Ruthenium Catalyzed C–C Bond Formation and Its Application Developed by Michael J. Krische

2024.6.8. Literature Seminar
D3 Yuto Hikone

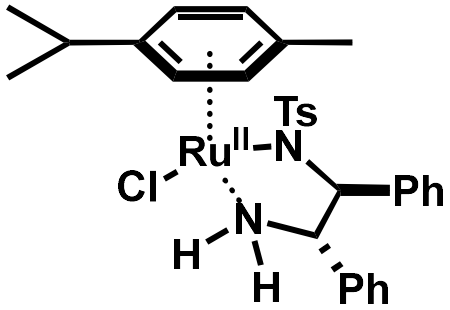
Contents

Ruthenium

^{44}Ru

group 8, period 5
electron configuration: [Kr] $4d^7\ 5s^1$
wide scope of oxidation states: –2, 0~+8

representative ruthenium catalysts

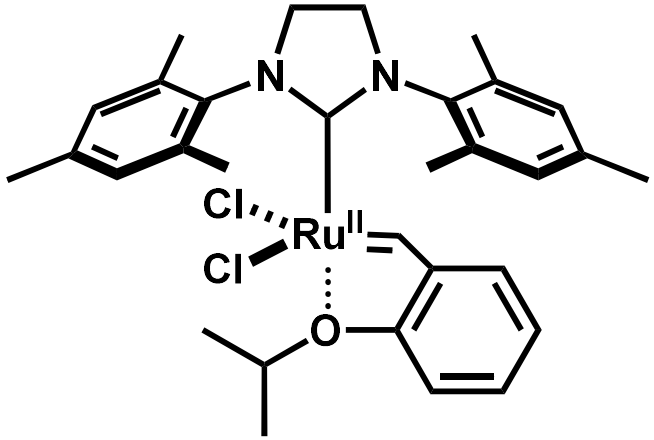


RuCl(η^6-cymene)(Ts-DPEN)

Noyori asymmetric
transfer hydrogenation

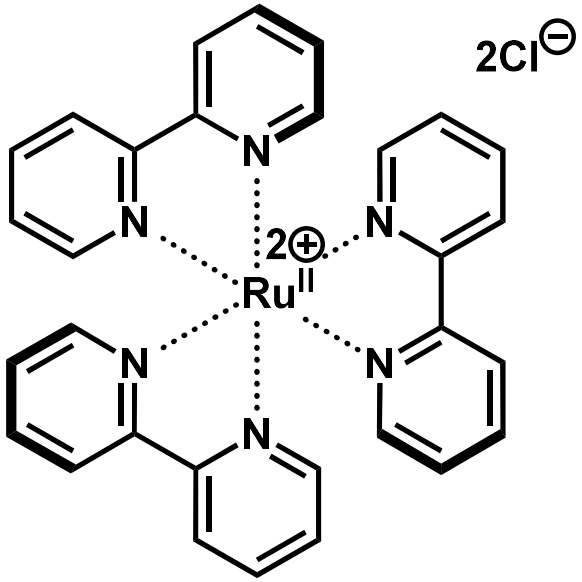
n-$Pr_4Ru^{IV}O_4$

oxidation of alcohols



Hoveyda-Grubbs
second generation
olefin metathesis

Ru^VO_4
(from $Ru^{III}Cl_3 \cdot nH_2O$, $NaIO_4$)
strong oxidant
oxidation of aromatic ring, C–H bond
cis-dihydroxylation of alkene

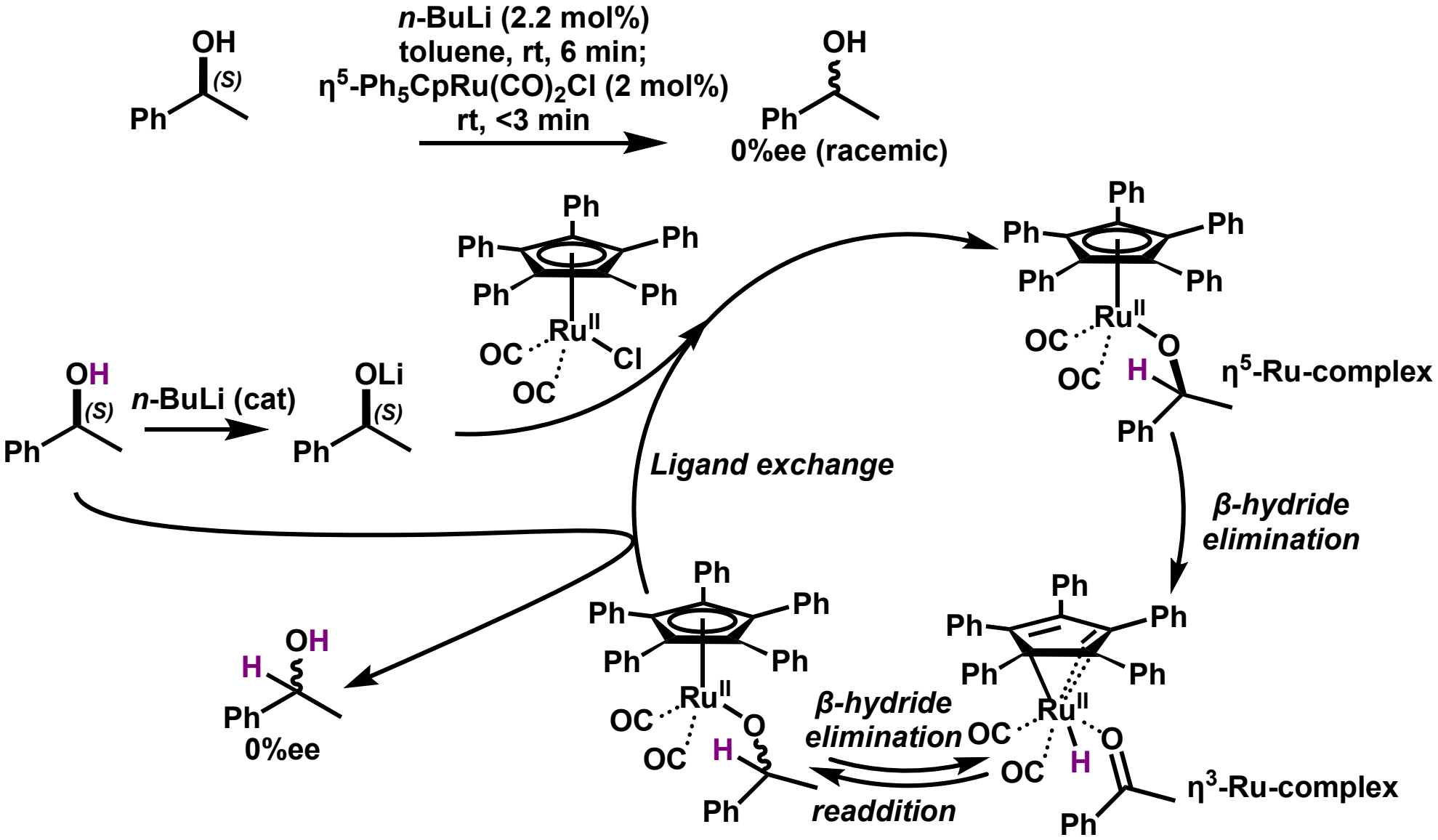


$Ru^{II}(bpy)_3Cl_2$

photoredox reactions

Transfer Hydrogenation (1)

- **transfer hydrogenation**
  - **(i) transfer hydrogenation catalyzed by Ru^{II} catalyst**



Martín-Matute, B.; Åberg, J. B.; Edin, M.; Bäckvall, J.-E. *Chem. - Eur. J.* **2007**, *13*, 6063.

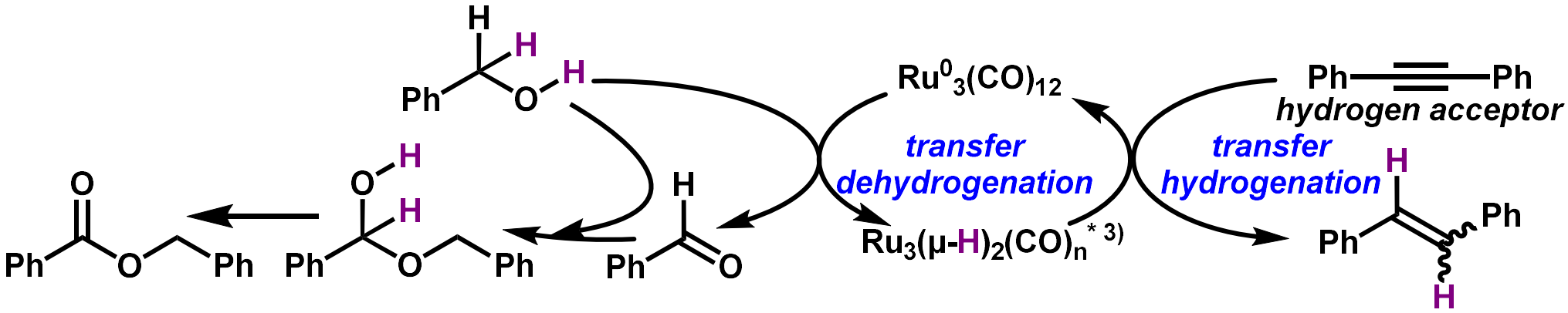
Transfer Hydrogenation (2)

(ii) transfer hydrogenation catalyzed by Ru^0 catalyst

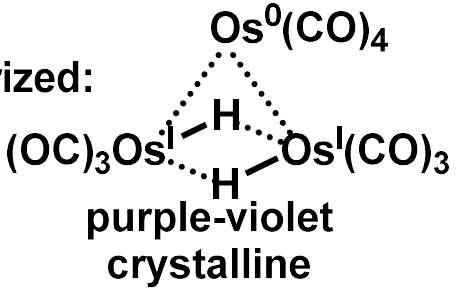
conditions A[1]: $Ru^0_3(CO)_{12}$ (0.3 mol%)
Ph—≡—Ph
147 °C, 2 h, 87%

conditions B[2]: $Ru^{II}H_2(PPh_3)_4$ (2 mol%)
mesitylene (1,3,5-trimethylbenzene)
180 °C, 24 h, 95%

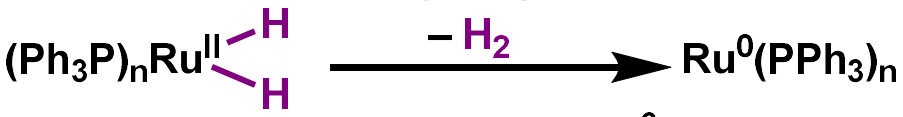
reaction mechanism
conditions A (hydrogen acceptor required):



* As for ^{76}Os (group 8), related dihydride Os cluster is characterized: $Os^0(CO)_4[Os^I(CO)_3(\mu\text{-}H)]_2$



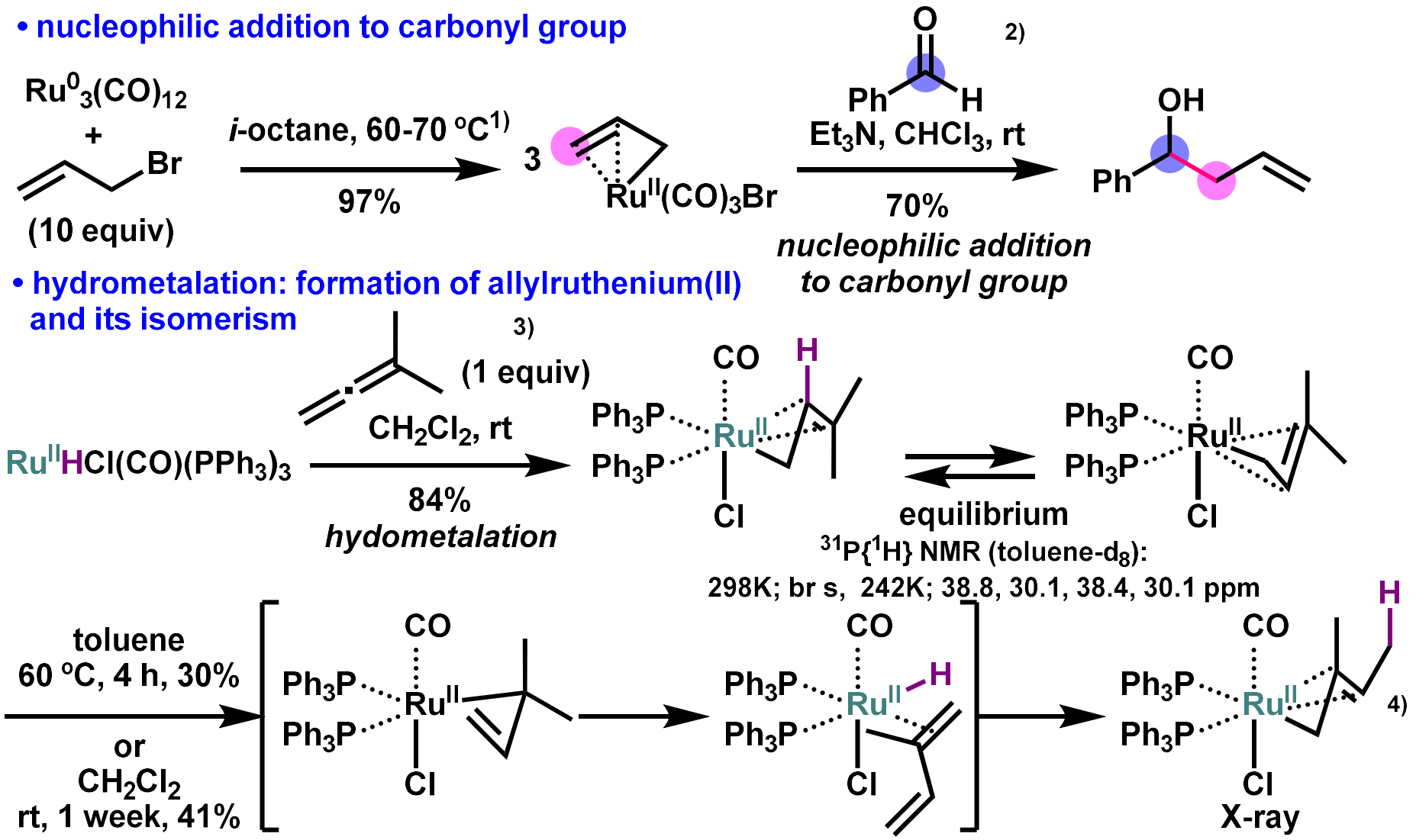
conditions B (no hydrogen acceptor):



generation of active Ru^0 species via dissociation of H_2

1) Blum, Y.; Reshef, D.; Shvo,Y. *Tetrahedron Lett*. **1981**, *22*, 1541.
2) Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319.
3) Al-Ibadi, M. A. M.; Duckett, S. B.; McGrady, J. E. *Dalton Trans.* **2012**, *41*, 4618.

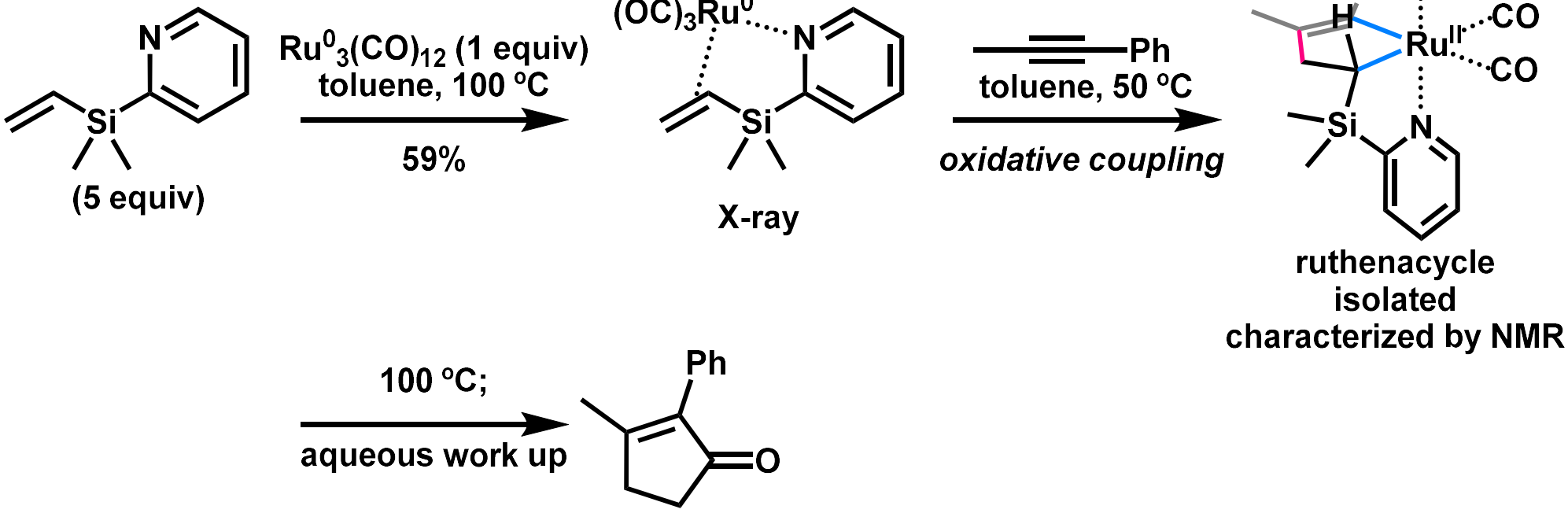
Nucleophilic Addition to Carbonyl Group and Hydrometalation



1) Sbrana, G.; Braca, G.; Piacenti, F.; Pino, P. *J. Organomet. Chem.* **1968**, *13*, 240.
2) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T. A.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945.
3) Xue, P.; Bi, S.; Sung, H. H. Y.; Williams, I. D.; Lin, Z.; Jia, G. *Organometallics* **2004**, *23*, 4735.
4) This complex can also be synthesized from $Ru^{II}HCl(CO)(PPh_3)_3$ and isoprene. see Hiraki, K.; Ochi, N.; Sasada, Y.; Hayashida, H.; Fuchita, Y.; Yamanaka, S. *J. Chem. Soc., Dalton Trans.* **1985**, *873*.

Ru-Catalyzed C–C Bond Formation (2): Oxidative Coupling

• oxidative coupling



Itami, K.; Mitsudo, K.; Fujita, K.; Ohashi, Y.; Yoshida, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 11058.

