LSPN Group Seminar

Dearomatisation as a strategy for the synthesis of complex targets: highlight on arenophile-mediated dearomatisations

Rémi Andres

Outline

1) Introduction

2) Dearomative reactions classification

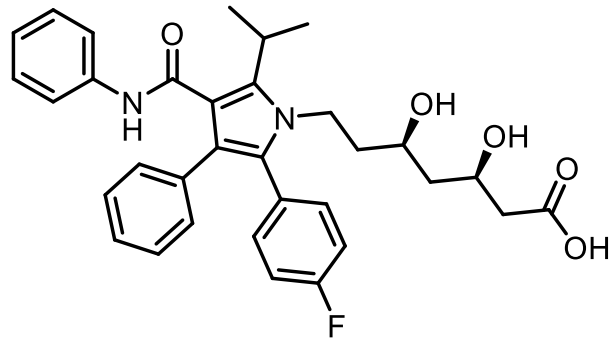
3) Arenophile-mediated dearomatisation

4) Application to the total synthesis of isocarbostyril alkaloids

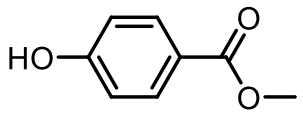
1) Introduction

Importance of aromatic compounds:

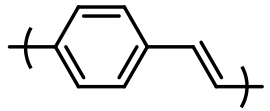
- Widely used in every field of molecular sciences
- Essential in nature
- Versatile substrates in organic chemistry
- Readily available building blocks



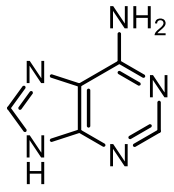
Lipitor



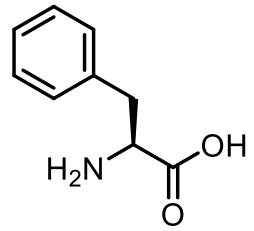
Methylparaben



Poly(phenylenevinylene) PPV



Adenine

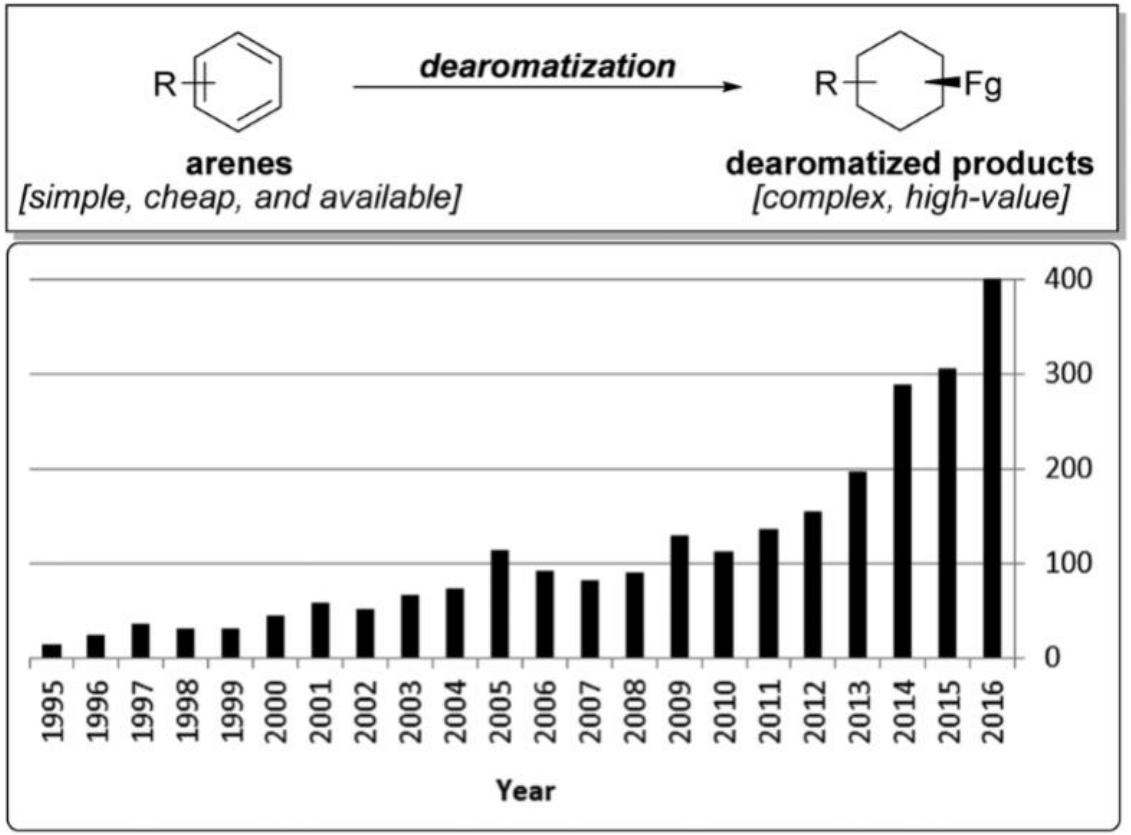


Phenylalanine

1) Introduction

Importance of dearomative reactions:

- Rapid access to saturated or non-aromatic unsaturated complex molecules
- Possibility of introducing functional groups
- Interesting tool to create new C-C bonds
- Way to control the generation of new stereocenters
- Very useful in industry (hydrogenation…)



Number of publications using the term ‘‘dearomatisation’’ since 1995

D. Sarlah et al., *Chem. Soc. Rev.* **2018**, *47*, 7996

1) Introduction

Importance of dearomative reactions in nature:

- Essential to many biosynthetic pathways (catabolic and anabolic processes, hormone and antiobiotic biosyntheses, degradation of xenobiotics…)

- Many known enzyme-catalysed transformations of aromatic substrates (hydration, dihydroxylation, epoxidation, ring opening, reduction…)

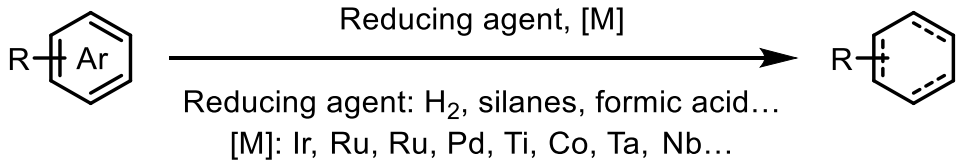
- Very mild conditions

Dearomatise… but how?

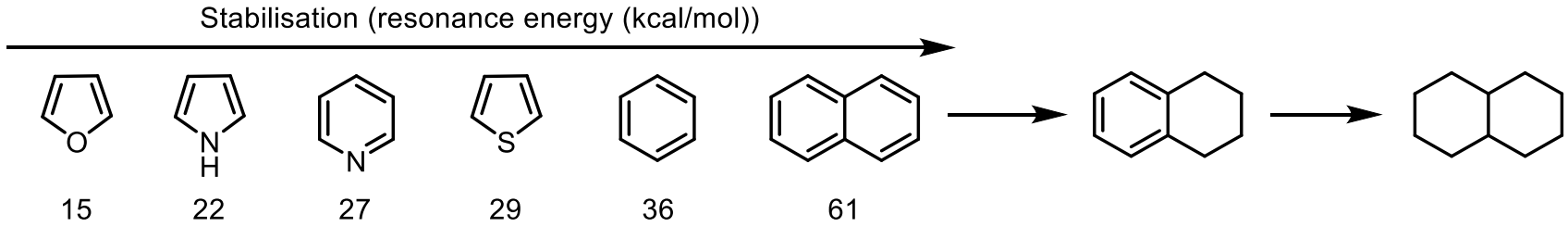
Annu. Rev. Microbiol. **1992**, *46*, 601; *Biochim. Biophys. Acta* **2005**, *1707*, 34; *Curr. Opin. Chem. Biol.* **2002**, *6*, 604; *Annu. Rev. Microbiol.* **2002**, *56*, 345; *FEMS Microbiol. Rev.* **1999**, 22, 439

2) Dearomative reactions classification

a) Reductive dearomatisation: hydrogenation



Rule: the ring with the lowest resonance energy is generally hydrogenated in preference
⇔ the least stable ring generally gets reduced first



Advantages:

- Regioselective reduction possible
- *Syn*-hydrogenation (in most cases)
- Enantioselective hydrogenation well-known

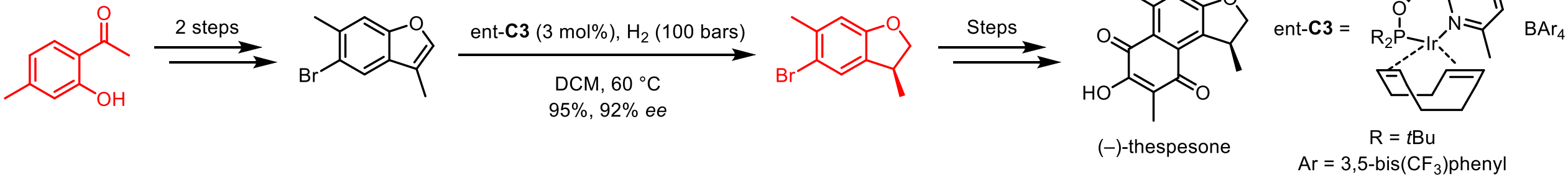
Challenges and drawbacks:

- Suitable equipment needed (high pressure)
- Regio-/chemoselectivity issues
- Ligand design often required for asymmetric synthesis
- Hydrogenation of the most stable aromatic challenging

