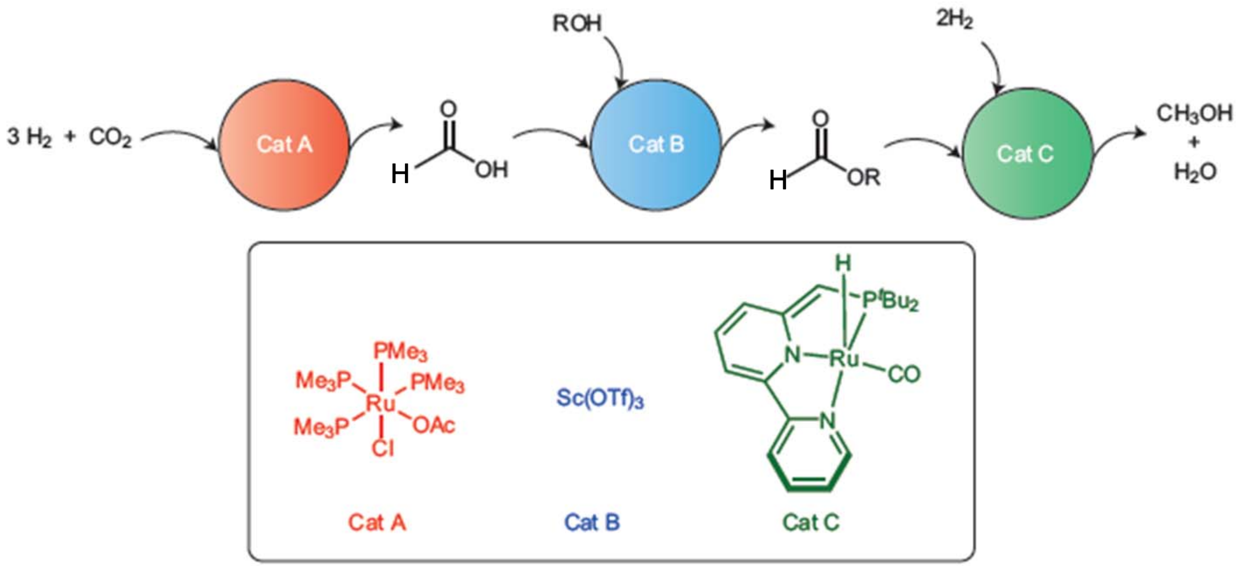
中国科学院上海有机化学研究所
Shanghai Institute of Organic Chemistry, CAS

Orthogonal tandem catalysis



Jian Rong（荣 健）

June 15th , 2015

The Hu Group

Outline

✓ **Introduction**

— *Tandem catalytic reaction*

— *Orthogonal tandem catalytic reaction*

— *Cascade and domino*

— *Advantages, Challenges and Solutions*

✓ **Orthogonal tandem catalytic reaction**

— *Addressing catalyst incompatibility*

— *Hydrocarbon upgrading*

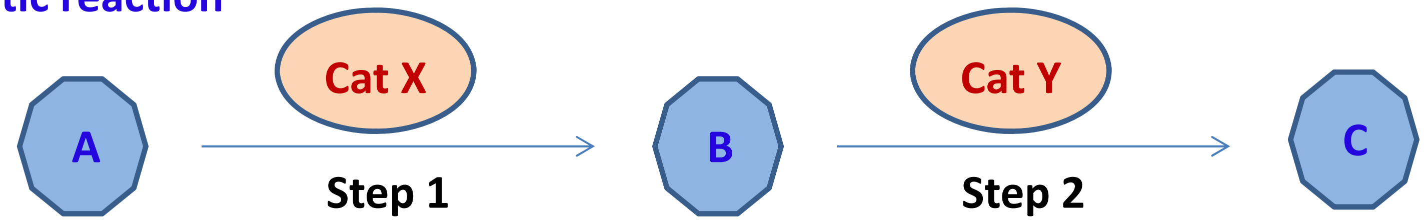
— *Thermodynamic leveraging*

✓ **Summary**

Introduction

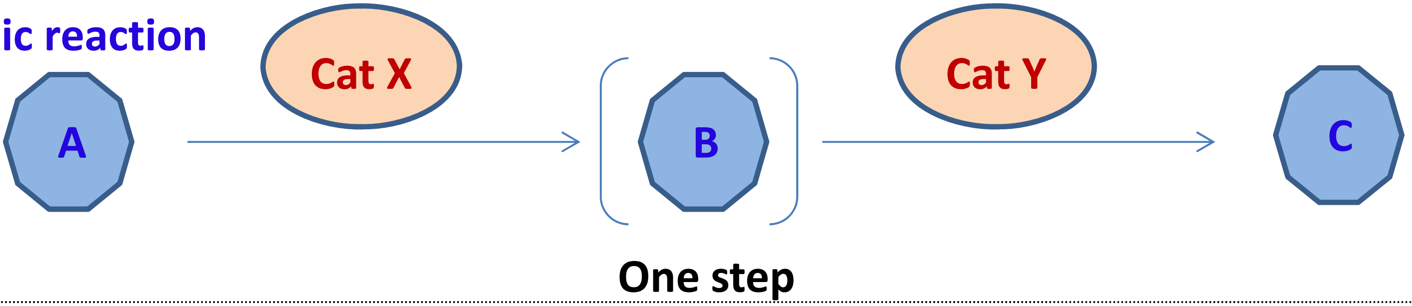
assemble complex organic molecules → discover or optimize new catalytic transformations

Isolated catalytic reaction



Dual-catalytic reaction

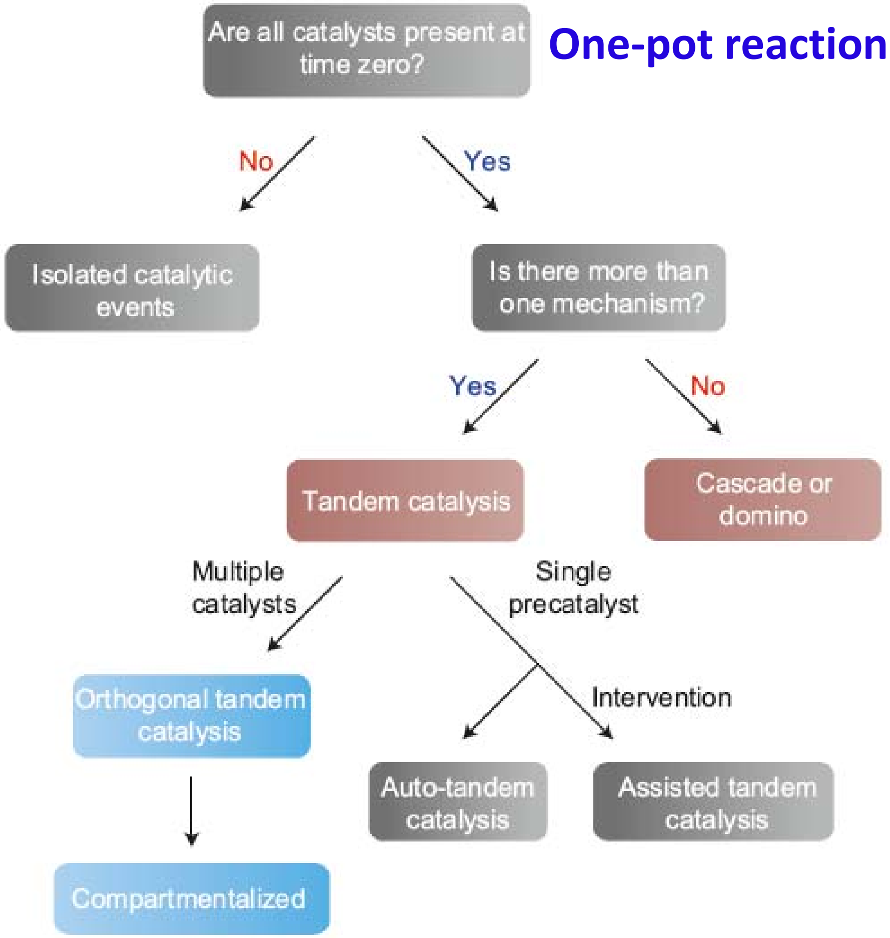
Tandem catalytic reaction



Concept: (Orthogonal) tandem catalysis

Tandem catalytic reaction, where multiple catalysts and reagents, combined in a single reaction vessel undergo a sequence of precisely staged catalytic steps, in which several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding reagents.

Orthogonal tandem catalytic reaction is a subset of tandem catalytic reactions in which more than one catalyst is used to promote two or more mechanistically distinct reaction steps.

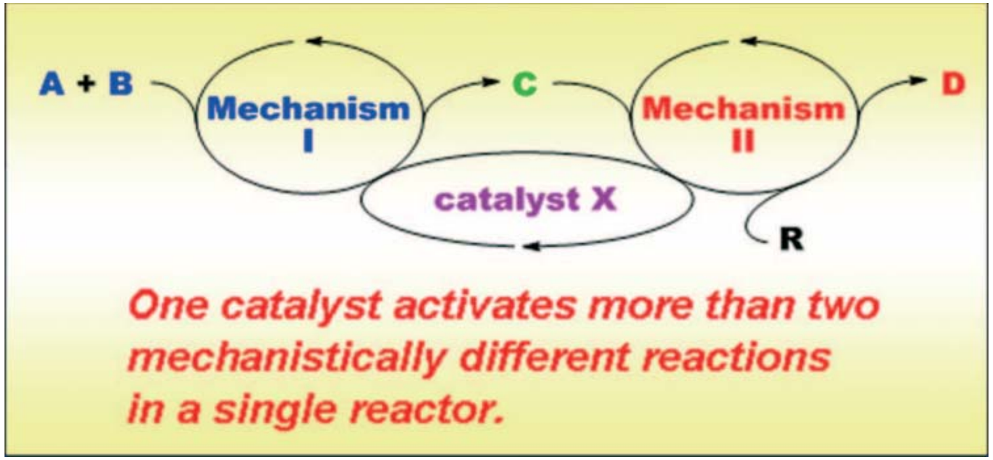


One-pot reaction

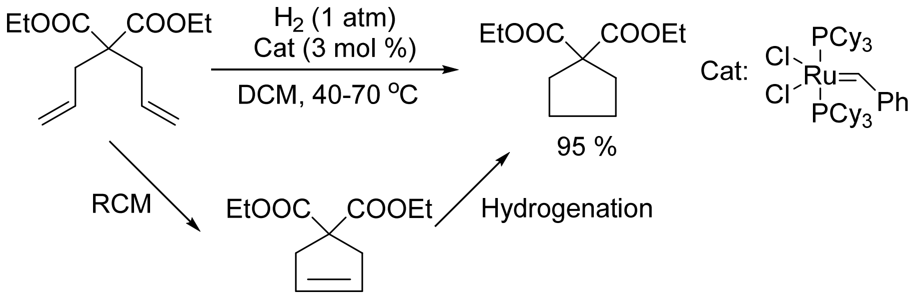
Marks, T. J. *et al*. Orthogonal tandem catalysis. *Nature Chem*. **2015**, *7*, 477–482.

Concept: Auto-tandem catalysis

Auto-tandem catalysis is defined as a process in which one catalyst promotes more than two fundamentally different reactions in a single reactor.



