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Ruthenium catalyzed diastereo- and enantioselective coupling of propargyl ethers with alcohols

T. Liang, W. Zhang, T.-Y. Chen, K. D. Nguyen, M. J. Krische, *JACS*, DOI : 20,1021/jacs.5b08019

Mylène ROUDIER, RCC seminar group, october 20th, 2015

Aix*Marseille université

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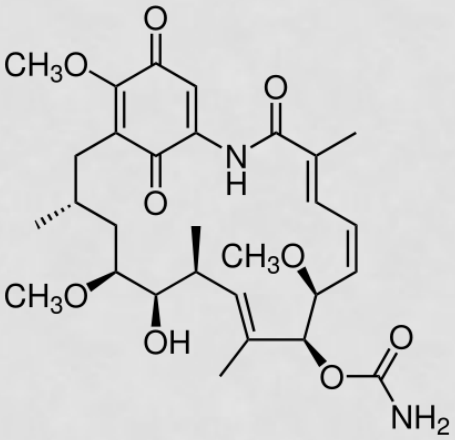
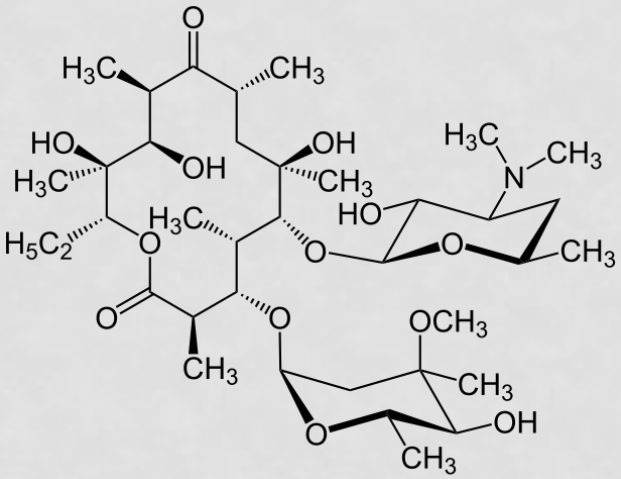
POLYKETIDES

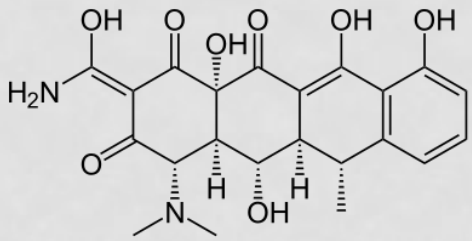


Geldanamycin



Erythromycin

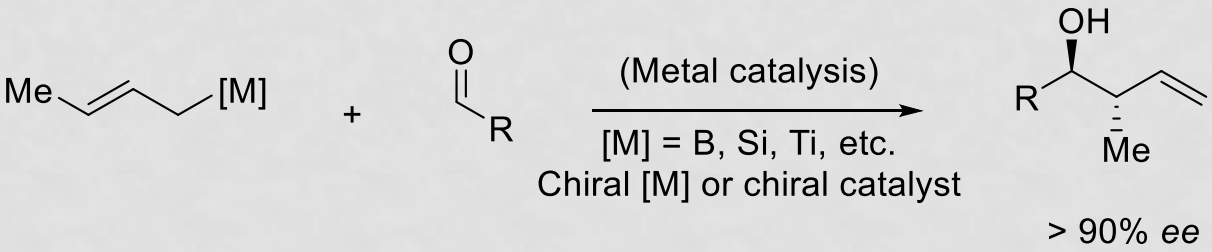
- Use in human medicine
- Prepared by fermentation
- New methods for the synthesis of polyketides
  - Diastereo- and –enantioselective carbonyl crotylation has proven to be efficient



Doxycycline

STATE OF THE ART

- Asymmetric crotylation of aldehydes : Hoffman 1978



Stoechiometric amount of allylmetal reactants

T. Herold, R. W. Hoffman, *Angew. Chem. Int. Ed. Engl.*, **1978**, 768
R. W. Hoffman, W. Ladner, *Tetrahedron Lett.*, **1979**, 4653

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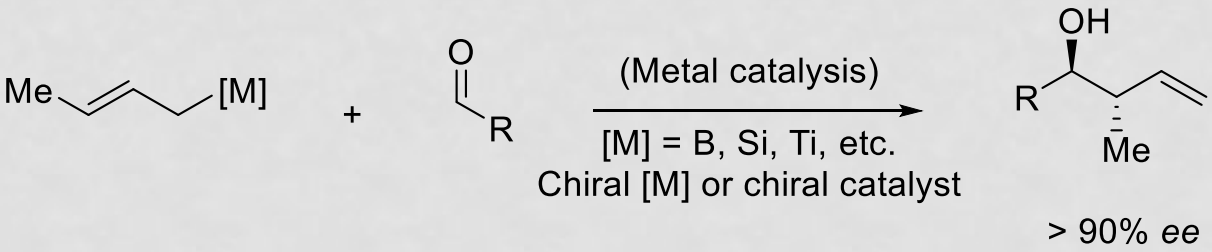

