Recent Advances in the use of Silicon Tethers in Metal-Mediated Reactions

Literature Review
20th November 2009

Sonia Bracegirdle

Overview

1. Introduction
2. Common methods for incorporating a tether
3. Application in metal-mediated reactions
    i. Metathesis
    ii. Cross-coupling and Heck chemistry
    iii. Cycloadditions
    iv. Hydrosilylation and carbosilylation
    v. Allylation
    vi. Other reactions
4. Removal and use of silicon-tethered products

Introduction

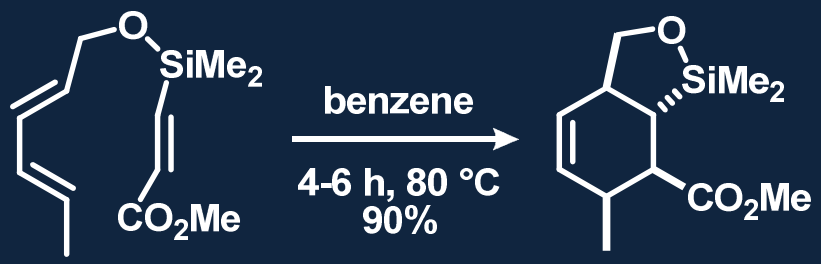
- A reaction can be made intramolecular through the use of a tether:

INTERMOLECULAR

INTRAMOLECULAR

Introduction

- What are the benefits of intramolecularity?
  - ➢ A considerable rate increase is observed over the intermolecular system
    - – Proximity effects give a higher effective concentration of the reacting partners
    - – Lower activation entropy
  - ➢ Greater regio- and stereoselectivity due to increased conformational restriction in the TS

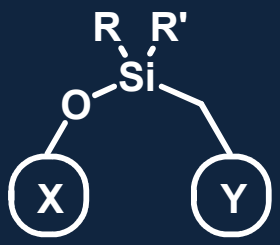


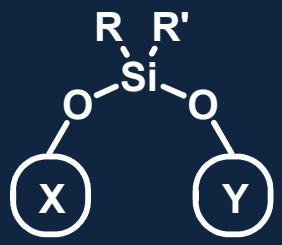
1. Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578

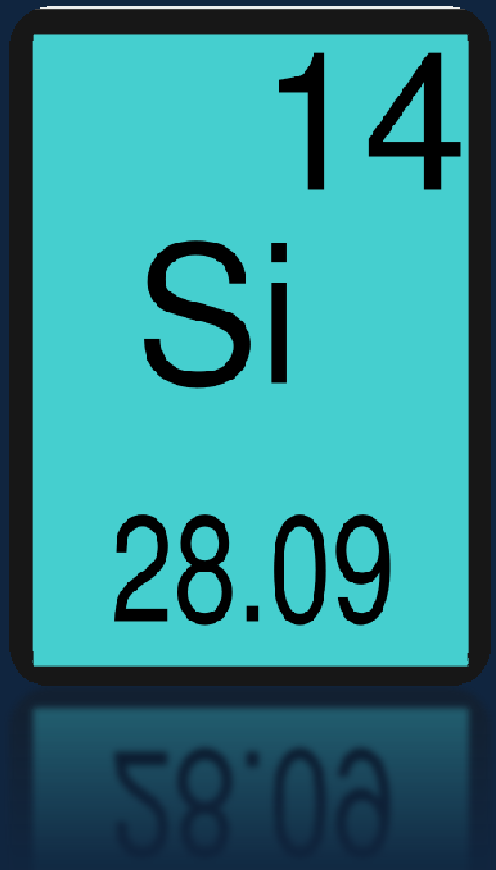
Introduction

- Important properties of a tether:
  - ➢ Readily introduced in high yields
  - ➢ Stable to the reaction conditions
  - ➢ Easily removed or functionalised – incorporates latent functionality

- Silicon is ideal for this purpose – the siloxane or disiloxane linkers are the most common







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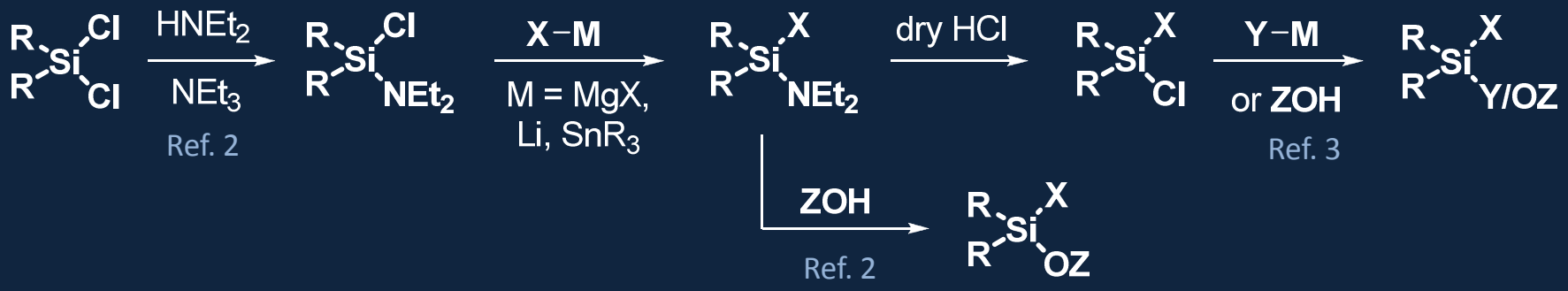
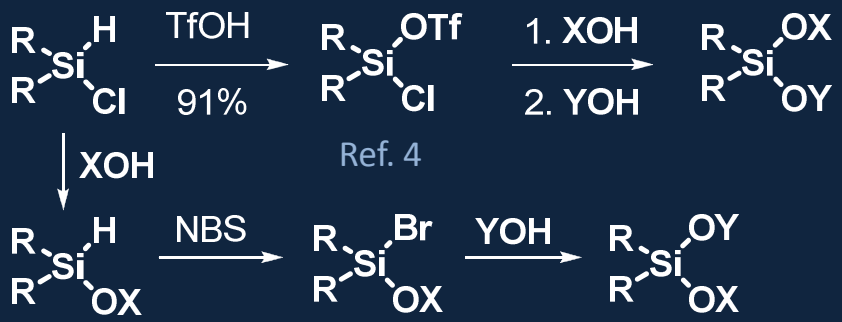
Silicon tether incorporation

FROM $ClSiR_2(NEt)_2$:



FROM $ClSiR_2H$:



- There are a number of further methods for the facile incorporation of silicon tethers

2. Tamao, K.; Nakajo, E.; Ito, Y. *Tetrahedron* **1988**, *44*, 3997
3. Stork, G.; Keitz, P. F. *Tetrahedron Lett.* **1989**, *30*, 6981
4. Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145; Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 2037