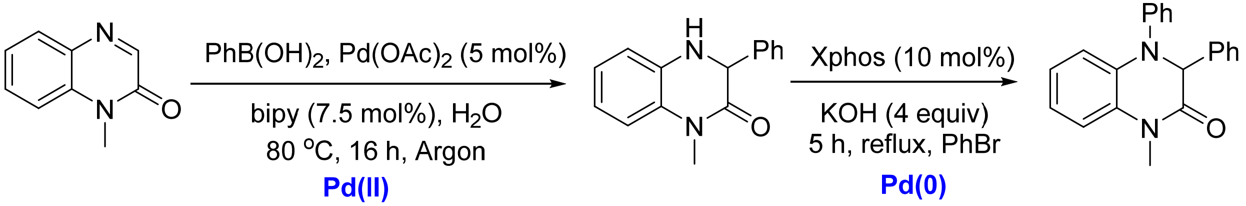
One catalyst activates more than two mechanistically different reactions in a single reactor.



Grubbs, R. H. *et al. J. Am. Chem. Soc.* **2001**, *123*, 11312–11313.

Concept

Assisted tandem catalysis, on which one precactalyst was used in different oxidation states to preform two mechanismtically distinct bond forming reactions in presence of a reagent that triggers this change in mechanism.



Alami, M.; Messaoudi, S. *et al. Adv. Synth. Catal.* **2014**, *356*, 3821–3830.

Cascade and domino

“Cascade reaction”, Tietze and Beifuss suggest to avoid its further usage because of its wide-spread use in several independent contexts.

Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

Orthogonal tandem catalysis : concept and advantages

Orthogonal tandem catalytic reaction is a subset of Tandem catalytic reactions in which more than one catalyst is used to promote two or more mechanistically distinct reaction steps.

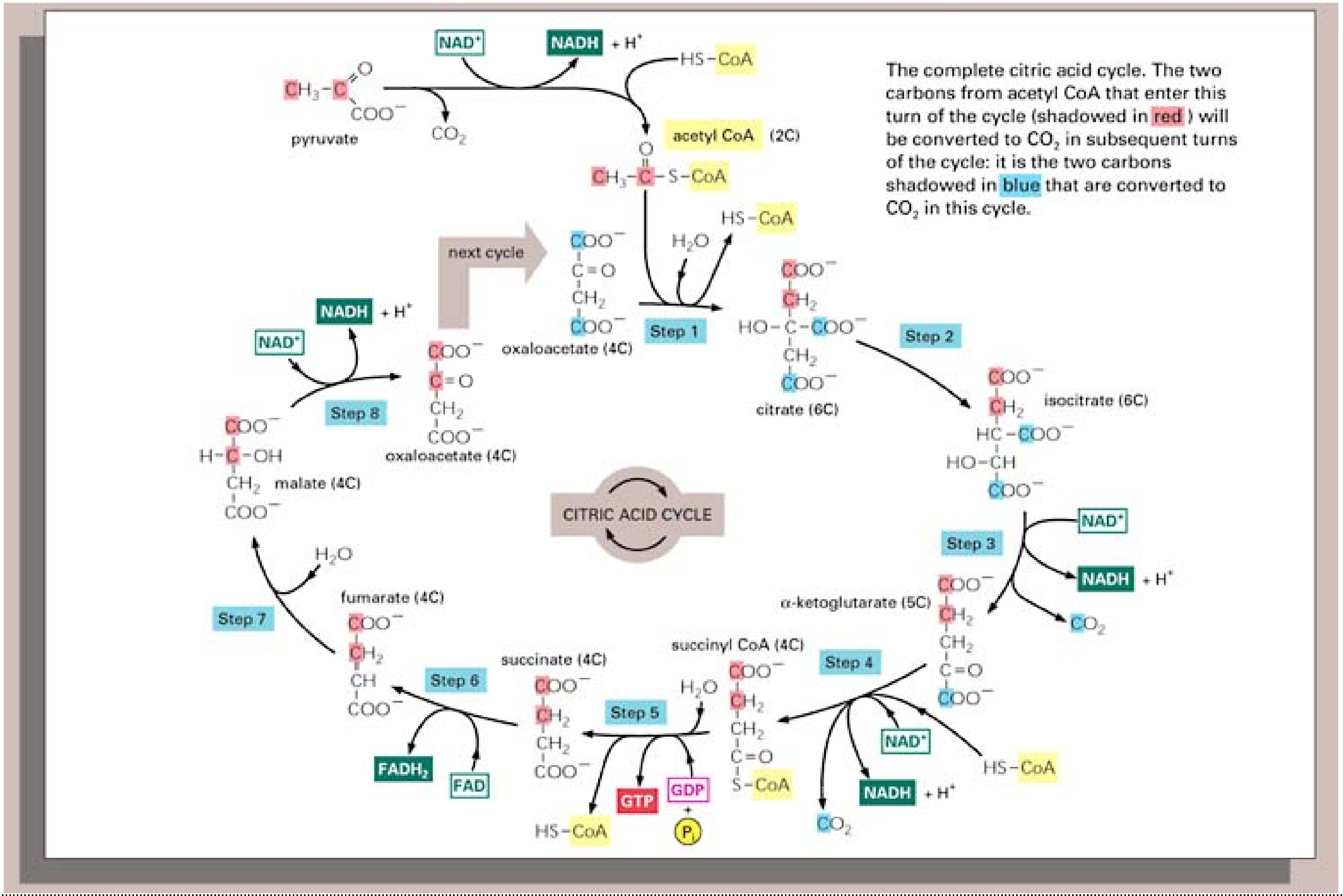
Advantages:

Greater economy of time and energy maximize resources and overall process simplicity, as well as decreasing materials loss from multiple iterations of reaction, workup and purification; help lower the risk in the storage, transportation, and the handling of toxic, unstable, or explosive intermediates, and promote equilibrium reactions to full conversion by directly coupling them in the following reaction cycle.

Marks, T. J. *et al*. Orthogonal tandem catalysis. *Nature Chem*. **2015**, *7*, 477–482.

Orthogonal tandem catalysis in nature

Multienzymatic systems that perform multistep reactions in nature have been a model for the development of artificial systems in an attempt to mimic different aspects of synthetic strategies.



The complete citric acid cycle. The two carbons from acetyl CoA that enter this turn of the cycle (shadowed in red) will be converted to CO_2 in subsequent turns of the cycle: it is the two carbons shadowed in blue that are converted to CO_2 in this cycle.

Challenges and Solutions

Challenges:

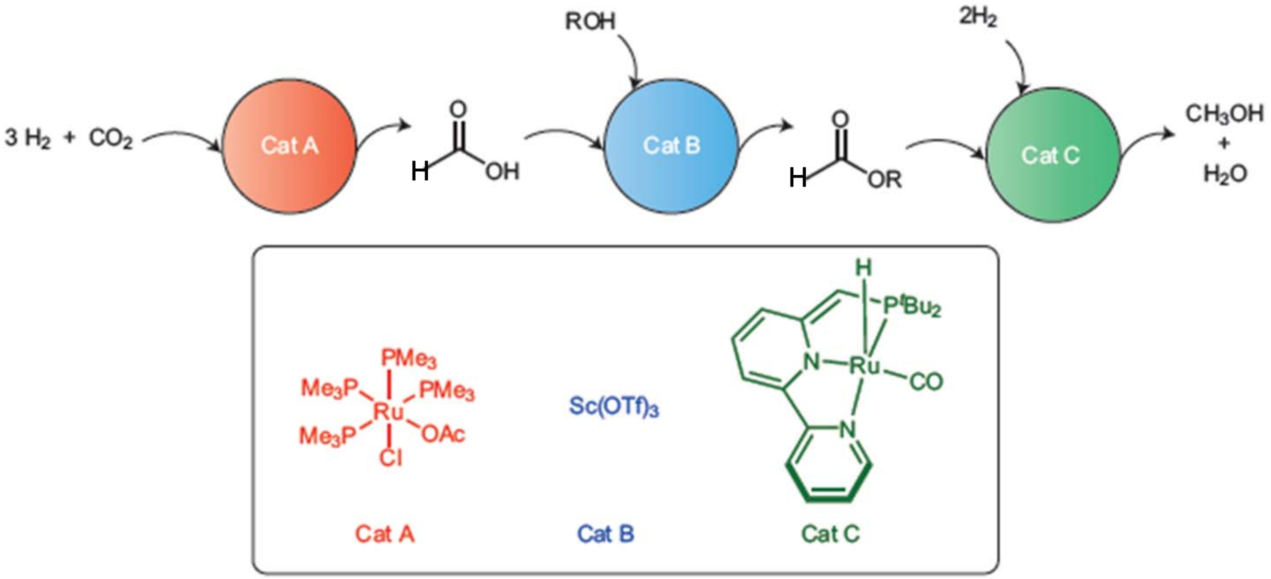
1) **Catalyst compatibility**: each catalyst must be compatible with each other, and with other reaction species (substrates, solvent, additives, intermediates, and so on);
2) **Reaction selectivity**: every step of a tandem reaction should strictly follow the designed sequence to avoid the generation of side products or termination of the tandem reaction;
3) Furthermore, each step should have high **regioselectivity, diastereoselectivity, and enantioselectivity**. Otherwise, the tandem reaction will produce many isomers that are difficult to purify.

Solutions:

1) **Use of compatible catalysts system**. For example, fine tuning the hardness and softness of the catalysts;
2) **Use of site-isolated techniques**. For example, the use of a microencapsulated multicatalyst system to avoid catalyst interference;
3) **Use of phase-separation techniques.** For example, taking advantage of the hydrophobic property of the substrates with similar reactivity, using aqueous and organic biphasic system to accomplish the desired reaction sequence;
4) Sequential addition of catalyst and substrates.(for other one-pot reactions)

Addressing catalyst incompatibility

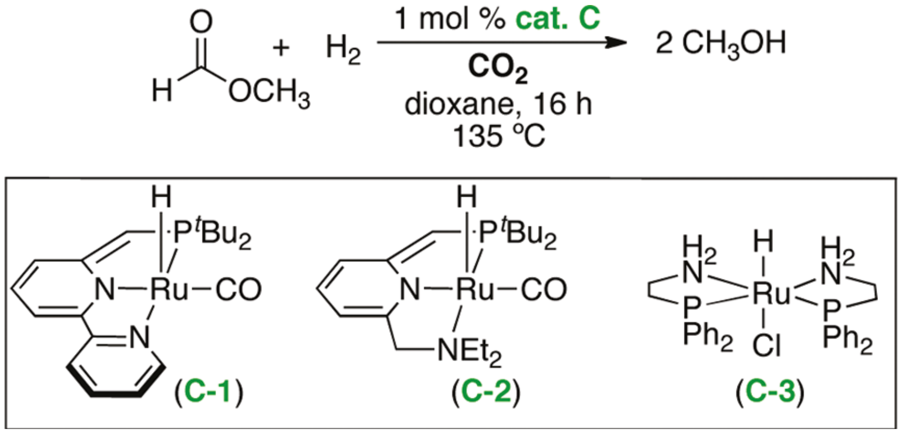
Homogeneous hydrogenation of CO_2 to methanol