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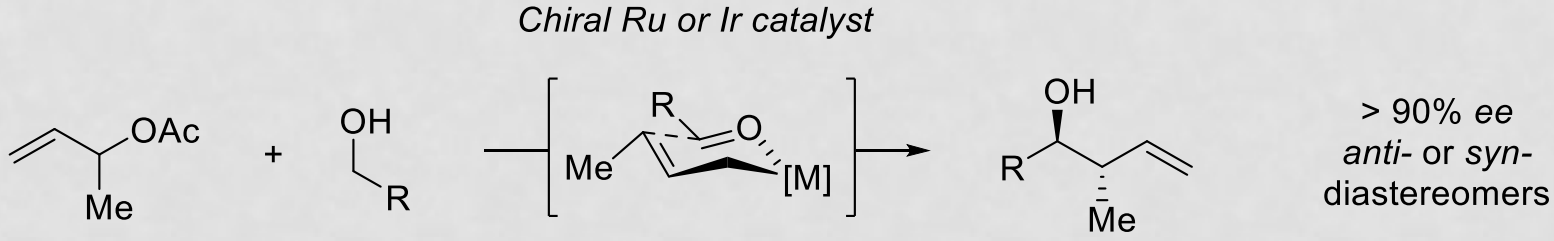
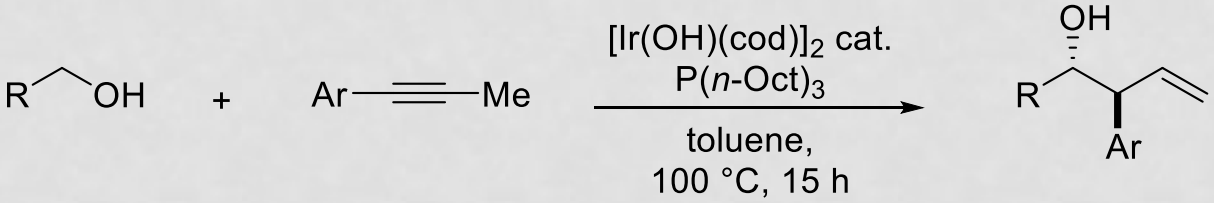
- Alcohols and allyl acetates as redox pairs for carbonyl additions



STATE OF THE ART

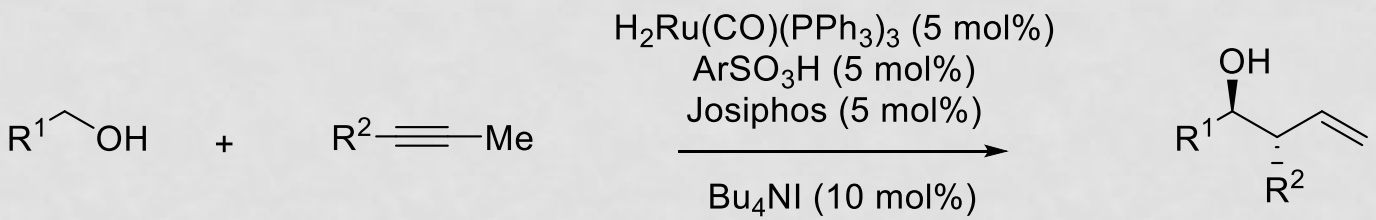
- Iridium-Catalyzed Coupling Reaction of Primary Alcohols with 1-Aryl-1-propynes



65-92 % yield

Y.Obora, S. Hatanaka, Y. Ishii, *Org. Lett.*, **2009**, 3510

- Ruthenium-Catalyzed carbonyl allylation

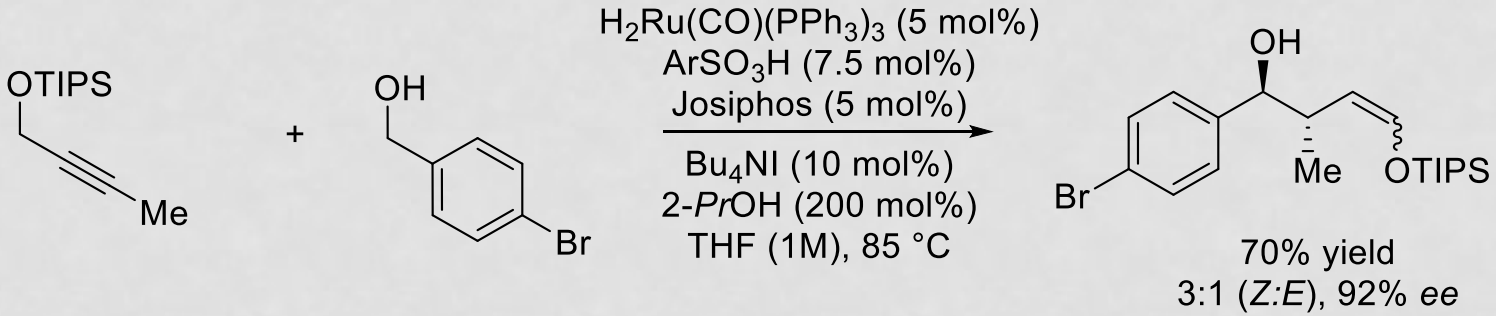


61-90% yield
>20:1 *dr*, 86-96% *ee*

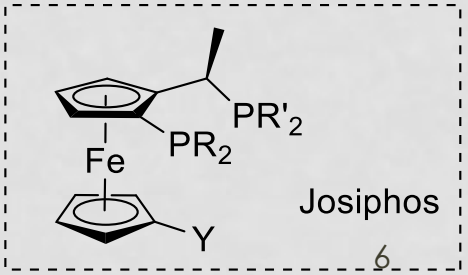
T. Liang, K. D. Nguyen, W. Zhang, M. J. Krische, *JACS*, **2015**, 3161

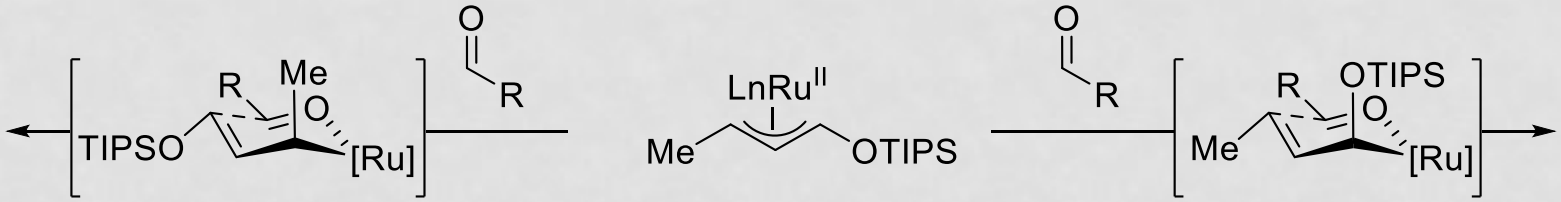
THIS WORK

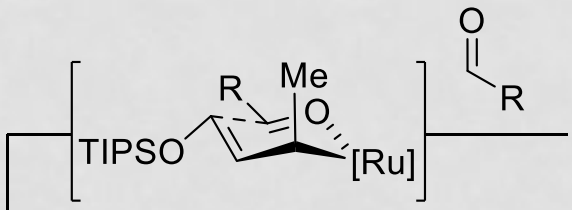
- Diastereo- and enantioselective alkyne-mediated carbonyl crotylation



