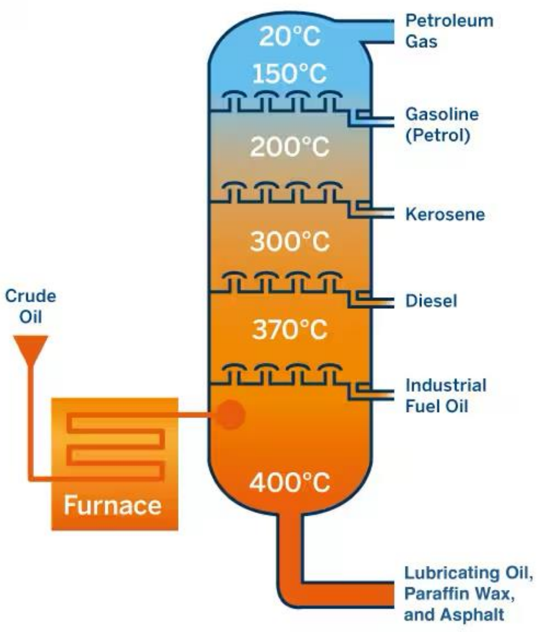
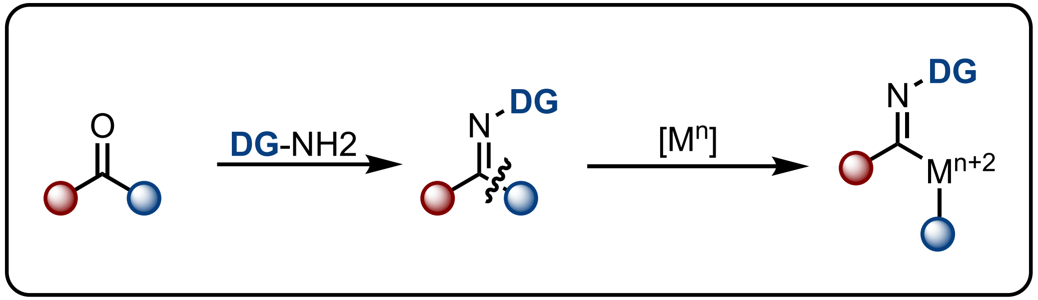
C–C Bond Activation via Rhodium Catalysis: Strategies Beyond Strain-Release



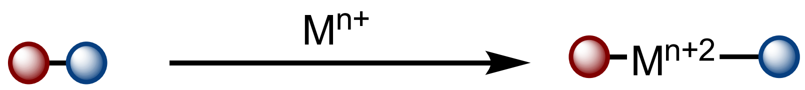


Dongchen Ouyang

Denmark Group Meeting
2025-06-17

Challenges in C-C bond Activation

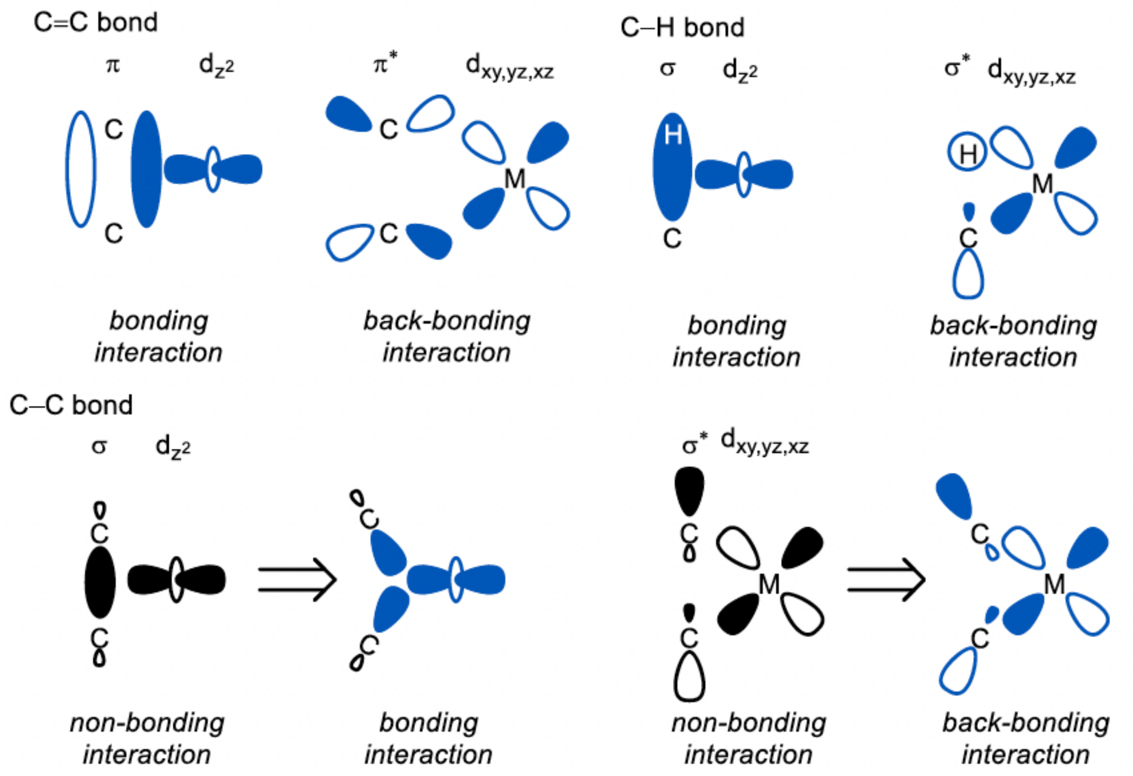
Thermodynamic



C-C BDE = ~90-105 kcal/mol

The reverse process, reductive elimination is usually more thermodynamically favorable.

Kinetic



- ***C−C single bond is barely polarized, lacking strong orbital overlap with transition metals***
- ***The π-orbitals of the olefin can effectively overlap with the d-orbitals of a transition metal, enabling facile coordination.***
- ***The spherical nature of the hydrogen orbitals allows for good overlap with the metal orbitals***
- ***C−C bond is highly directional and does not allow for significant overlap.***

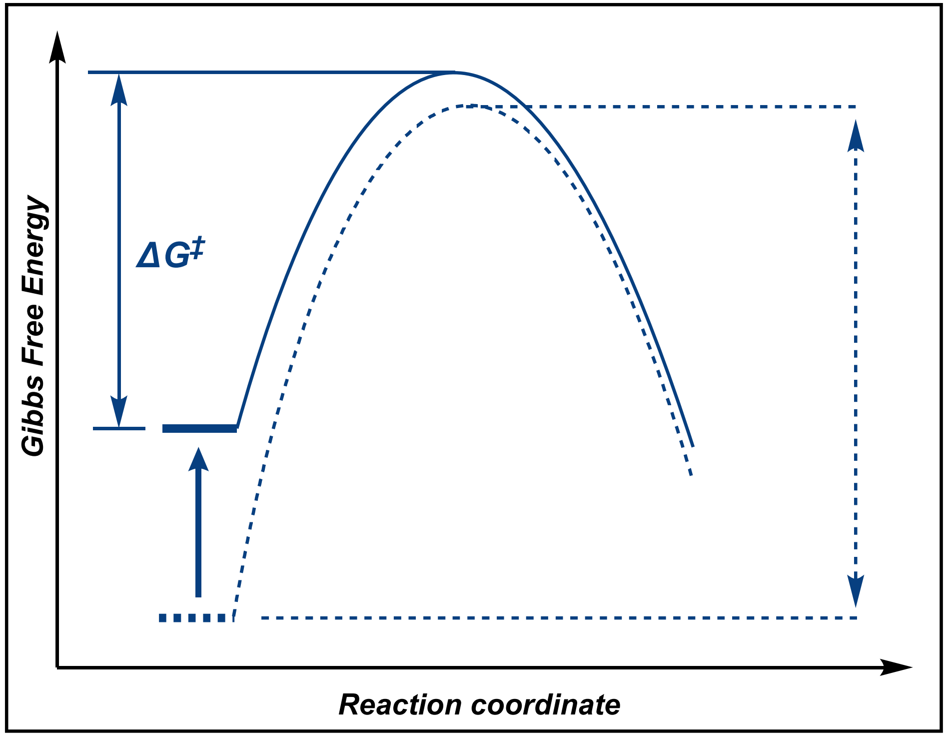
C−C Bond Activations via Ring Strain-Release

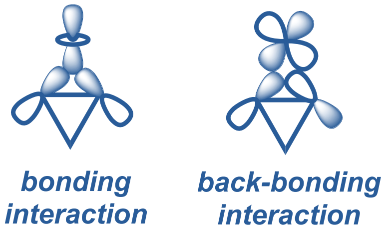
- **C−C Bond Activations via Oxidative Addition**

Ring Strain-Release

strain energies in kcal/mol

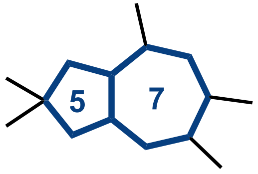
increasing ring strain



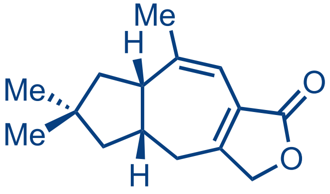


Walsh orbitals can show interactions between transition metals and cyclopropanes

Transition-metal-catalyzed carbocyclizations are used to build polycyclic scaffolds

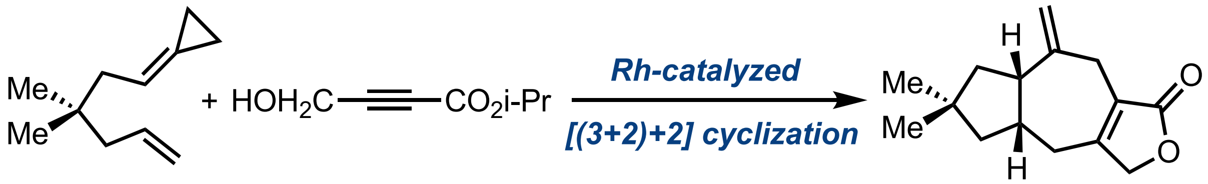


Lactarane



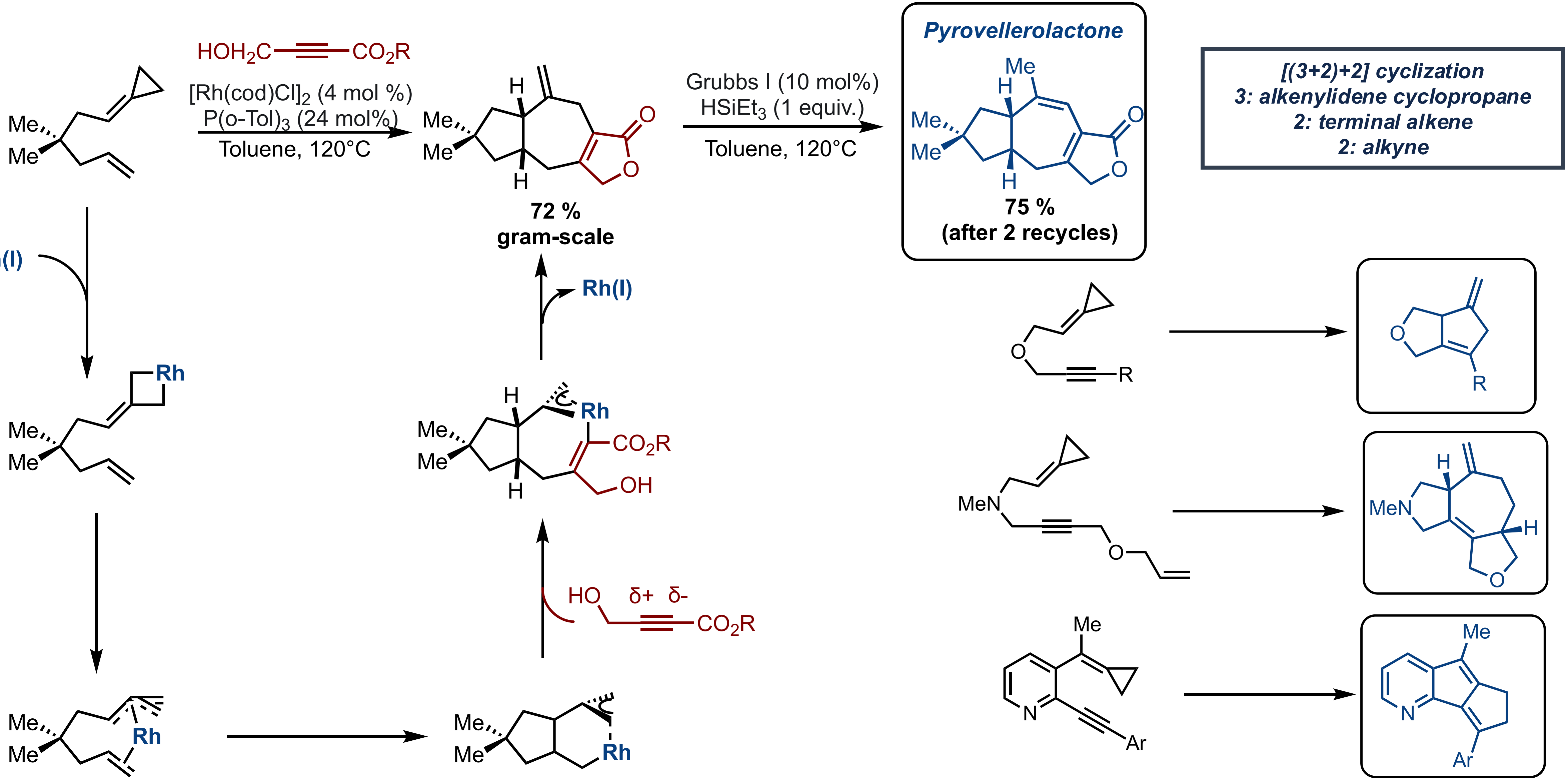
Pyrovellerolactone

Strain-release C-C activation builds 3 rings in one single step.



