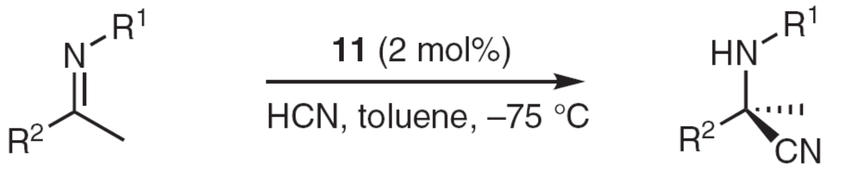
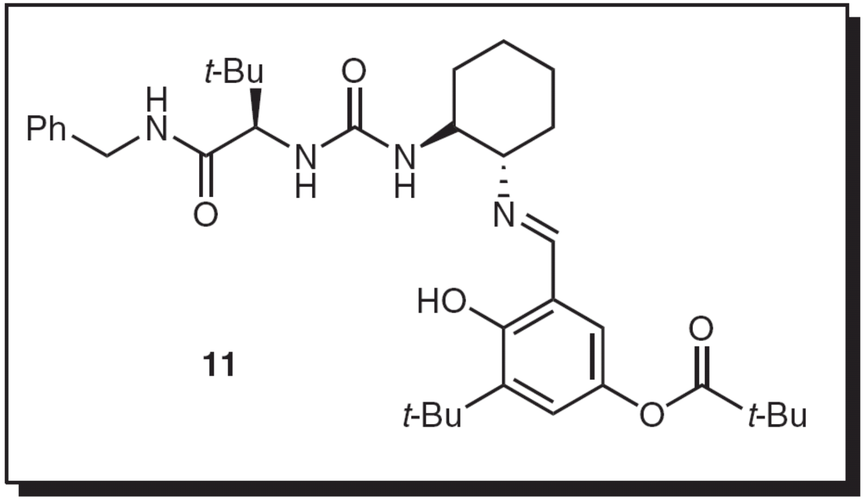
Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem. Eur. J.* ***2008, 14, 8094.***
Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* ***2005, 44, 2896.***

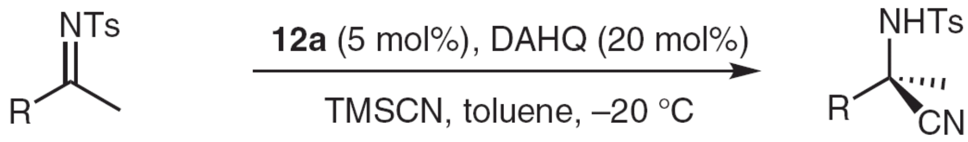
Strecker Reaction



R^1 = Ph, Allyl
R^2 = Ar, *t*-Bu

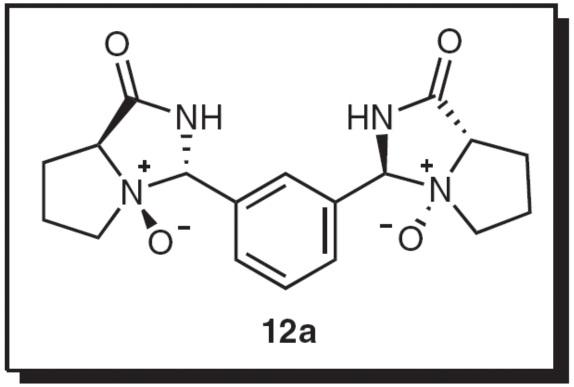
42–97% ee
45–99% yield





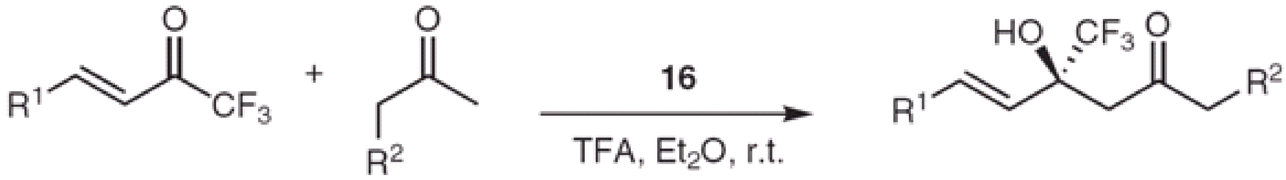
R = Ph, aryl, 2-thienyl,
c-Hex, *t*-Bu

61–91% ee
82–99% yield



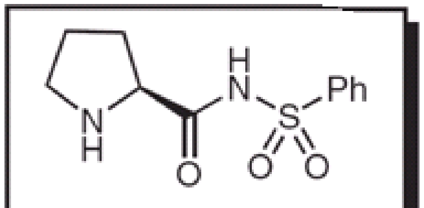
(a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* ***2000, 2, 867.***(b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* ***2002, 124,*** 10012.
(a) Huang, X.; Huang, J.; Wen, Y.; Feng, X. *Adv. Synth. Catal.* ***2006, 348, 2579. (b) Hou, Z.; Wang, J.; Liu, X.;*** Feng, X. *Chem. Eur. J.* ***2008, 14, 4484.***

Aldol and Related Reactions:



R^1 = Ph, 5-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4,
4-$MeOC_6H_4$, 4-MeC_6H_4, 1-naphthyl,
1-furyl, PhC≡C, PhCH=CH, $Ph(CH_2)_3$
R^2 = H, Me, Et