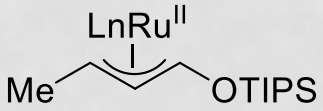
$ArSO_3H$ = 2,4,6-(2-Pr)$_3$PhSO$_3$H

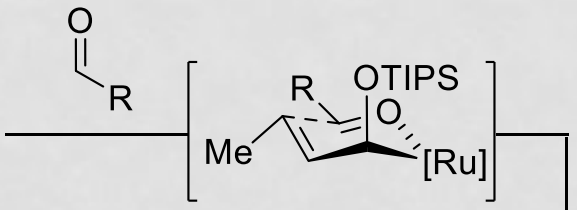



TIPSO
R
Me
O
[Ru]
O
R
LnRu^II
Me
OTIPS
O
R
R
OTIPS
O
Me
[Ru]



8 stereoisomeric transition structures





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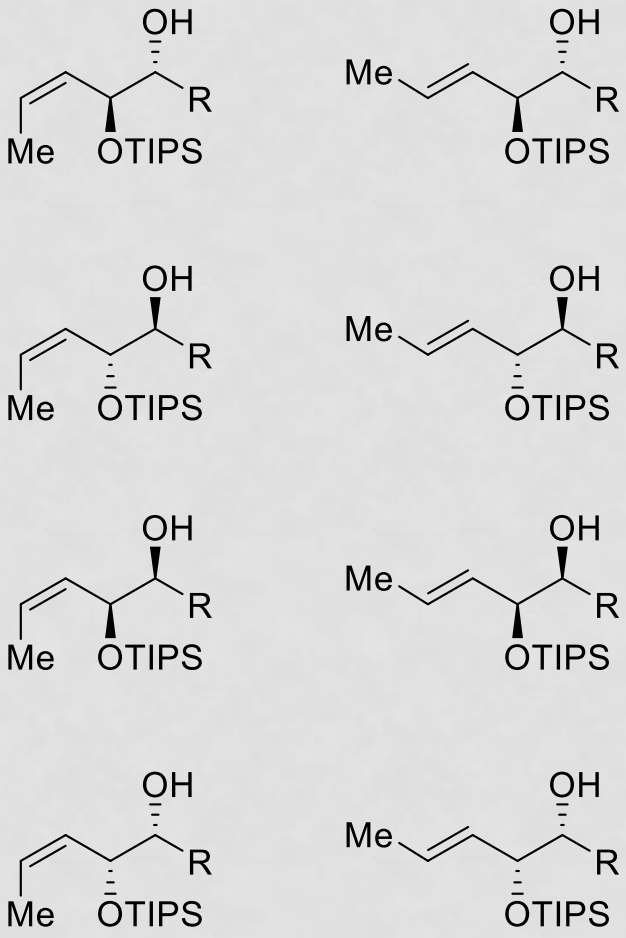
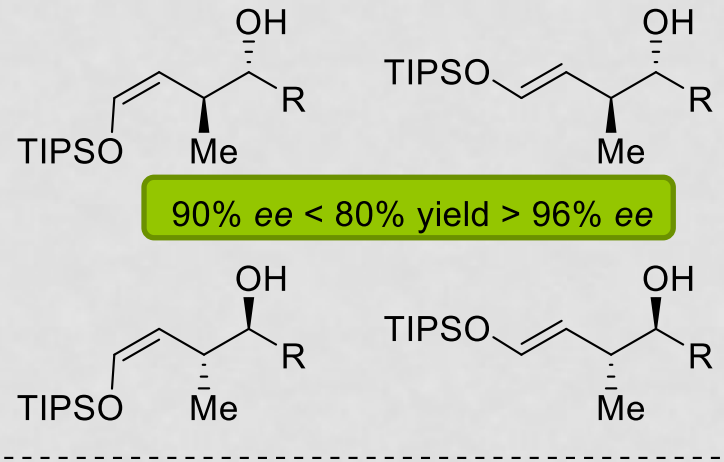
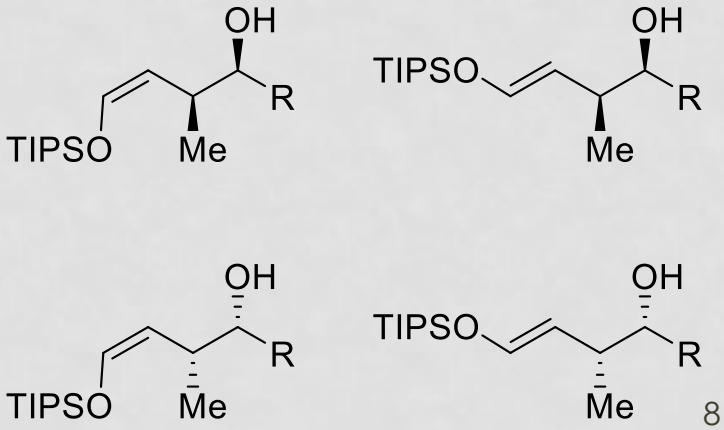
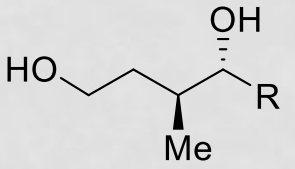




