MacMillan Group Meeting

4th March 2009

Mark Pickworth

Nucleophilic Dearomatisation Reactions with Synthetic Applications

D_NAr

Lead references

Lopez-Ortiz, F.; Iglesias, M. J.; Fernandez, I.; Sanchez, C. M. A.; Gomez, G. R. *Chem. Rev.* **2007**, *107*, 1580

Clayden, J.; Kenworthy, M. *Synthesis* **2004**, 1721

Overview

- Introduction to Dearomatisation Reactions
- Introduction to Nucleophilic Dearomatisation Reactions (D_NAr)
- D_NAr with Synthetic Applications Spotlighted
- Recent Highlights
- Summary

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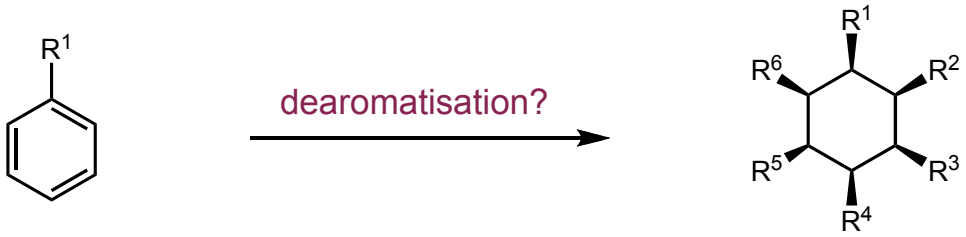
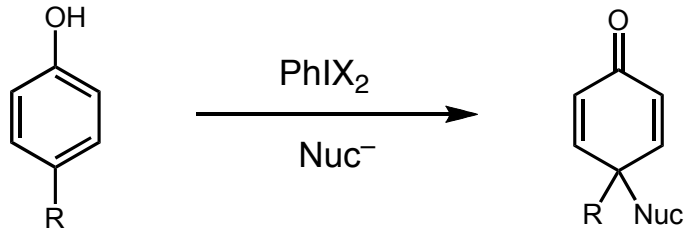


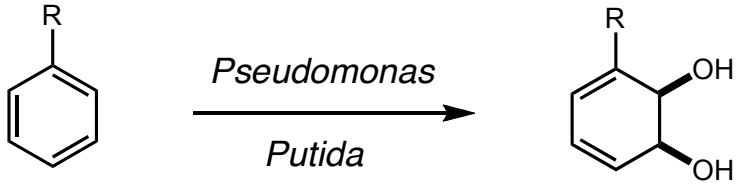
Dearomatising Reactions - a long list!

■ Oxidation

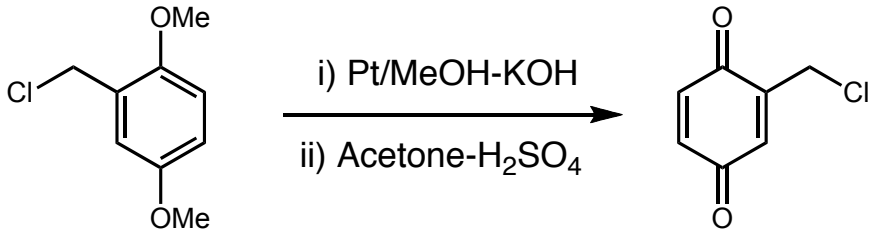
– Chemical:



– Microbial:

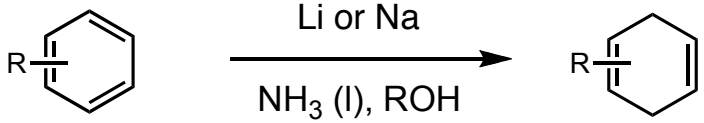


– Electrolysis:



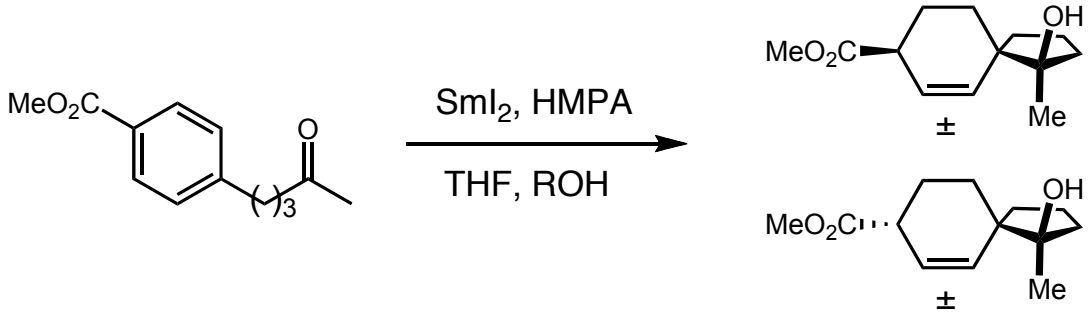
■ Hydrogenation

– Birch Reduction



Dearomatising Reactions - a long list!

■ Radical Cyclisation



Dearomatising Reactions - a long list!

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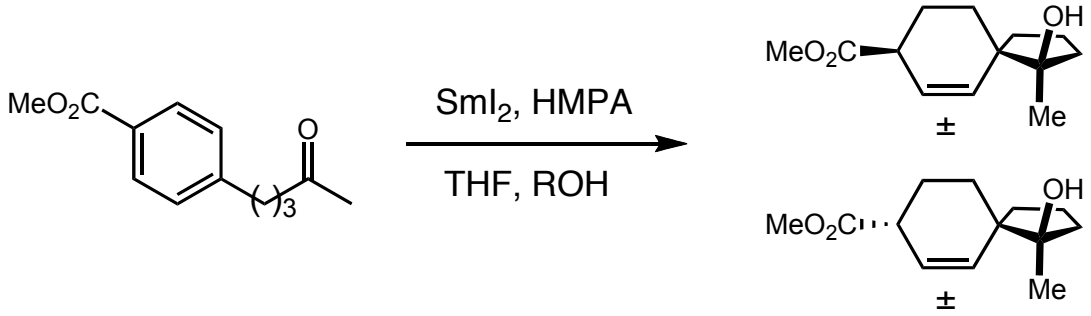
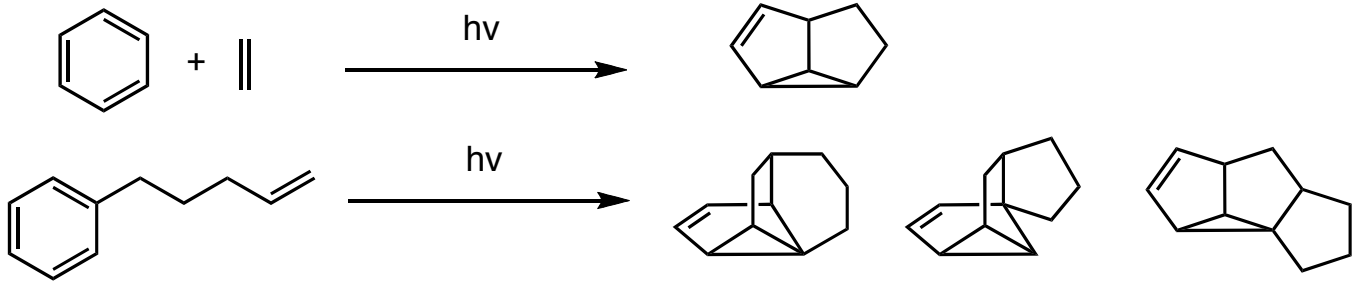
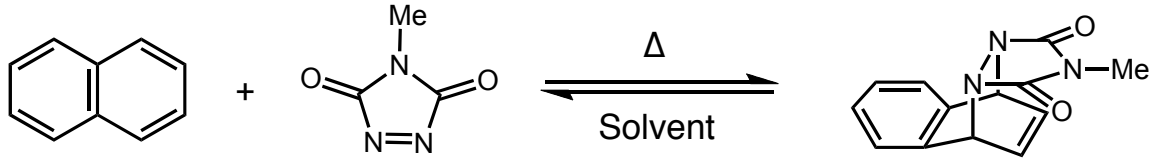


■ Cycloaddition

Photo-:

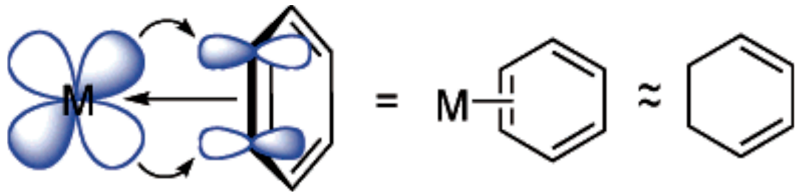


Thermo-:

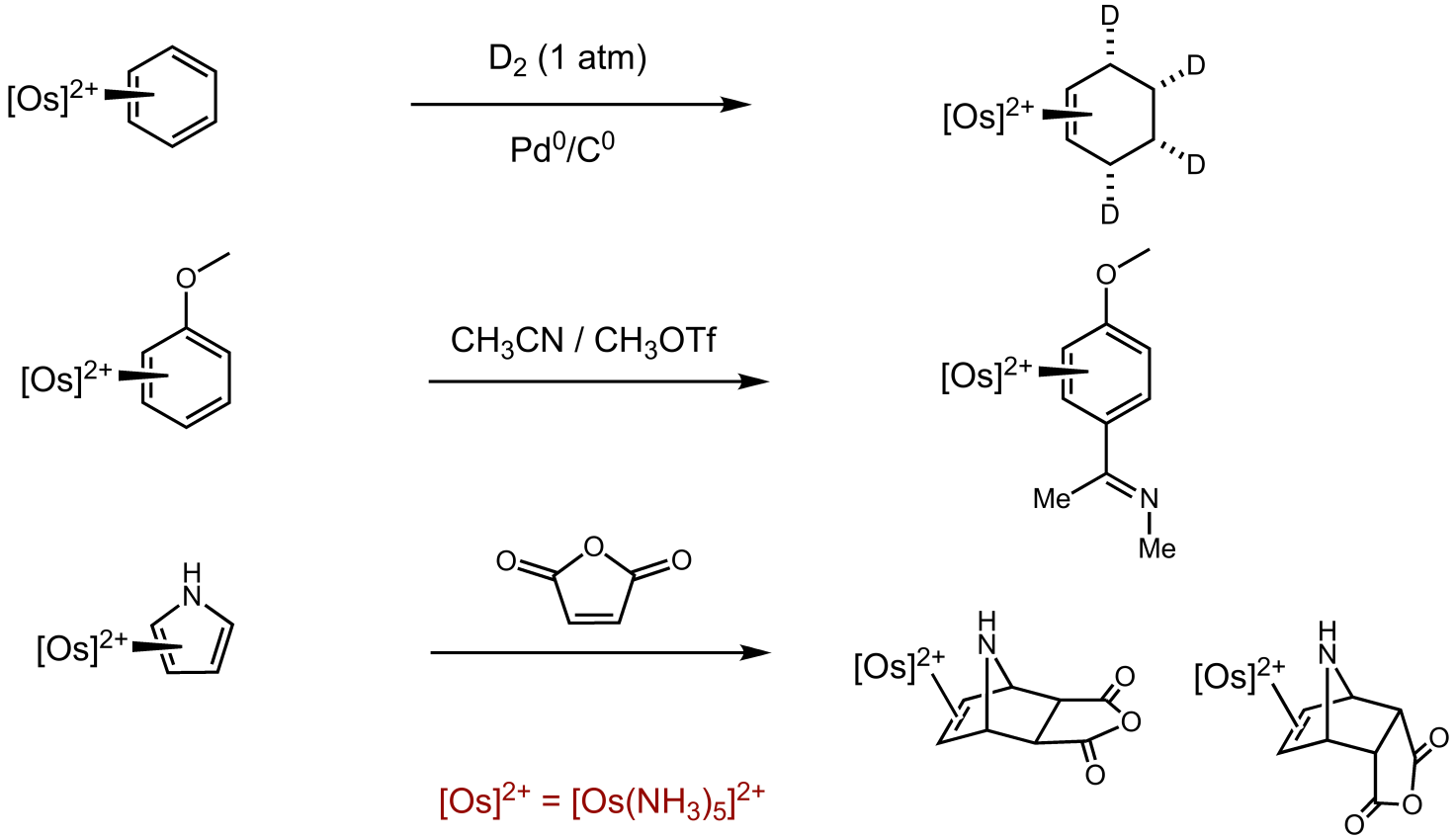


Dearomatising Reactions - a long list!

■ Electrophilic Addition



- η^2 coordination stabilised through π-donation of electron density

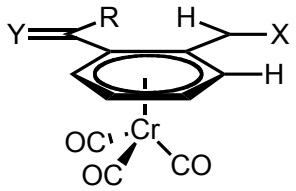


Dearomatising Reactions - a long list!

■ Nucleophilic Addition

Selective side chain reactions

Nucleophilic addition to ring carbons

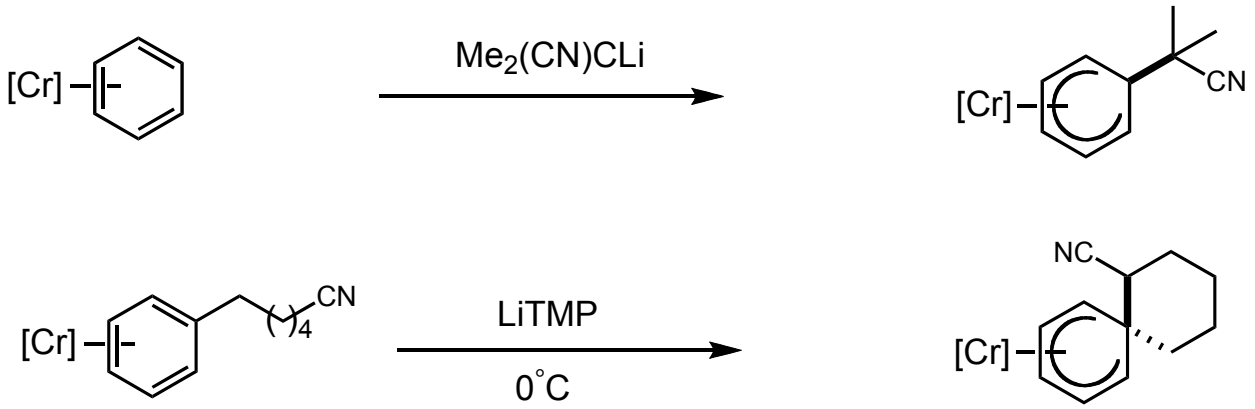


Steric directing group

Stabilisation of benzylic carbanions and carbocations

Increased acidity of ring hydrogens

● Complexation with $Cr(CO)_3$ changes arene reactivity

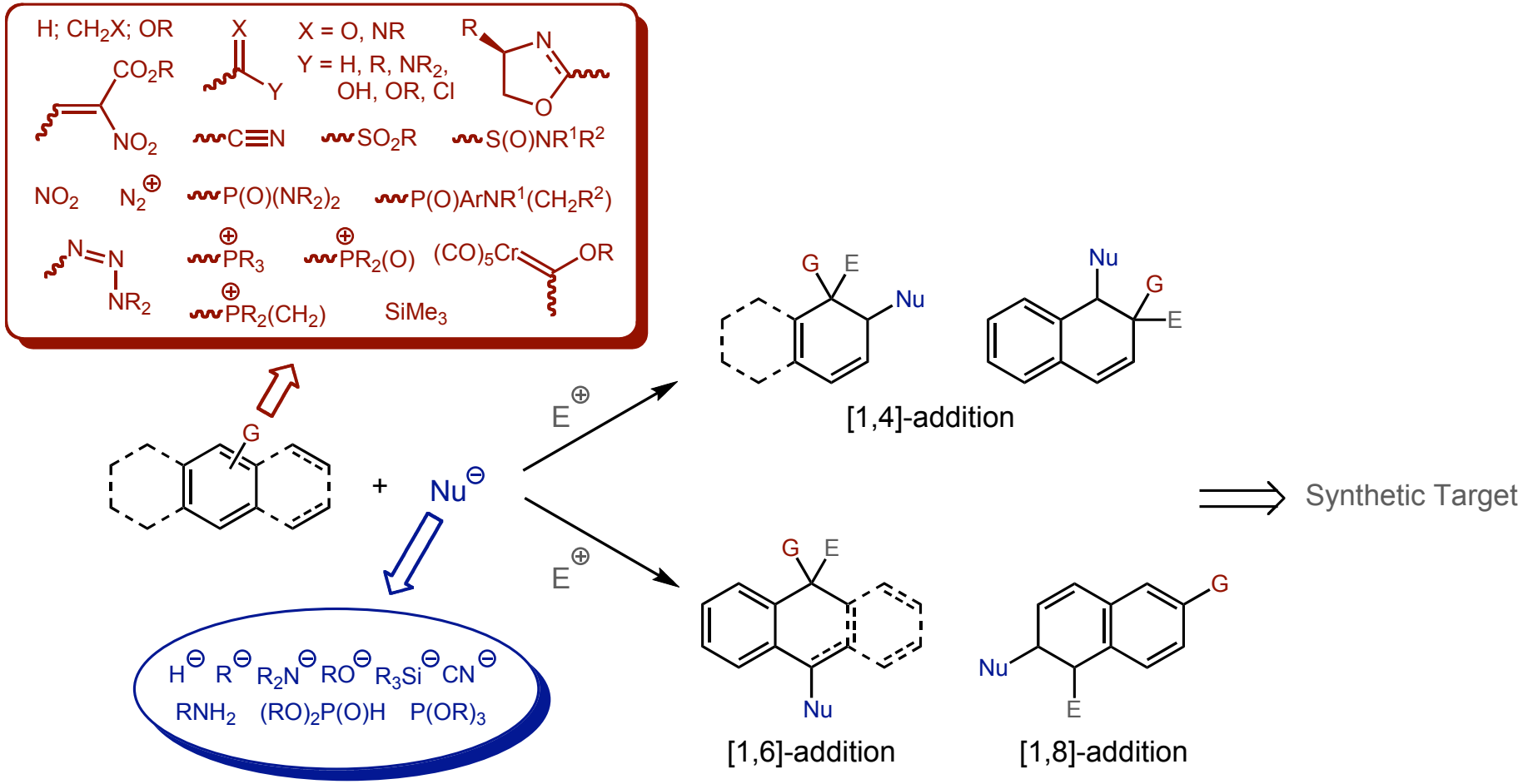


[Cr] = $[Cr(CO)_3]$

■ Can Nucleophilic Dearomatising Addition be accomplished without TM complexation?

Nucleophilic Dearomatising Reactions without TM Coordination

■ Quite a few examples!

