Universität Konstanz

Ti-Metallacycle-Mediated Cross Coupling Chemistry

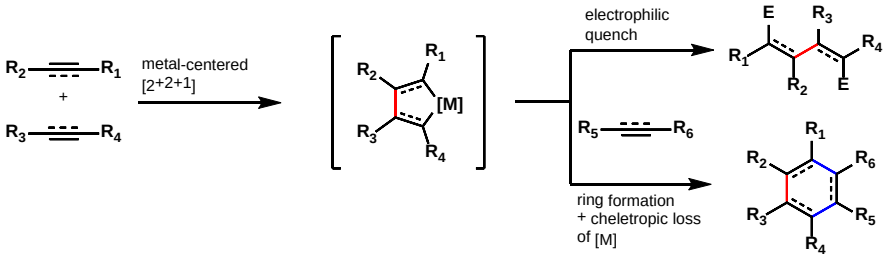
Modern Developments by Glenn C. Micalizio

Till Vogel

Konstanz, 17.08.2022

1 Background & Overview

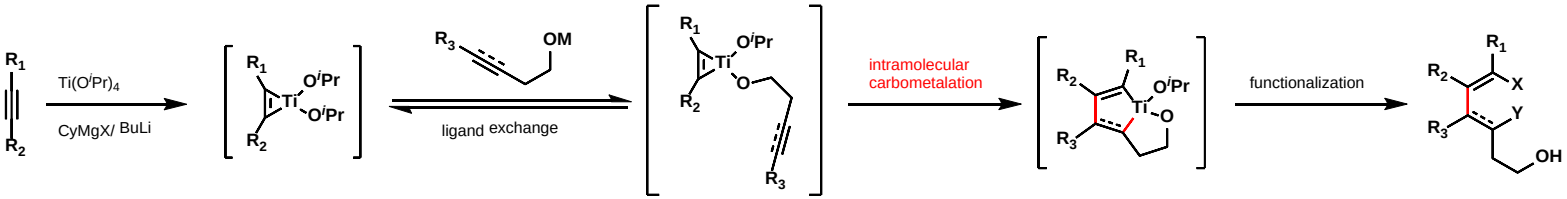
1.1 General depiction of metal-centered alkyne/ alkene coupling



Challenges:

- Cross-coupling vs. homo-dimerization
- Regioselectivity (with unsymmetric π-systems
- Stereoselectivity
- Functional group compatibility

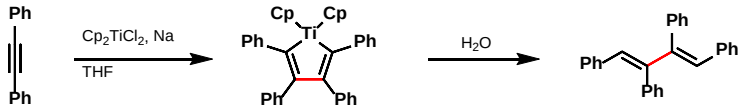
1.2 Main focus of the talk – Micalizio‘s hydroxyl-directed metallacycle-mediated cross-coupling



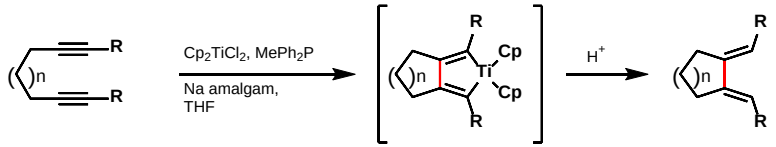
Micalizio *et al. Eur. J. Org. Chem.* **2010**, 391–409

2 Historic Developments

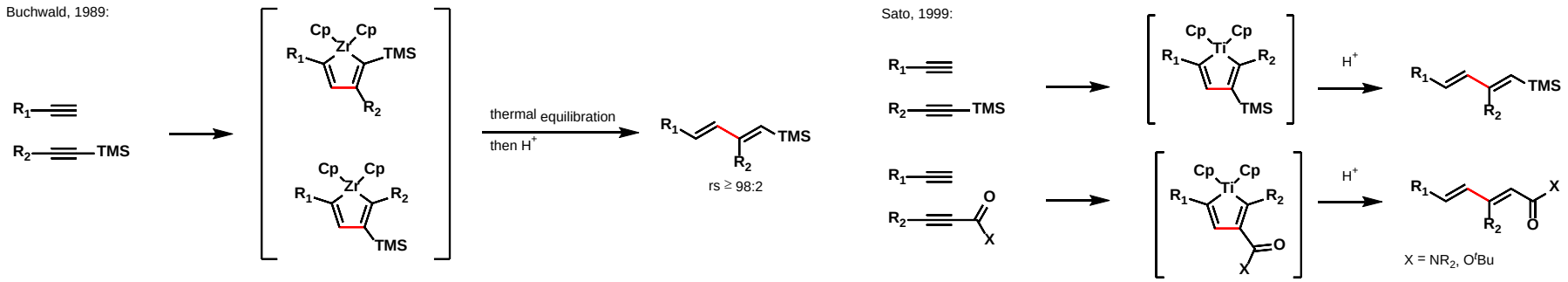
Dimerization of diphenylacetylene, 1963 [1]



Cyclization of diynes, 1984 [2]