90% *ee* < 80% yield > 96% *ee*



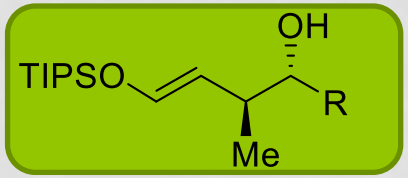
FUNCTIONALIZATION



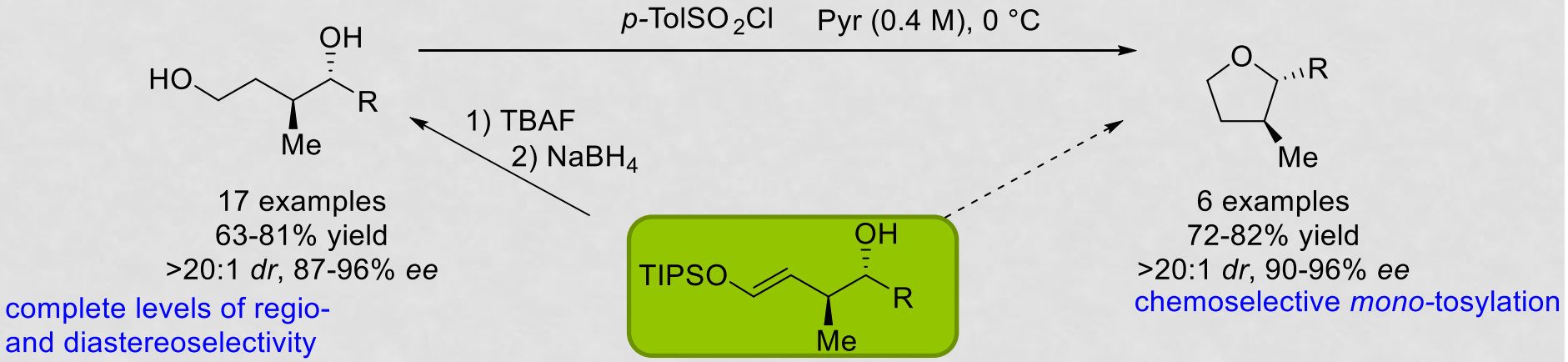
1) TBAF
2) $NaBH_4$

17 examples
63-81% yield
>20:1 *dr*, 87-96% *ee*

complete levels of regio- and diastereoselectivity



FUNCTIONALIZATION



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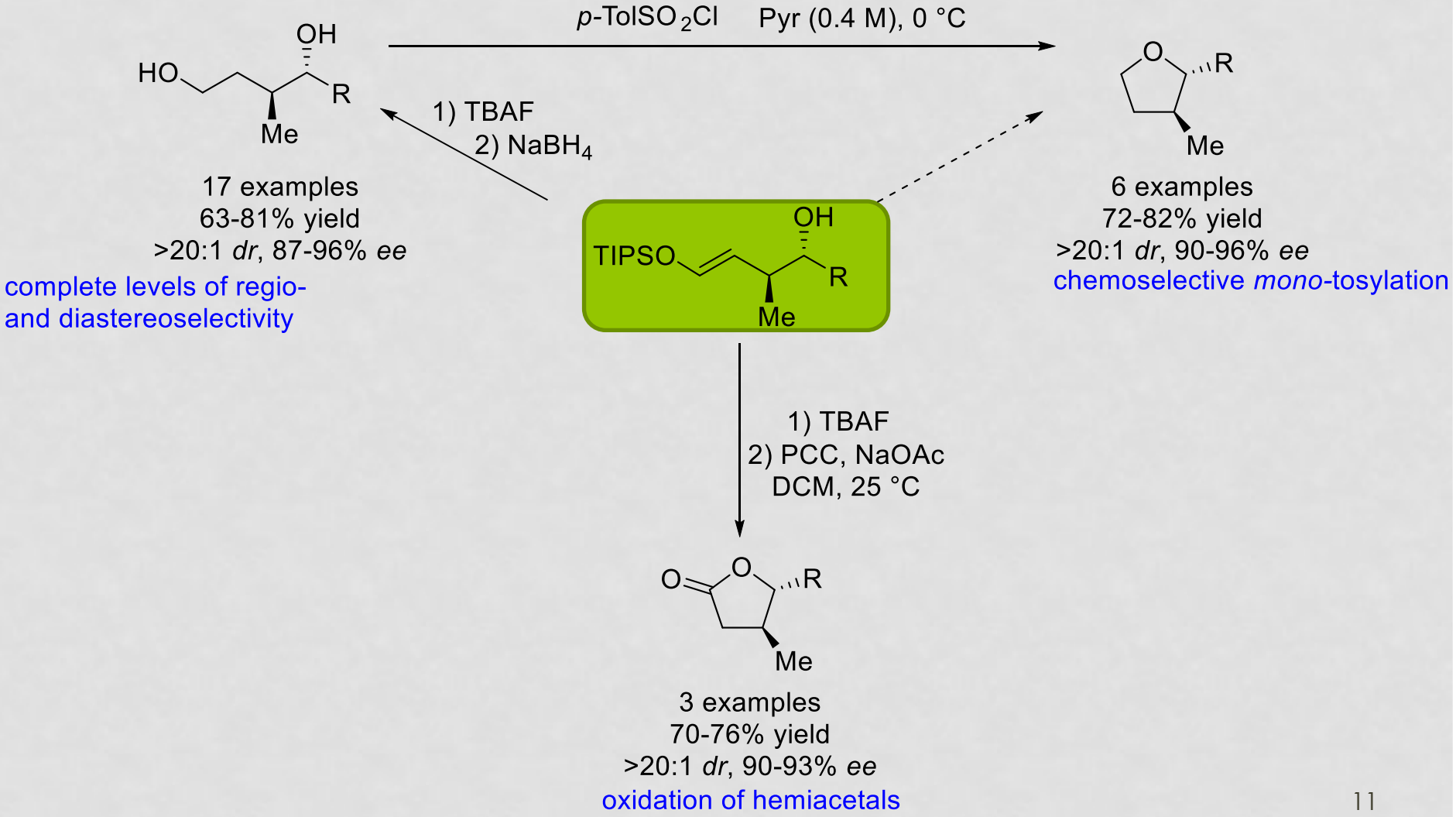