81–95% ee
76–99% yield



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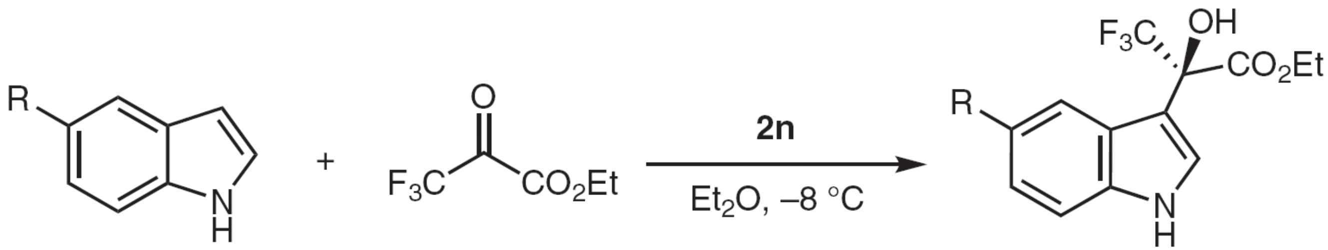
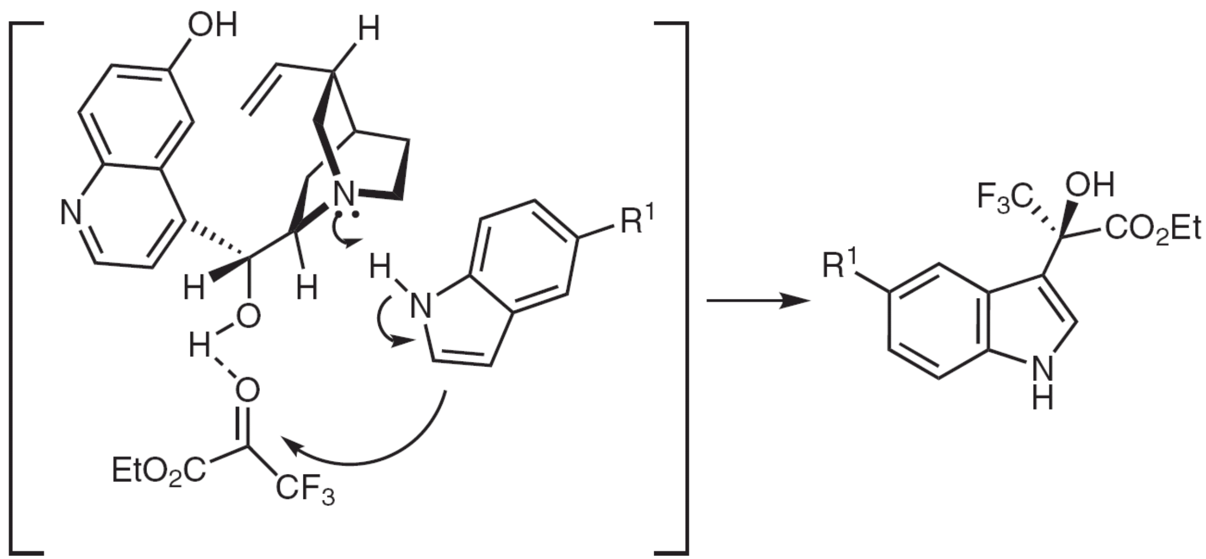
Wang, X. J.; Zhao, Y.; Liu, J.-T. *Org. Lett.* ***2007, 9, 1343.***

Aldol and Related Reactions:

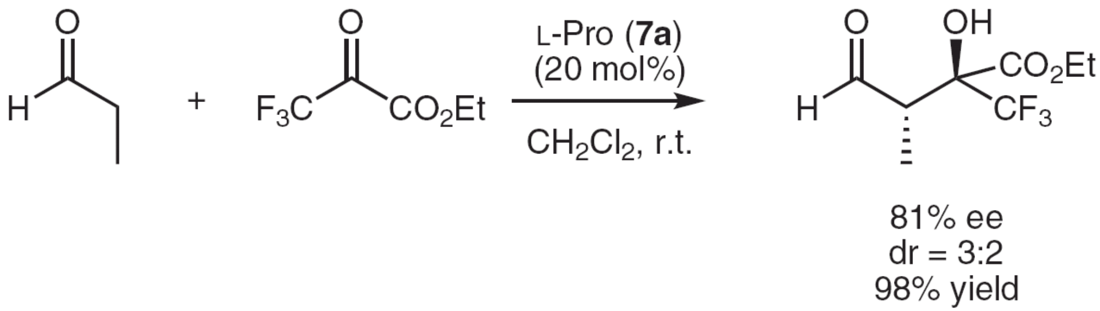


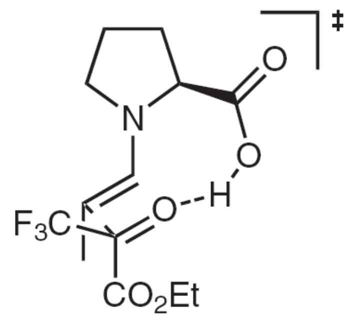
R = H 90% ee, 99% yield
R = Me 92% ee, 99% yield
R = OMe 83% ee, 96% yield
R = Cl 86% ee, 98% yield



Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem. Int. Ed.* ***2005, 44, 3086.***