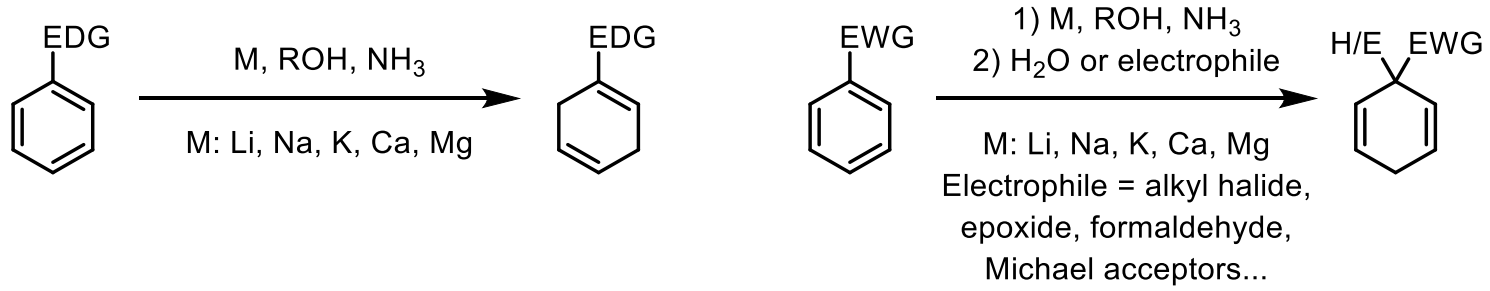
D. Sarlah et al., *Chem. Soc. Rev.* **2018**, *47*, 7996; S. Y. Liu et al., *Coord. Chem. Rev.* **2016**, *314*, 134; F. Glorius et al., *Angew. Chem. Int. Ed.* **2019**, *58*, 10460

a) Reductive dearomatisation: hydrogenation

Formal synthesis of (–)-thespesone:



a) Reductive dearomatisation: Birch reduction/alkylation

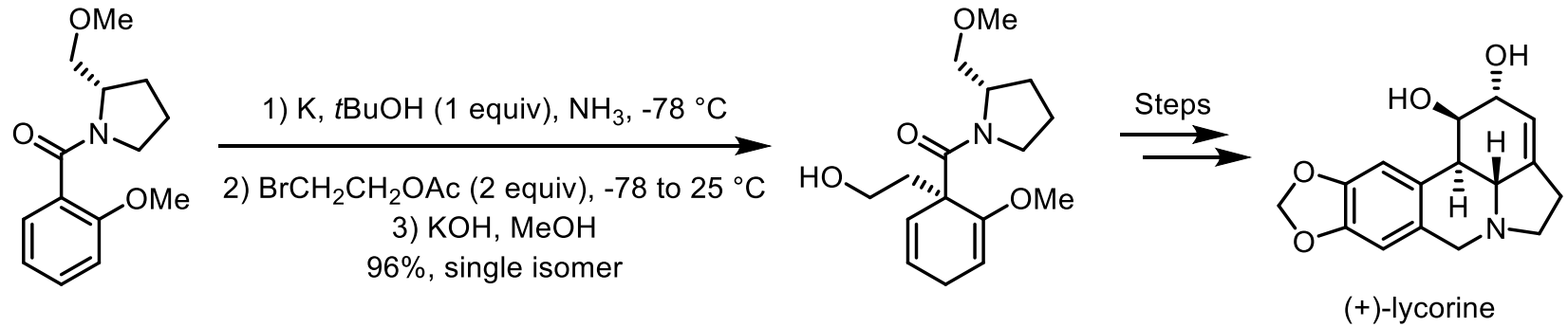


Advantages:

- Surprisingly good functional group tolerance
- Diastereoselective Birch alkylation known (chiral auxiliaries)
- Possibility to create new C-C bonds

Challenges and drawbacks:

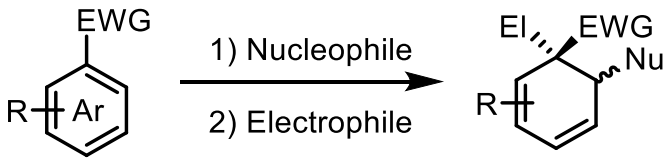
- Harsh conditions
- Selectivity issues
- Over-reduction issues
- Possible isomerisation of double bonds
- No (direct) enantioselective report

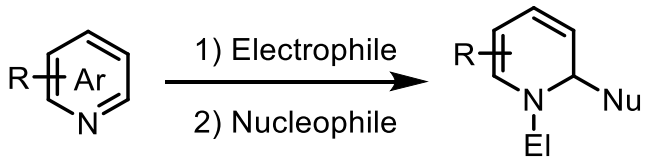


(+)-lycorine

A. J. Birch, *J. Chem. Soc.* **1944**, 430; J. M. Hook et al., *Nat. Prod. Rep.* **1986**, *3*, 35; A. G. Schultz et al., *Tet. Lett.* **1984**, *25*, 4591; A. G. Schultz et al., *J. Am. Chem. Soc.* **1996**, *118*, 6210

b) Nucleophilic dearomatisation





Advantages:

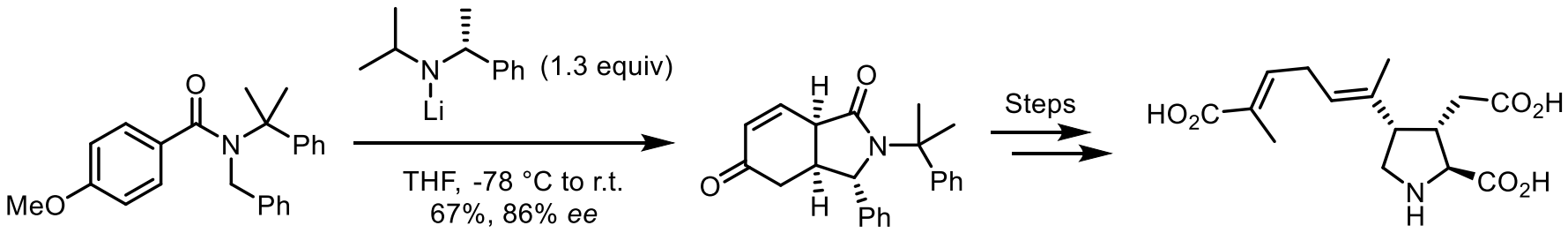
- Multi-functionalisation possible
- Creation of new C-C bonds
- Single double bond touched (most cases)
- Significant complexification in a single step
- Regioselectivity predictable and controllable (heteroatoms, DG…)
- Diastereoselective and enantioselective processes possible

Challenges and drawbacks:

- Diastereoselectivity issues
- Regioselectivity issues

Often:

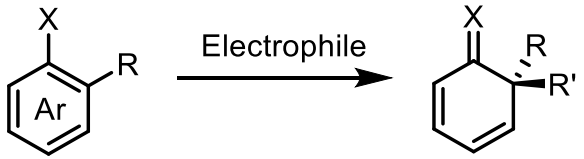
- Harsh conditions
- Low functional group tolerance

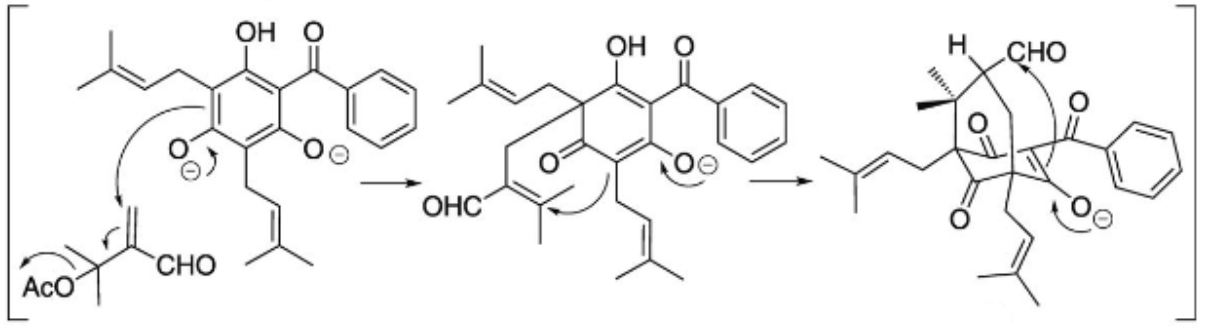


(–)-isodomic acid B

J. Clayden et al., *Chem. Commun.* **2011**, *47*, 3745; F. Ortiz et al., *Chem. Rev.* **2007**, *107*, 1580; S. L. You et al., *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; D. Sarlah et al., *Chem. Soc. Rev.* **2018**, *47*, 7996

c) Alkylative dearomatisation



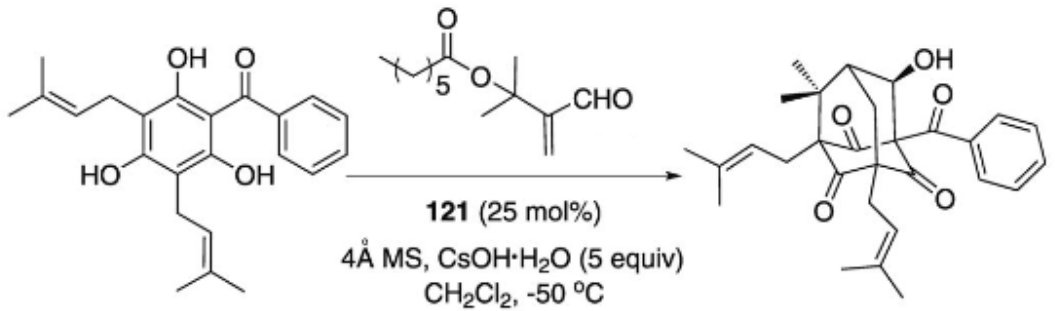


Advantages:

- Means to introduce functional groups
- Tool to create new C-C bonds
- Single double bond touched only
- Enantioselective alkylation possible
- Mild conditions (usually)

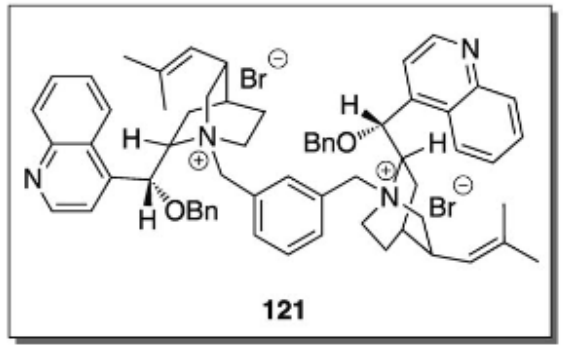
Challenges and drawbacks:

- Regioselectivity issues (*m*'-, *p*-positions)
- Chemoselectivity issues (X-alkylation)
- Only few reports of catalytic enantioselective processes
- Limited to phenol and aniline derivatives



clusiaphenone B

71% yield, 90% *ee*



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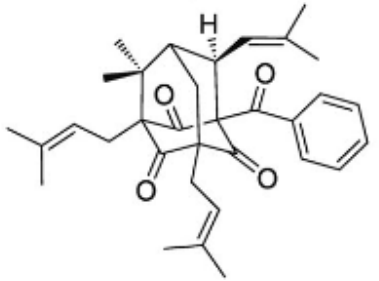
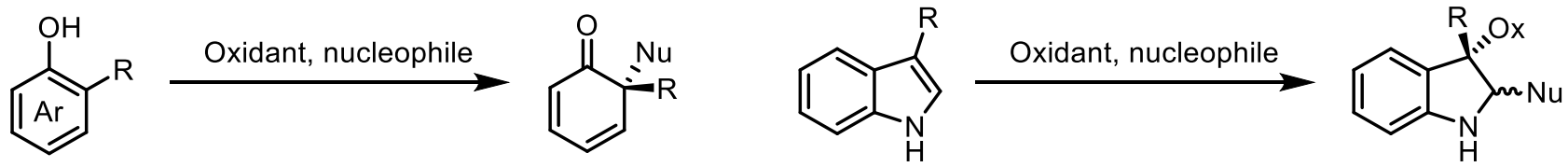