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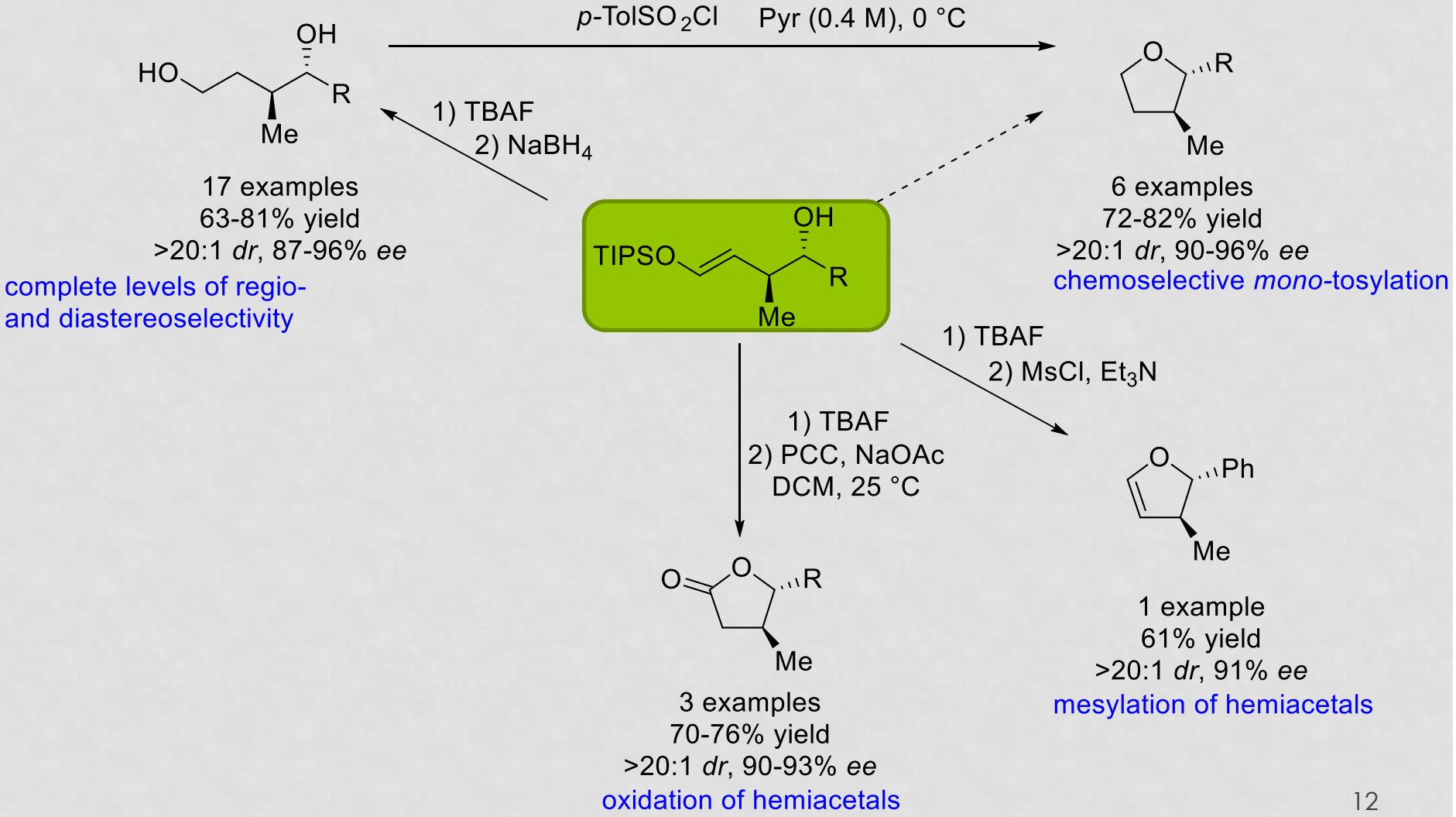

