

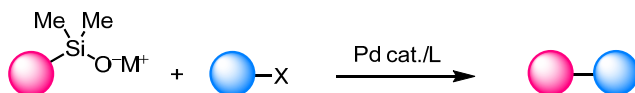
Five years in the Denmark Group

Andrea Ambrosi
July 19, 2016

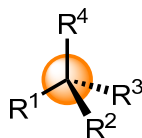


Projects

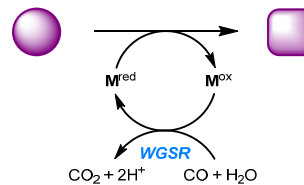
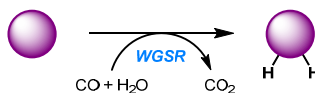
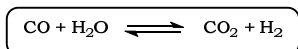
- Organosilicon cross-coupling: mechanistic studies



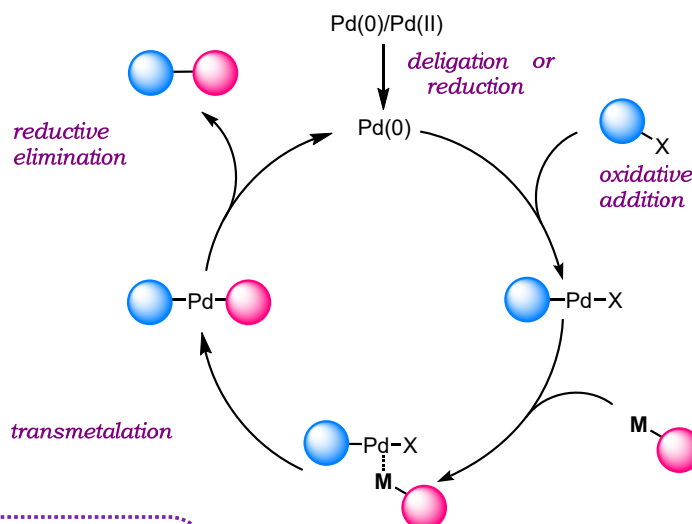
- New approaches to the enantioselective synthesis of quaternary stereocenters



- Use of the Water-Gas Shift Reaction to drive reductive processes in organic synthesis



Catalytic cycle for cross-coupling reactions

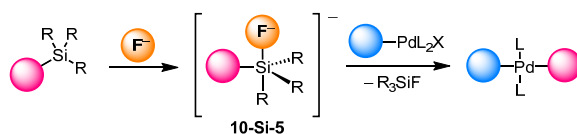


M = Mg (Kumada)
 Zn (Negishi)
 Sn (Stille)
 B (Suzuki-Miyaura)
 Si (Hiyama-Denmark)

- **Oxidative addition** and **Reductive elimination** have been studied extensively
- The **Transmetalation** step differentiates the various cross-coupling processes and is more difficult to study

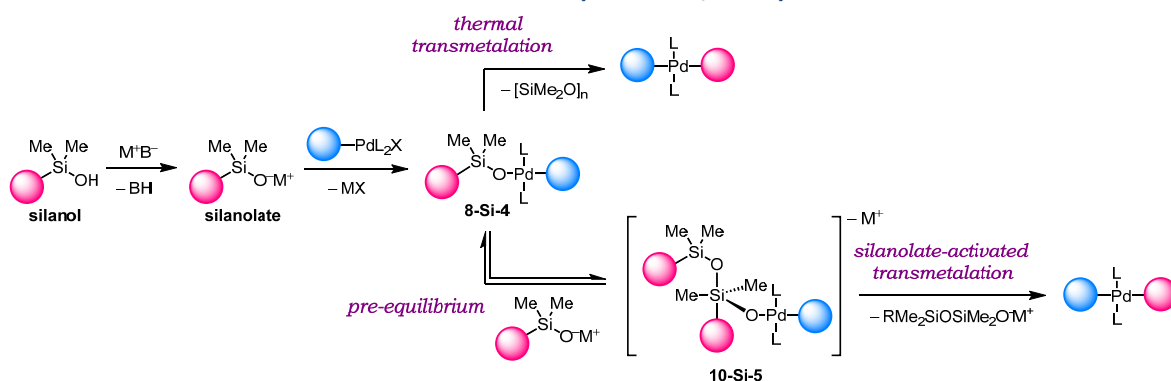
Modes of transmetalation of organosilanes

- **Fluoride-activated transmetalation (Hiyama-Hatanaka, 1988)**



Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, 53, 918

- **Brønsted base-activated transmetalation (Denmark, 2001)**

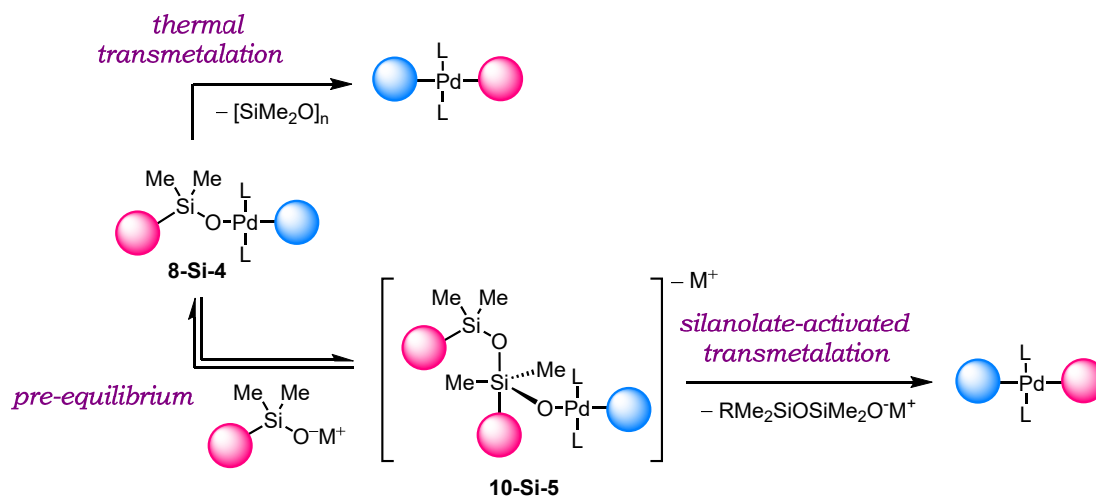


Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, 123, 6439

Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, 137, 6192

Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Ober, M. H.; Wang, H.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, 137, 6200

Modes of transmetalation of organosilanes

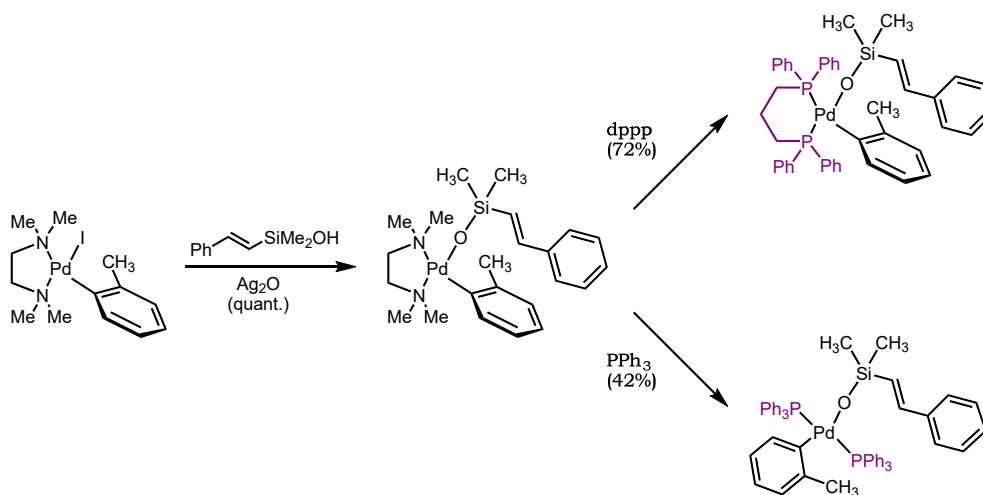


Are both modes of transmetalation viable?

Which one is preferred?

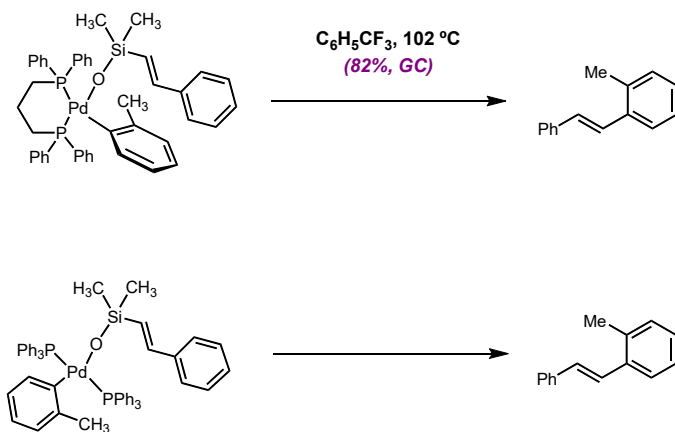
J. Am. Chem. Soc. **2015**, *137*, 6192
J. Am. Chem. Soc. **2015**, *137*, 6200

Alkenylsilanolate arylpalladium complexes



Tymonko, S. A.; Smith, R. C.