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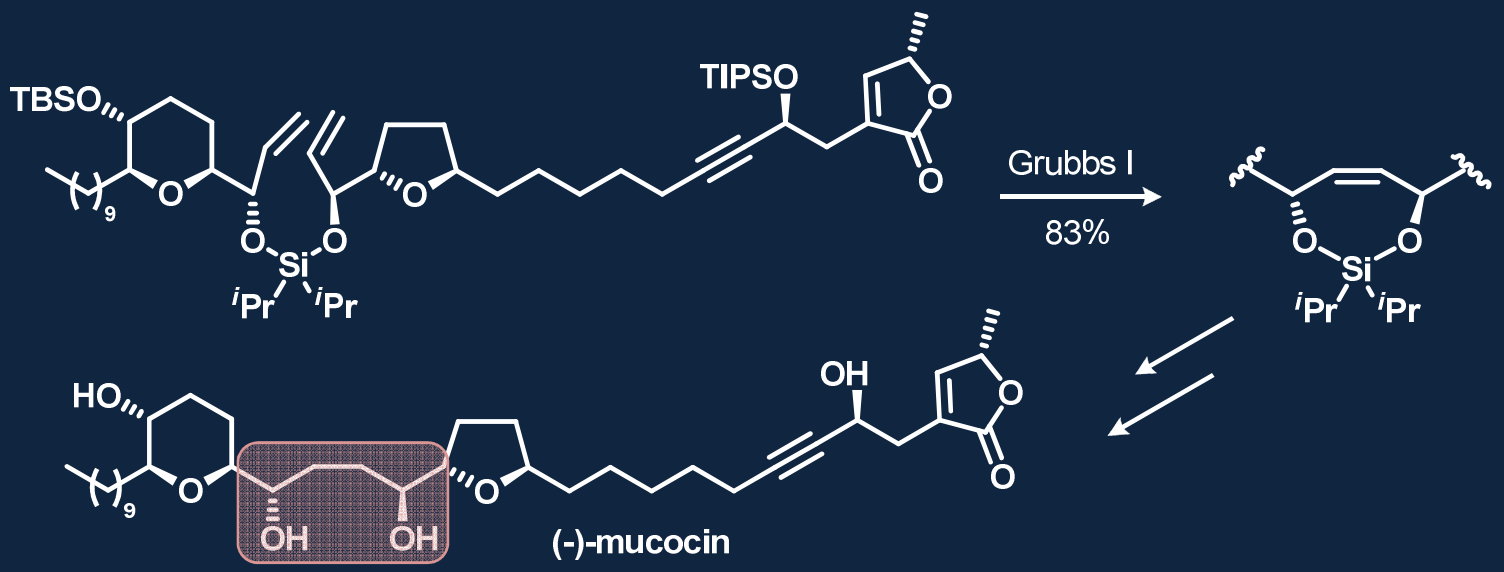
Use in metal-mediated reactions

METATHESIS

- The use of silicon tethers allows a cross-metathesis reaction to become a ring closing metathesis, enhancing selectivity, efficiency and yield
- Silicon-tethered RCM is a well-established strategy, but has only recently been applied to natural product synthesis[5]

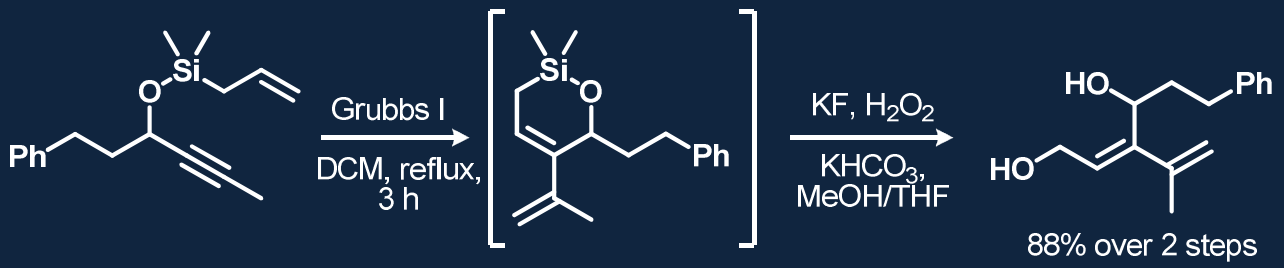


5. Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125,* 14702

Use in metal-mediated reactions

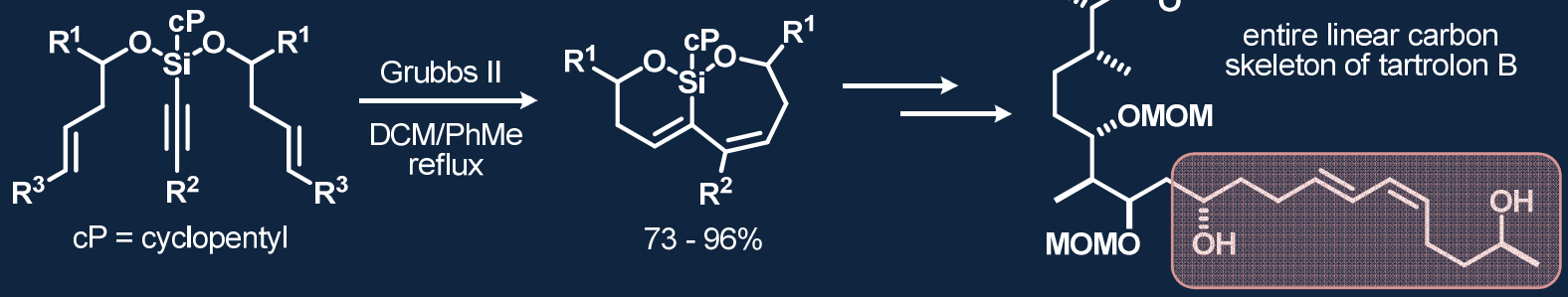
METATHESIS

- Silicon tethers have also been applied to other forms of RCM, namely enyne[6] and dienyne[7] metathesis



Enyne RCM – a trisubstituted double bond is readily formed

Dienyne RCM



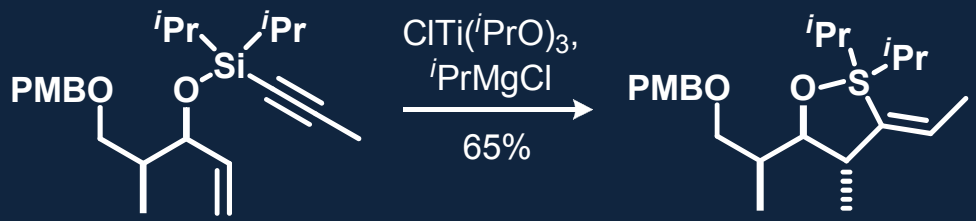
6. Yao, Q. *Org. Lett.* **2001**, *3,* 2069

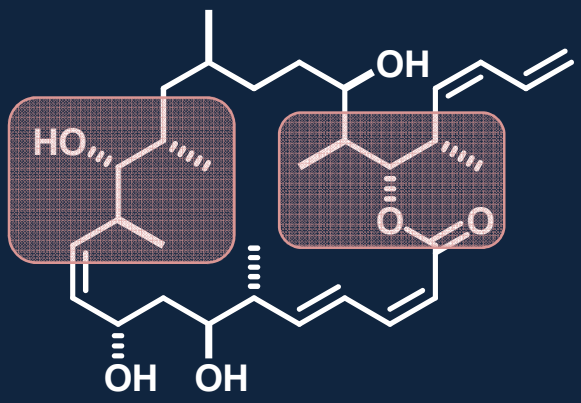
7. Grimm, J. B.; Otte, R. D.; Lee, D. *J. Organomet. Chem.* **2005**, *690,* 5508; Kim, Y. J; Lee, D. *Org. Lett.* **2006**, *8,* 5219

Use in metal-mediated reactions

METATHESIS

- The Phillips group have developed a novel Ti(II)-mediated enyne cyclization, and subsequently applied it to the total synthesis of dictyostatin[8]





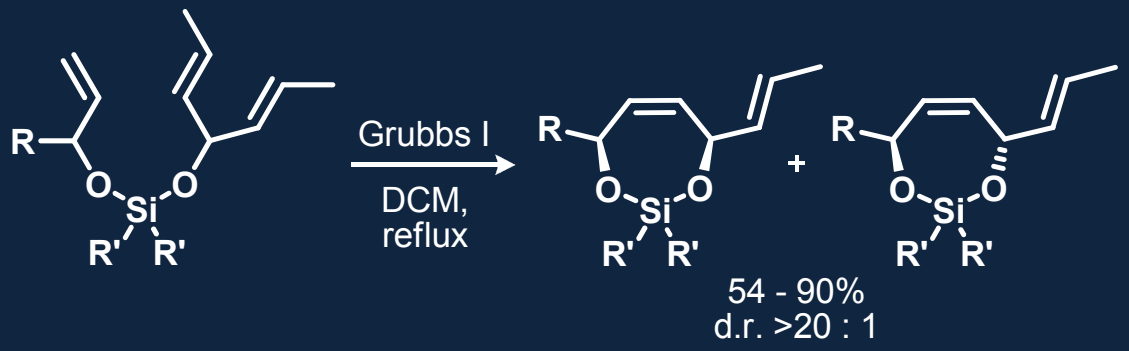
- The reaction produces only the *anti*-diastereomer
- The active species (non-catalytic) is (η^2-propene)Ti(^{i}PrO)$_2$, generated *in situ*