Souillart, L. & Cramer, N. *Chem. Rev.* **115**, 9410–9464 (2015). Evans, P. A., Inglesby, P. A. & Kilbride, K. *Org. Lett.* **15**, 1798–1801 (2013)

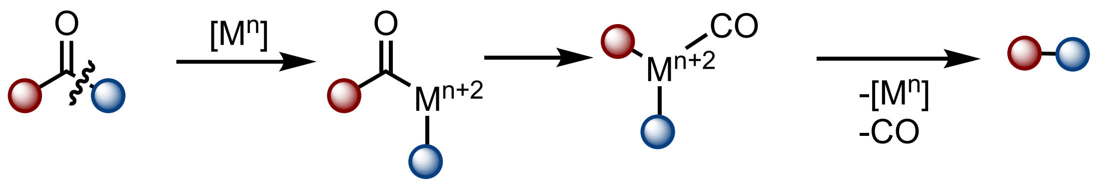
Ring Strain-Release: Total synthesis example



Souillart, L. & Cramer, N. *Chem. Rev.* **115**, 9410–9464 (2015). Evans, P. A., Inglesby, P. A. & Kilbride, K. *Org. Lett.* **15**, 1798–1801 (2013) Bhargava, G. et al. *Chem. Commun.* **46**, 270–272 (2010).

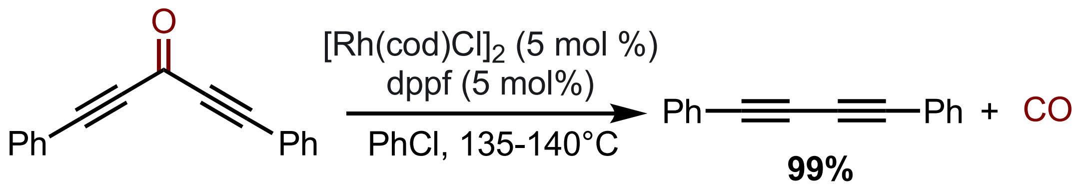
Overview: Strategies for Breaking a σ C–C Bond

Decarbonylation



Decarbonylation drives reactions via CO release and entropy gain.

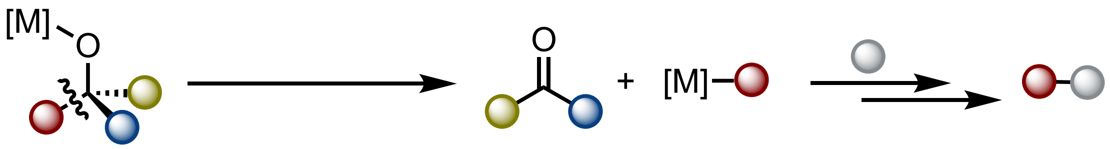
Dong (2013)



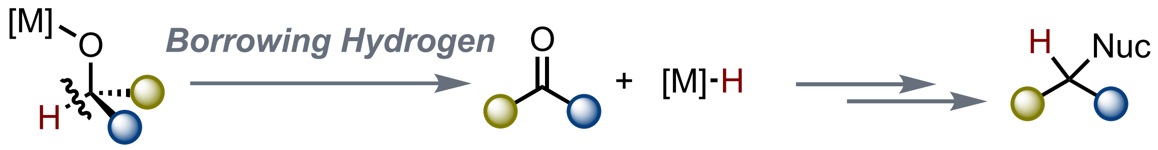
β-Carbon Elimination

Tertiary alcohols essentially act as nucleophiles masked by ketones

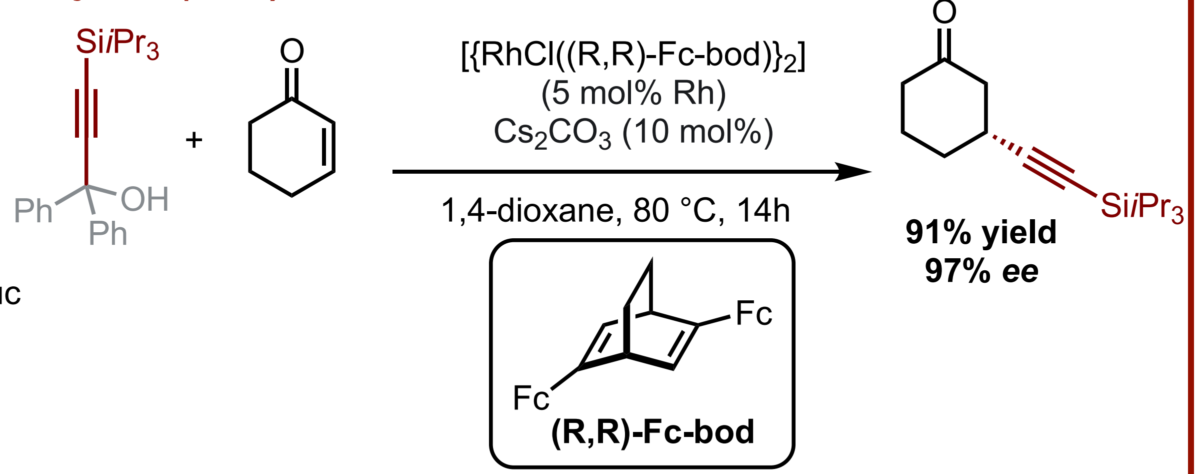
β-Carbon Elimination



β-Hydride Elimination



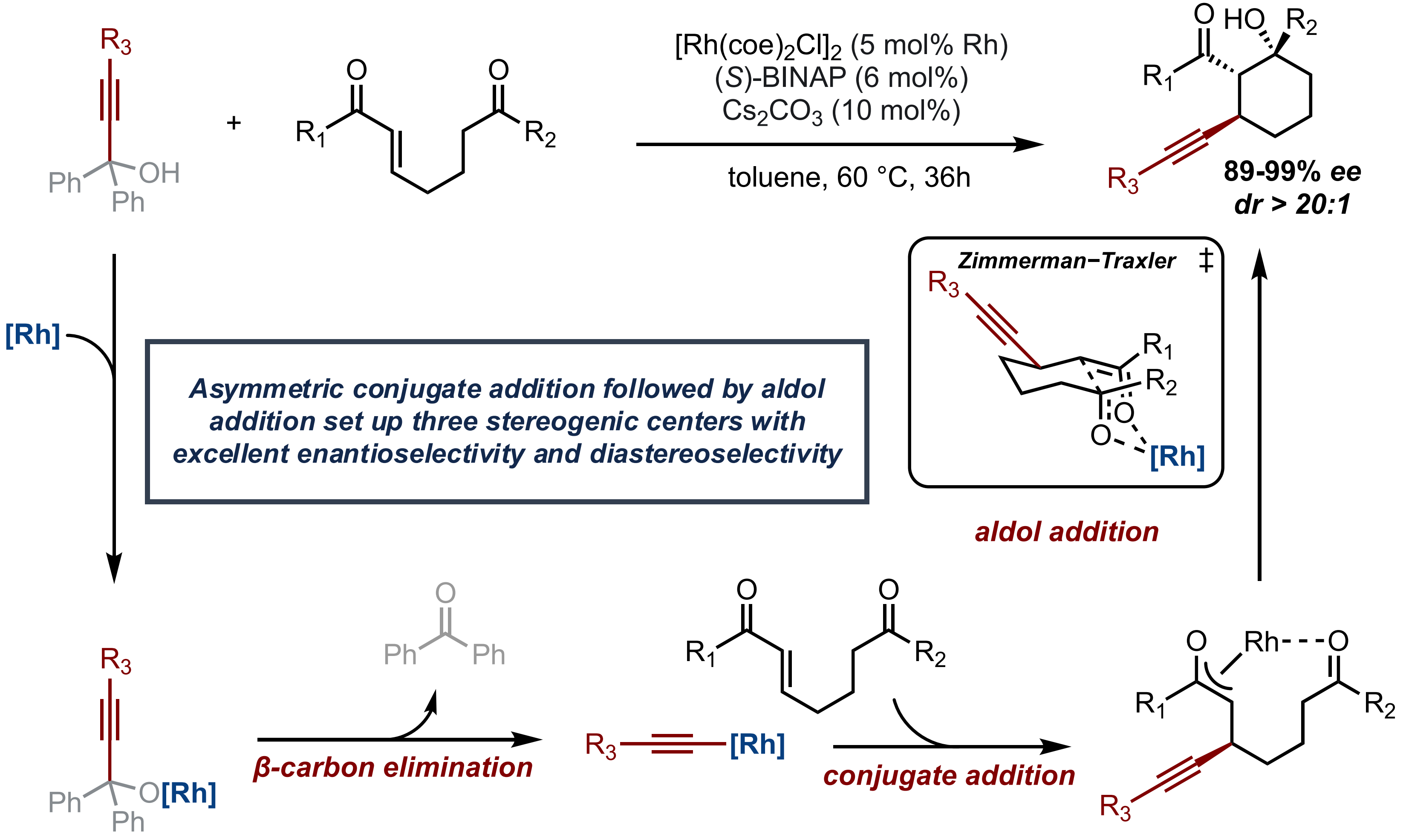
Hayashi (2016)



Souillart, L. & Cramer, N. *Chem. Rev.***115**, 9410–9464 (2015); Dermenci, A., Whittaker, R. E. & Dong, G. *Org. Lett*. **15**, 2242–2245 (2013).

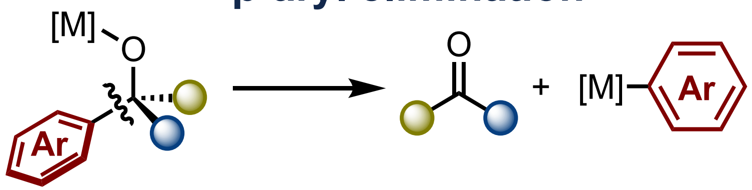
Overview: Strategies for Breaking a σ C–C Bond

Lautens (2018)

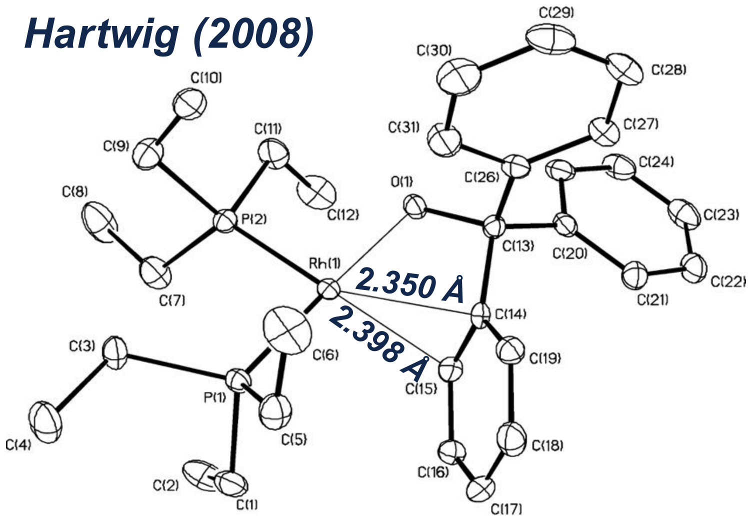


Asymmetric conjugate addition followed by aldol addition set up three stereogenic centers with excellent enantioselectivity and diastereoselectivity

β-aryl elimination

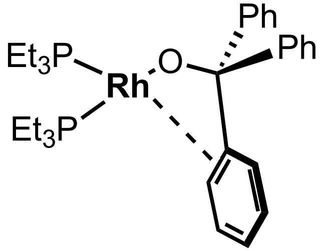


Hartwig (2008)



X-ray structure

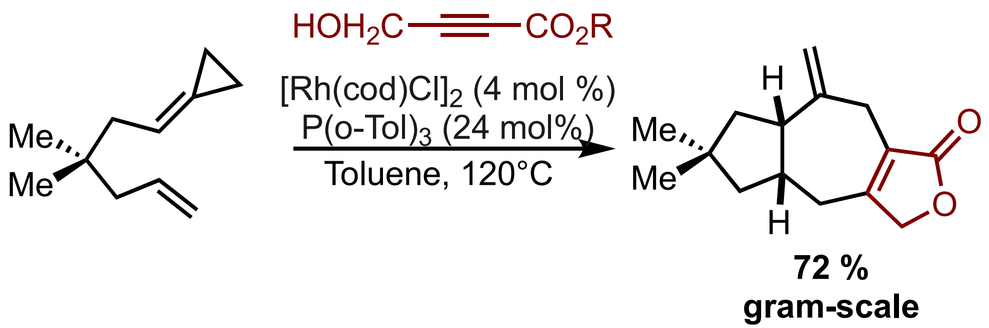
C(13)-C(14) was lengthened compared to other C(sp3)−C(sp2) bonds, implying the involvement of η2-interaction in the TS of β-phenyl elimination