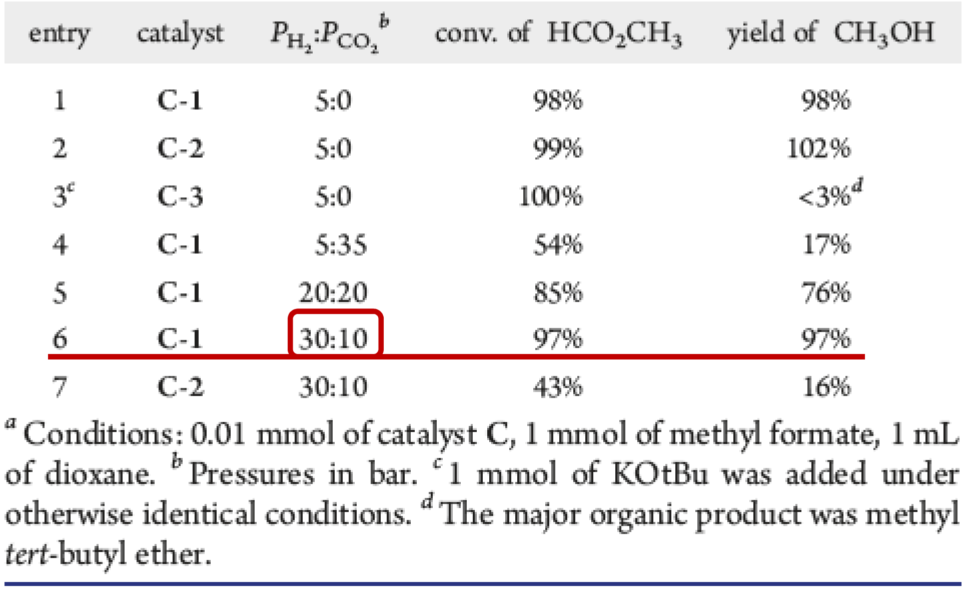


Cat A [Ru]: hydrogenation of CO_2
Cat B $Sc(OTf)_3$: esterification
Cat C (PNN)Ru: hydrogenation of the formate

Sanford, M. S. *et al*. *J. Am. Chem. Soc.* **2011**, *133,* 18122–18125.

Hydrogenation of CO_2 to methanol



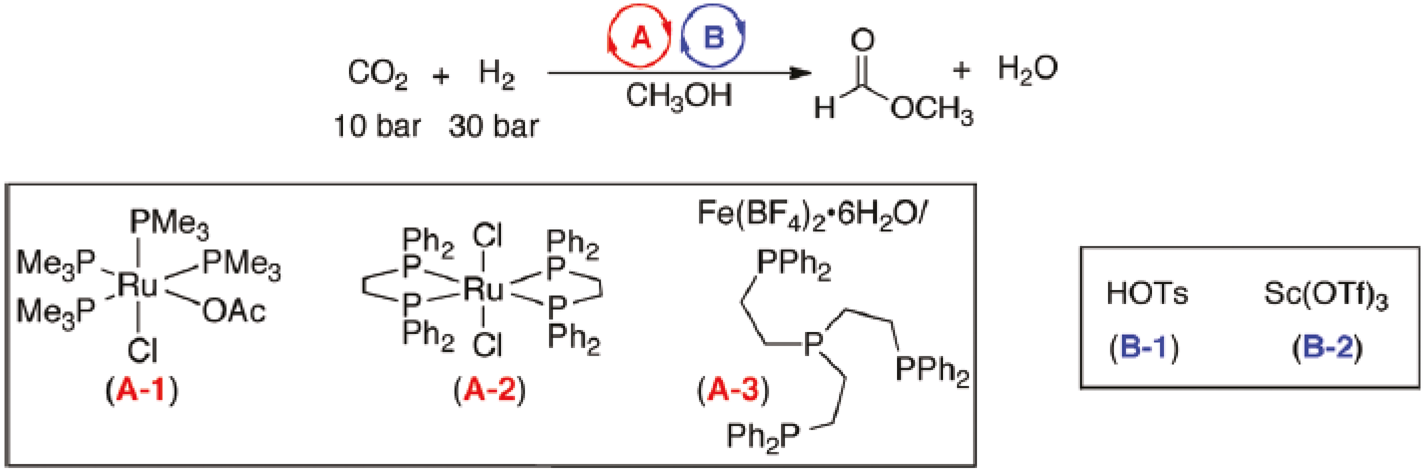


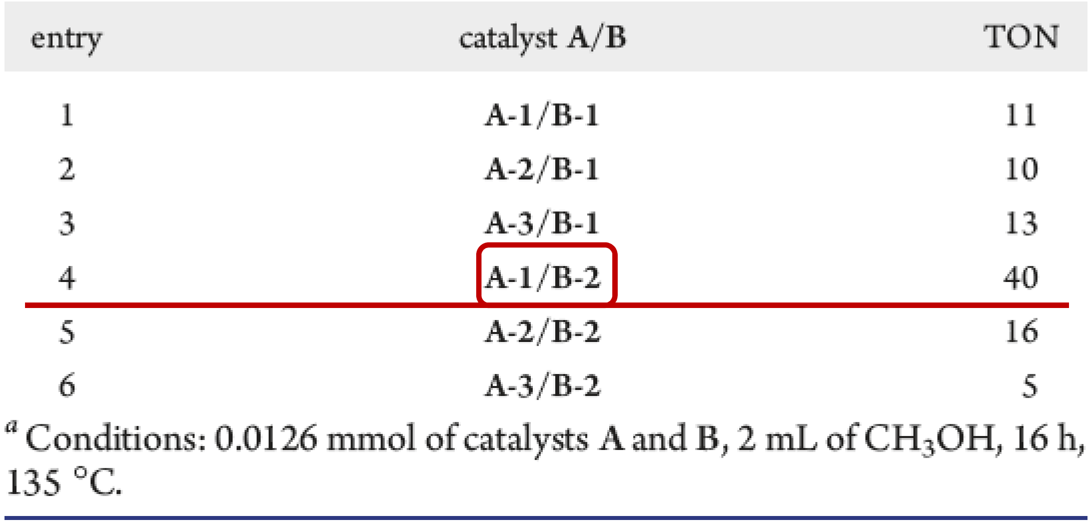
entry	catalyst	$P_{H_2}:P_{CO_2}$[b]	conv. of HCO_2CH_3	yield of CH_3OH
1	C-1	5:0	98%	98%
2	C-2	5:0	99%	102%
3[c]	C-3	5:0	100%	<3%[d]
4	C-1	5:35	54%	17%
5	C-1	20:20	85%	76%
6	C-1	30:10	97%	97%
7	C-2	30:10	43%	16%

[a] Conditions: 0.01 mmol of catalyst C, 1 mmol of methyl formate, 1 mL of dioxane. [b] Pressures in bar. [c] 1 mmol of KOtBu was added under otherwise identical conditions. [d] The major organic product was methyl *tert*-butyl ether.

Sanford, M. S. *et al. J. Am. Chem. Soc.* **2011**, *133,* 18122–18125.

Hydrogenation of CO_2 to methanol



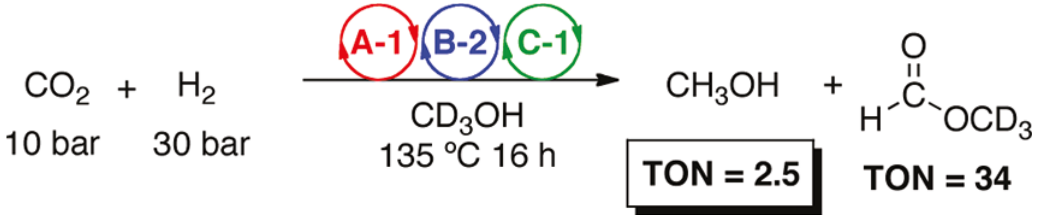


entry	catalyst A/B	TON
1	**A-1/B-1**	11
2	**A-2/B-1**	10
3	**A-3/B-1**	13
4	**A-1/B-2**	40
5	**A-2/B-2**	16
6	**A-3/B-2**	5

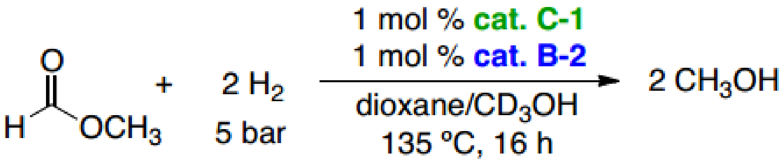
[a] Conditions: 0.0126 mmol of catalysts A and B, 2 mL of CH_3OH, 16 h, 135 °C.

Sanford, M. S. *et al*. *J. Am. Chem. Soc.* **2011**, *133,* 18122–18125.

Hydrogenation of CO_2 to methanol



Hydrogenation of ester in the Presence of B-2

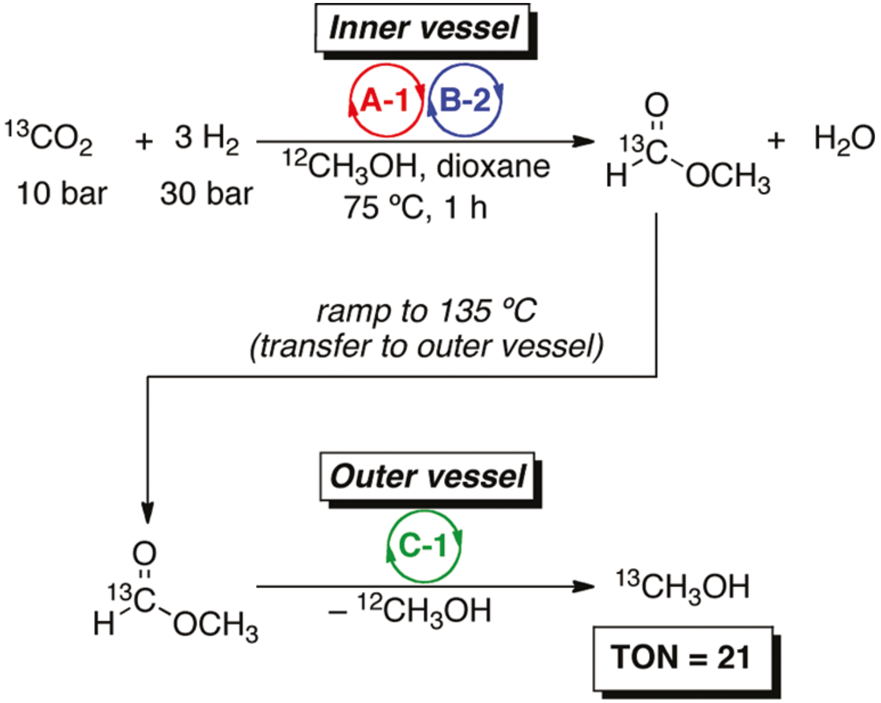


Entry[a]	Additive	Conversion HCO_2CH_3	Yield CH_3OH
1	none	100%	103%
2[b]	**B-2**	22%	31%

[a] Conditions: 1 mmol HCO_2CH_3, catalyst **C-1** (0.0126 mmol), 1 mL dioxane, 40 µL CD_3OH, 135 C, 16 h. Note: CD_3OH used to solvate **B-2**. [b] Catalyst **B-2** (0.0126 mmol).

Sanford, M. S. *et al. J. Am. Chem. Soc.* **2011**, *133,* 18122–18125.