8. O'Neil, G. W.; Phillips, A. J. *Tetrahedron Lett.* **2004**, *45*, 4253; O'Neil, G. W.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 5340

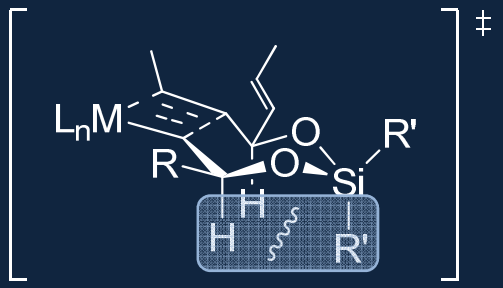
Use in metal-mediated reactions

METATHESIS

- A tethering approach can be used to induce long-range asymmetric selectivity in a metathesis process[9]



Favoured TS



Cis selectivity is observed – steric clashing is minimised in the favoured transition state

9. Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734

Use in metal-mediated reactions

METATHESIS

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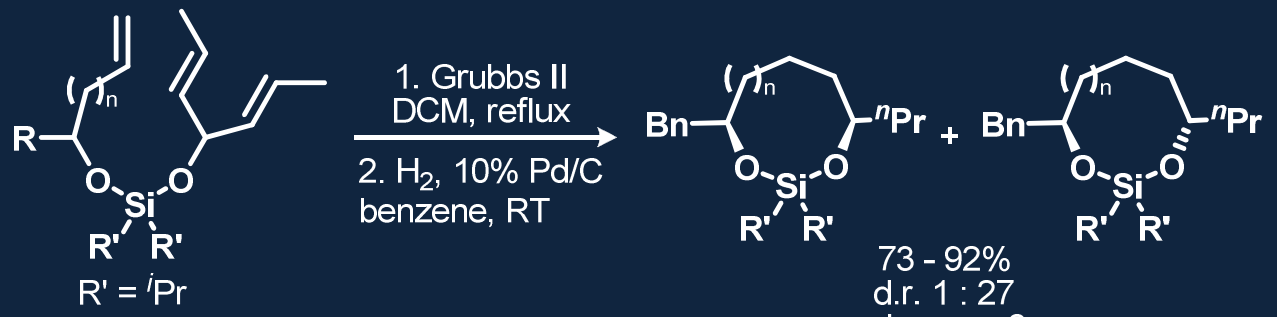
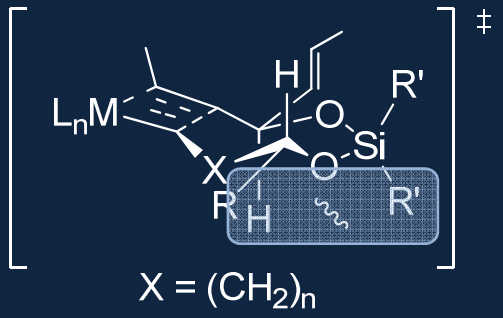


Favoured TS



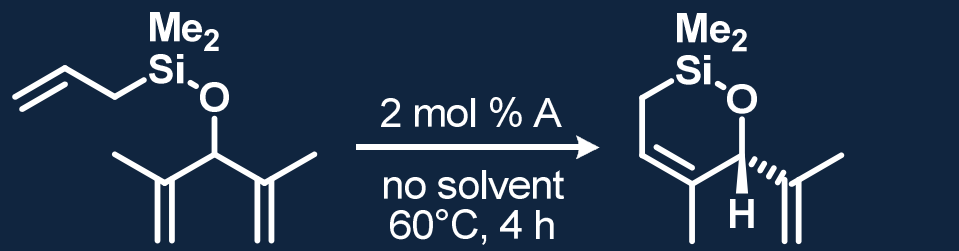
Trans selectivity is observed – the extra linkers give a different transition state structure

9. Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734

Use in metal-mediated reactions

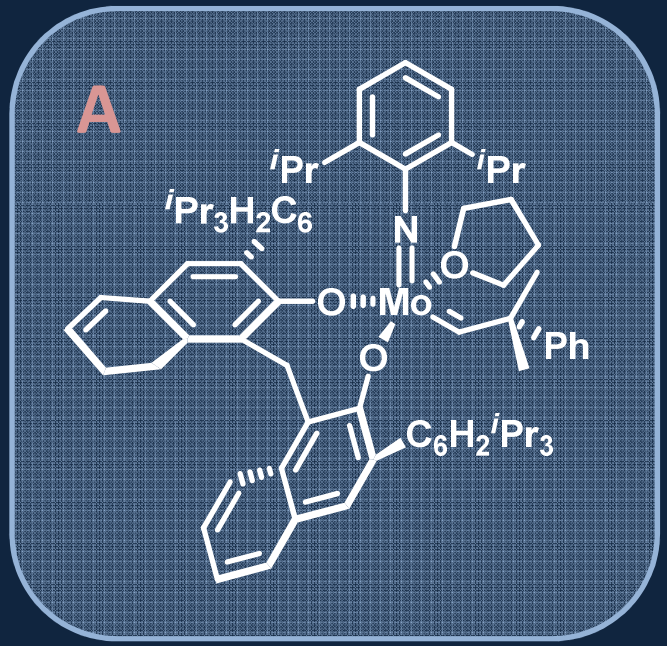
METATHESIS

- Desymmetrisation may also be achieved through a silicon-tethered RCM approach, using a chiral molybdenum complex[10]



>98% ee, 98% yield

Molybdenum-catalysed asymmetric RCM utilising silicon tethers has also been applied to the synthesis of medium ring siloxanes



10. For a review, see Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42,* 4592

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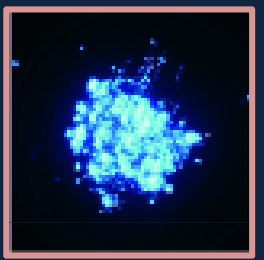
Use in metal-mediated reactions

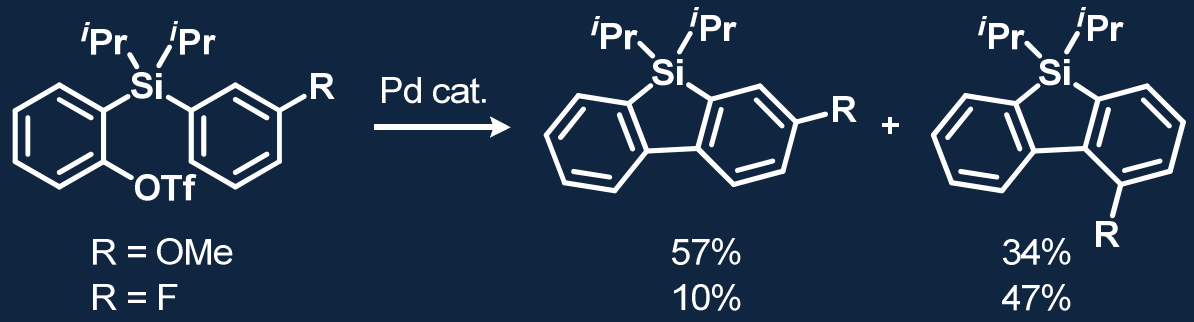
Pd-CATALYSED COUPLING

- Silicon-bridged biaryls can be approached via a direct intramolecular coupling – some of the resulting products display photoluminescent properties[11]

bulky substitutents increase yield through the Thorpe-Ingold and *gem*-dialkyl effects



- Regioselectivity studies were also carried out:



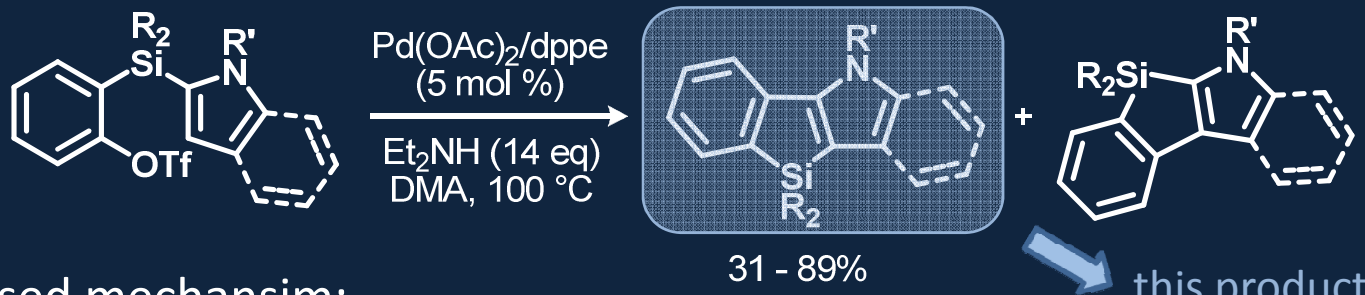
Heteroaromatic biaryl couplings could be achieved *via* this methodology