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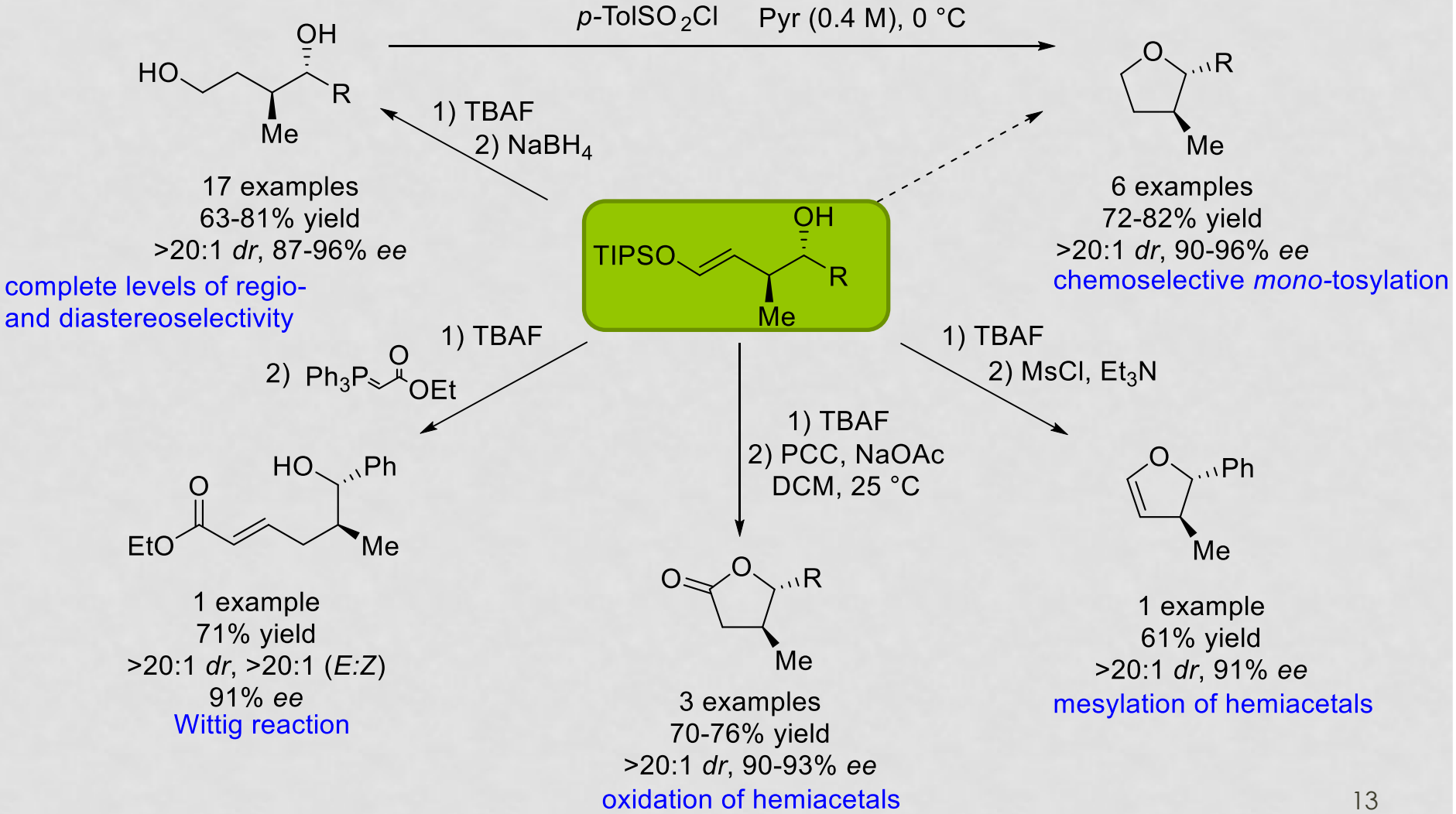
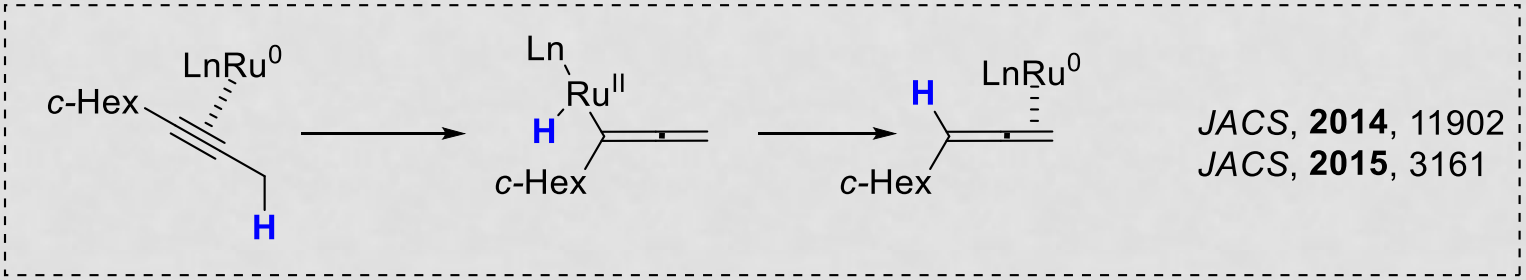


MECHANISM INVESTIGATION

- Isomerization of alkyne to allene with ruthenium



JACS, **2014**, 11902
JACS, **2015**, 3161

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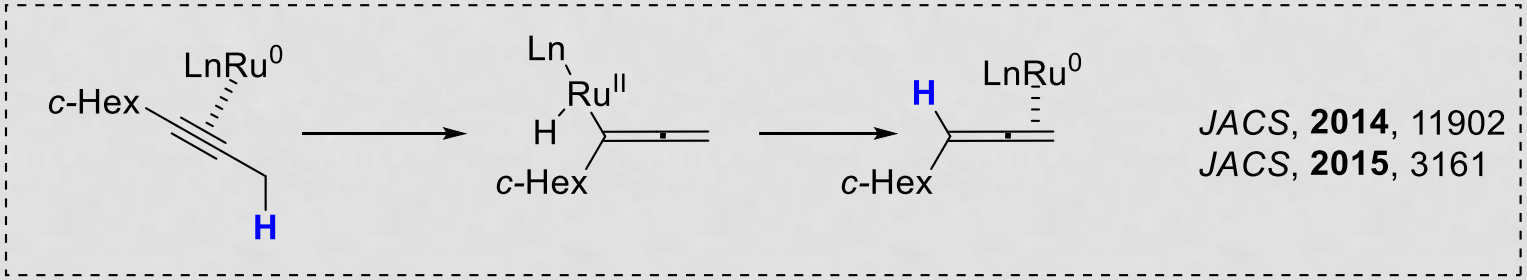