Hydrogenation of CO_2 to methanol

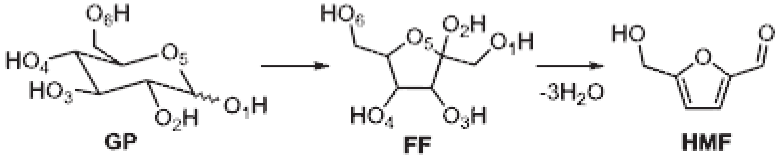


Placing a physical barrier between catalysts while allowing full access to catalytic reactants and intermediates can be achieved by means of equipment design.

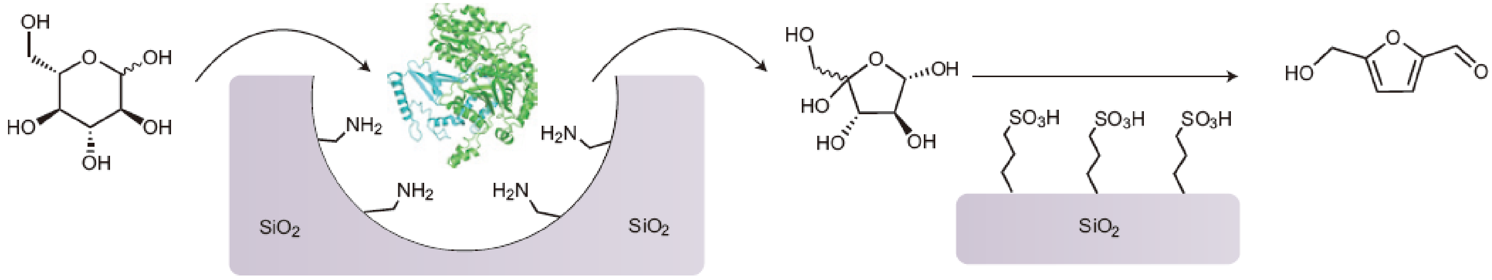
Sanford, M. S. *et al. J. Am. Chem. Soc.* **2011**, *133,* 18122–18125.

Conversion of cellulosic biomass to renewable chemicals

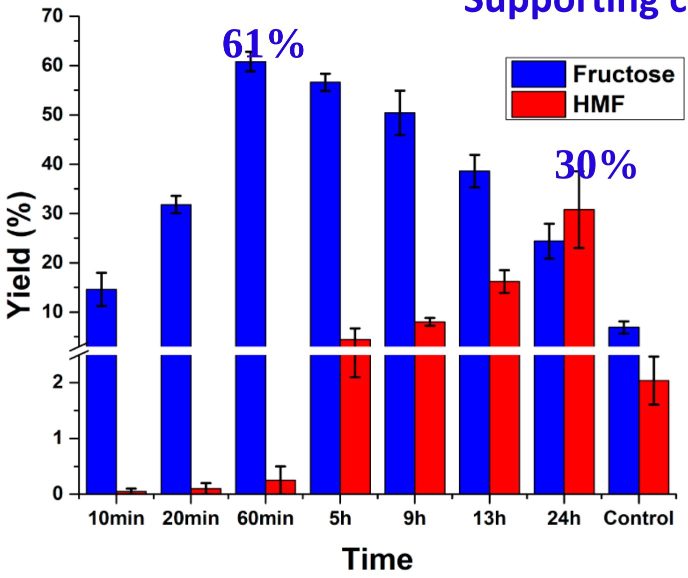
Tandem Catalytic Conversion of Glucose to 5-Hydroxymethylfurfural



THF:H_2O (4:1 v/v) , 363 K , 24 h.



Supporting catalysts on a protective solid phase



A thermophilic glucose isomerase enzyme on an amine (–NH_2)-functionalized mesoporous silica.

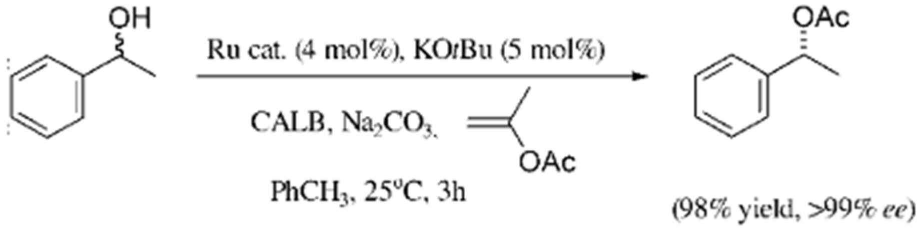
For glucose isomerization to fructose and a solid acid catalyst for fructose dehydration to HMF.

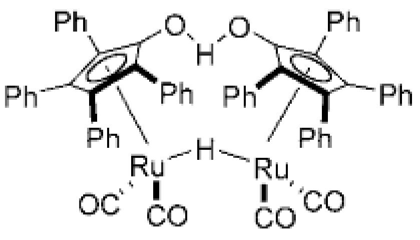
Results in a higher enzyme activity and stability in buffer, but also affords moderate protection in organic solvents at 363 K.

Huang, H. *et al. ACS Catal.* **2014***, 4*, 2165–2168.

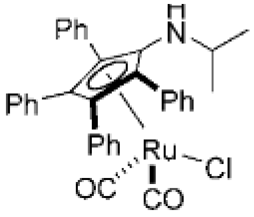
Efficient dynamic kinetic resolution of alcohols

Highly compatible metal and enzyme catalysts for efficient dynamic kinetic resolution of alcohols at ambient temperature

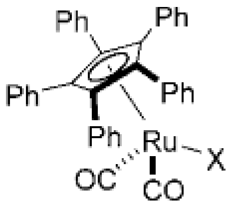




1



2



3a: X = Cl
3b: X = Br
3c: X = I

CALB: *Candida antarctica lipase B*

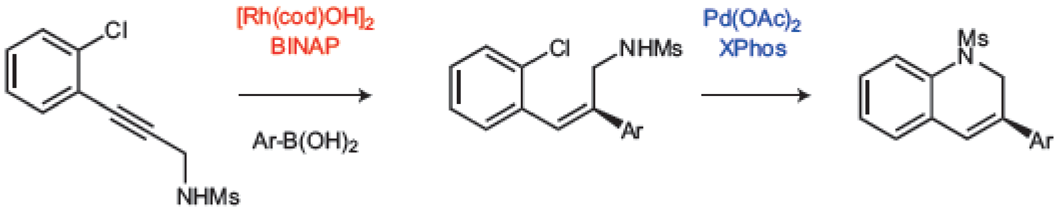
Complex 1 is activated at high temperature; Complex 2 takes very long reaction times when combined with an enzyme (lipase) in DKR at room temperature.

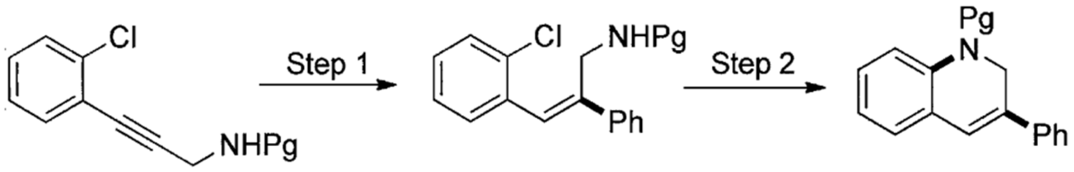
Conditions: enabled dynamic kinetic resolution at almost the same rate as the individual steps (**alcohol racemization** and **enzymatic esterification**) via catalyst selection and by allowing the pre-catalysts to react before substrate addition

Bäckvall, J. E. *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 6535–6539.

Addressing catalyst incompatibility

Tandem rhodium-catalyzed alkyne arylation/palladium-catalyzed N arylation: a mechanistic investigation





Step 1: 77 %
Step 2: 92 %

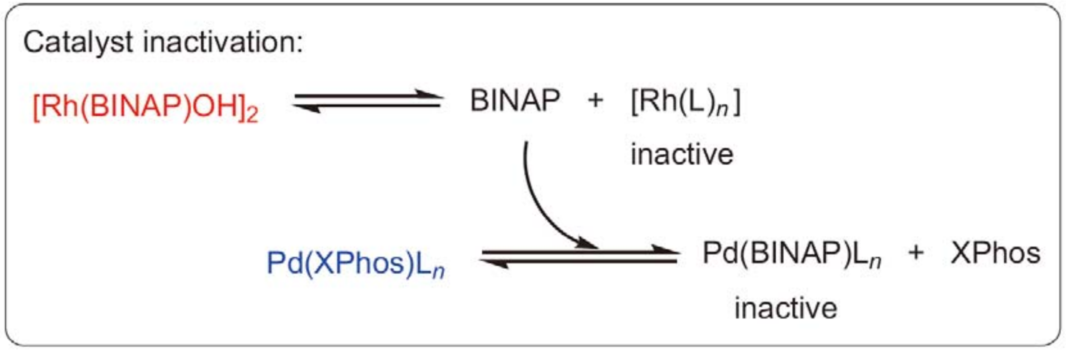
Step 1: [Rh(cod)OH]$_2$ (5 mol % [Rh]), ligand (5.2 mol %)
Ph-B(OH)$_2$ (2 equiv), K_2CO_3 (1.1 equiv), dioxane/additive

Step 2: Pd(OAc)$_2$ (2 mol %), ligand (4 mol %)
K_2CO_3 (1.1 equiv) or Cs_2CO_3 (1.4 equiv), dioxane

Together: 5 % + 0 %

Lautens, M. *et al*. *Angew. Chem. Int. Ed.* **2011**, *50*, 9089–9092.

Addressing catalyst incompatibility



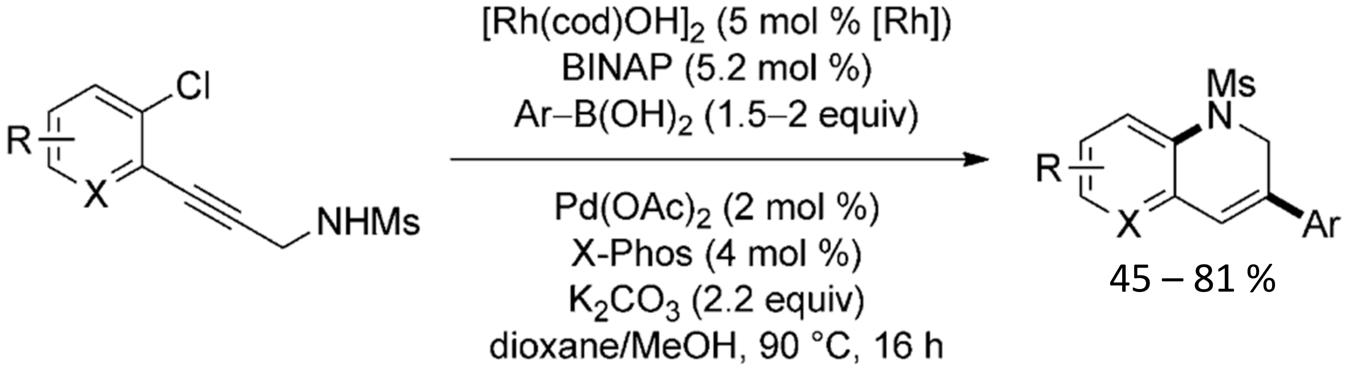
Catalyst inactivation:

$[Rh(BINAP)OH]_2 \rightleftharpoons$ BINAP + $[Rh(L)_n]$ inactive

$Pd(XPhos)L_n \rightleftharpoons Pd(BINAP)L_n$ + XPhos inactive

Premixing precatalyst and ligands before catalytic runs

Stock catalyst solutions ([Rh] with BINAP, and $Pd(OAc)_2$ with X-Phos), were mixed separately in dioxane at 50 °C for 15 min; then 0.5 mL of each solution was added to a vial.