11. Shimizu, M.; Mochida, K.; Hiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 9760

Use in metal-mediated reactions

Pd-CATALYSED COUPLING

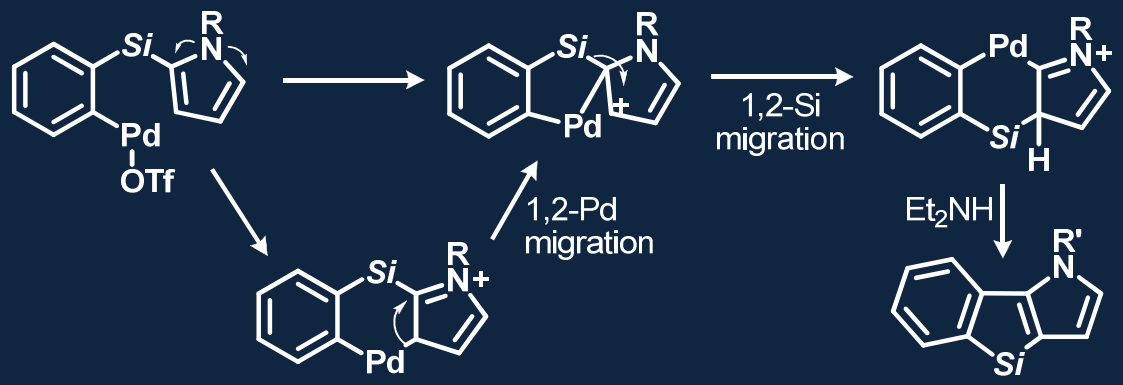
- Further work by the Hiyama group found that regioisomeric silicon-bridged biaryls could be synthesised when coupling with indole or pyrrole-based systems[12]



31 - 89%

this product is favoured when using Et_2NH in large excess

- Proposed mechansim:



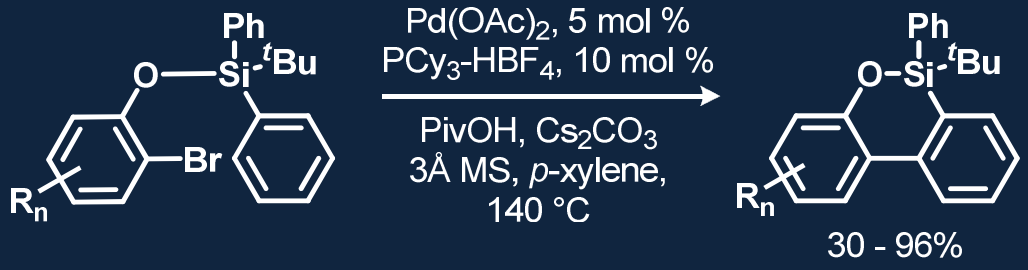
A 1,2-silicon migration was proposed to explain the selectivity observed

12. Mochida, K.; Shimizu, M.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 8350

Use in metal-mediated reactions

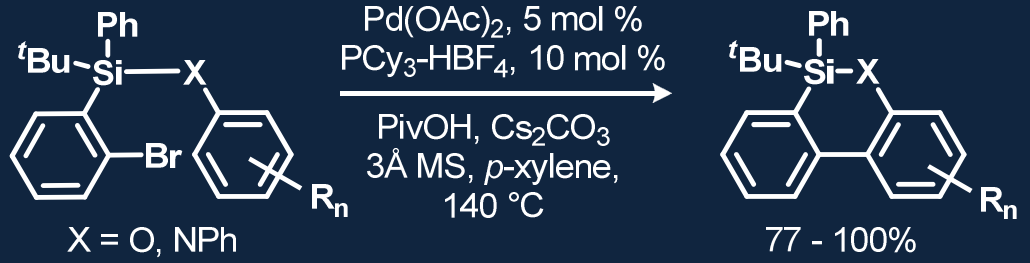
Pd-CATALYSED COUPLING

- A temporary silicon connection method has been used in intramolecular C-H arylation reactions[13]



The reactivity and regioselectivity is improved over intermolecular C-H arylation processes

- The position of the bromine can be moved to allow arylation of simple phenols and anilines

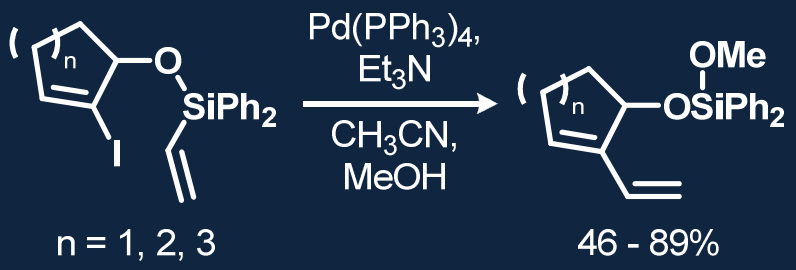


13. Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2009**, *131*, 10844

Use in metal-mediated reactions

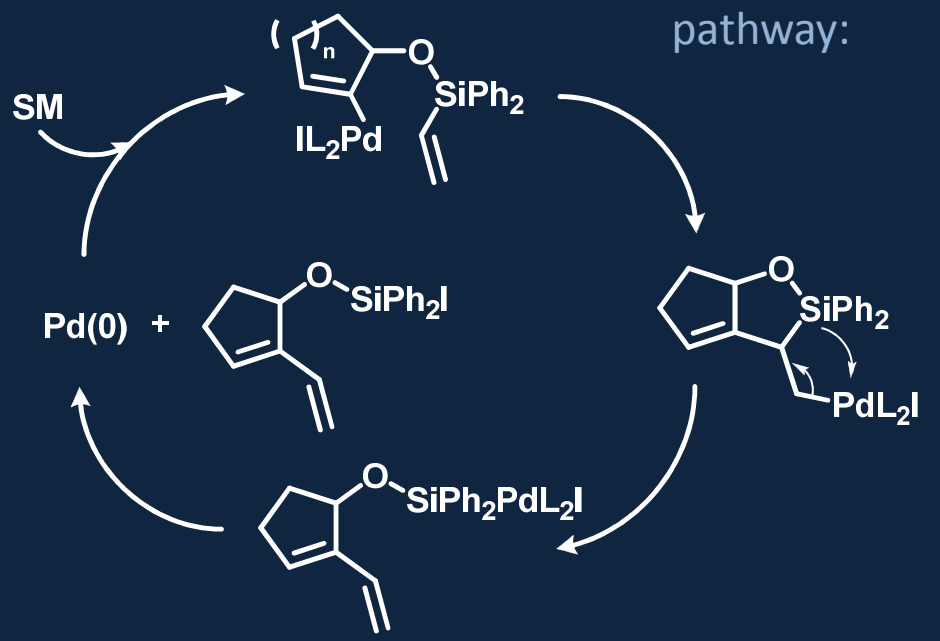
Pd-CATALYSED COUPLING

- The Young group has developed a silicon-tethered Heck reaction, allowing a vinyl substituent to be readily attached to a 5, 6 or 7-membered ring[14]



- the yield is lowest for the seven-membered system
- the proposed mechansim involves a β-silyl elimination step

Proposed pathway:



14. Mayasundari, A.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 203

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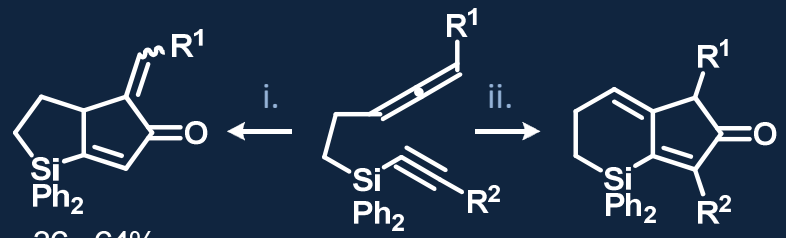
Use in metal-mediated reactions

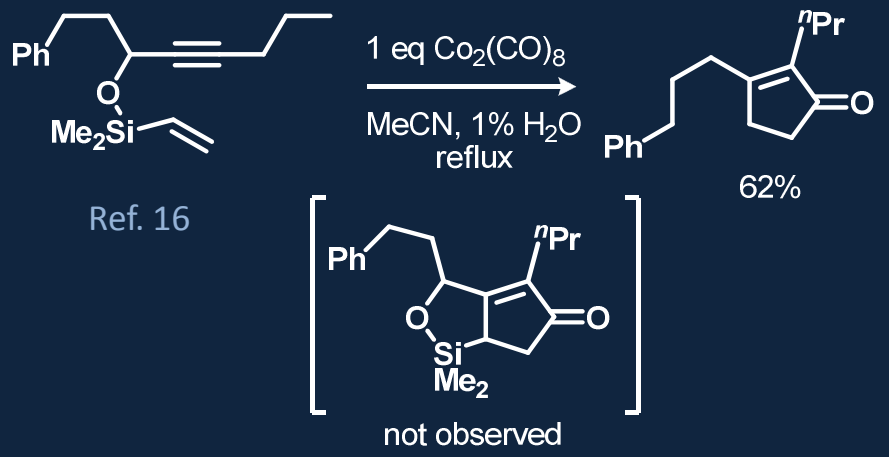
CYCLOADDITIONS

- Silicon tethers have had some use in cyclocarbonylation processes, such as the Pauson-Khand reaction



i. 1.2 eq $Mo(CO)_6$, DMSO, PhMe, 90 °C; ii. 5 mol % $[Rh(CO)_2Cl]_2$, CO (1 atm), PhMe, 90 90 °C

Only limited success was achieved with silyl ether tethers and non-allenic systems



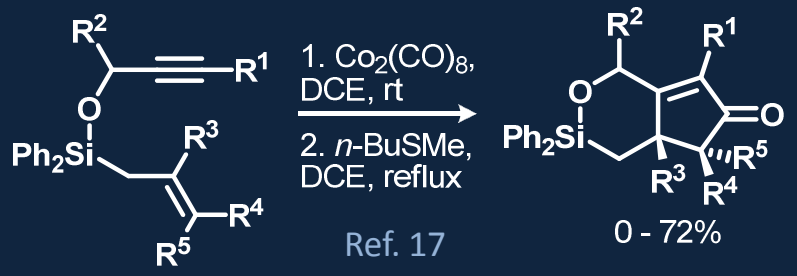
In most examples, reduction of the propargylic alcohol was observed under the reaction conditions

15. Brummond, K. M.; Sill, P. C.; Rickards, B.; Geib, S. J. *Tetrahedron Lett.* **2002**, *43*, 3735
16. Reichwein, J. F.; Iacono, S. T.; Patel, M. C.; Pagenkopf, B. L *Tetrahedron Lett.* **2002**, *43*, 3739

Use in metal-mediated reactions

CYCLOADDITIONS

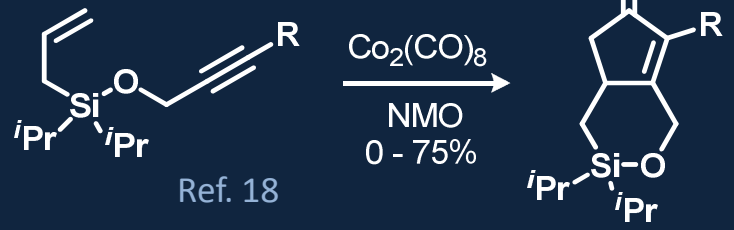
- Further attempts at applying a silicon-tethering concept to the Pauson-Khand reaction have had limited success



Ref. 17

0 - 72%

The substrate scope for this process is very limited, with most substitution patterns returning starting material



Ref. 18

The substrate scope for this variation is also limited

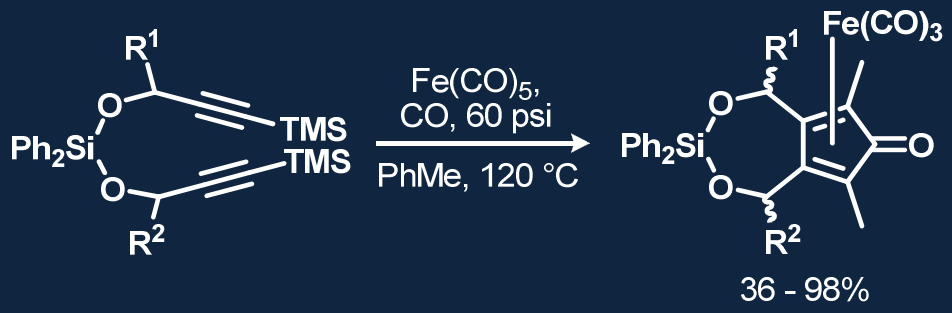
Silicon tether methodology has not yet been effectively applied to the intramolecular P-K reaction

17. Ishaq, S.; Porter, M. J. *Synthetic Communications*, **2006**, *36*, 547
18. Dobbs, A. P.; Miller, I. J.; Martinovic, S. *Beilstein J. Org. Chem.* **2007**, *3*, No. 21

Use in metal-mediated reactions

CYCLOADDITIONS

- Silicon tethering has been applied to another cyclocarbonylation process, mediated by $Fe(CO)_5$ in this instance[19]



Tethering allows heterocoupling of two alkynes – only homocoupling has been reported in the intermolecular case

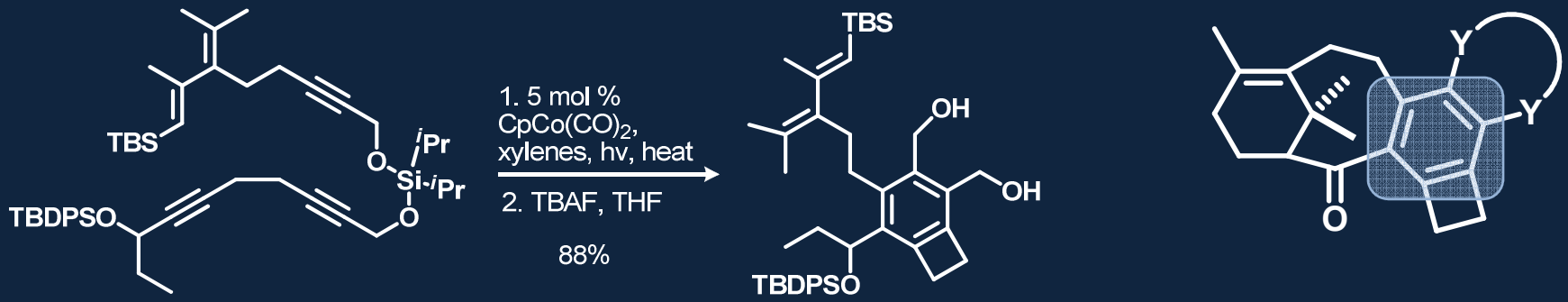
- In a similar fashion, the regio- and chemoselectivity of the cobalt-mediated [2+2+2] cyclotrimerisation can be enhanced through the use of a temporary silicon tether[20]

19. Pearson, A. J.; Kim, J. B. *Org. Lett.* **2002**, *4,* 2837
20. For a review, see Gandon, V.; Aubert, C.; Malcria, M. *ChemComm.* **2006**, 2209