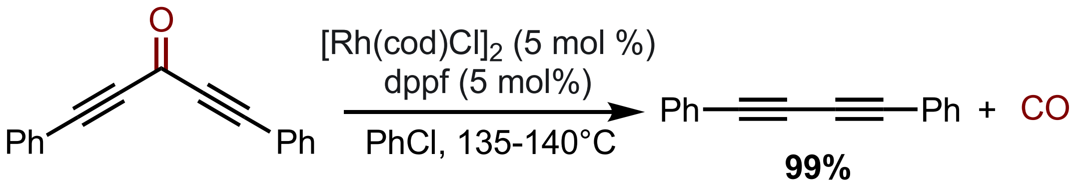
Souillart, L. & Cramer, N. *Chem. Rev.* **115**, 9410–9464 (2015); Choo, K.-L. & Lautens, M. *Org. Lett.* **20**, 1380–1383 (2018); Zhao, P. & Hartwig, J. F. *Organometallics* **27**, 4749–4757 (2008)

Overview: Strategies for Breaking a σ C–C Bond

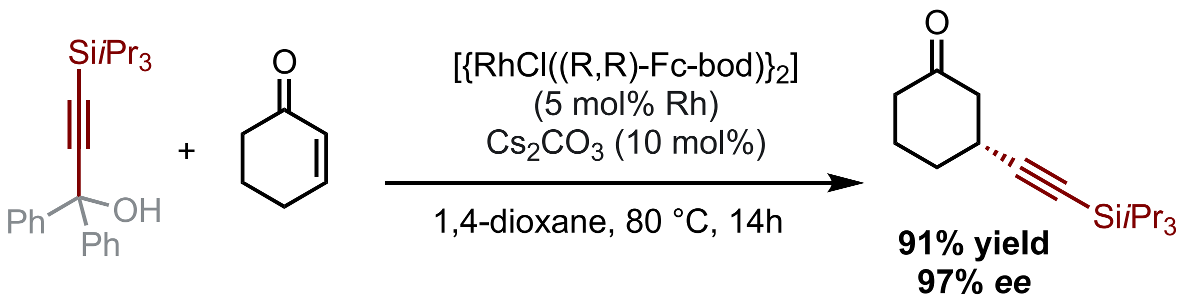
Ring Strain-Release

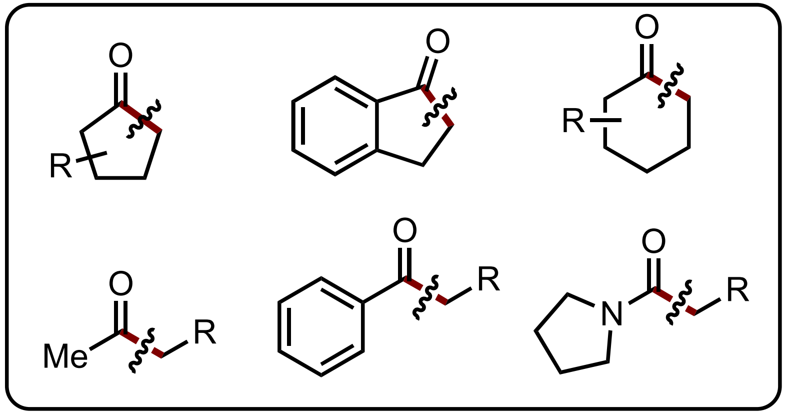


Decarbonylation



β-Carbon Elimination



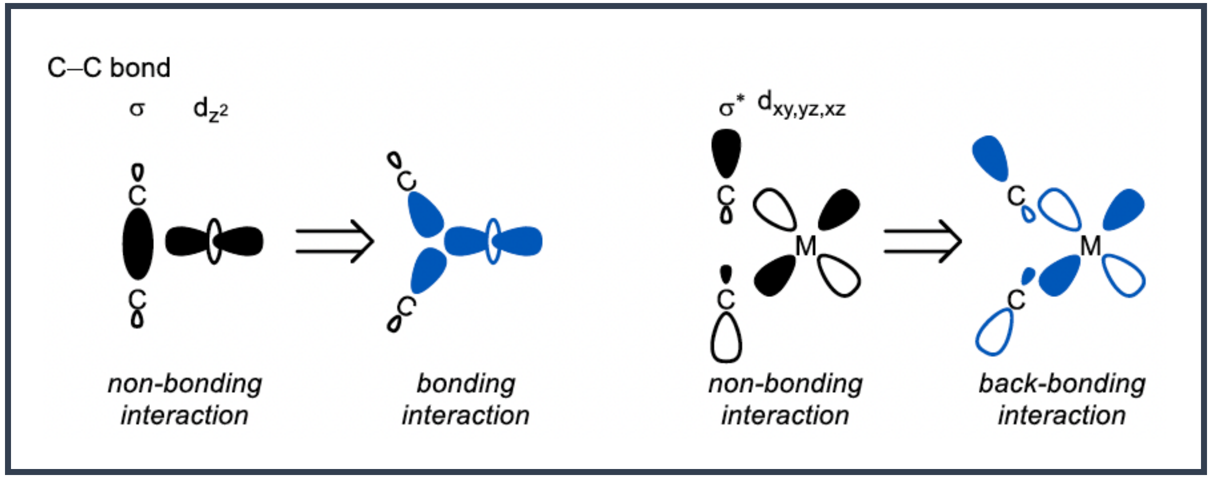


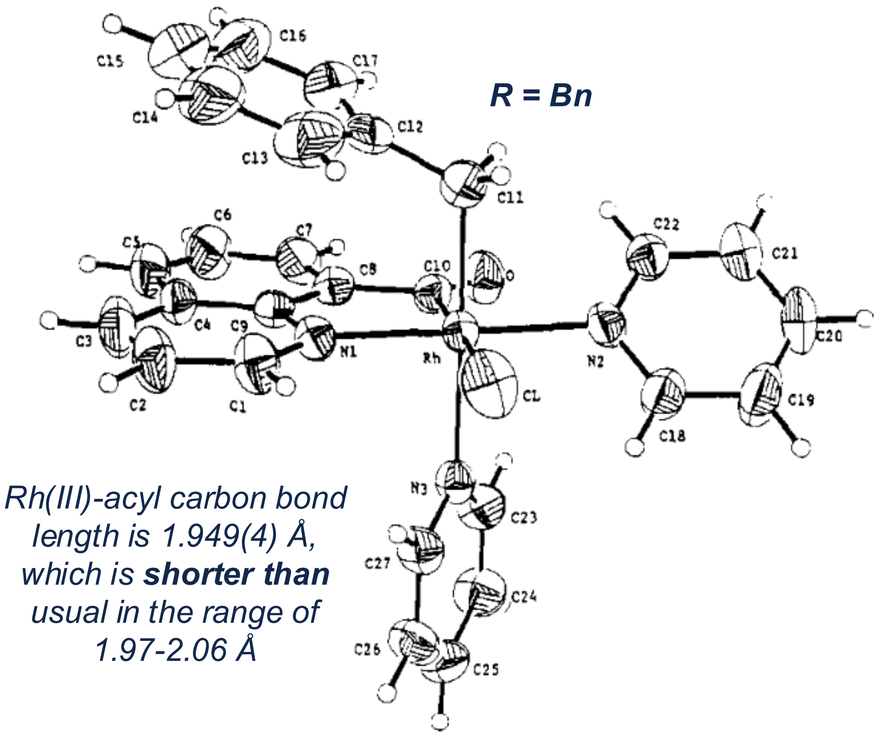
What about unstrained C-C bond activation?

Outline

- **Historical perspective into Directed Unstrained C-C Bonds Activation**
- **Rhodium-Catalyzed C–C Activation of Ketones**
- **Rhodium-Catalyzed C–C Activation of Amides**
- **Summary and Perspective**

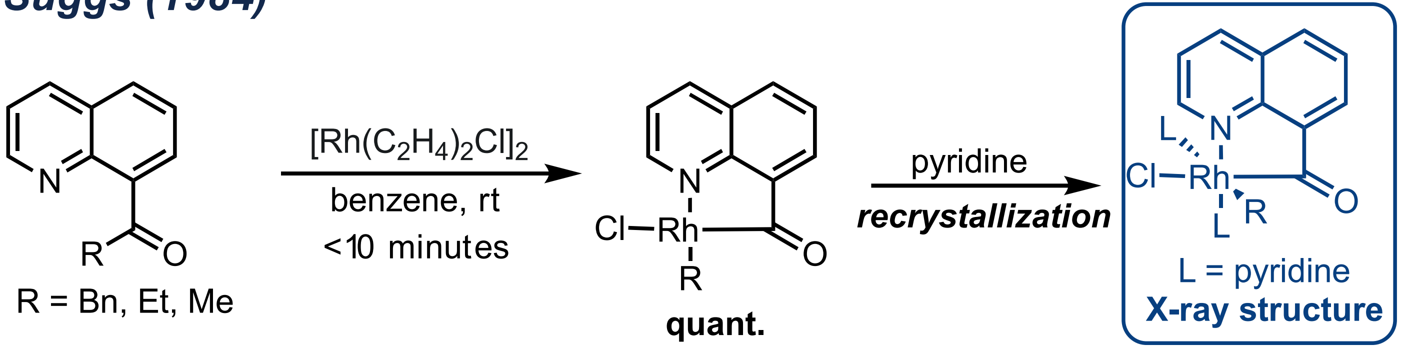
Quinolinyl Alkyl Ketones as Prototypical Directing Groups

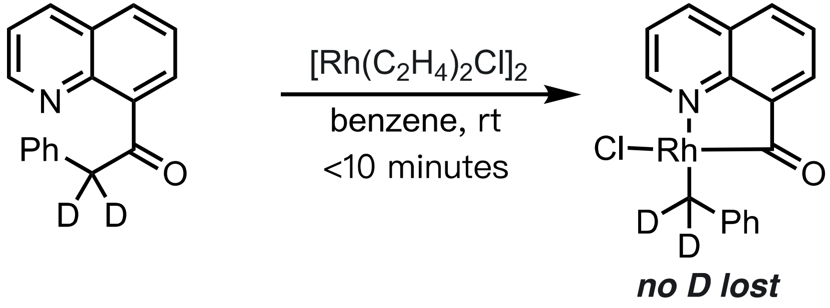




Rh(III)-acyl carbon bond length is 1.949(4) Å, which is **shorter than** usual in the range of 1.97-2.06 Å

Suggs (1984)



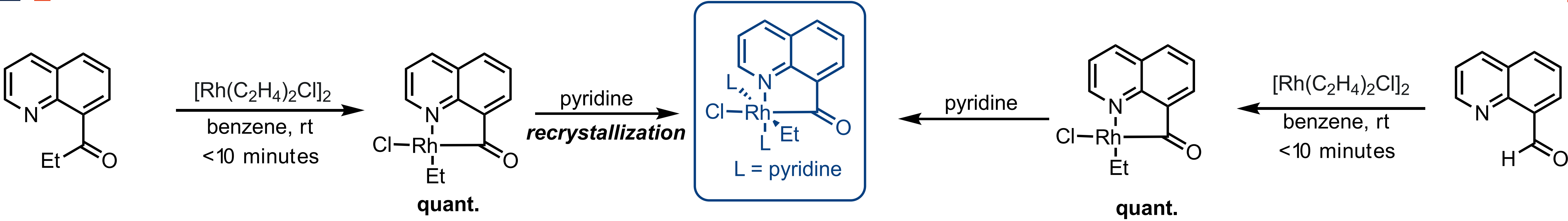


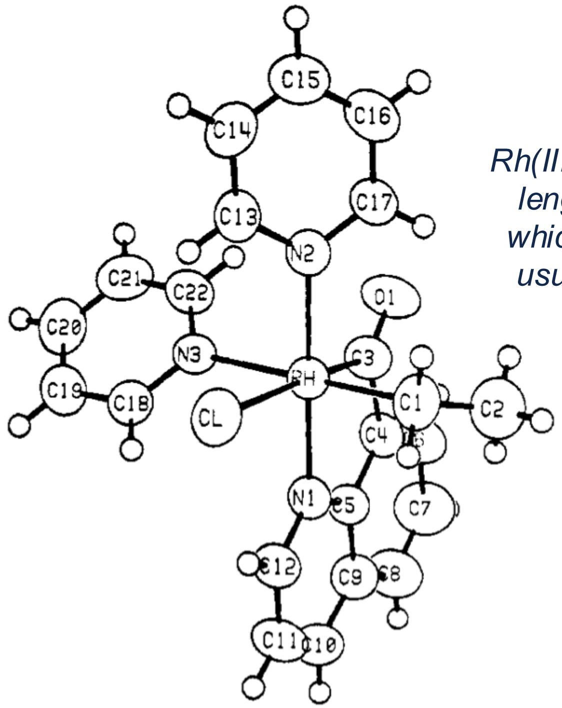
- *Five is the favored cyclometalation ring size, so Rh is only directed to the α-ketone C-C bond.*

- *α-Ketone C-C bond is slightly weaker than other C-C single bonds (BDE_{ethane} = 88 kcal/mol vs $BDE_{acetone}$= 82 kcal/mol)*