(–)-hyperibone K

S. L. You et al., *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; S. L. You et al., *Chem. Soc. Rev.* **2016**, *45*, 1570; R. Fan et al., *Synthesis* **2013**, *45*, 1; J. A. Porco et al., *J. Am. Chem. Soc.* **2010**, *132*, 13642

d) Oxidative dearomatisation



Advantages:

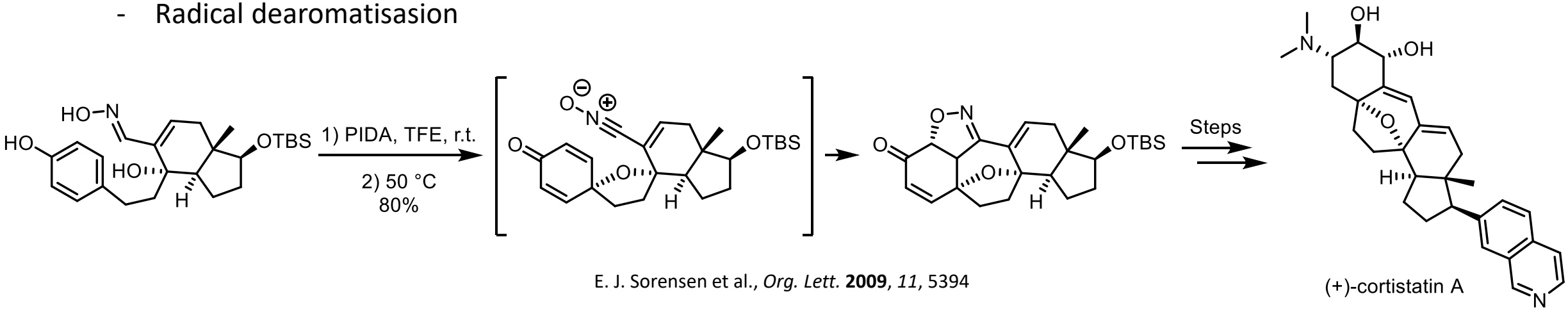
- Low toxicity of chiral iodanes
- Multi-functionalisation possible
- Tool to create new C-C bonds
- Enantioselective processes possible
- Mild conditions (usually)

Challenges and drawbacks:

- Limited to indole and phenol derivatives (most cases)
- Regioselectivity issues (*m*'-, *p*-positions)
- Catalytic enantioselective processes particularly challenging
- Price and explosivity of chiral hypervalent iodines
- Preparation of chiral iodanes

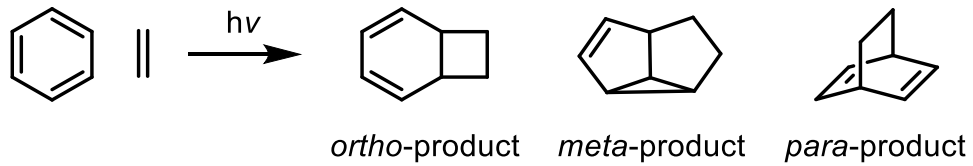
Variant:

- Radical dearomatisasion



E. J. Sorensen et al., *Org. Lett.* **2009**, *11*, 5394

e) Dearomative cycloaddition

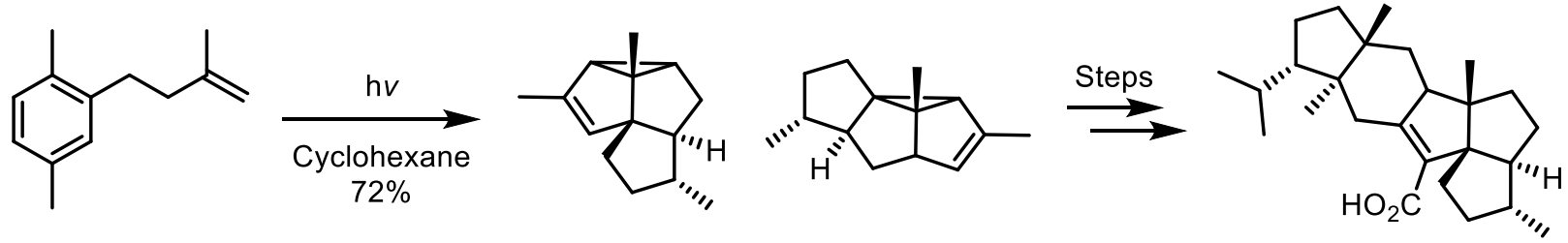


Advantages:

- Significant complexification in a single step
- Creation of several new C-C bonds/stereocenters
- Catalytic enantioselective processes well-known
- Ring contraction/expansion feasible

Challenges and drawbacks:

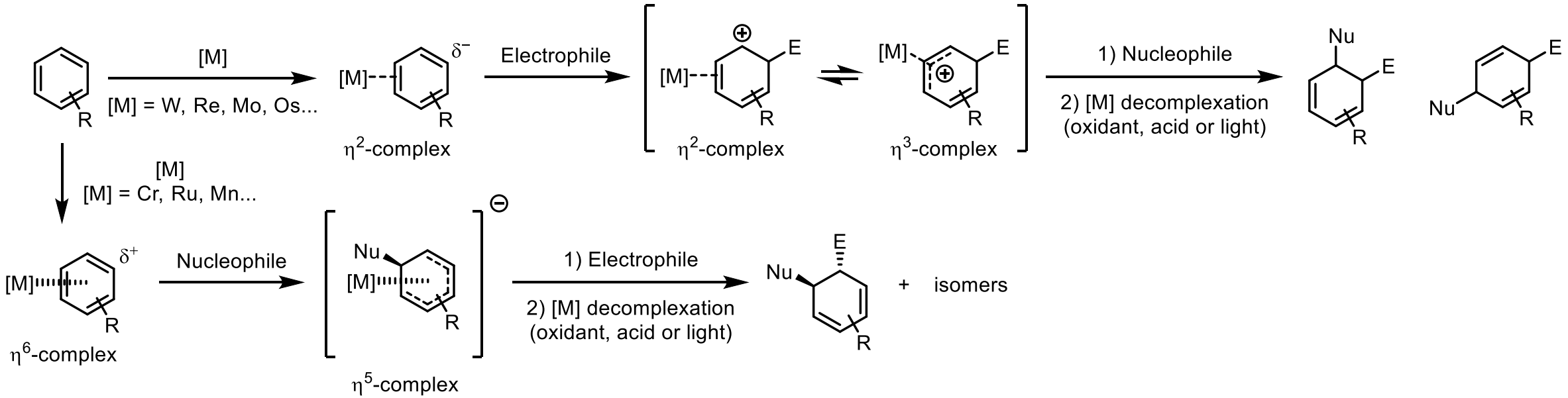
- Regioselectivity issues (*o*-, *m*-, *p*-products)
- Endo/exo selectivity issues
- Reversibility of the processes
- *O*-, *p*-selectivities underdevelopped



(–)-retigeranic acid

Chem. Soc. Rev. **2018**, *47*, 7996; *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Chem. Rev.* **2016**, *116*, 9816; *Beilstein J. Org. Chem.* **2011**, *7*, 525; *Tet. Lett.* **1990**, *31*, 2517

f) Transition metal-mediated/catalysed dearomatisation



Advantages:

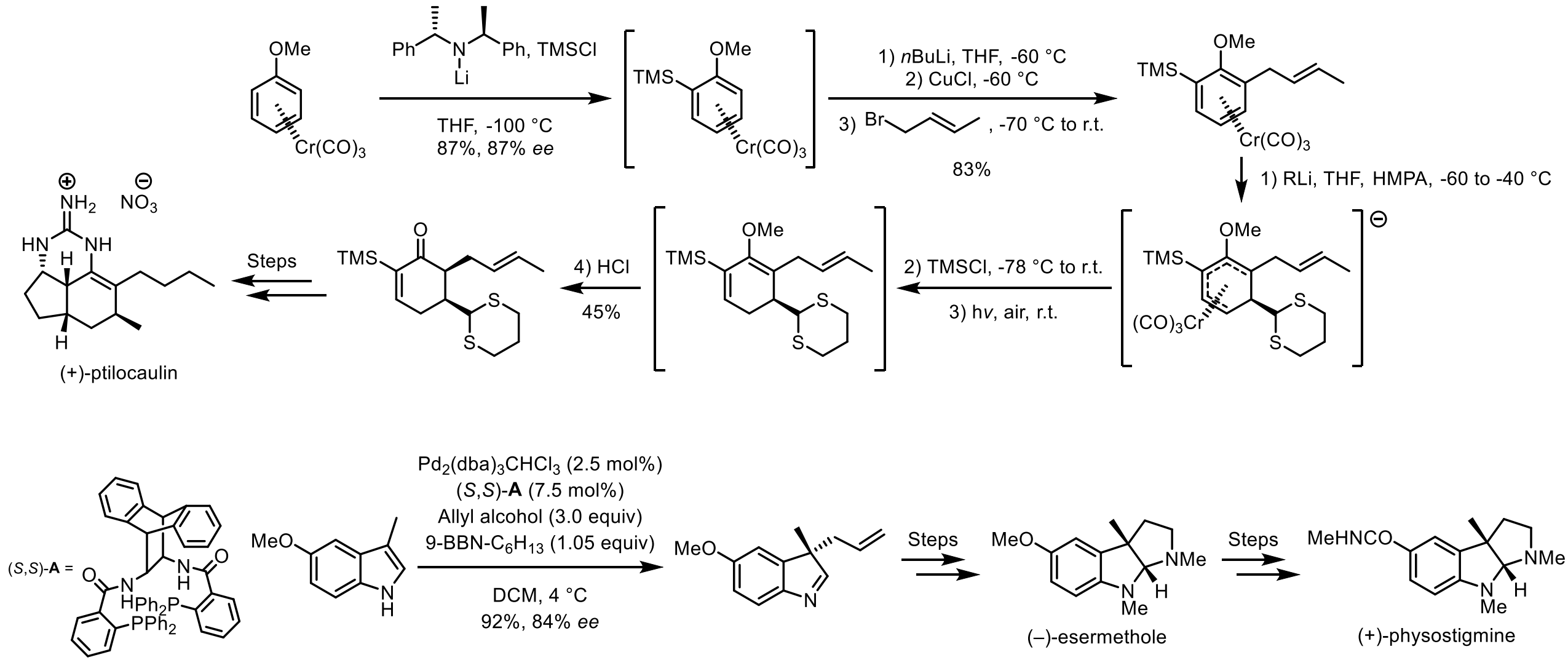
- Multi-functionalisation possible
- Creation of new C-C bonds
- Significant complexification in a single step
- Broad range of metal known
- Enantioselective processes possible