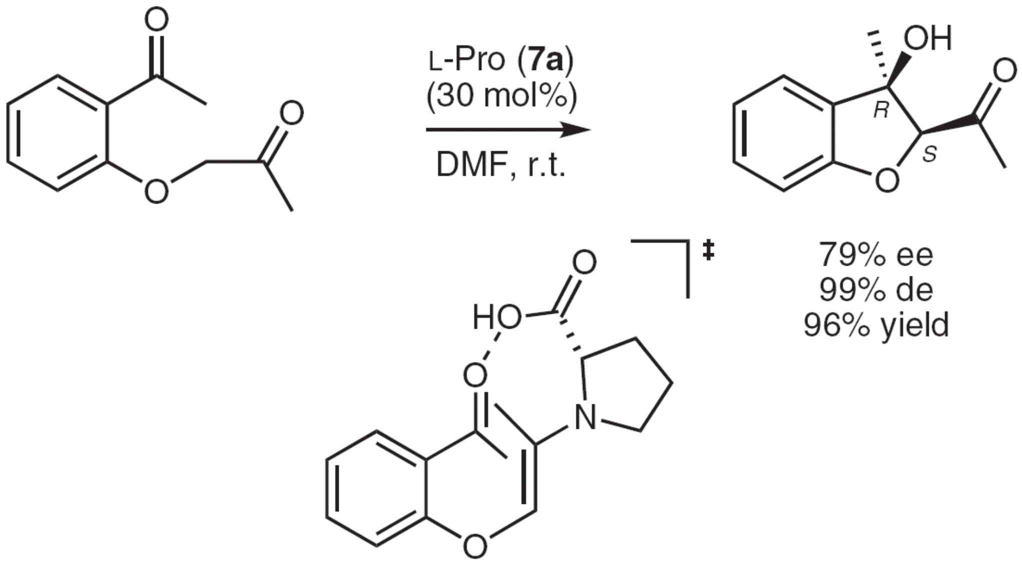
Direct Aldol Reaction





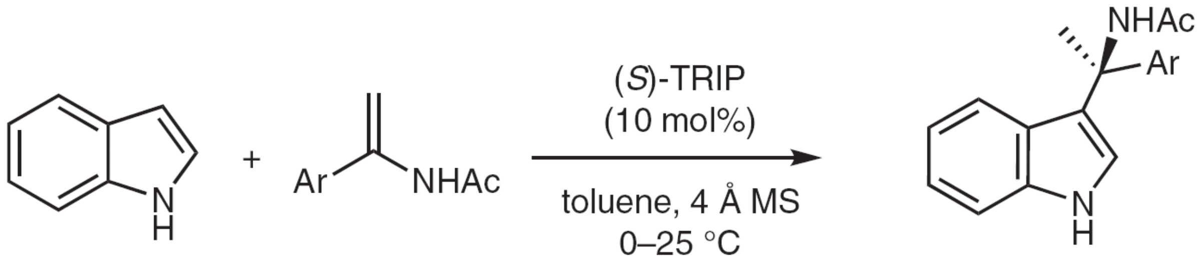
Proposed transition state

Intramolecular cross-coupling



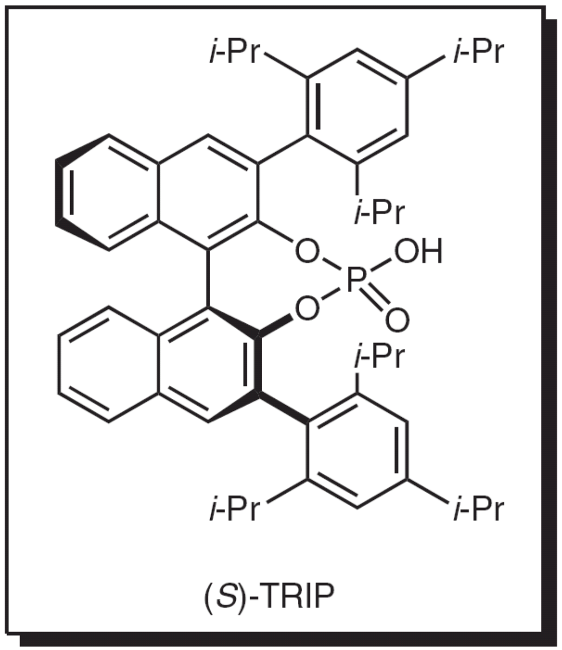
Bøgevig, A.; Nagaswamy, K.; Jørgensen, K. A. *Chem. Commun.* ***2002, 620.***
Zheng, C.; Wu, Y.; Wang, X.; Zhao, G. *Adv. Synth. Catal.* **2008, *350, 2690.***

Brønsted Acid organocatalyzed Formation of Nitrogen- Containing Quaternary Stereocenters :



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 3,4-$Me_2C_6H_3$, 3-MeC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl

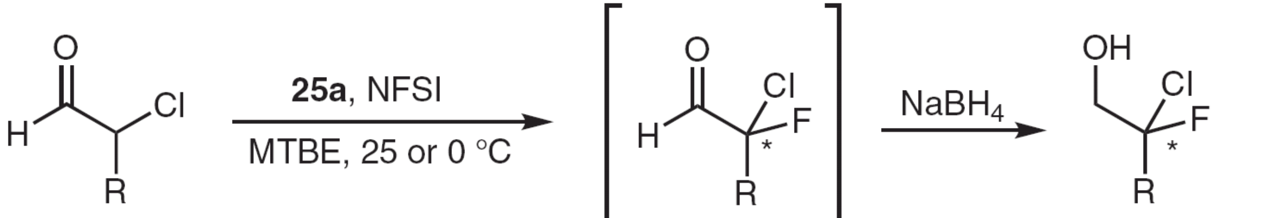
90–97% ee
95–99% yield



Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* ***2007, 46, 5565.***

Halogenation and Pseudohalogenation Reactions :

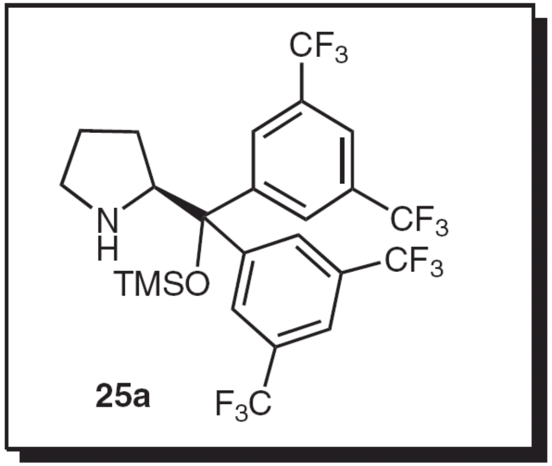
Fluorination



(racemic)