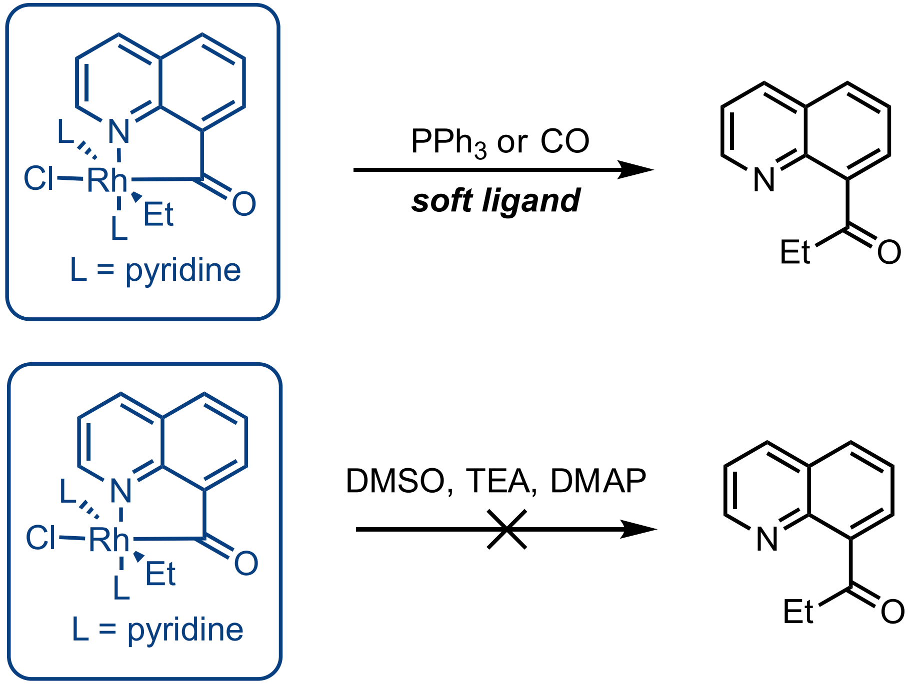
Gordon, A. J.; Ford, R. A. "The Chemist's Companion;" Wiley; New York, 1972; p 113; Suggs, J. W. & Jun, C. H. *J. Am. Chem. Soc.* **106**, 3054–3056 (1984)

Quinolinyl Alkyl Ketones as Prototypical Directing Groups





Rh(III)-acyl carbon bond length is 1.938(6) Å, which is ***shorter than*** *usual in the range of 1.97-2.06 Å*



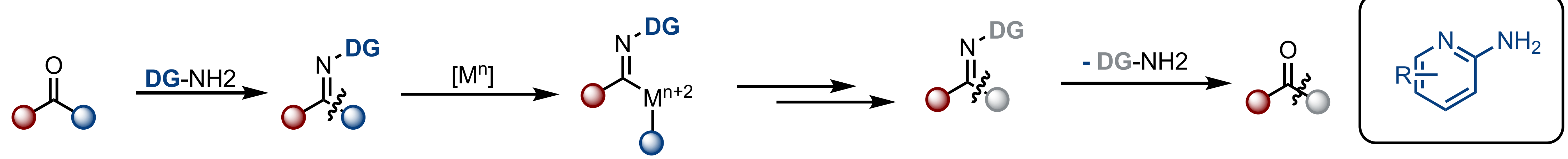
rapid reductive elimination

no reductive elimination

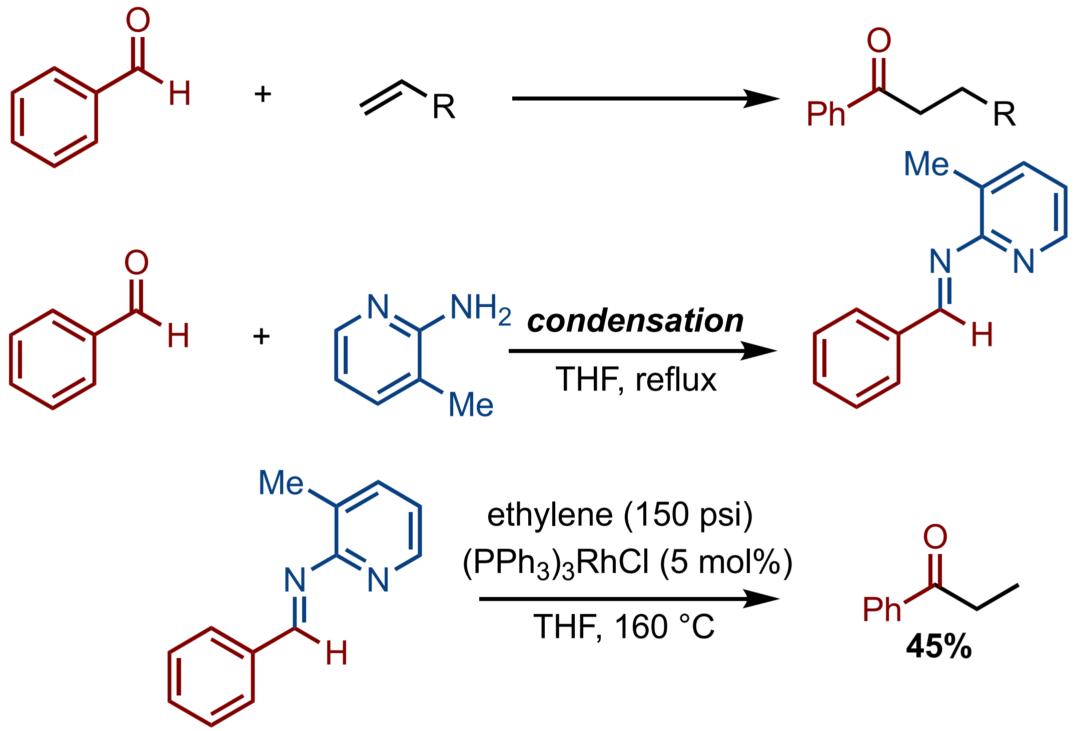
Gordon, A. J.; Ford, R. A. “The Chemist’s Companion;” Wiley; New York, 1972; p 113; Suggs, J. W. & Jun, C. H. *J. Am. Chem. Soc.* **106**, 3054–3056 (1984); Suggs, J. William., Wovkulich, M. J. & Cox, S. D. *Organometallics* **4**, 1101–1107 (1985)

2-Amino Pyridines as Removable Directing Groups

removable directing group



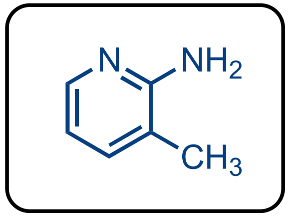
Suggs (1979)

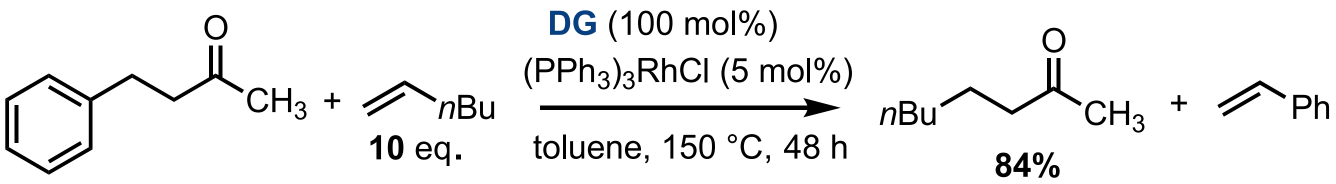


Although the yield was modest, this result clearly demonstrated that imines derived from 2-amino pyridine could undergo Rh-catalyzed oxidative addition and subsequent transformation

Jun (1999)

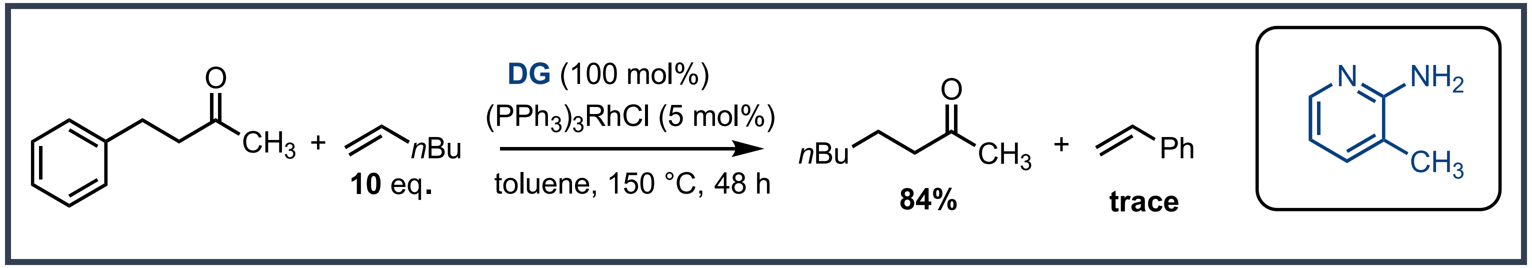
Jun was a Suggs' student and the author of the quinoline system

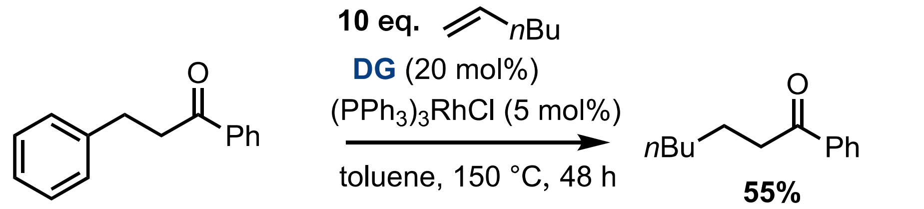




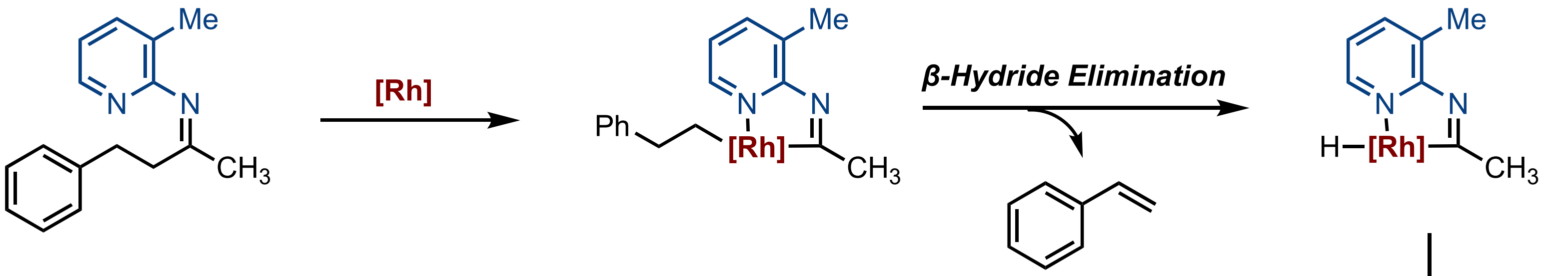
Suggs, J. W. *J. Am. Chem. Soc.* **101**, 489–489 (1979); Jun, C.-H. & Lee, H. *J. Am. Chem. Soc.* **121**, 880–881 (1999)

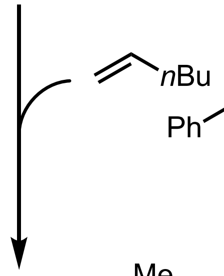
2-Amino Pyridines as Removable Directing Groups

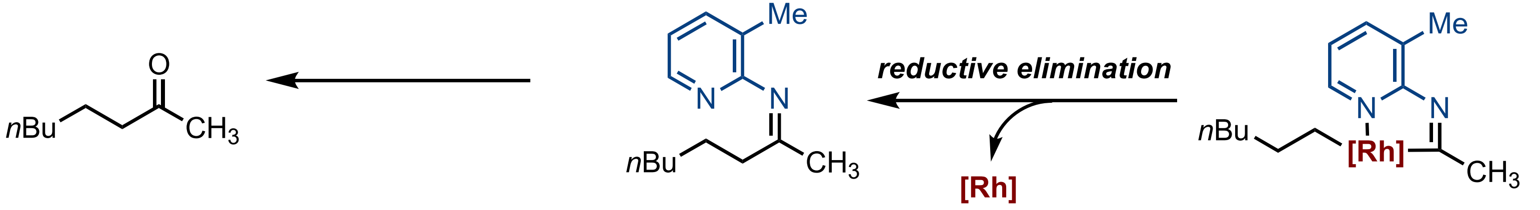


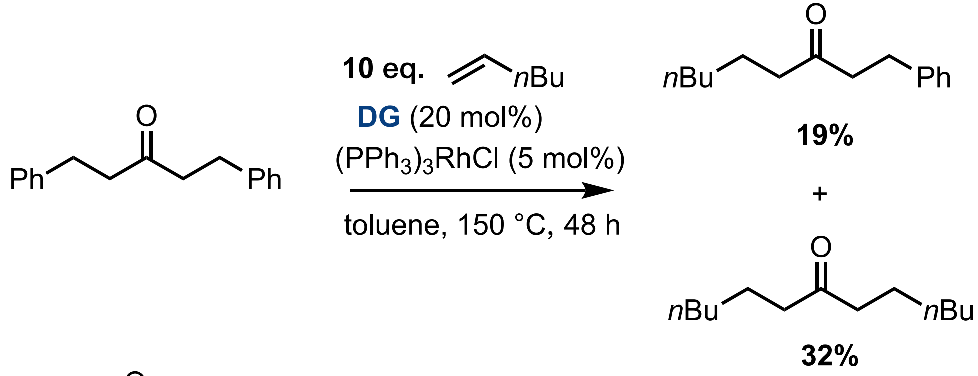


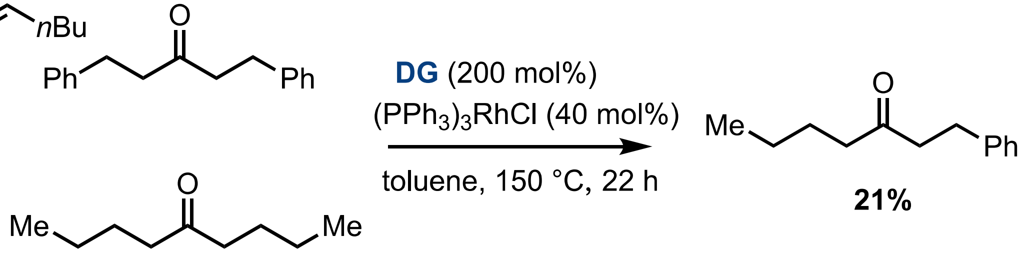
- *Styrene was polymerized at this temperature, especially in the presence of Rh complex.*