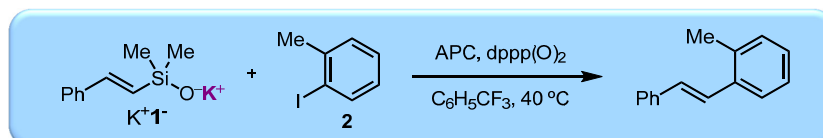
Alkenylsilanolate arylpalladium complexes



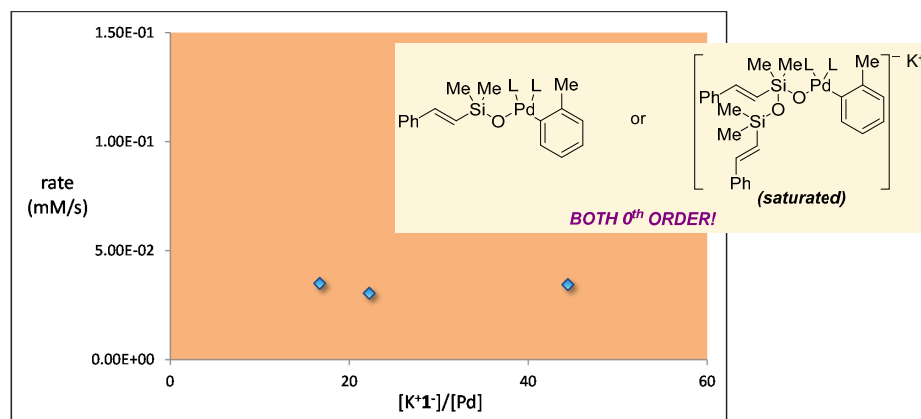
- Species with a **Si-O-Pd linkage** are **competent intermediates**
- Alkenylsilanolates are capable of **direct, thermal transmetalation**

What is the preferred transmetalation mode in the CATALYTIC reaction?

Kinetic studies – potassium silanolate



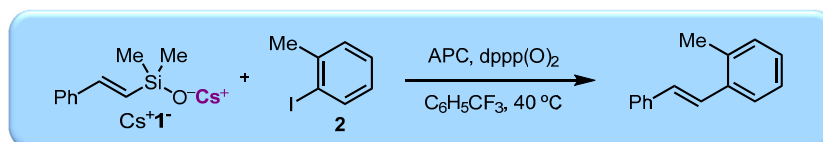
$$\text{rate} = k_{\text{obs}} [\text{K}^+\text{silanolate}]^0 [\text{Ar-I}]^0 [\text{dppp(O)}_2]^0 \quad \text{with } k_{\text{obs}} = k [\text{Pd}]$$



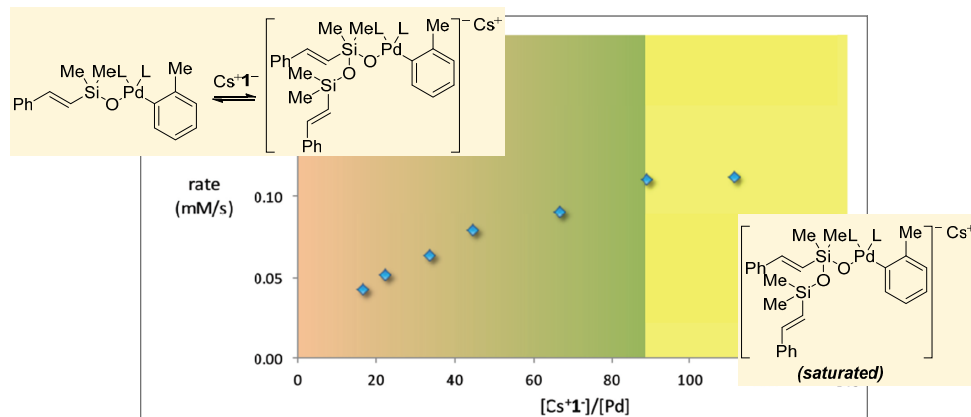
0th order in silanolate is consistent with:

- Turnover-limiting **thermal transmetalation**
- Turnover-limiting **activated transmetalation** from a **saturated 10-Si-5 intermediate**

Kinetic studies – cesium silanolate



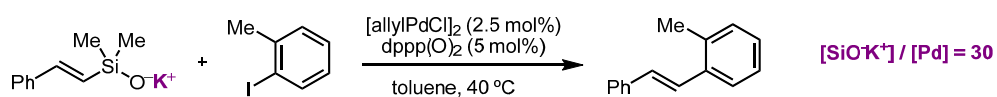
$$\text{rate} = k_{obs} [\text{Cs}^+\text{silanolate}]^{0.55} [\text{Ar-I}]^0 [\text{dppp(O)}_2]^0 \quad \text{with } k_{obs} = k [\text{Pd}]$$



- **Partial order** in silanolate indicates rapid equilibration of 8-Si-4 and 10-Si-5 intermediates. **Both modes of transmetalation** are operative.
- **0th order** in silanolate at higher concentrations is consistent with **complete saturation as the 10-Si-5 species**. Only activated transmetalation is operative.

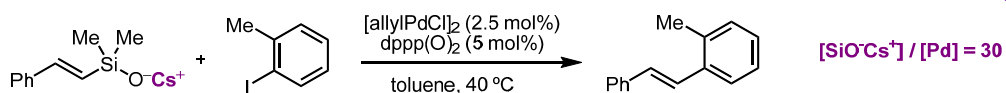
Alkenylsilanolates – summary

▪ POTASSIUM ALKENYLSILANOLATES



The preferred transmetalation pathway is **thermal**

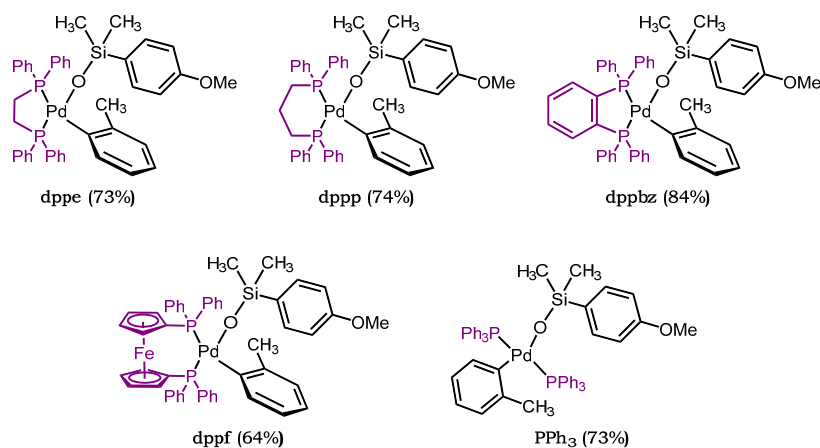
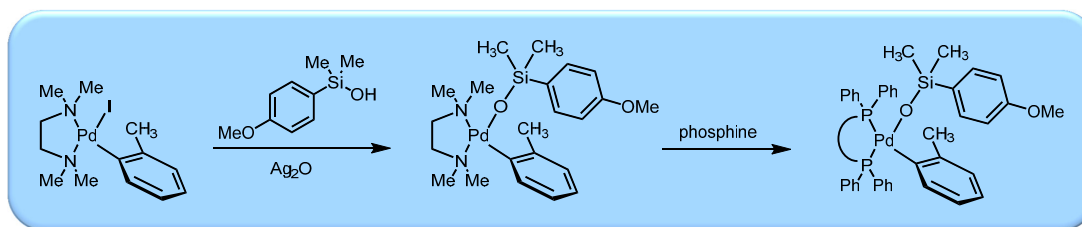
▪ CESIUM ALKENYLSILANOLATES



Both **thermal** and **activated** transmetalation are operative

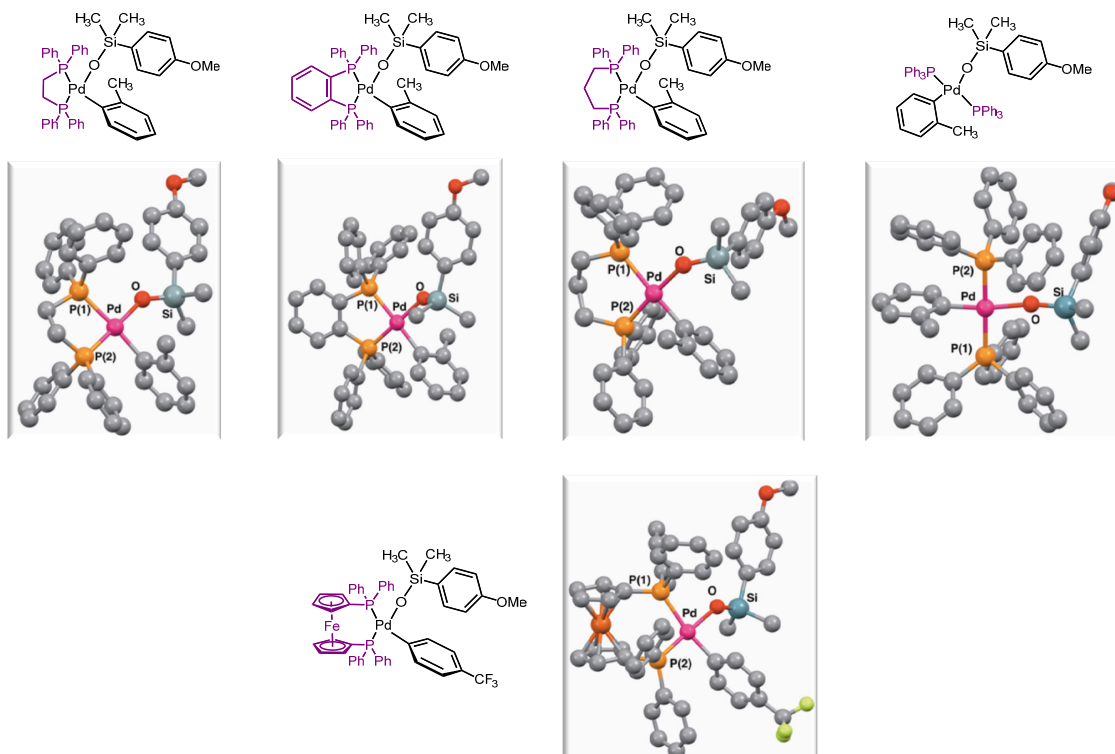
These conclusions are **in contrast** with the **reigning paradigm** that organosilicon cross-coupling must be **anionically activated** (**Hiyama-Hatanaka paradigm**)

Arylsilanolate arylpalladium complexes



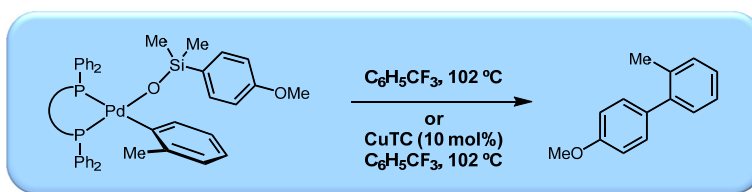
Tymonko, S. A.; Smith, R. C.