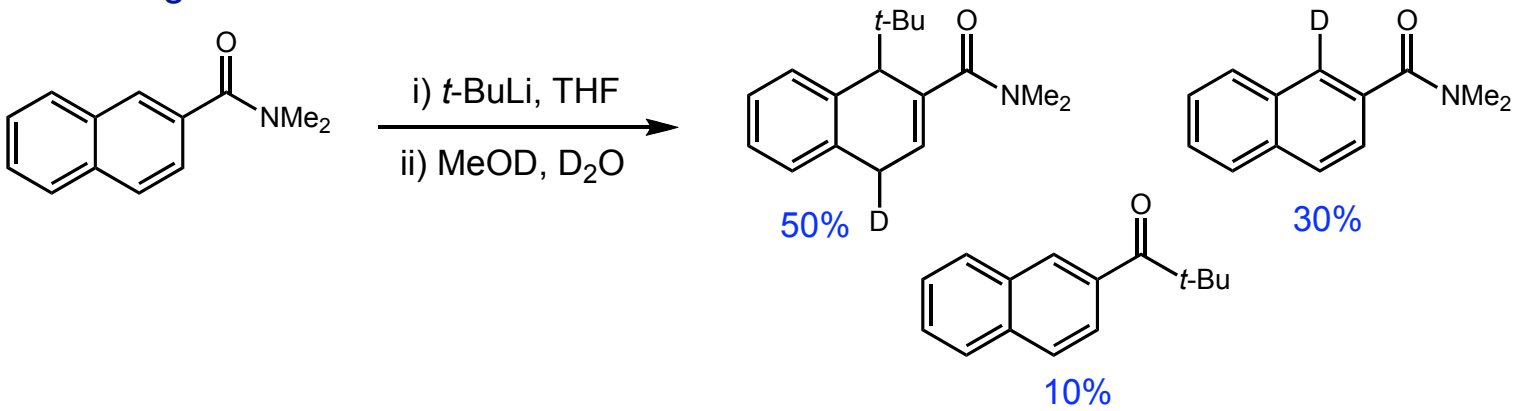


■ Focus on D_NAr systems which have been applied to Natural Product Synthesis

● Activation by carboxamide, oxazoline, oxazolidine, nitro, phosphinamide & sulfone groups

D_NAr with Activation by a Carboxamide Group : Intermolecular

■ Pioneering work:



Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107

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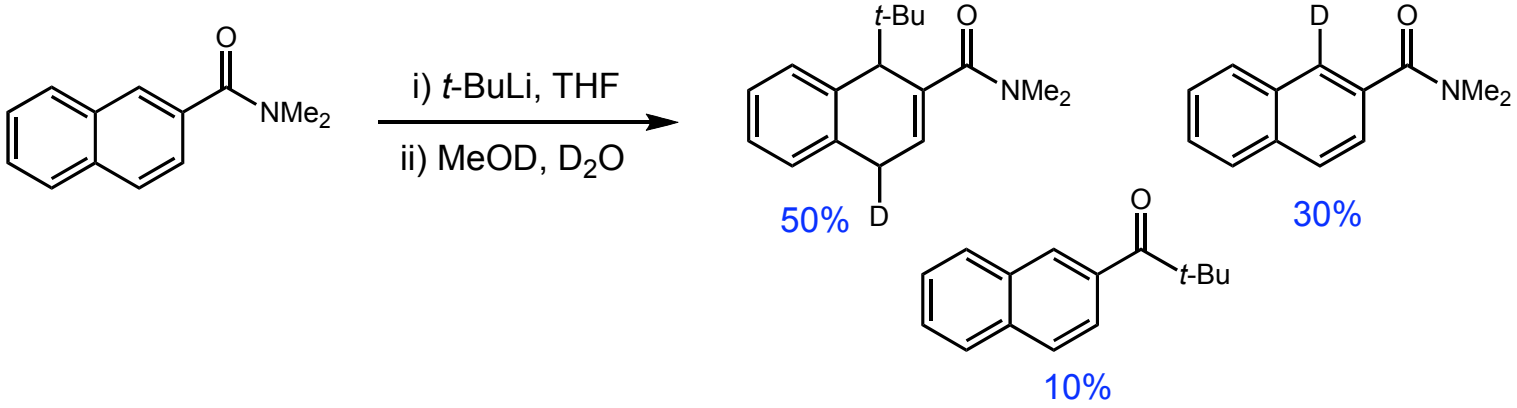
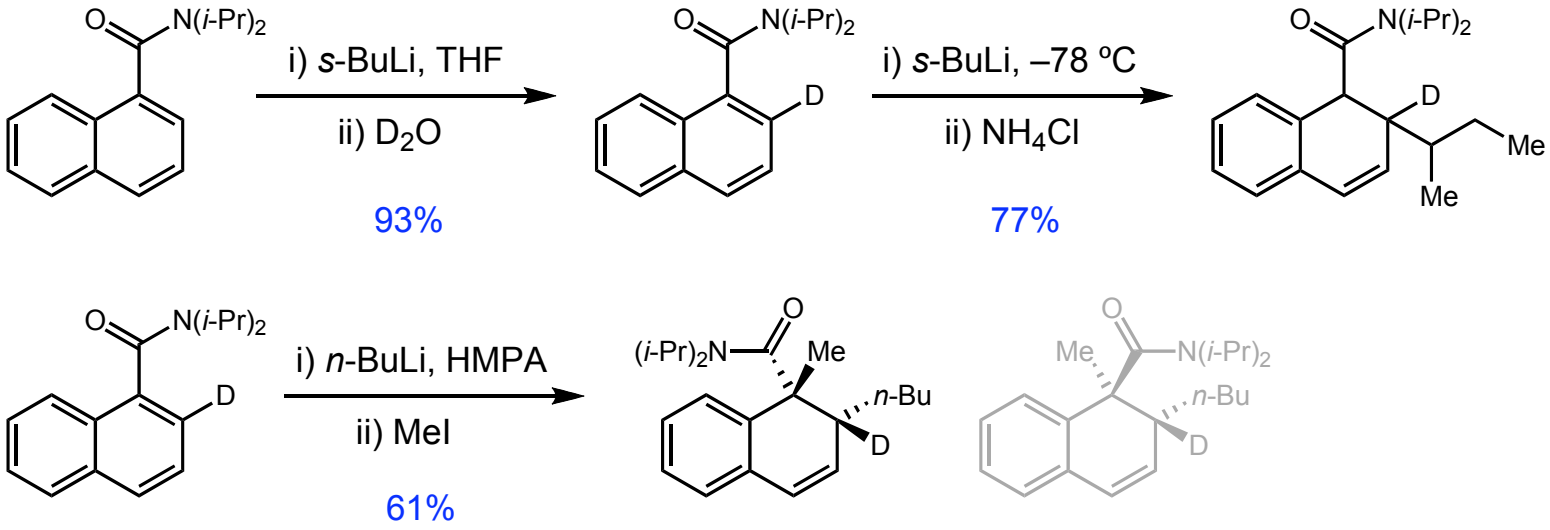


Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107

■ 10 years later

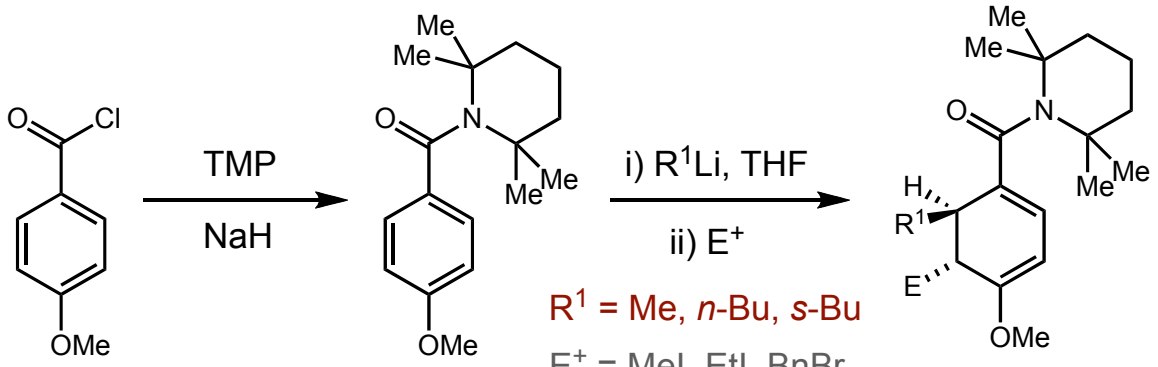


Clayden, J.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1998**, *39*, 8377

Clayden, J.; Frampton, C. S.; McCarthy, C.; Westlund, N. *Tetrahedron* **1999**, *55*, 14161

D_NAr with Activation by a Carboxamide Group : Intermolecular

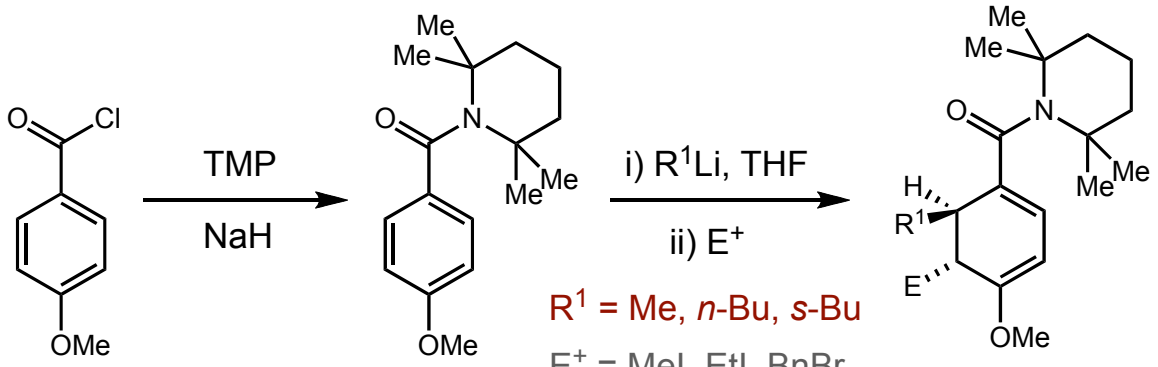
- Steric hindrance prevents amide addition or *ortho*-lithiation



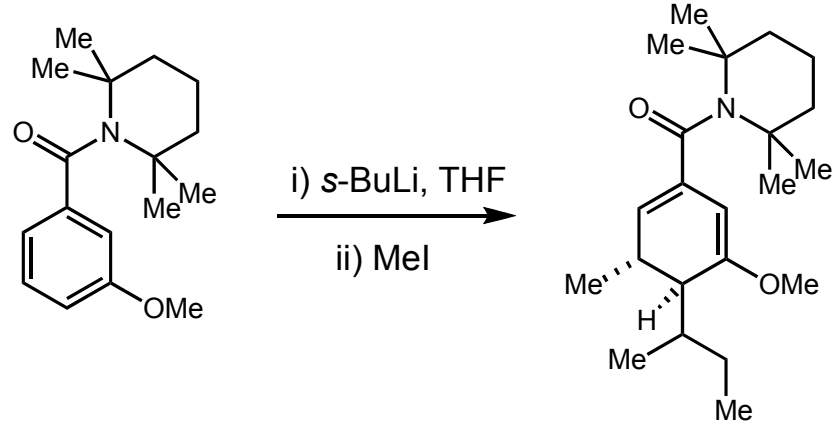
22-76% y

D_NAr with Activation by a Carboxamide Group : Intermolecular

- Steric hindrance prevents amide addition or *ortho*-lithiation



- Regiochemistry controlled by OMe group

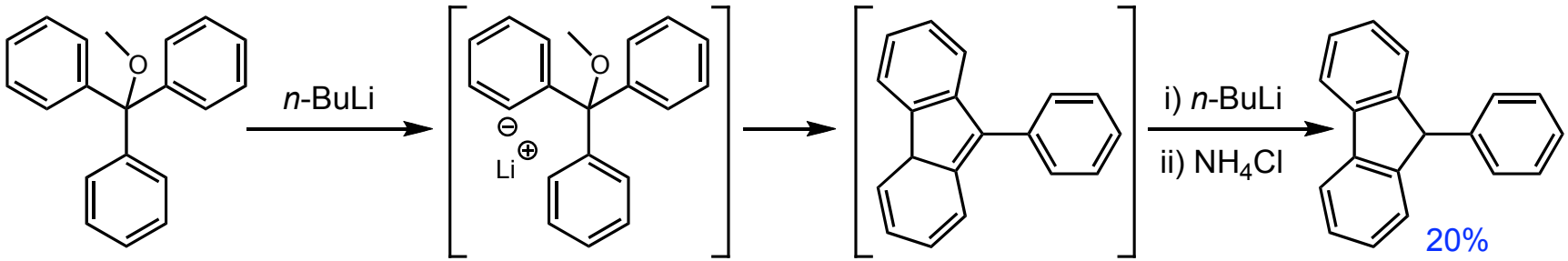


Clayden, J.; Foricher, Y. J. Y.; Lam, H. K. *Chem. Commun.* **2002**, 2138

Clayden, J.; Foricher, Y. J. Y.; Lam, H. K. *Eur. J. Org. Chem.* **2002**, 3558

D_NAr with Activation by a Carboxamide Group : Intramolecular

- Anionic cyclisation: carbon-carbon bond formation



Gilman, H.; Meikle, W. J.; Morton, J. W. *J. Am. Chem. Soc.* **1952**, *74*, 6282

- Only re-aromatised product isolated

D_NAr with Activation by a Carboxamide Group : Intramolecular

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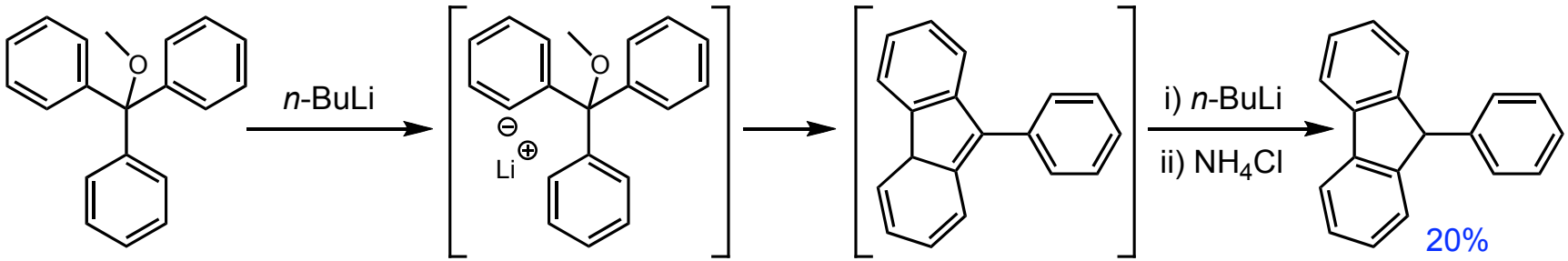

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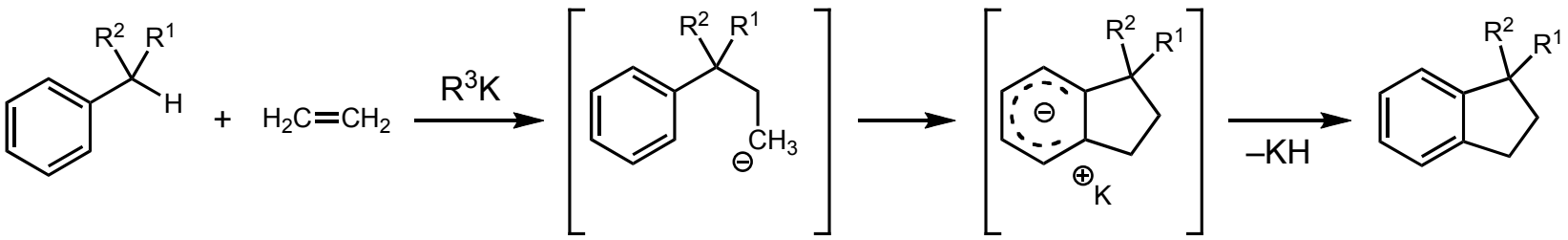
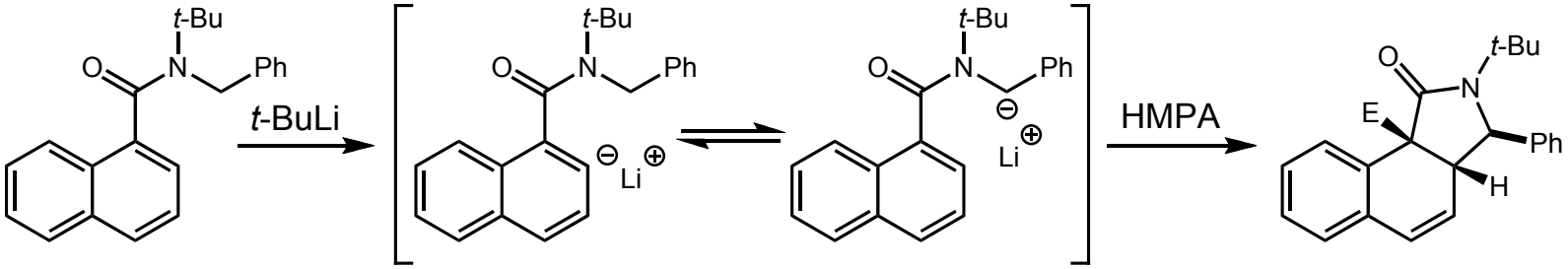


Schaap, L.; Pines H. *J. Am. Chem. Soc.* **1957**, *79*, 4967

- How to stabilise dearomatised intermediate?

D_NAr with Activation by a Carboxamide Group : Intramolecular

- Anionic cyclisation: isolation of dearomatised products

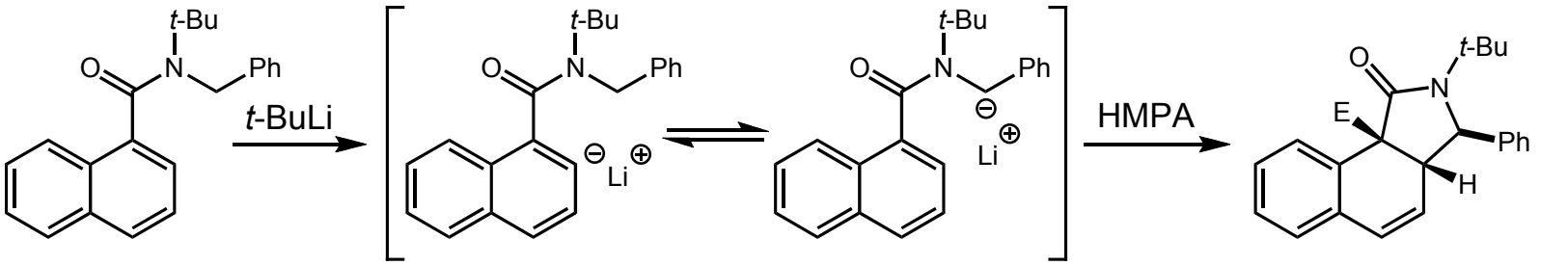


E = H, Me, Et, allyl, *n*-Bu, Bn, *n*-PrCHOH, PhCHOH

Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.* **1998**, 297

D_NAr with Activation by a Carboxamide Group : Intramolecular

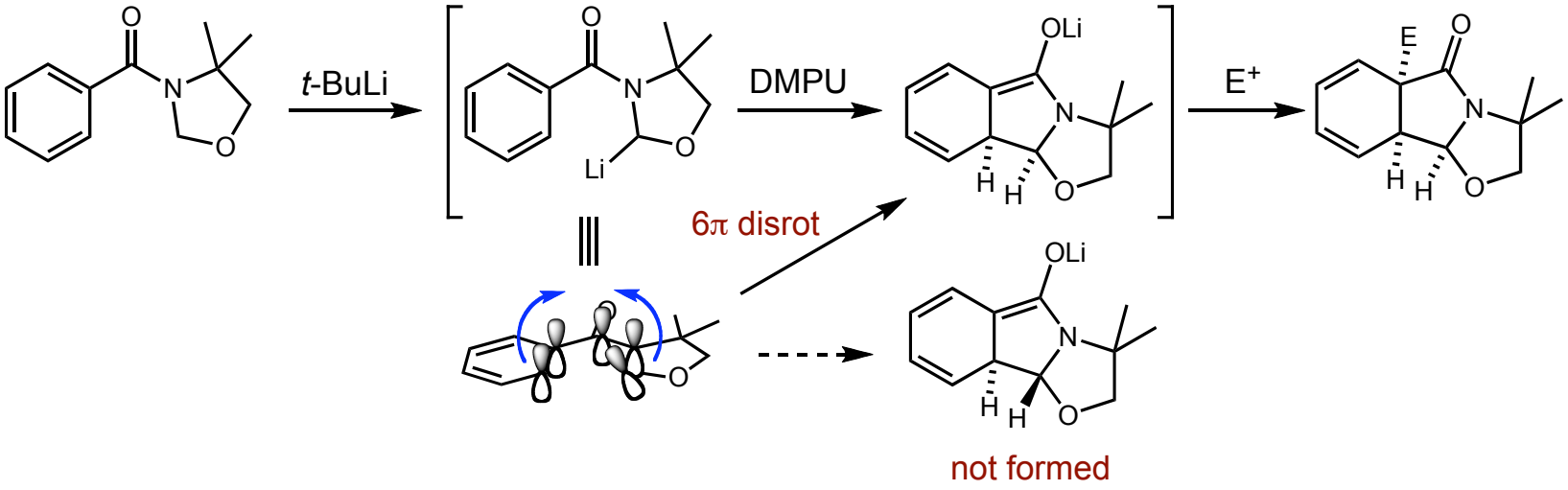
■ Anionic cyclisation: isolation of dearomatised products