- ***Rh faces two possible C–C cleavage sites***
- ***The reaction stalls and simply reverts to the starting complex when breaking into methyl-C bonds.***

The coordination of the olefin to Rh is reversible

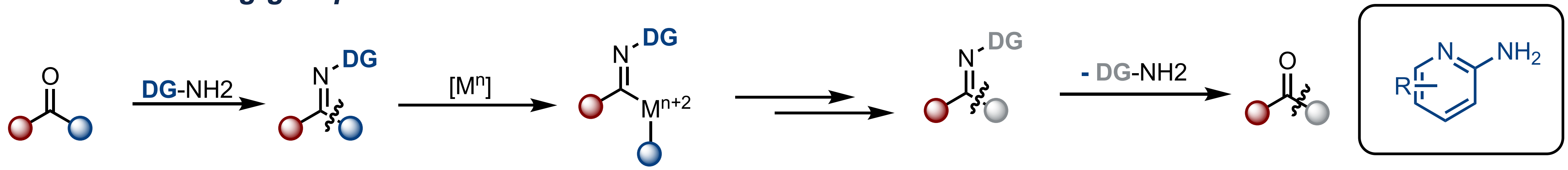
Jun, C.-H. & Lee, H. *J. Am. Chem. Soc.* **121**, 880–881 (1999)

Outline

- Historical perspective into Directed Unstrained C-C Bonds Activation
- **Rhodium-Catalyzed C–C Activation of Ketones**
- Rhodium-Catalyzed C–C Activation of Amides
- Summary and Perspective

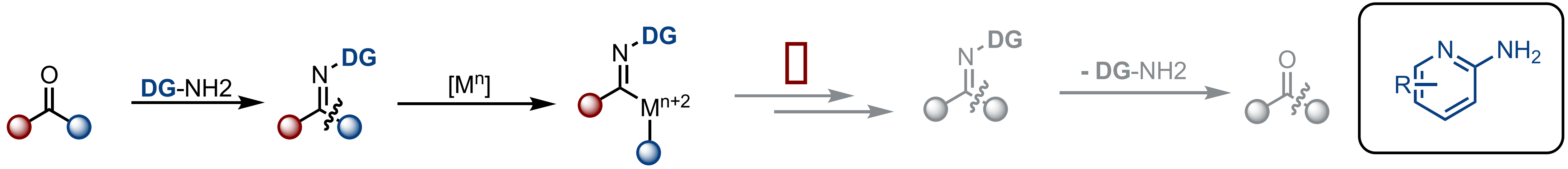
Rhodium-Catalyzed C–C Activation of Ketones

removable directing group



DGs can effectively reduce the kinetic barriers, but…

- *The unstrained substrates are special and lack structural complexity*
- *The types of downstream transformations are limited*
- *High catalyst loadings and high reaction temperature are often required*



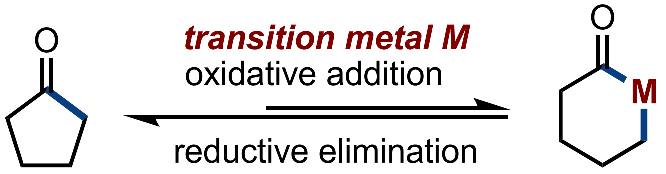
What else can we do with this removable directing group system?

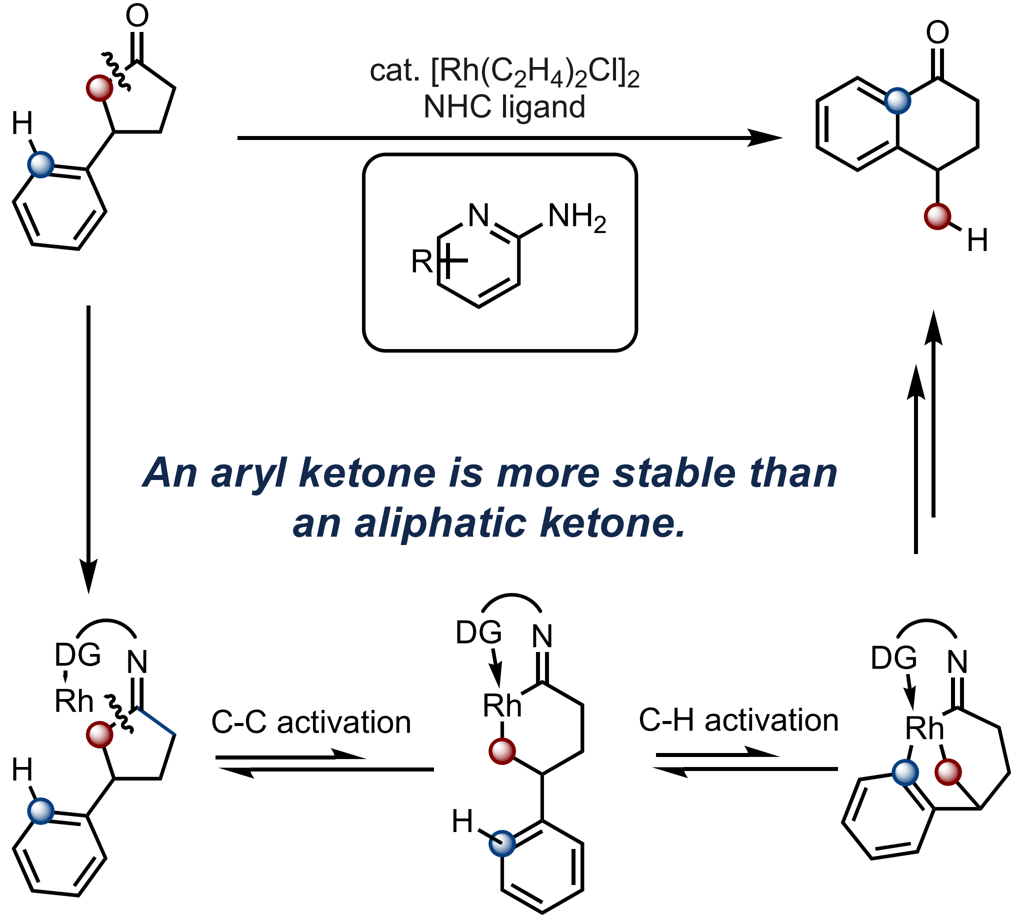
a new, broadly useful, and practical transformation—without increasing the system's energy

Jun, C.-H. & Lee, H. *J. Am. Chem. Soc.* **121**, 880–881 (1999)

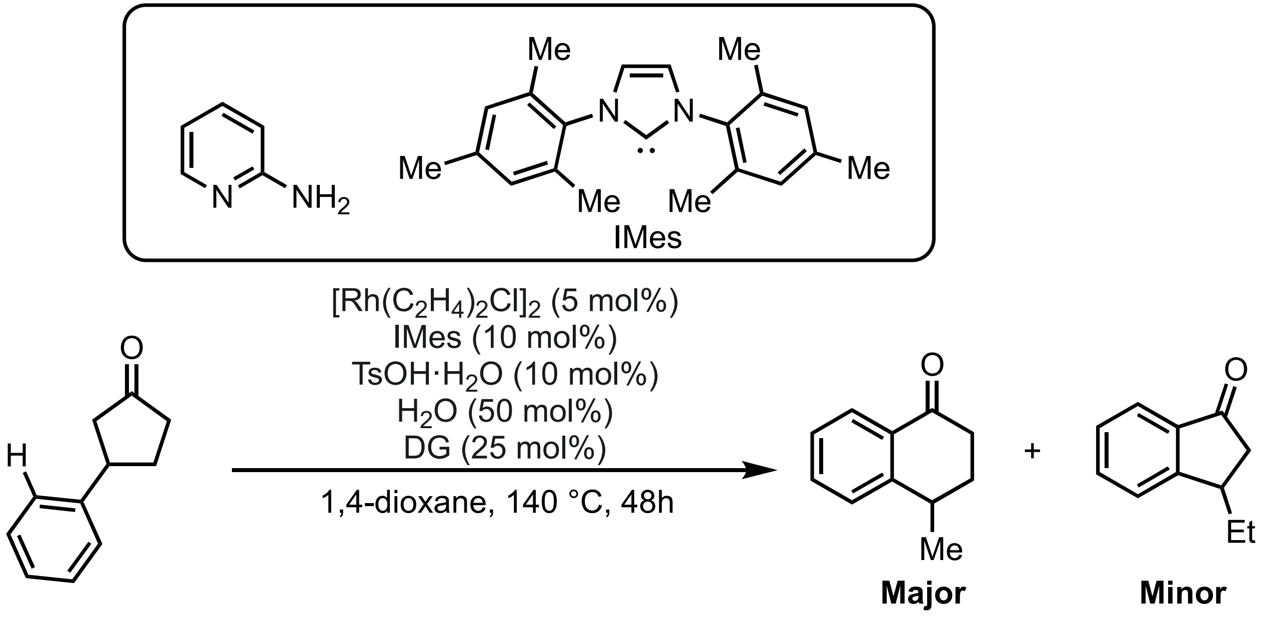
Rhodium-Catalyzed C–C Activation of Ketones

Dong (2016)



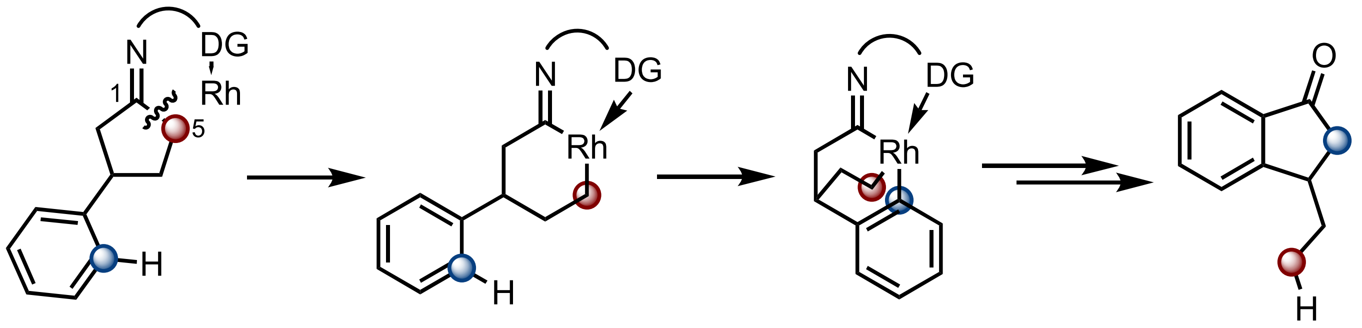


An aryl ketone is more stable than an aliphatic ketone.