Challenges and drawbacks:

- (Very high) toxicity of the complexes
- Regioselectivity issues (metal-, substrate- and electrophile-dependant)
- Diasteroselectivity issues
- Low reactivity of electron-poor aromatics
- Functional group tolerance

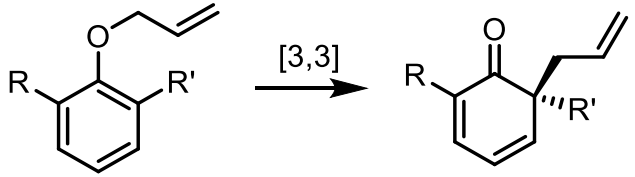
Chem. Soc. Rev. **2018**, *47*, 7996; *Chem. Rev.* **2000**, *100*, 2917; *Chem. Soc. Rev.* **2007**, *36*, 1589; *Chem. Rev.* **2017**, *117*, 13721; *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Chem. Soc. Rev.* **2016**, *45*, 1570

f) Transition metal-mediated/catalysed dearomatisation



H. G. Schmalz et al., *Chem. Eur. J.* **1998**, *4*, 57; H. G. Schmalzand and K. Schellhaas, *Angew. Chem.Int. Ed. Engl.* **1996**, *35*, 2146; B. M. Trost and J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6315

g) Dearomative rearrangement (excluding η-arene-[M] complexes)

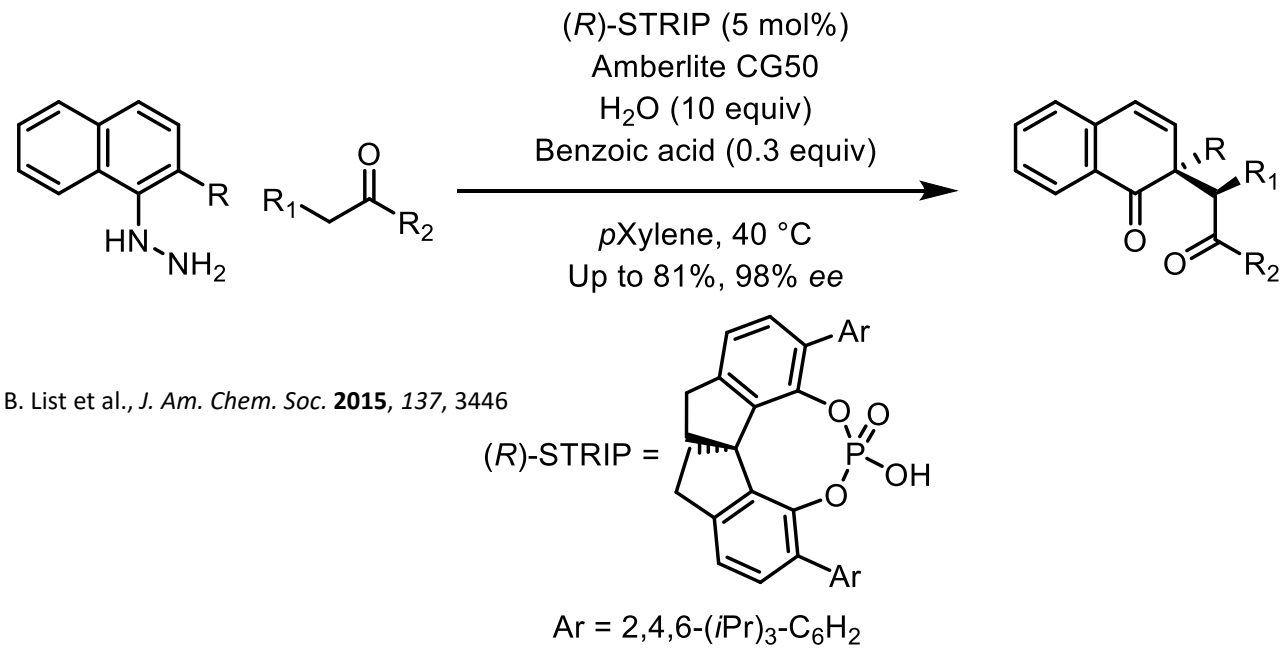


Advantages:

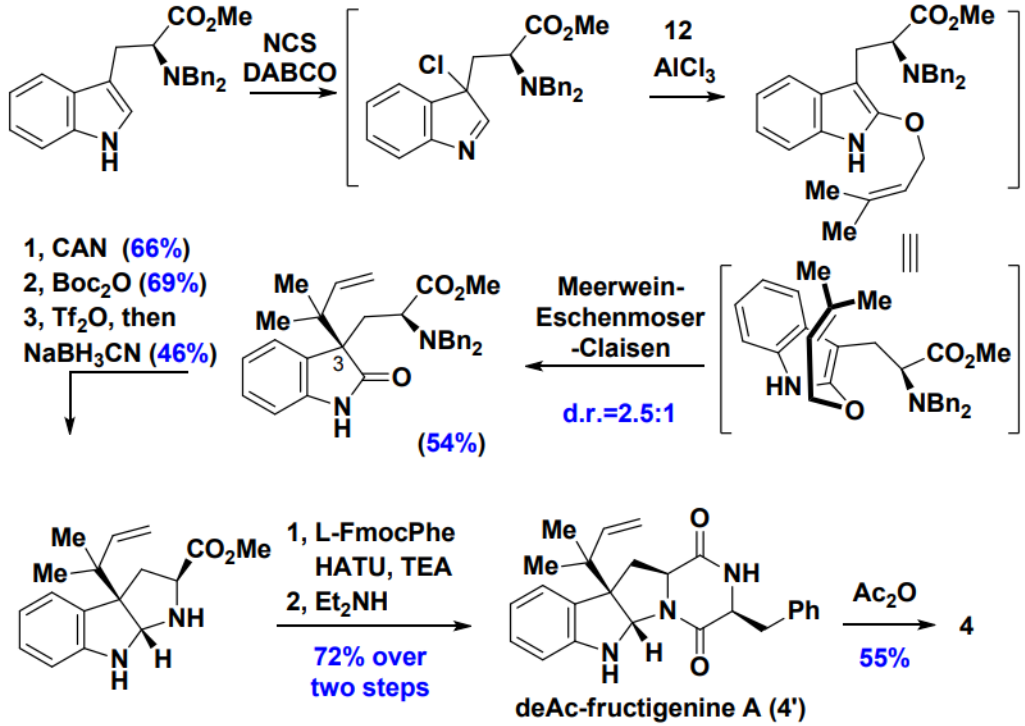
- Multi-functionalisation possible
- Tool to create new C-C bonds
- Enantioselective processes possible
- Significant complexification in a single step

Challenges and drawbacks:

- Challenging reaction to develop
- Limited examples (Claisen-type rearrangements mostly)
- Regioselectivity issues (*m'*-position)



B. List et al., *J. Am. Chem. Soc.* **2015**, *137*, 3446



Scheme 2 Synthesis of fructigenine A (**4**) and penicimutatin (**5**).

T. Xu et al., 10.1039/C9SC05252F

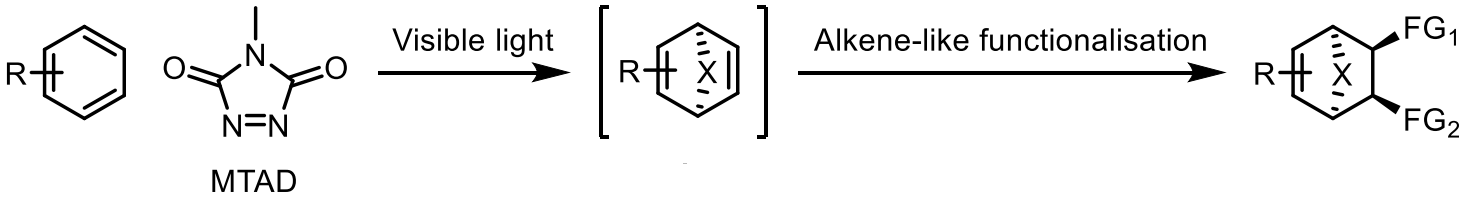
h) Arenophile-mediated dearomatisation

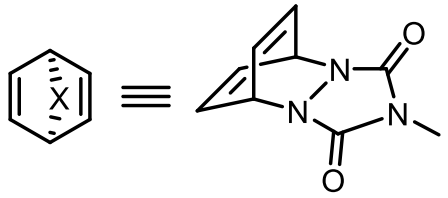
Advantages:

- (Heavy-) functionalisation directly on the aromatic ring possible
- Very simple unactivated aromatic substrates utilizable
- Halogens, free-benzylic positions, heteroaromatics, free functional groups tolerated
- Excellent diastereocontrol
- Possibility to render the process enantioselective (transition-metals)

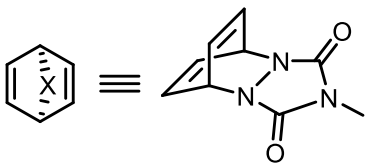
Challenges and drawbacks:

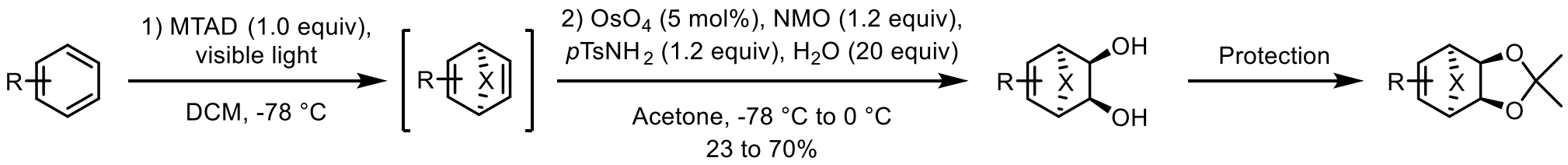
- Fine-tuning of the conditions and ligand needed for enantioselective reactions
- Moderate yields (usually)