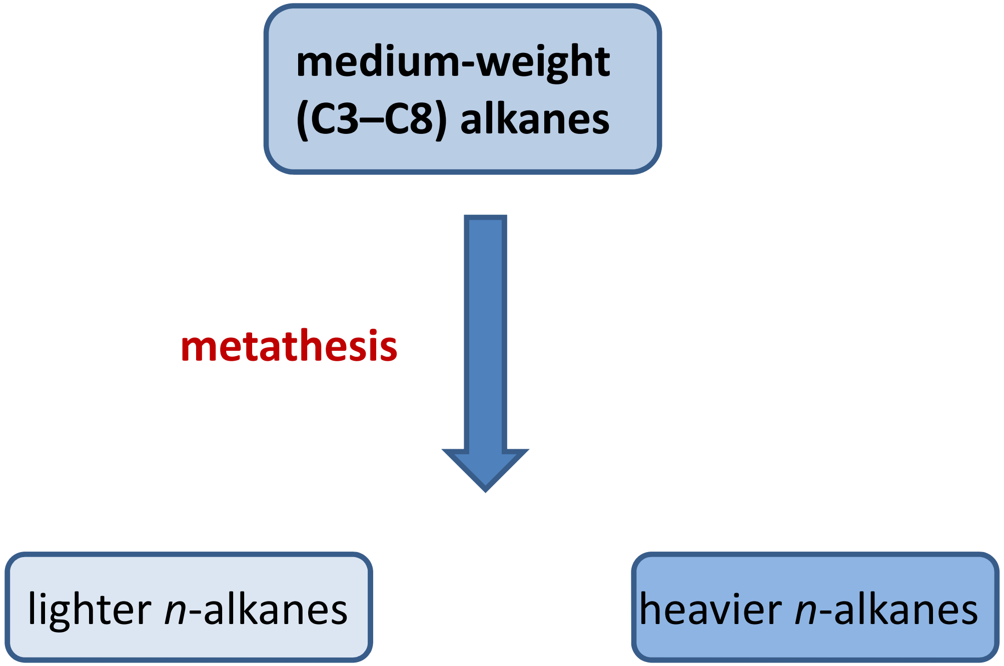


45 – 81 %

Lautens, M. *et al*. *Angew. Chem. Int. Ed.* **2011**, *50*, 9089–9092.

Hydrocarbon upgrading

Olefin hydrogenation/dehydrogenation with olefin metathesis

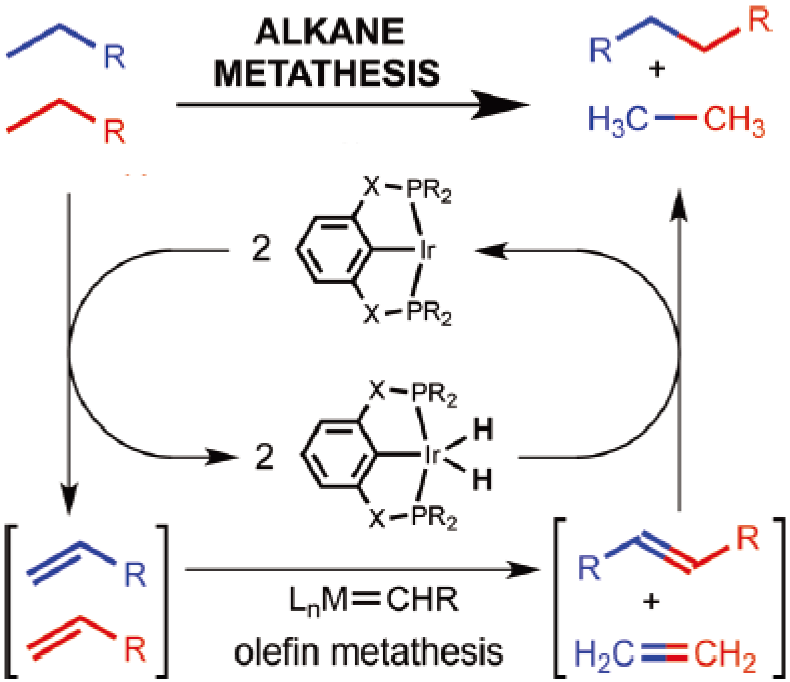


medium-weight (C3–C8) alkanes

metathesis

lighter *n*-alkanes

heavier *n*-alkanes

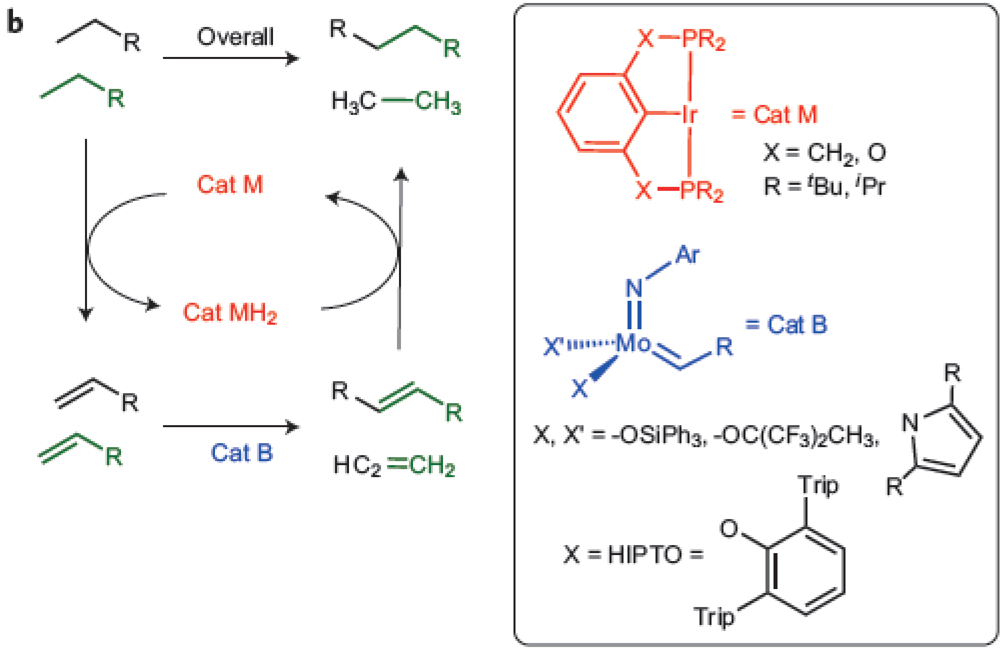


Liquid natural gas

Diesel and jet fuels

Homogeneous hydrocarbon upgrading

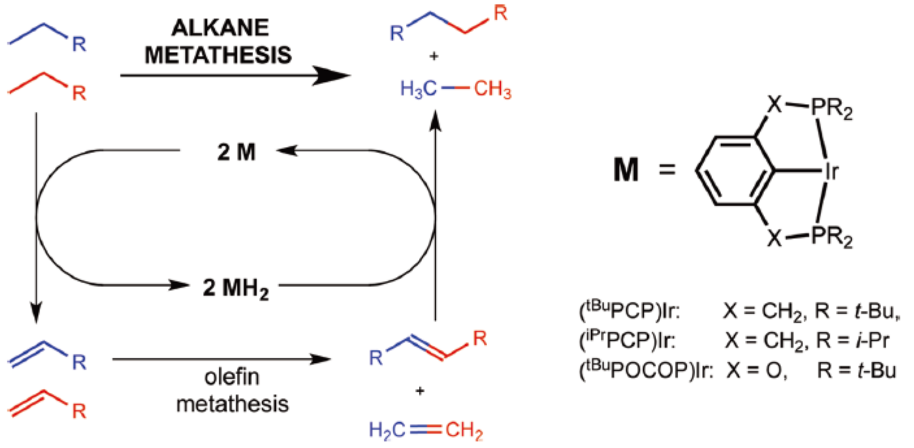
Alkane metathesis by tandem alkane-dehydrogenation olefin-metathesis catalysis



Brookhart, M.; Goldman, A. S. *et al. Acc. Chem. Res.* **2012**, *45*, 947–958.

Homogeneous hydrocarbon upgrading

Alkane metathesis by tandem alkane-dehydrogenation olefin-metathesis catalysis



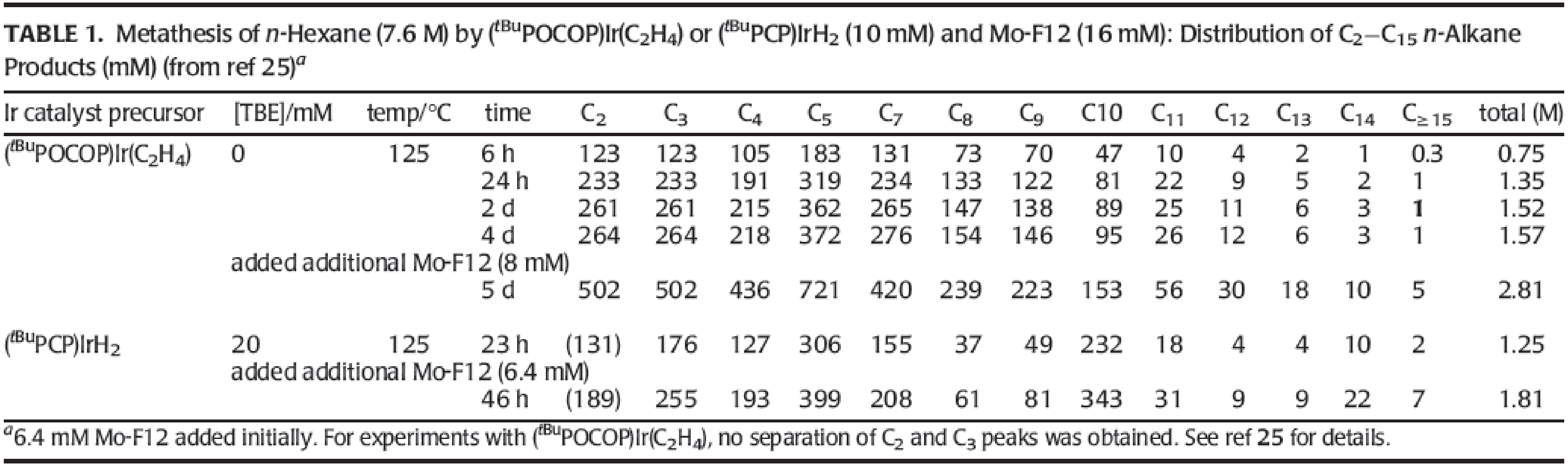


TABLE 1. Metathesis of *n*-Hexane (7.6 M) by (^{tBu}POCOP)Ir(C_2H_4) or (^{tBu}PCP)IrH_2 (10 mM) and Mo-F12 (16 mM): Distribution of C_2–C_{15} *n*-Alkane Products (mM) (from ref 25)[a]