Arylsilanolate arylpalladium complexes



Tymonko, S. A.; Smith, R. C.

Arylpalladium arylsilanolate complexes

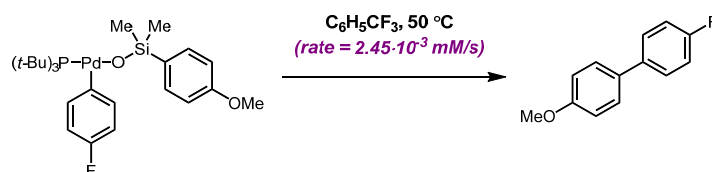
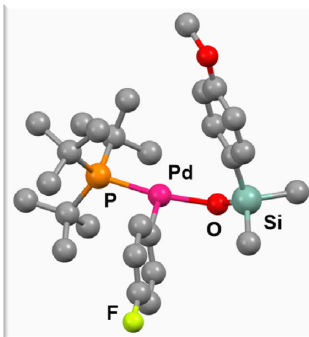
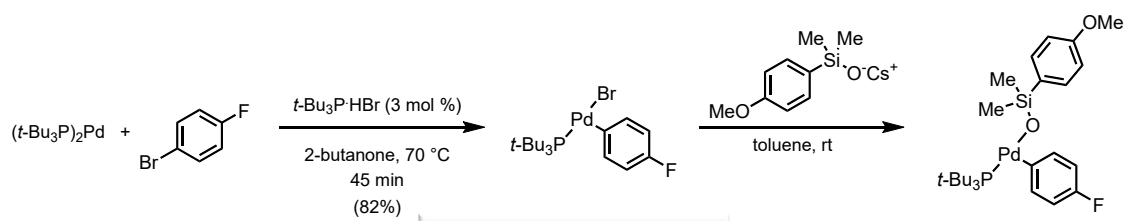


ligand	rate (10^{-2} mM/s)	rate with CuTC	increase
PPh ₃	1.77	4.76	2.7
dppe	0.671	0.815	1.2
dppp	0.139	1.84	13.3
dppf	0.0941	9.21	97.9
dppbz	0	0	0

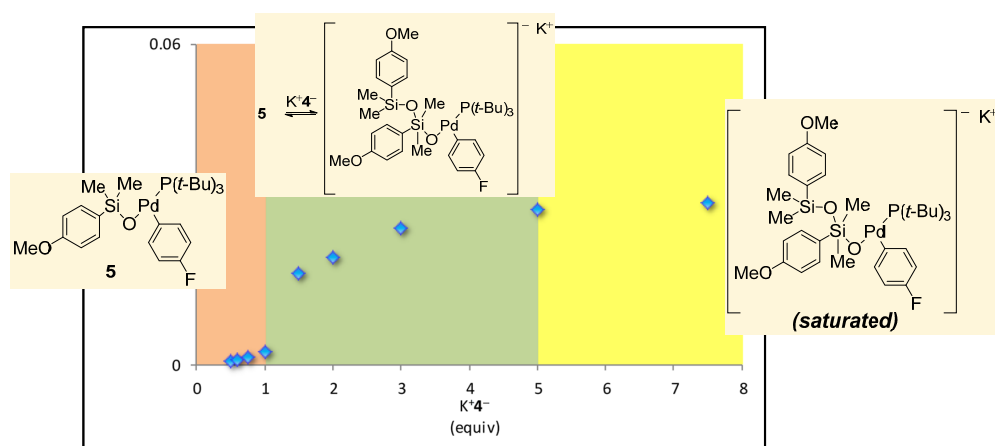
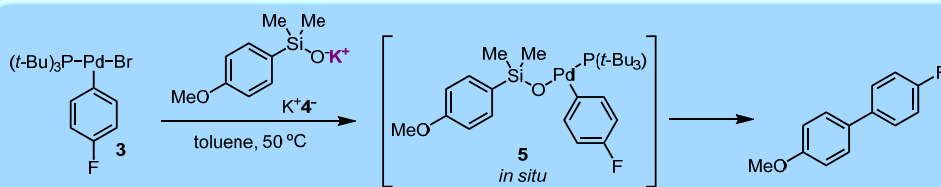
- Arylsilanolates are capable of **direct, thermal transmetalation**
- CuTC facilitates transmetalation by decomposition of phosphine ligands

What is the preferred transmetalation mode in the CATALYTIC reaction?

T-shaped arylsilanolate complexes

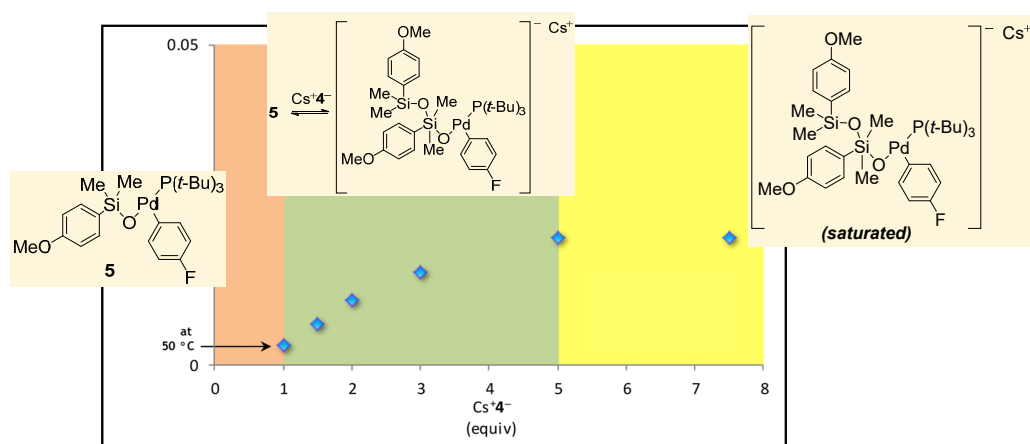
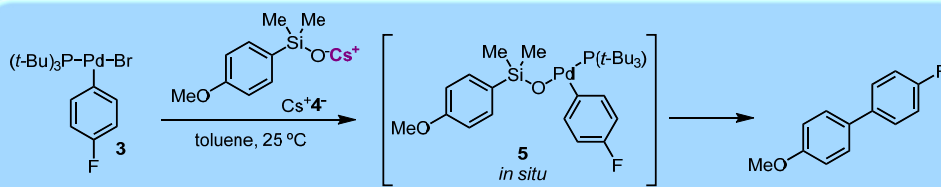


Kinetic studies – potassium silanolate



- K⁴⁻ ≤ 1 equiv (with respect to **3**): slow reaction, **thermal transmetalation**
- 1 equiv < K⁴⁻ < 5 equiv: sudden increase in rate, **activated transmetalation**
- K⁴⁻ > 5 equiv: no increase in rate, **activated transmetalation (saturated)**

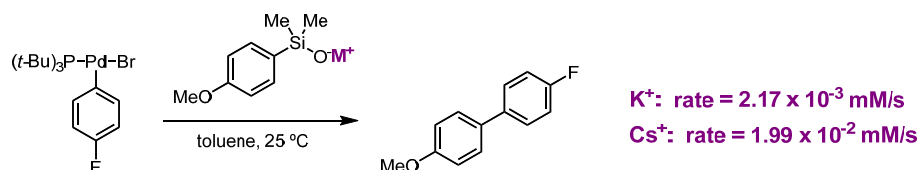
Kinetic studies – cesium silanolate



- Cs⁴⁻ = 1 equiv (with respect to **3**): same rate as with K⁴⁻, **thermal transmetalation**
- 1 equiv < Cs⁴⁻ < 5 equiv: sudden increase in rate, **activated transmetalation**
- Cs⁴⁻ > 5 equiv: no increase in rate, **activated transmetalation (saturated)**

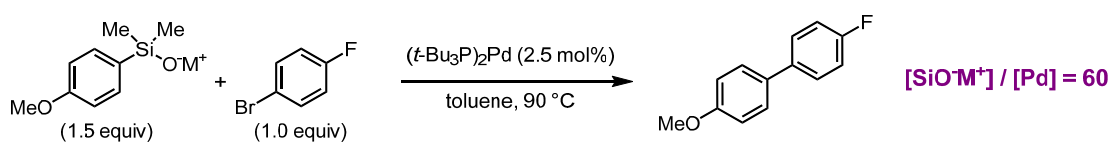
Saturation point

- Cs-silanolate reacts much faster than the K-silanolate; kinetics had to be run at room temperature (vs. 50 °C for the K-silanolate)
- **Initial hypothesis:** higher nucleophilicity of the Cs-silanolate accounts for the increased rate
- However, saturation points for K and Cs-silanolates are identical
- **Rates at 25 °C are different**

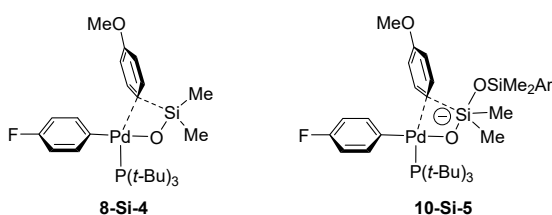


- **New hypothesis:** in toluene, ion pairs are not separated; higher reactivity of the Cs-silanolate arises from the greater negative charge localized on the 10-Si-5 intermediate