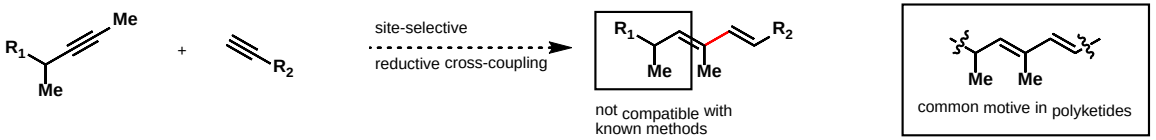
Intermolecular hetero coupling [3],[4]



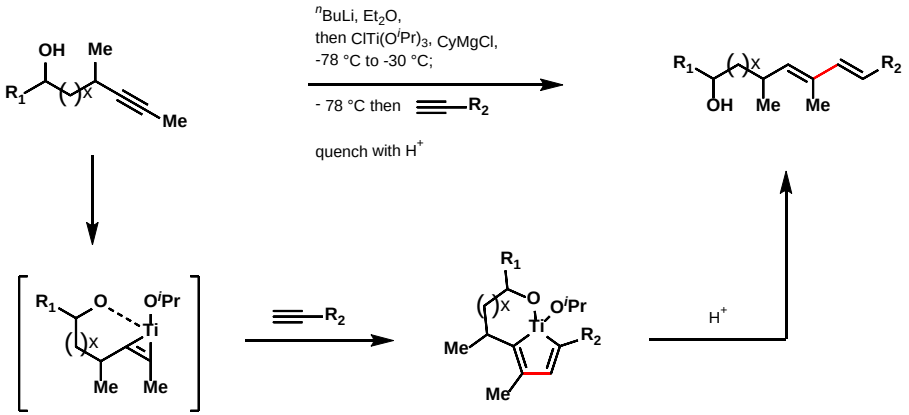
[1] Kursanov *et al. Dokl Akad. Nauk SSSR* **1963**, 151, 1100– 1103; [2] Nugent *et al. J. Am. Chem. Soc.* **1984**, 106, 6422– 6424; [3] *Buchwald et al*. J. Am. Chem. Soc. **1989**, 111, 2870– 2874;
[4] Sato *et al. J. Am. Chem. Soc.* **1999**, 121, 7342– 7344

3 Alkoxide directed alkyne-alkyne cross-coupling – polyketide synthesis

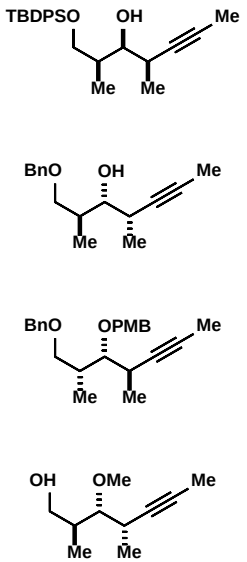
3.1 Desired process



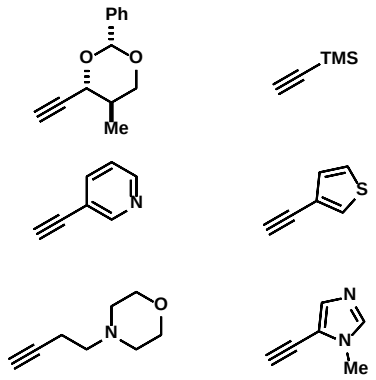
3.2 Solution – alkoxide-direction



selected internal alkynes:



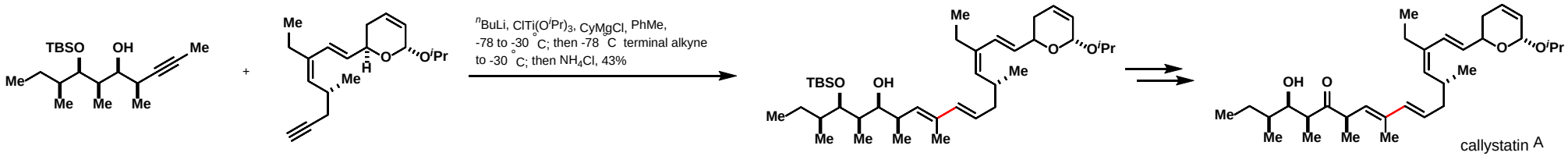
selected terminal alkynes:



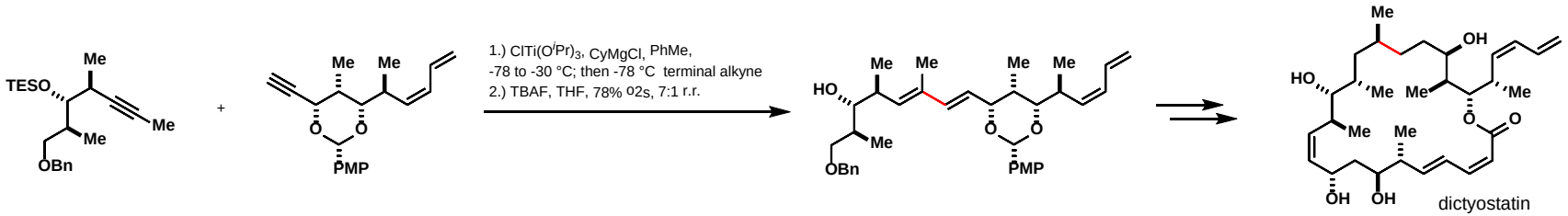
Micalizio *et al. J. Org. Lett.* **2005**, 7, 5111-5114