E = H, Me, Et, allyl, *n*-Bu, Bn, *n*-PrCHOH, PhCHOH

Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.* **1998**, 297

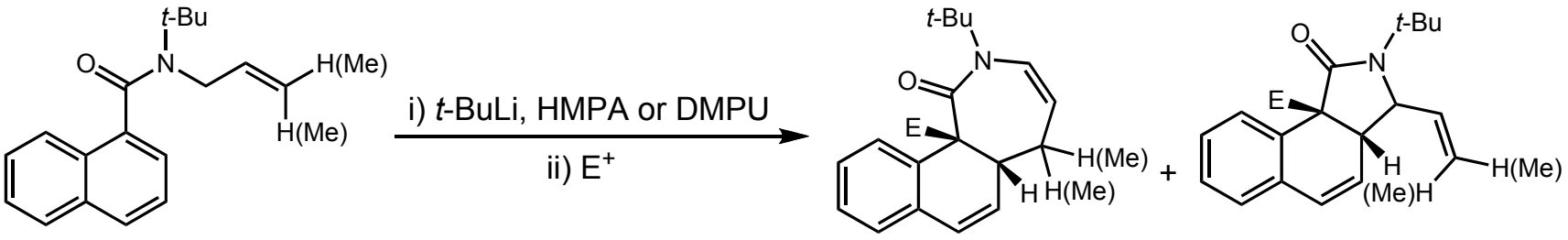
■ 6-π disrotatory electrocyclic ring closure



Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1049

D_NAr with Activation by a Carboxamide Group : Intramolecular

- Anionc cyclisation : first example of a seven-membered ring product



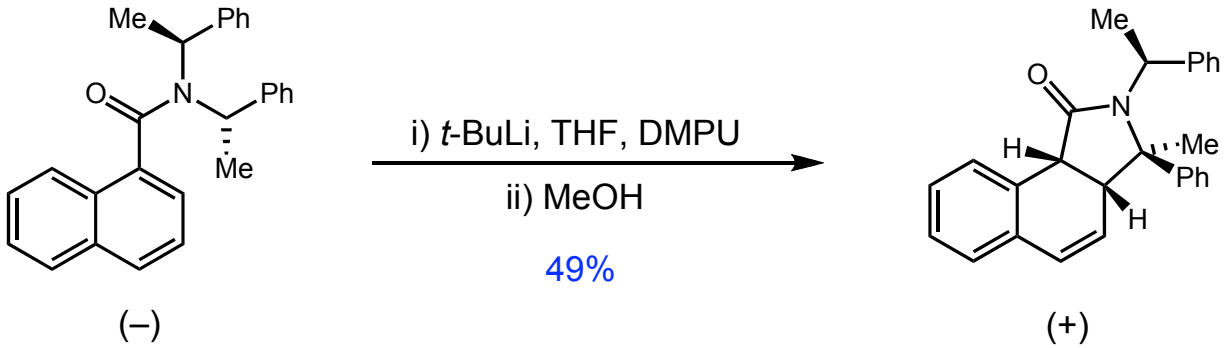
5-2 : 1

E = H, Me, Et, Bn, PhCHOH

Ahmed, A.; Clayden, J.; Rowley, M. *Synlett.* **1999**, 1954

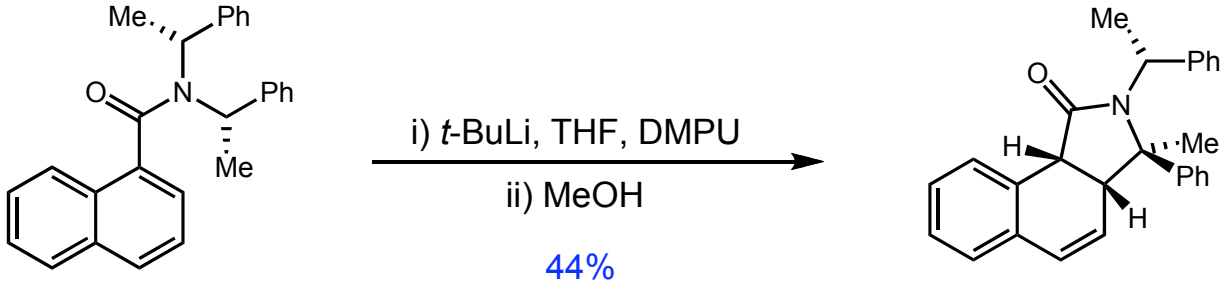
Asymmetric D_NAr with Activation by a Carboxamide Group

■ Chiral substrates



(–) (+)

single diastereomers



(*meso*) (±)

Bragg, R.; Clayden, J. *Tetrahedron Lett.* **1999**, *40*, 8323

Bragg, R.; Clayden, J. *Tetrahedron Lett.* **1999**, *40*, 8327

Asymmetric D_NAr with Activation by a Carboxamide Group

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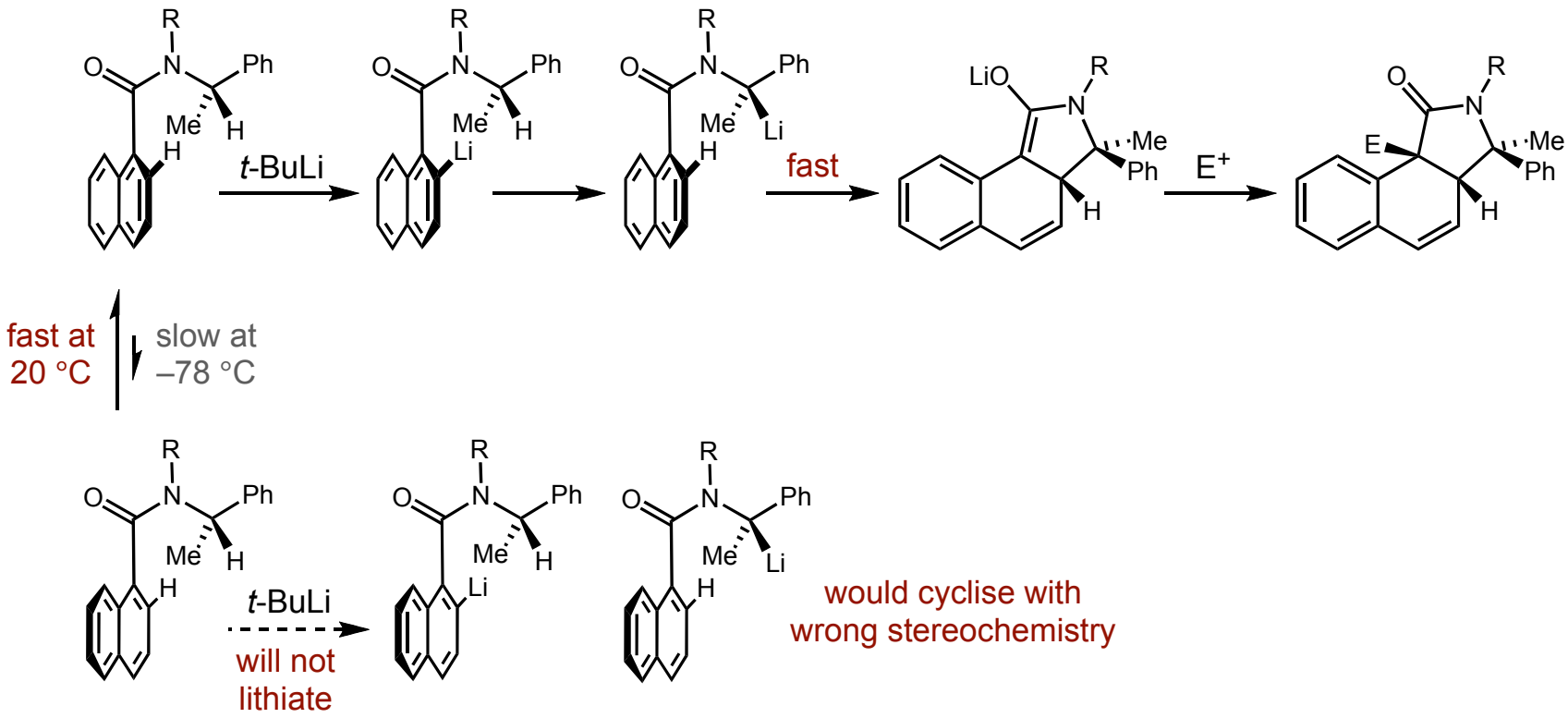
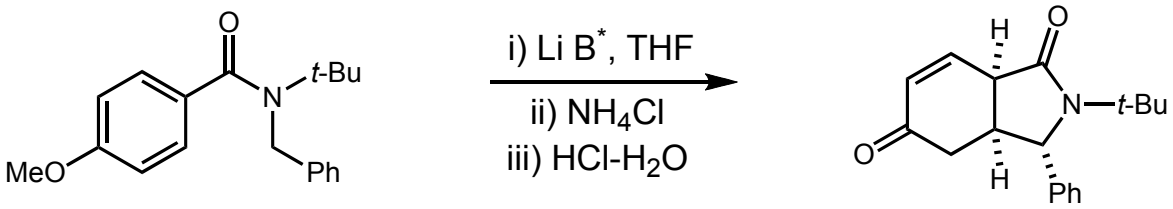


Bragg, R.; Clayden, J. *Tetrahedron Lett.* **1999**, *40*, 8323

Bragg, R.; Clayden, J. *Tetrahedron Lett.* **1999**, *40*, 8327

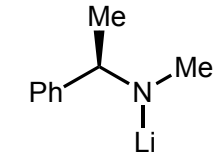
Asymmetric D_NAr with Activation by a Carboxamide Group

■ Enantioselective Deprotonation with Chiral Bases

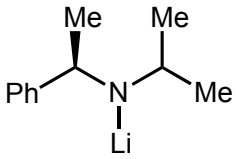


s-BuLi / (–)-sparteine — racemic

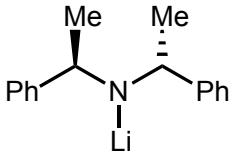
Li B* =



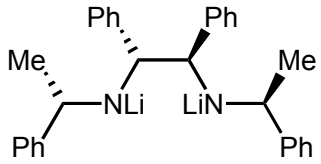
72% y 17% ee



72% y 80% ee



73% y 80% ee

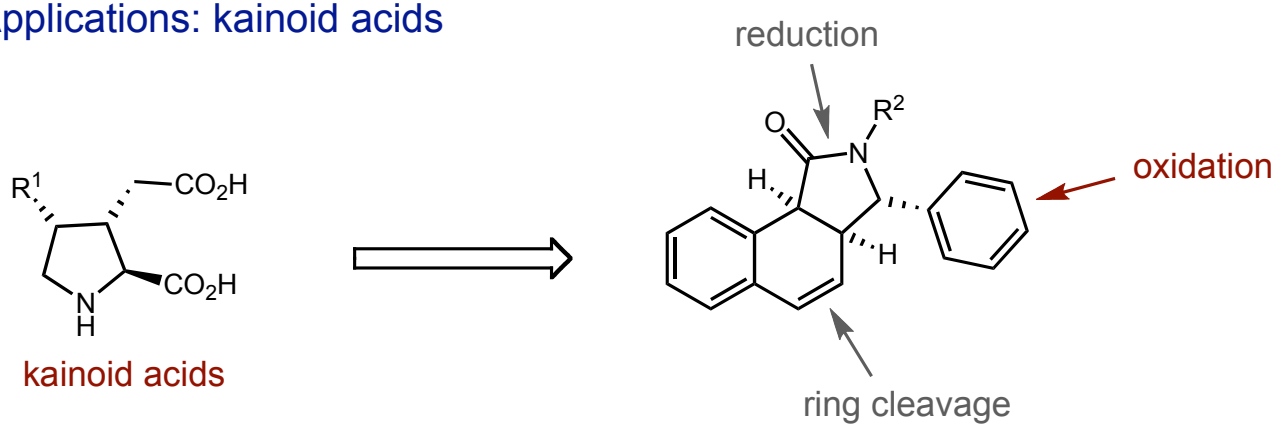


38% y 75% ee

Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38

Asymmetric D_NAr with Activation by a Carboxamide Group

- Synthetic Applications: kainoid acids



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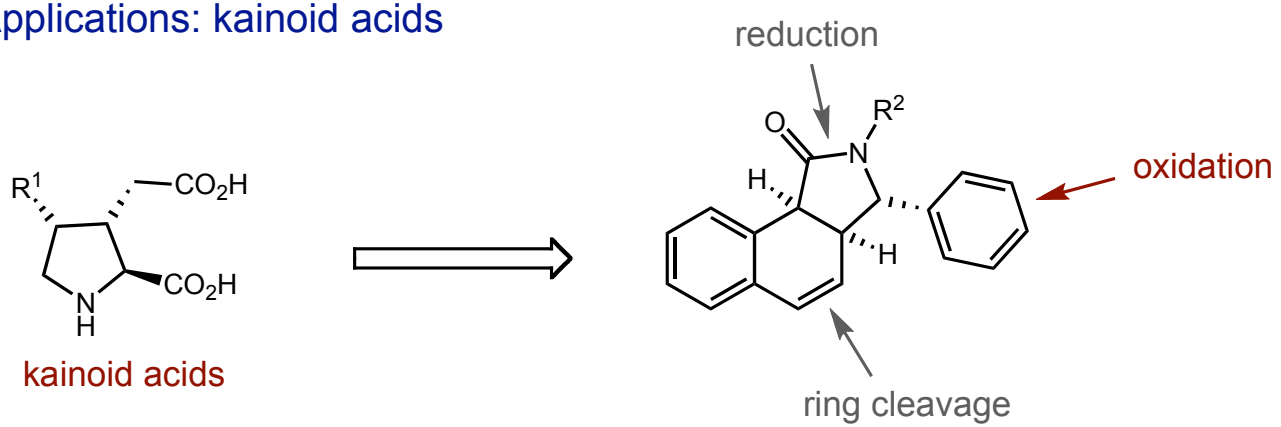
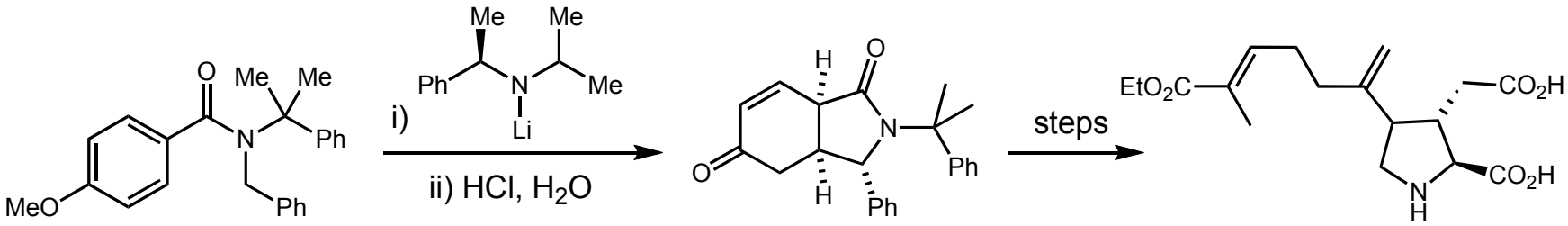
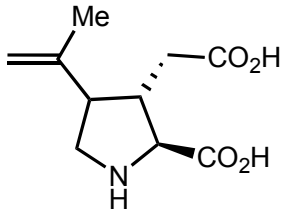




Clayden, J.; Knowles F. E.; Baldwin, I. R. *J. Am Chem. Soc.* **2005**, *127*, 2412

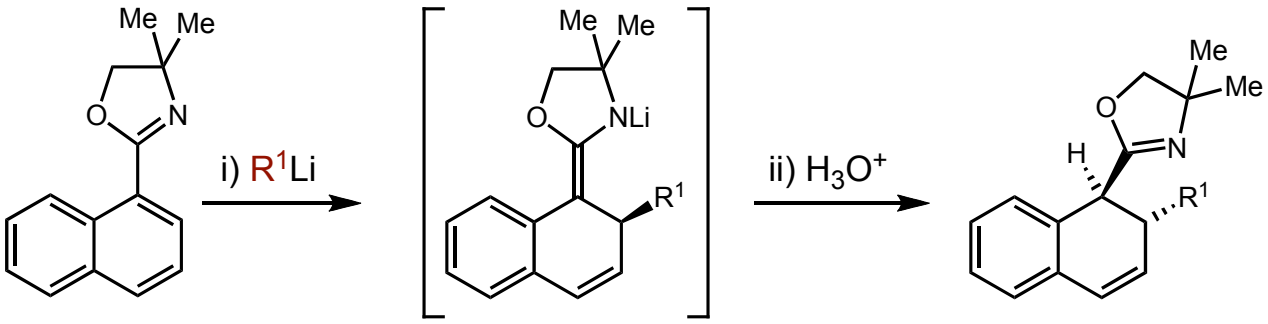


(–)-α-kainic acid

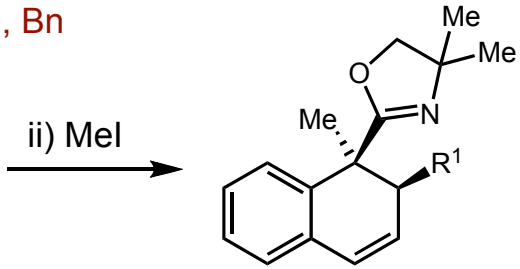
Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38

D_NAr with Activation by an Oxazoline: C Nucleophiles

■ Pioneering work:

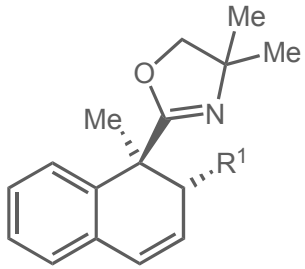


R^1 = vinyl, allyl, Me, *i*-Pr,
c-Pr, *n*-Bu, *s*-Bu, *t*-Bu, Bn



78-99% y

+

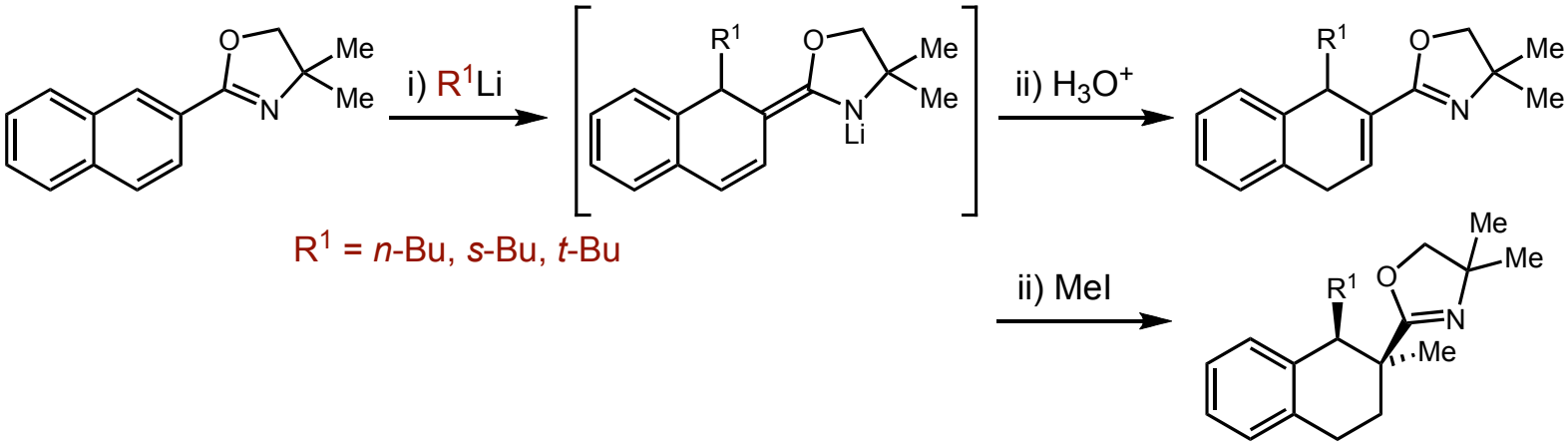


only observed for
R^1 = vinyl (2 : 1 ratio)

Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107

D_NAr with Activation by an Oxazoline: C Nucleophiles

■ Oxazoline at the 2-position



90-91% y

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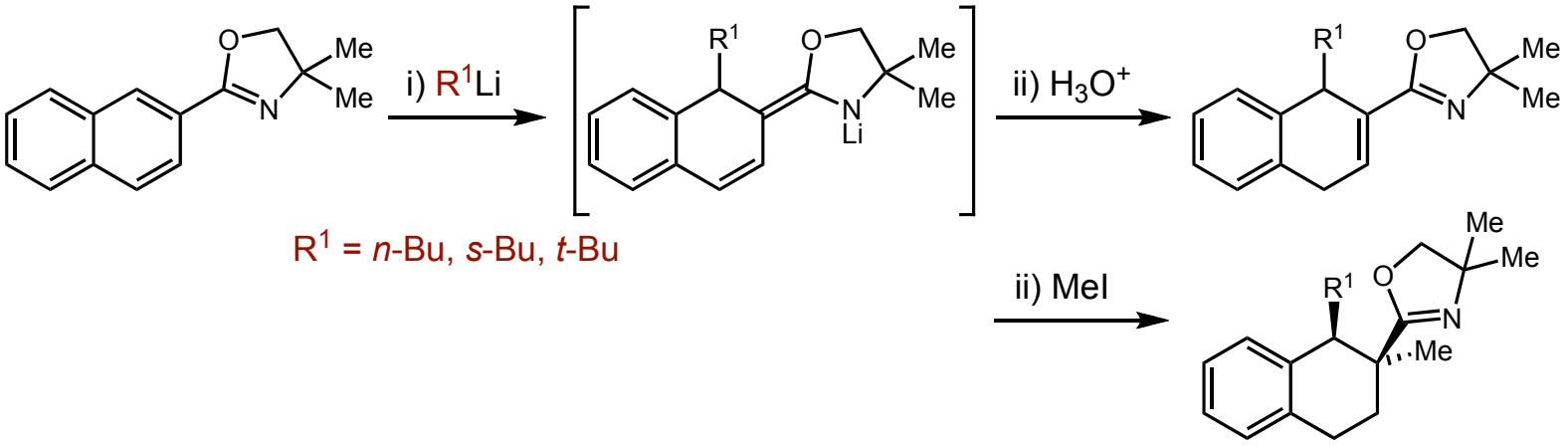
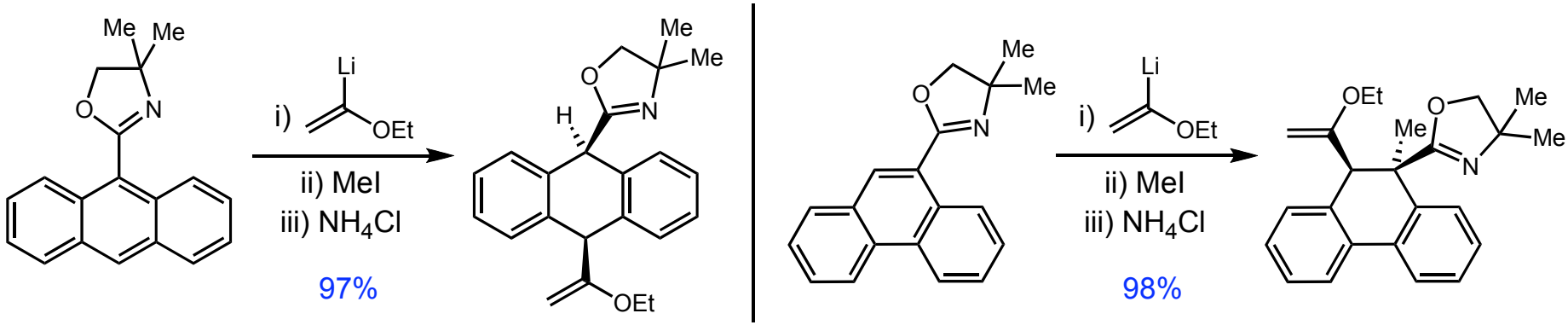


Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107

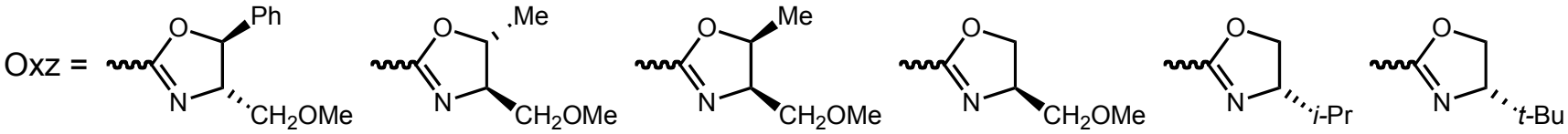
■ Only examples of non-naphthalene oxazolines

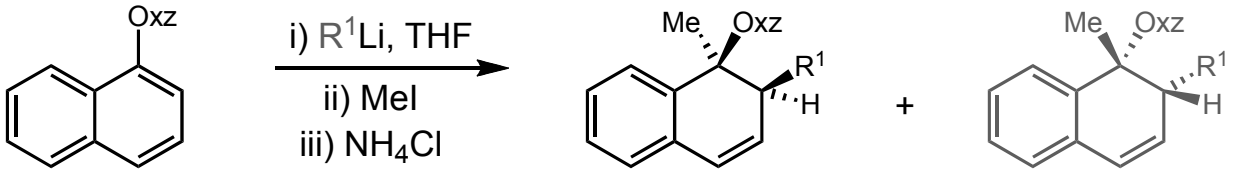


James, B.; Meyers, A. I. *Tetrahedron Lett.* **1998**, *39*, 5301

D_NAr with Activation by an Oxazoline: C Nucleophiles

- Oxazolines can be chiral



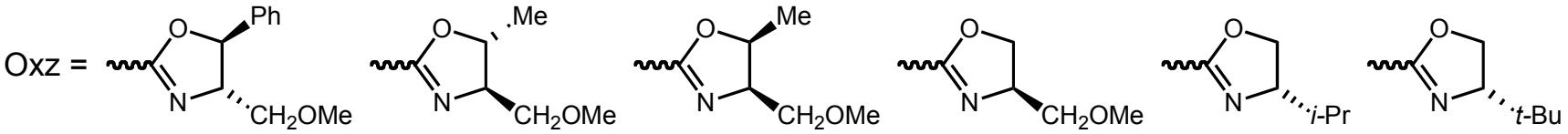


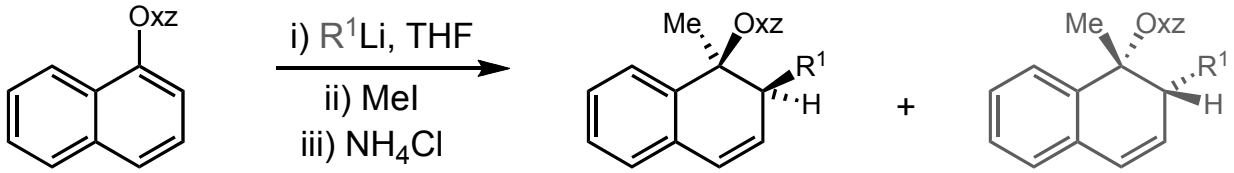
R^1 = Me, Et, Ph, *i*-Pr, allyl, *n*-BuLi, *s*-BuLi, *t*-BuLi, vinyl

66-99% y & upto >99% ee

D_NAr with Activation by an Oxazoline: C Nucleophiles

- Oxazolines can be chiral

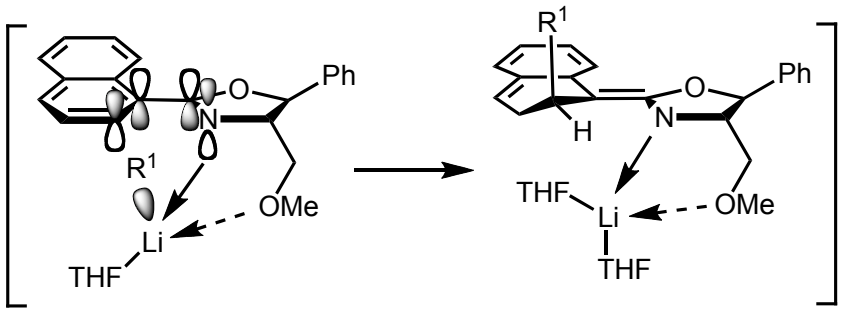




R^1 = Me, Et, Ph, *i*-Pr, allyl, *n*-BuLi, *s*-BuLi, *t*-BuLi, vinyl

66-99% y & upto >99% ee

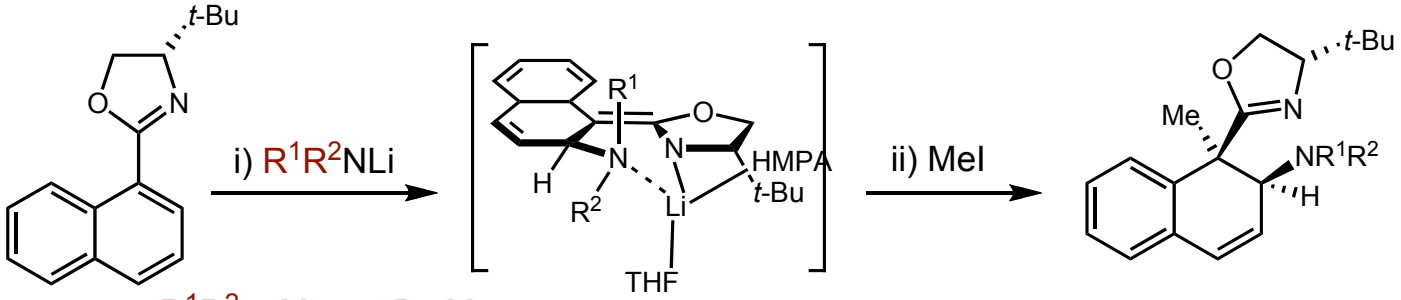
- Stereocentre at C4 of oxazoline controls facial selectivity



Rawson D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292

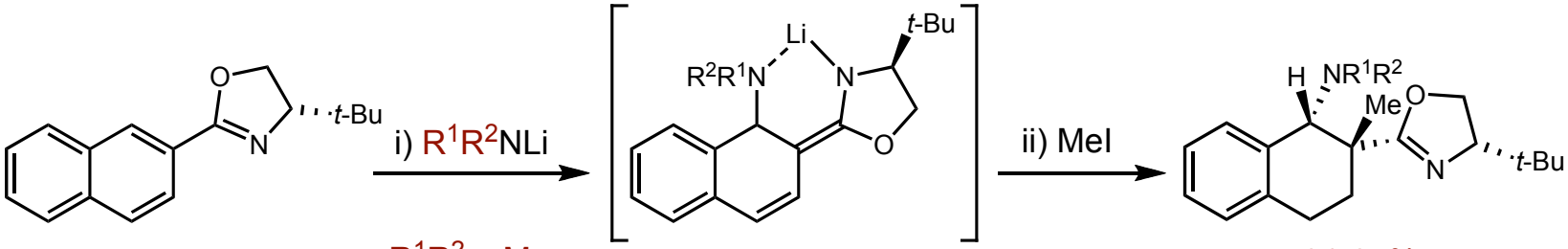
D_NAr with Activation by an Oxazoline: N Nucleophiles

- First direct amination of naphthalene nucleus



R^1R^2 = Me_2, *n*-Bu Me, *n*-C_5H_{11} Me, $(CH_2)_5$

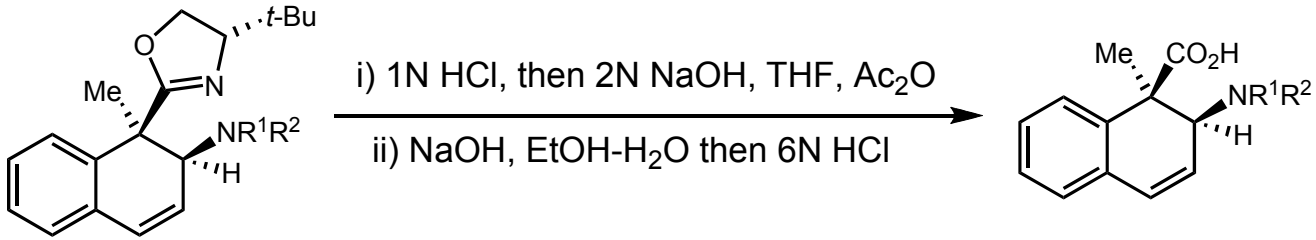
92-96% y



R^1R^2 = Me_2, $(CH_2)_4$, $(CH_2)_5$

91-94% y

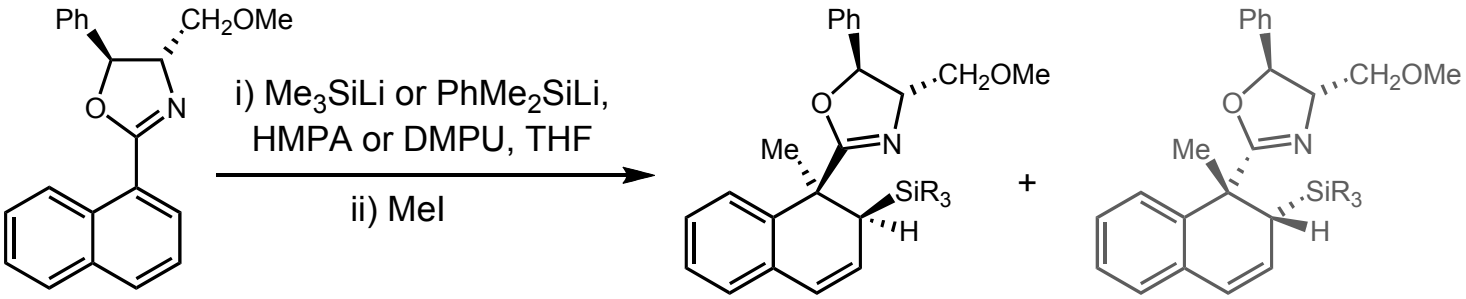
- Products could be converted to β-amino acids



Shimano M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7445

D_NAr with Activation by an Oxazoline: Si Nucleophiles

- Contrasting reactivity with Si nucleophiles

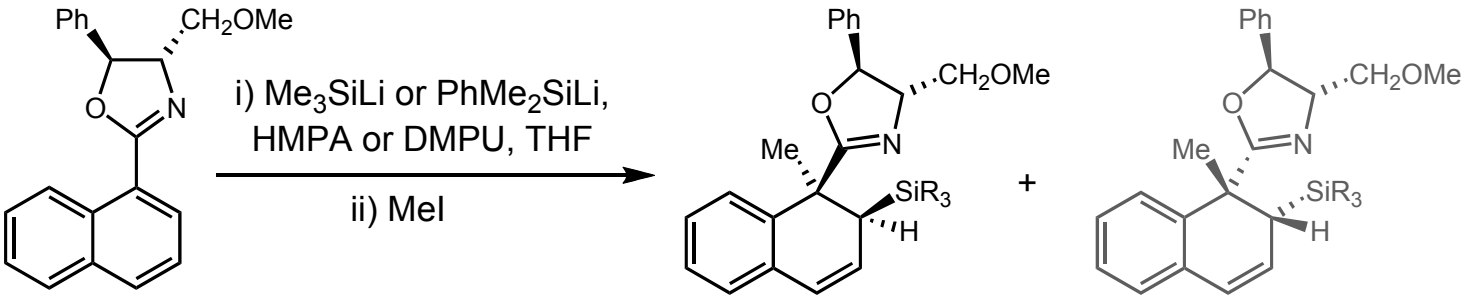


70-76% y in ~ 1 : 1 ratio

3 : 1 Et_2O : THF = >90% ee

D_NAr with Activation by an Oxazoline: Si Nucleophiles

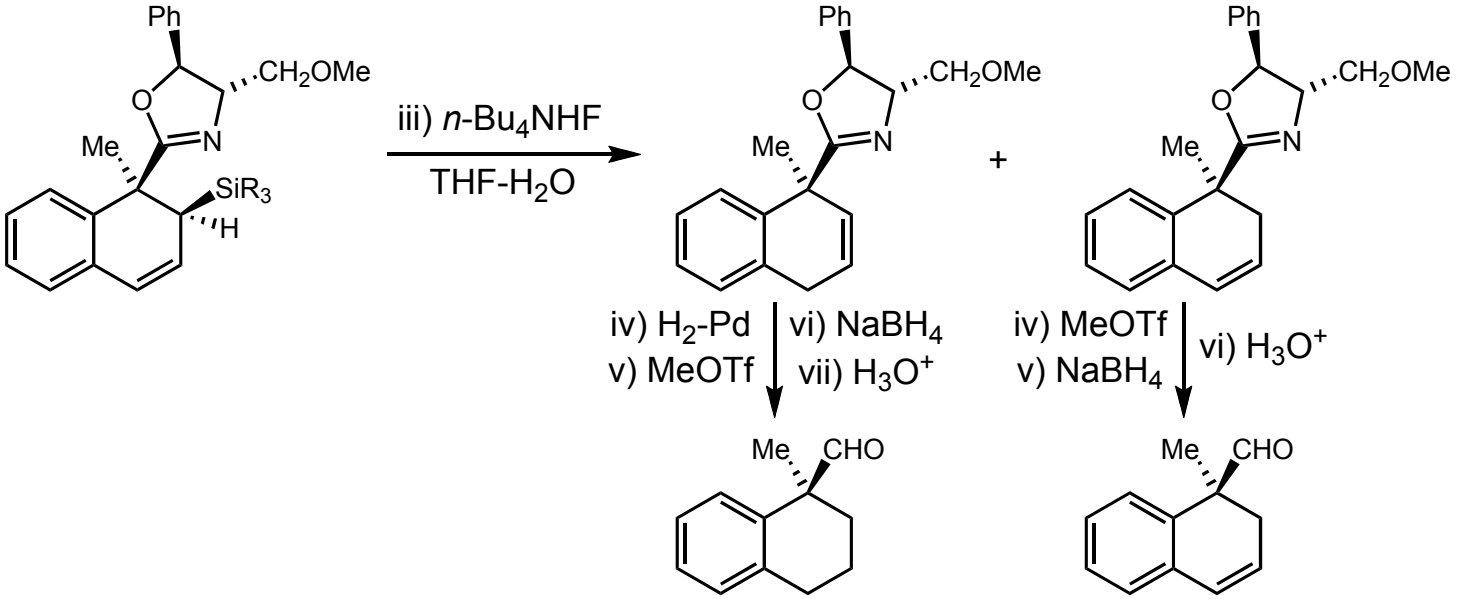
■ Contrasting reactivity with Si nucleophiles