Arylsilanolates – summary

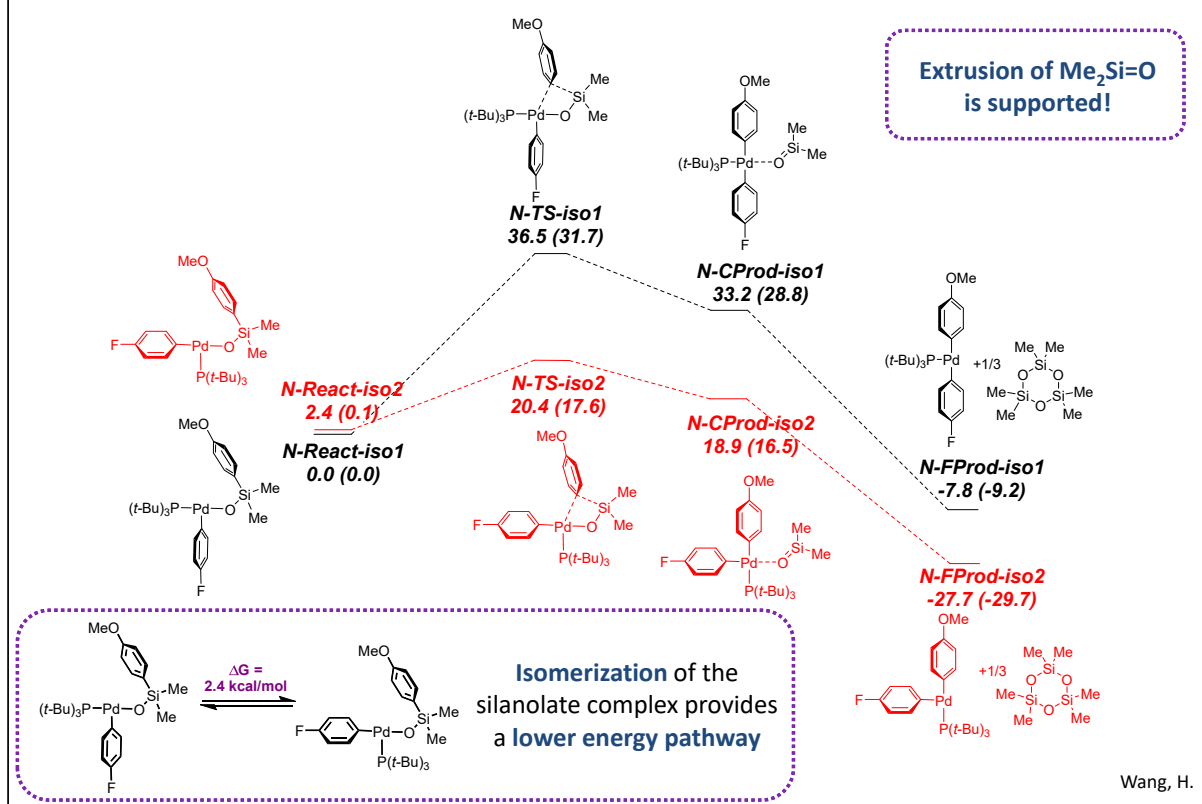


Regardless of the cation employed (K^+ or Cs^+), arylsilanolates undergo **activated** transmetalation under catalytic conditions

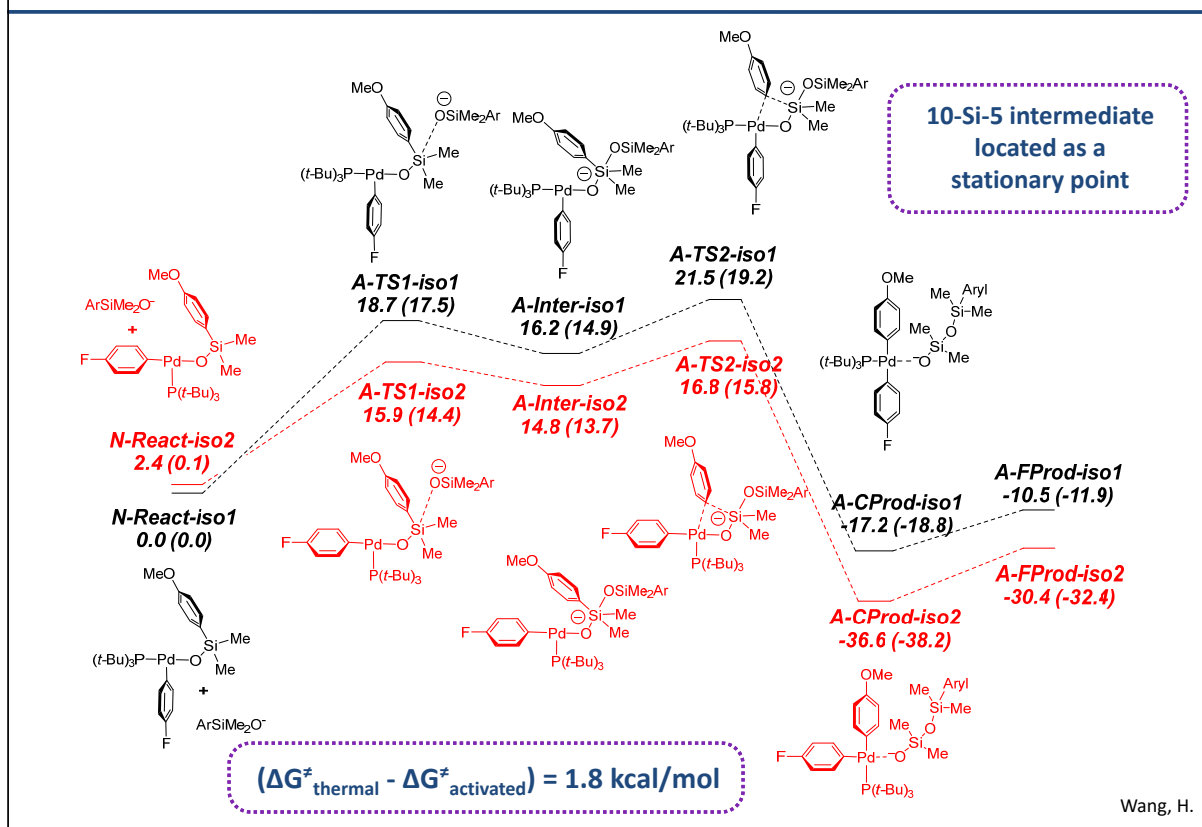


Transmetalation proceeds via $\text{S}_{\text{E}}\text{Ar}$ mechanism (requires interruption of aromaticity)

Computational studies – thermal transmetalation

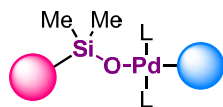


Computational studies – activated transmetalation

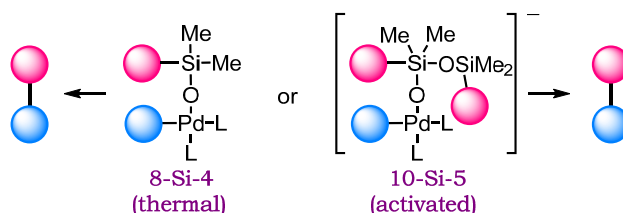


Summary of transmetalation modes

- Intermediates containing the critical **Si-O-Pd linkage** were isolated and shown to be kinetically competent



- Both **thermal and activated transmetalation** are viable, depending on the conditions (stoichiometric or catalytic) and the organic moiety used (alkenyl or aryl)

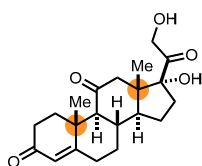


- The understanding of the mechanism of cross-coupling of organosilanolates can guide the design and optimization of synthetic methods
- Stimulated similar studies for the transmetalation step in the Suzuki coupling

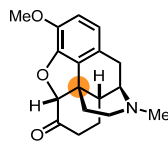
J. Am. Chem. Soc. **2015**, *137*, 6192
J. Am. Chem. Soc. **2015**, *137*, 6200

Quaternary stereocenters in organic synthesis

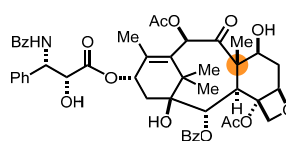
- Among the drugs currently on the market, **nearly 300 contain a quaternary stereocenter**



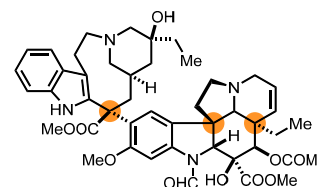
Cortisone
anti-inflammatory



Hydrocodone
analgesic/anti-tussive



Paclitaxel
mitotic inhibitor

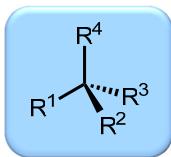


Vincristine
mitotic inhibitor

- Among the drugs on the market containing quaternary stereocenters, **no instances are found where the stereocenter is forged via asymmetric synthesis!**
- Stereoselective synthesis is made difficult by the **steric repulsion** between the substituents
- Existing methods **lack generality**

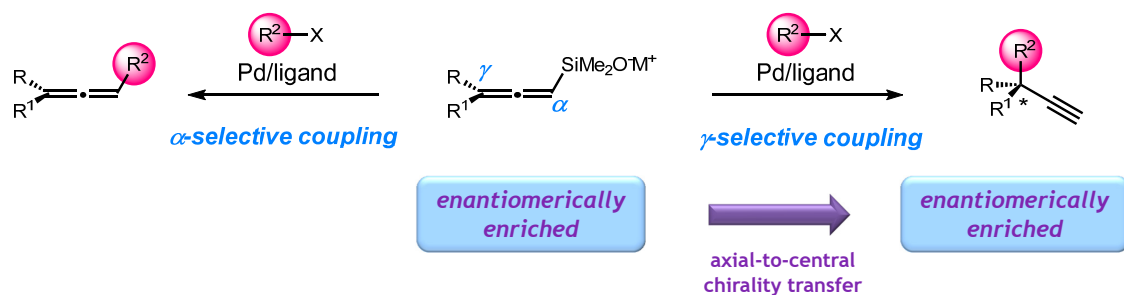
de Vries, J. G., Important Pharmaceuticals and Intermediates. In *Quaternary Stereocenters*, Wiley-VCH Verlag GmbH & Co. KGaA: 2006; 25-50.
 Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D., Pharmaceutical Substances - Syntheses, Patents and Applications of the Most Relevant AIPs. Thieme.
 Quasdorf, K. W.; Overman, L. E., Catalytic enantioselective synthesis of quaternary carbon stereocentres. *Nature* **2014**, *516* (7530), 181-191.