3.3 Aplication in Total Synthesis

Total Synthesis of Callystatin A[1]:



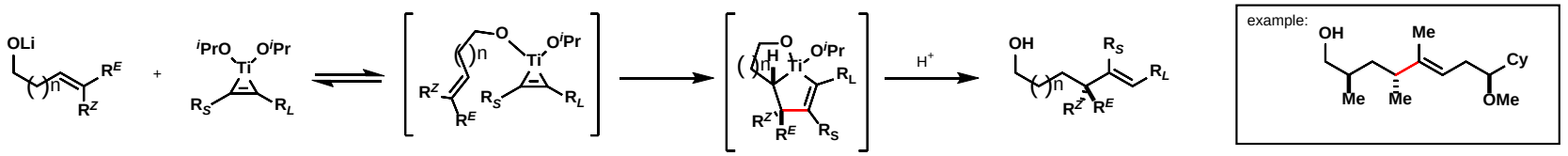
Formal Total Synthesis of Dictyostatin[2]:



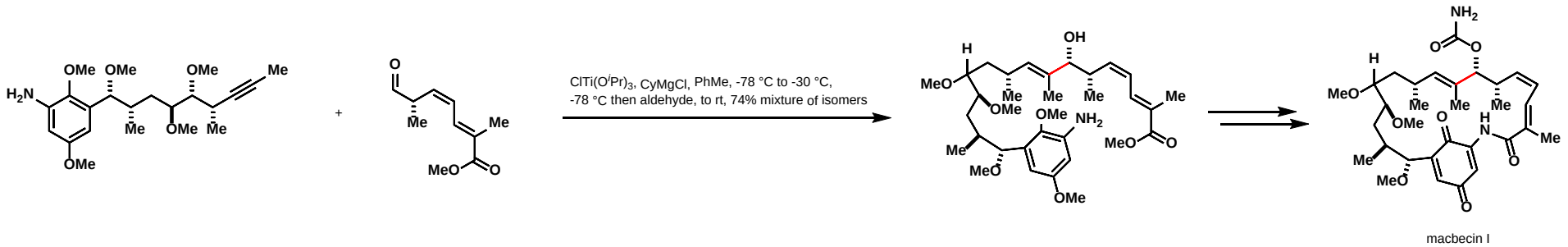
[1] Micalizio *et al. Angew. Chem. Int. Ed.* **2008**, 47, 7837–7840
[2] Micalizio *et al. Tetrahedron* **2009**, 65, 5908–5915

3.4 Variations – Coupling with Alkenes & Aldehydes

Alkyne-Alkene Coupling:



Alkyne-Aldehyde Coupling – Synthesis of Macbecin I:

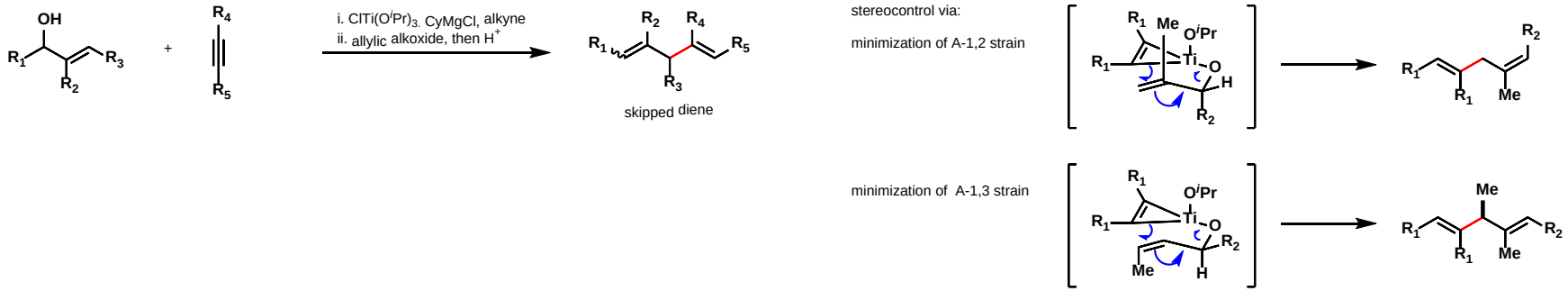


macbecin I

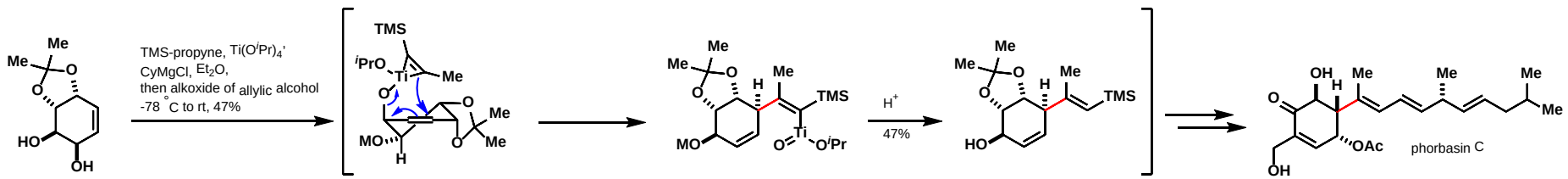
[1] Micalizio *et al. Angew. Chem. Int. Ed.* **2007**, 46, 1440–1443
[2] Micalizio *et al. Angew. Chem. Int. Ed.* **2008**, 47, 4005–4008

4 Deoxygenative Alkylation of Allylic Alcohols

4.1 General Mechanism [1]



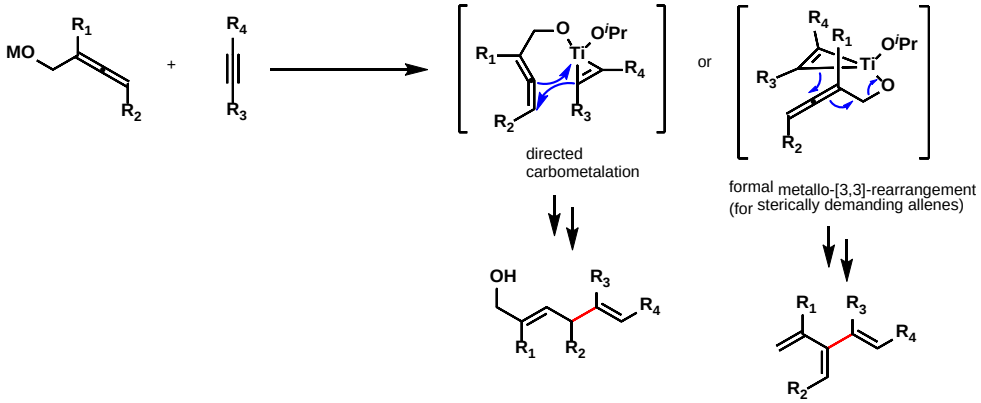
4.2 Application in the Synthesis of (+)-Phorbasin C [2]



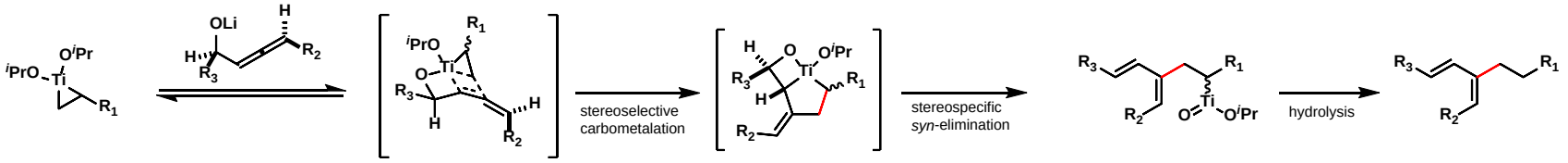
[1] Micalizio *et al. J. Am. Chem. Soc.* **2007**, 129, 49, 15112–15113
[2] Micalizio *et al. J. Am. Chem. Soc.* 2009, 131, 4, 1392–1393

5 Reaction of Allenes with Alkynes and Alkenes in Ti-mediates cross-couplings

5.1 Allenyl Alcohol-Alkyne Cross-Coupling for Stereoselective Synthesis of 1,4-dienes



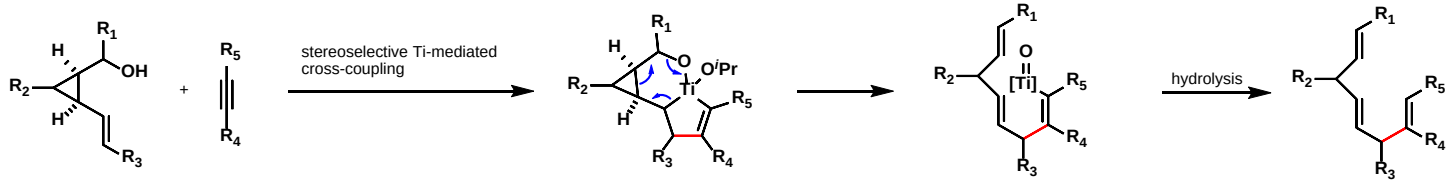
5.2 Allenyl Alcohol-Alkene Cross-Coupling