Contents

Prof. Michael J. Krische

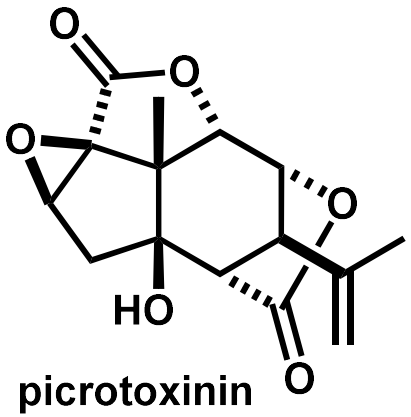
Career:

1986-1989 : B.S. @ Univ. of California at Berkely (Prof. Henry Rapoport)
1989-1990 : Fulbright Fellow @ Helsinki University (Prof. Ari M. P. Koskinen)
1990-1996 : Ph.D. @ Stanford University (Prof. Barry M. Trost)
1997-1999 : National Institutes of Health Postdoctoral Fellow @Université Louis Pasteur (Prof. Jean-Marie Lehn)
1999-2003 : Assistant Professor @ University of Texas at Austin
2004-Present : Professor @ University of Texas at Austin

Reasearch interests:

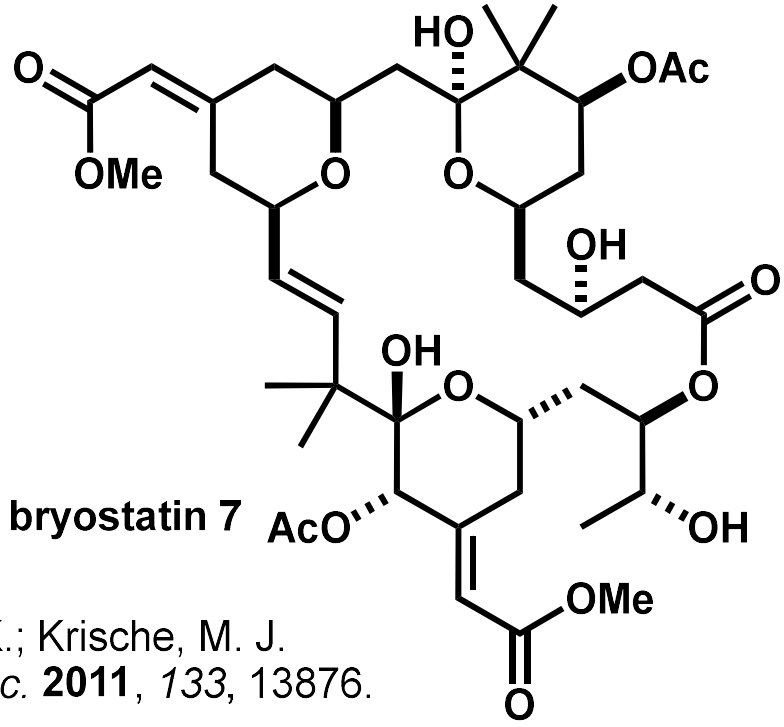
Development of new synthetic methods with attendant applications in natural product synthesis

- **identification of new reactivity patterns**
- **evolution of related catalytic processes**
- **development of new synthetic strategies**



picrotoxinin

Trost, B. M.; Krische, M. J.
J. Am. Chem. Soc. **1996**, *118*, 233.



bryostatin 7

Lu, Y.; Woo, S. K.; Krische, M. J.
J. Am. Chem. Soc. **2011**, *133*, 13876.

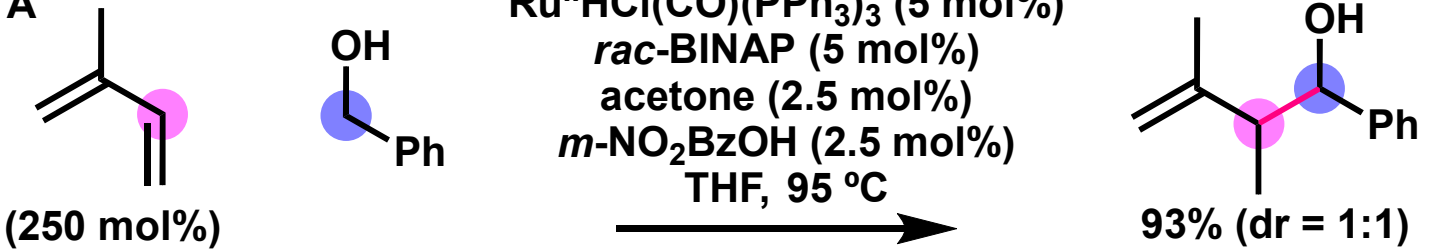
https://sites.google.com/a/utexas.edu/the-krische-research-group/michael-j-krische?authuser=1

Ru-Catalyzed Allylation

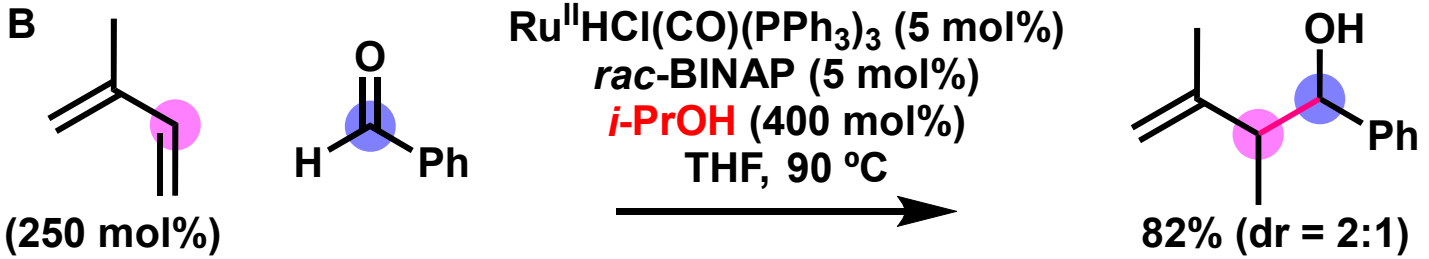
Concept: merging hydrometalation, nucleophilic addition and transfer hydrogenation

- **General reactions**

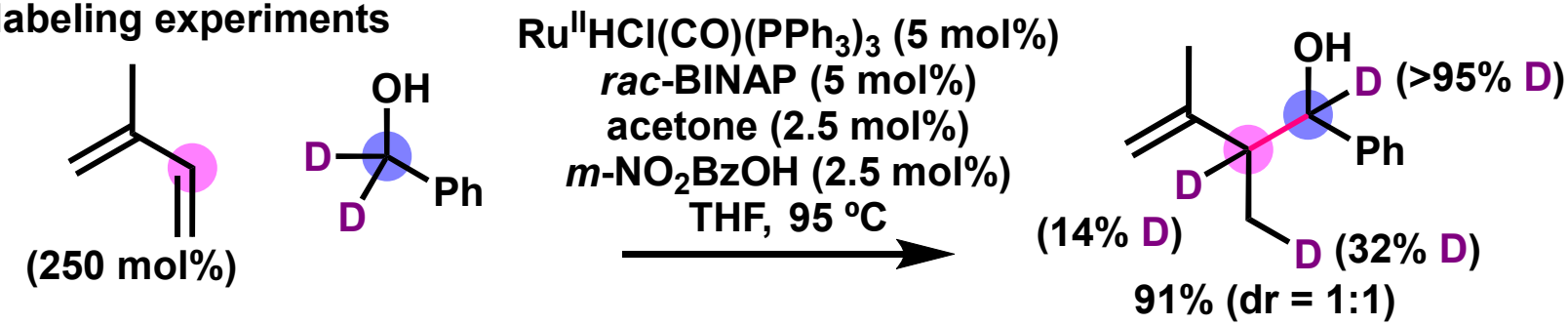
***conditions* A**

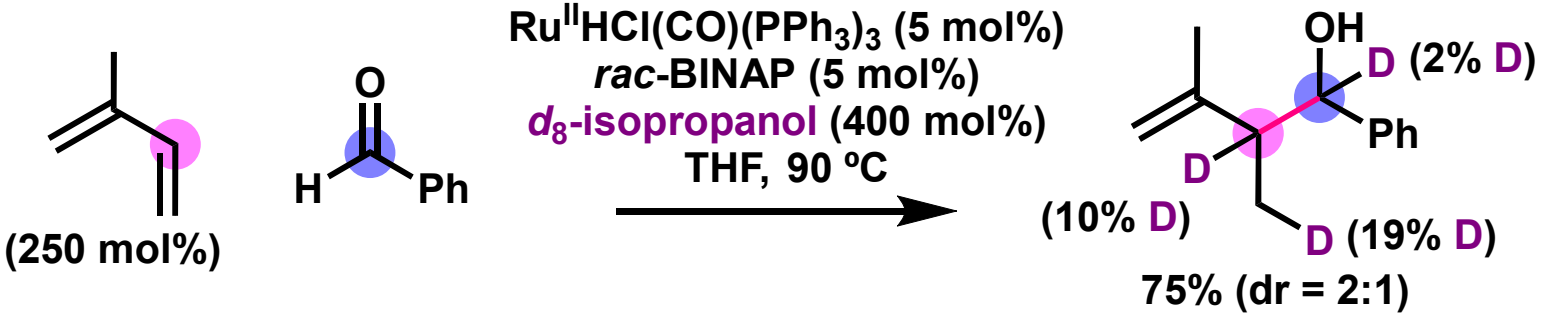


***conditions* B**



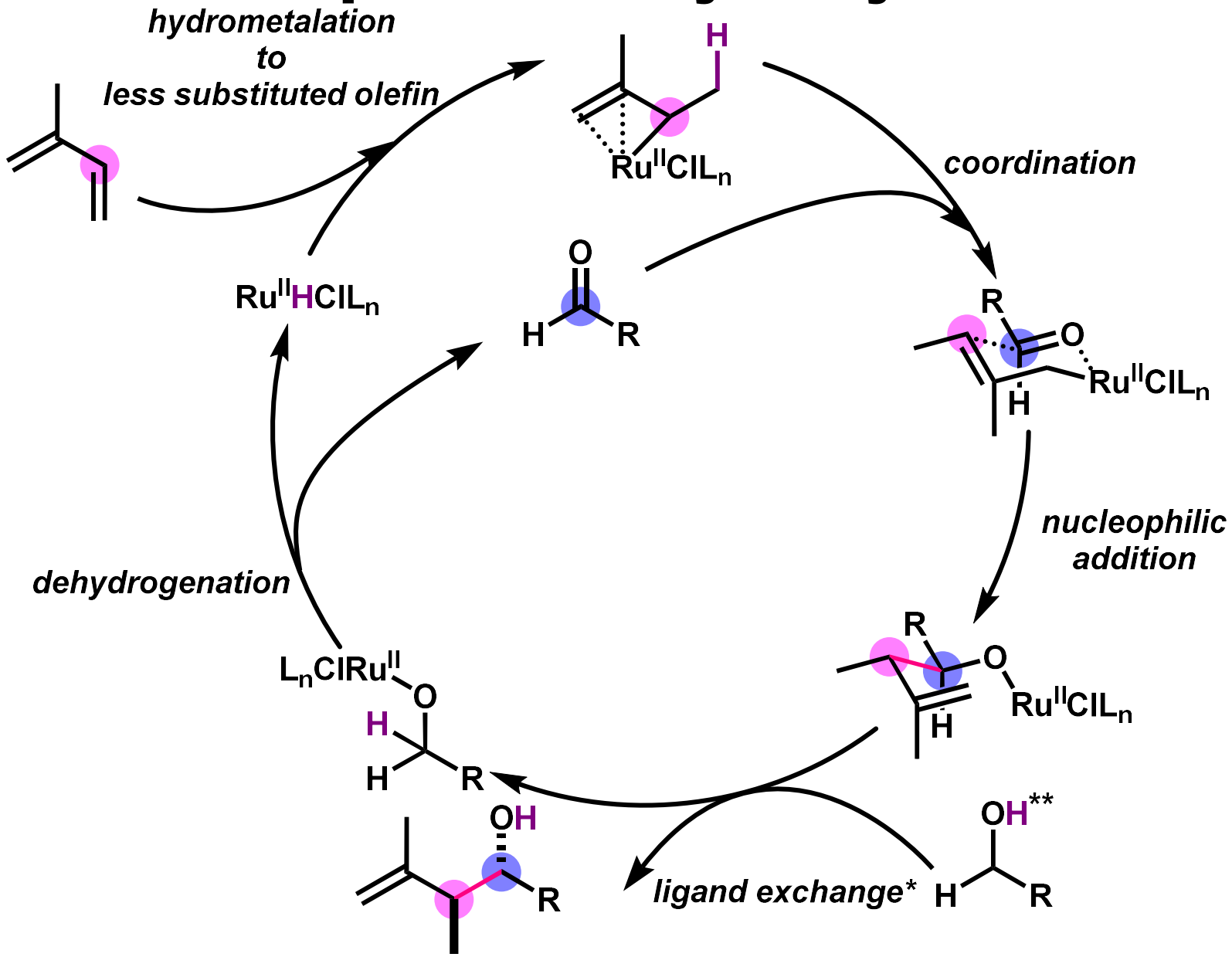
- **Deuterium labeling experiments**





Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338.

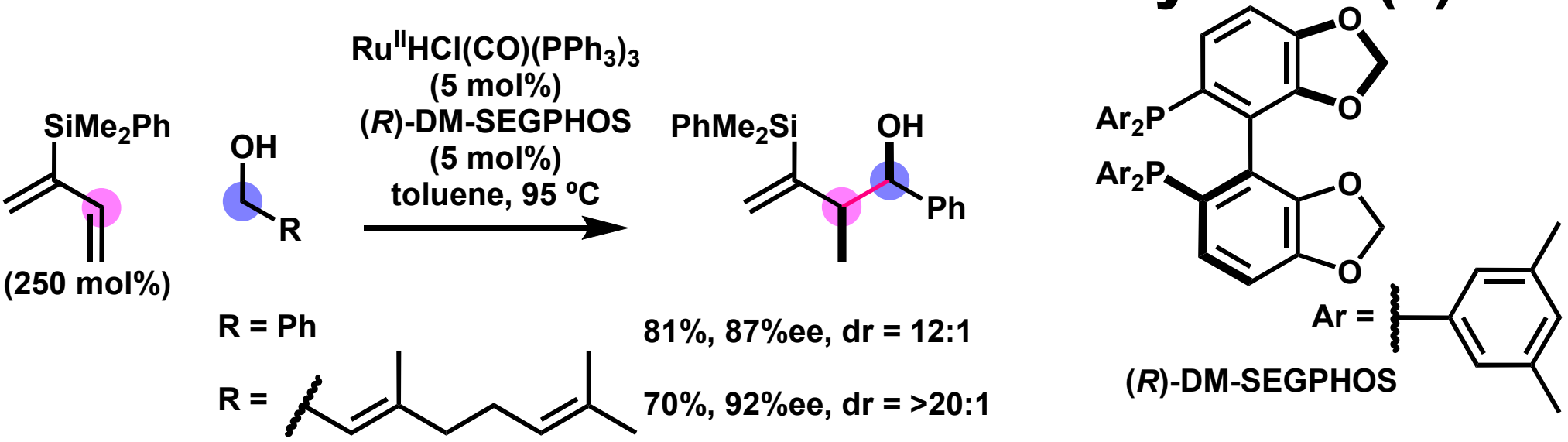
Proposed Catalytic Cycle



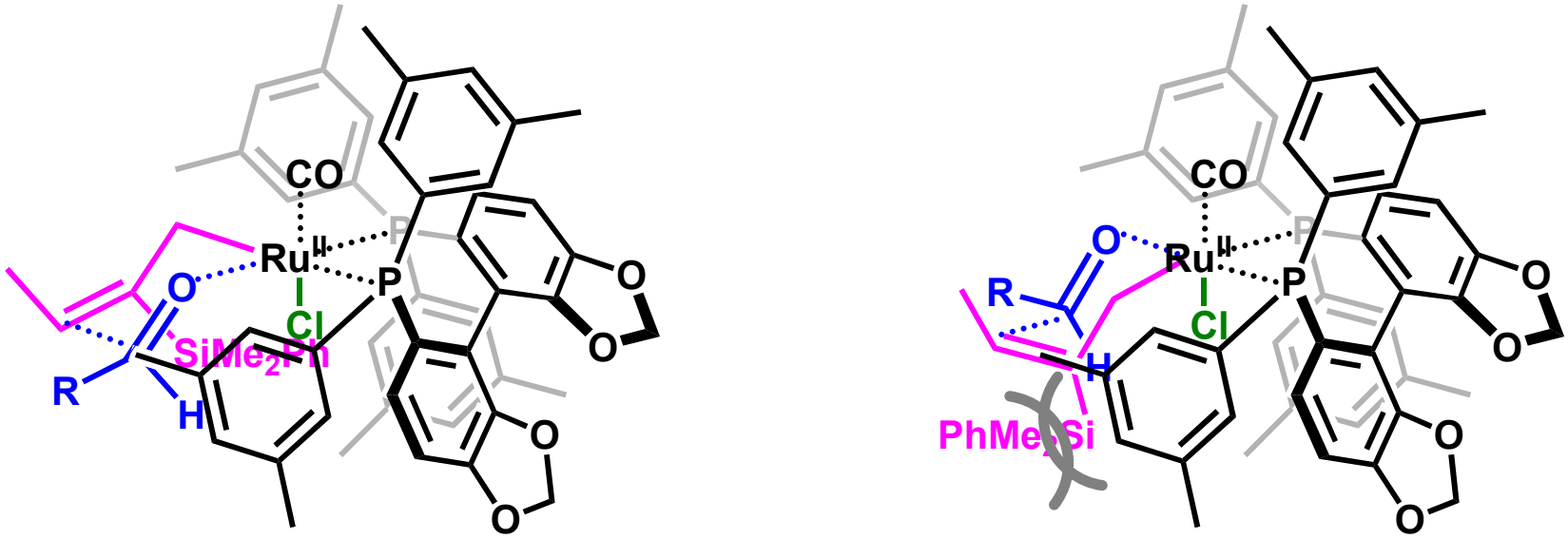
* *m*-NO_2BzOH facilitates this steps in conditions A.
** Isopropanol participates in conditions B.

Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338.

Enantio- and Diastereoselective Allylation (1)

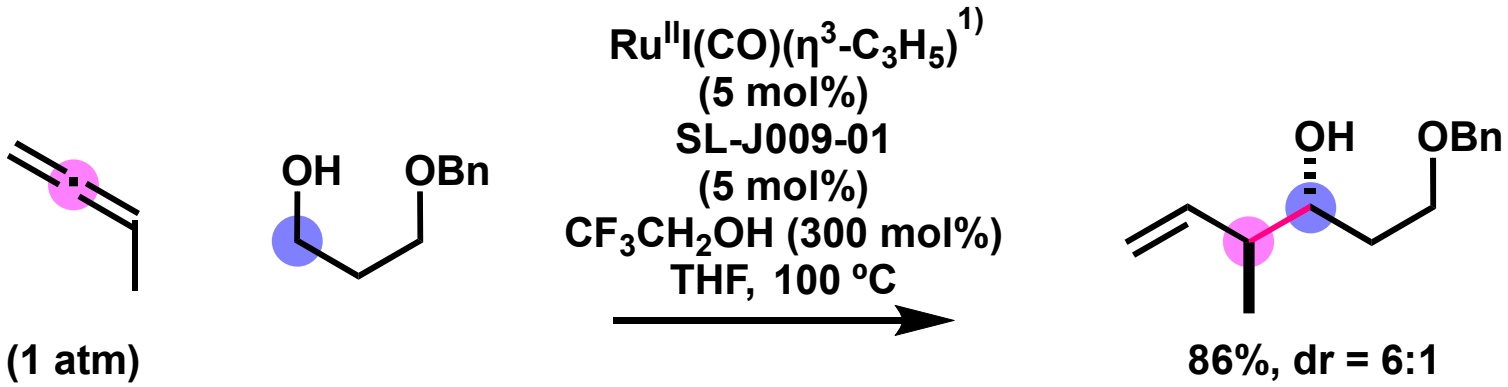


- Rational for enantio/diastereoselectivity



Zbieg, J. R.; Moran, J.; Krische M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582.