Enantioselective synthesis of quaternary stereocenters

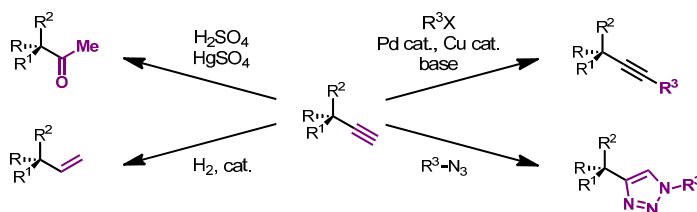


- **Ongoing challenge** in organic synthesis
- The majority of the methods target **cyclic structures**
- **Acyclic structures** are more challenging due to the increased degrees of freedom
- **Limitation of existing methods:**
 - Limited to very specific substitution patterns in the starting material/product
 - Cannot generate isolated stereocenters
 - Are not catalytic (rely on a chiral auxiliary, a stoichiometric chiral reagent, or a resolution process as the source of the stereocenter)
 - Are overengineered
 - Utilize expensive and/or sensitive reagents/catalysts, therefore not scalable

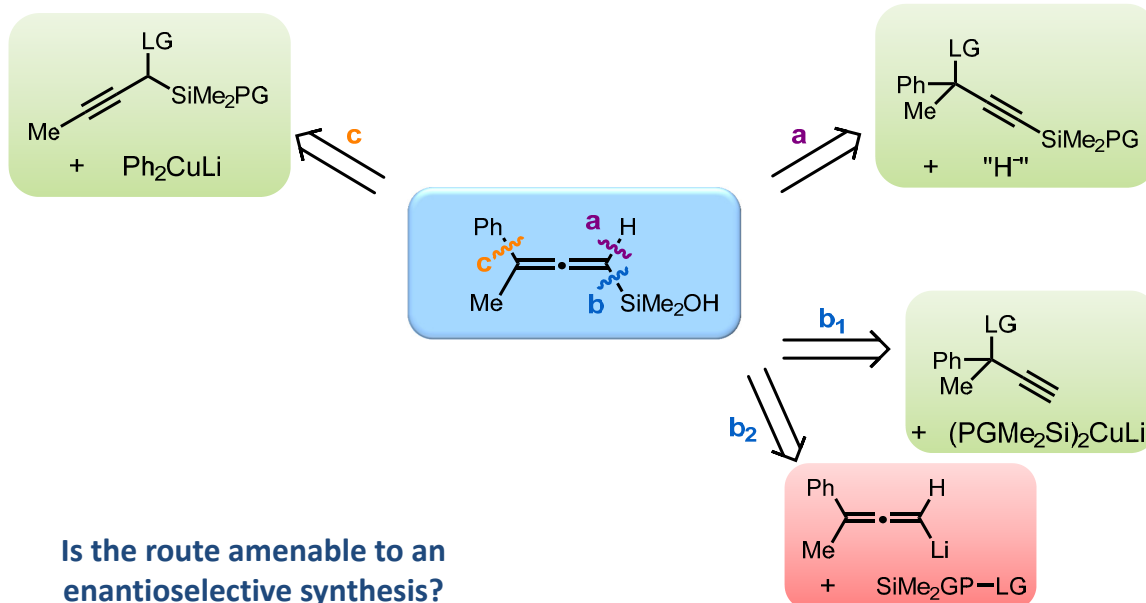
Cross-coupling of allenylsilanolates



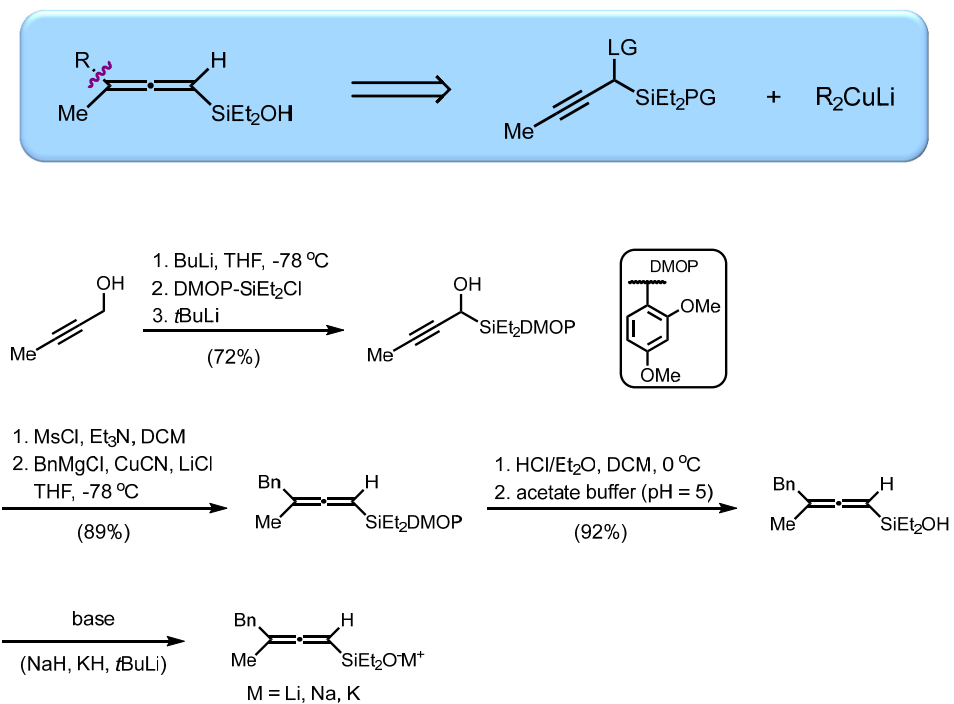
- Advantages of **silanol cross-coupling**
- Stereocontrol imparted by the **chirality of the substrate** (no chiral reagent/catalyst needed)
- The resulting **alkyne** is a **versatile intermediate**



Synthesis of allenylsilanolates: retrosynthetic analysis



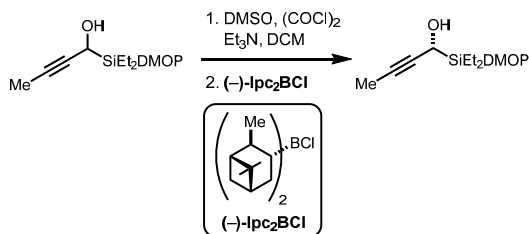
Synthesis of allenylsilanolates



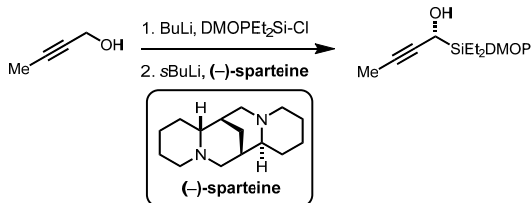
Synthesis of allenylsilanolates

Enantioselective synthesis of allenylsilanols:

- Oxidation/stereoselective reduction

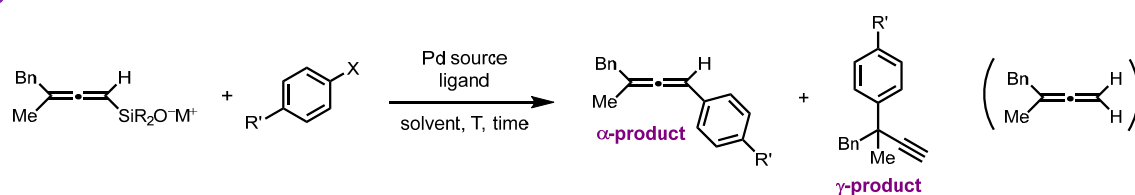


- Asymmetric reverse Brook rearrangement



- A **synthesis of allenylsilanols/silanolates** was developed (4 steps, 59% overall yield, potentially enantioselective)
- Flexible enough to accommodate structural variations
- Introduction of a new **protecting group** for sterically encumbered silanes

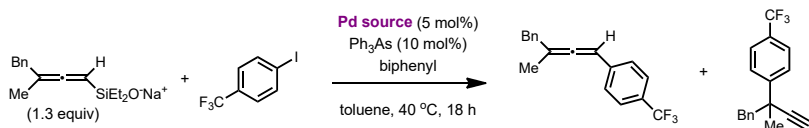
Cross-coupling optimization



Optimization with respect to:

- Pd source
- Ligand
- Electrophile
- R group (Et, iPr)
- M (Li, Na, K, Cs)
- Temperature
- Solvent