66% (>10:1)

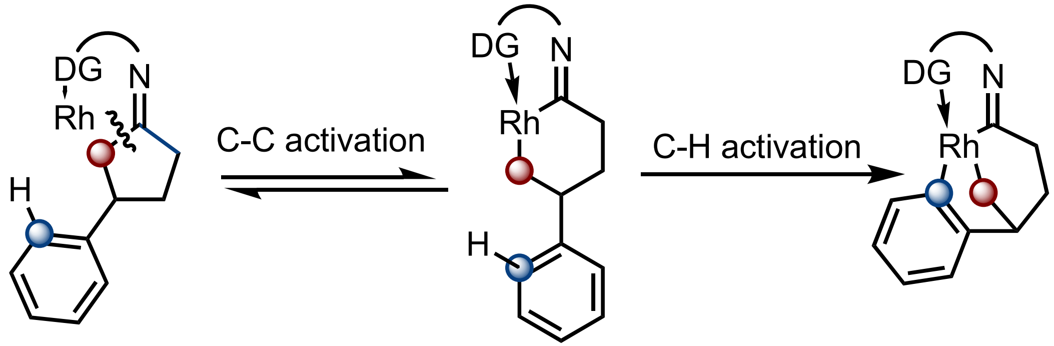
Oxidative addition could occur at both sides of the ketone



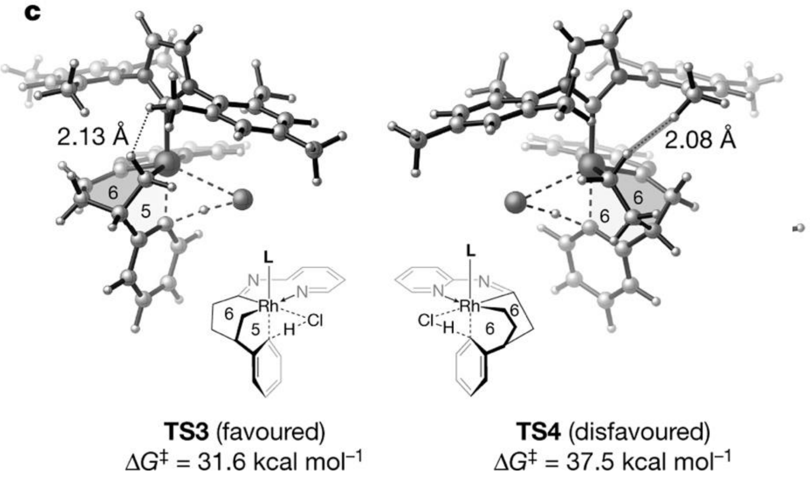
Xia, Y., Lu, G., Liu, P. & Dong, G. *Nature* **539**, 546–550 (2016).

Rhodium-Catalyzed C–C Activation of Ketones

DFT study



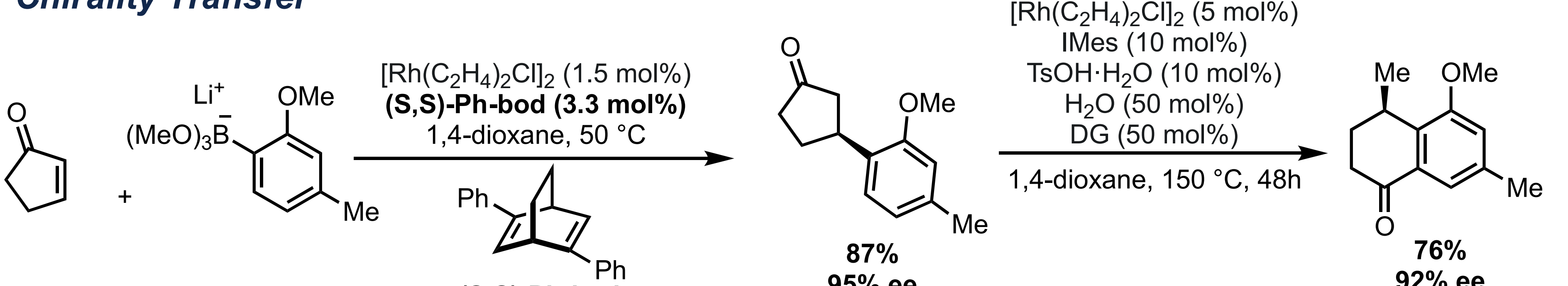
- *C-C activation is reversible, and the ΔG‡ difference is negligible*
- *C-H activation proceeds through a concerted metalation-deprotonation(CMD) pathway, with a significant ΔG‡ difference.*

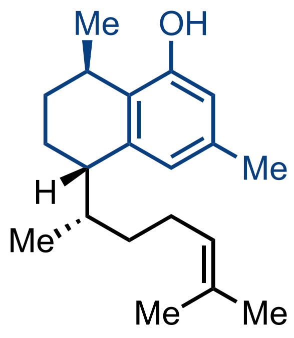


proximal activation

distal activation

Chirality Transfer



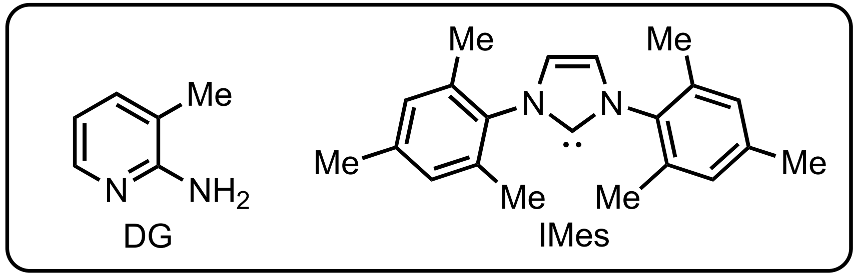


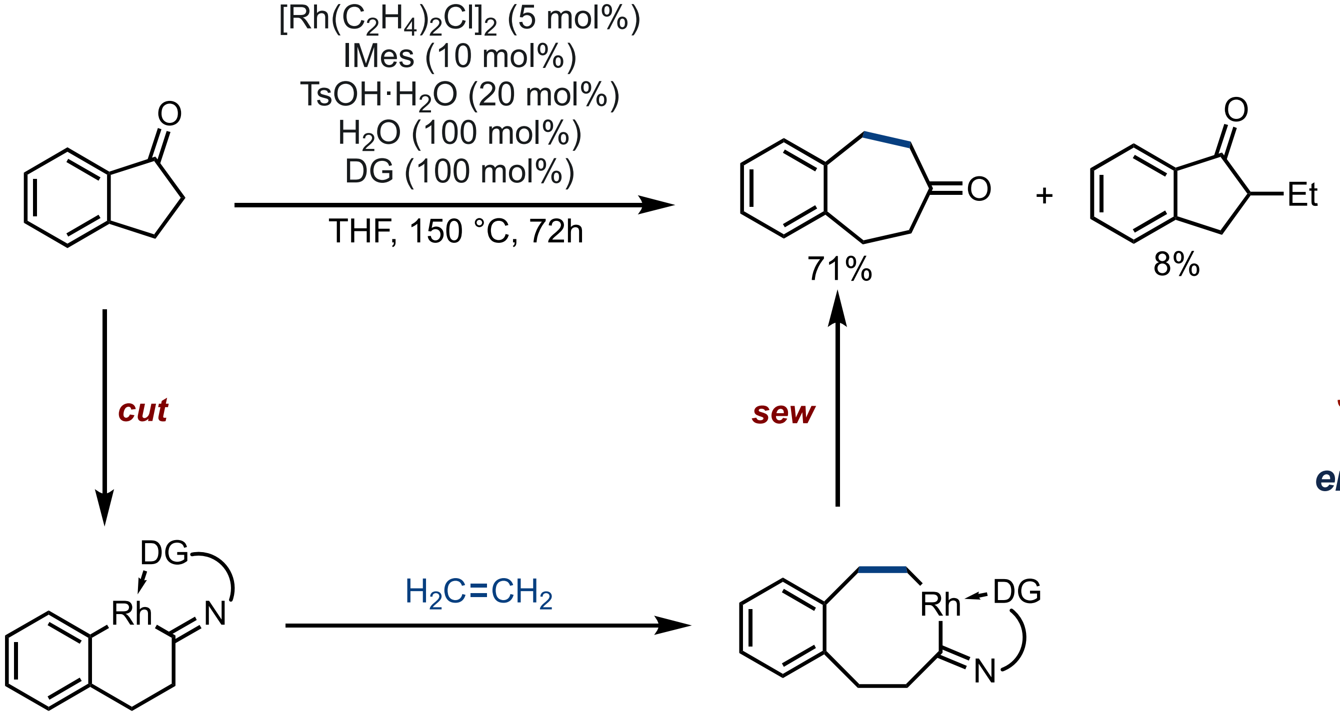
(-)-leubethanol

This strategy has been successfully applied in total synthesis

Xia, Y., Lu, G., Liu, P. & Dong, G. *Nature* **539**, 546–550 (2016); Hou, S., Prichina, A. Y., Zhang, M. & Dong, G. *Angewandte Chemie* **132**, 7922–7930 (2020).

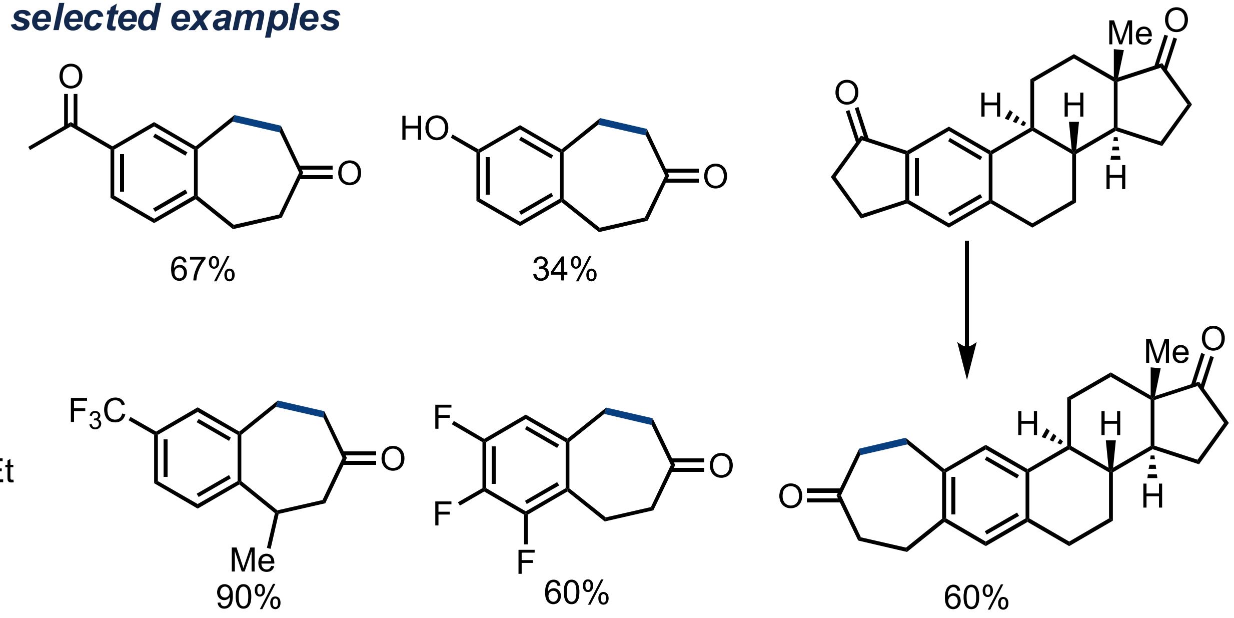
Rhodium-Catalyzed C–C Activation of Ketones





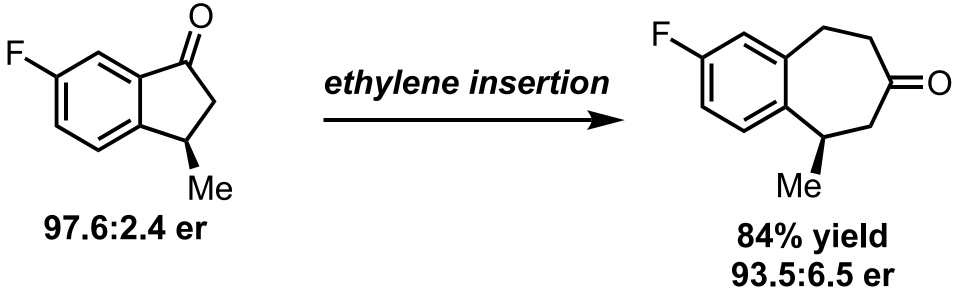
The 'cut and sew' involve ***oxidative addition*** *to a C–C bond, followed by* ***migratory insertion*** *of an unsaturated unit and* ***reductive elimination****, leading to ring expansion.*

selected examples



Substituted alkenes are not reactive under the current conditions

enantioselectivity erosion



Unproductive C–C activation at the C1–C2 position leads to reversible β-hydride elimination

Xia, Y., Ochi, S. & Dong, G. *J. Am. Chem. Soc.* **141**, 13038–13042 (2019)

Outline

- Historical perspective into Directed Unstrained C-C Bonds Activation
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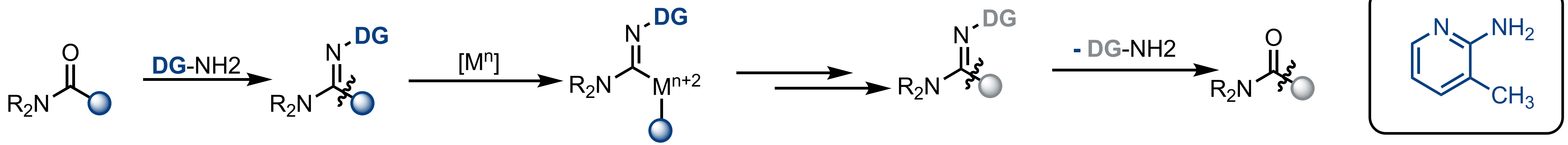
- **Rhodium-Catalyzed C–C Activation of Amides**
- Summary and Perspective