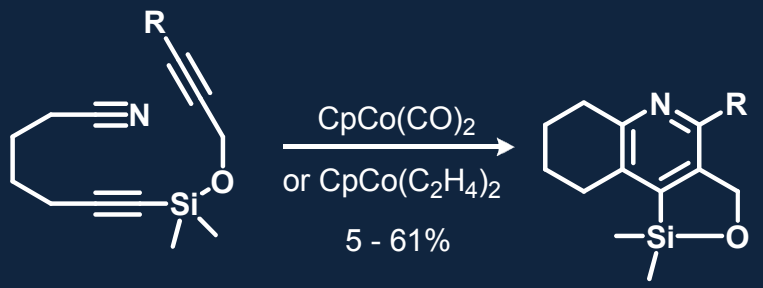
Use in metal-mediated reactions

CYCLOADDITIONS

- The Malacria group have carried out extensive research into the cyclotrimerisation of silicon-tethered alkynes,[21] and have applied this work to the synthesis of the taxane framework[22]



- Tetrahydroquinolines may also be synthesised using similar methodology[23]

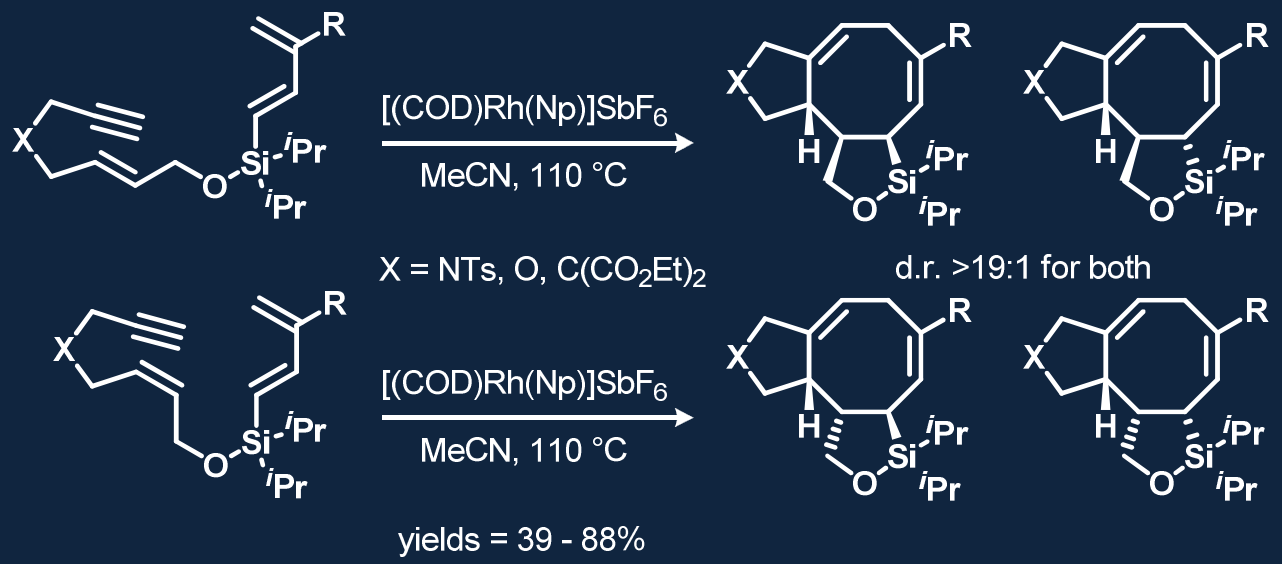


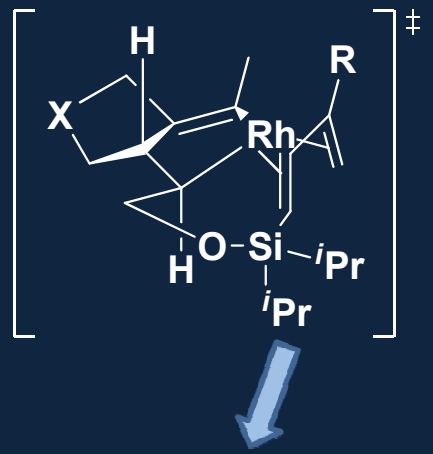
21. Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6,* 1519
22. Chouraqui, G.; Petit, M.; Phansavath, P.; Aubert, C.; Malacria, M. *Eur. J. Org. Chem.* **2006**, 1413
23. Groth, U.; Huhn, T.; Kesenheimer, C.; Kalogerakis, A. *Synlett* **2005**, *11,* 1758

Use in metal-mediated reactions

CYCLOADDITIONS

- A tethering approach has allowed the regioselectivity and reactivity of the rhodium-catalysed [4+2+2] cycloisomerisation reaction to be enhanced[24]





No clashing between the diene and the ^{i}Pr groups in the favoured TS

24. Evans, P. A.; Baum, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 11150

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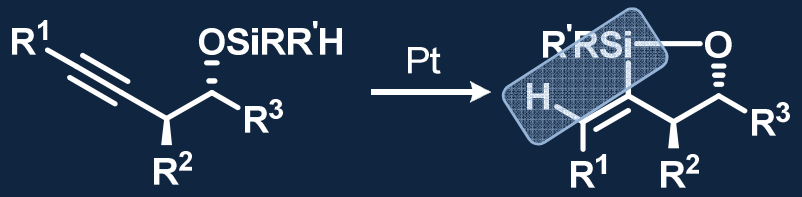
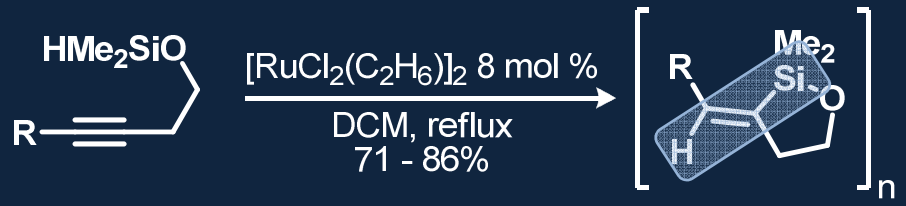
Use in metal-mediated reactions

SILYLATION REACTIONS

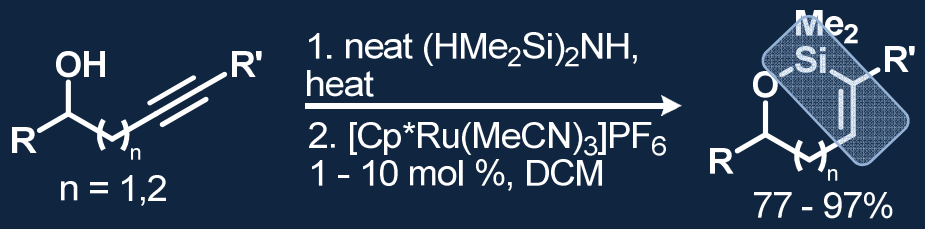
- A number of groups have reported the development of silicon-tethered hydrosilylation reactions, the selectivity of which is dependent upon the catalyst used



When a platinum catalyst is used, syn hydrosilylation is observed[25]



Denmark has found that ruthenium will give the anti exo-dig product[26] – product oligomerisation occurs



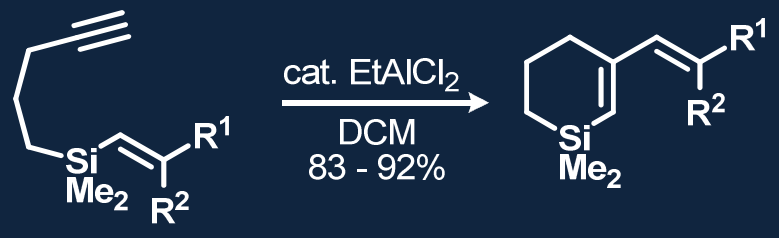
In contrast, Trost has found that a different Ru catalyst will give the endo-dig product[27]

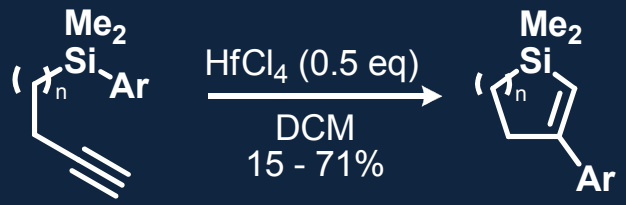
25. Tamao, K.; Maeda, K; Tanaka, T.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 6955; Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173; Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61; Denmark, S. E.; Pan, W. *Org. Lett.* **2003**, *5*, 1119
26. Denmark, S. E.; Pan, W. *Org. Lett.* **2002**, *4*, 4162; Denmark, S. E.; Pan, W. *Org. Lett.* **2003**, *3*, 1119
27. Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30