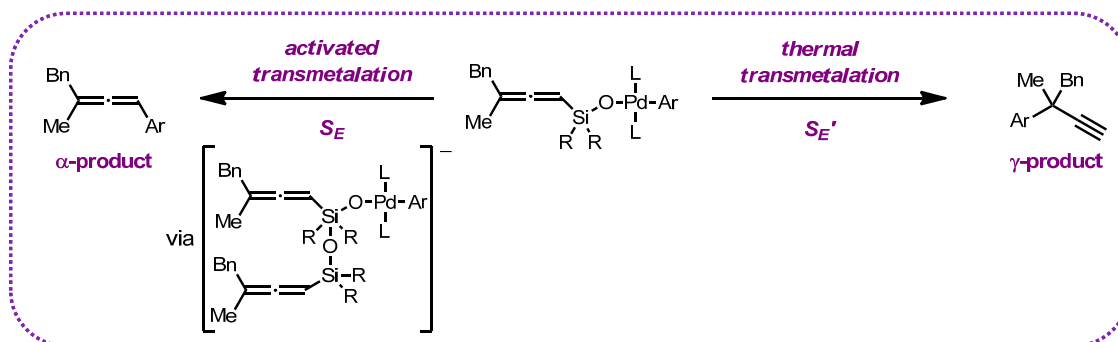
Survey of Pd sources



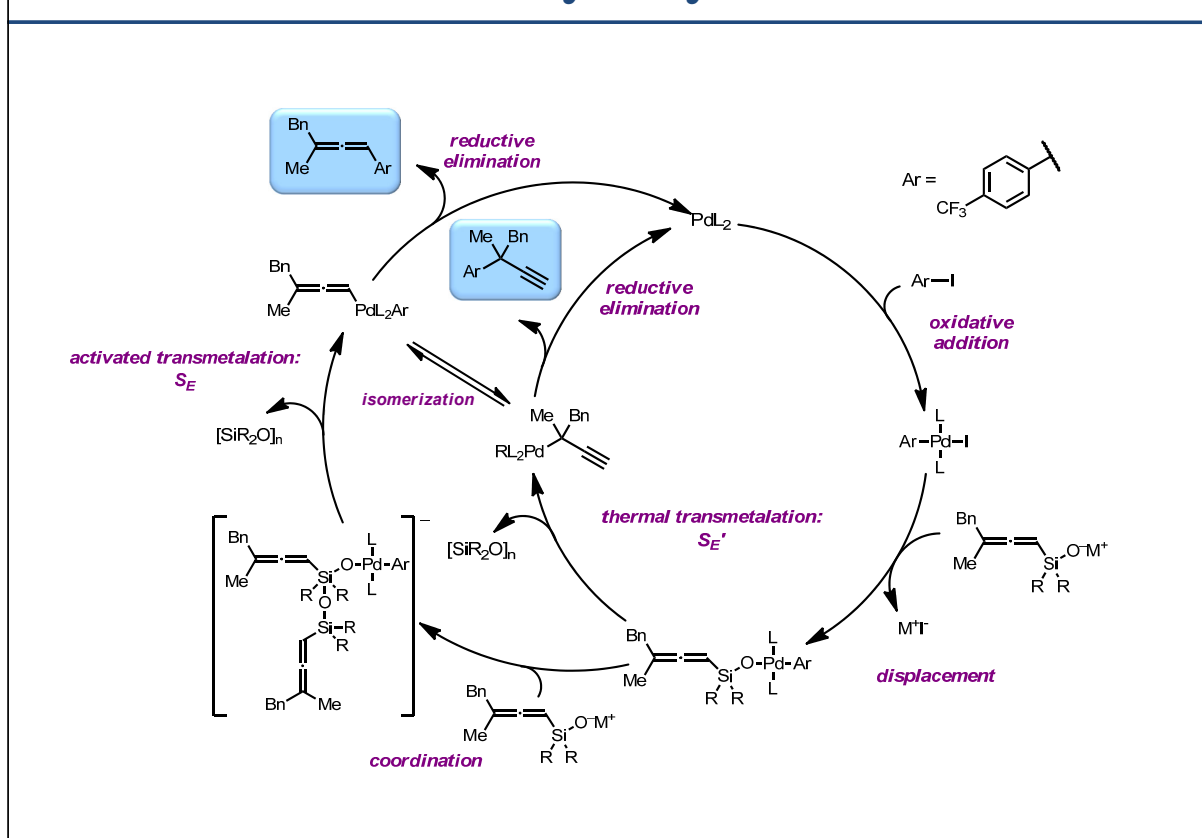
Pd source	time	α -product (%)	γ -product (%)	silanol (%)	halide (%)	allene (%)	α : γ ratio
Pd ₂ (dba) ₃	1 h	36	-	46	54	3	100:0
	18 h	37	5	20	37	5	88:12
Pd(4,4'-CF ₃ -dba) ₂	1 h	33	-	55	61	2	100:0
	18 h	34	4	27	45	4	89:11
APC	1 h	22	0	25	46	-	100:0
	18 h	25	5	4	-	-	82:18
PdCl ₂ (PhCN) ₂	1 h	15	-	63	77	4	100:0
	18 h	25	5	18	48	4	82:18
PdCl ₂ (CH ₃ CN) ₂	1 h	12	1	55	78	5	93:7
	18 h	14	10	12	49	6	58:42
Pd(acac) ₂	1 h	15	-	57	77	4	100:0
	18 h	15	9	14	51	6	62:38
PdBr ₂	1 h	12	1	28	73	2	96:4
	18 h	12	7	7	34	2	62:38
Pd(OAc) ₂	1 h	10	2	50	82	6	83:17
	18 h	10	10	14	61	9	49:51
Pd(OCOCF ₃) ₂	1 h	8	1	55	85	3	90:10
	18 h	10	11	10	53	6	47:53

Mechanistic hypothesis

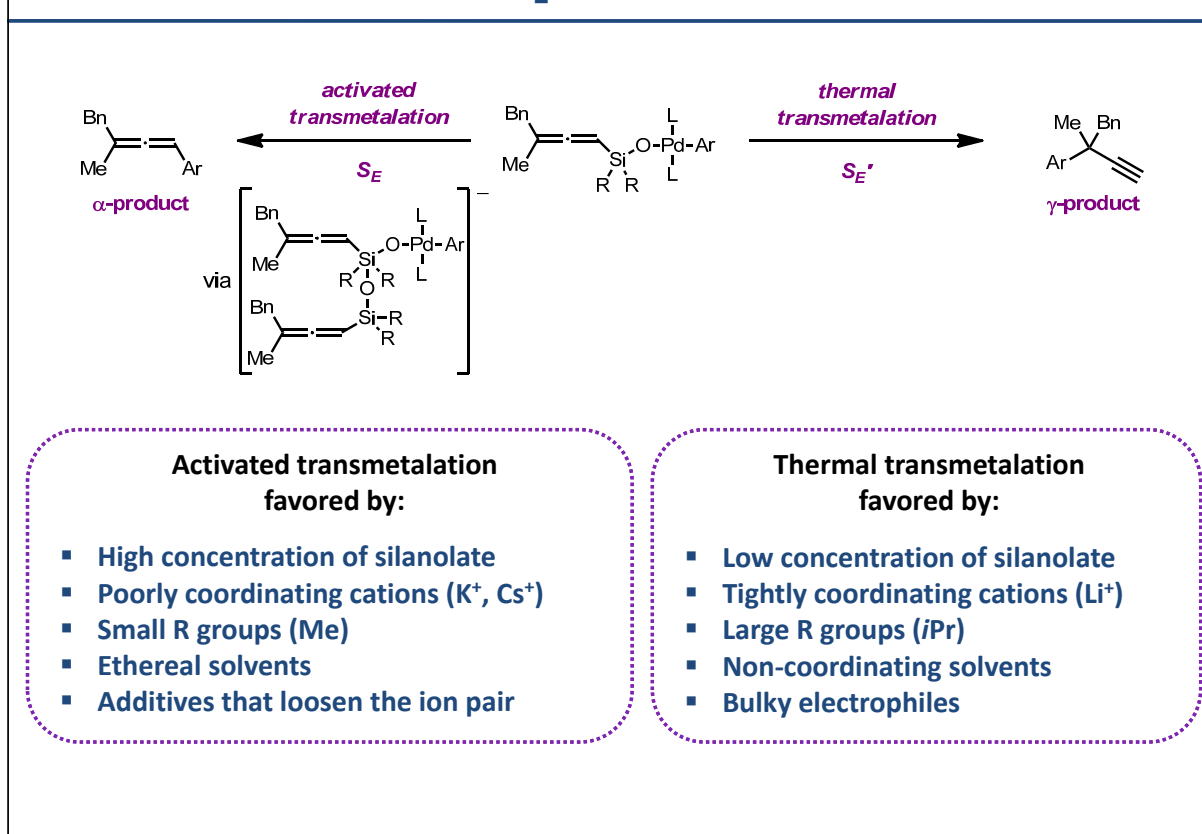
- The α : γ ratio decreases over the course of the reaction
- Products/byproducts are not responsible for a change in the mechanism (tested by addition of NaI, arsine-oxide, product)
- **Thermal transmetalation** for the γ -product / **Activated transmetalation** for the α -product?