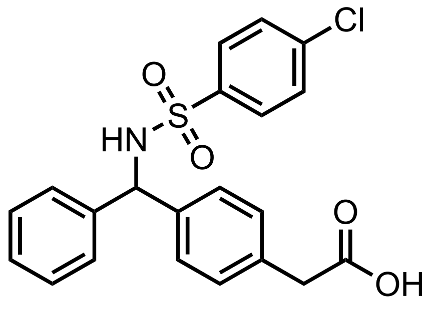
Hook-and-slide: Rhodium catalyzed amide homologation

removable directing group

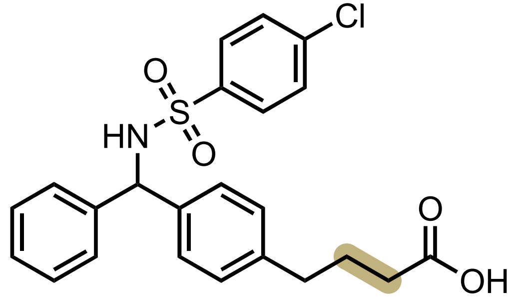


Homologs refers to a series of molecules with different carbon-chain lengths but otherwise identical functionality

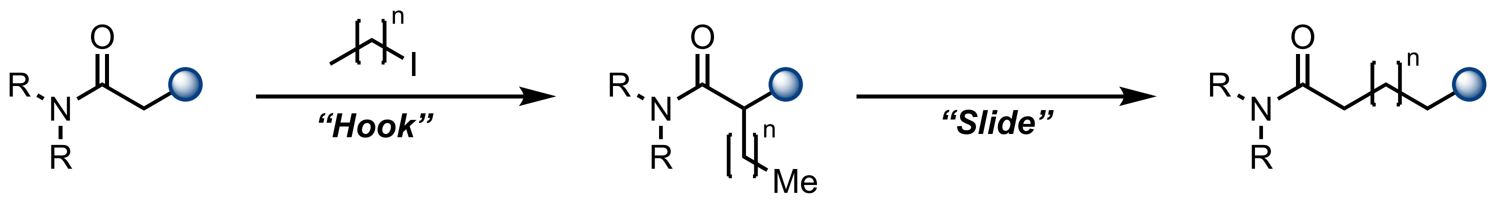
Thromboxane A_2 receptor antagonists



IC_{50} = 100 μM

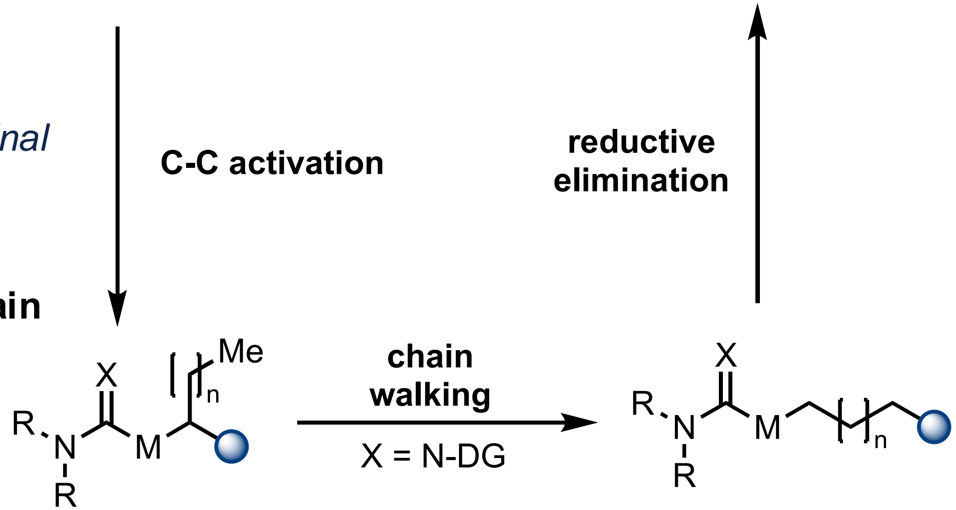


IC_{50} = 0.20 μM



- *"Hook": enolate alkylation*
- *"Slide" : shift the metal to the alkyl terminal position*

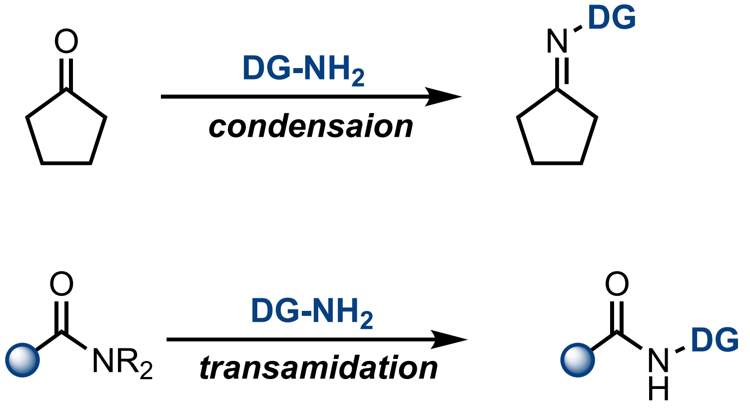
The length of the homologation is determined by the length of the alkyl chain

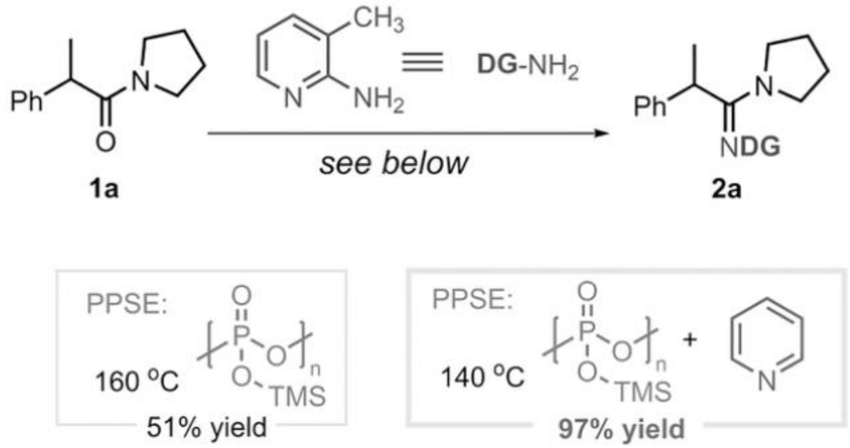


Zhang, R., Yu, T. & Dong, G. *Science* **382**, 951–957 (2023); Ogata, S., Mochizuki, A., Kakimoto, M. & Imai, Y. *Bulletin of the Chemical Society of Japan* **59**, 2171–2177 (1986)

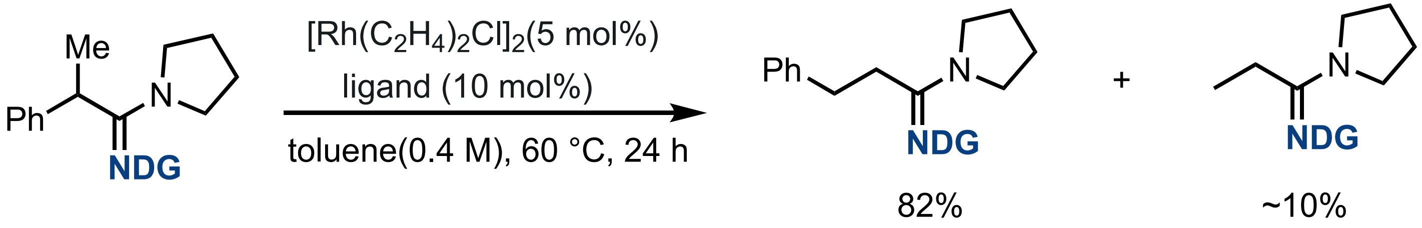
Hook-and-slide: Rhodium catalyzed amide homologation

Installation of DG

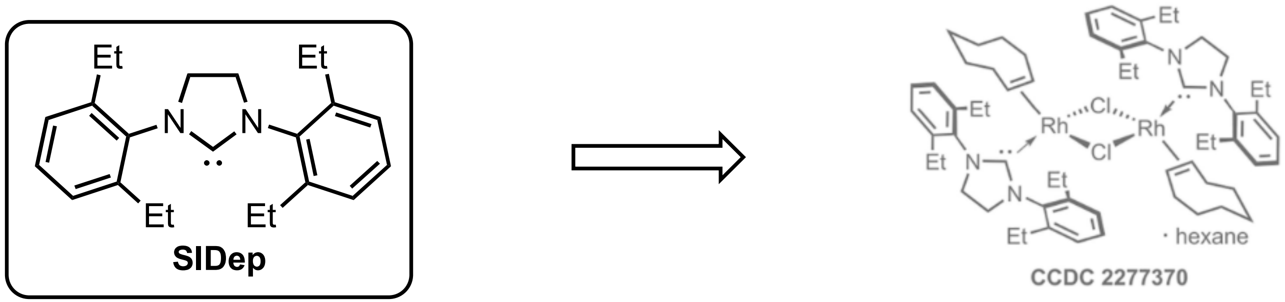




The polyphosphoric acid trimethylsilyl ester (PPSE) condition was first developed by Kakimoto in 1986



The use of the pre-catalyst $[Rh(C_2H_4)_2Cl]_2$ leads to side reactions.



CCDC 2277370

5 mol% $[Rh(coe)(SIDep)Cl]_2$· hexane

Replacement of $[Rh(C_2H_4)_2Cl]_2$ with $[Rh(coe)(SIDep)Cl]_2$·hexane improves the yield to 96%

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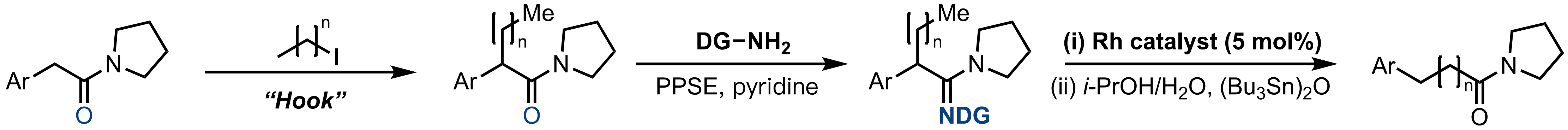
Hook-and-slide: Rhodium catalyzed amide homologation

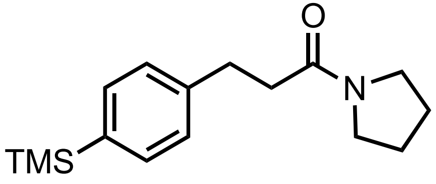
Overall homologation reaction sequence



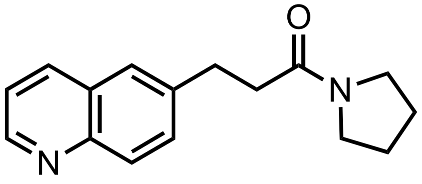
Stage I **Stage II** **Stage III**

The amide activation requires additional steps for DG installation and removal

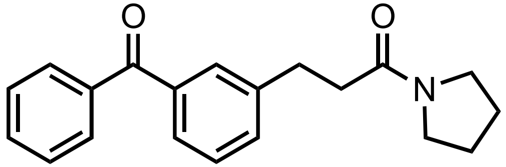
Yield
Stage II/Stage III



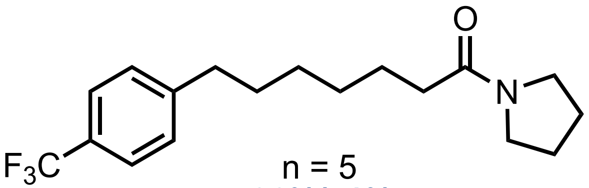
56%/89%



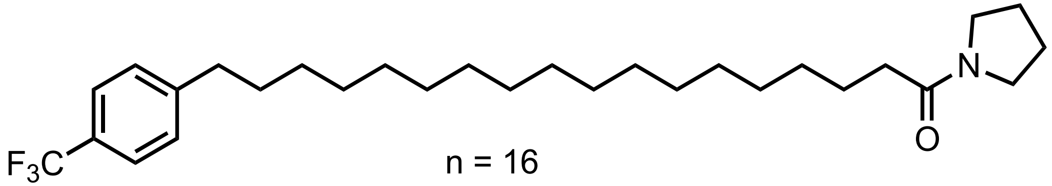
86%/63%



80%/79%



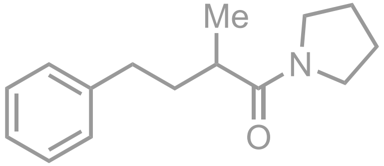
n = 5
96%/71%

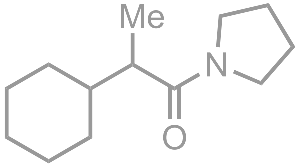


n = 16
87%/33%

Excellent linear selectivity was observed across all examples with no detectable formation of branched intermediates