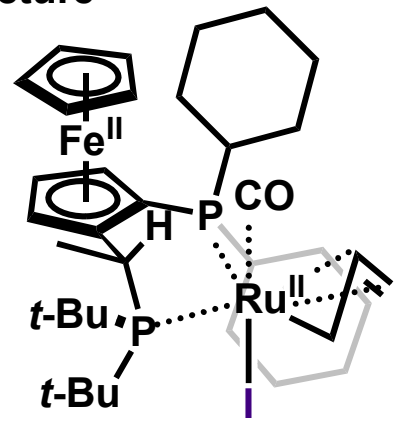
Enantio- and Diastereoselective Allylation (2)



(1 atm)

86%, dr = 6:1

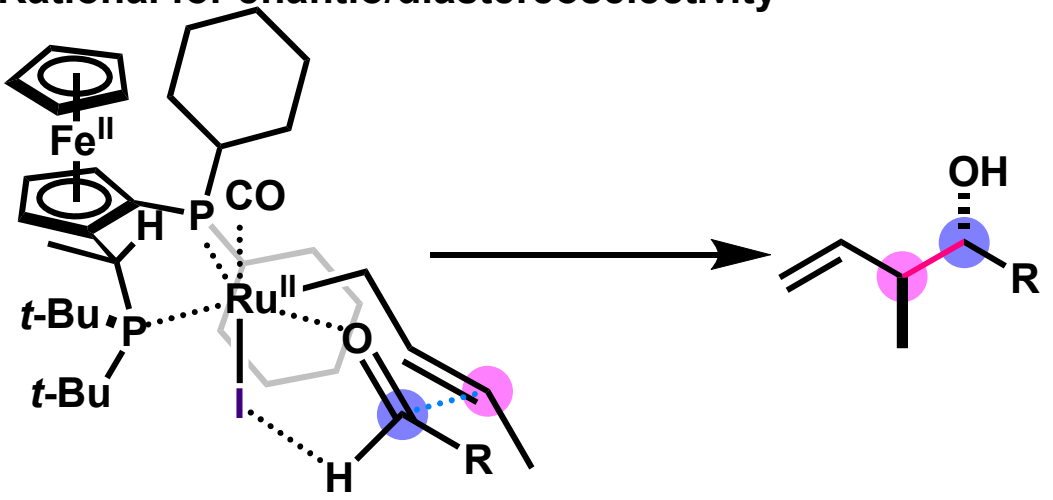
- X-ray structure 2)



$Ru^{II}I(CO)(SL\text{-}J009\text{-}01)(\eta^3\text{-}C_3H_5)$

Axial site occupancy	π-allyl
Cl: Cl vs CO = 3:1	highly disordered
Br: B vs CO = 1:1	moderately disordeed
I : I vs CO = 1:0	not disordered

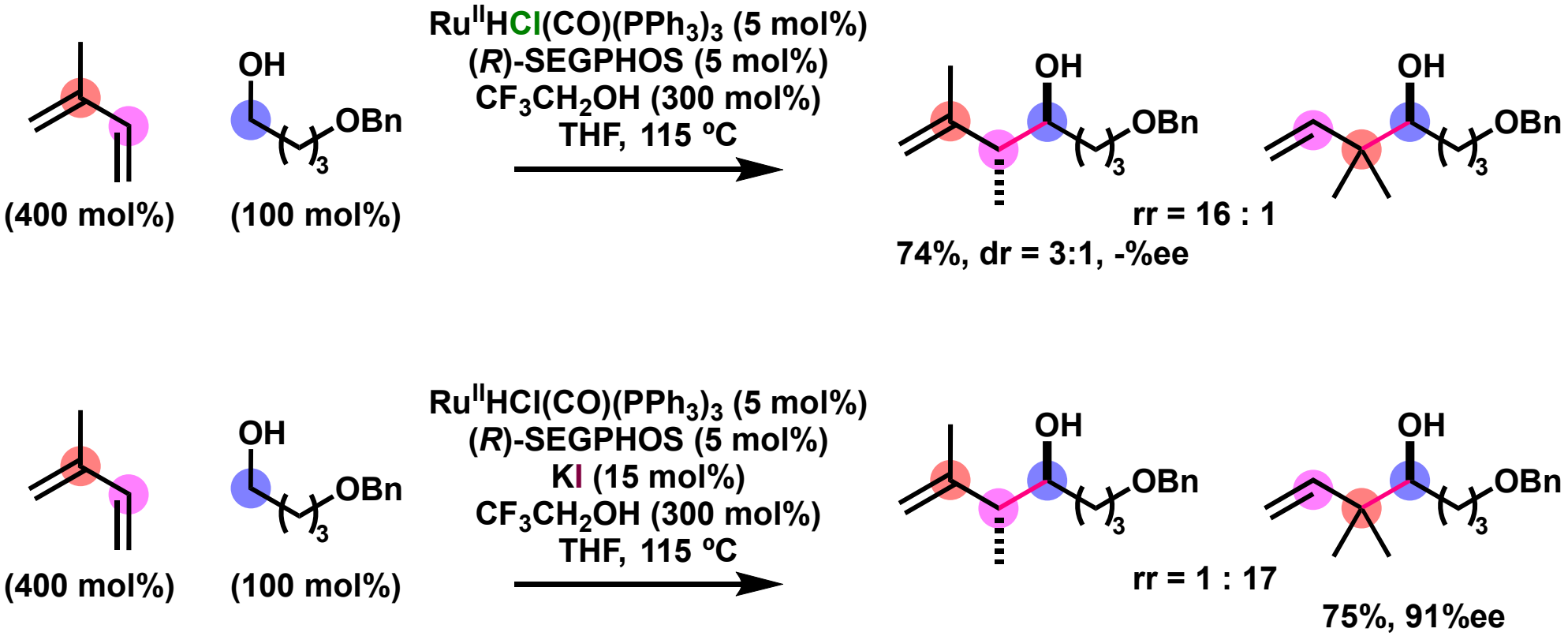
- Rational for enantio/diastereoselectivity



I-bounded π-allylRu-SL-J009-01 catalyst unambiguously defines Ru-centered stereogenicity, which leads to high enantio- and diastereoselectivities.

1) Ortiz, E.; Spinello, B. J.; Cho, Y.; Wu, J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2022**, *61*, e202212814.
2) Ortiz, E.; Shezaf, J. Z.; Chang, Y.-H.; Gonçalves, T. P.; Huang, K.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2021**, *143*, 16709.

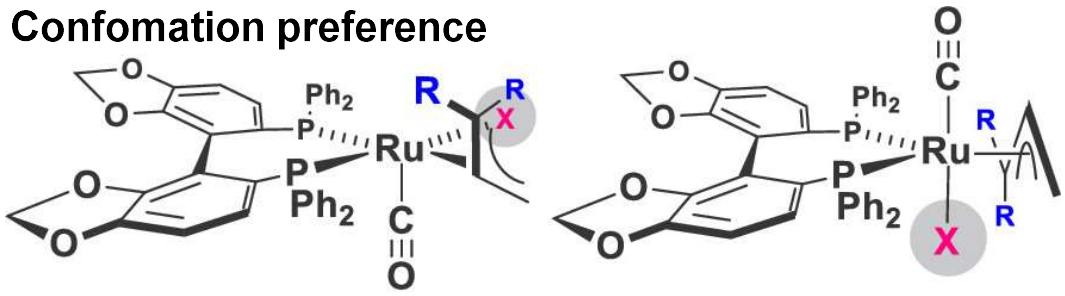
Enantio- and Diastereoselective Allylation (3)



Shezaf, J. Z.; Santana, C. G.; Saludares, C.; Briceno, E. S.; Sakata, K.; Krische, M. J.
J. Am. Chem. Soc. **2023**, *145*, 18676.

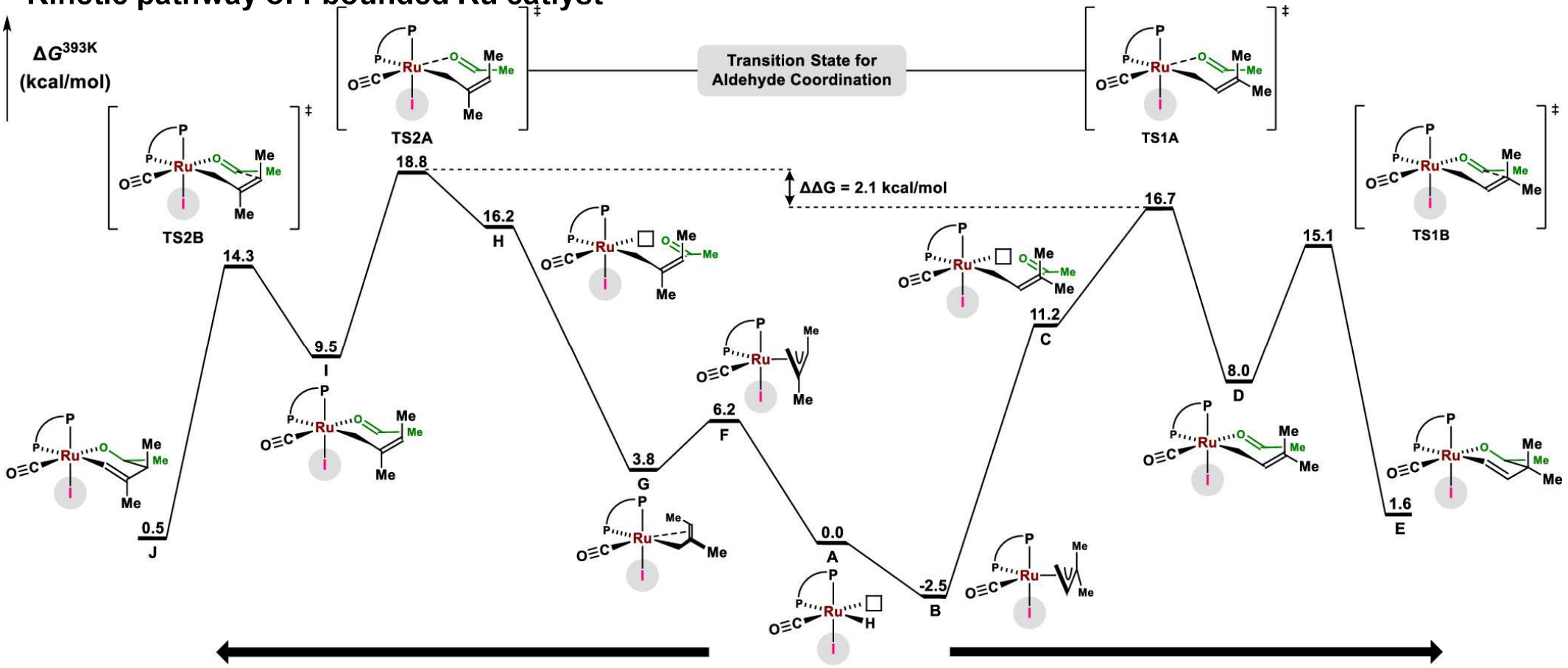
Enantio- and Diastereoselective Allylation (4)

Confomation preference



Halide & CO = *cis*			Halide & CO = *trans*
$\Delta\Delta G^{393K}$	R	X	$\Delta\Delta G^{393K}$
0.3 Kcal/mol	H	Cl	0.0 Kcal/mol (X-ray)
0.8 Kcal/mol	Me	Cl	0.0 Kcal/mol
(X-ray) 0.0 Kcal/mol	H	I	4.3 Kcal/mol
0.0 Kcal/mol	Me	I	1.4 Kcal/mol

Kinetic pathway of I-bounded Ru catlyst



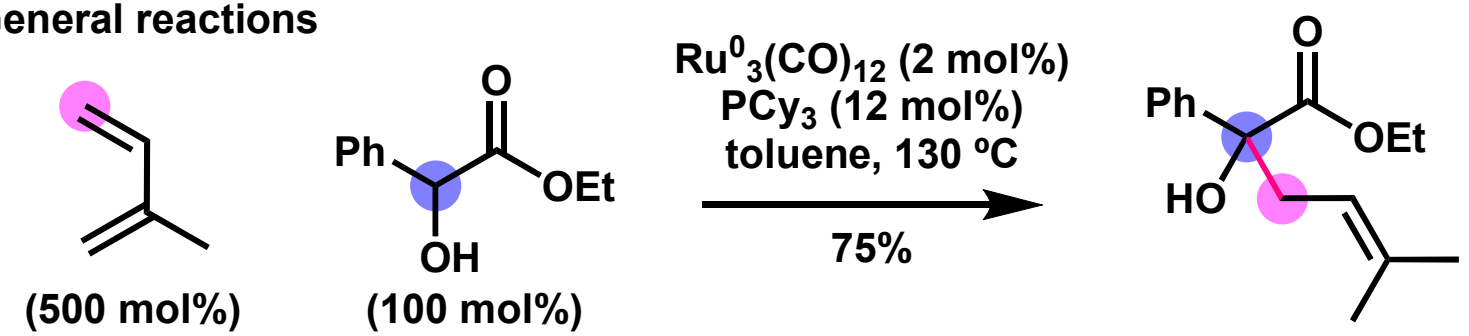
ωB97X-D(IEF-PCM)/Def2-TZVPP//ωB97X-D/[SDD, 6-311G(d, p)] level of theory.

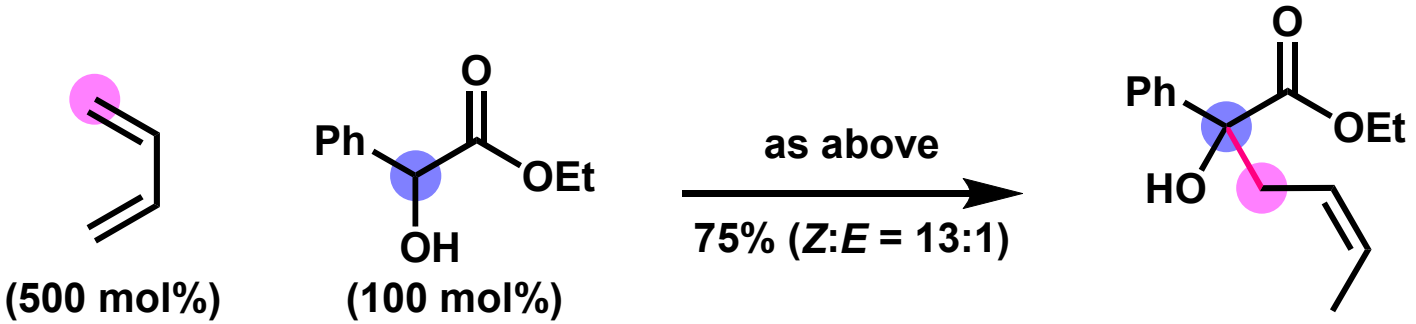
Shezaf, J. Z.; Santana, C. G.; Saludares, C.; Briceno, E. S.; Sakata, K.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 18676.

Ru-Catalyzed Diene-Carbonyl Oxidative Coupling (1)

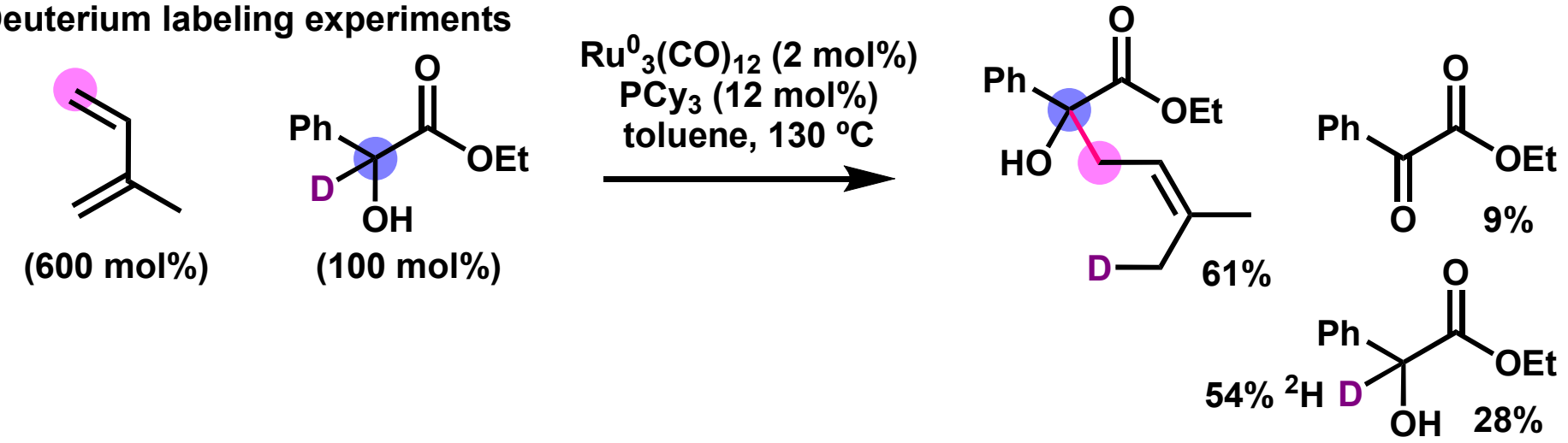
Concept: merging oxidative coupling and transfer hydrogenation