R = Ph, Bn, Hex, *t*-Bu

88–99% ee
62–86% yield



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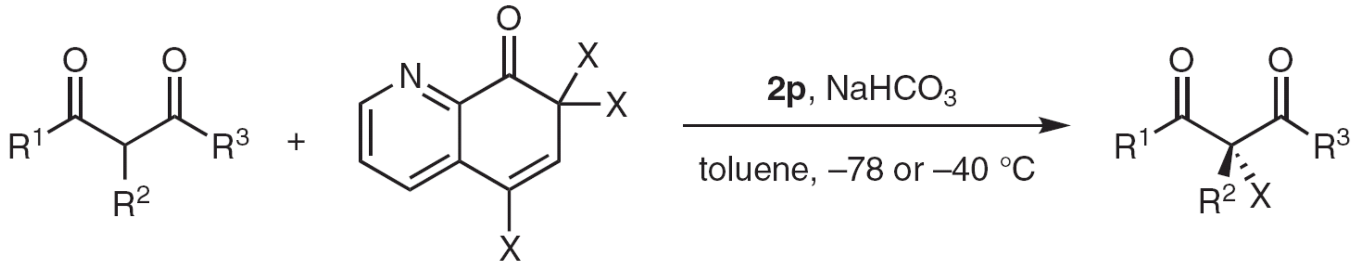
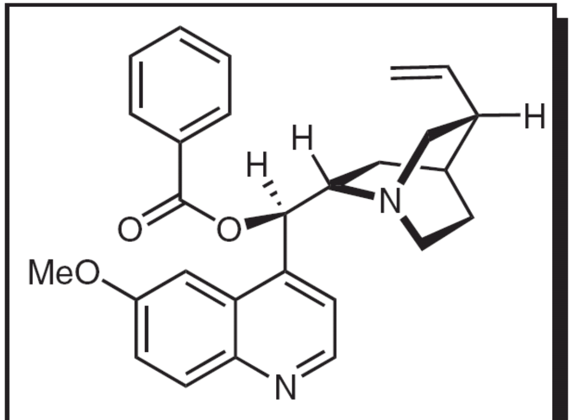
Chlorination and Bromination



X = Cl, 7 examples, 59-96 % ee
55-99 % yield

X = Br, 2 examples, 83-84 % ee
67-82 % yield



2p

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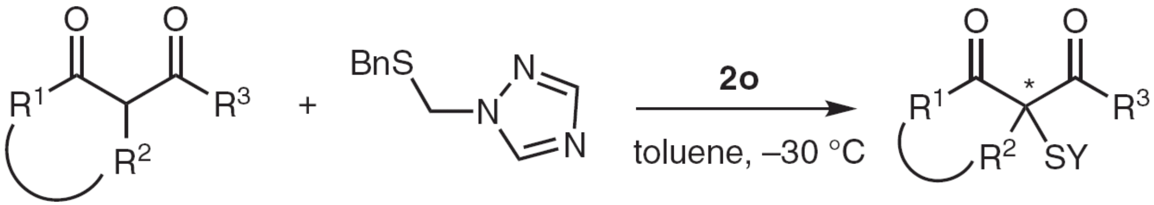
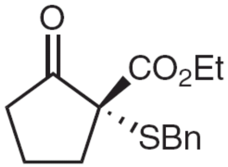
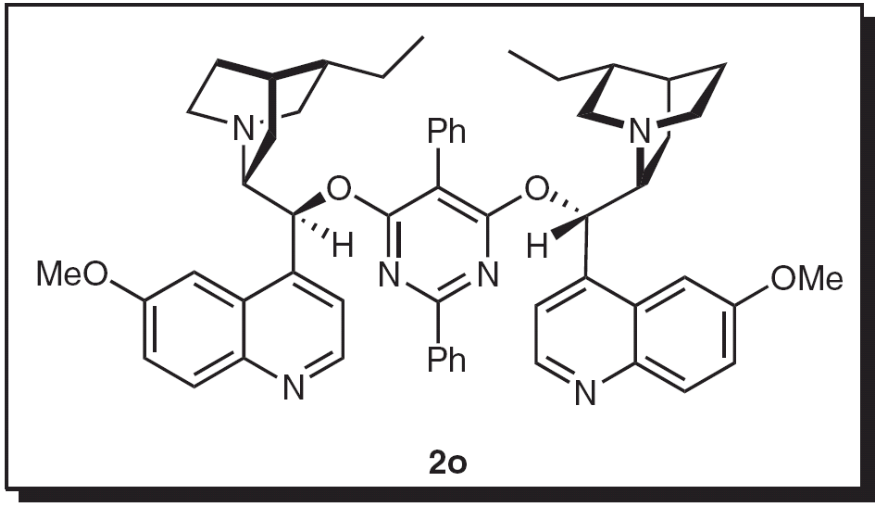
Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem. Int. Ed.* ***2005, 44,*** 6219.