70-76% y in ~ 1 : 1 ratio

3 : 1 Et_2O : THF = >90% ee

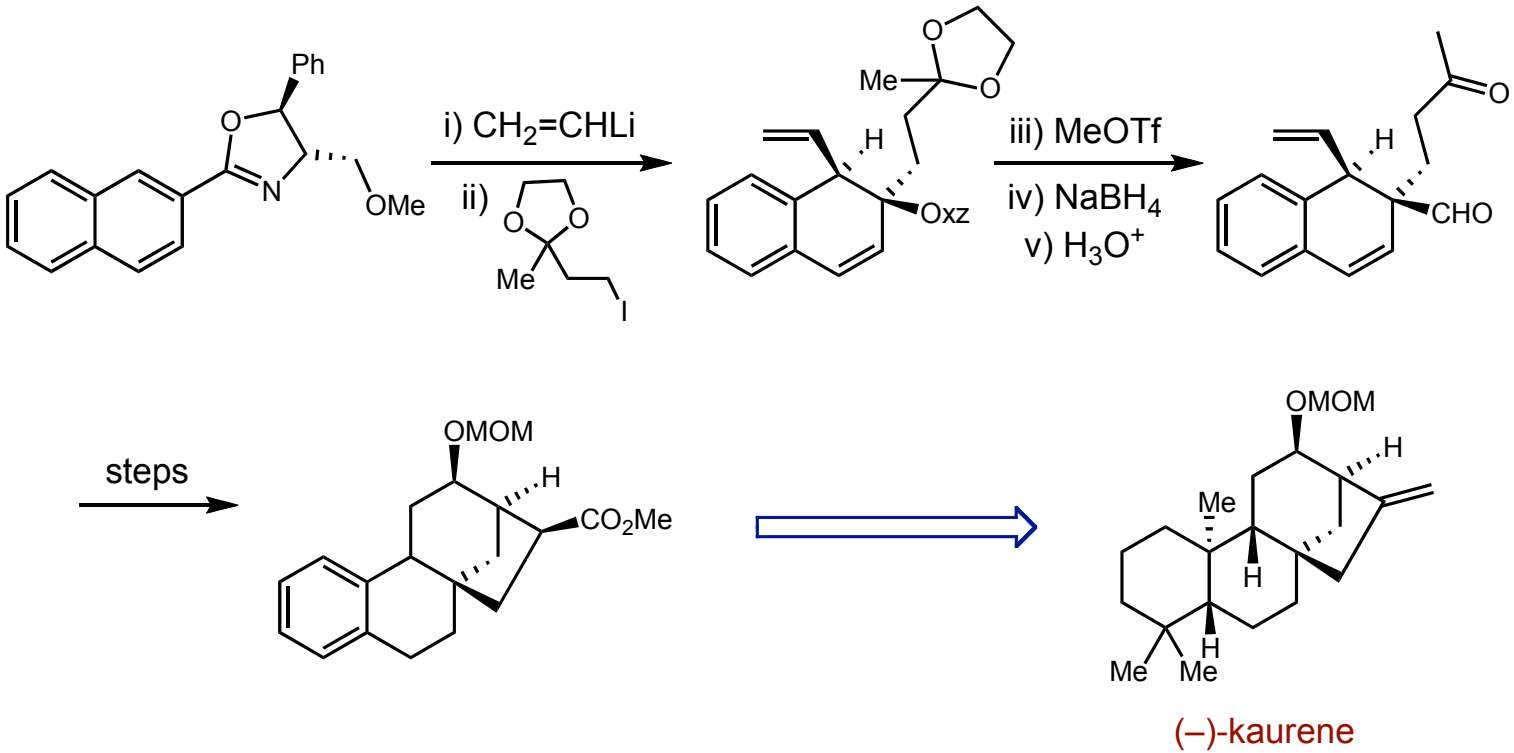
■ Oxazoline product could be converted to two quarternary substituted aldehydes



Hulme, A.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 952

D_NAr with Activation by an Oxazoline

- Synthetic Applications: many examples in natural product chemistry
- Limited to condensed aromatic hydrocarbons



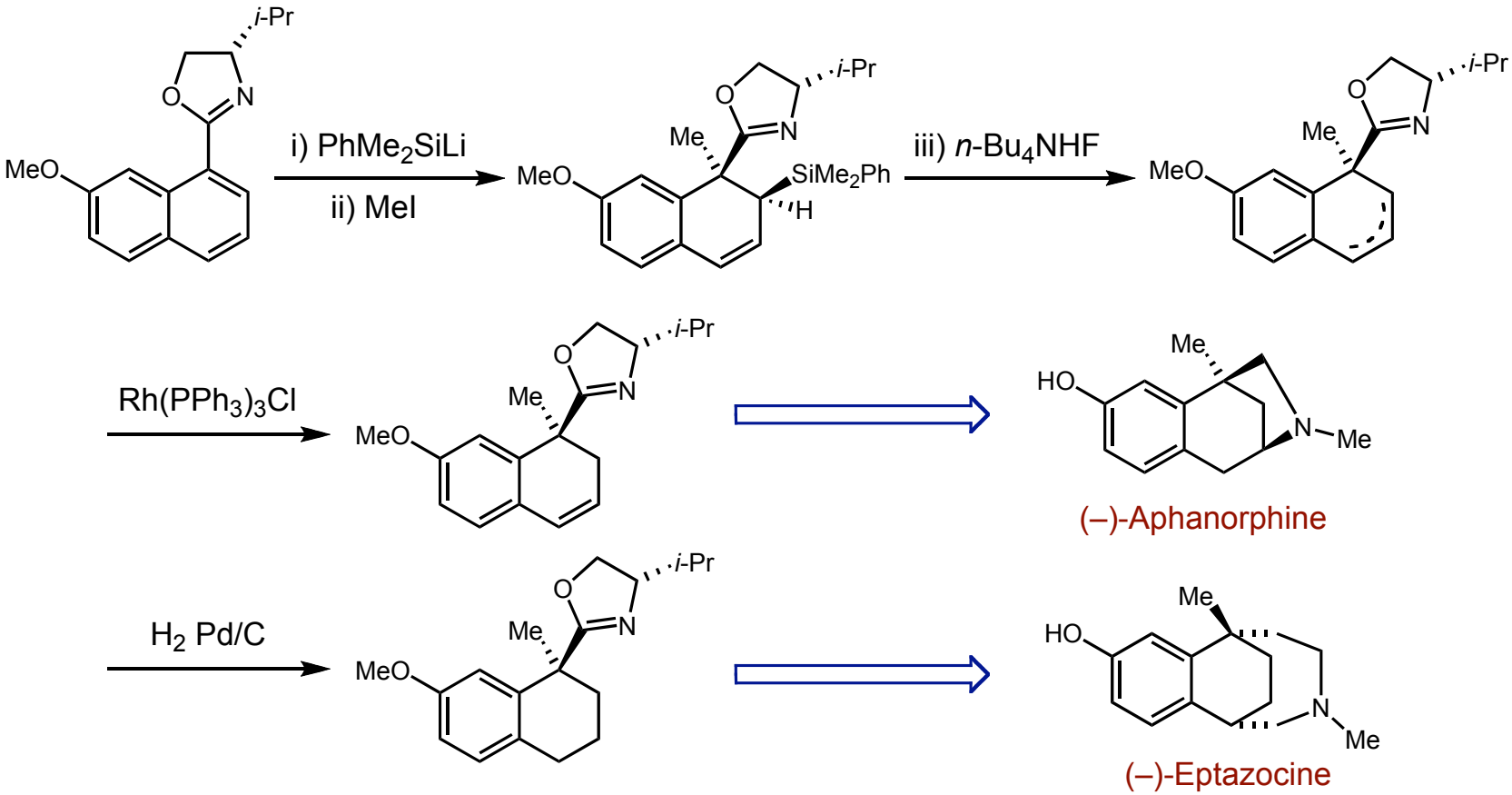
(–)-kaurene

- Tetracyclic ring system present in diterpenes of kaurane family

Robichaud A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607

D_NAr with Activation by an Oxazoline

- Synthetic Applications: many examples in natural product chemistry
- Limited to condensed aromatic hydrocarbons

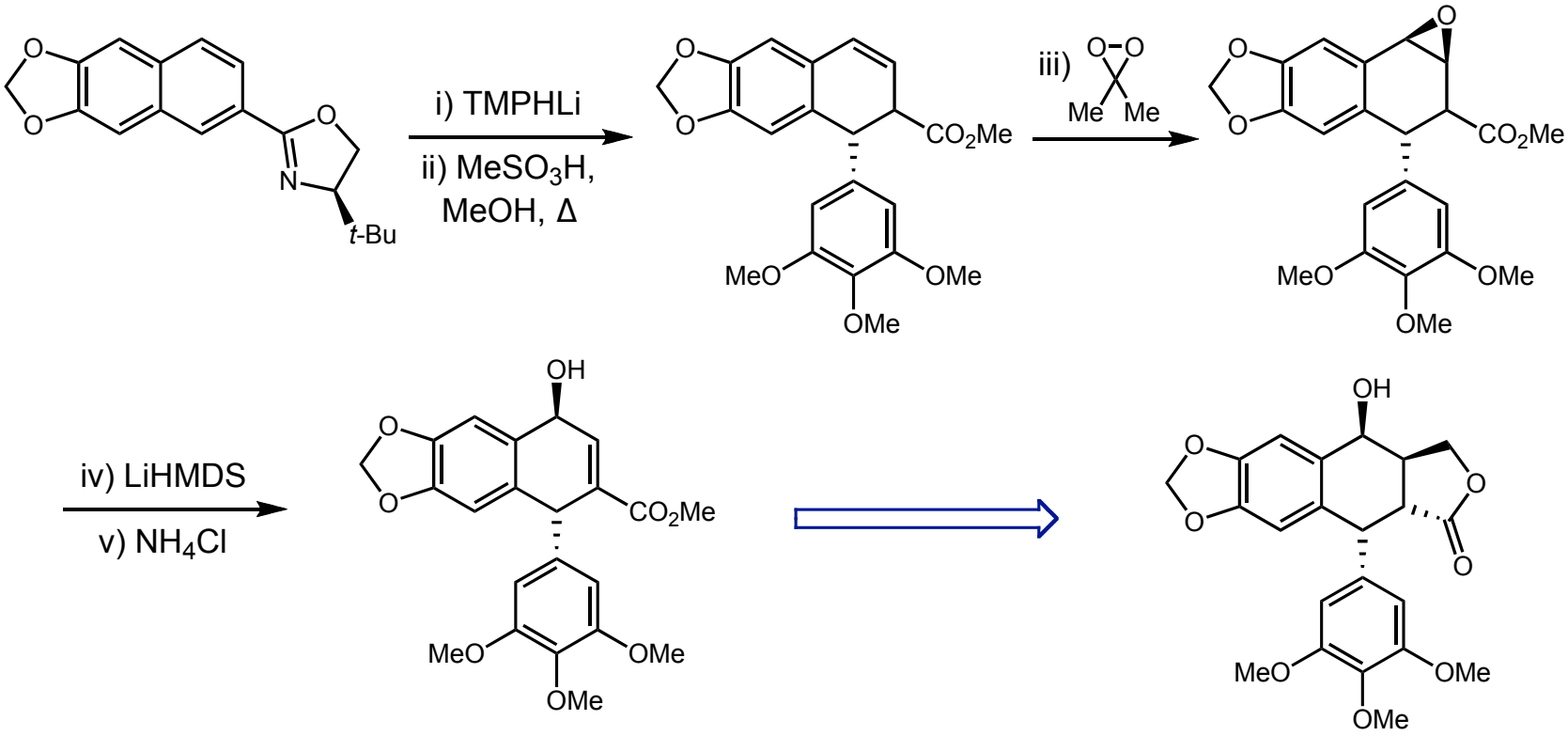


- Known precursors for two alkaloids (a narcotic and an analgesic)

Hulme A. N.; Henry S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265

D_NAr with Activation by an Oxazoline

- Synthetic Applications: many examples in natural product chemistry
- Limited to condensed aromatic hydrocarbons



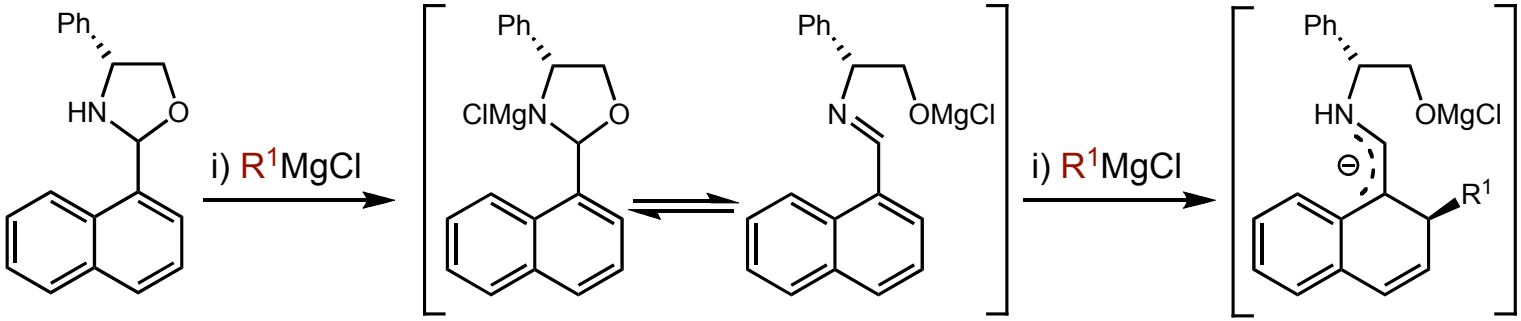
(–)-epi-podophyllotoxin

- Four additional steps gave the natural product

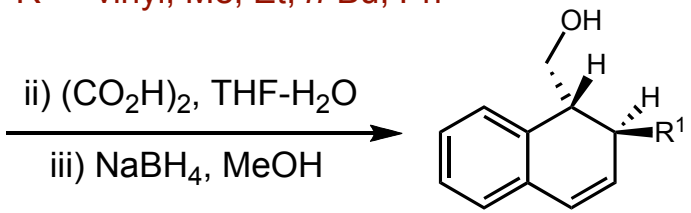
Engelhardt, U.; Sarkar, A.; Linker, T. *Angew. Chem. Int. Ed.* **2003**, *42*, 2487

D_NAr with Activation by an Oxazolidine

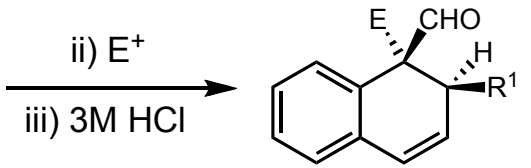
- Developed in parallel to oxazoline studies by Meyers' Group



R^1 = vinyl, Me, Et, *n*-Bu, Ph



65-83% y 93-96% ee

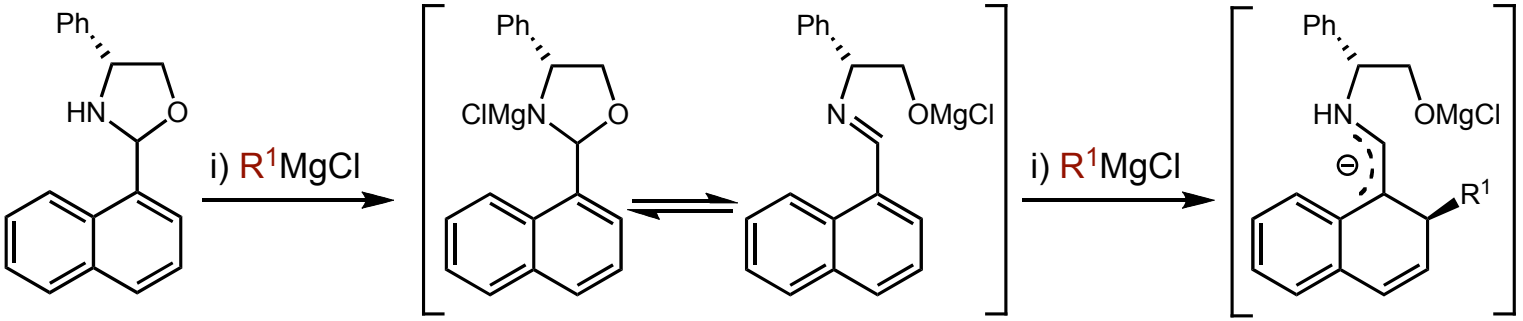


70-89% y 74-99% ee

Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237

D_NAr with Activation by an Oxazolidine

- Developed in parallel to oxazoline studies by Meyers' Group



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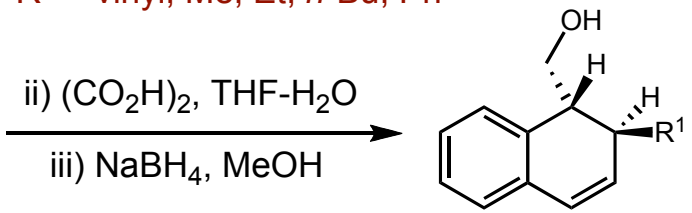

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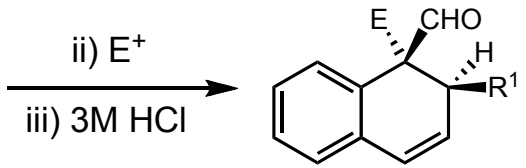
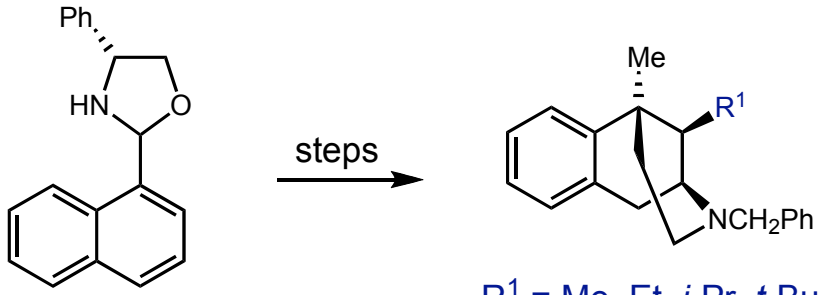


70-89% y 74-99% ee

Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237

- Synthetic Applications: synthesis of (–)-morphine analogues (benzomorphans)



33-53% overall yield
all >99% ee

R^1 = Me, Et, *i*-Pr, *t*-Bu

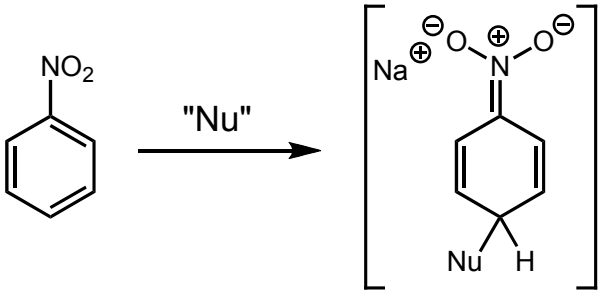
Carroll, F. I.; Bai, X.; Dehghami, A.; Mascarella, S. W.; Williams, W.; Bowen, W. D. *J. Med. Chem.* **1999**, *42*, 4621

D_NAr with Activation by a Nitro Group

- Best substituent for making an aromatic ring electron-deficient
- Has been reviewed a number of times