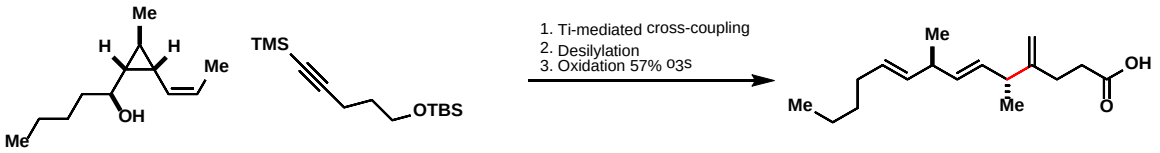
[1] Micalizio *et al. Chem. Commun.* **2007**, 43, 4531-4533
[2] Micalizio *et al. Tetrahedron* ***2010***, 66 4775–4783

6 Preparation of Skipped Polyenes by Alkyne-Alkene Coupling and Vinylcyclopropane Opening

6.1 General Mechanism



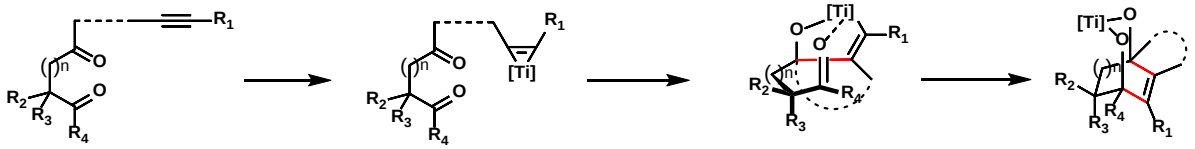
5.2 Application in the Synthesis of Polyunsaturated Fatty Acids



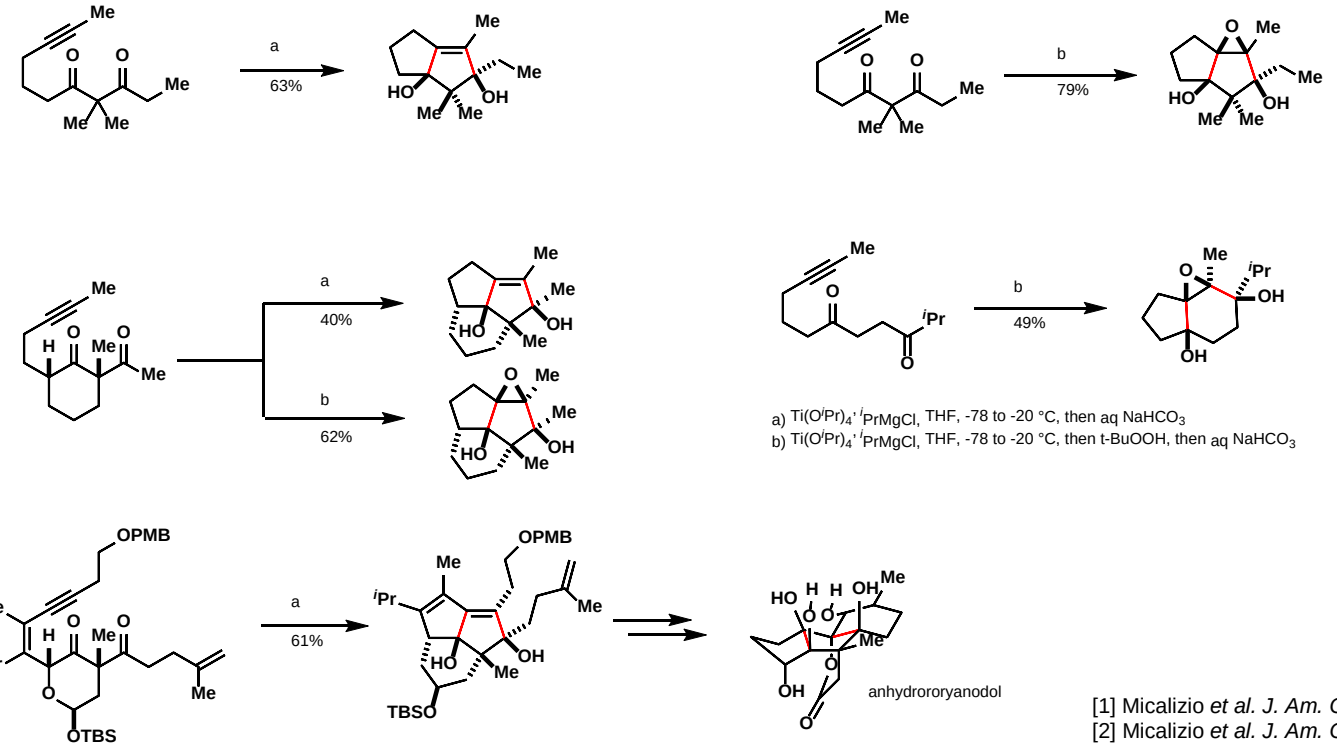
Micalizio *et al. Nature Chem.* **2010**, 2, 638–643