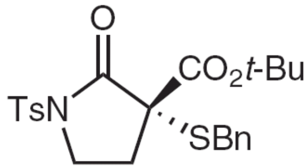
Sulfenylation



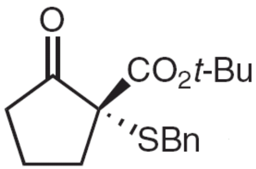


63% ee
91% yield

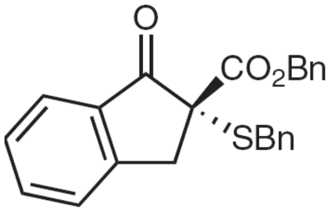




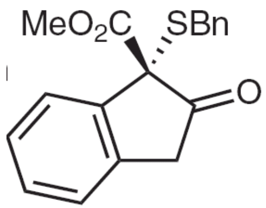
85% ee
87% yield



88% ee
89% yield



60% ee
84% yield

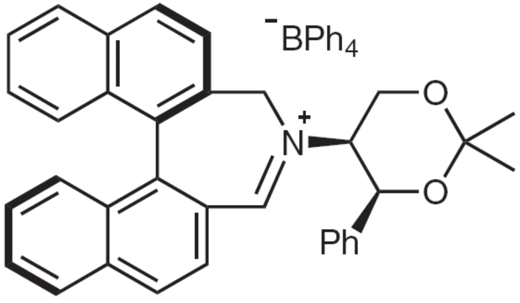


53% ee
94% yield

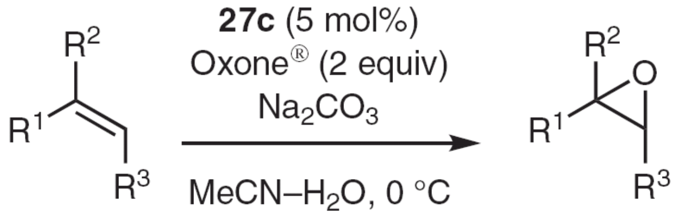
Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem. Eur. J.* ***2005, 11, 5689.***

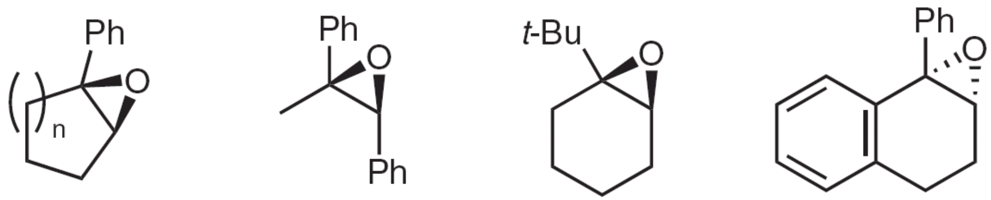
Epoxidation :