- General reactions



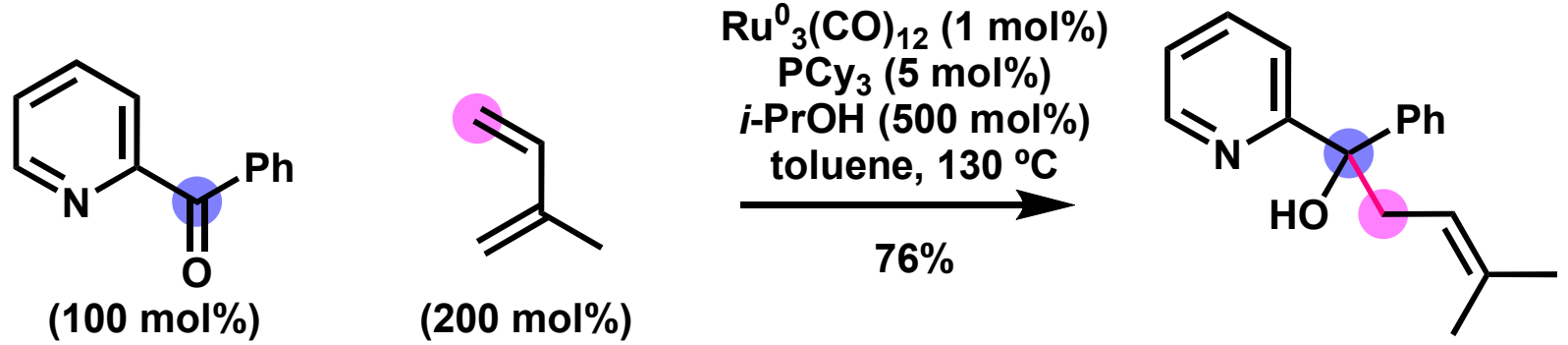


- Deuterium labeling experiments

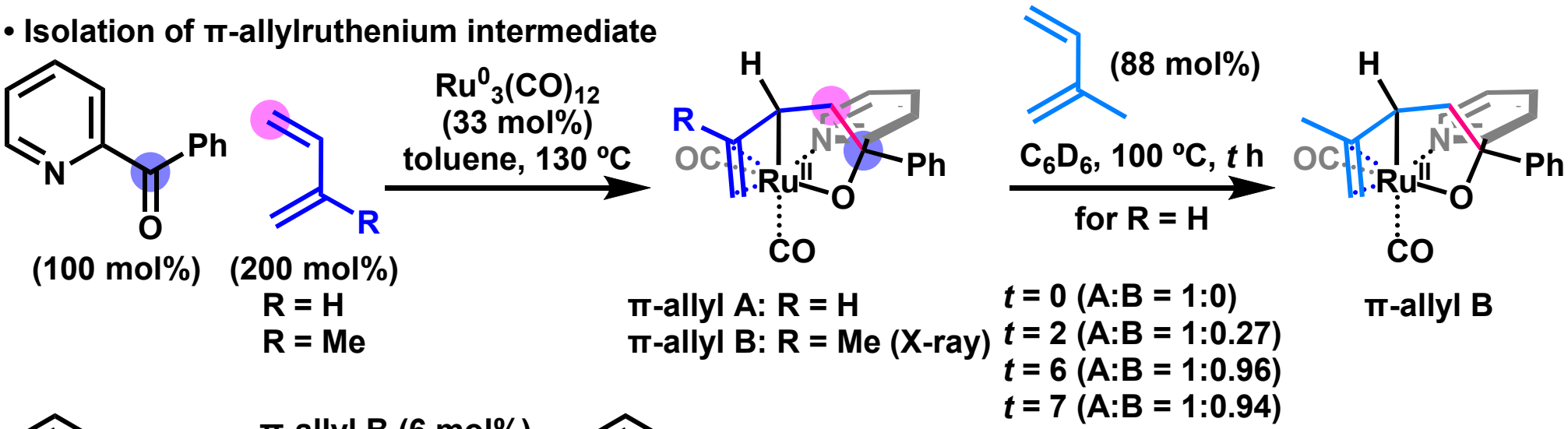


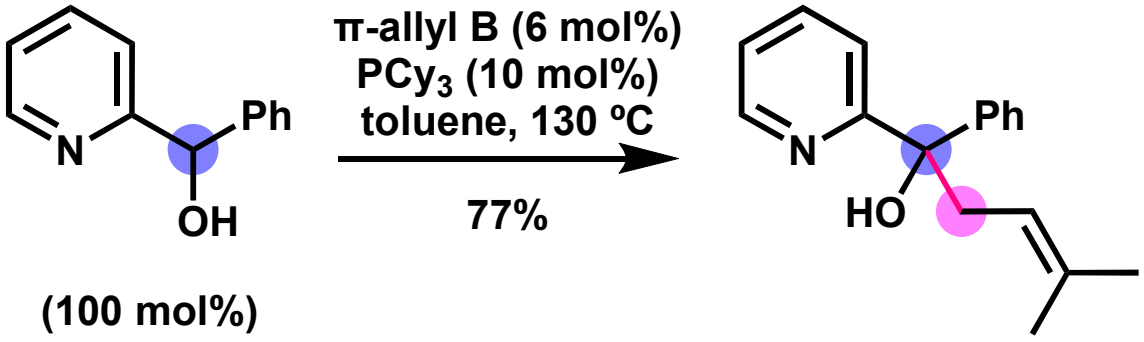
Leung, J. C.; Geary, L. M.; Chen, T.-Y.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 15700.

Ru-Catalyzed Diene-Carbonyl Oxidative Coupling (2)



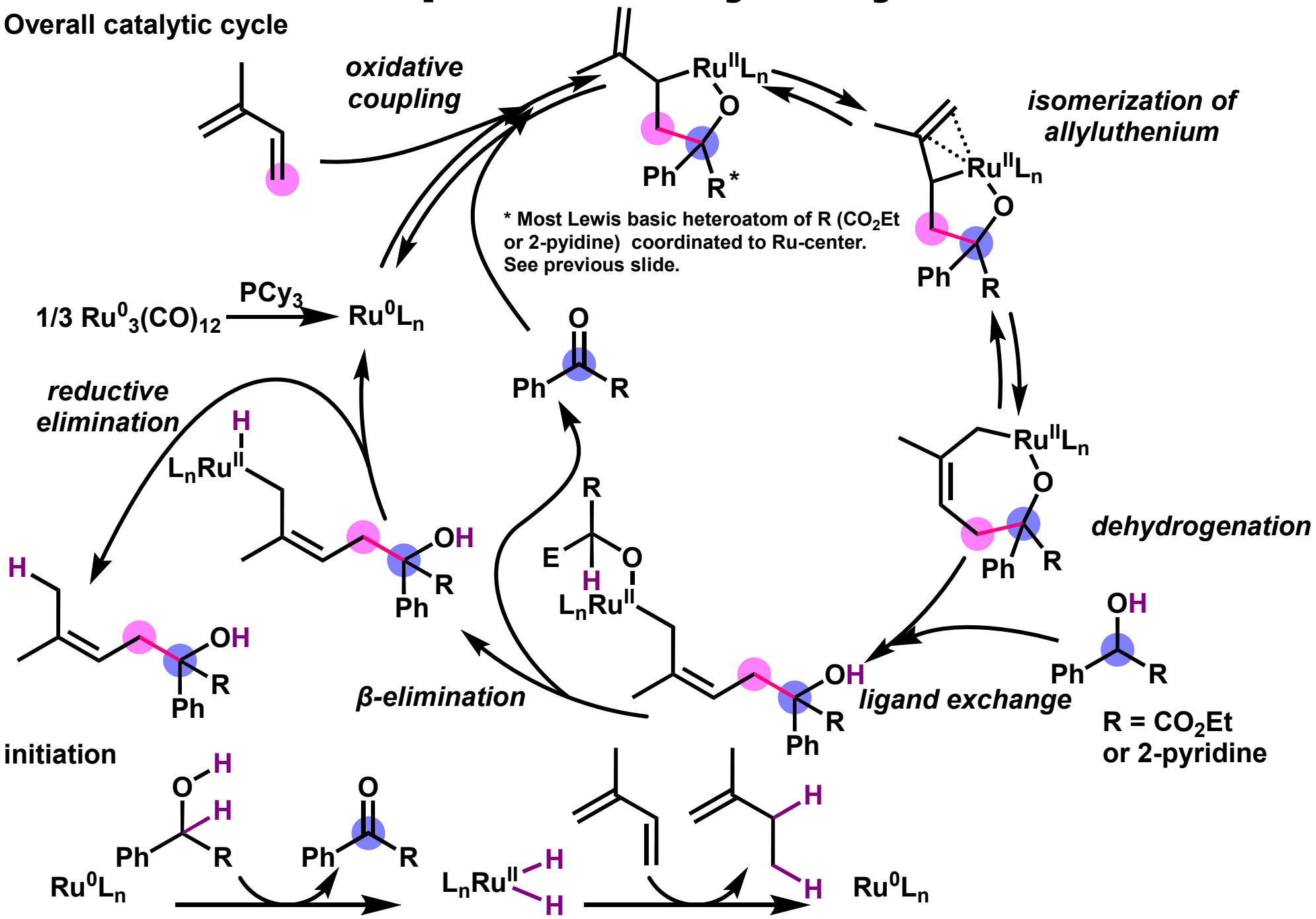
• Isolation of π-allylruthenium intermediate





Park, B. Y.; Montgomery, T. P.; Garza, V.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 16320.

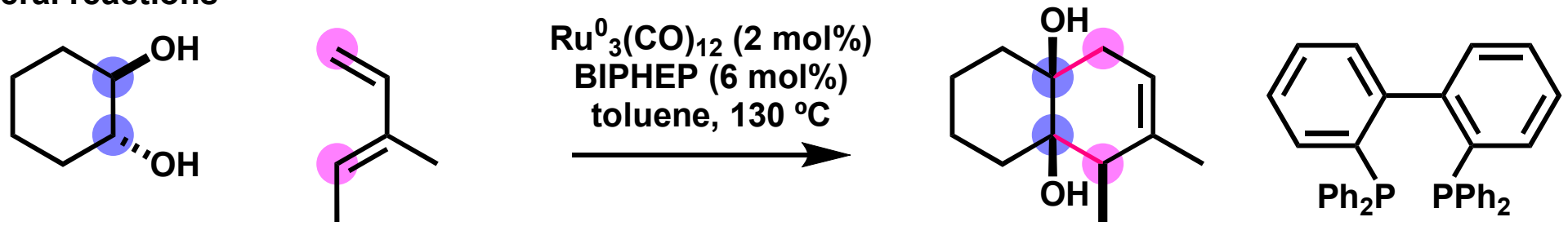
Proposed Catalytic Cycle



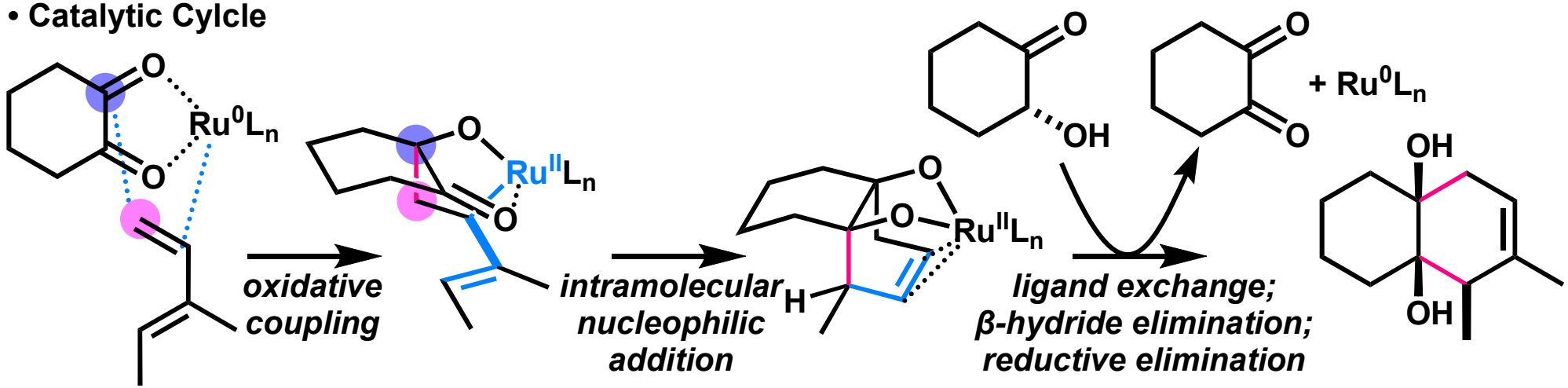
Ru-Catalyzed Diene-Diol Cycloaddition

Concept: merging oxidative coupling, intramolecular nucleophilic addition and transfer hydrogenation

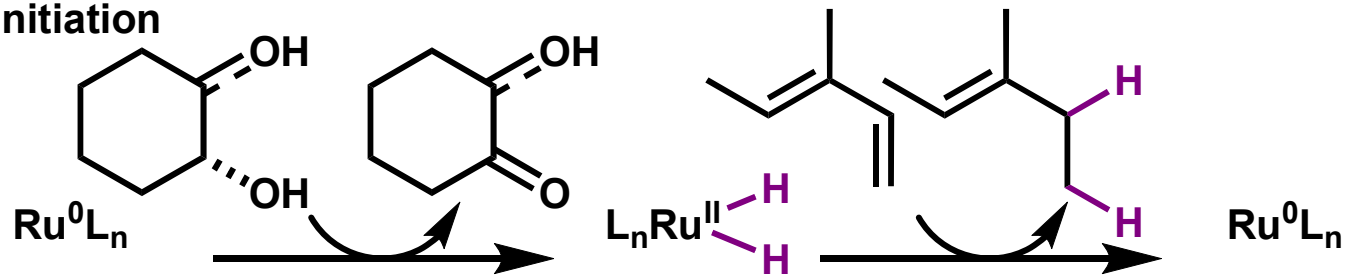
- **General reactions**



- **Catalytic Cylcle**



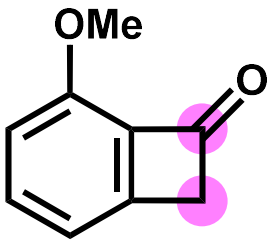
- **Initiation**



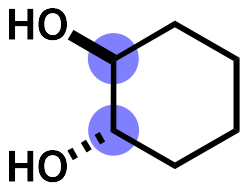
1) Glasspoole, B. W.; Kim, M. M. Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 3796.

Ru-Catalyzed Benzocyclobutenone-Diol/Ketol/Diketone Cycloaddition

Concept: merging oxidative coupling, double nucleophilic addition and transfer hydrogenation



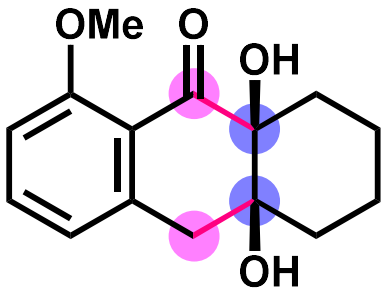
(200 mol%)



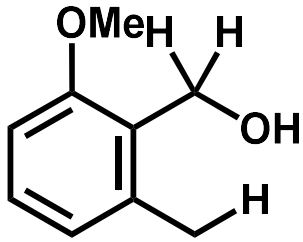
(100 mol%)

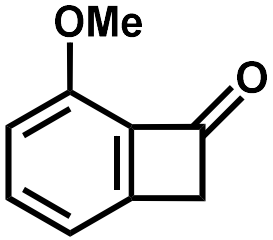
$Ru^0_3(CO)_{12}$ (2 mol%)
dppp (6 mol%)
m-xylene, 150 °C

dppp

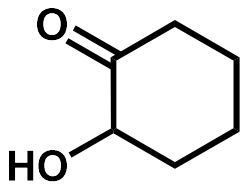


88%, dr >20:1





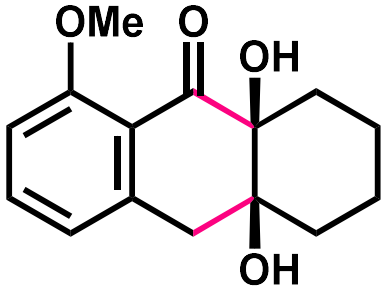
(100 mol%)



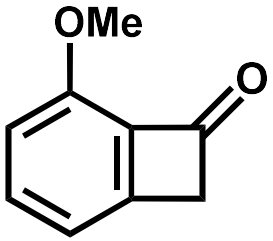
(100 mol%)

$Ru^0_3(CO)_{12}$ (2 mol%)
dppp (6 mol%)
m-xylene, 150 °C

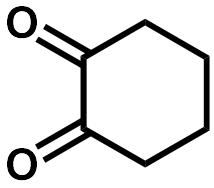
87%



no stoichiometric byproducts



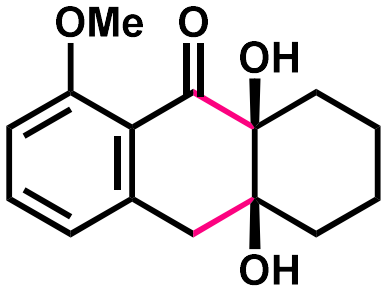
(200 mol%)

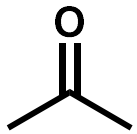


(100 mol%)

$Ru^0_3(CO)_{12}$ (2 mol%)
dppp (6 mol%)
i-PrOH (300 mol%)
m-xylene, 150 °C

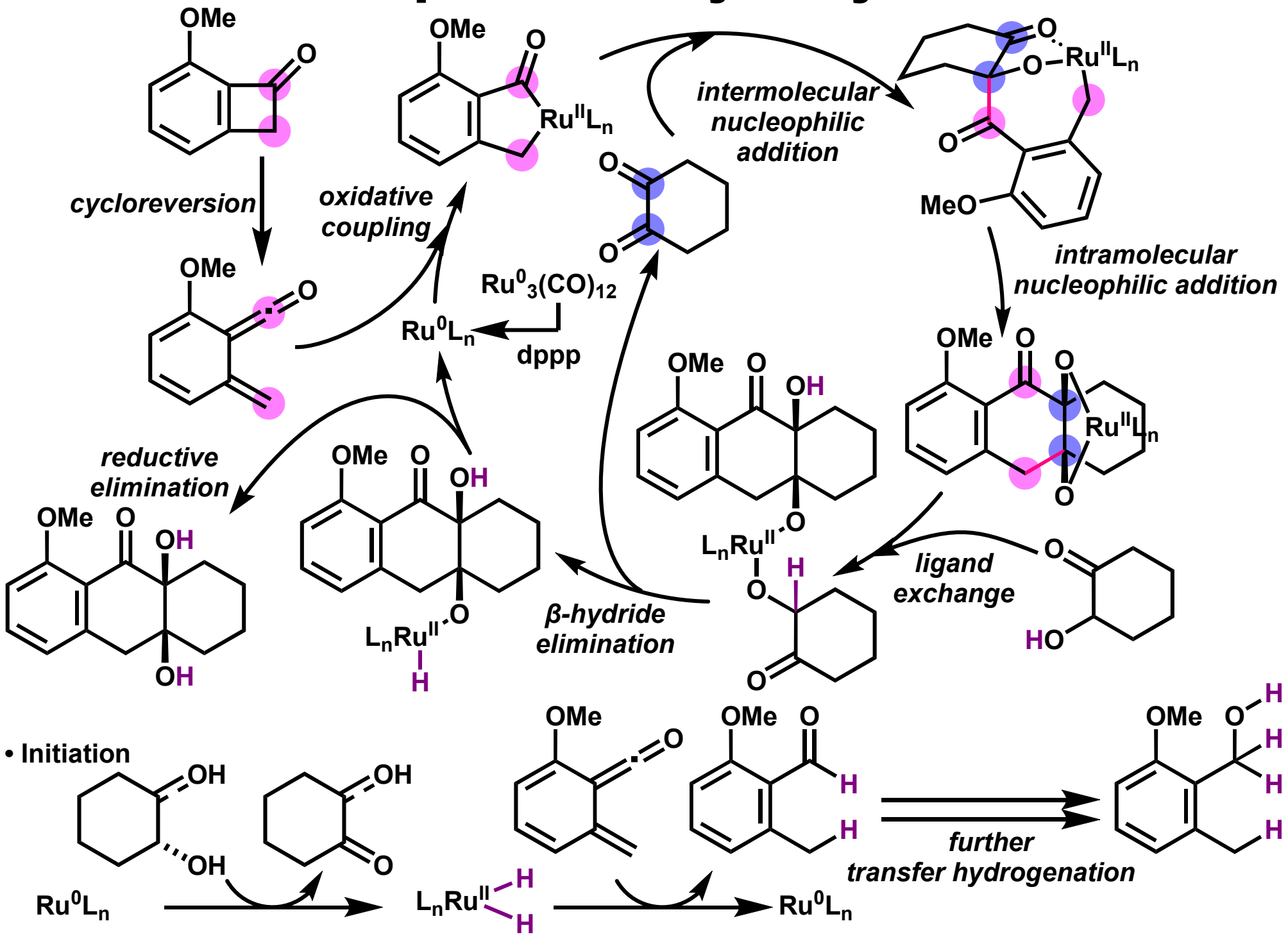
56%



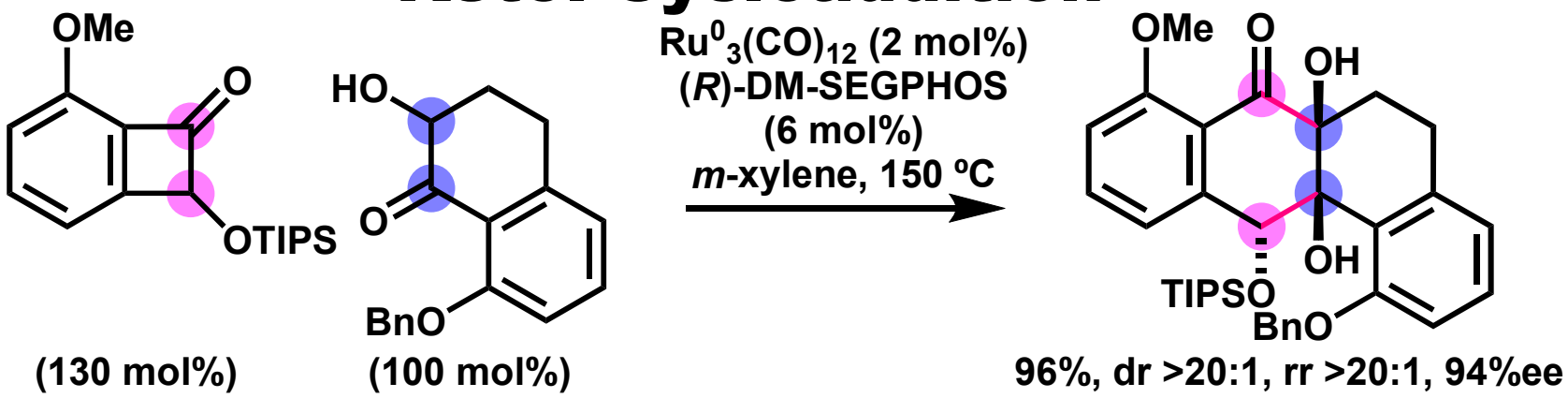


Bender, M.; Turnbull, B. W. H.; Ambler, B. R.; Krische, M. J. *Science*, **2017**, *357*, 779.