Strauss, M. *Chem. Rev.* **1970**, *70*, 667

Makosza, M; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631



Nu = oxygen nucleophile - Meisenheimer complex

Nu = nitrogen nucleophile - Jackson- Meisenheimer complex

Nu = carbon nucleophile - Janovsky complex

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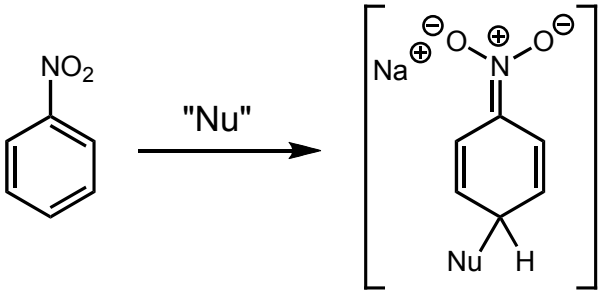
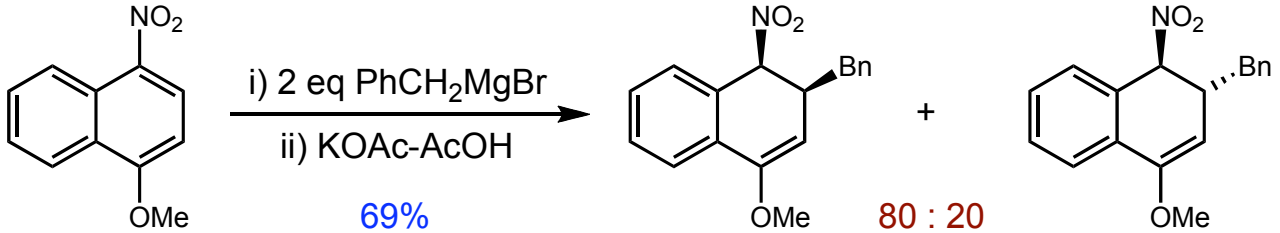


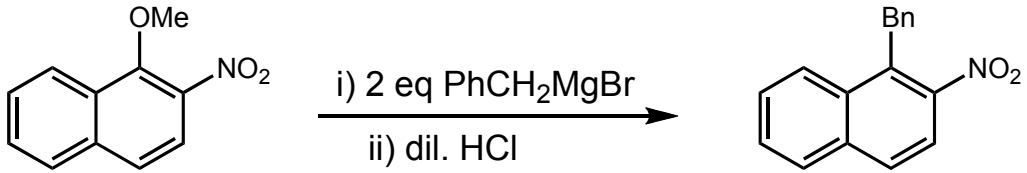
Nu = oxygen nucleophile - Meisenheimer complex

Nu = nitrogen nucleophile - Jackson- Meisenheimer complex

Nu = carbon nucleophile - Janovsky complex

- General patterns of reactivity



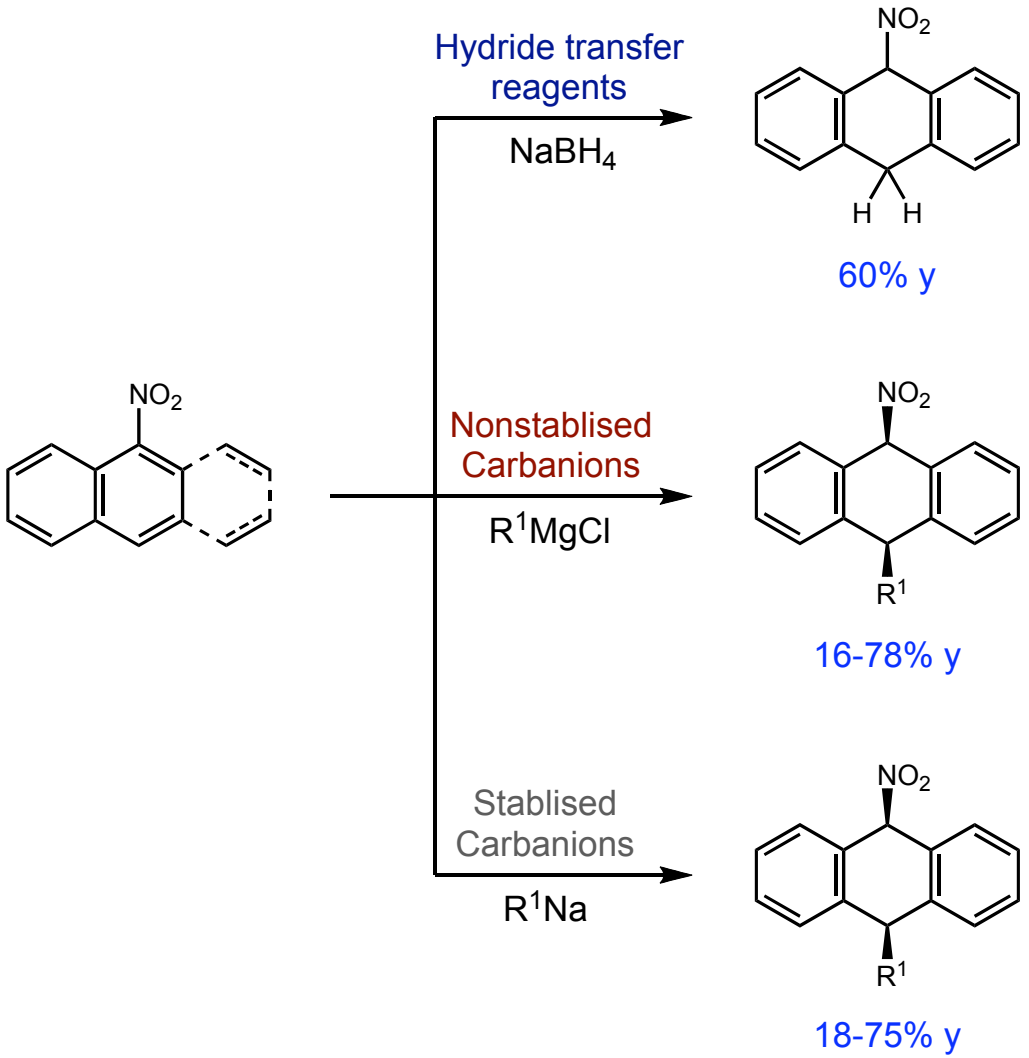


Bartoli, G.; Bosco, M.; Baccolini G., *J. Org. Chem.* **1980**, *45*, 2649

Bartoli, G.; Bosco, M.; Melandri A.; Boicelli A. C. *J. Org. Chem.* **1979**, *44*, 2089

D_NAr with Activation by a Nitro Group

- Reaction with many nucleophiles has been observed - mono-nitro arenes



Ortiz, F. L.; Iglesias, M. J.; Fernandez, I.; Sanchez, C. M. A.; Gomez, G. R. *Chem. Rev.* **2007**, *107*, 1580

D_NAr with Activation by a Nitro Group

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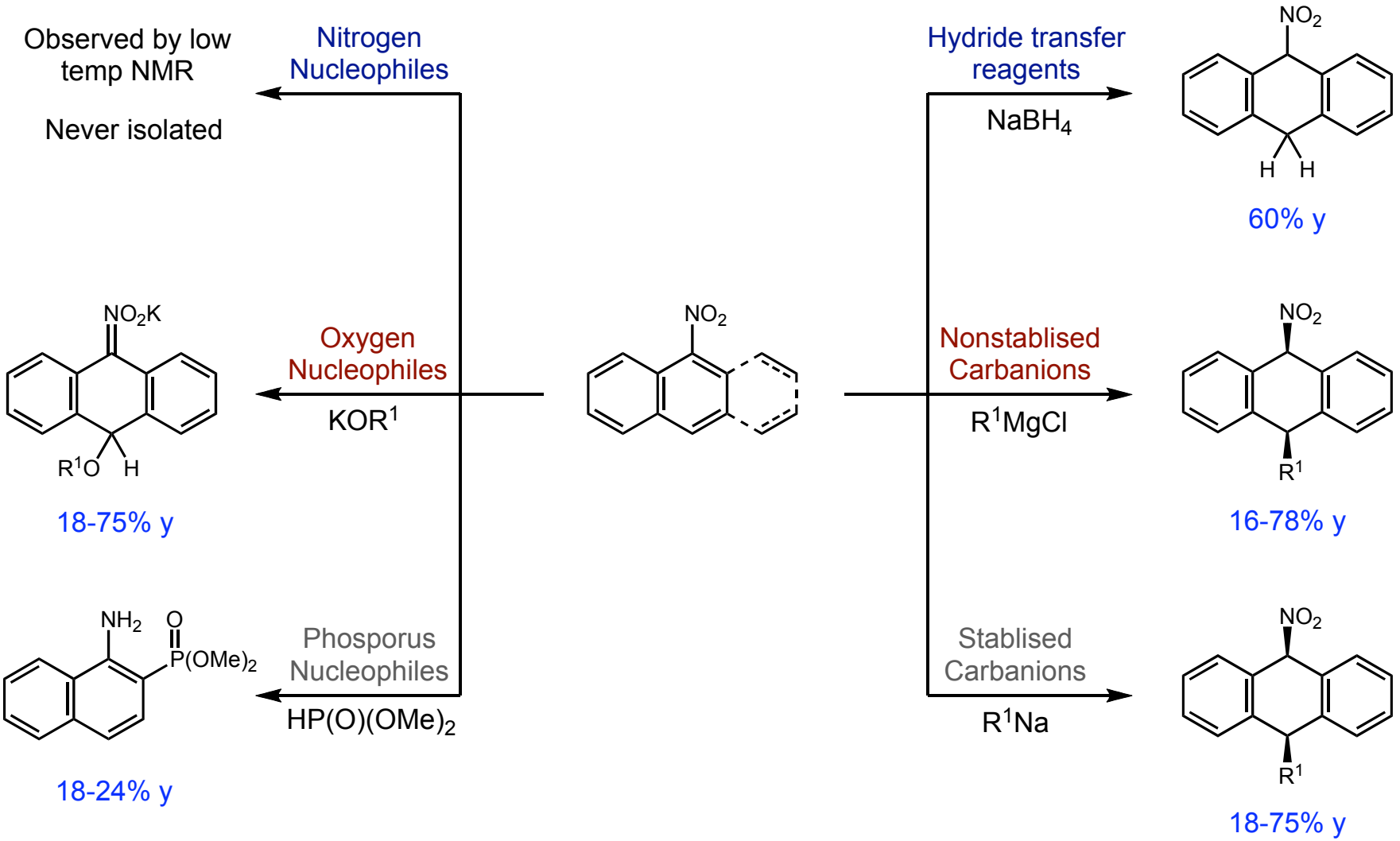
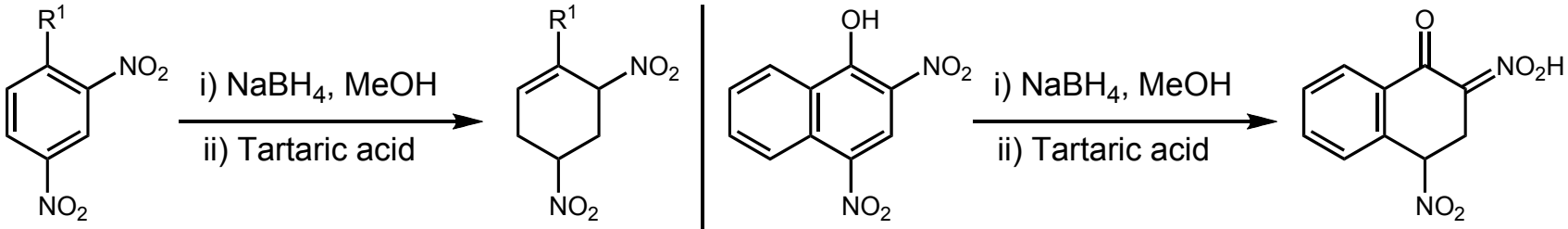


Ortiz, F. L.; Iglesias, M. J.; Fernandez, I.; Sanchez, C. M. A.; Gomez, G. R. *Chem. Rev.* **2007**, *107*, 1580

D_NAr with Activation by a Nitro Group

- Reaction with many nucleophiles has been observed - di-nitro arenes



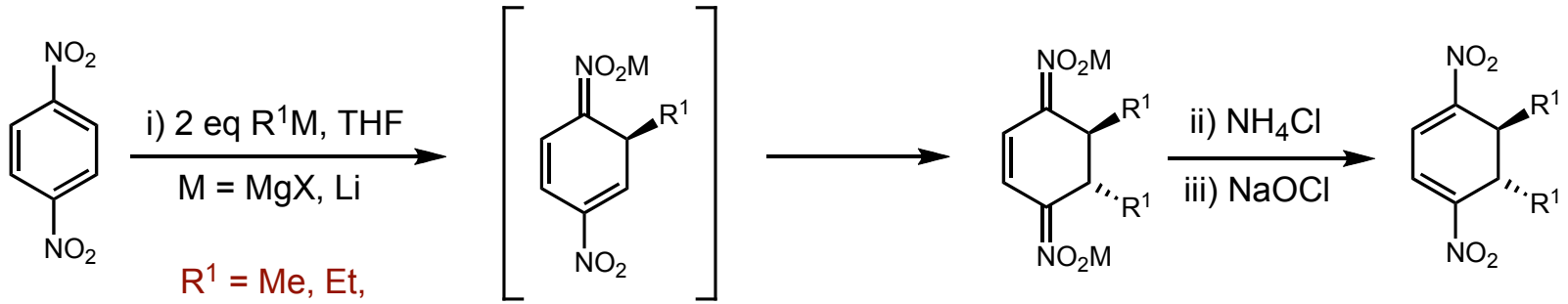
R^1 = Cl, Br, Me, CO_2H, CH=CHPh

22-55% y

90% y

Severin, T.; Schmitz, R. *Chem. Ber.* **1962**, *95*, 1417

- Increasing the electron deficiency of the arene allows double alkylation

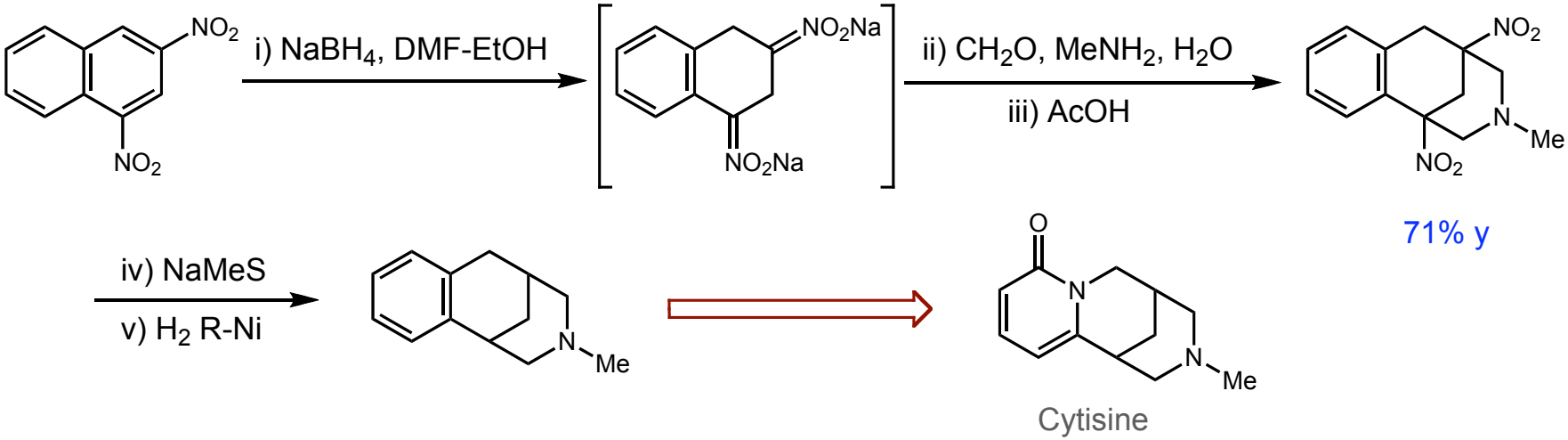


17-56% y

Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R.; Ciminale, F. *J. Chem. Soc. Perkin Trans. 2* **1985**, 773

D_NAr with Activation by a Nitro Group

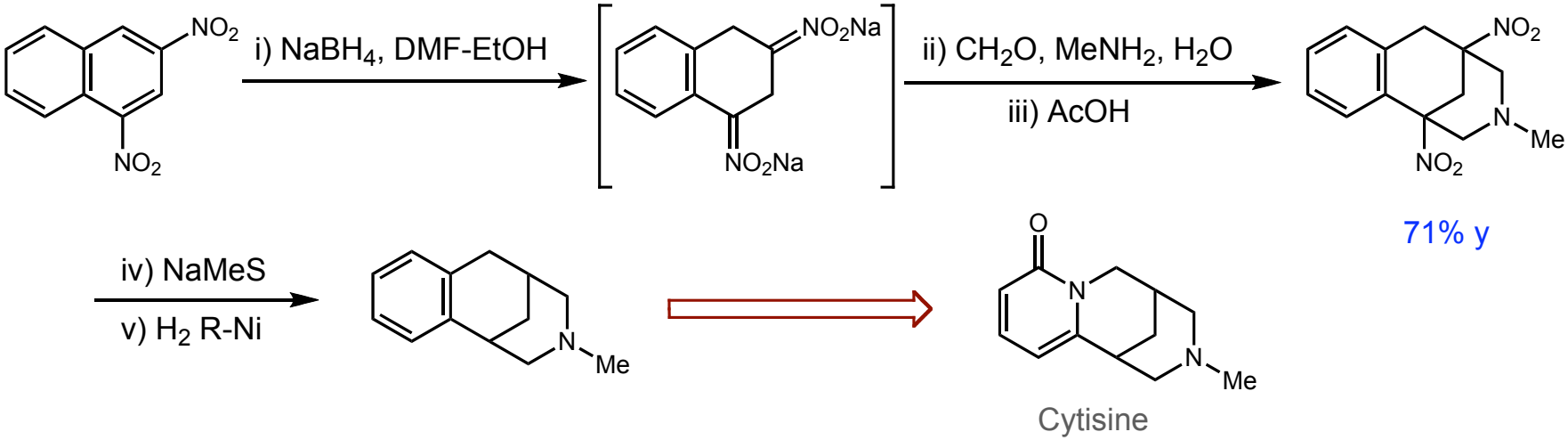
- Synthetic Applications - di-nitro arenes



Blackall, K. J.; Hendry, D.; Pryce, R. J.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2767

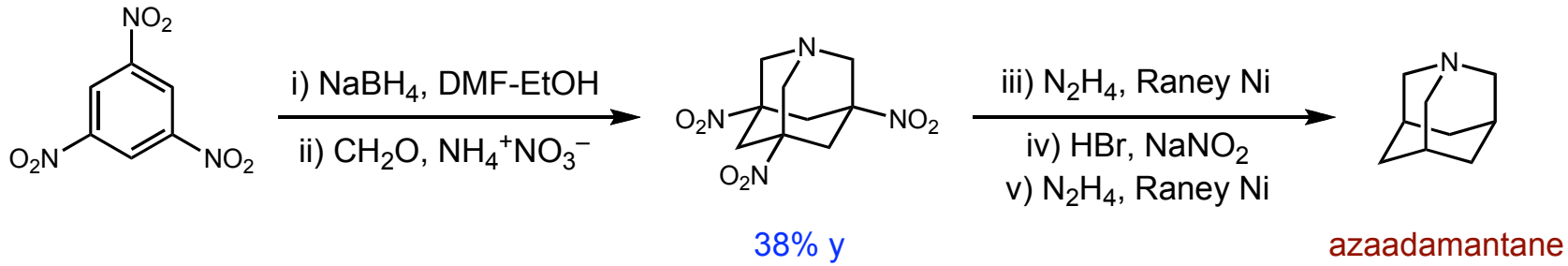
D_NAr with Activation by a Nitro Group

Synthetic Applications - di-nitro arenes



Blackall, K. J.; Hendry, D.; Pryce, R. J.; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1995**, 2767