Iminium Salt Catalyzed Epoxidation



27c





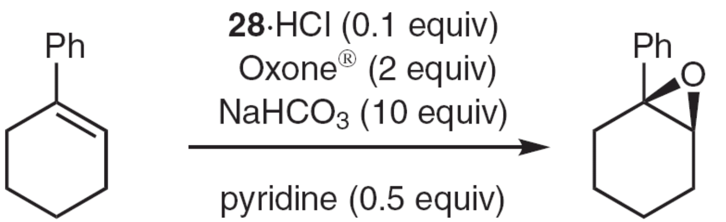
n = 1–3
55–91% ee
52–54% yield

49% ee
58% yield

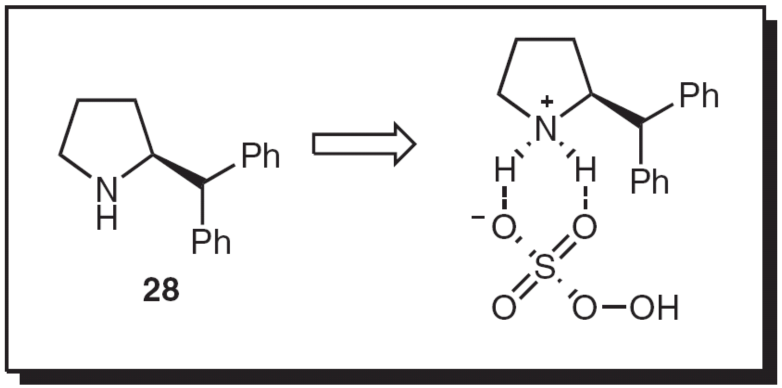
25% ee
63% yield

95% ee
66% yield

Amine Catalyzed Epoxidation



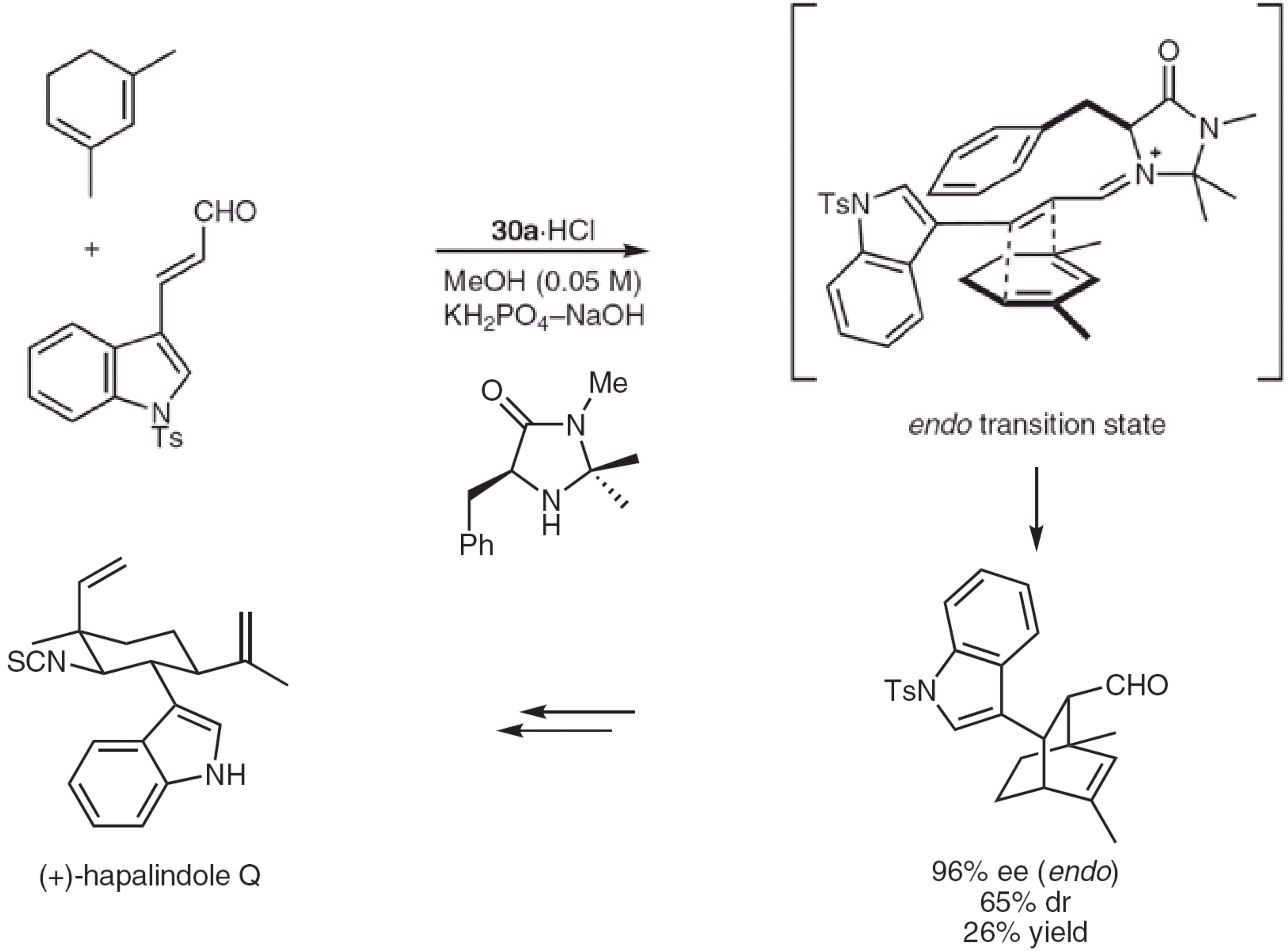
25% ee
93% yield



Page, P. C. B.; Buckley, B. R.; Blaker, A. J. *Org. Lett.* ***2004**, 6*, *1543.*
Peris, G.; Jakobsche, C. E.; Miller, S. *J. Am. Chem. Soc.* **2007, *129*, *8710.***

Diels-Alder reaction:

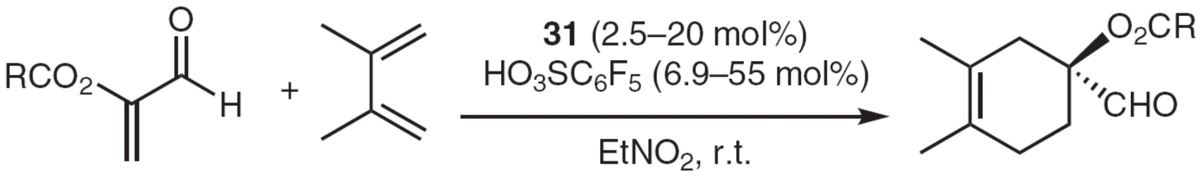
MacMillan's approach



Limitations : nature of the dienophile

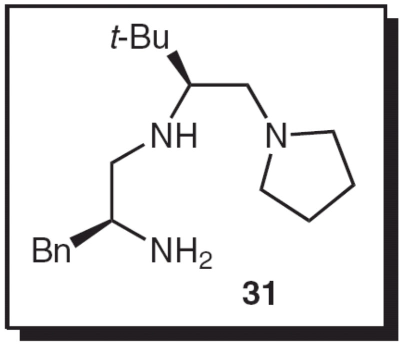
Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* ***2003, 125,*** 14120.
Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* ***2000, 122, 4243.***

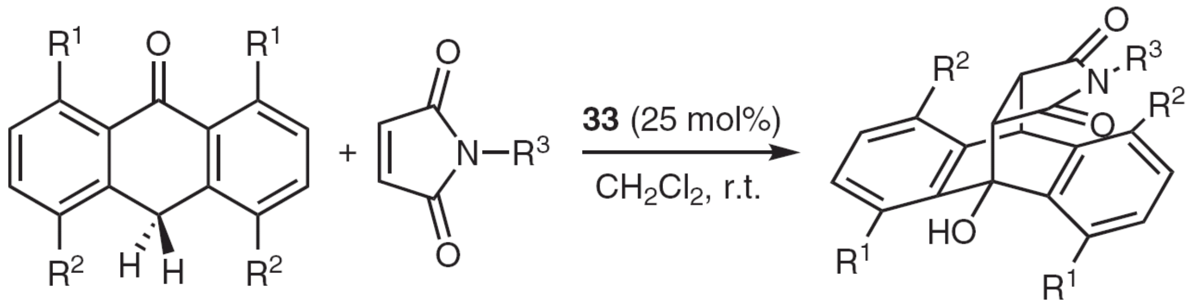
Diels-Alder reaction:



R = Me, Ph, Ar

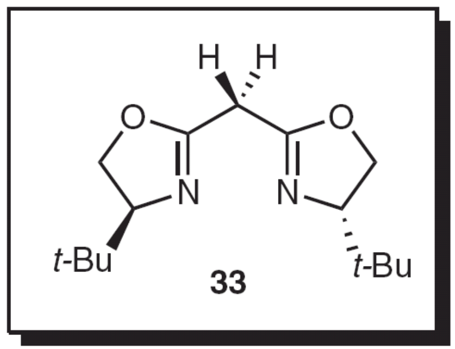
exo/*endo* = 6.7:1 to 99:1
72–92% ee
81–99% yield