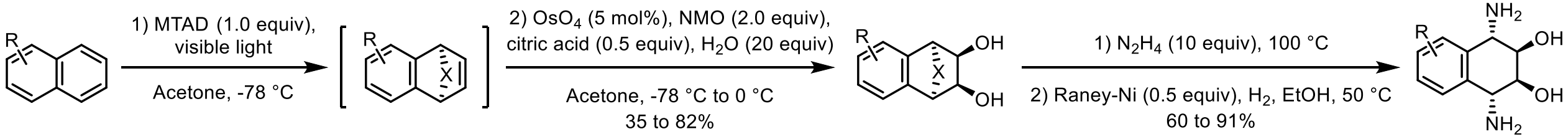




h) Arenophile-mediated dearomatisation

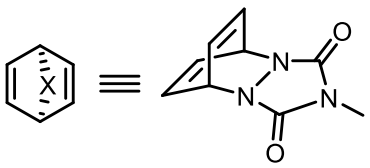


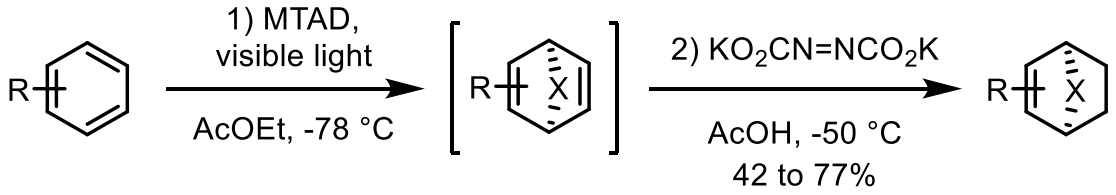


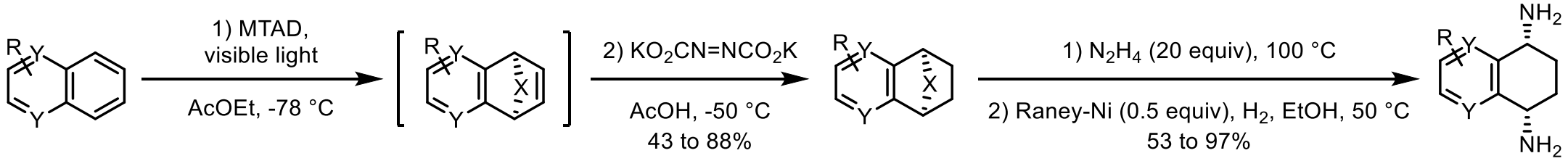


D. Sarlah et al., *Chem. Soc. Rev.* **2018**, *47*, 7996; D. Sarlah et al., *Nat. Chem.* **2016**, *8*, 922

h) Arenophile-mediated dearomatisation

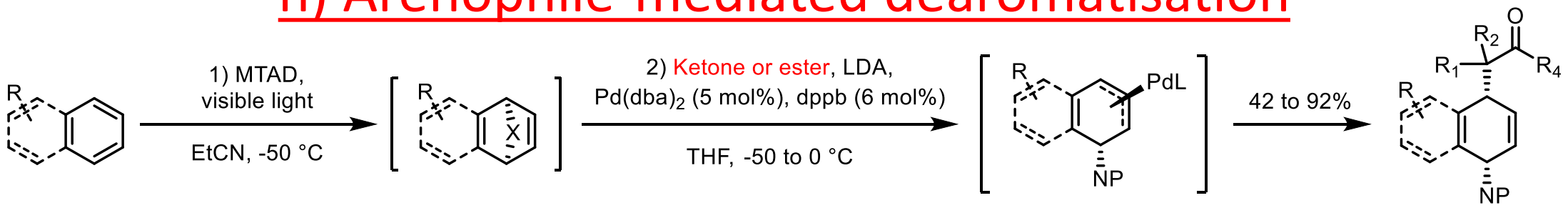


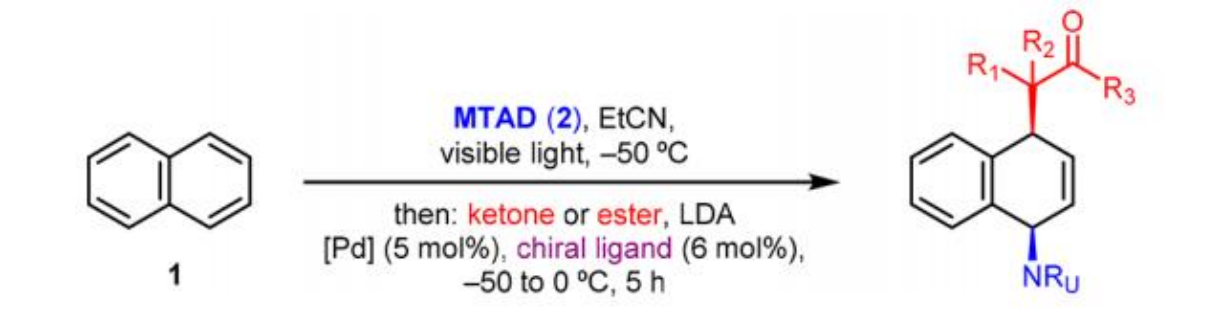




D. Sarlah et al., *Chem. Soc. Rev.* **2018**, *47*, 7996; D. Sarlah et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 15910

h) Arenophile-mediated dearomatisation



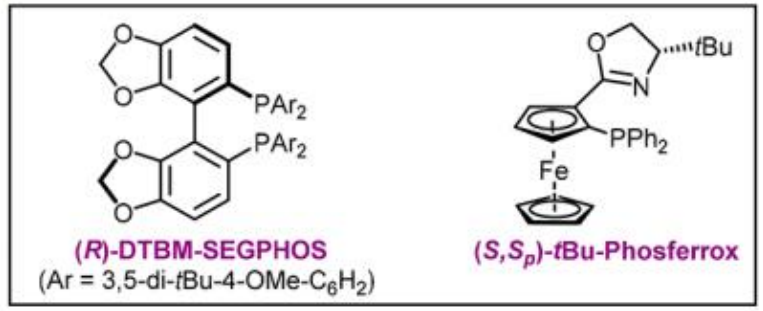


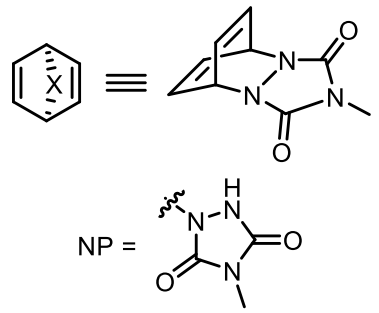
4 (R_1 = R_2 = H, R_3 = *p*-MeO-C_6H_4), 75%, 95:5 er
13 (R_1 = Me, R_2 = H, R_3 = Ph), 60%, 82:18 er, 20:1 dr
16 (R_1 = R_2 = H, R_3 = ^{i}Pr), 45%, 94:6 er
17 (R_1 = R_2 = H, R_3 = Cy), 68%, 97:3 er

KETONES

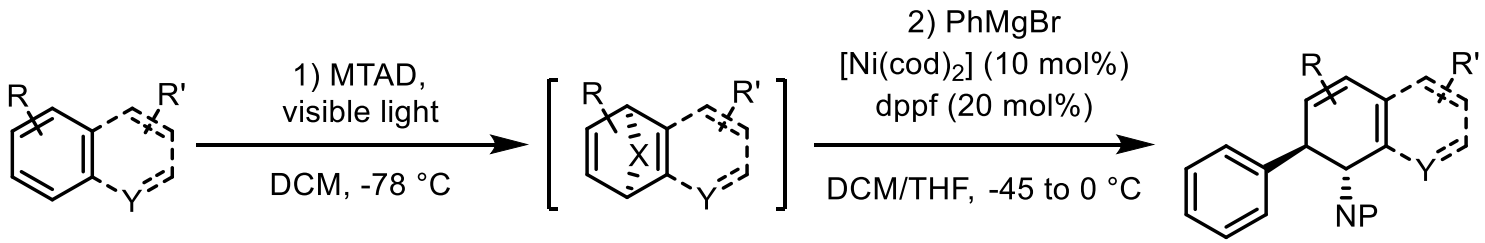
26 (R_1 = R_2 = Me, R_3 = OMe), 61%, 95:5 er
27 (R_1 = R_2 = $(CH_2)_5$, R_3 = OMe), 72%, 95:5 er