7 Annulative Coupling of Alkynes and 1,3 and 1,4 Diketones

7.1 General Mechanism



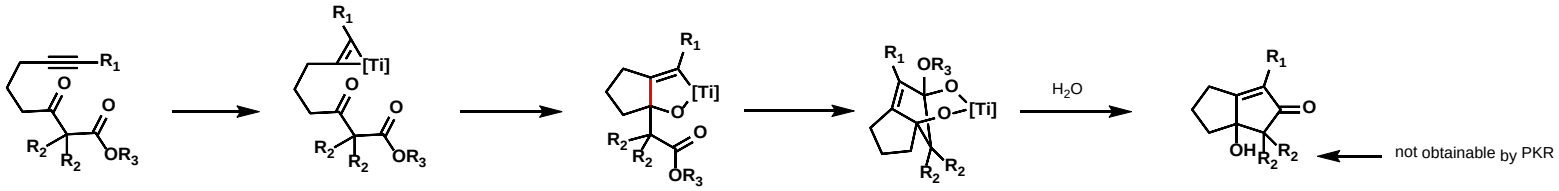
7.2 Synthetic Examples [1],[2]



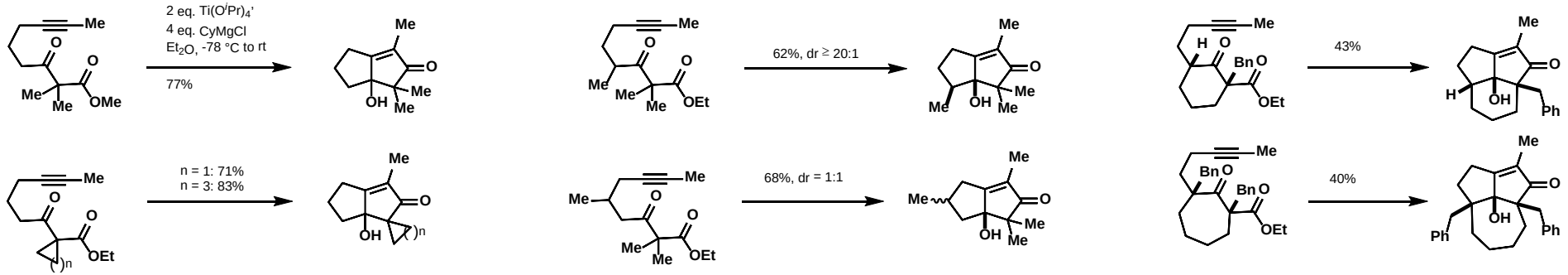
[1] Micalizio *et al. J. Am. Chem. Soc.* **2017**, 139, 36, 12374–12377
[2] Micalizio *et al. J. Am. Chem. Soc.* **2020**, 142, 30, 12937–12941

7.3 Extension to Keto-Esters – a Pauson-Khand Alternative

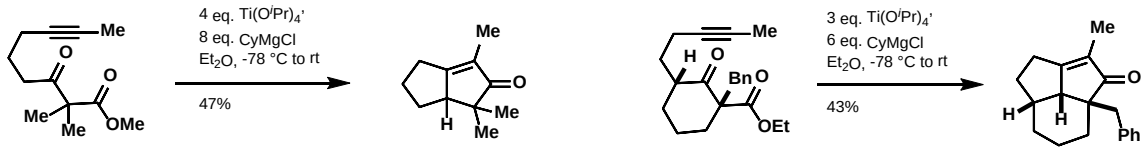
Mechanism:



Examples



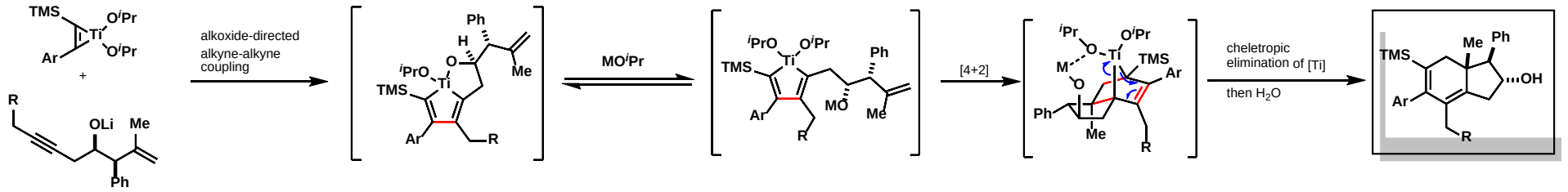
Interesting Side Reaction – Deoxygenation under the Reaction Conditions:



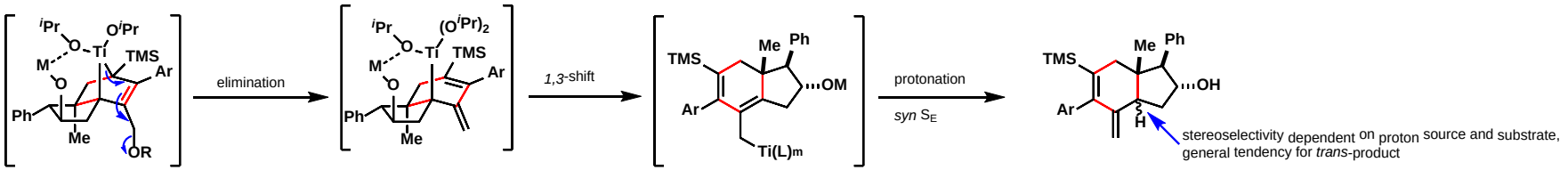
Micalizio *et al. Org. Lett.* **2019**, 21, 2, 567–570

8 Annulative Ti-mediated Coupling of Alkynes and Alkenes – [2+2+2]-Annulation

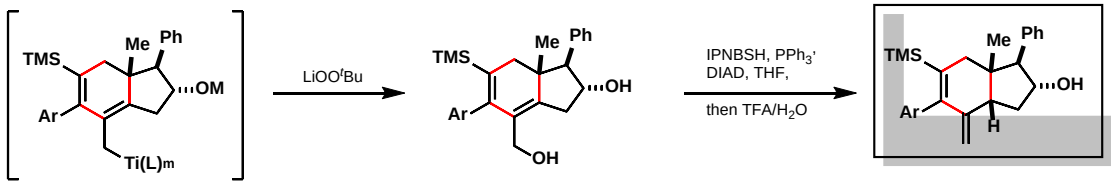
8.1 General Mechanism & Potentially Usable Side-Reactions



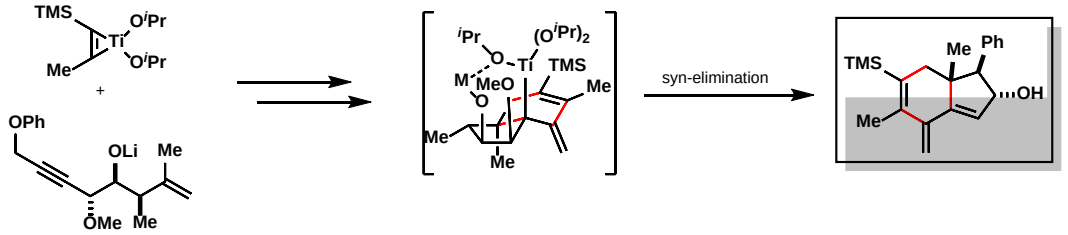
If R = OAr:



If R = OAr, trapping with LiOO^{t}Bu:



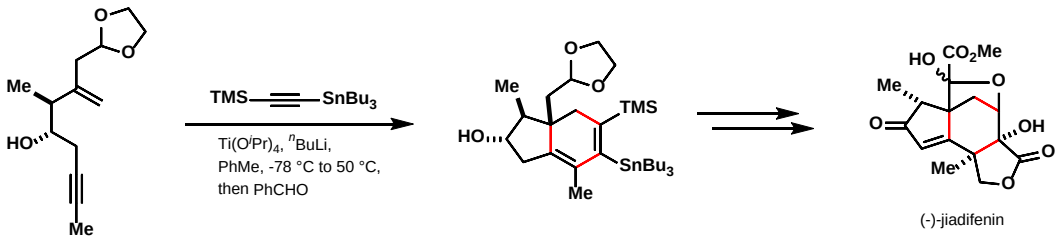
With additional LG:



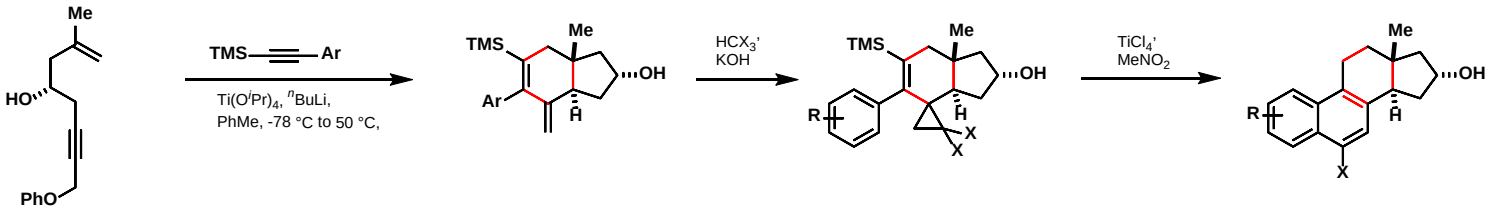
[1] Micalizio *et al. J. Am. Chem. Soc.* **2012**, 134, 2766–2774
[2] Micalizio *et al. J. Am. Chem. Soc.* **2012**, 134, 5, 2766–2774
[3] Micalizio *et al. Tet. Lett.* ***2015***, *56,* 3557 – 3559
[4] Micalizio *et al. Org. Lett.* **2014**, 16, 19, 5144–5147