R^1 = H, Cl
R^2 = H, Cl
R^3 = Ph, Bn, Ar, *i*-Pr, *t*-Bu, *c*-Hex

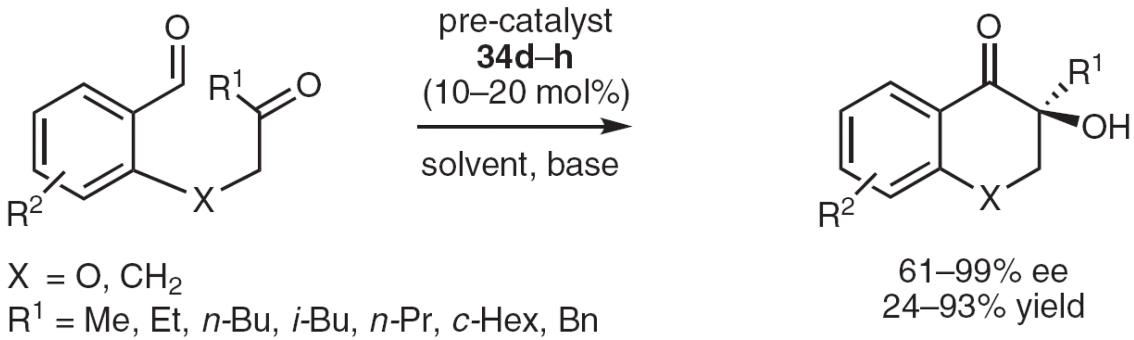
39–70% ee
67–99% yield



Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* ***2005, 127,*** 10504.
Akalay, D.; Dürner, G.; Göbel, M. W. *Eur. J. Org. Chem.* **2008, 2365.**

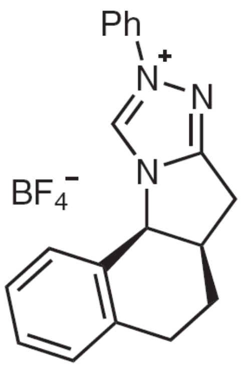
N-Heterocyclic Carbene Catalysis :

Assymetric intramolecular crossed-benzoin reaction

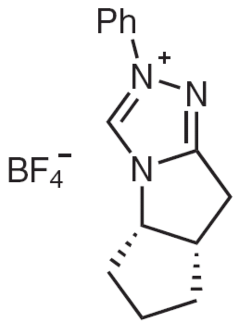


X = O, CH_2
R^1 = Me, Et, *n*-Bu, *i*-Bu, *n*-Pr, *c*-Hex, Bn
R^2 = H, 2,4-Br_2, 2-NO_2, 2,4-(*t*-Bu)$_2$,
2,3-methylenedioxo

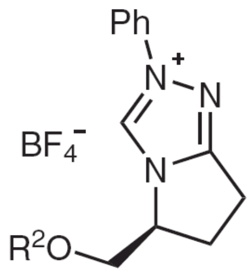
pre-catalyst =



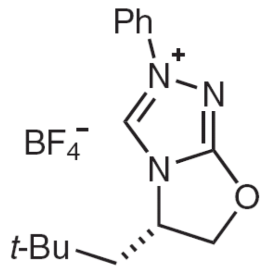
34d



34e



R^2 = TBS, TIPS
34f,g

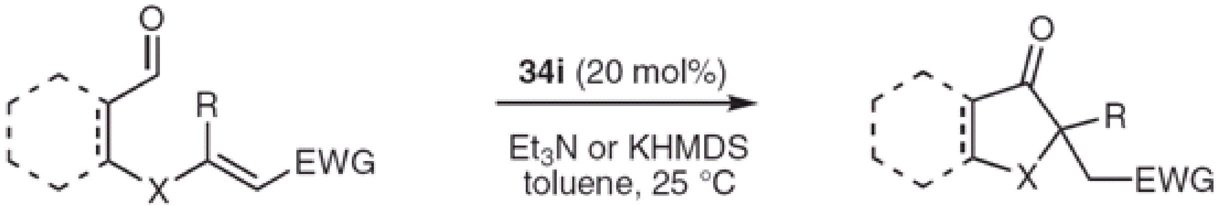


34h

(a) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem. Int. Ed.* **2006, 45, 1463. (b) Enders, D.; Niemeier, O.;** Raabe, G. *Synlett* **2006, 2431.**

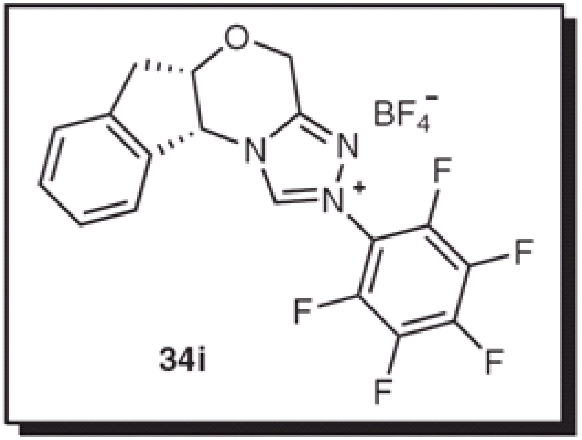
N-Heterocyclic Carbene Catalysis :

Catalytic asymmetric Stetter reaction

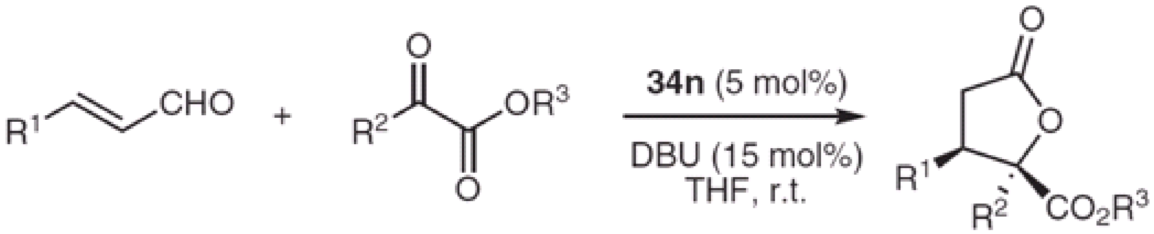


X = CH_2, O, S
R = Me, Et, *n*-Bu, CO_2Me
EWG = CO_2Me, CO_2Et, COMe, COPh

84–99% ee
55–96% yield

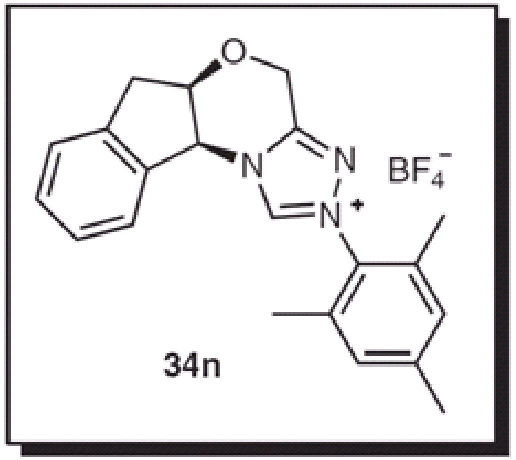


Annulation of enals and keto esters



R^1 = Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$,
2-furyl, *n*-Pr
R^2 = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4,
4-ClC_6H_4, 2-MeC_6H_4, CF_3,
2-thienyl, *c*-Hex, Me
R^3 = Bn, Et, Me