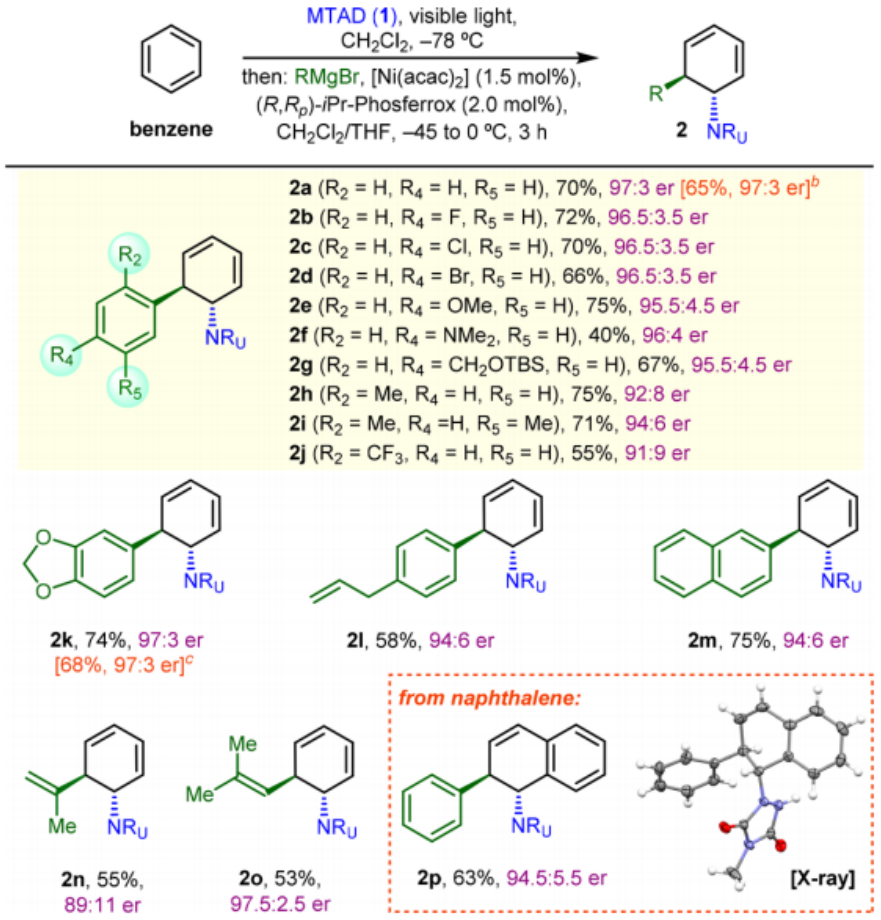
ESTERS

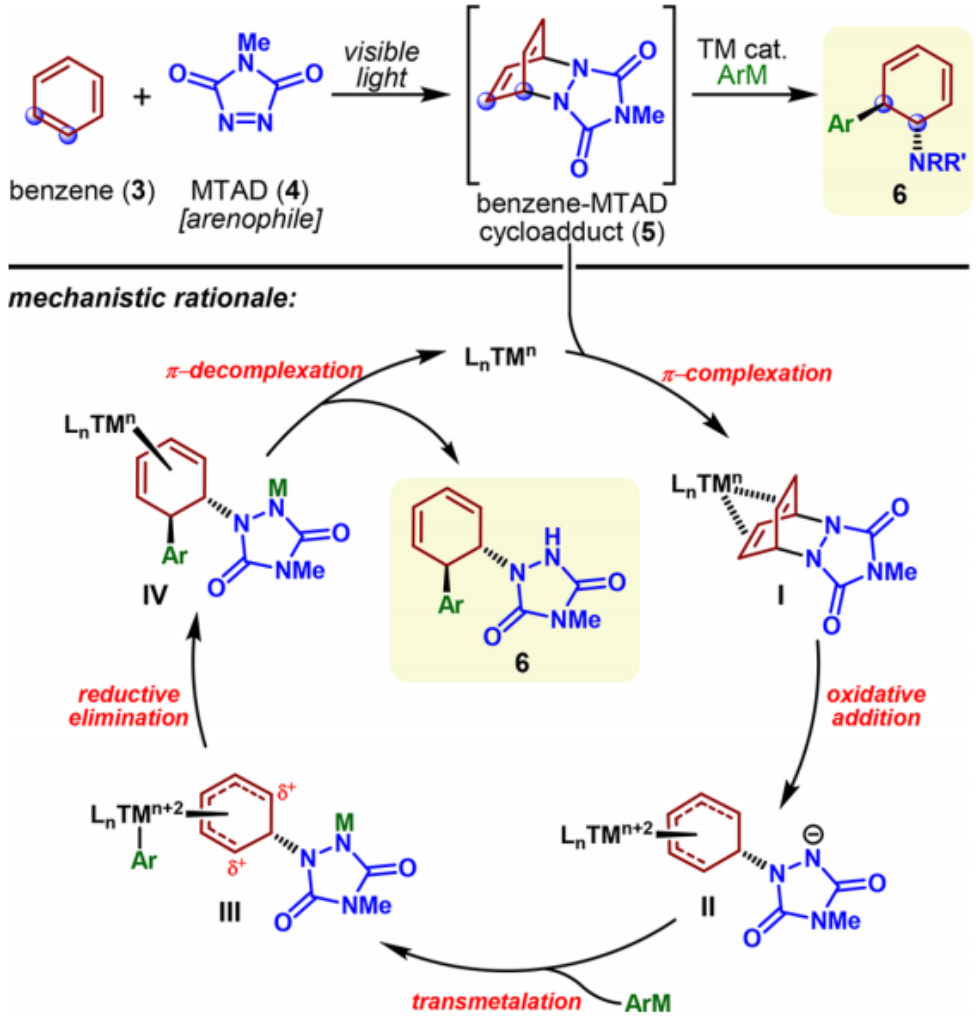




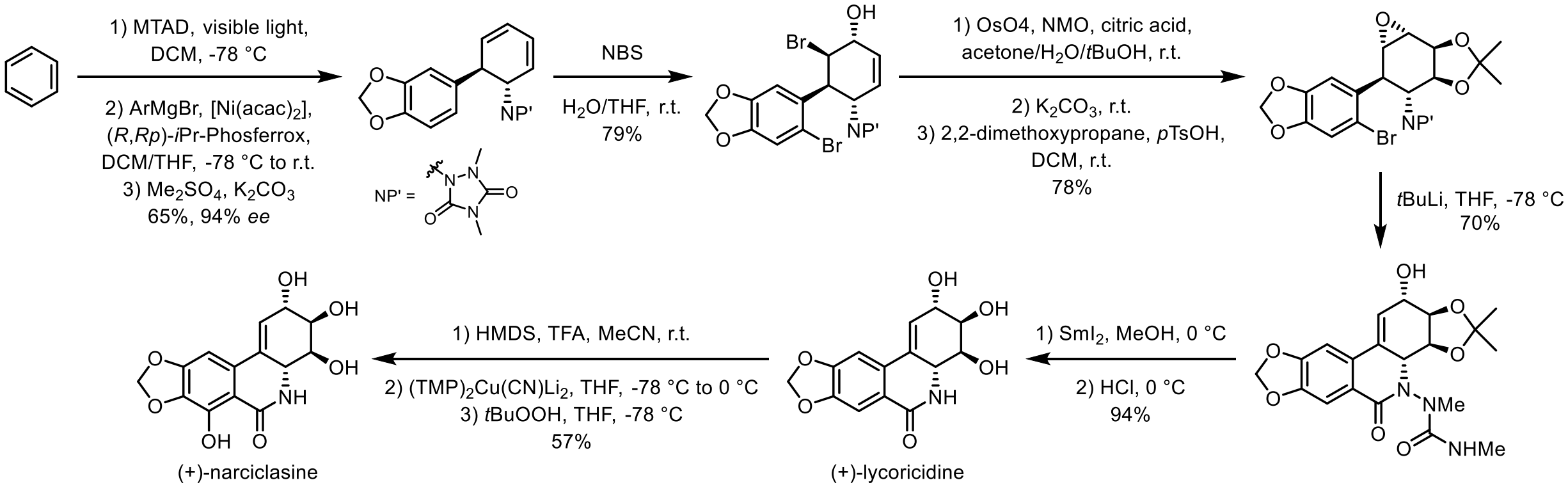
h) Arenophile-mediated dearomatisation



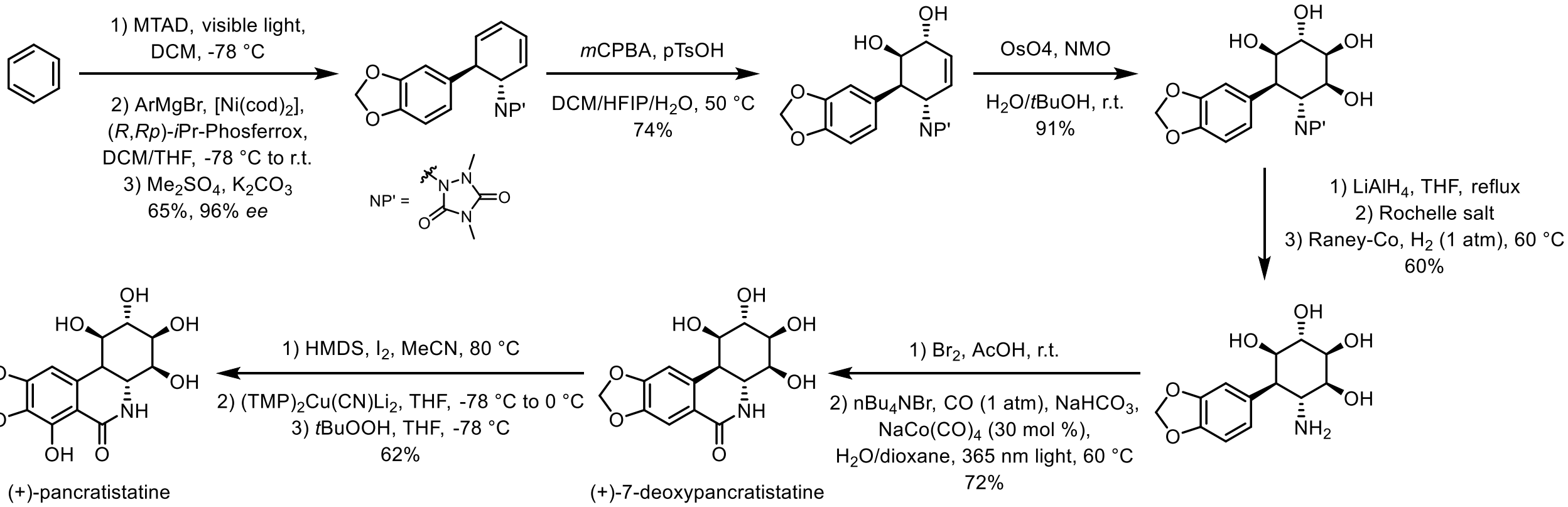




10) Application: total synthesis of isocarbostyril alkaloids



10) Application: total synthesis of isocarbostyril alkaloids



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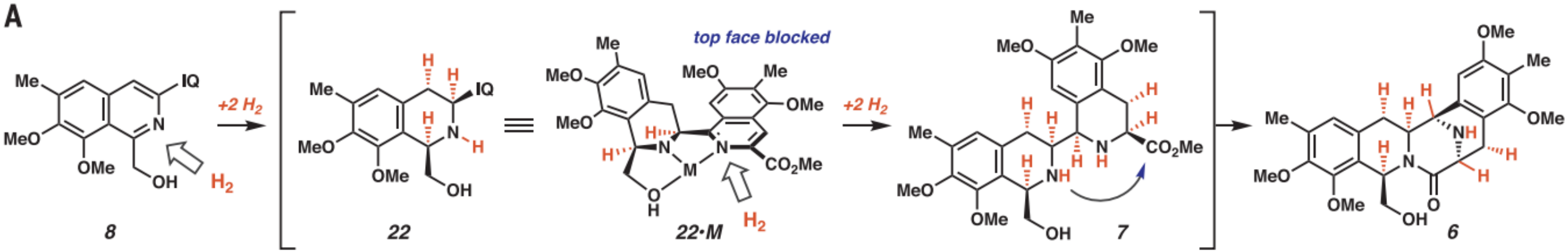
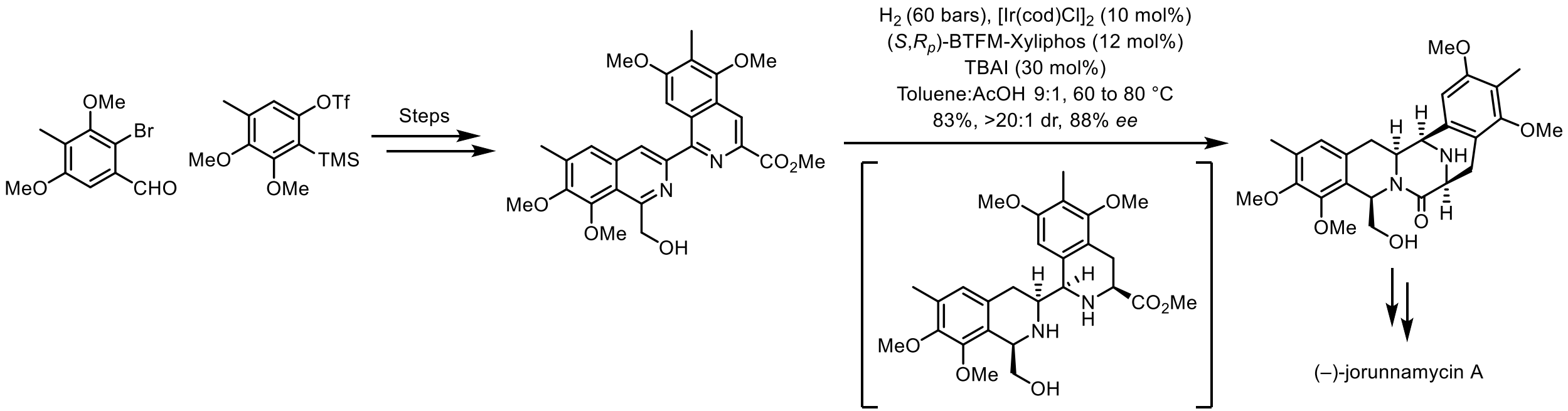
Thanks for your attention