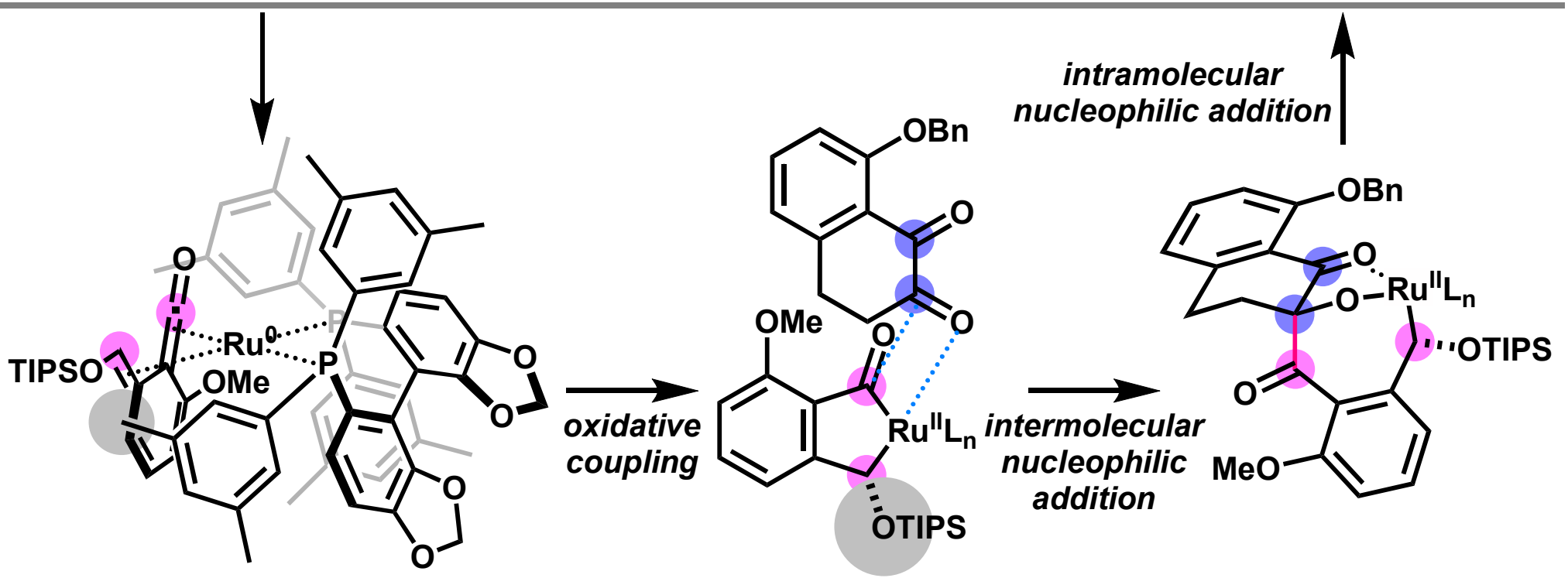
Proposed Catalytic Cycle



Enantioselective Benzocyclobutenone-Ketol Cycloaddition



(130 mol%) (100 mol%) 96%, dr >20:1, rr >20:1, 94%ee

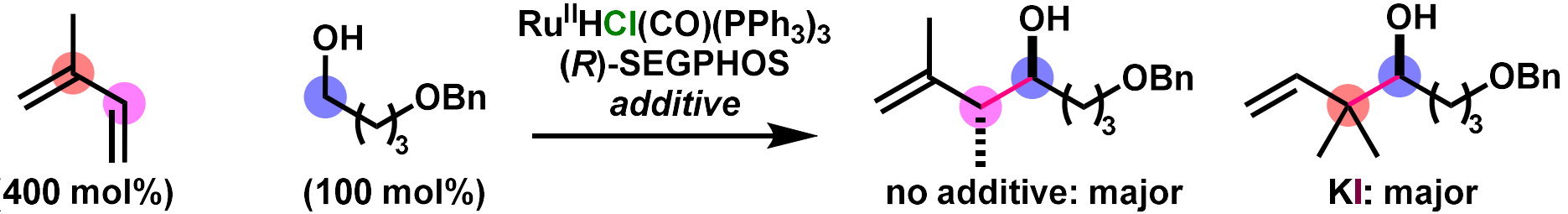


OMe goup avoids steical repulsion from methyl goup highlighted grey.

Ambler, B. R.; Turnbull, B. W. H.; Suravarapu, S. R.; Uteuliyev, M. M.; Huynh, N. O.; Krische, M. J. *J. Am. Chem. Soc.* **2018**, *140*, 9091.

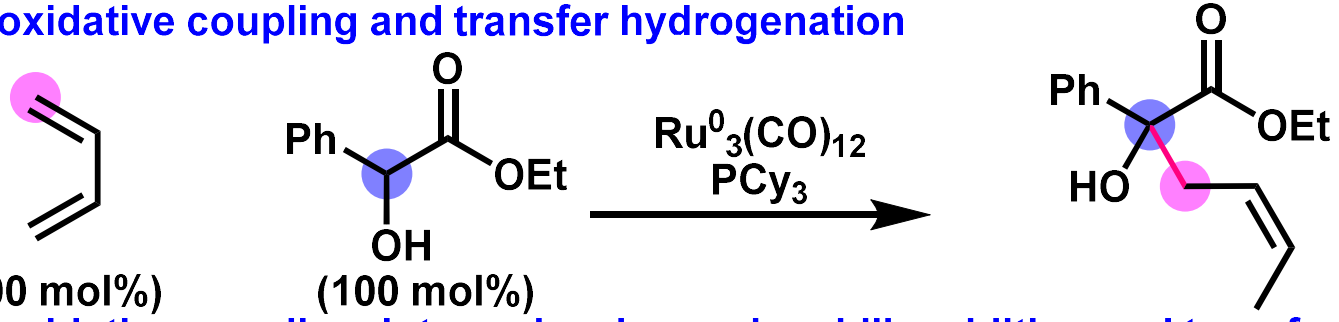
Short Summary

- Merging hydrometalation, nucleophilic addition and transfer hydrogenation



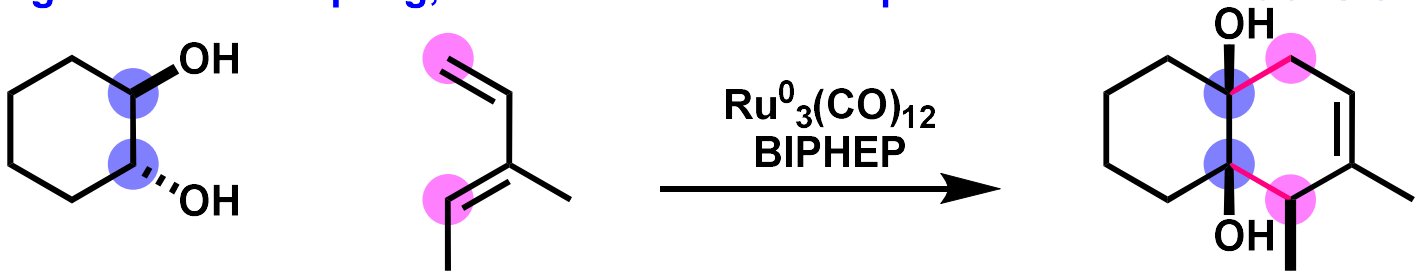
(400 mol%) (100 mol%) no additive: major KI: major

- Merging oxidative coupling and transfer hydrogenation



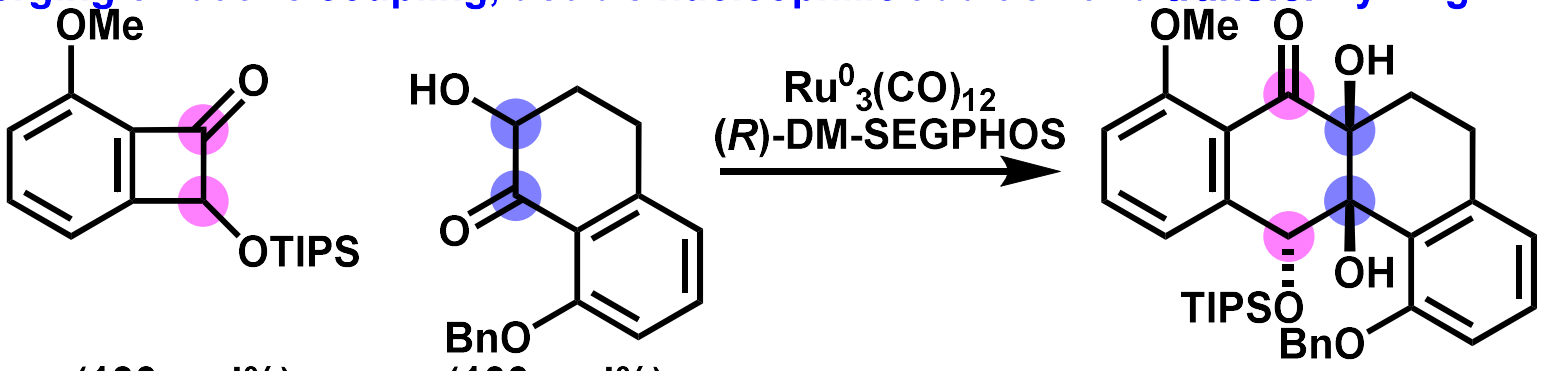
(500 mol%) (100 mol%)

- Merging oxidative coupling, intramolecular nucleophilic addition and transfer hydrogenation



(racemic, 100 mol%) (500 mol%)

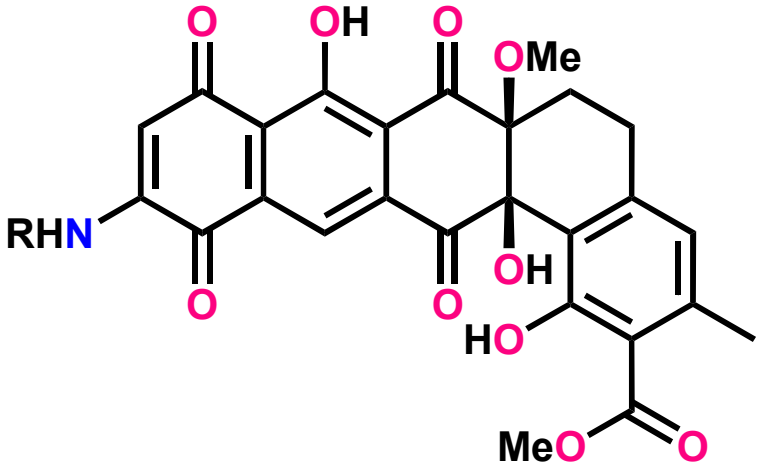
- Merging oxidative coupling, double nucleophilic addition and transfer hydrogenation

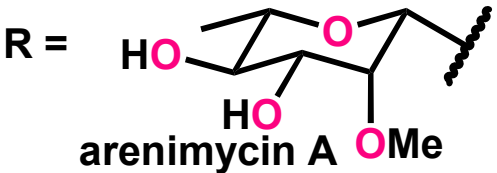


(130 mol%) (100 mol%)

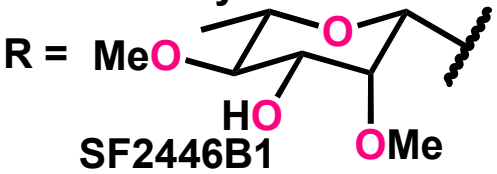
Contents

SF2446 B3: Aglycon of Arenimycins





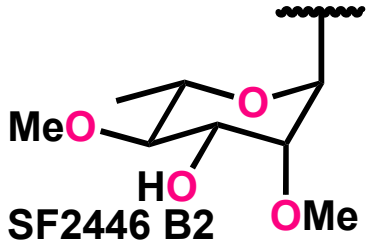
arenimycin A



SF2446B1

R = H

SF2446 B3



SF2446 B2

Isolation

arenimycin A : marine actinomycete *Salinispora arenicola* (strain CNR-647) in 2010

SF2446B1/B2/B3: soil actinomycete *Streptomyces* SF2446 in 1987

Biological activity

arenimycin A: antimicrobial activity against rifampin and methicillin-resistant *Staphylococcus aureus* : MIC (minimal inhibitory concentration) 1.06 μg/mL

Structual features of

benzo[α]naphthacene quinone ring system, bridgehead diol motif

Structure determination

arenimycin A : deduced from ^{13}C NMR of SF2446B1 (Δ≤0.3 ppm)

SF2446B3 (aglycon of SF2446B1/B2): NMR, relative stereochemistry

glycoside of SF2446B1/B2: NMR, absolute stereochemistry compared with optical rotation of synthetic glycoside

SF2446B1 or B2 $\xrightarrow{\text{1 N HCl/MeOH}}$ SF2446B3 + 2,4-di-*O*-methyl-α-rhamnopyranoside

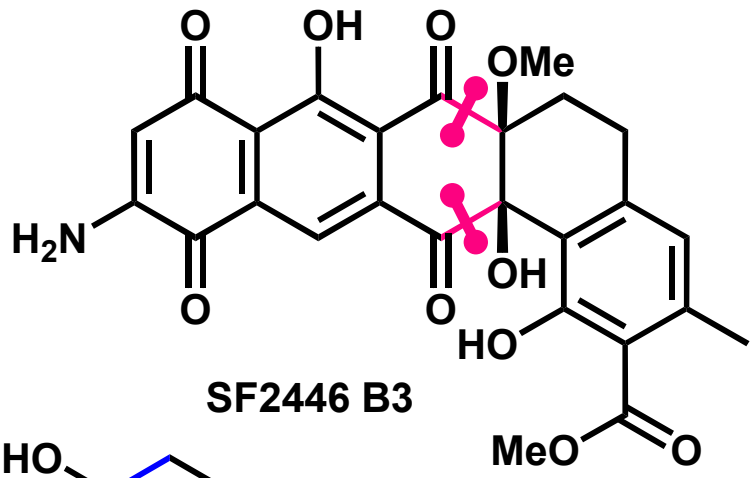
Total synthesis

Krische group (enantioselective synthesis of SF2446B3, 2023)

---

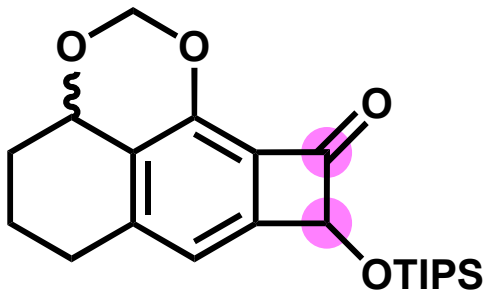
1) Asolkar, R. N.; Kirkland, T. N.; Jensen, P. R.; Fenical, W. *J. Antibiot. (Tokyo)* **2010**, *63*, 37. 2) (a) Takeda, U.; Okada, T.; Takagi, M.; Gomi, S.; Itoh, J.; Sezaki,M.; Ito, M.; Miyahdoh, S.; Shomura, T. *J.Antibiot. (Tokyo)* **1988**, *41*, 417. (b) Gomi, S.; Sasaki, T.; Itoh,J.; Sezaki, M. *J. Antibiot. (Tokyo)* **1988**, *41*,425.