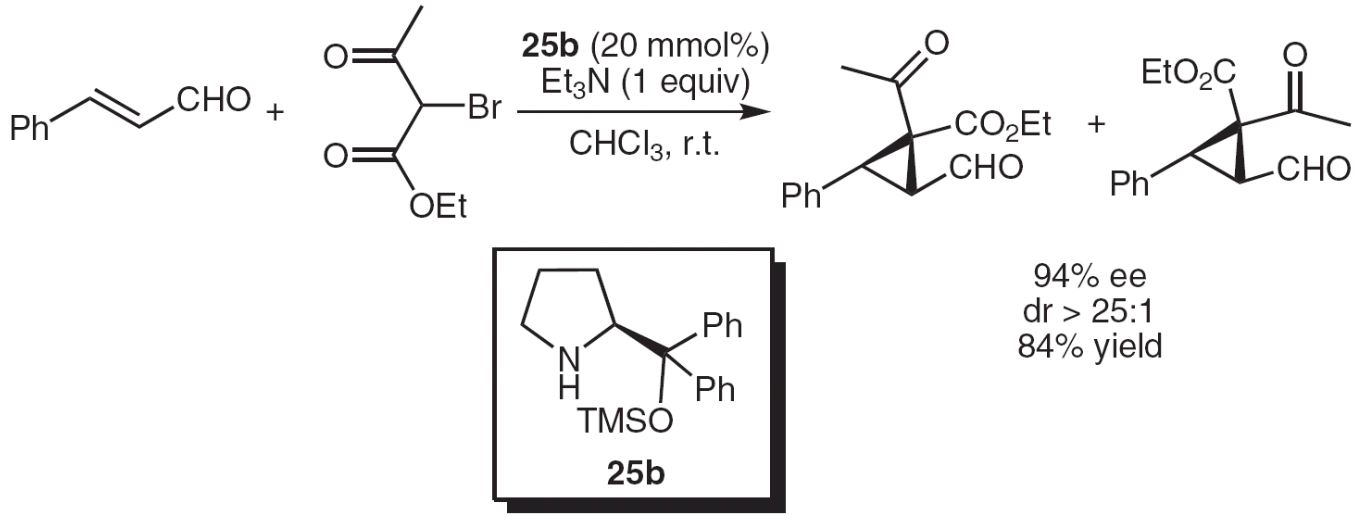
cis/*trans* = 55:45 to 83:17
14–55% ee (*cis*)
14–78% ee (*trans*)
45–98% yield



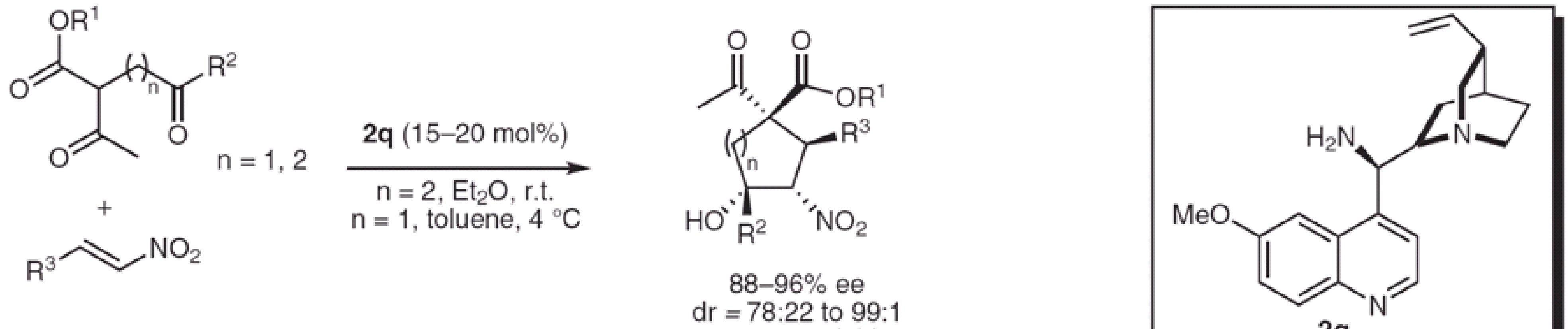
(a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* ***2004, 126,*** 8876. (b) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* ***2005,*** *127, 6284*
Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Catal.* **2008, *350, 1885*.**.

Cascade reactions:

One-pot organocatalytic domino Michael-α-alkylation reactions : direct catalytic enantioselective cyclopropanation



Tandem Michael/Henry reaction and domino double Michael-reaction



R^1 = Me, Et, Bn
R^2 = Me, Ph, Ar
R^3 = Ph, Ar

Ibrahem, I.; Zhao, G. L.; Rios, R.; Vesely, J.; Sundén, H.; Dziedzic, P.; Córdova, A. *Chem. Eur. J.* ***2008, 14, 7868.***
Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* ***2008, 10,*** 3425.

Conclusion :

Several optimized catalytic systems with excellent enantioselectivity

Several new transformations

Unresolved problems : - electrophile addition to double bond

- alkylation of aldehydes
- addition to sterically hindered double bonds