Unsuccessful substrates





α-Aryl–substituted amides are required

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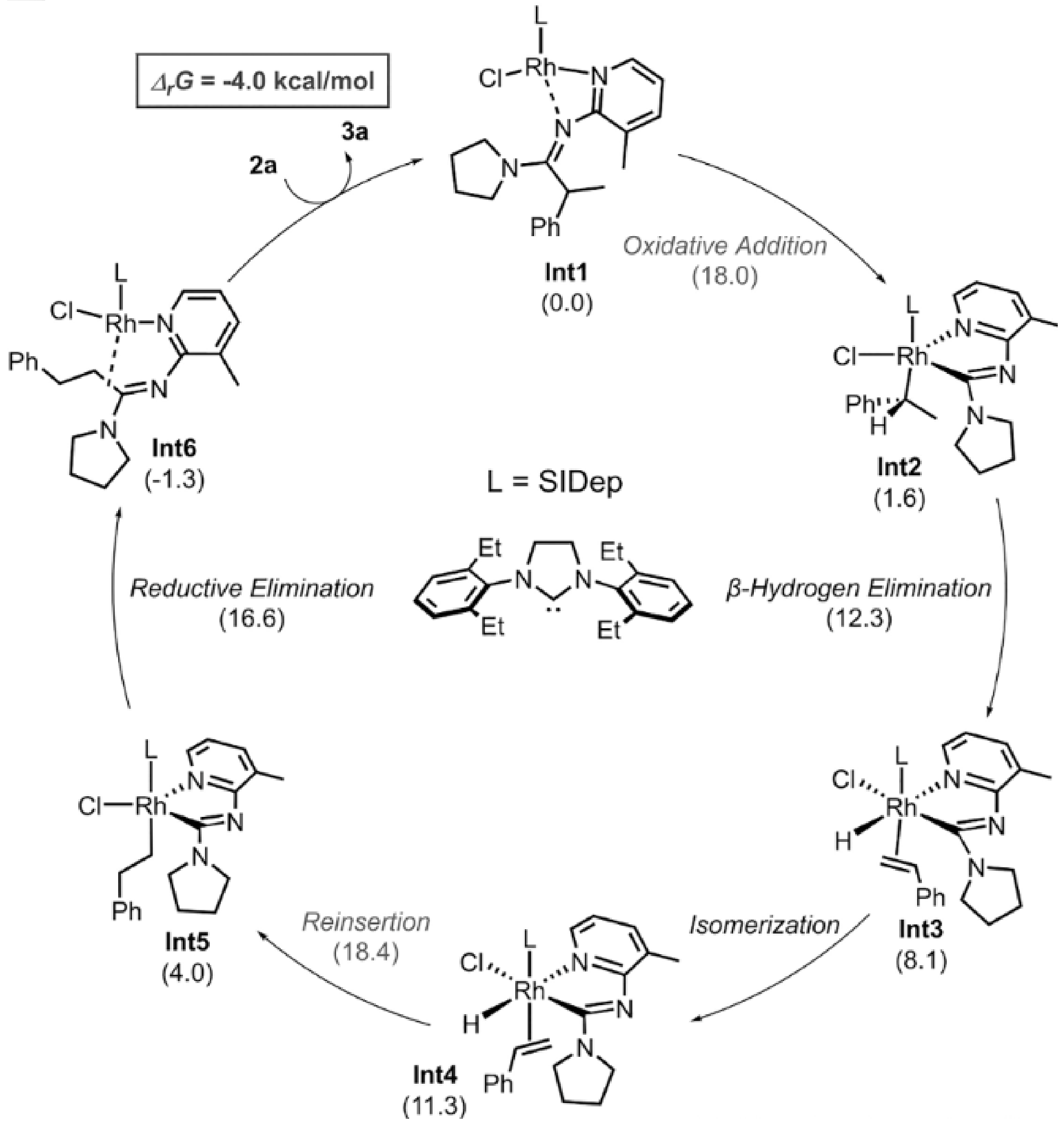
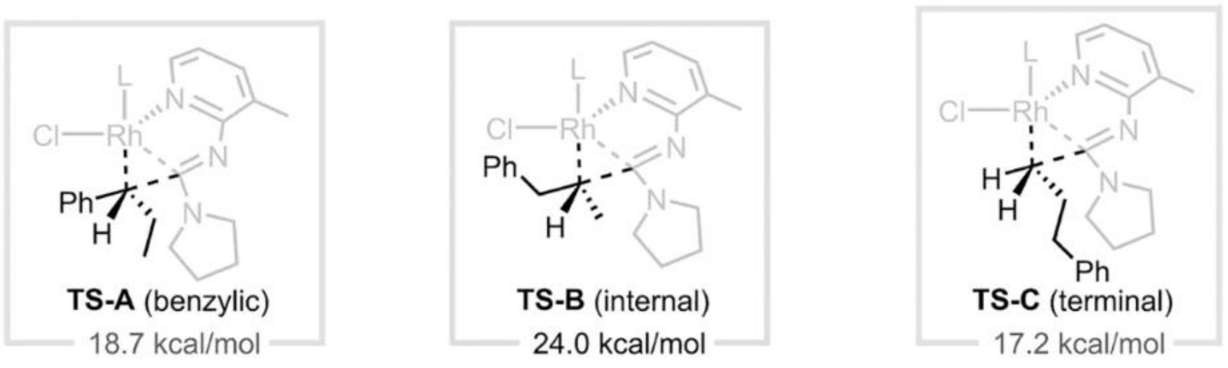
Hook-and-slide: Rhodium catalyzed amide homologation



- *Overall free energy change of the reaction is −4.0 kcal/mol, suggesting that the linear product is thermodynamically more stable*



- *Reductive elimination and oxidative addition are favorable at benzylic or terminal positions under standard conditions.*
- *No branched intermediates were observed.*
- *α-Aryl–substituted amides were required.*

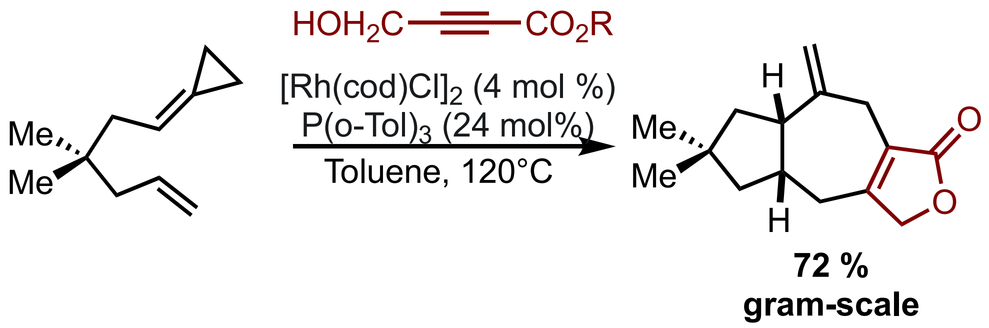
Zhang, R., Yu, T. & Dong, G. *Science* **382**, 951–957 (2023); Ogata, S., Mochizuki, A., Kakimoto, M. & Imai, Y. *Bulletin of the Chemical Society of Japan* **59**, 2171–2177 (1986)

Outline

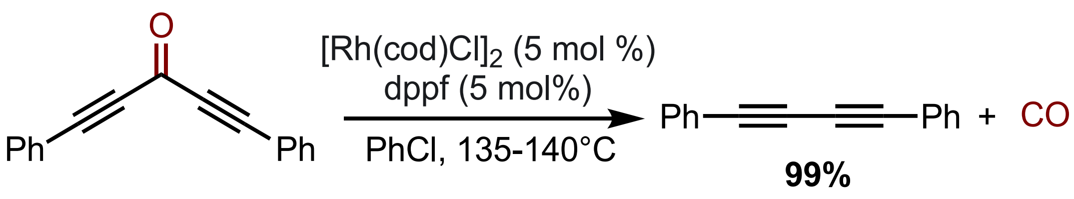
- Historical perspective into Directed Unstrained C-C Bonds Activation
- Rhodium-Catalyzed C–C Activation of Ketones
- Rhodium-Catalyzed C–C Activation of Amides
- **Summary and Perspective**

Summary

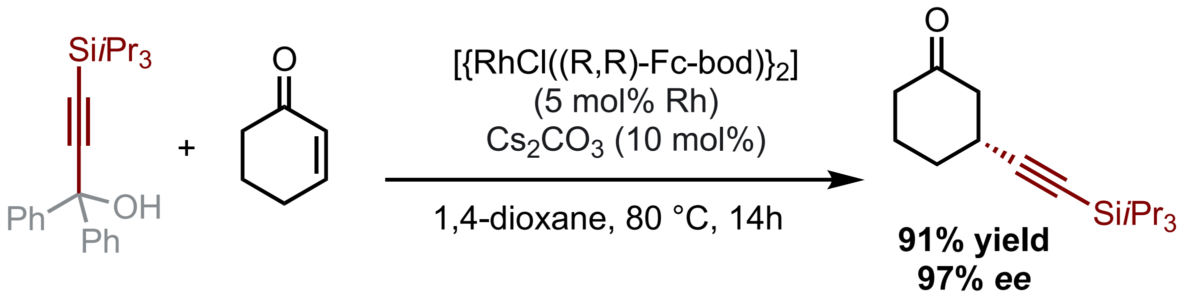
Ring Strain-Release



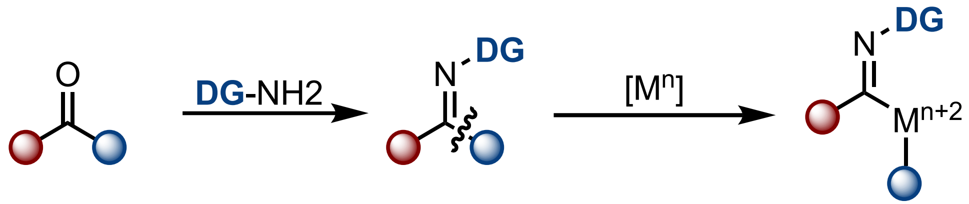
Decarbonylation



β-Carbon Elimination



Directing group

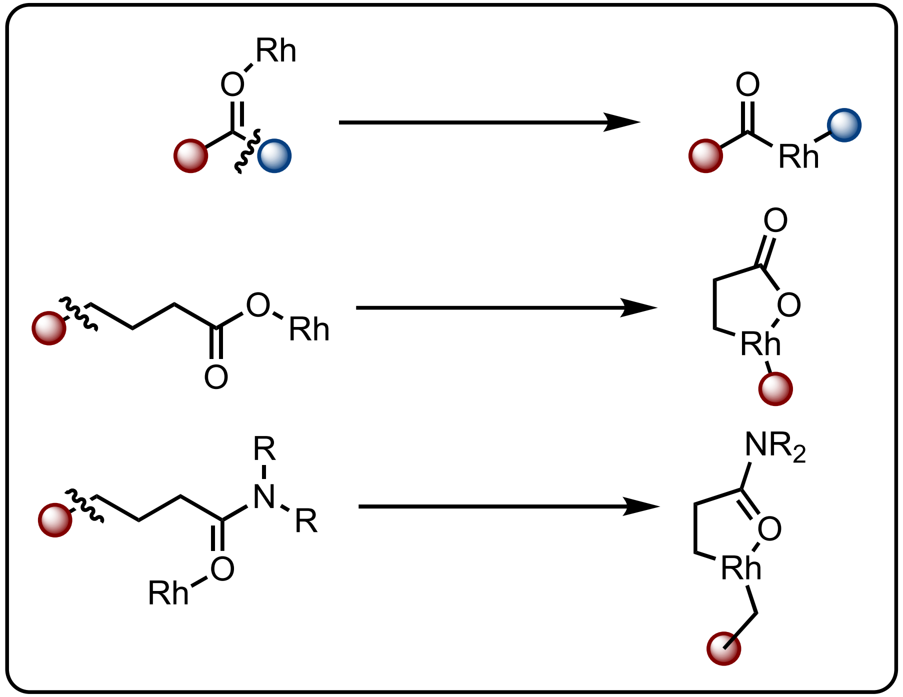


Pre-functionalized substrates or structurally biased systems are required

Activation of bonds between two unactivated sp³ carbons is still a major challenge

Perspective

- **New removable DG or native DG**



Rh ⇒ Ni, Co, Fe …

- *Design new catalytic systems utilizing native functional groups, which could potentially simplify the reaction conditions.*

- *Replace Rh with earth-abundant metals, such as Ni, Co, Fe…*

Further Reading

- **Reviews**

Transition metal-catalyzed carbon–carbon bond activation

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Received 26th February 2004
First published as an Advance Article on the web 4th November 2004

CHEMICAL REVIEWS
Review
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Catalytic C–C Bond Activations via Oxidative Addition to Transition Metals

Laetitia Souillart and Nicolai Cramer*
Laboratory of Asymmetric Catalysis and Synthesis, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne 1015, Switzerland

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Review

Metal-Catalyzed Carbon–Carbon Bond Cleavage of Unstrained Alcohols

Marius D. R. Lutz and Bill Morandi*

ACCOUNTS of chemical research
pubs.acs.org/accounts
Article

Skeletal Modification via Activation of Relatively Unstrained C–C Bonds

Published as part of Accounts of Chemical Research special issue "Skeletal and Stereochemical Editing".

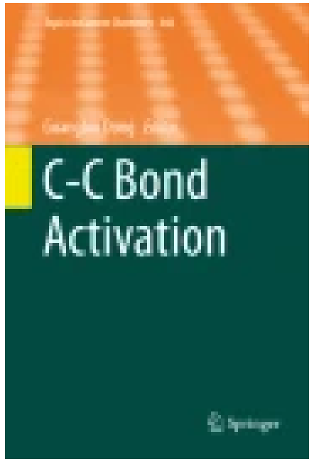
Rui Zhang and Guangbin Dong*

Cite This: *Acc. Chem. Res.* 2025, 58, 991–1002
Read Online

- **Books**

C-C Bond Activation https://doi.org/10.1007/978-3-642-55055-3

This book was published in 2014, so it doesn't provide the most up-to-date review of C–C bond activation. However, some chapters cover interesting topics that are not included in this presentation, such as asymmetric transformations via C–C bond cleavage and related developments.



Questions?