Retrosynthetic Analysis

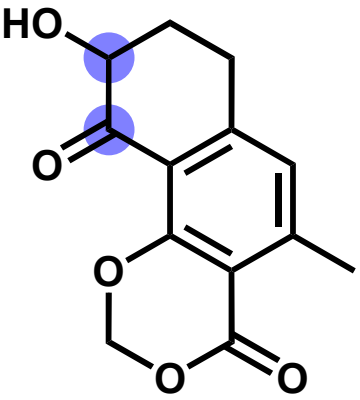


SF2446 B3

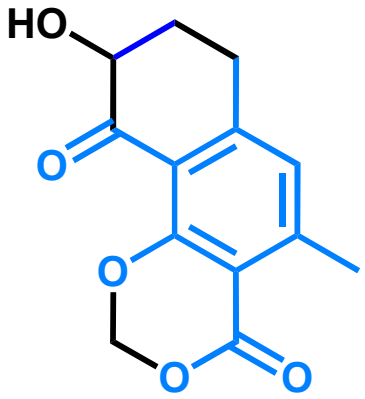
Ru-catalyzed coupling



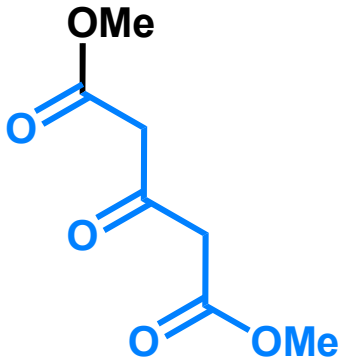
Western fragment (racemic)

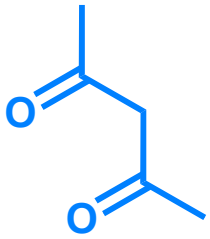


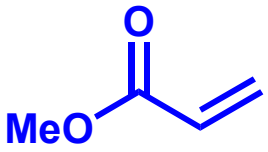
Eastern fragment (racemic)

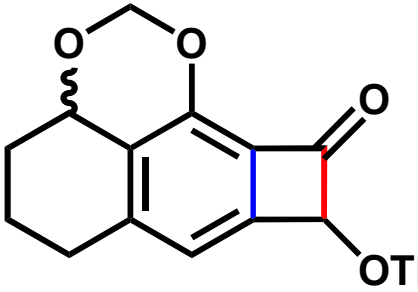


Eastern fragment (racemic)

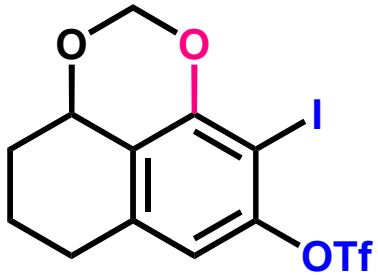




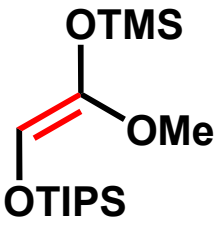


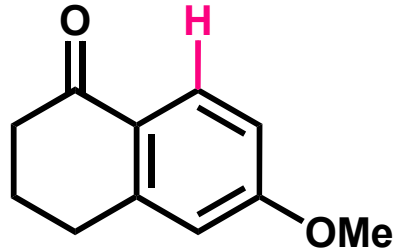


Western fragment (racemic)



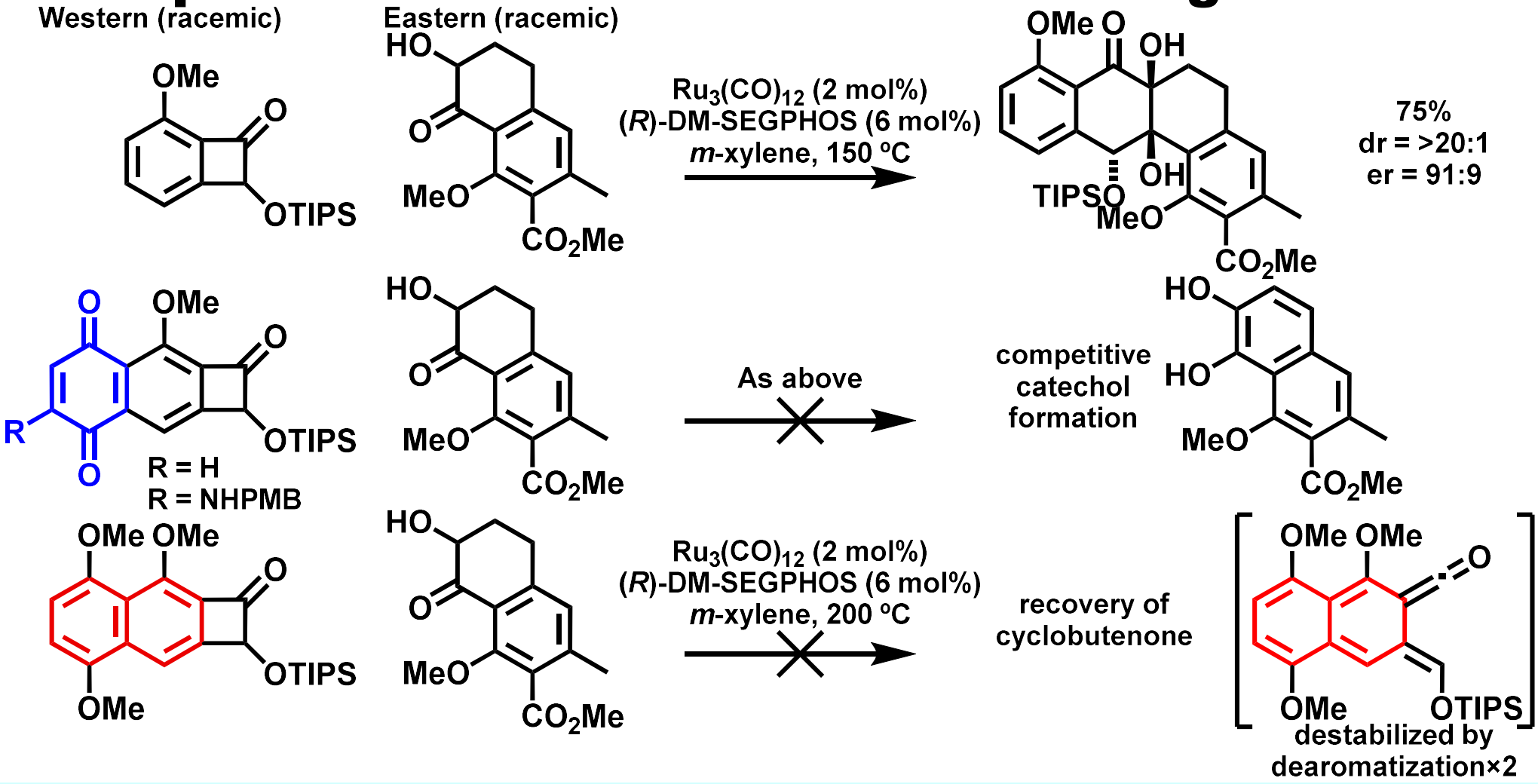
(racemic)



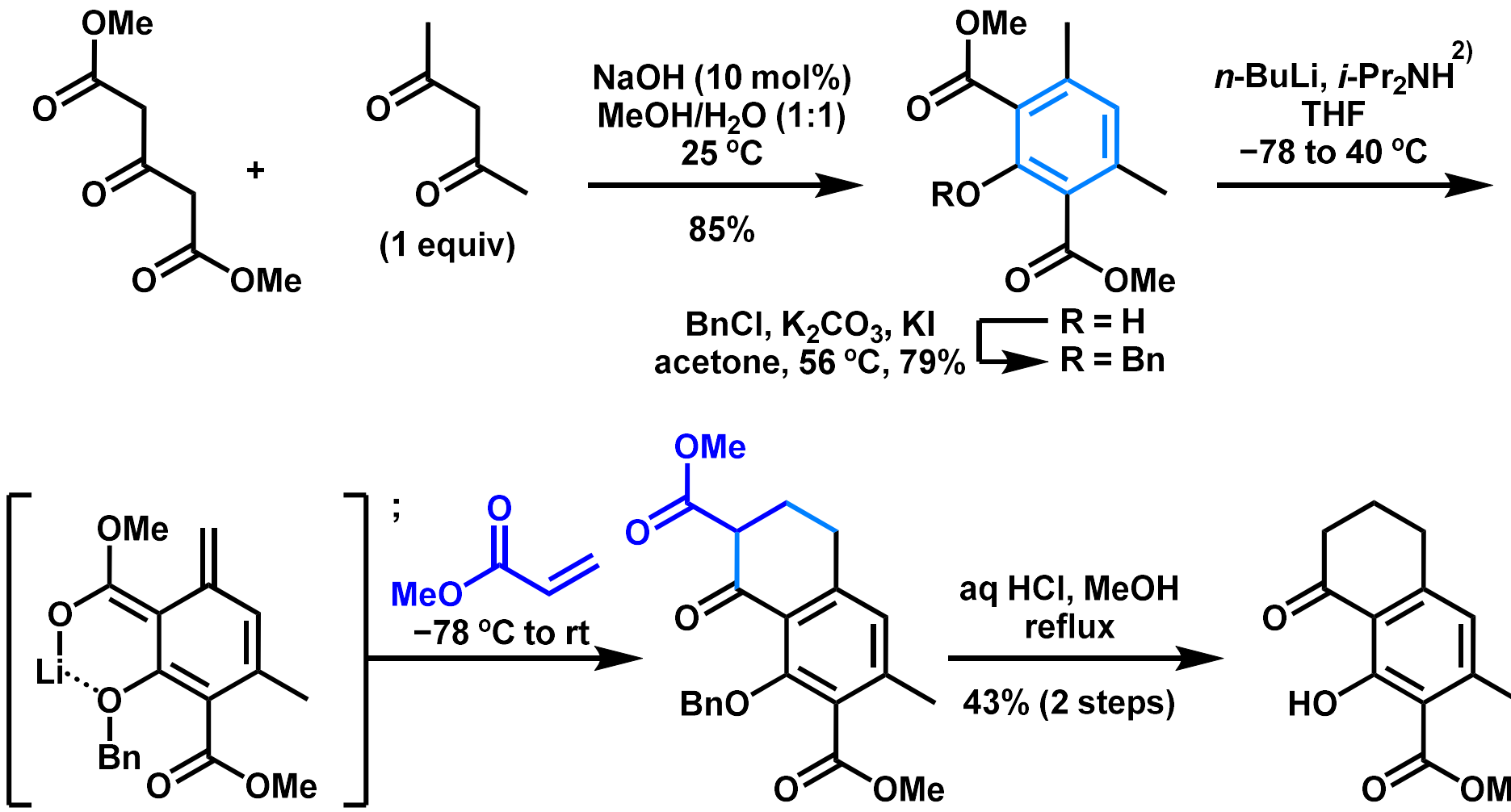


Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.

Optimization of Western/Eastern Fragments

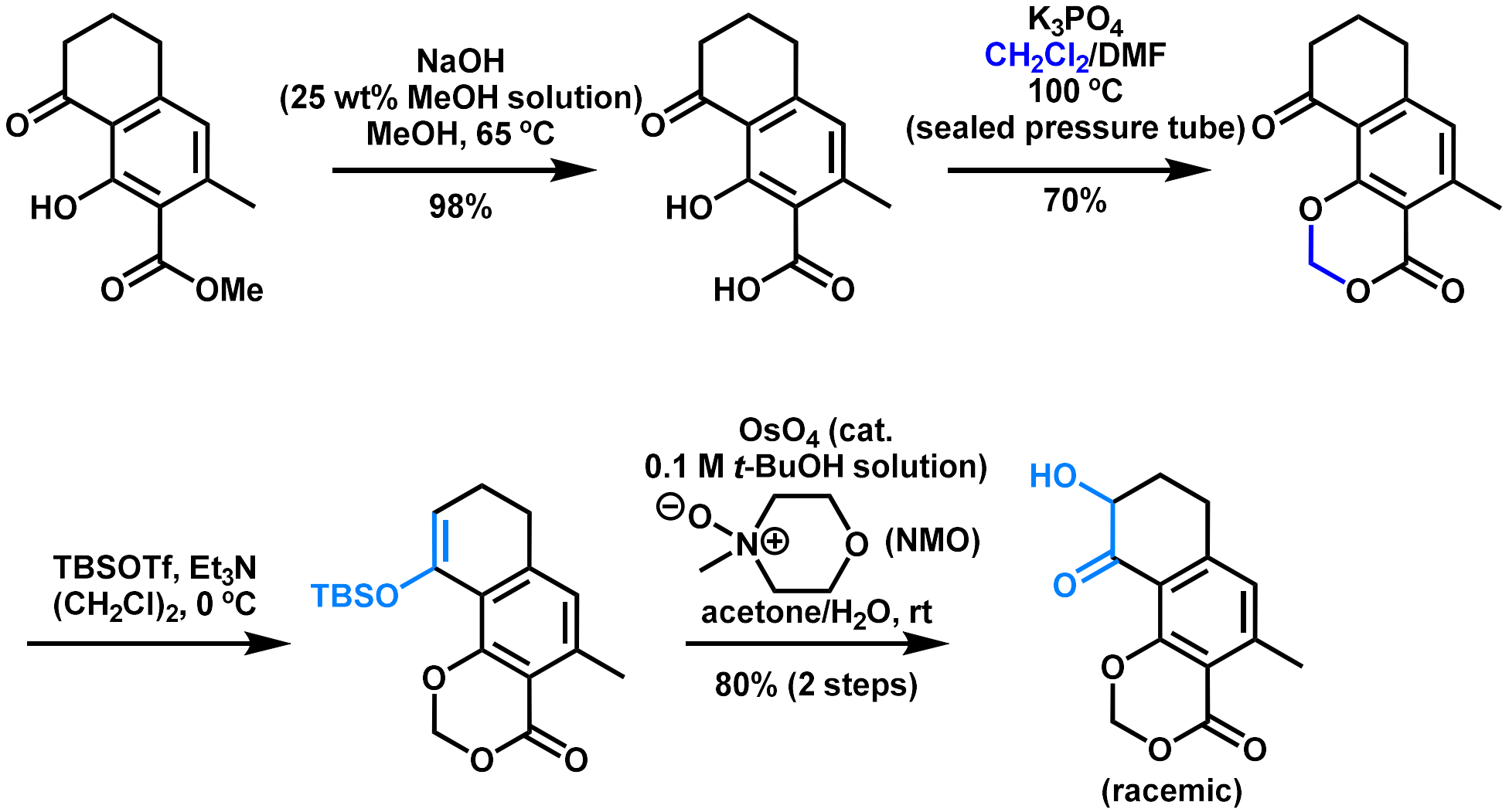


Synthesis of Eastern Fragment(1)[1)]



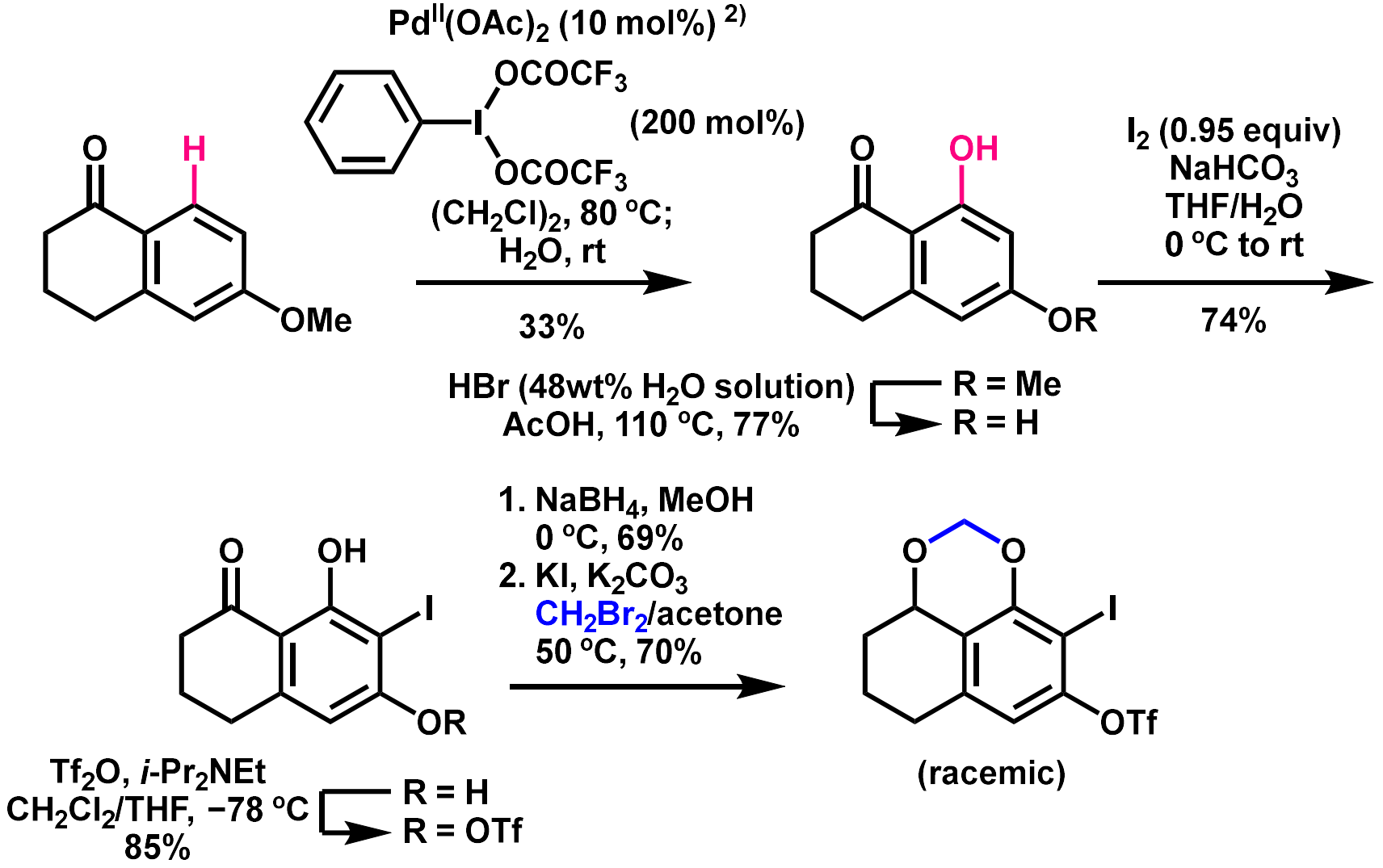
1) Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.
2) (a) Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Synthesis* **1986**, *1986*, 785. (b) Caron, B.; Brassard, P. *Tetrahedron* **1993**, *49*, 771.

Synthesis of Eastern Fragment (2)



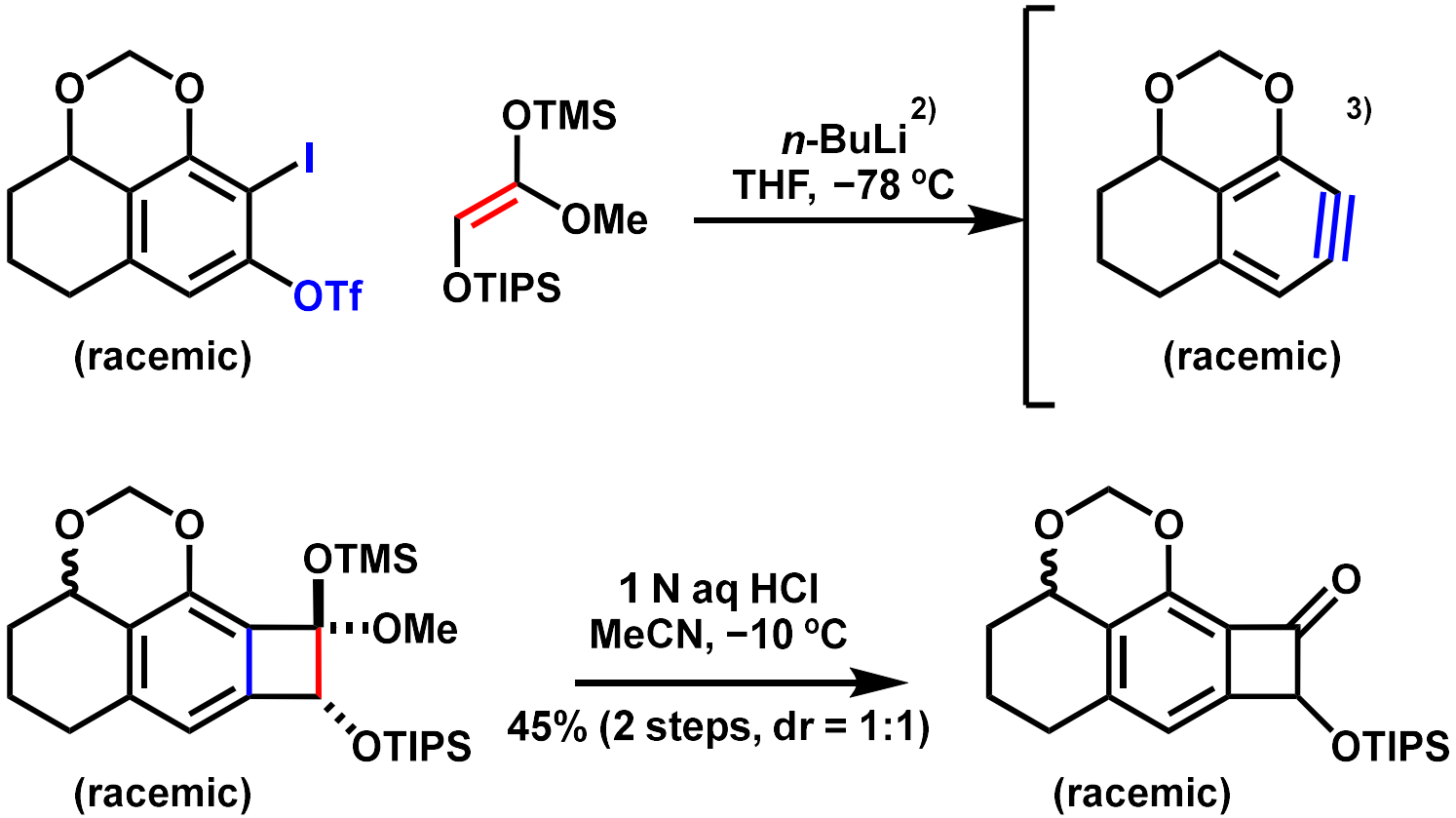
Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.