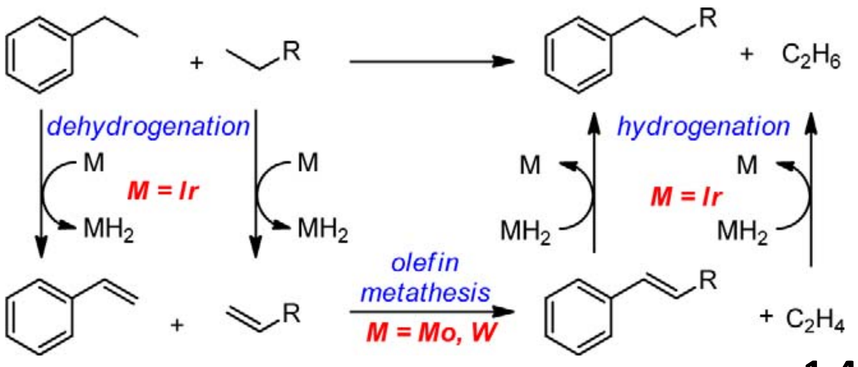
Ir catalyst precursor	[TBE]/mM	temp/°C	time	C_2	C_3	C_4	C_5	C_7	C_8	C_9	C10	C_{11}	C_{12}	C_{13}	C_{14}	$C_{\geq 15}$	total (M)
(^{tBu}POCOP)Ir(C_2H_4)	0	125	6 h	123	123	105	183	131	73	70	47	10	4	2	1	0.3	0.75
			24 h	233	233	191	319	234	133	122	81	22	9	5	2	1	1.35
			2 d	261	261	215	362	265	147	138	89	25	11	6	3	1	1.52
			4 d	264	264	218	372	276	154	146	95	26	12	6	3	1	1.57
	added additional Mo-F12 (8 mM)																
			5 d	502	502	436	721	420	239	223	153	56	30	18	10	5	2.81
(^{tBu}PCP)IrH_2	20	125	23 h	(131)	176	127	306	155	37	49	232	18	4	4	10	2	1.25
	added additional Mo-F12 (6.4 mM)																
			46 h	(189)	255	193	399	208	61	81	343	31	9	9	22	7	1.81

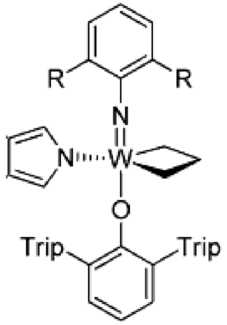
[a] 6.4 mM Mo-F12 added initially. For experiments with (^{tBu}POCOP)Ir(C_2H_4), no separation of C_2 and C_3 peaks was obtained. See ref 25 for details.

Brookhart, M.; Goldman, A. S. *et al. Acc. Chem. Res.* **2012**, *45*, 947–958.

Homogeneous hydrocarbon upgrading

Catalytic Synthesis of *n*-Alkyl Arenes through Alkyl Group Cross-Metathesis

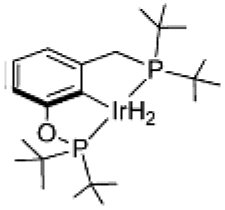




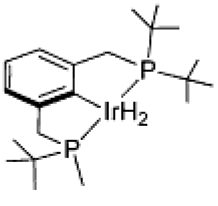
1a; R = i-Pr
1b; R = Me

Trip = 2,4,6-i-$Pr_3C_6H_2$

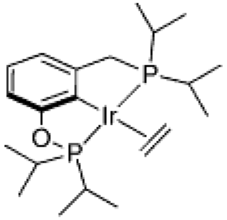
1:4 (v/v) n-octane/ethylbenzene at 150 °C for 2 days using 16 mM 1a and 10 mM $(^{tBu}POCOP)Ir(C_2H_4)$



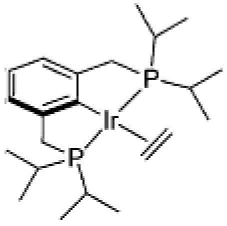
$(^{tBu}PCOP)IrH_2$



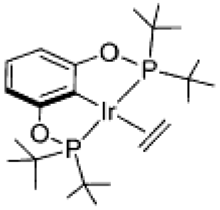
$(^{tBu3Me}PCP)IrH_2$



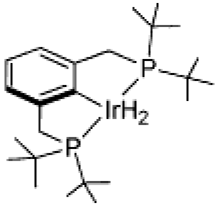
$(^{iPr}PCOP)Ir(C_2H_4)$



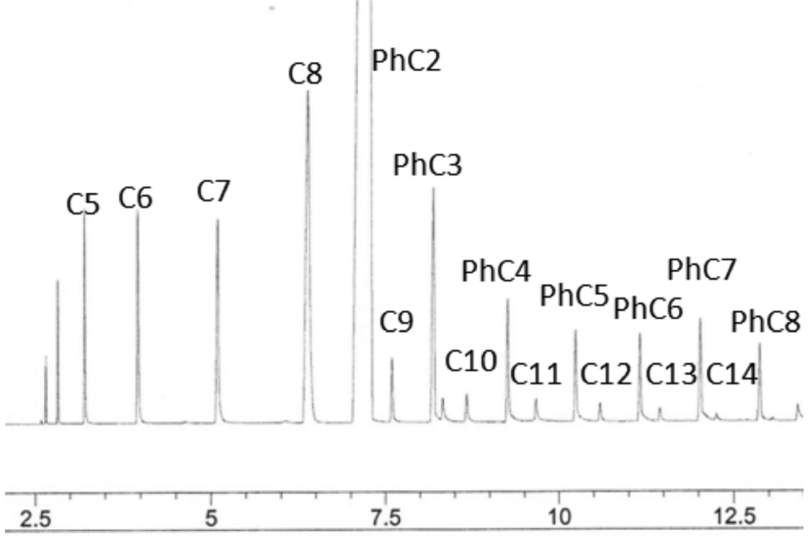
$(^{iPr}PCP)Ir(C_2H_4)$



$(^{tBu}POCOP)Ir(C_2H_4)$



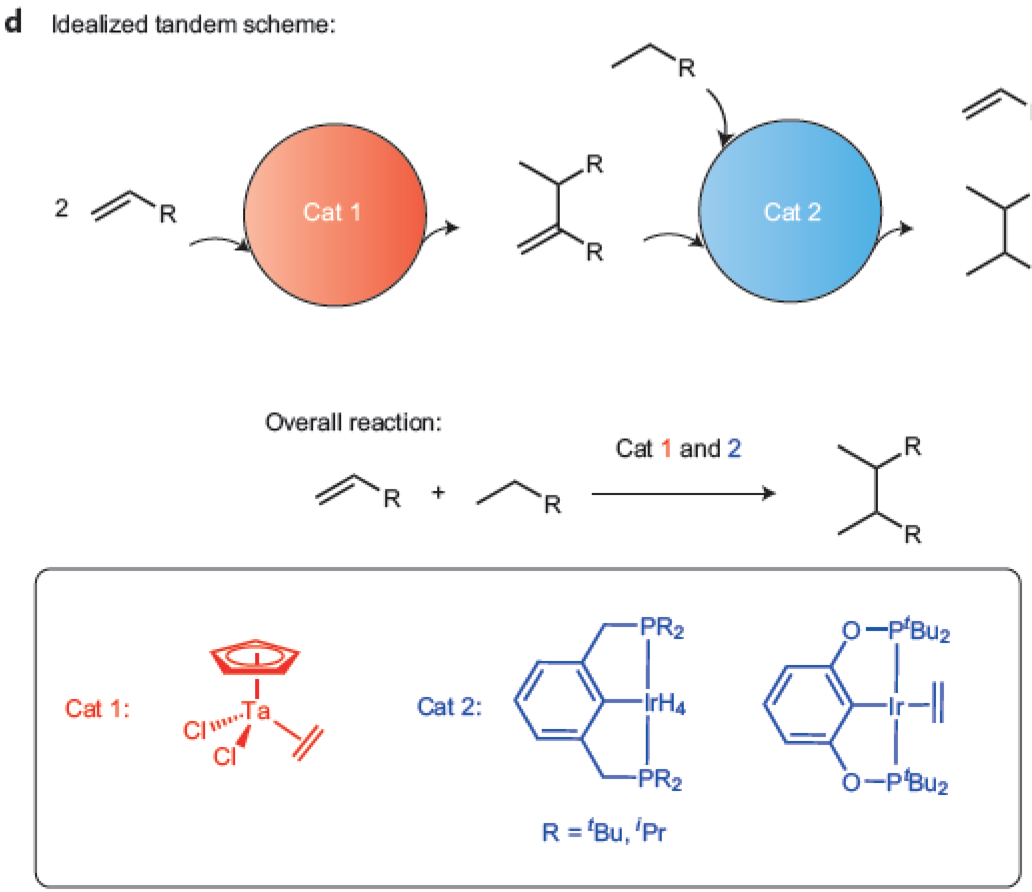
$(^{tBu}PCP)IrH_2$



Schrock, R. R. *et al. J. Am. Chem. Soc.* **2013***, 135***,** 12572–12575.