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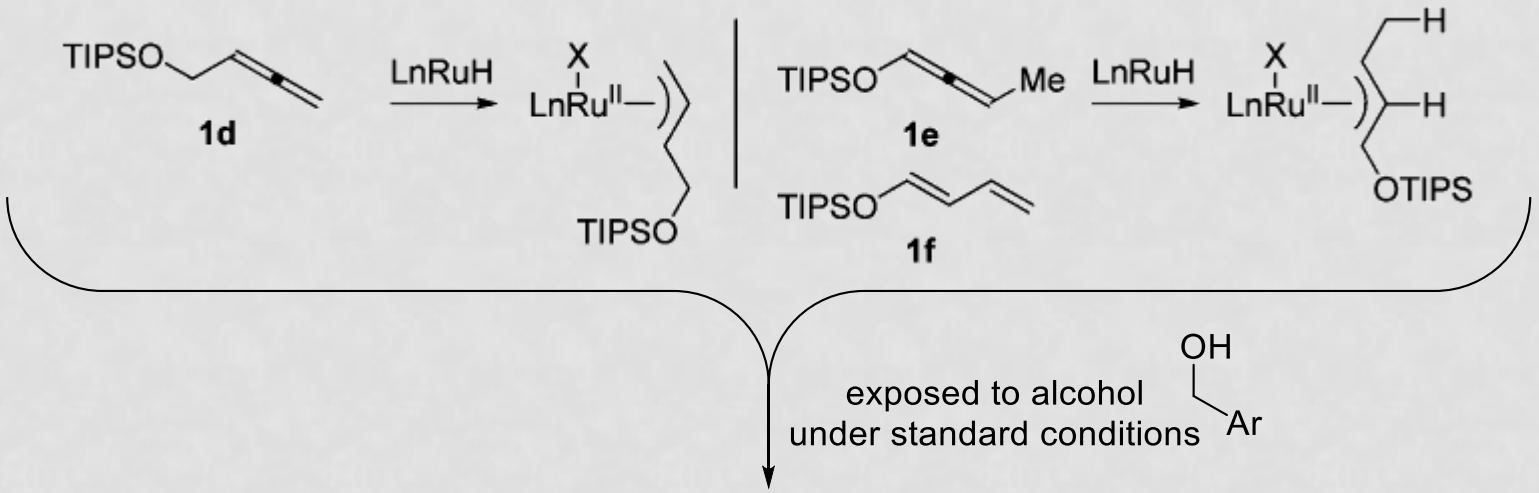
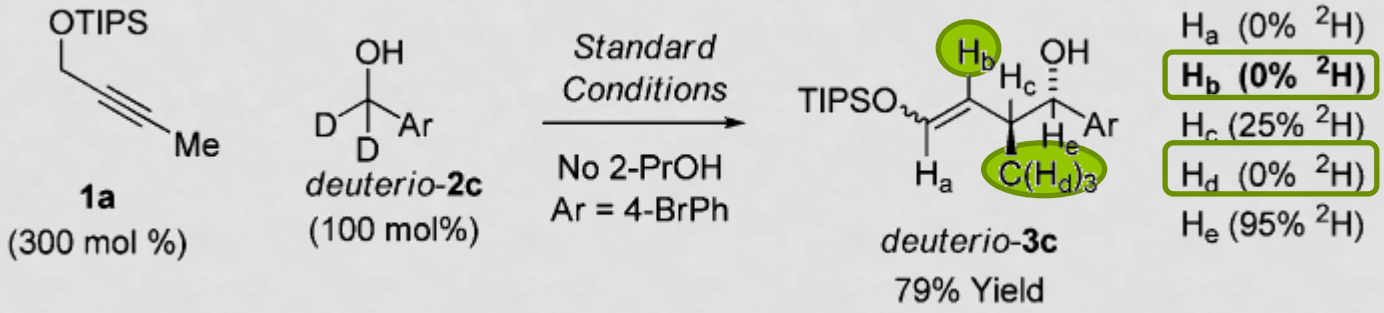
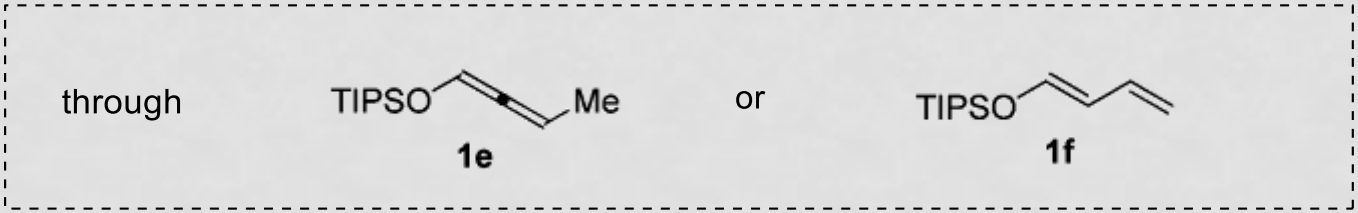