Synthesis of Western Fragment (1)[1)]



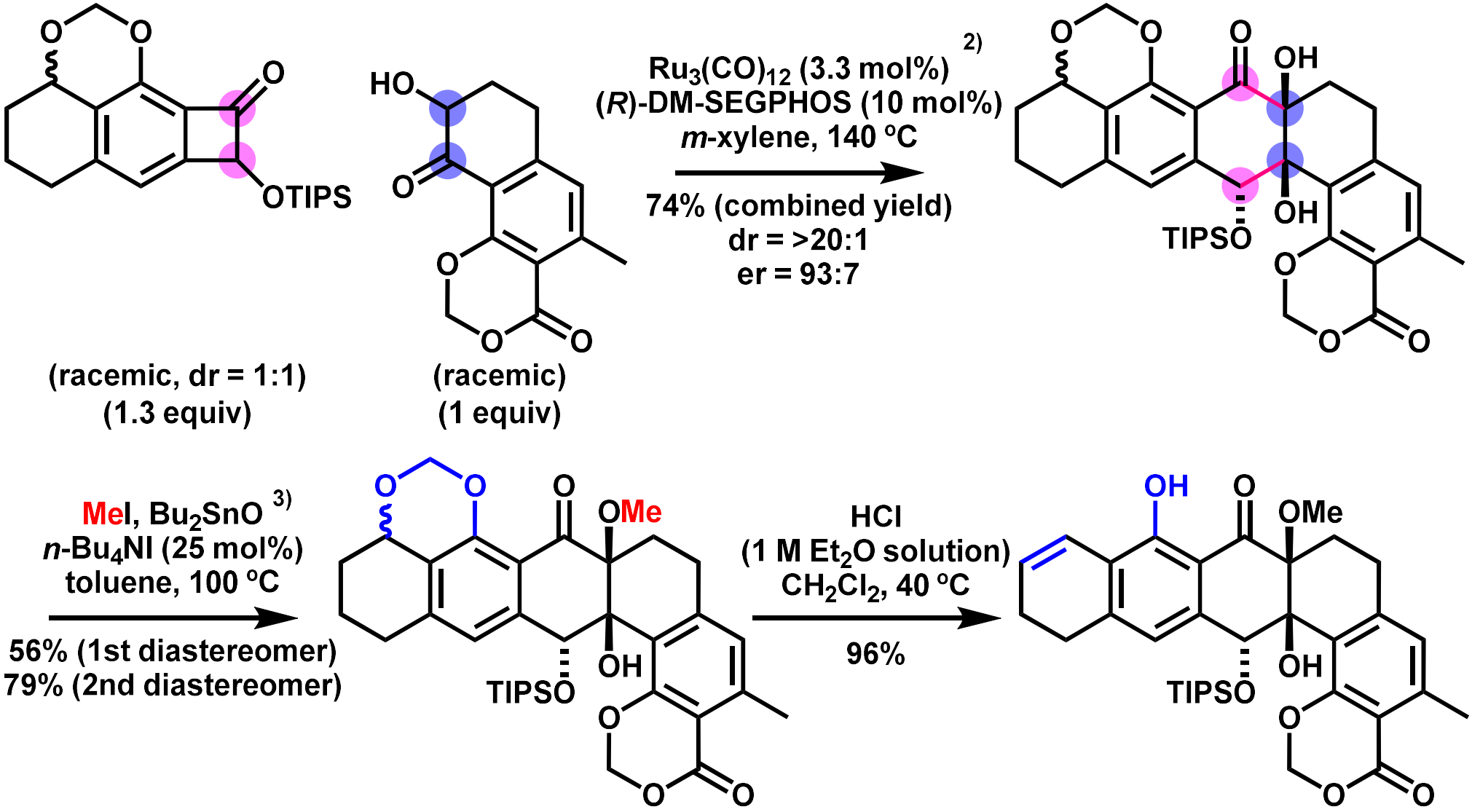
1) Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.
2) (a) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070. (b) Mo, F.; Trzepkowski, L. J.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 13075. (c) Choy, P. Y.; Kwong, F. Y. *Org. Lett.* **2013**, *15*, 270.

Synthesis of Western Fragment (2)[1)]



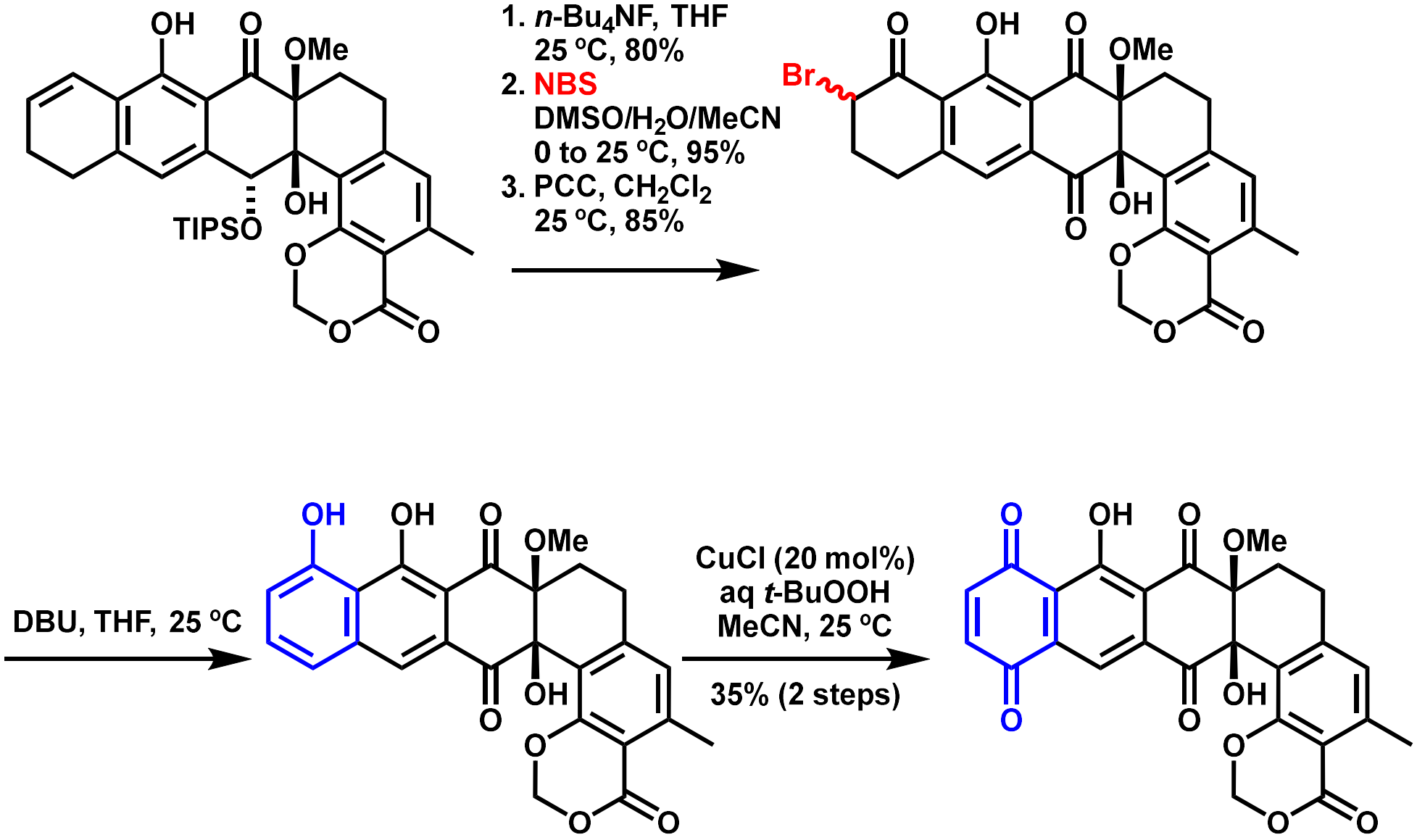
1) Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.
2) (a) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589. (b) Takemura, I.; Imura, K.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2004**, *6*, 2503.
3) For aryne distortion and regioselectivity, see Medina, J. M.; Mackey, J. L. Garg, N. K. Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798.

Enantioselective Benzocyclobutenone-Ketol Cycloaddition[1)]



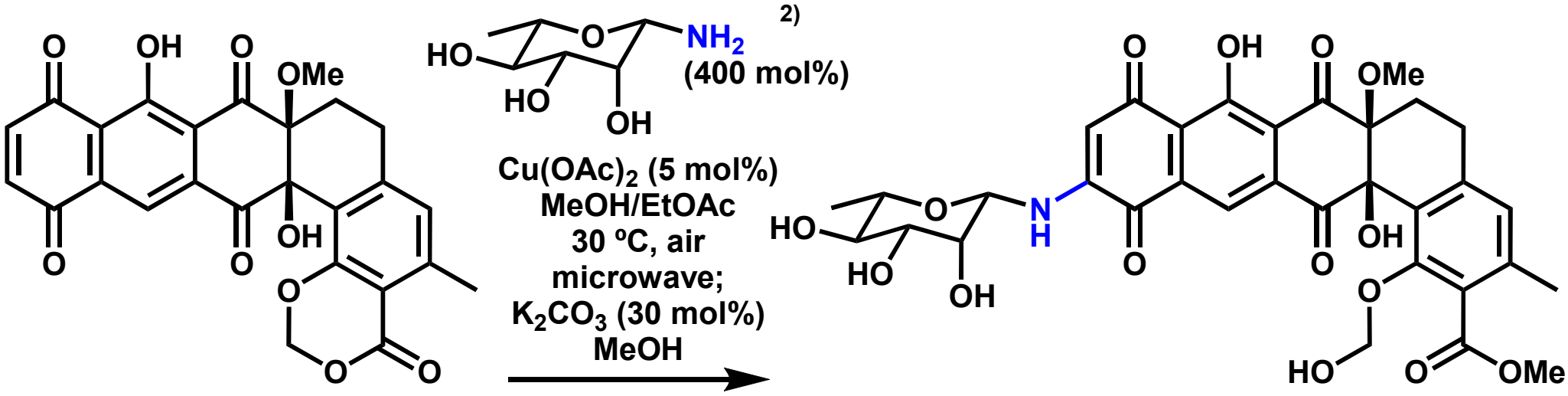
1) Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.
2) Ambler, B. R.; Turnbull, B. W. H.;Suravarapu, S. R.; Uteuliyev, M. M.; Huynh, N. O.; Krische, M. *J. J. Am. Chem. Soc*. **2018**, *140*, 9091.
3) Haque, M. E.; Kikuchi, T.; Yoshimoto, K.; Tsuda, Y. *Chem. Pharm. Bull*. **1985**, *33*, 2243.

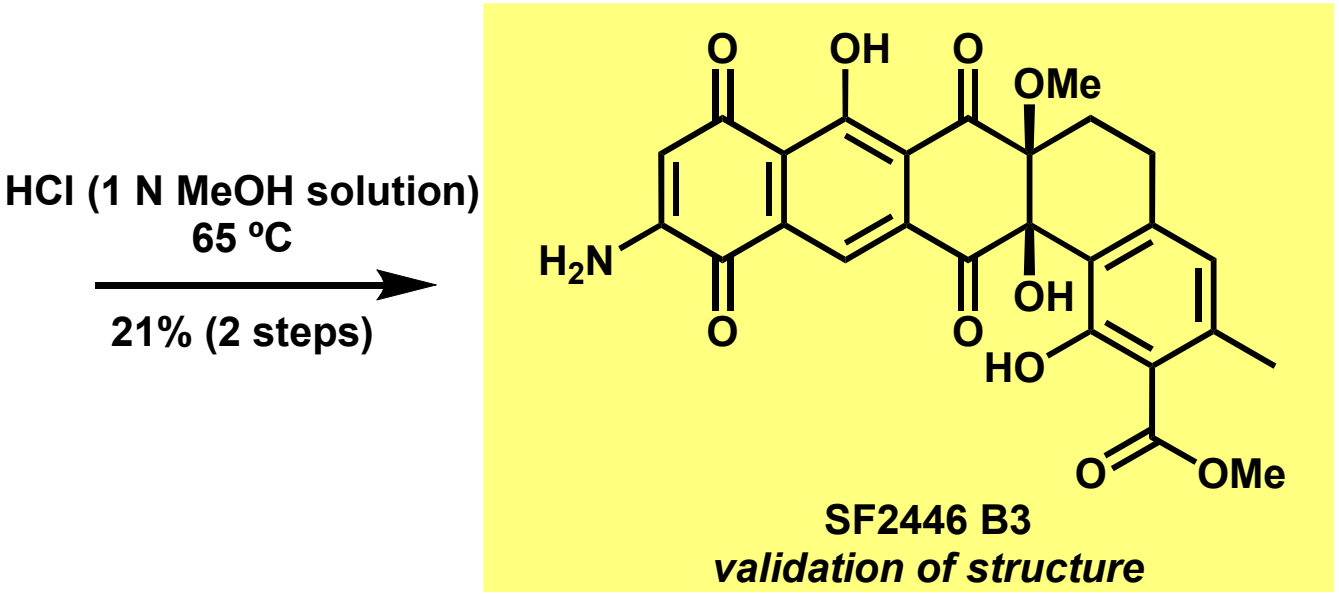
Construction of Quinone



Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.

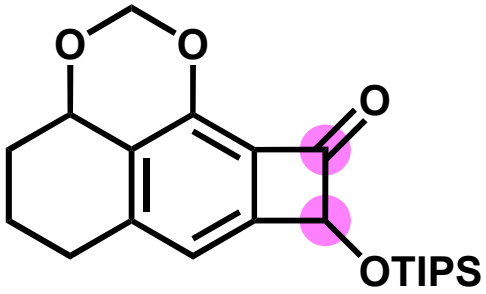
Total Synthesis of SF2446 B3[1)]



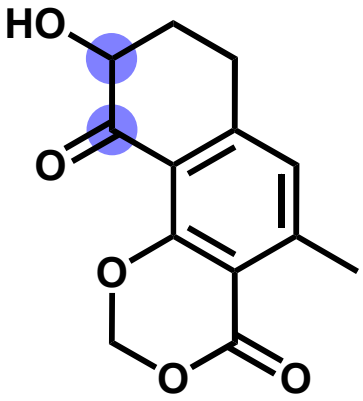


1) Huynh, N. O.; Hodík, T.; Krische, M. J. *J. Am. Chem. Soc.* **2023**, *145*, 17461.
2) Lisboa, C. d. S.; Santos, V. G.; Vaz, B. G.; De Lucas, N. C.; Eberlin, M. N.; Garden, S. J. *J. Org. Chem.* **2011**, *76*, 5264.

Summary

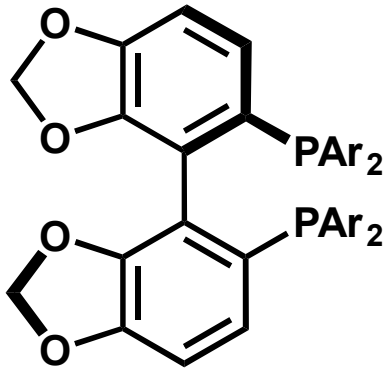


(racemic, dr = 1:1)

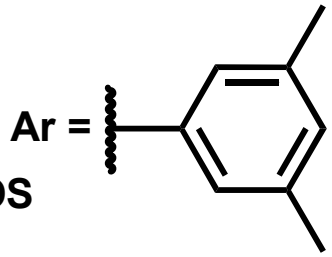


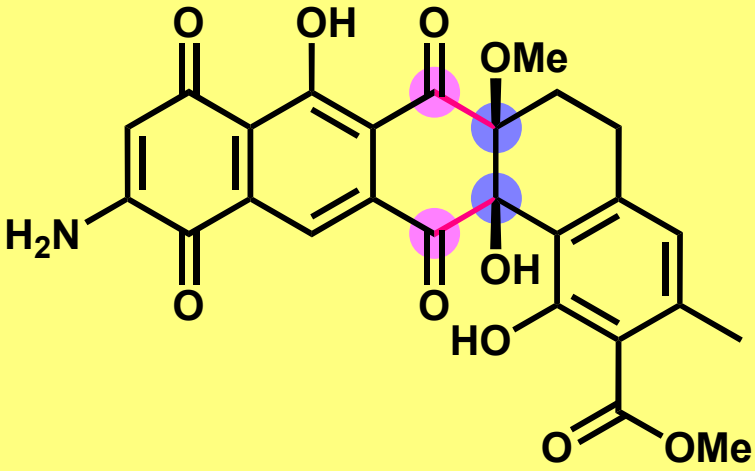
(racemic)