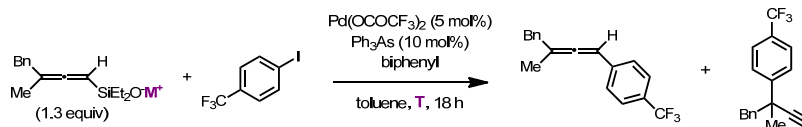
Catalytic cycle



Implications



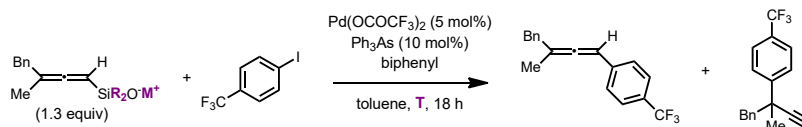
Effect of the cation



conditions	time	α -product (%)	γ -product (%)	silanol (%)	halide (%)	allene (%)	α : γ ratio
Li-silanolate 40 °C	18 h	1	4	69	92	1	10:90
Li-silanolate 60 °C	1 h	-	5	76	88	-	0:100
	18 h	1	13	8	77	-	8:92
Na-silanolate 40 °C	1 h	8	1	55	85	3	90:10
	18 h	10	11	10	53	6	47:53
K-silanolate 40 °C	1 h	35	-	47	67	9	100:0
	18 h	45	1	18	53	34	98:2
K-silanolate 80 °C	1 h	57	1	22	42	12	98:2
	18 h	82	7	2	-	20	93:7
Silanol + Cs ₂ CO ₃ 80 °C	18 h	29	7	17	-	-	81:19

Tight ion pair → γ -selectivity (but lower reactivity)

Effect of the R groups on silicon

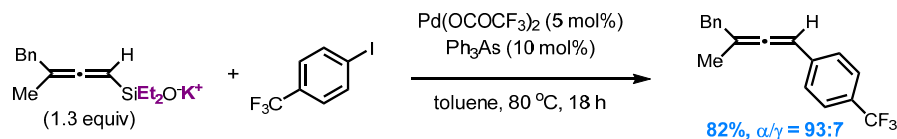


conditions	time	α -product (%)	γ -product (%)	silanol (%)	halide (%)	allene (%)	α : γ ratio
Na / Et ₂ 40 °C	1 h	8	1	55	85	3	90:10
	18 h	10	11	10	53	6	47:53
Na / <i>i</i> Pr ₂ 40 °C	18 h	-	-	52	85	-	-
Na / <i>i</i> Pr ₂ 80 °C	1 h	2	1	74	76	1	77:23
	18 h	1	6	14	11	1	8:92
K / Et ₂ 80 °C	1 h	57	1	22	42	12	98:2
	18 h	82	7	2	-	20	93:7
K / <i>i</i> Pr ₂ 80 °C	1 h	13	1	61	85	14	94:6
	18 h	16	23	11	43	28	41:59
Et ₂ + Cs ₂ CO ₃ 80 °C	18 h	29	7	17	-	-	81:19
<i>i</i> Pr ₂ + Cs ₂ CO ₃ 80 °C	1 h	1	1	84	76	-	54:46
	18 h	3	23	9	-	1	11:89

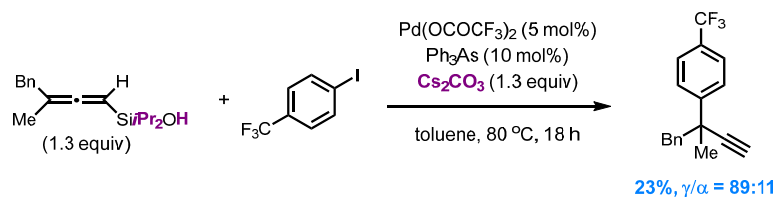
Bulky R group → γ -selectivity (but lower reactivity)

Optimized cross-coupling reaction

- Optimization of α -selective cross-coupling conditions

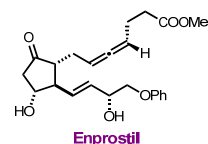
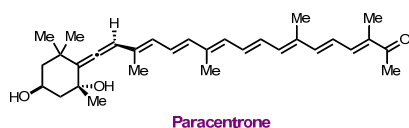
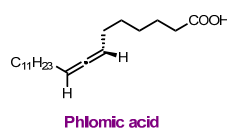
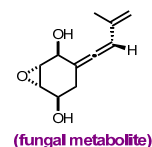
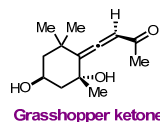
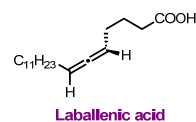


- Unsuccessful optimization of γ -selective cross-coupling conditions (α -coupling is preferred, unless Si bears bulky substituents)



Conclusions

- The enantioselective synthesis of quaternary stereocenters could not be achieved through the proposed methods
- Allenyloxy silanes prefer to undergo cross-coupling at the α -position
- The **enantioretentive α -selective cross-coupling** of allenylsilanols is open to further exploration

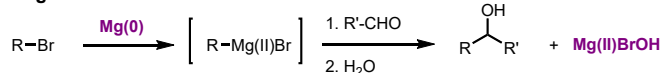


- C-C activation of 3,3-disubstituted cyclobutanones is challenging and complicated by several competing processes

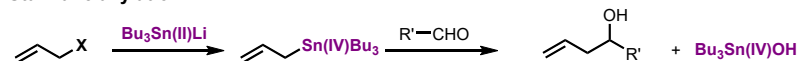
Reductive processes in organic synthesis

- A large number of organic reactions are **overall reductive** and rely on a pre-reduced starting material
- Issues: waste stream, poor atom economy**

Grignard



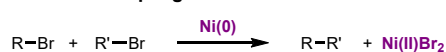
Stannane allylation



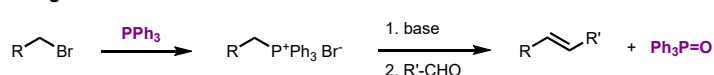
Nozaki-Hiyama-Kishi



Reductive coupling



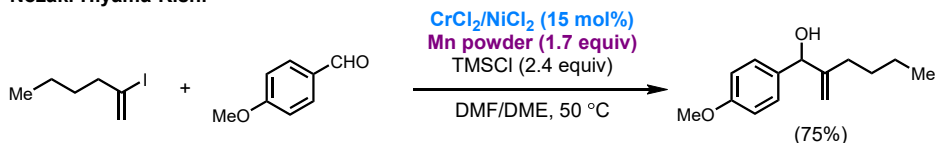
Wittig



Catalytic variants

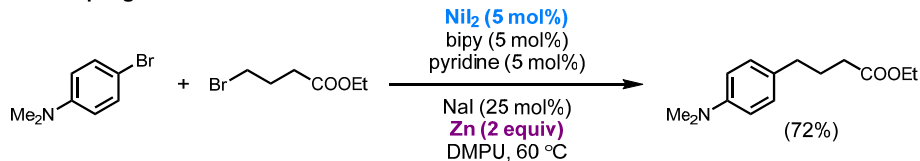
- Solution: use of a terminal reducing agent**
- This approach does not solve the problem of waste generation – it just replaces a reducing agent with another (perhaps more tractable) stoichiometric reducing agent

Nozaki-Hiyama-Kishi



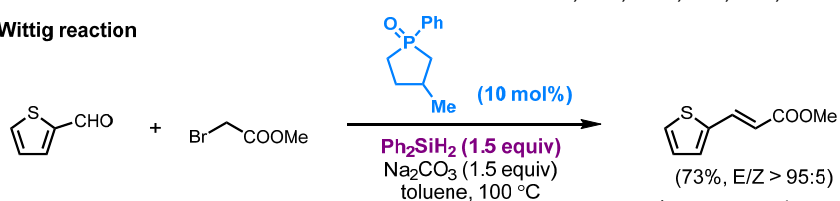
Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349

Halide coupling



Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146

Wittig reaction



O'Brien, C. J. et al. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836

Truly catalytic variants

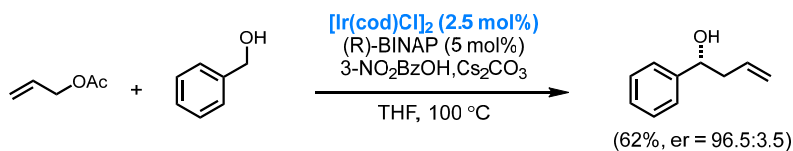
Grand Challenge:

Discover ways to carry out fundamentally new chemical transformations utilizing green and sustainable chemistry and engineering, based on the ultimate premise that **it is better to prevent waste than to clean it up after it is formed.**

Sustainability in the Chemical Industry: Grand Challenges and Research Needs – A Workshop Report; The National Academies Press, Washington, DC, 2005.

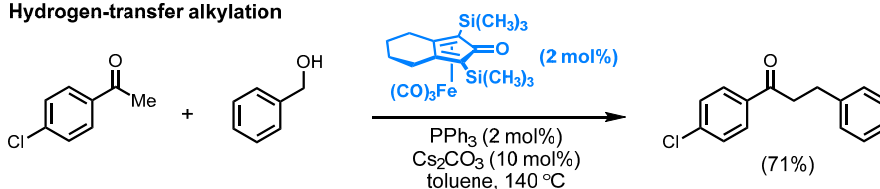
▪ Better solution: redox-neutral transformations

Hydrogen-transfer allylation



Kim, I. S.; Ngai, M.-Y.; Krische, M. J. . *J. Am. Chem. Soc.* **2008**, *130*, 14891

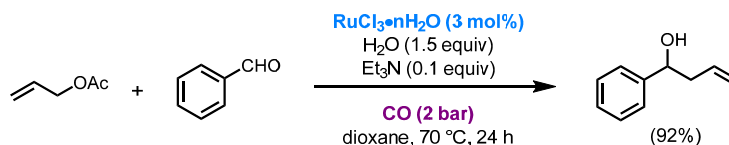
Hydrogen-transfer alkylation



Elangovan, S.; Sortais, J.-B.; Beller, M.; Darcel, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 14483

