Metal Catalyzed Redox Reactions

Nathan Jui

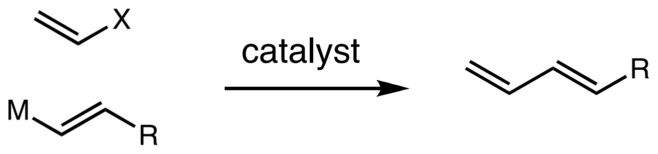
MacMillan Group Meeting

January 27, 2010

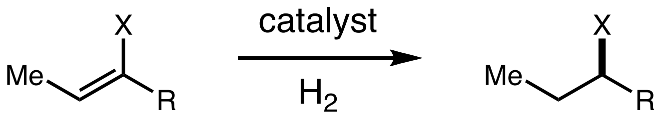
Metal Catalyzed Redox Reactions

- Many metal-catalyzed reactions involve redox processes

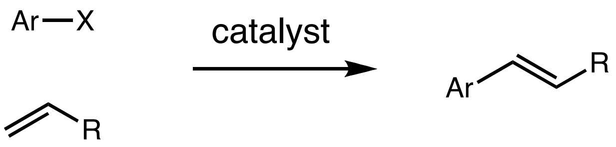
Cross-Coupling Chemistry



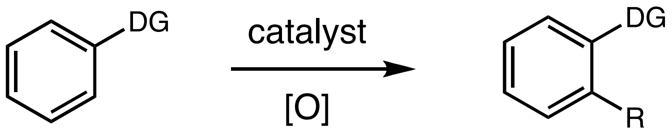
Reduction Chemistry



Heck-Type Chemistry



Oxidation Chemstry



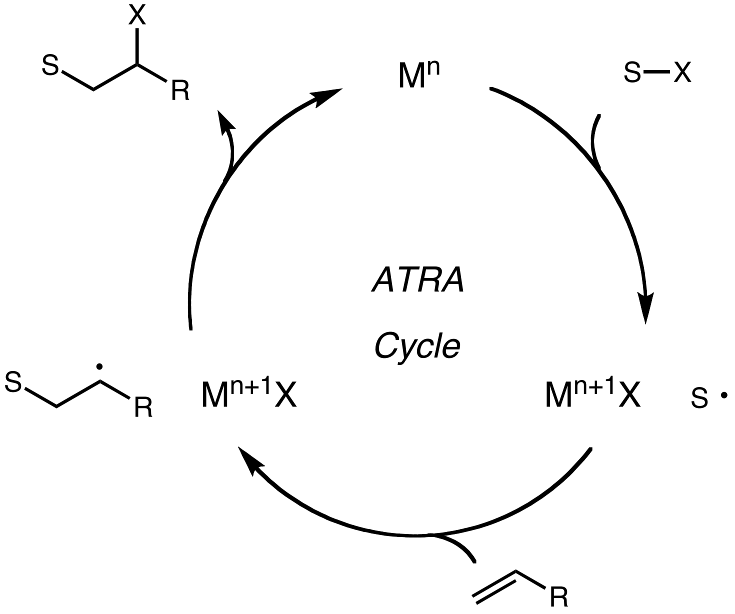
- These reactions and their mechanisms will not be addressed

Metal Catalyzed Redox Reactions

- Many metal-catalyzed reactions involve redox processes

Constraints Applied

1. Catalytic in metal
2. Single electron transfer processes
3. Net redox neutral (no terminal oxidant)
4. No light (purely chemical activation)
5. Selective generation of organic radicals



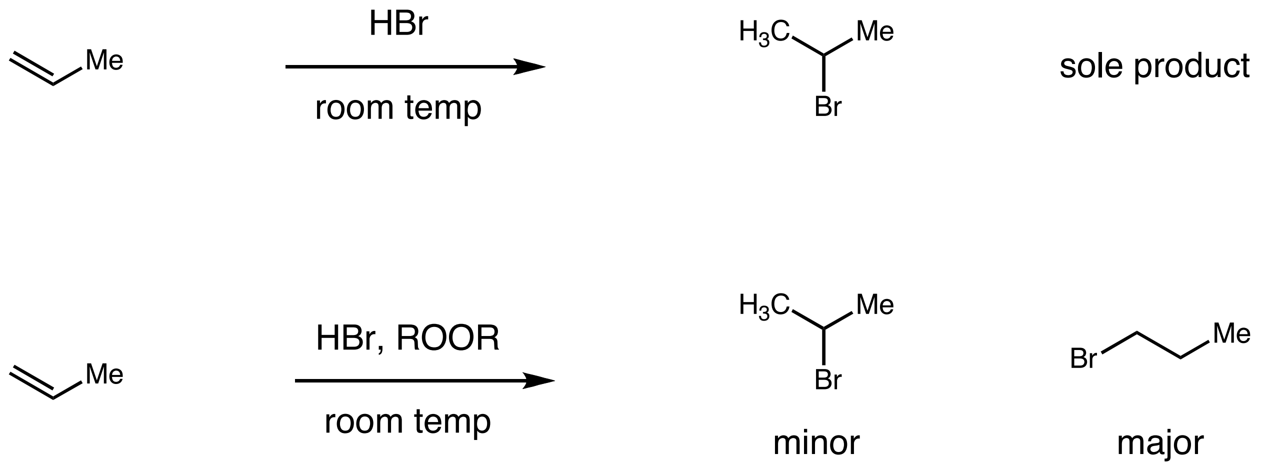
If electron transfer is accompanied occurs via inner-sphere mechanism