Use in metal-mediated reactions

SILYLATION REACTIONS

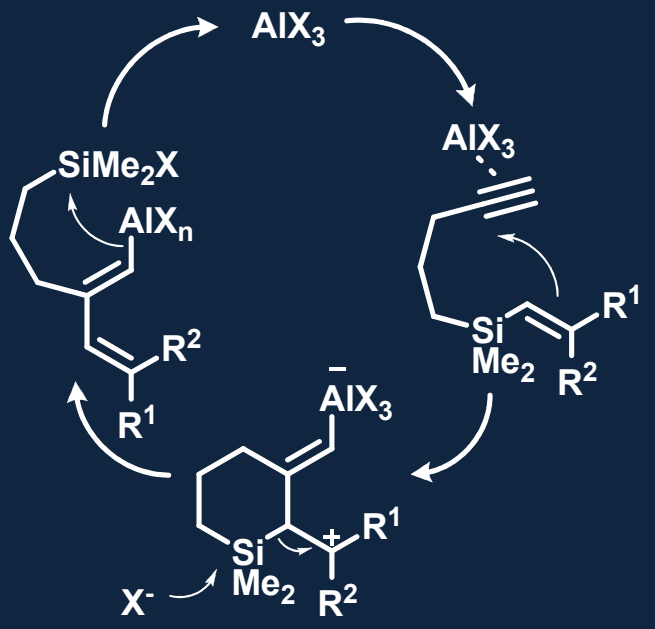
- A *trans* carbosilylation process has also been reported by the Yamamoto group[28]





Both processes utilise the ability of silicon to stabilise a β-carbocation

Mechanistic proposal:

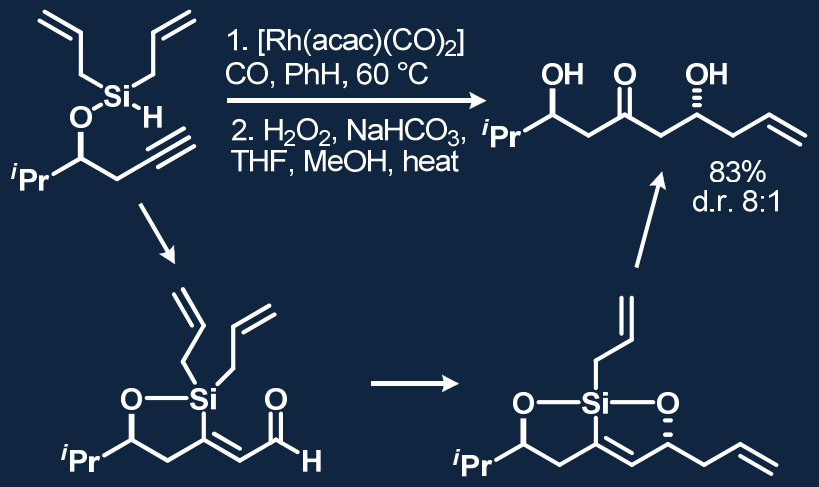


28. Asao, N.; Shimada, T.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10899

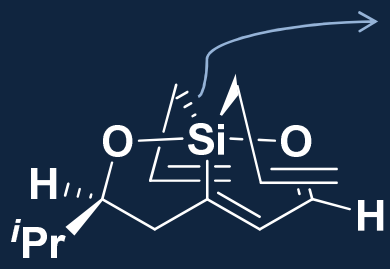
Use in metal-mediated reactions

SILYLATION REACTIONS

- Work by the Leighton group has led to the development of a tandem silylformylation-allyl/crotylsilylation of alkenes and alkynes[29]

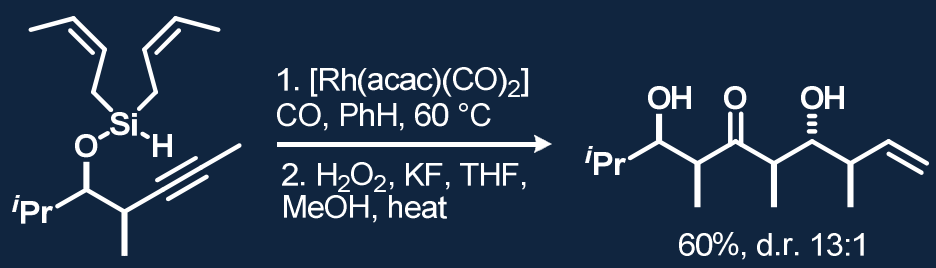


1,5-asymmetric induction is observed here



The least hindered allyl group is transferred

Polyketide-like fragments can be readily synthesised



28. Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587; O'Malley, S. J.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 2915; Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890; Spletstoser, J. T.; Zacuto, M. J.; Leighton, J. L. *Org. Lett.* **2008**, *10*, 5593

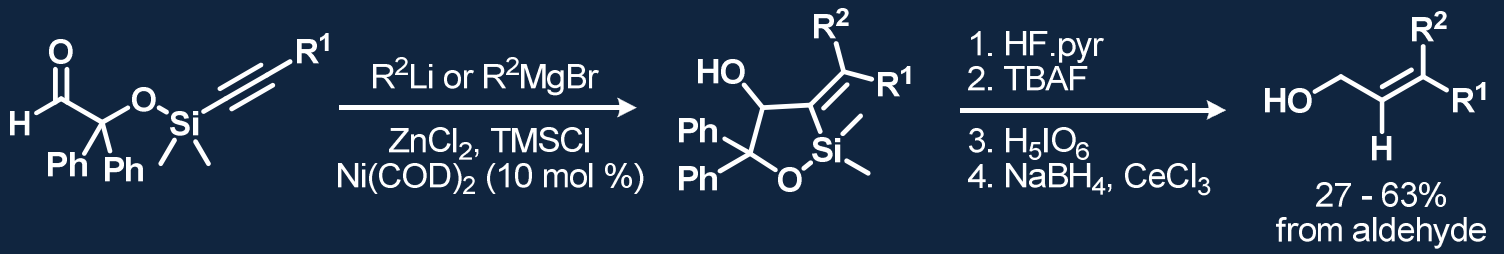
Overview

1. Introduction
2. Common methods for incorporating a tether
3. Application in metal-mediated reactions
    i. Metathesis
    ii. Cross-coupling and Heck chemistry
    iii. Cycloadditions
    iv. Hydrosilylation and carbosilylation
    v. Allylation
    vi. Other reactions
4. Removal and use of silicon-tethered products

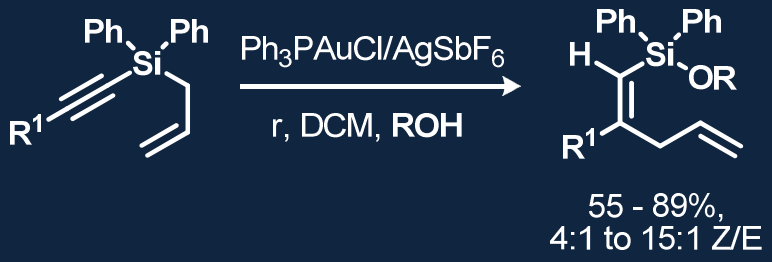
Use in metal-mediated reactions

ALLYLATION

- Several examples of allylation reactions utilising silicon tethers have been reported, allowing good levels of control over double bond geometry



Ref. 29, >95:5 E/Z selectivity



Ref. 30 – intramolecular allylation is induced by silane alcoholysis.
A wide variety of alcohol substituents are tolerated, including alkenyl and alkynyl groups.