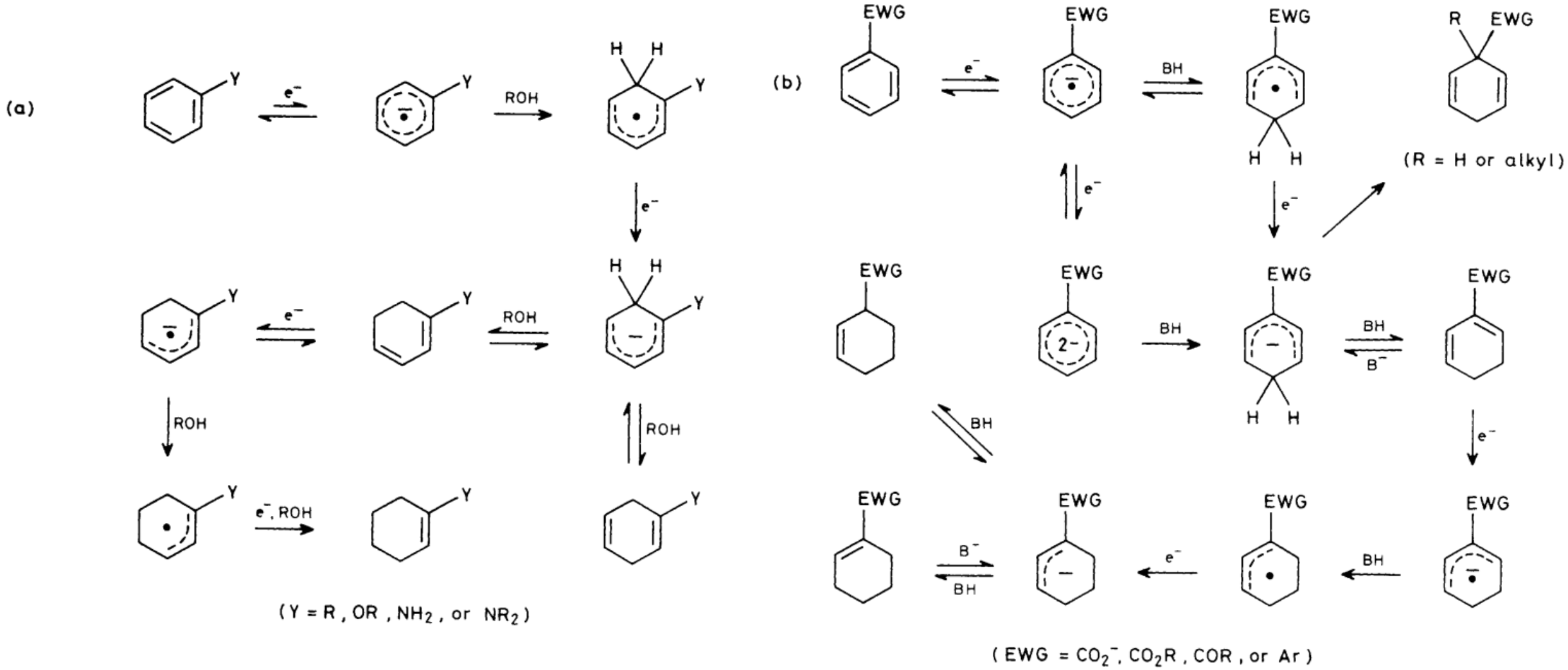
Any questions?

Total synthesis of (–)-jorunnamycin



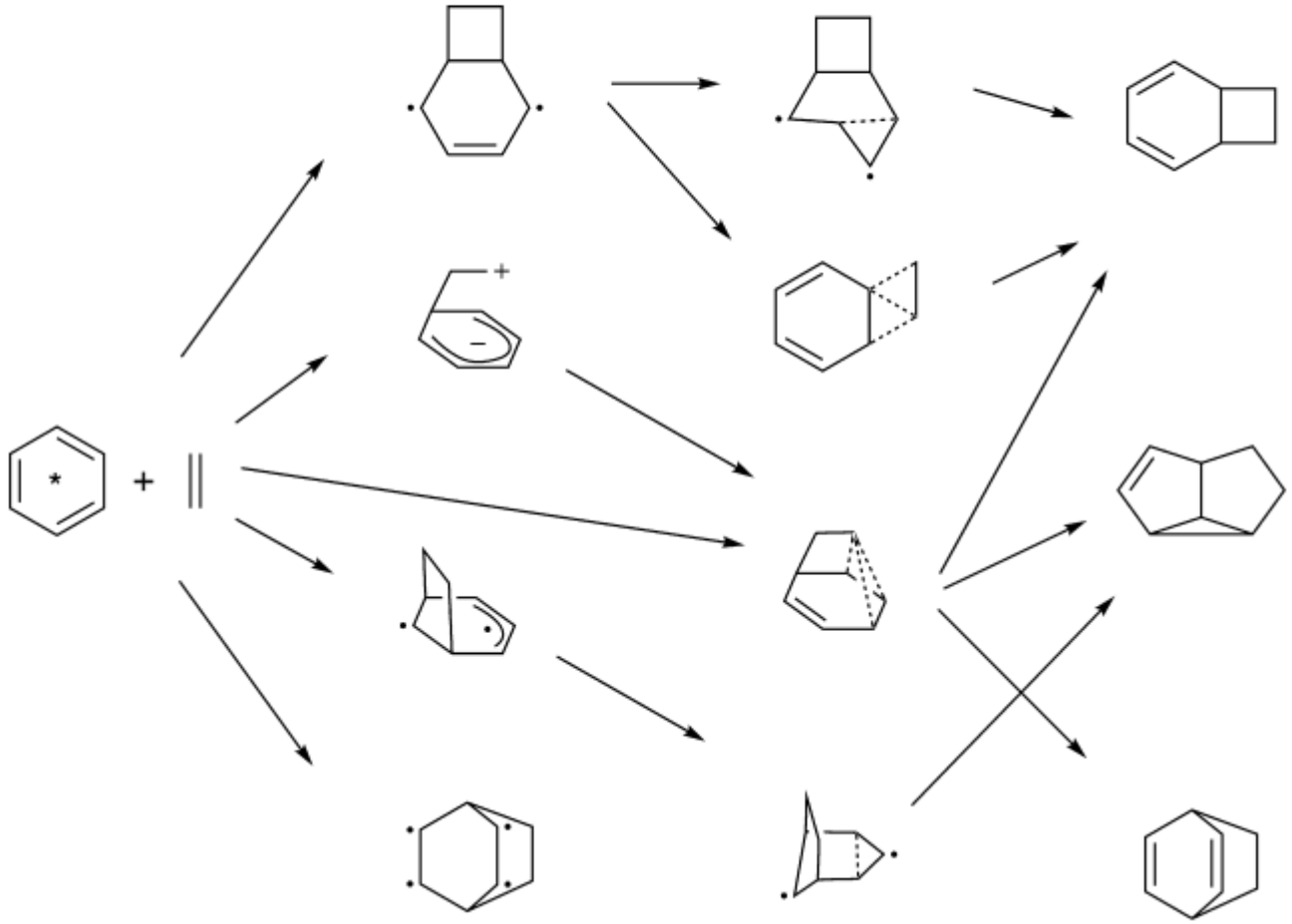


Mechanism Birch reduction/alkylation

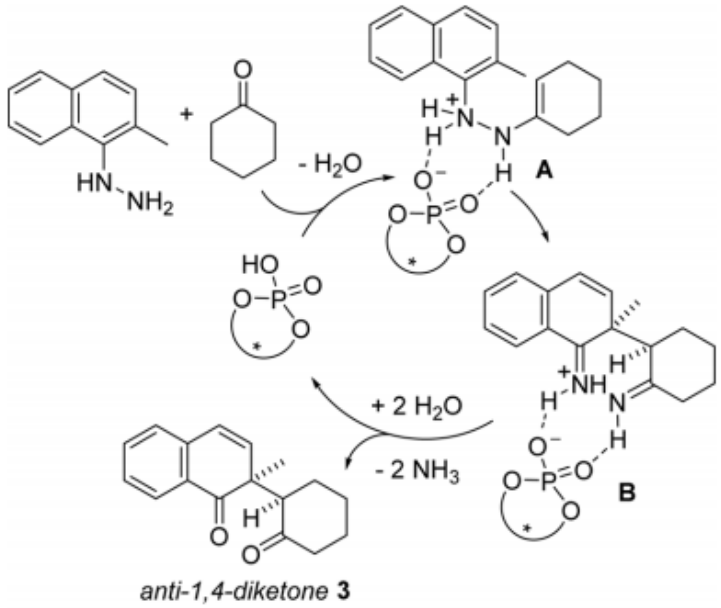


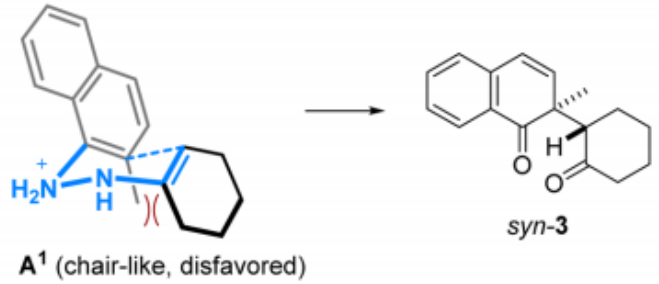
Mechanism [2+2] photo-cycloaddition

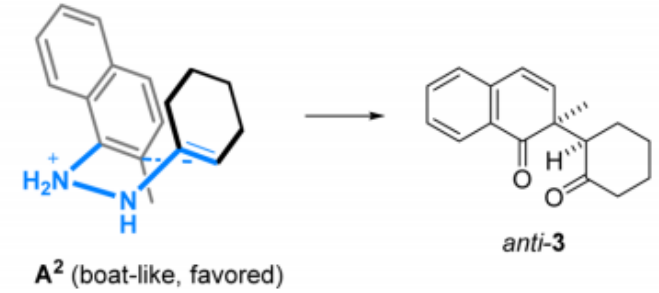
Scheme 6. Reaction Mechanism between Excited Benzene and Ethylene As Predicted by Computation