8.2 Application in Total Synthesis

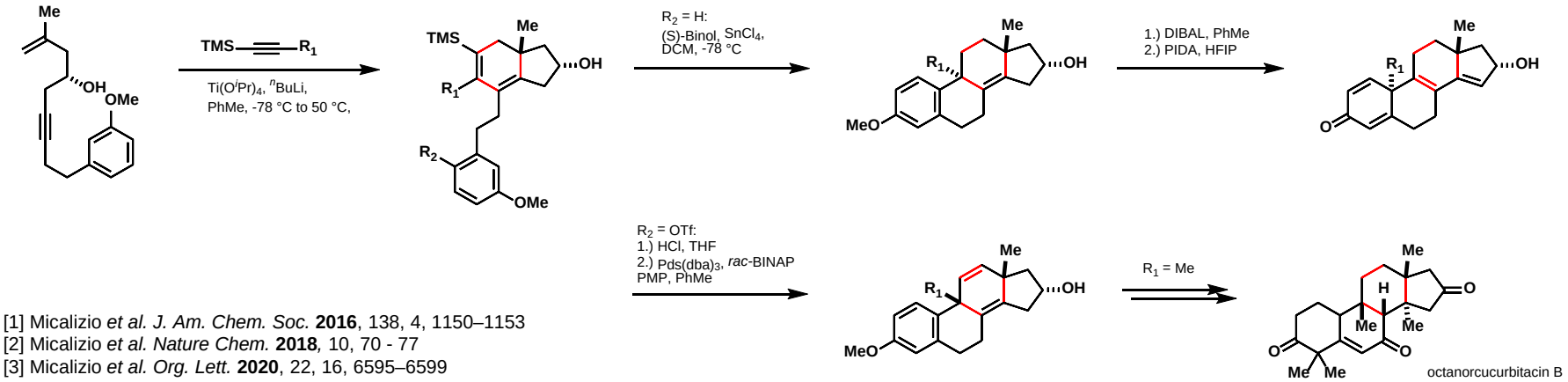
Total Synthesis of Jiadifenin[1]:



Synthesis of *nat*- and ent-Steroids and Derivatives[2]:

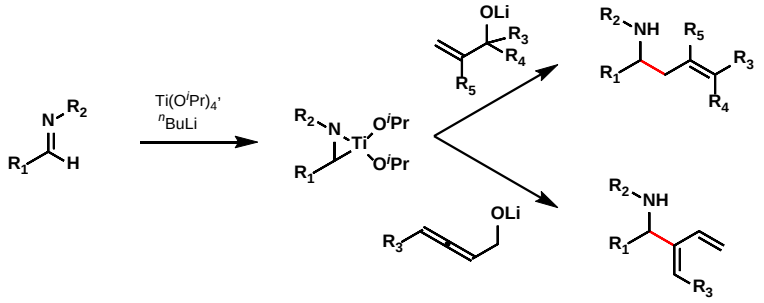


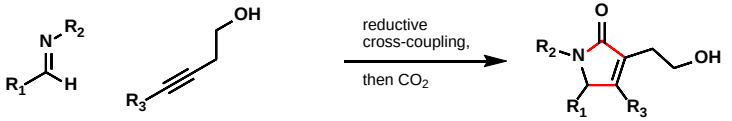
Synthesis of Different Tetracyclic Steroidal Skeletons, Total Synthesis of Octanorcucurbitacin B[3],[4]:

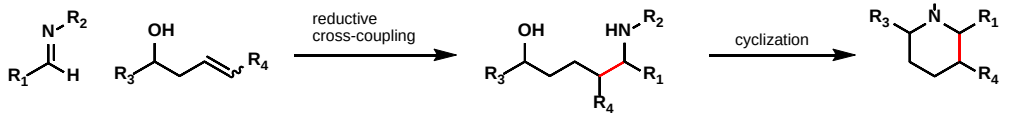


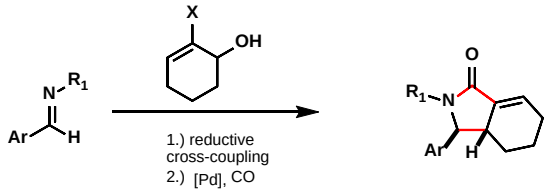
[1] Micalizio *et al. J. Am. Chem. Soc.* **2016**, 138, 4, 1150–1153
[2] Micalizio *et al. Nature Chem.* **2018**, 10, 70 - 77
[3] Micalizio *et al. Org. Lett.* **2020**, 22, 16, 6595–6599
[4] Micalizio *et al. J. Am. Chem. Soc.* **2022**, 144, 19, 8493–8497

8 Not covered in this talk – Reductive Cross-Couplings Using Imine-Complexes









[1] Micalizio *et al. Org. Lett.* **2009**, 11, 20, 4596–4599
[2] Micalizio *et al. Angew. Chem. Int. Ed.* **2007**, 46, 3912 –3914
[3] Micalizio *et al. J. Am. Chem. Soc.* **2007**, 129, 24, 7514–7516
[4] Micalizio *et al. Org. Lett.* **2009**, 11, 23, 5402–5405