29. Lozanov, M.; Montgomery, J. *Tetrahedron Lett.* **2001**, *42*, 3259
30. Park, S.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 10664

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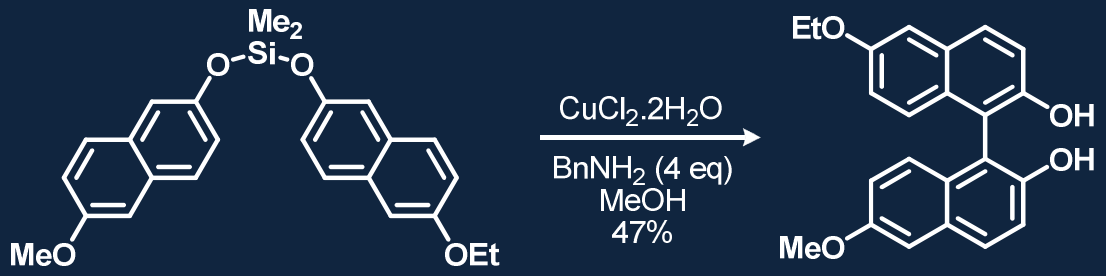
Use in metal-mediated reactions

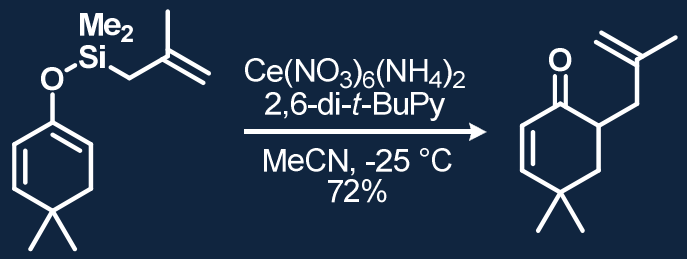
MISCELLANEOUS

- The formation of unsymmetrical binapthols has been achieved *via* silicon-tethered oxidative coupling[31]



This process is *ortho*-selective, and only the unsymmetrically coupled product is observed

- An intramolecular oxidative allylation can also be achieved[32]



The intermolecular variant of this reaction required 10 eq of silane to proceed to completion

31. Schmittel, M.; Haeuseler, A. *Z. Natruforsch*, **2003**, *58b*, 211
32. Konkol, L. C.; Jones, B. T.; Thomson, R. J. *Org. Lett.* ASAP

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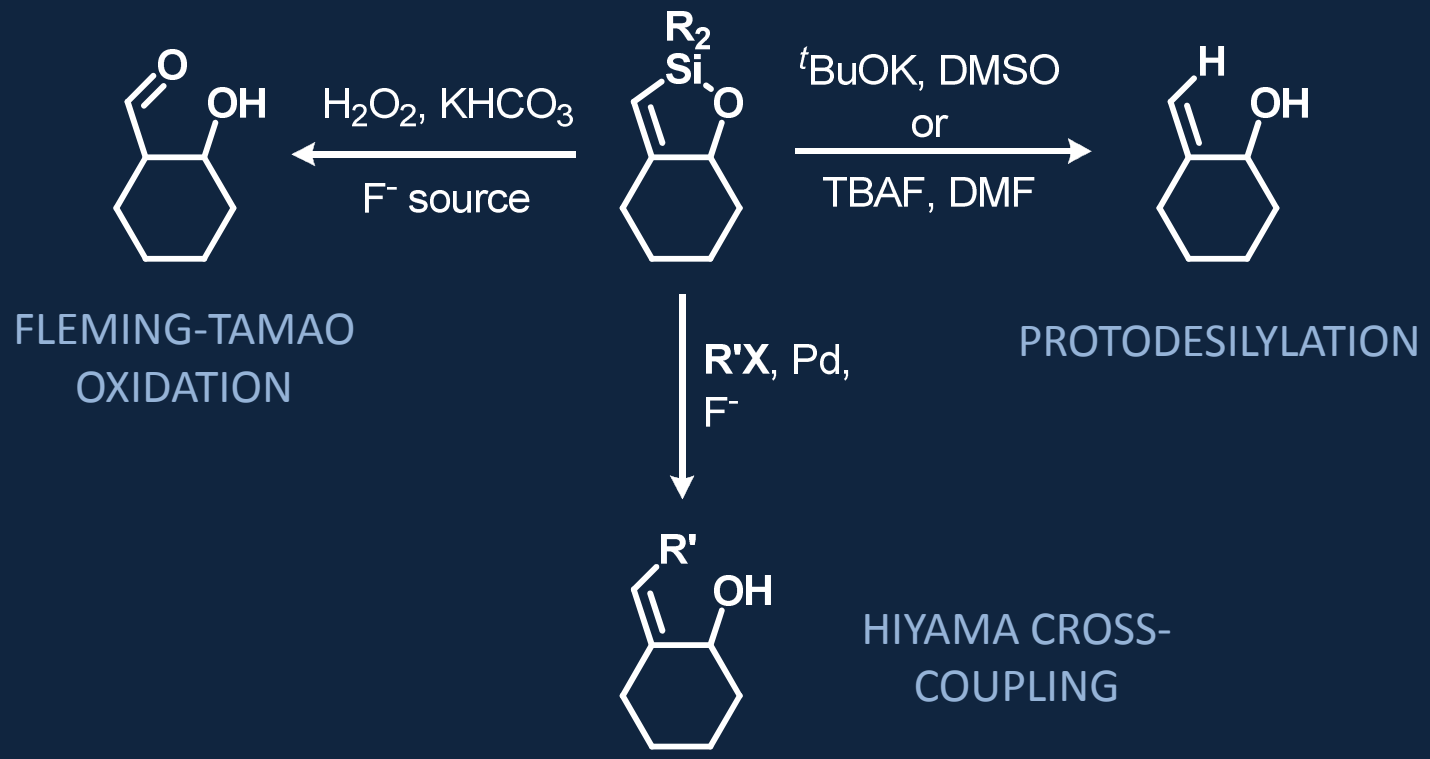
Reaction of Tethered Products

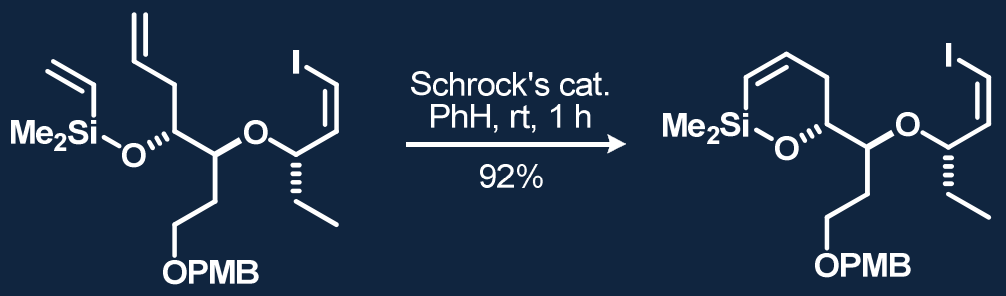


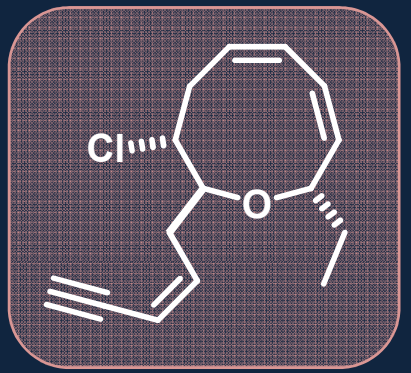
33. Fleming, I. *ChemTracts – Organic Chemistry* **1996**, *9*, 1

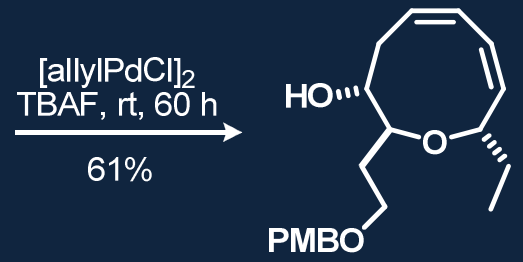
Reaction of Tethered Products

HIYAMA CROSS-COUPLING

- Denmark's synthesis of (+)-brasilenyne highlights the utility of silicon tethers, and their potential for application in total synthesis[34]







The key step in this synthesis was the use of a sequential RCM/silicon-assisted intramolecular cross-coupling process

34. Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124,* 2102; Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196; Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126,* 12432; Denmark, S. E.; Yang, S.-M. *Tetrahedron* **2004**, *60*, 9695

Acknowledgements