Our solution

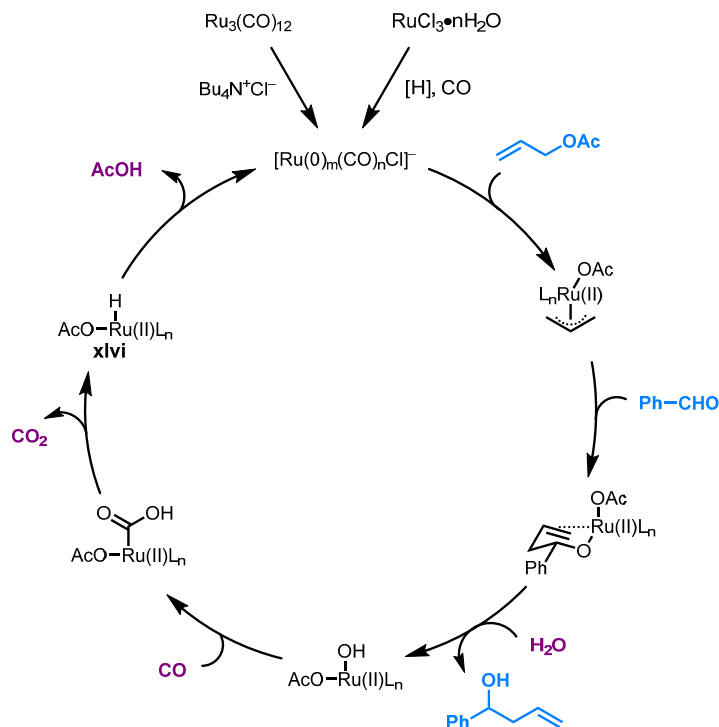
Use of **CO** as the terminal reducing agent exploiting the reducing potential of the **Water-Gas Shift Reaction**



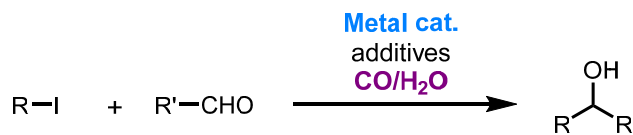
- Cheap, traceless reducing agent
- **CO₂** and **acetic acid** are the only byproducts

Denmark, S. E.; Nguyen, S. T. *Org. Lett.* **2009**, *11*, 781
Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79*, 5970

Our solution

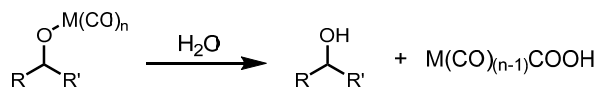


1. Addition of organometallic reagents to carbonyls

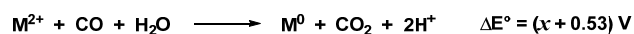
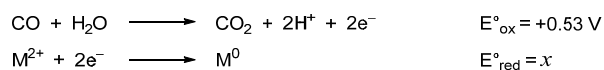


- WGSR reduces the metal that accomplishes the transformation
- Studied using DoE approaches with Cr, Mn, Ru, Pd, Ni
- Turnover was never observed
- Issues: *Compatibility with water*

Cleavage of the alkoxide

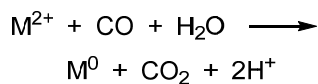
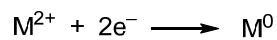


Electrochemical limitations



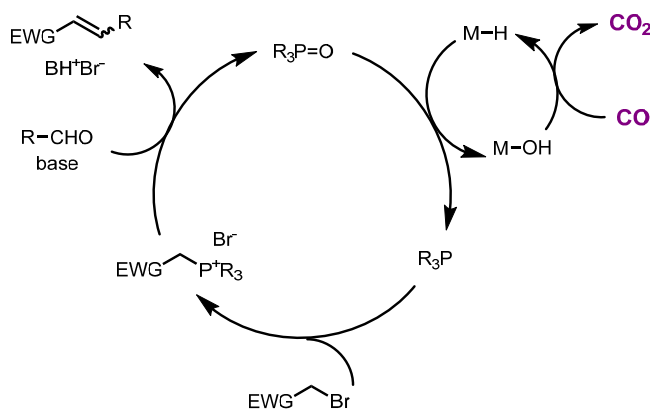
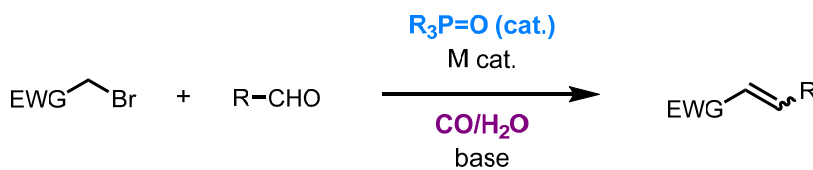
*If $E^\circ_{\text{red}} > -0.53 \text{ V}$,
the reaction can be driven by the WGSR*

Electrochemical requirements



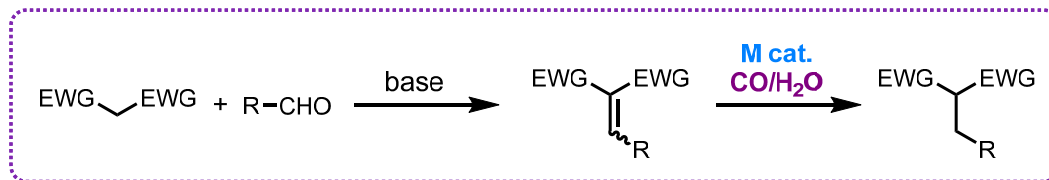
<i>Cr</i>	<i>Mn</i>	<i>Fe</i>	<i>Co</i>	<i>Ni</i>	<i>Cu</i>	<i>Zn</i>
-0.91 -0.38	-1.19 -0.66	-0.45 0.08	-0.28 0.25	-0.26 0.27	0.34 0.87	-0.76 -0.23
<i>Mo</i>	<i>Tc</i>	<i>Ru</i>	<i>Rh</i>	<i>Pd</i>	<i>Ag</i>	<i>Cd</i>
		0.45 0.98	0.60 1.13	0.95 1.48		-0.40 0.13
<i>W</i>	<i>Re</i>	<i>Os</i>	<i>Ir</i>	<i>Pt</i>	<i>Au</i>	<i>Hg</i>
				1.18 1.71		0.85 1.38

2. Catalytic Wittig olefination

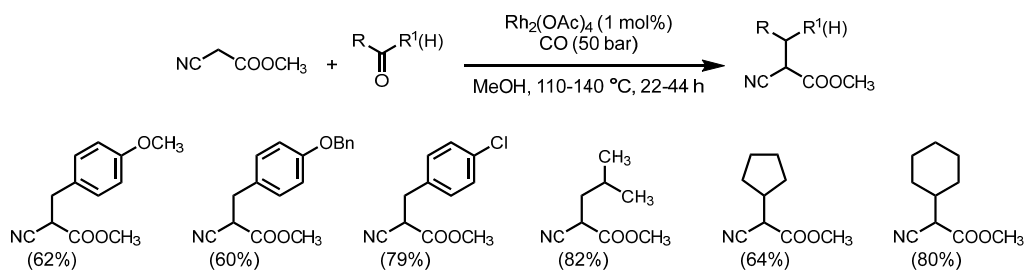


- WGS turns over an **organocatalyst**
- The metal is NOT involved in the transformation being accomplished

3. Reductive alkylation

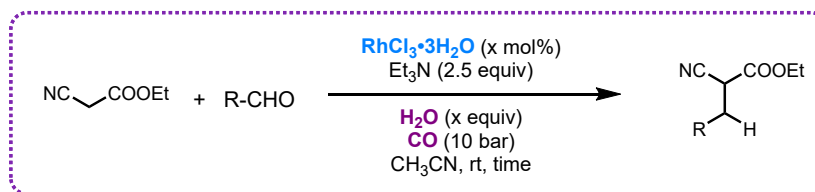


- WGSR and C-C bond forming event happen in **two separate steps**
- WGSR acts as a **source of H₂**
- Benefits:** tandem reaction; higher functional group compatibility vs standard hydrogenation
- Previous reports: user-unfriendly protocol, high T and P



Kolesnikov, P. N.; Usanov, D. L.; Barablina, E. A.; Maleev, V. I.; Chusov, D. *Org. Lett.* **2014**, *16*, 5068

Substrate scope

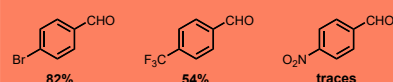
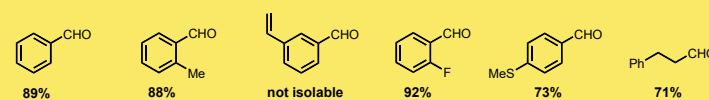
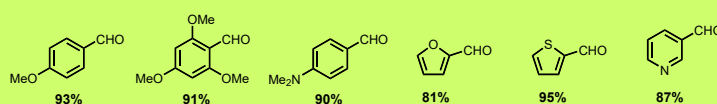
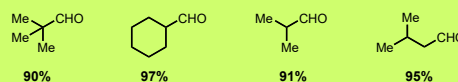


- Works at **room temperature!**
- Good functional group compatibility
- Significant impact of the **alkene's Lewis basicity**
- Being extended to ketones and other active-methylene compounds

RhCl₃ 2 mol%, H₂O 2 equiv, 18 h

RhCl₃ 2 mol%, H₂O 3 equiv, 24 h

RhCl₃ 3 mol%, H₂O 5 equiv, 36 h



WGSR summary

- The WGSR can be successfully used in organic synthesis to provide reducing power
- Different strategies can be envisioned:
 - Reduction of a metal catalyst*
 - Reduction of an organocatalyst*
 - Incorporation of H₂ in the substrate*
- The first two approaches are more challenging and need to take into account:
 - Electrochemical limits*
 - Ease of reduction (BDEs)*
 - Compatibility with water*

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 - Why You Really Should Consider Using Palladium-Catalyzed Cross-Coupling of Silanols and Silanolates
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 - Modern Allene Chemistry
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 - Catalytic enantioselective synthesis of quaternary carbon stereocentres
Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516* (7530), 181-191
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Dong, G., Ed. Springer Berlin Heidelberg: **2014**; Vol. 346
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Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115* (17), 9410-9464
- WGSR in organic synthesis
 - ACIE review coming soon... stay tuned