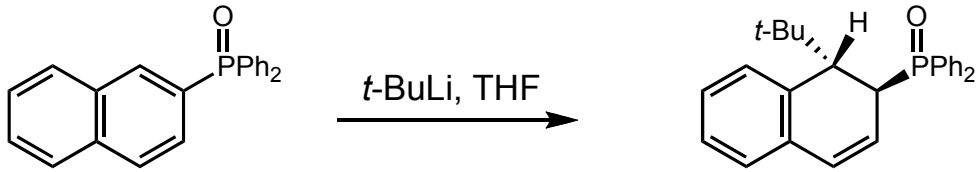
Synthetic Applications - tri-nitro arenes



Kutznezov, A. I.; Beer, A. M. *Chem. Abstr.* **1991**, *114,* 81541

D_NAr with Activation by a Phosphinamide Group

- Attempted *ortho*-lithiation led to addition product

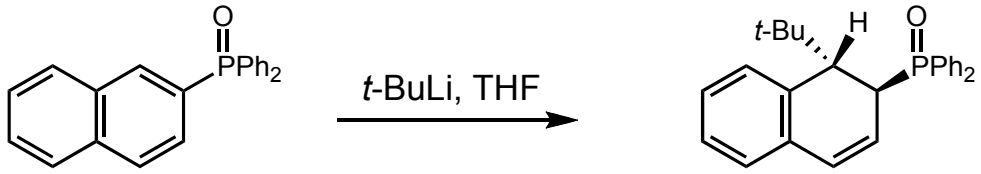


exclusive product

Alcock, N. W.; Brown, J. M.; Pearson, M.; Woodward, S. *Tetrahedron: Asymmetry* **1992**, *3*, 17

D_NAr with Activation by a Phosphinamide Group

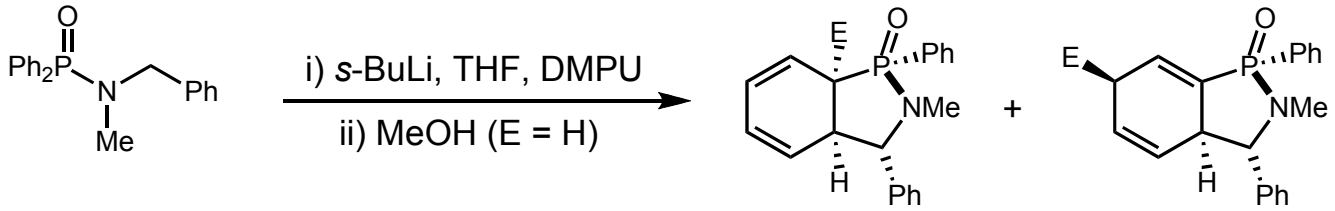
- Attempted *ortho*-lithiation led to addition product



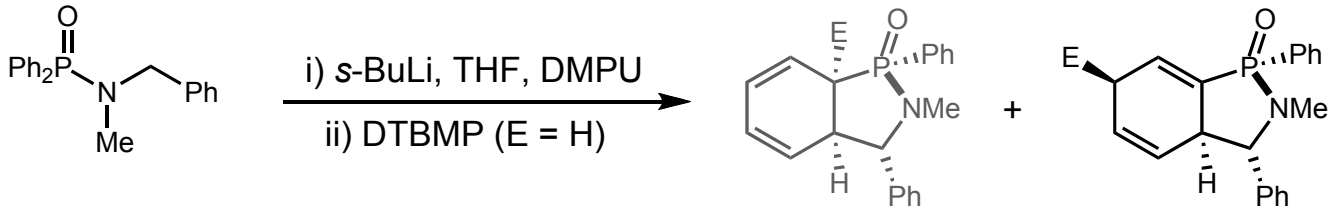
exclusive product

Alcock, N. W.; Brown, J. M.; Pearson, M.; Woodward, S. *Tetrahedron: Asymmetry* **1992**, *3*, 17

- Different proton sources led to different dearomatised products



65% y 18% y



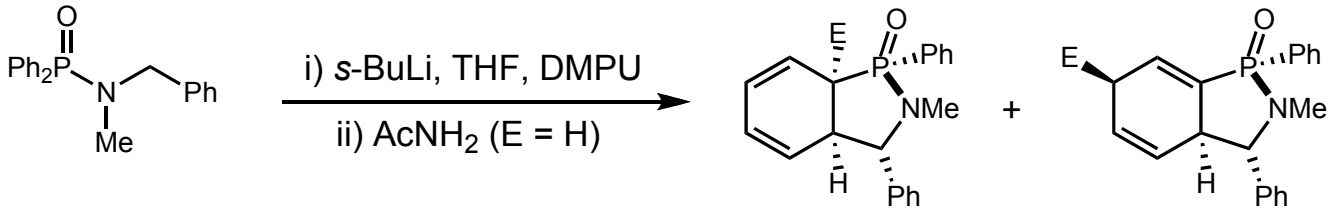
0% y 97% y

- Other electrophiles (MeI, EtI, BnBr, AllylBr) gave mixtures of all products

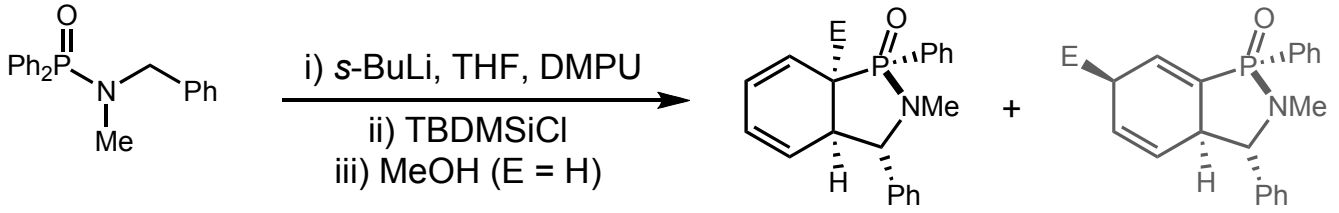
Fernandez, I; Lopez-Ortiz, F.; Garcia-Granda, S. *J. Org. Chem.* **2002**, *67* , 3852

D_NAr with Activation by a Phosphinamide Group

- Later results were greatly improved



81% y 91 : 9 ratio

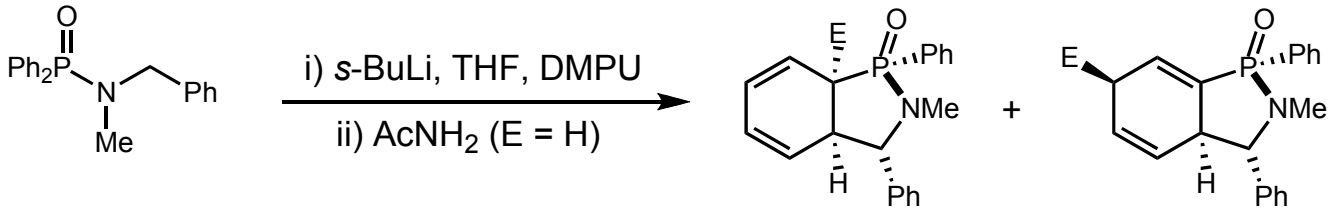


96% y 0% y

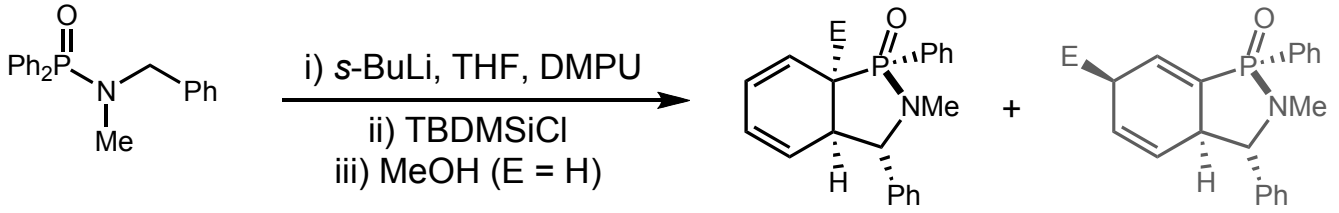
Fernandez, I; Lopez-Ortiz, F.; Garcia-Granda, S. *Chem. Commun.* **2005**, 5408

D_NAr with Activation by a Phosphinamide Group

■ Later results were greatly improved



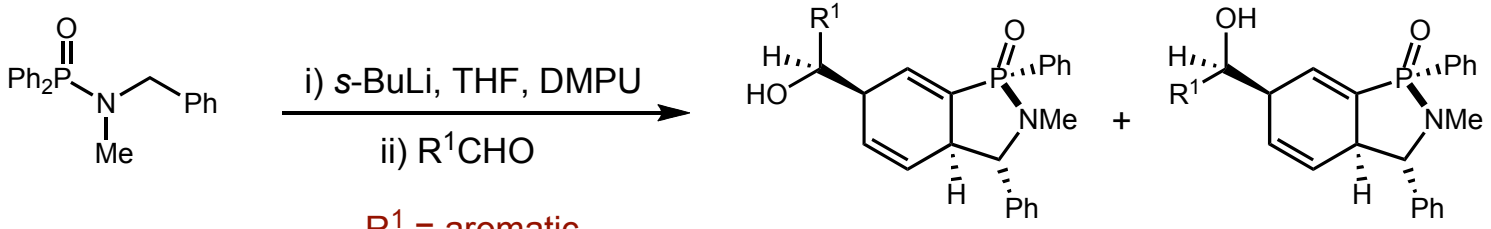
81% y 91 : 9 ratio



96% y 0% y

Fernandez, I; Lopez-Ortiz, F.; Garcia-Granda, S. *Chem. Commun.* **2005**, 5408

■ Aldehydes proved to be excellent electrophiles



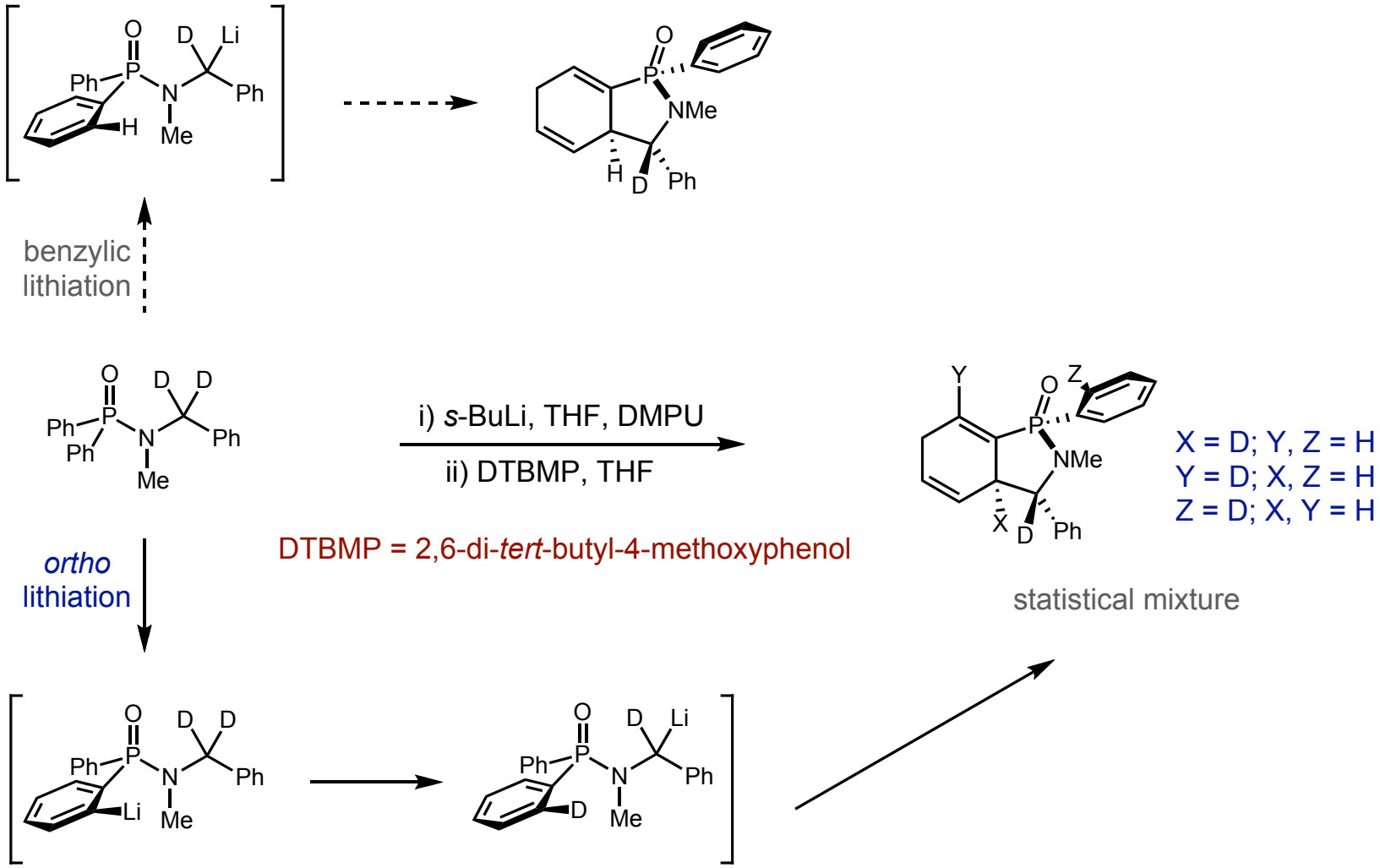
R^1 = aromatic or aliphatic

74 : 26 - 85 : 15 ratio

Fernandez, I; Lopez-Ortiz, F.; Garcia-Granda, S. *J. Org. Chem.* **2002**, *67* , 3852

D_NAr with Activation by a Phosphinamide Group

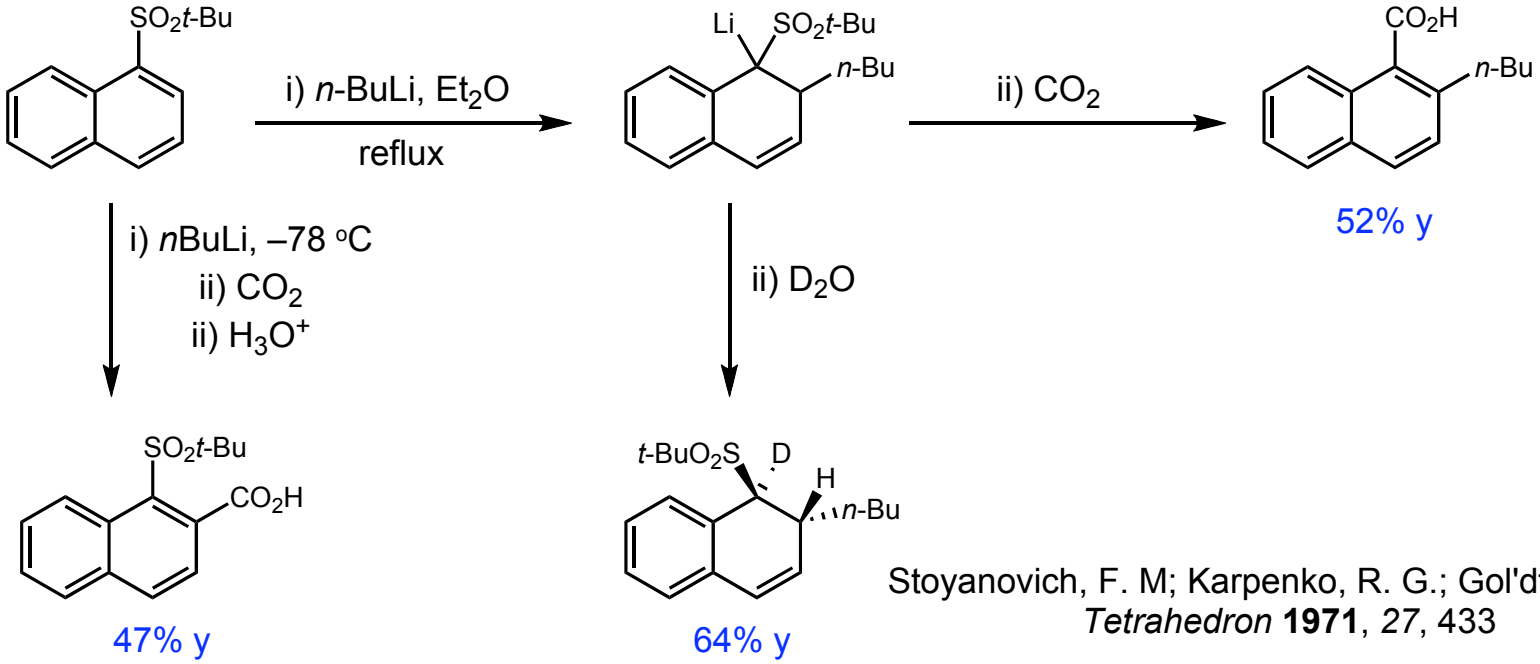
- Mechanistic insight: deuterium label studies



Fernandez, I; Lopez-Ortiz, F.; Garcia-Granda, S. *J. Am. Chem. Soc.* **2004**, *126*, 12551

D_NAr with Activation by a Sulfone Group

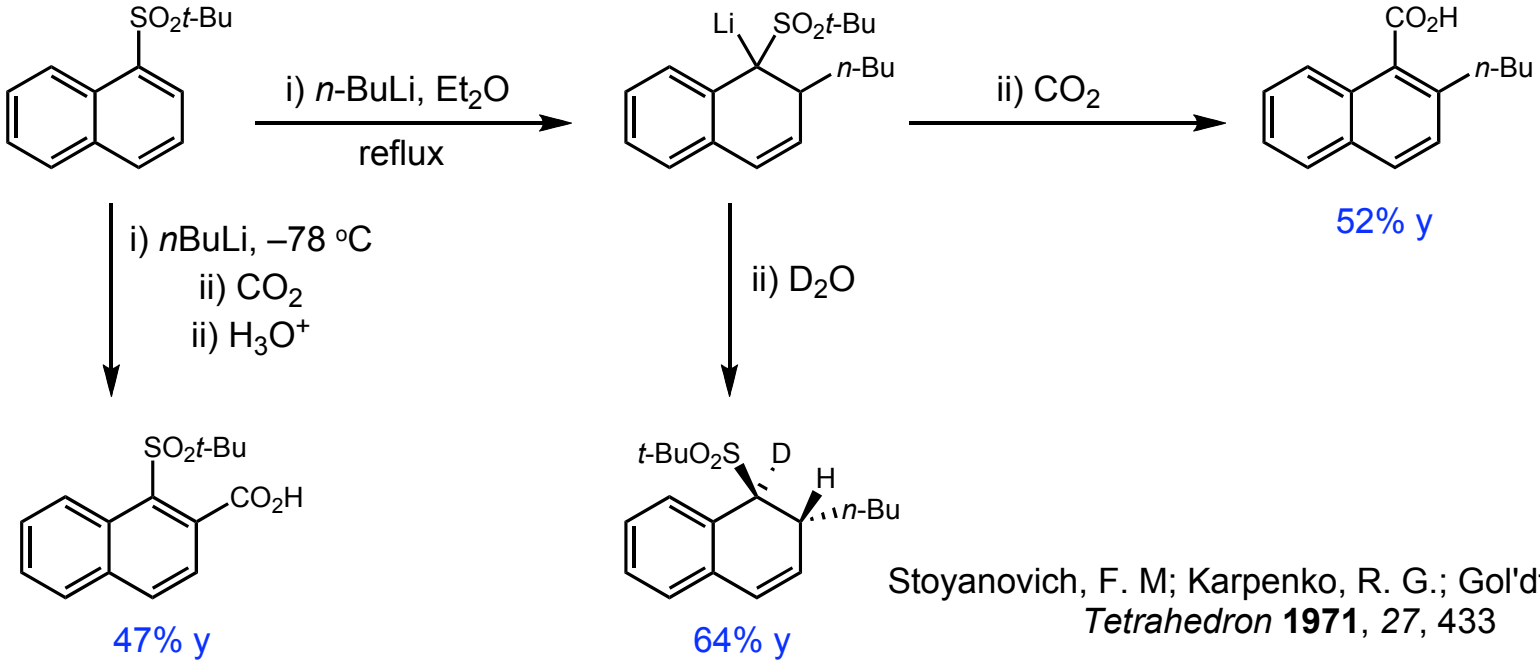
- First discovered by Stoyanovich *et al.*