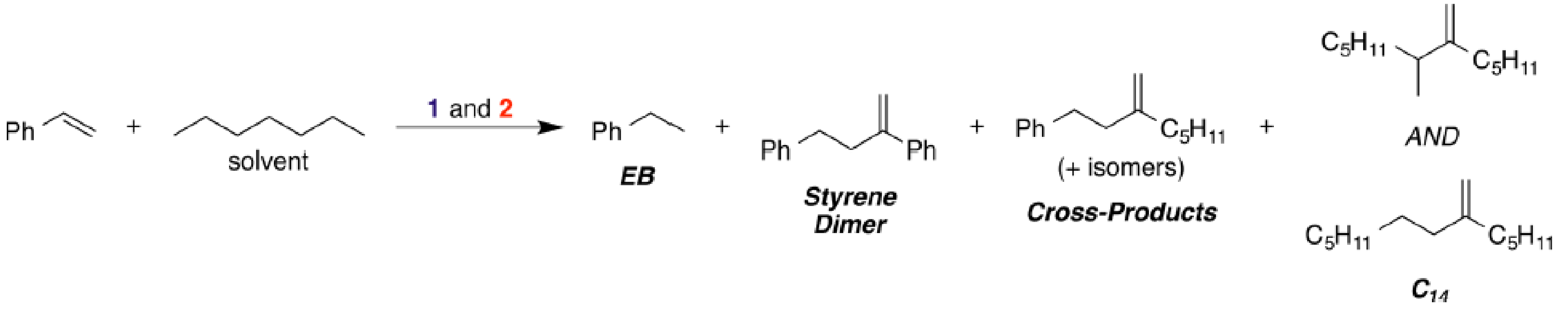
Hydrocarbon upgrading

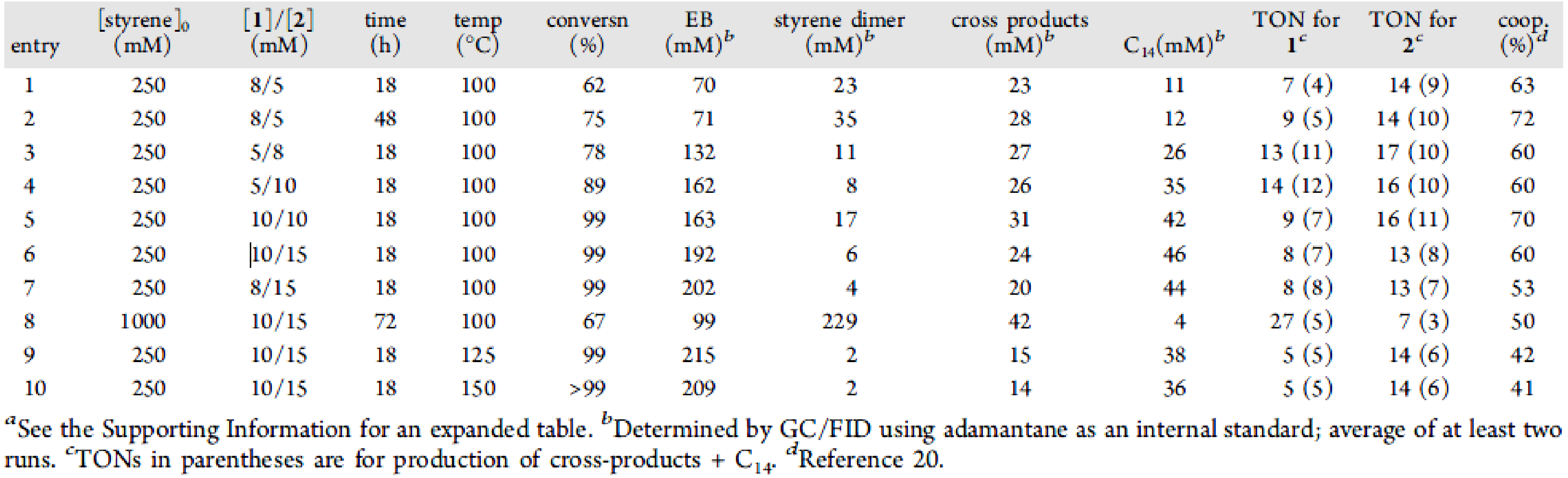
Tantalum/iridium tandem catalytic alkane/alkene upgrading



Bercaw, J. E. *et al*. *Organometallics*, **2014**, *33*, 3353–3365.

Hydrocarbon upgrading





entry	$[\text{styrene}]_0$ (mM)	[1]/[2] (mM)	time (h)	temp (°C)	conversn (%)	EB (mM)[b]	styrene dimer (mM)[b]	cross products (mM)[b]	C_{14}(mM)[b]	TON for 1[c]	TON for 2[c]	coop. (%)[d]
1	250	8/5	18	100	62	70	23	23	11	7 (4)	14 (9)	63
2	250	8/5	48	100	75	71	35	28	12	9 (5)	14 (10)	72
3	250	5/8	18	100	78	132	11	27	26	13 (11)	17 (10)	60
4	250	5/10	18	100	89	162	8	26	35	14 (12)	16 (10)	60
5	250	10/10	18	100	99	163	17	31	42	9 (7)	16 (11)	70
6	250	10/15	18	100	99	192	6	24	46	8 (7)	13 (8)	60
7	250	8/15	18	100	99	202	4	20	44	8 (8)	13 (7)	53
8	1000	10/15	72	100	67	99	229	42	4	27 (5)	7 (3)	50
9	250	10/15	18	125	99	215	2	15	38	5 (5)	14 (6)	42
10	250	10/15	18	150	>99	209	2	14	36	5 (5)	14 (6)	41

[a] See the Supporting Information for an expanded table. [b] Determined by GC/FID using adamantane as an internal standard; average of at least two runs. [c] TONs in parentheses are for production of cross-products + C_{14}. [d] Reference 20.

[Ta] catalyst operates most efficiently at **high [alkene]([4M])** and at **lower temperature**; In contrast, **[Ir] catalyst** is most active at **higher temperatures (125 °C)** with a rate law that is **inverse order in [alkene]**. Moderate temperatures (100 °C) and [alkene] 0.25M were choosed for both catalytic cycles.

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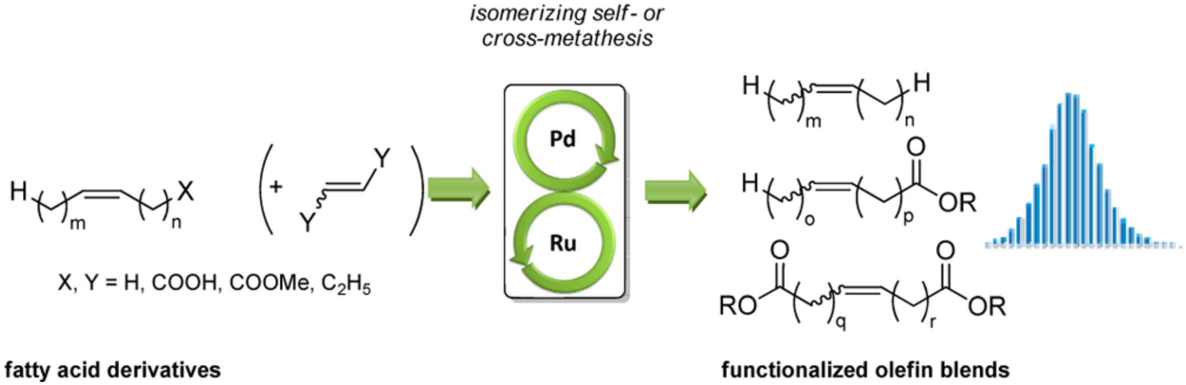
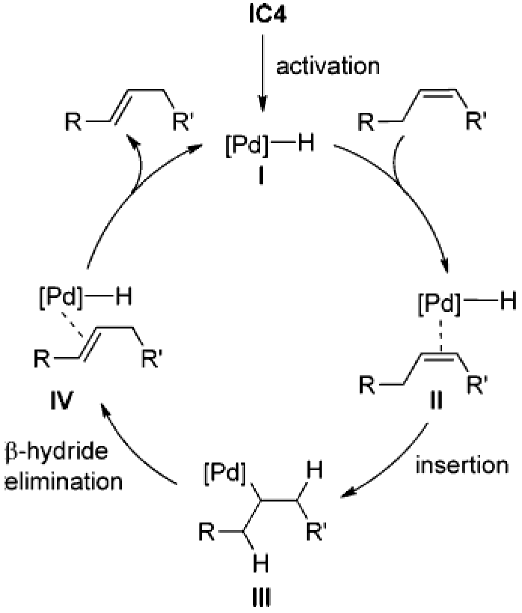
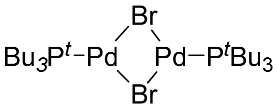
Hydrocarbon upgrading

Distributions of Unsaturated Compounds from Fatty Acids



[Pd]: migration of double bond
[Ru]: RCM reaction



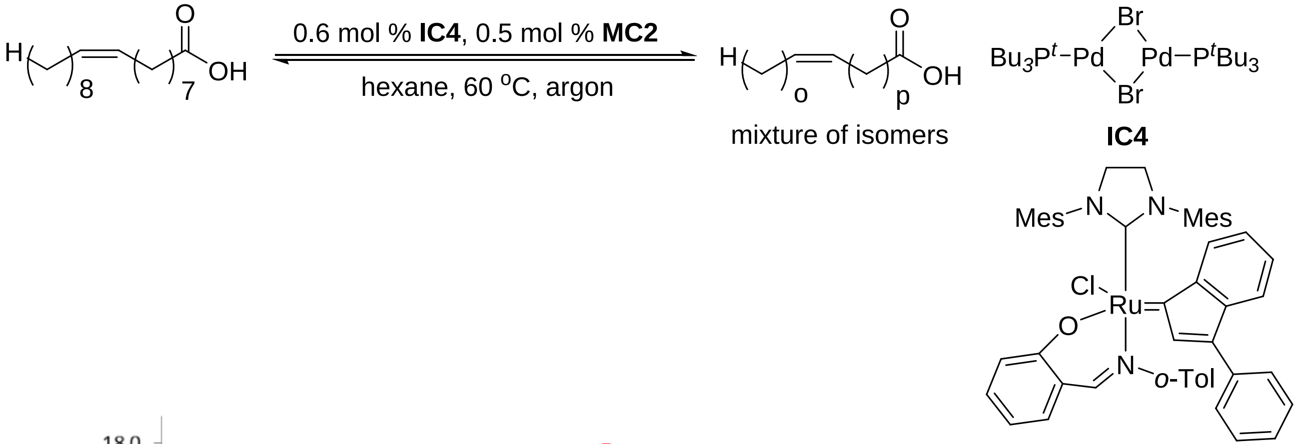


IC 4

Ohlmann, D. M. *et al*. *J. Am. Chem. Soc.* **2012**, *134*, 13716–13729.

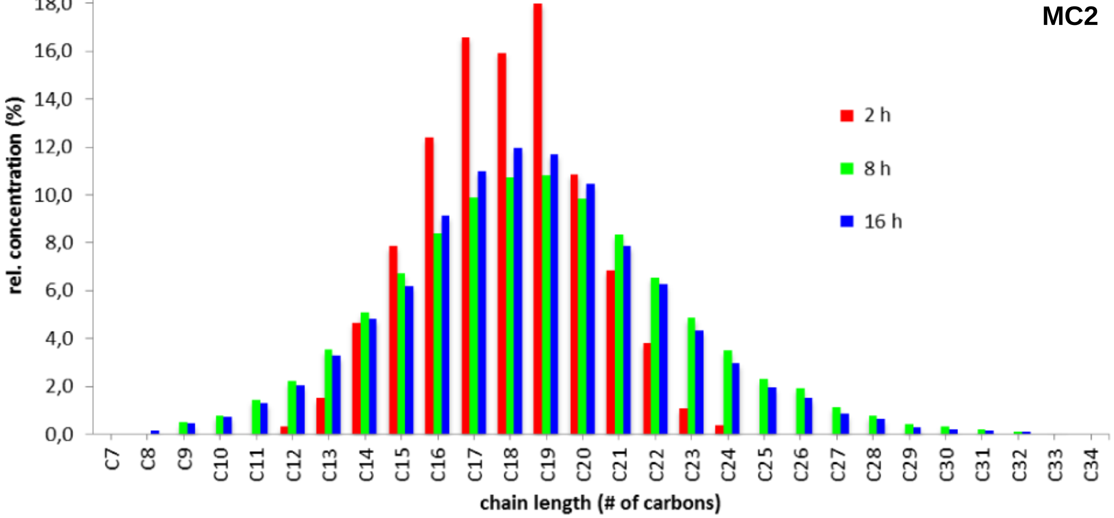
Hydrocarbon upgrading

Distributions of Unsaturated Compounds from Fatty Acids



IC4

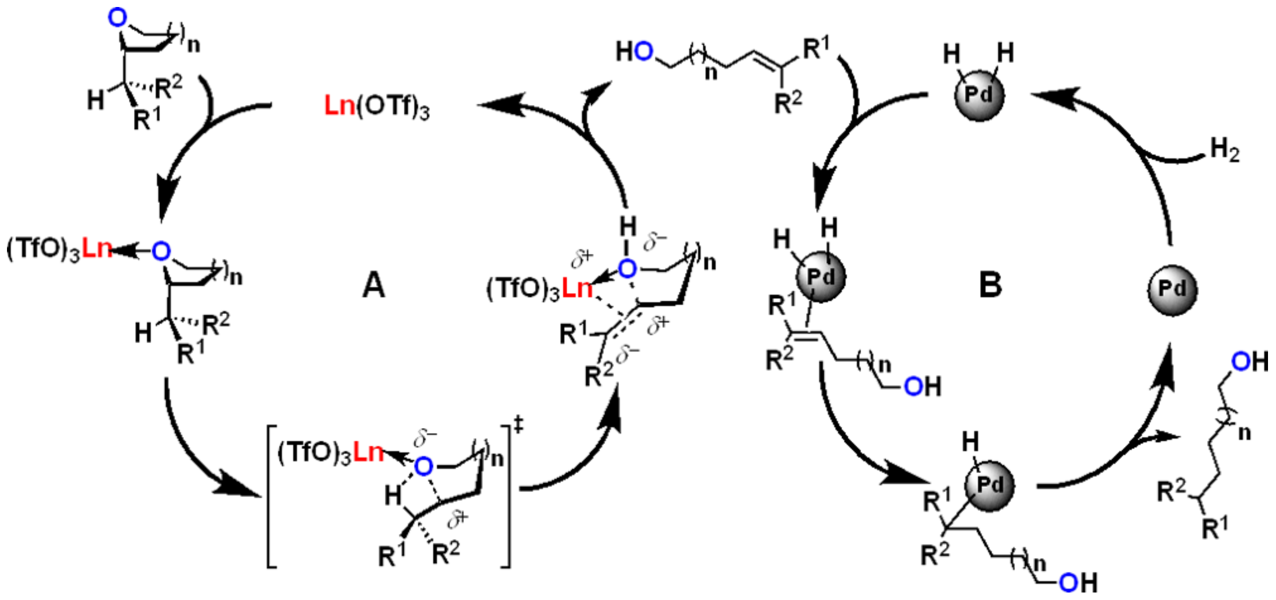
MC2



Ohlmann, D. M. *et al. J. Am. Chem. Soc.* **2012**, *134*, 13716–13729.