- dehydrogenation of alcohol observed
- no C-C coupling product detected

MECHANISM : DEUTERIUM LABELING





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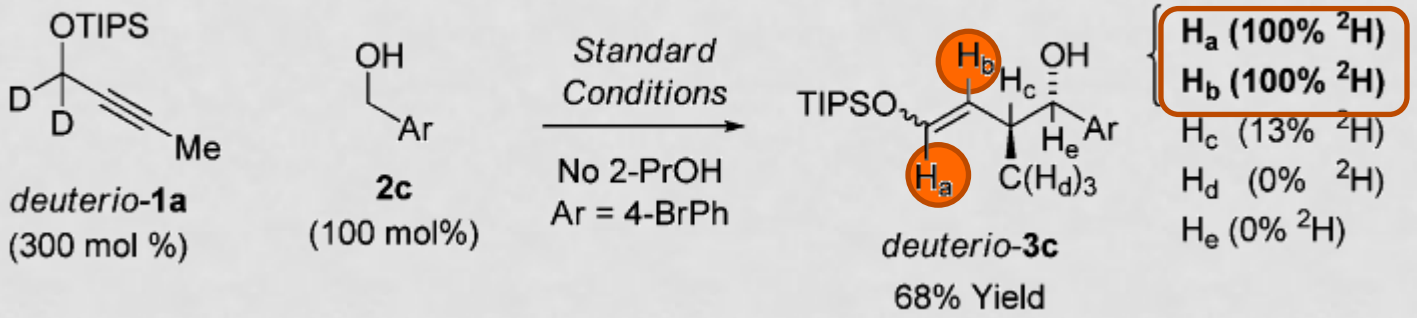
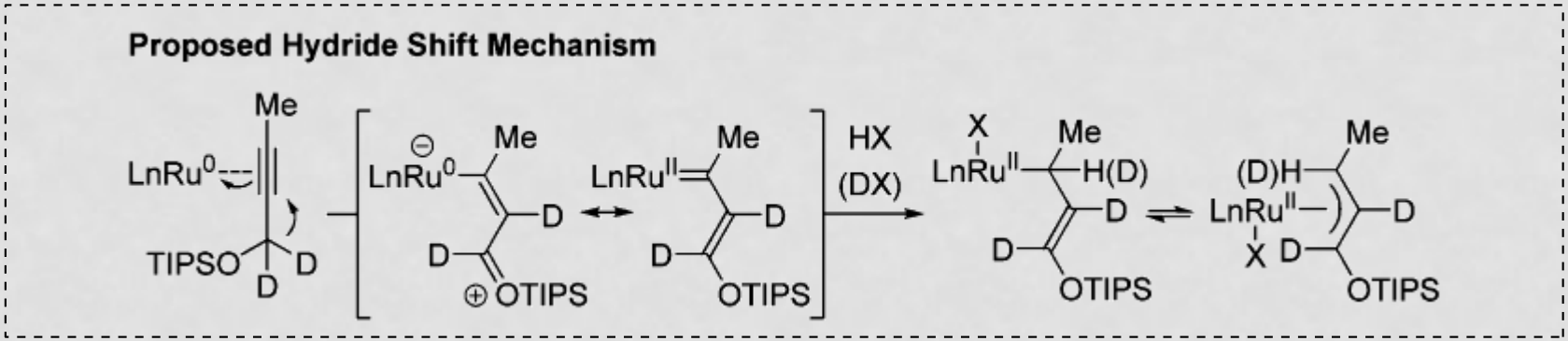
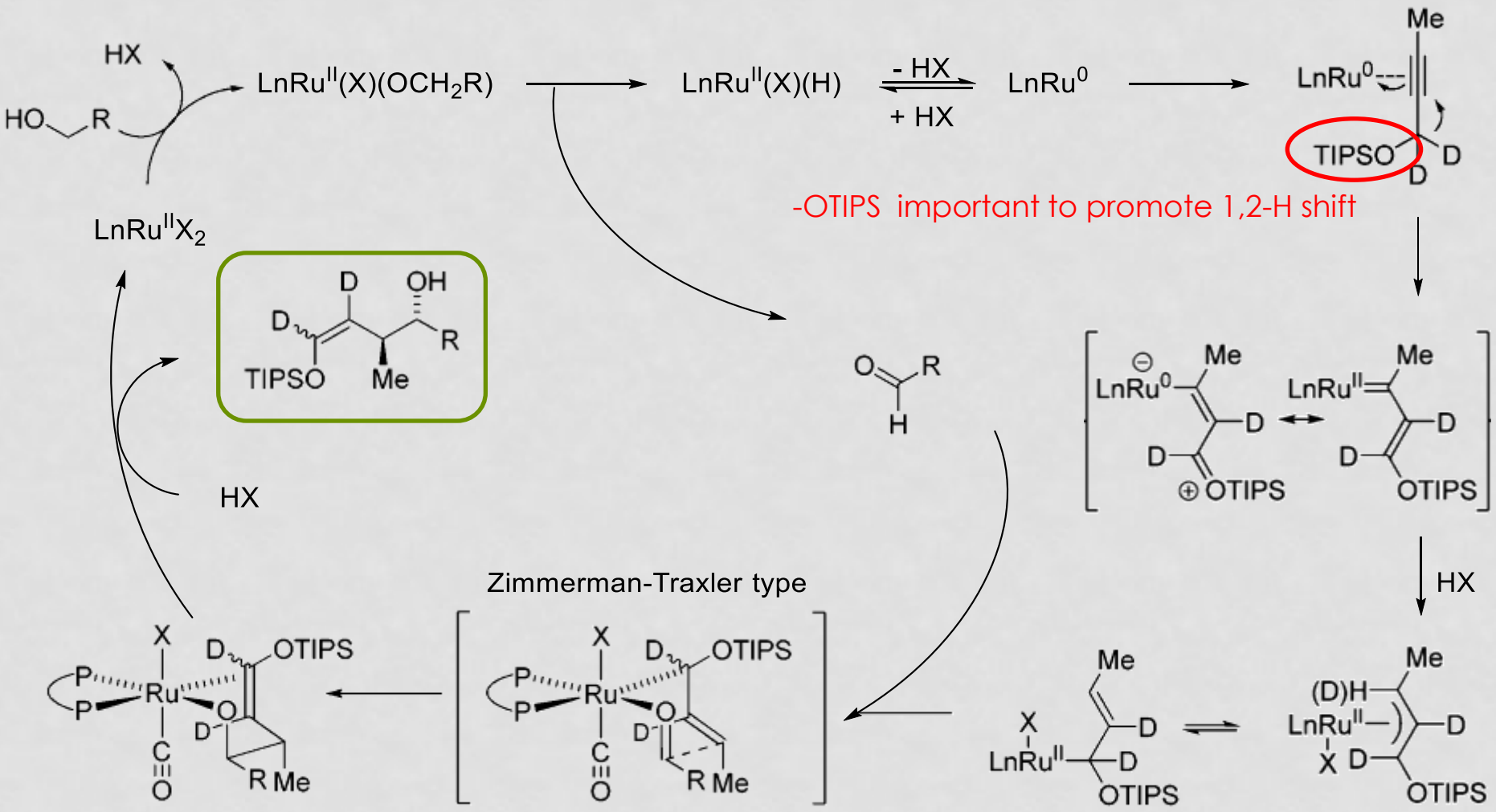




PROPOSED MECHANISM



CONCLUSION

- Development of a direct alkyne-mediated carbonyl crotylation via redox carbonyl addition
- Access to a lot of post-functionalization
- Discovery of a new 1,2-hydride shift mechanism confirmed by deuterium labeling

THANK YOU FOR YOUR ATTENTION