Stoyanovich, F. M; Karpenko, R. G.; Gol'dfarb, Y. L. *Tetrahedron* **1971**, *27*, 433

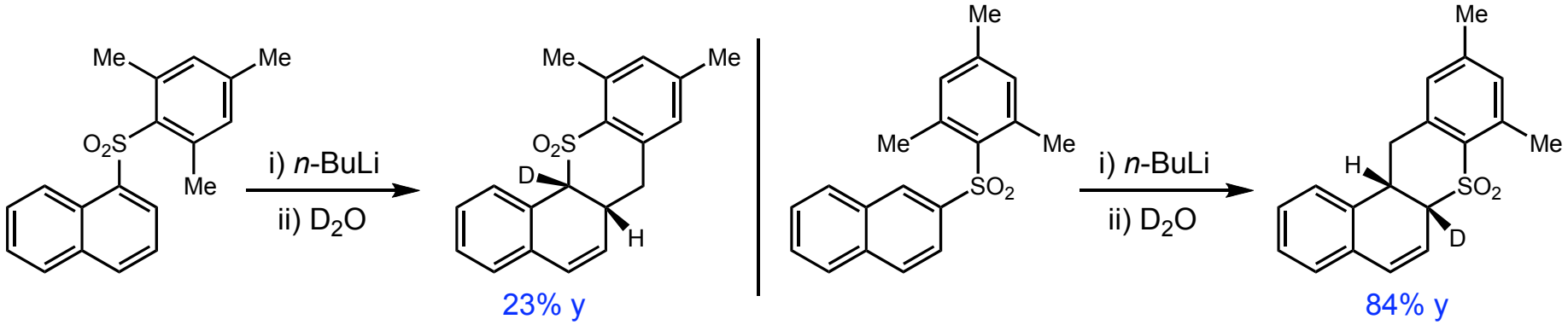
D_NAr with Activation by a Sulfone Group

■ First discovered by Stoyanovich *et al.*



Stoyanovich, F. M; Karpenko, R. G.; Gol'dfarb, Y. L. *Tetrahedron* **1971**, *27*, 433

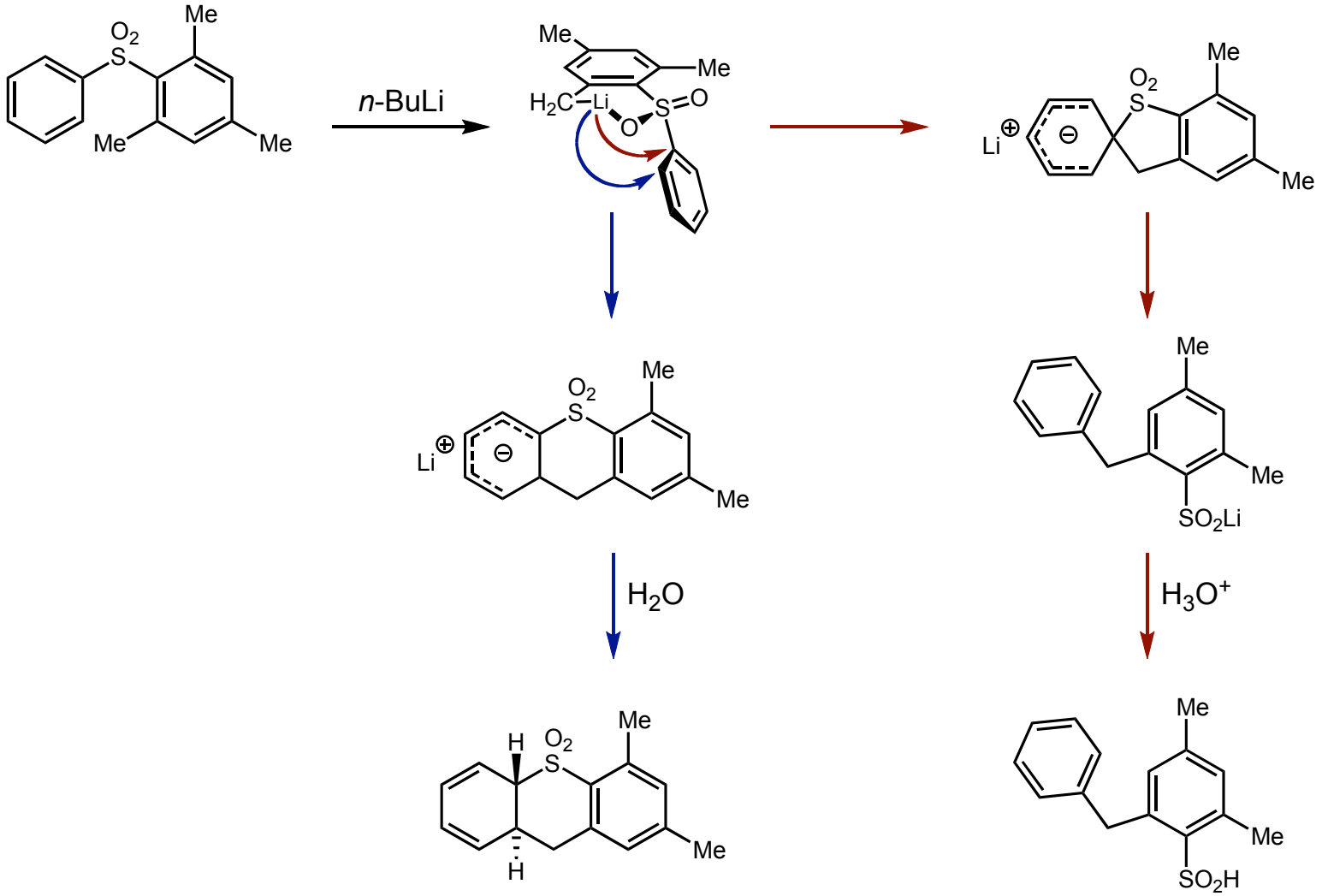
■ Tetracyclic products formed with mesityl sulfones



Drozd, V. N; Pak, K. A.; Ustynyuk, Y. A. *Russ. J. Org. Chem.* **1969**, *5*, 1258

D_NAr with Activation by a Sulfone Group

■ Mechanistic thoughts



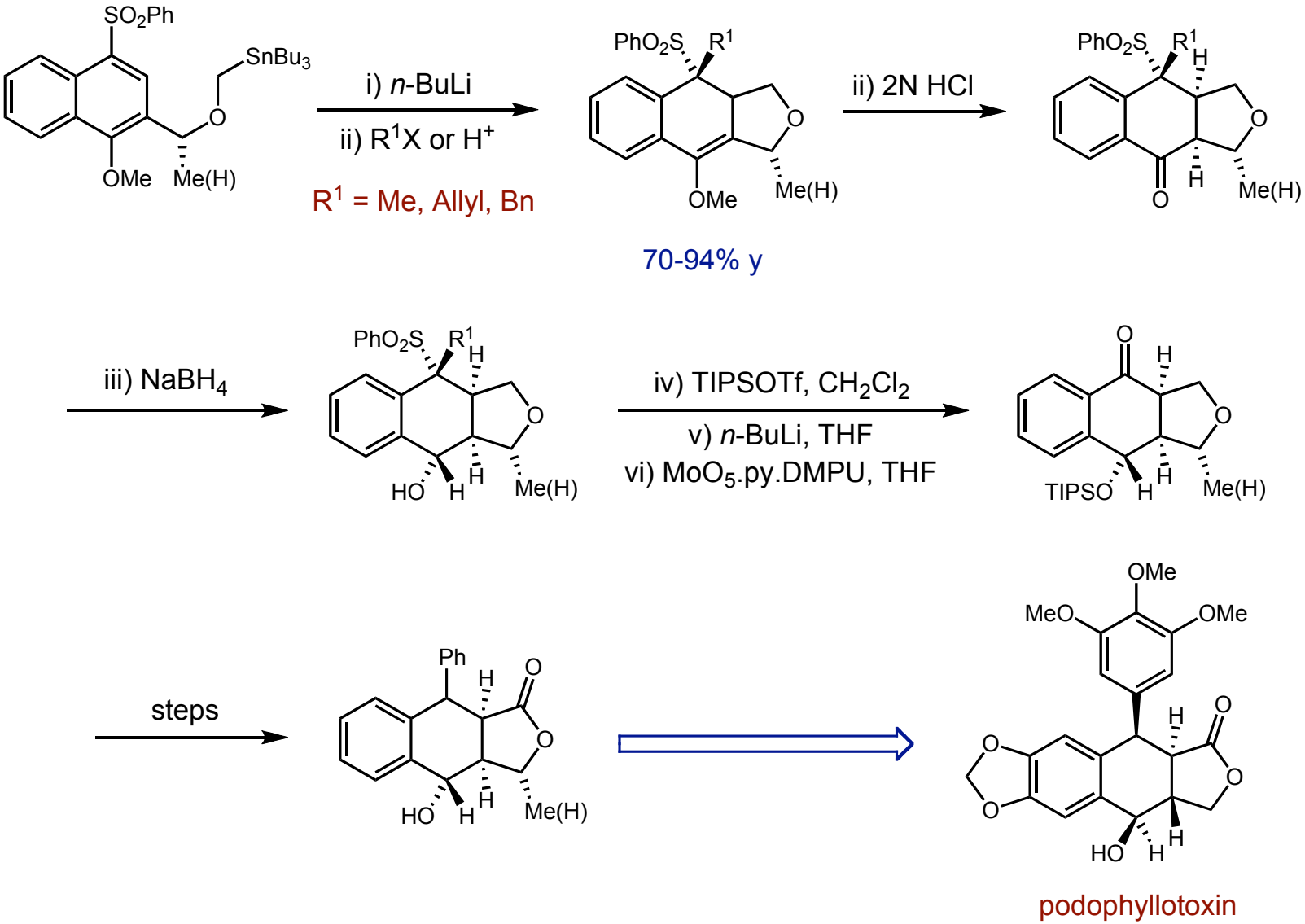
dearomatised product

Smiles product

Drozd, V. N; Pak, K. A.; Ustynyuk, Y. A. *Russ. J. Org. Chem.* **1969**, *5*, 1258

D_NAr with Activation by a Sulfone Group

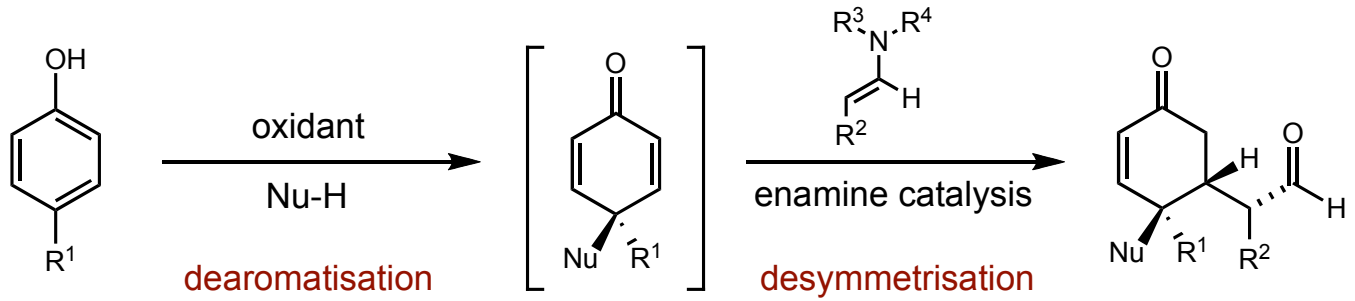
- Synthetic Applications: similar targets to carboxamide section



Clayden, J; Kenworthy, M. N.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831

Saving the best till last?

- An Enantioselective Organocatalytic Oxidative Dearomatisation Strategy
- The concept:



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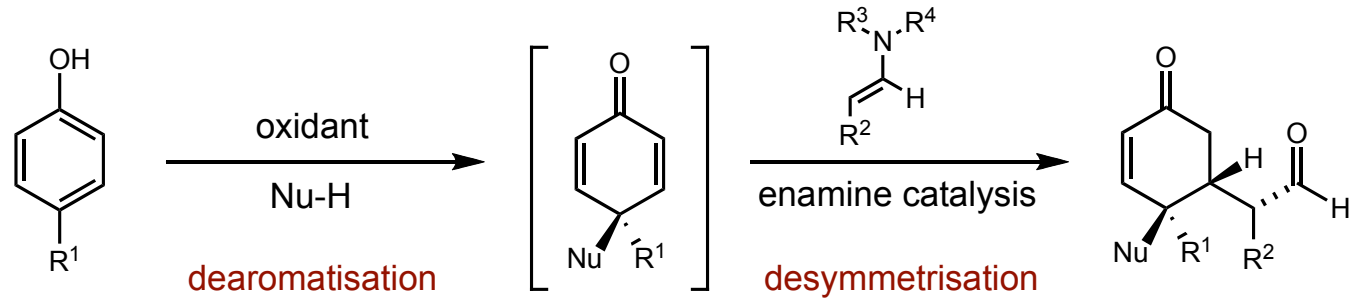
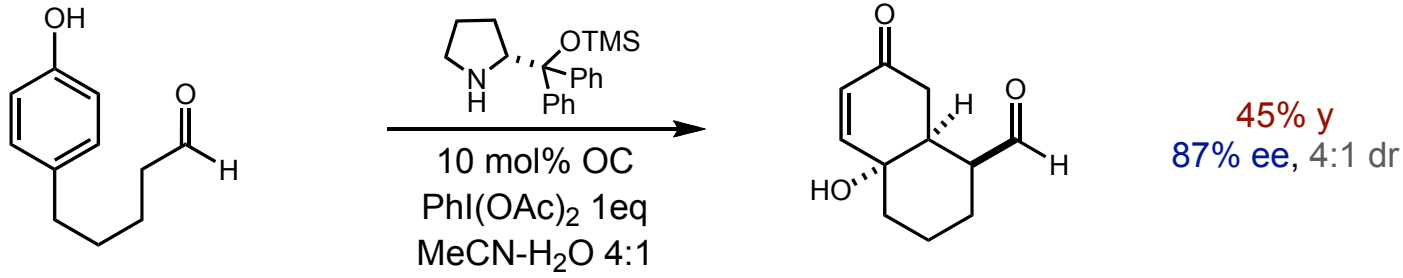


- Preliminary results:



45% y
87% ee, 4:1 dr

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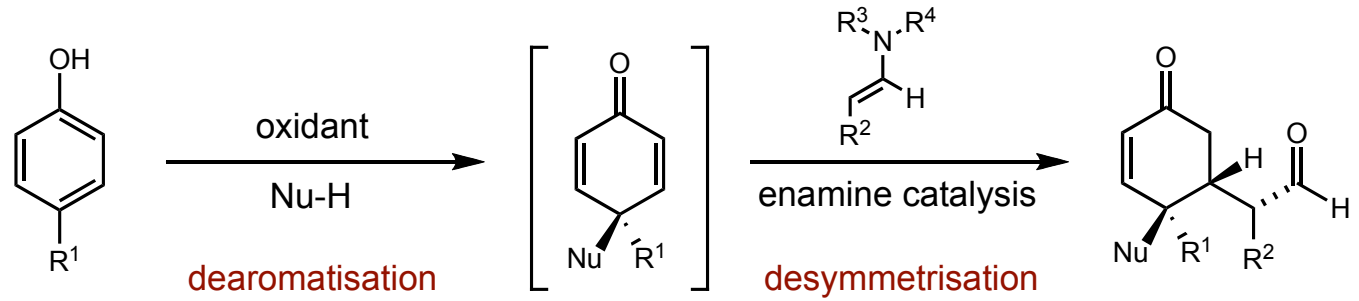
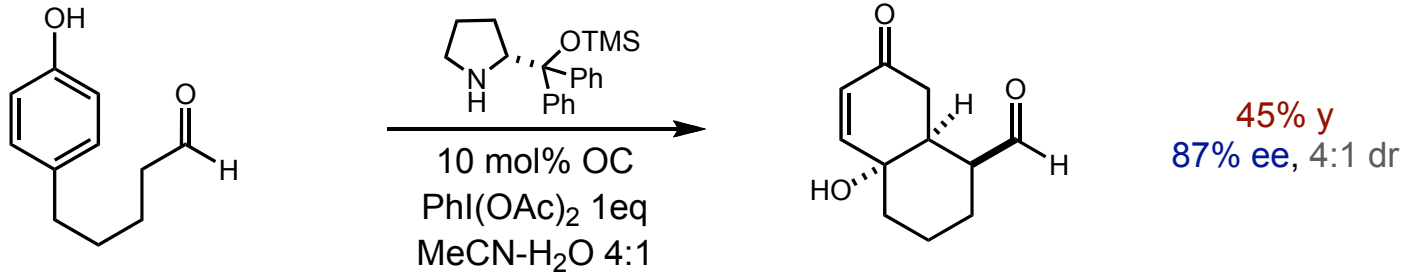
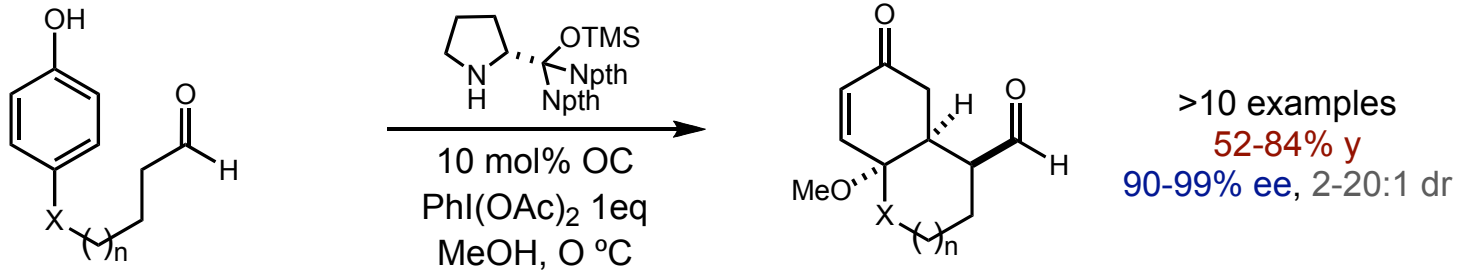


- Preliminary results:



- Optimisation of catalyst, solvent, temperature etc.



Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2007**, *130*, 404

Summary: Nucleophilic Dearomatisation Reactions

- A number of methods allow the nucleophilic dearomatisation of arenes
- Nucleophilic addition to the activating group inhibited by steric effects
- Coordinating solvents can control reaction pathway
- Efficient methods are available for inter- and intra-molecular nucleophilic addition
- Regio- and stereo-chemical outcome can be predicted
- Implemented towards natural product synthesis

- Atom efficiency is an issue

- The first organocatalytic dearomatisation reaction has been acheived

Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2007**, *130*, 404