Thermodynamic leveraging

Tandem etheric C–O Bond Hydrogenolysis



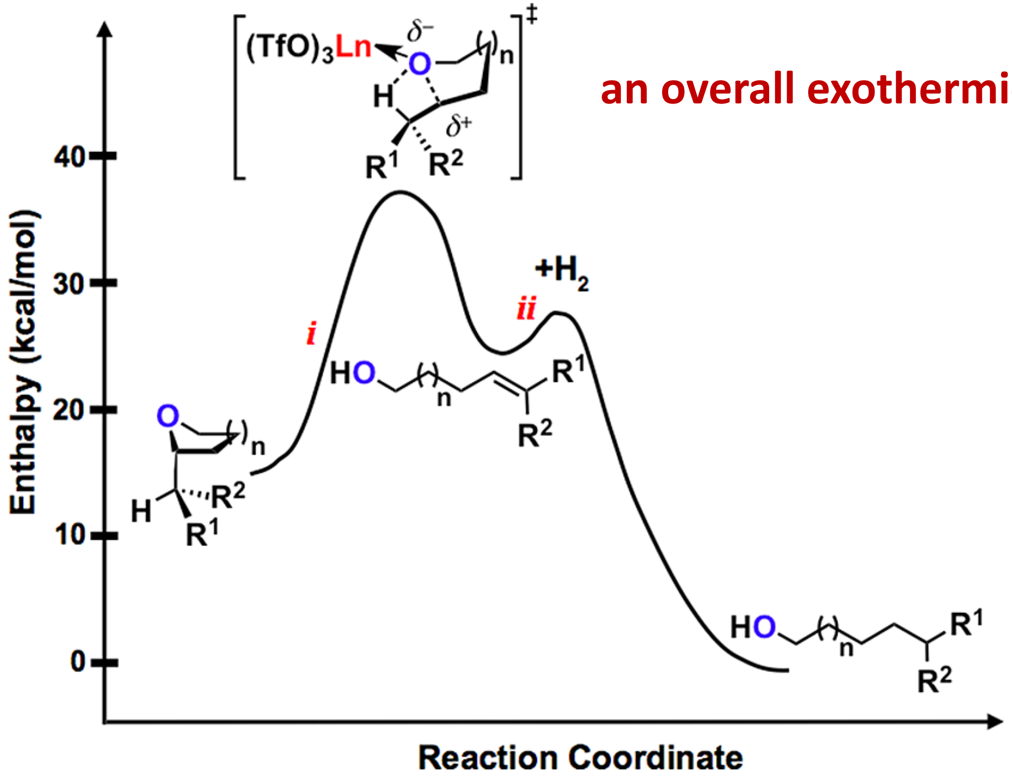
C–O scission

Hydrogenation of C=C

Marks, T. J. *et al. J. Am. Chem. Soc.* **2012**, *134*, 14682–14685.

Thermodynamic leveraging

Tandem etheric C−O Bond Hydrogenolysis



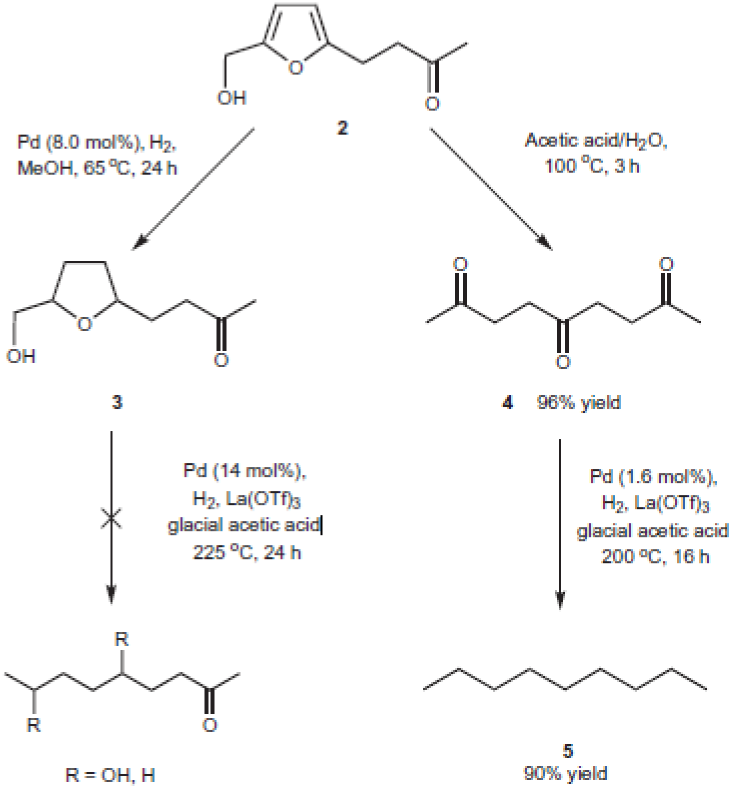
an overall exothermic/exoergic process

C−O bond scission process is endothermic (ΔH ≈ +14 kcal/mol) and C=C hydrogenation is exothermic (ΔH ≈ −25 kcal/mol).

Marks, T. J. *et al. J. Am. Chem. Soc.* **2012**, *134*, 14682–14685.

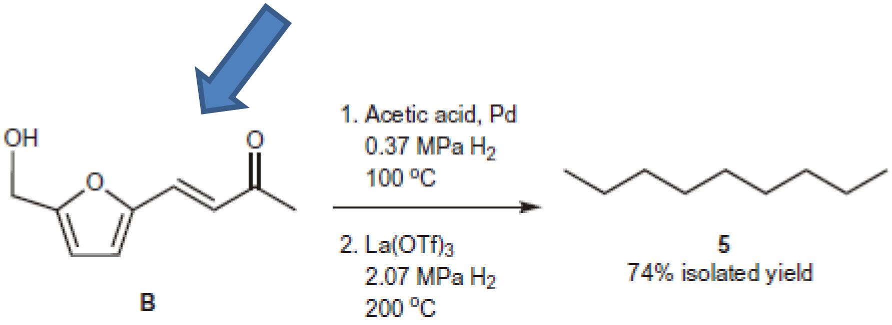
Thermodynamic leveraging

The hydrodeoxygenation of bioderived furans into alkanes



Glucose and xylose

biomass



Sutton, A. D. *et al.*. *Nature Chem.* **5,** 428–432 (2013).

Summary for orthogonal tandem catalysis

Advantages

Greater economy of time, energy and resources and overall process, workup and purification simplicity; lower the risk in the storage, transportation, and the handling of toxic, unstable, or explosive intermediates, and promote equilibrium reactions to full conversion by directly coupling them in the following reaction cycle.

Challenges:

1) **Catalyst compatibility: each catalyst must be compatible with each other, and with other reaction species (substrates, solvent, additives, intermediates, and so on);**
2) **Reaction selectivity: every step of a tandem reaction should strictly follow the designed sequence to avoid the generation of side products or termination of the tandem reaction;**
3) **Furthermore, each step should have high regioselectivity, diastereoselectivity, and enantioselectivity. Otherwise, the cascade reaction will produce many isomers that are difficult to purify.**

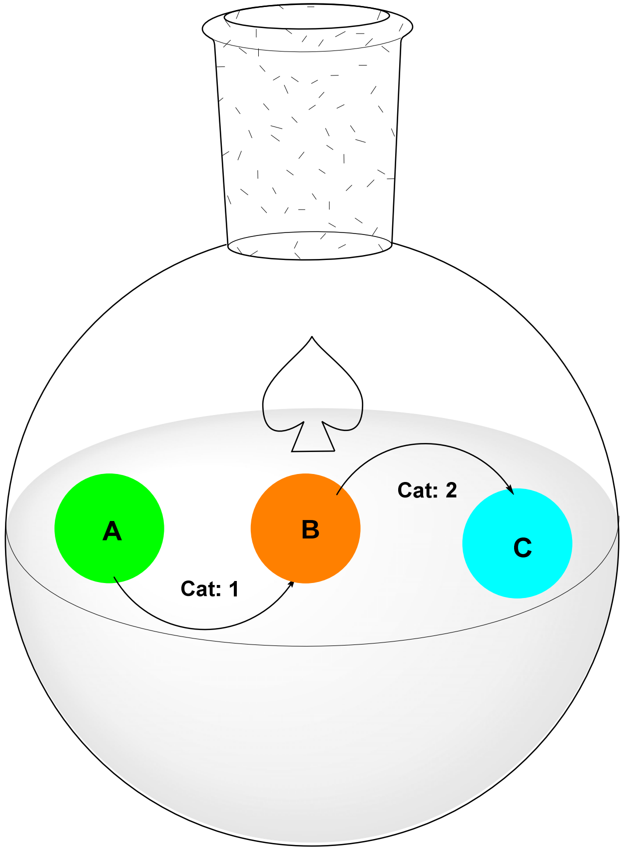
Summary for orthogonal tandem catalysis

Solutions:

1) **Different catalysts must accommodate the same reaction conditions and catalyst lifetimes over the relevant reaction times;**
2) **Placing a physical barrier between catalysts to avoid two component catalysts interacting directly or supporting one (or both) catalysts on a protective solid phase;**
3) **Premixing precatalyst and ligands before catalytic runs, while optimizing catalyst:ligand ratios, ligand poisoning effects can be significantly suppressed;**
4) **And so on · · ·**

New direction:

1) **We wish also to highlight the thermodynamic leveraging approach of coupling the endothermic/endergonic reverse of a well-characterized catalytic process with a second exothermic/exergonic process, to render the combined process thermodynamically favourable.**
2) **Indeed, there are multiple combinations of reactions and catalysts that are ripe for experimental and mechanistic study; for example, could this methodology be applied to other hydroelementation reactions and their reverse?**



Thanks for your attention!