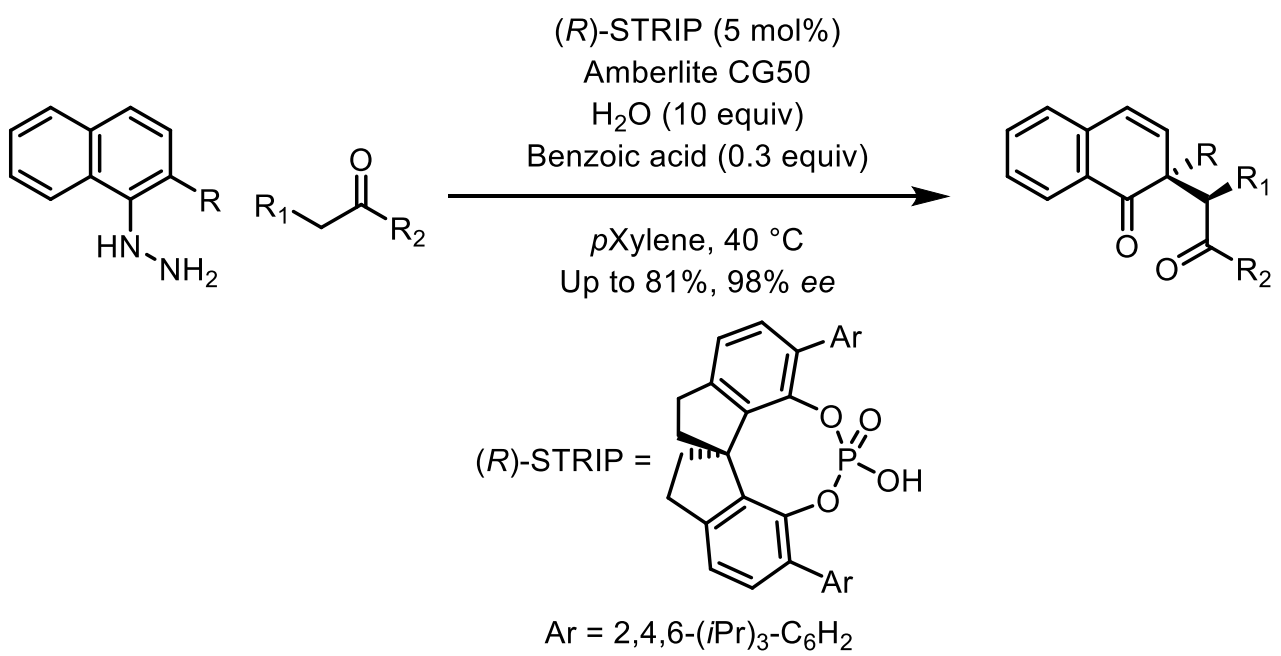


Diaza-Cope rearrangement mechanism

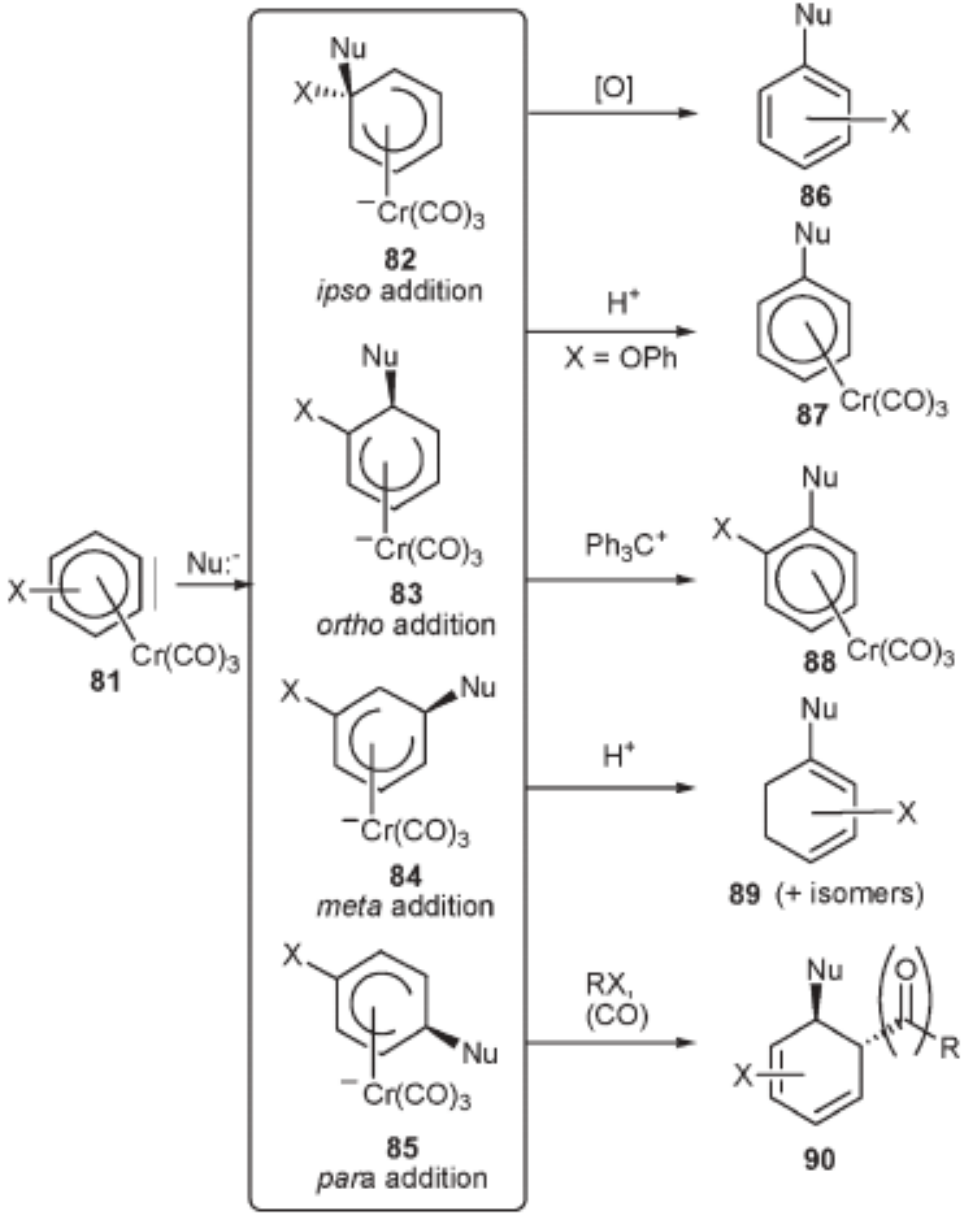








Possible products after addition with chromium-arene complexes



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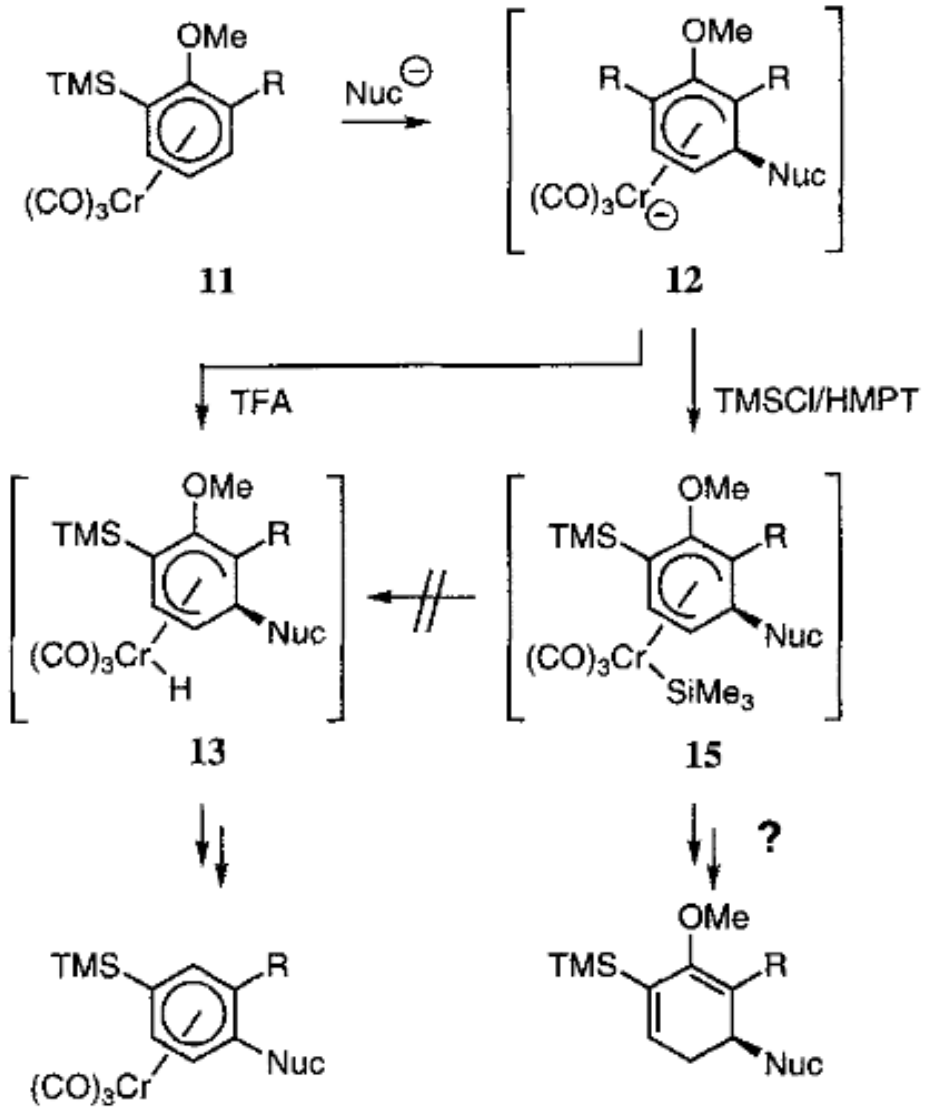
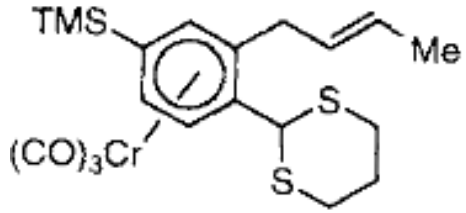
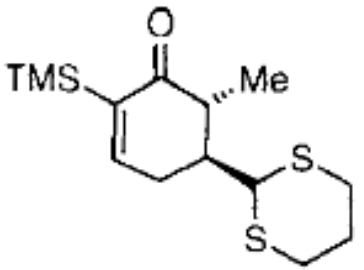
Mechanism total synthesis of (+)-ptilocaulin







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