$Ru_3(CO)_{12}$ (3.3 mol%)
(*R*)-DM-SEGPHOS (10 mol%)
m-xylene, 140 °C



(*R*)-DM-SEGPHOS

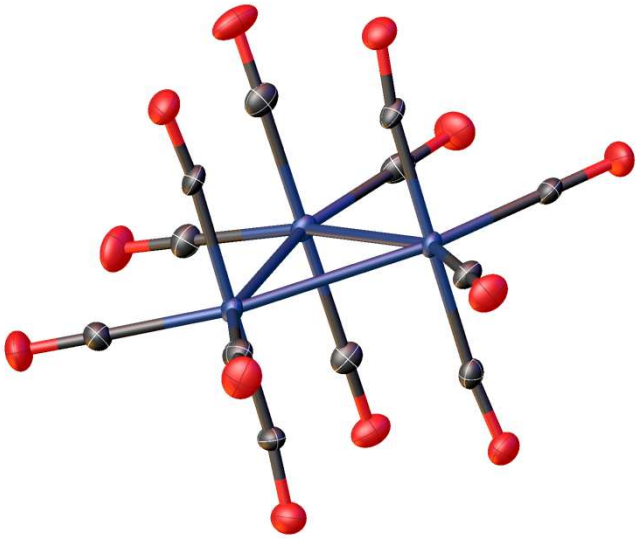




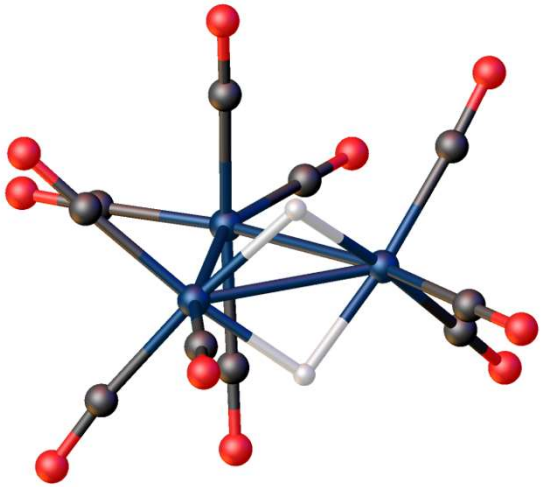
SF2446 B3

Appendix

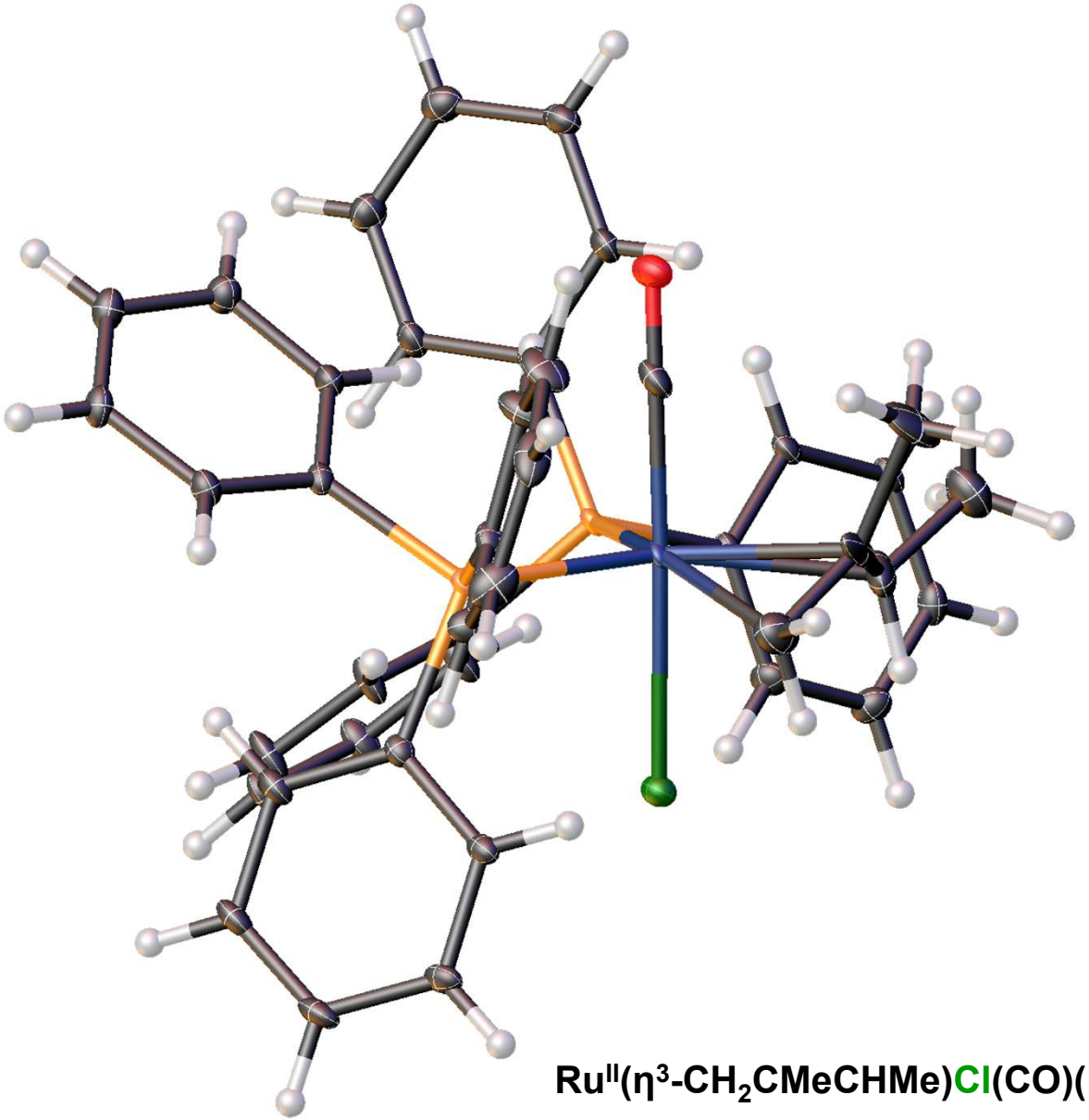
X-ray Structure (1)



$Ru^0_3(CO)_{12}$



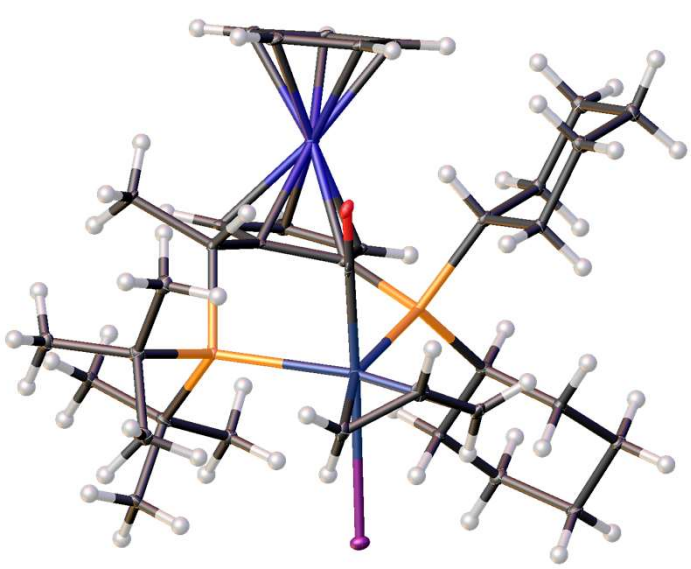
$Os^0(CO)_4[Os^I(CO)_3(\mu\text{-}H)]_2$



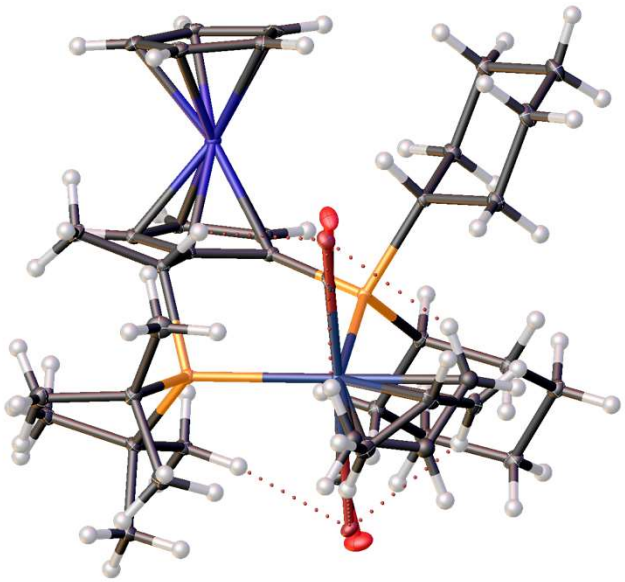
$Ru^{II}(\eta^3\text{-}CH_2CMeCHMe)Cl(CO)(PPh_3)_2$

$Ru_3(CO)_{12}$: *Inorg. Chem.* **2004**, *43*, 5245.
$(\mu\text{-}H)_2Os_3(CO)_{10}$: *Inorg. Chem.* **1977**, *16*, 2697.
Isoprene-derived allylruthenium(II) : *Organometallics* **2004**, *23*, 4735.

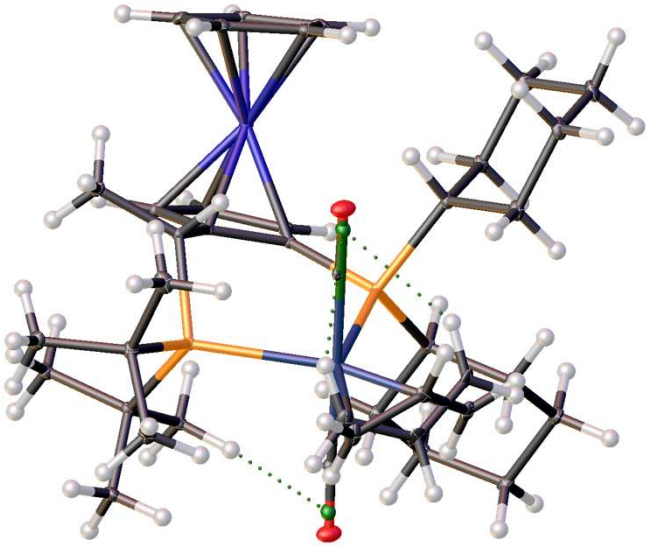
X-ray Structure (2)



$Ru^{II}I(CO)(SL\text{-}J009\text{-}01)(\eta^3\text{-}C_3H_5)$



$Ru^{II}Br(CO)(SL\text{-}J009\text{-}01)(\eta^3\text{-}C_3H_5)$



$Ru^{II}Cl(CO)(SL\text{-}J009\text{-}01)(\eta^3\text{-}C_3H_5)$

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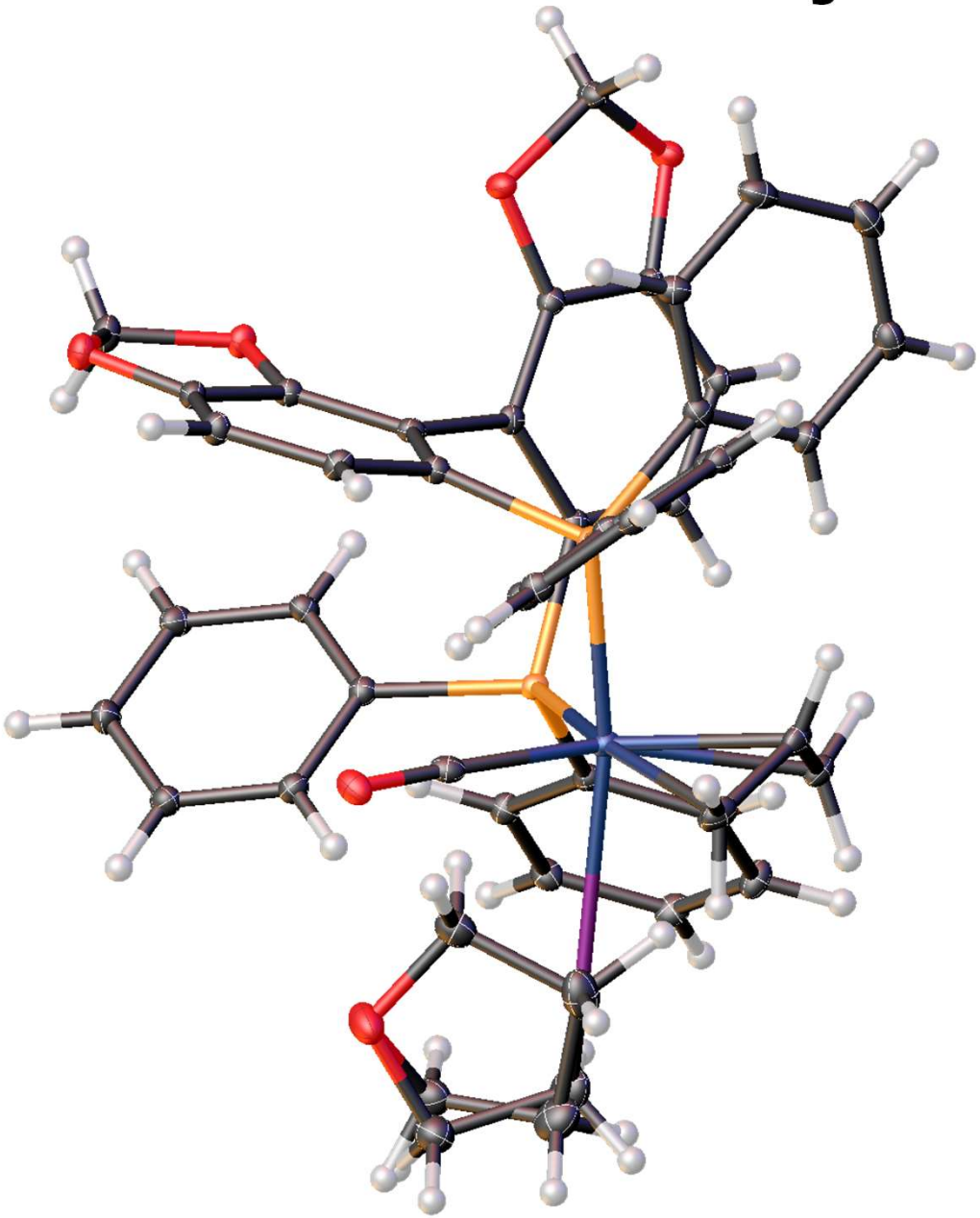
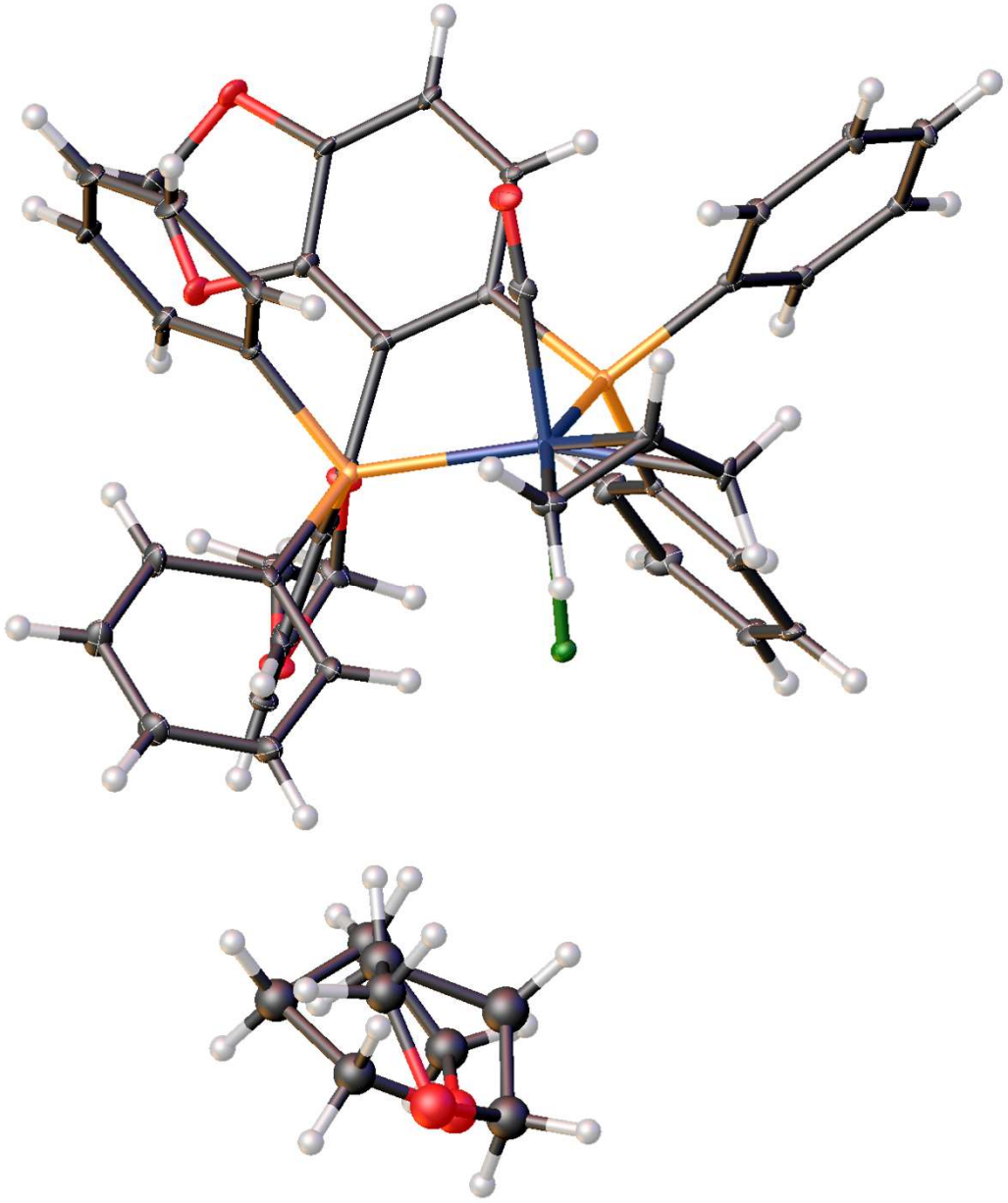
X-ray Structure (3)



$Ru^{II}I(CO)(SEGPHOS)(\eta^3\text{-}C_3H_5)\cdot THF$



$Ru^{II}Cl(CO)(SEGPHOS)(\eta^3\text{-}C_3H_5)\cdot THF$

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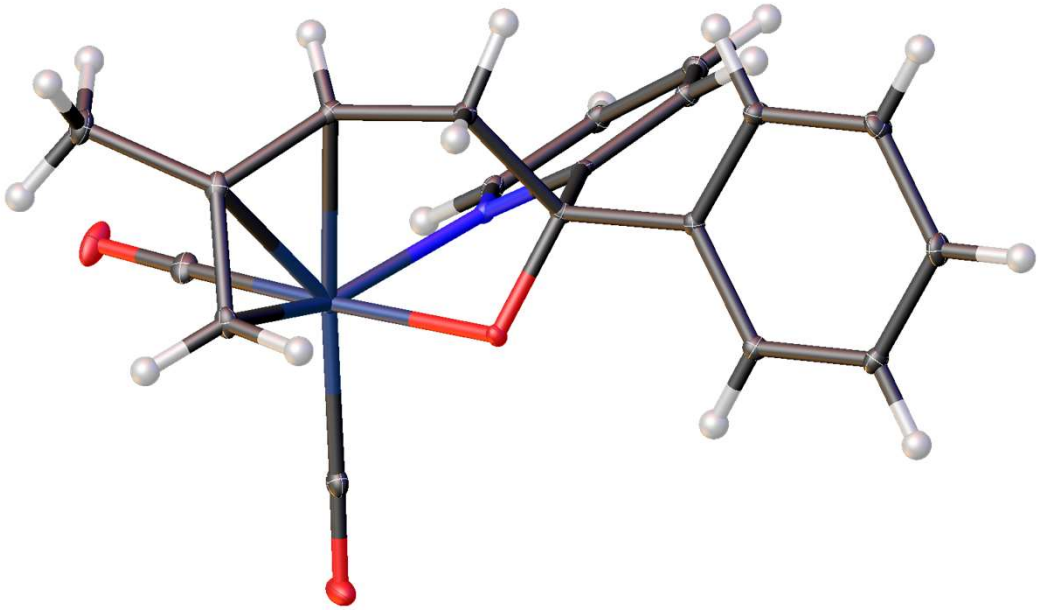
X-ray Structure (4)



Pyridine-chelated η^3-allylruthenium(II) complex

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