⇩

Atom Transfer Radical Chemistry

Radical Addition Mechanism as First Defined

- The 'Peroxide Effect' as observed by Kharasch and co-workers (1933)

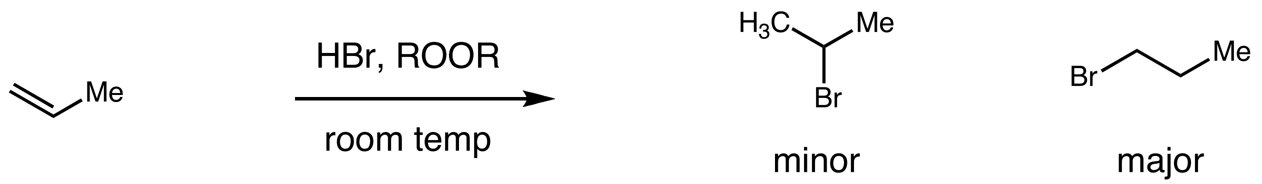


> *"The presence of benzoyl peroxide or ascaridole modified profoundly the course of the addition and the product of the reaction was largely, if not all, normal propyl bromide"*
>
> -Morris Kharasch

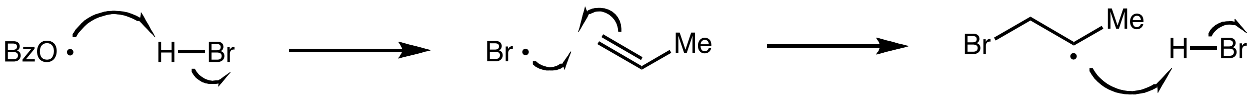
Kharasch, M. S. *J. Am. Chem. Soc.* **1933**, *55*, 2531.

Radical Addition Mechanism as First Defined

- The 'Peroxide Effect' independantly defined by Kharash et al. as well as Hey and Waters (1937)



> *"...it may be suggested that the addition process is one requiring the transient production of neutal atoms of hydrogen and broming from hydrogen bromide"*
>
> -Hey and Waters

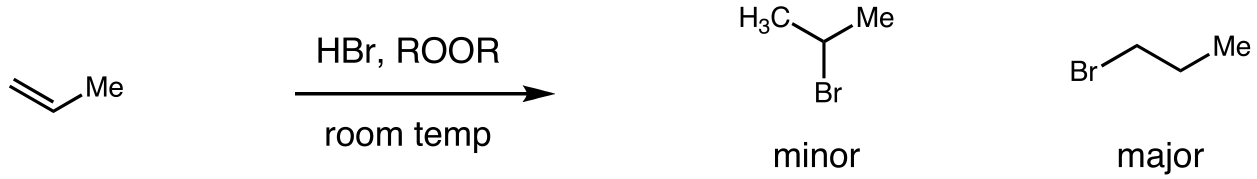


Kharasch, M. S. *J. Org. Chem.* **1937**, *2*, 288.

Hey, D.; Waters, W. *Chem. Rev.* **1937**, *21*, 1969.

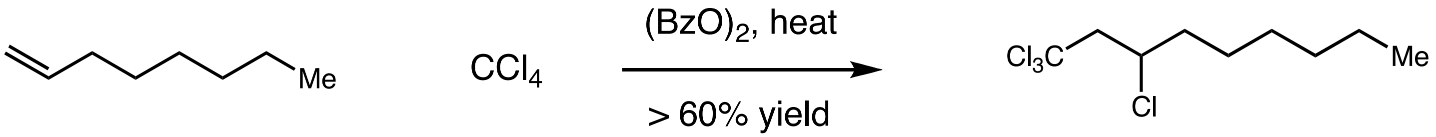
Radical Addition Mechanism as First Defined

- The 'Peroxide Effect' independantly defined by Kharash et al. as well as Hey and Waters (1937)



Kharasch, M. S. *J. Org. Chem.* **1937**, *2*, 288.

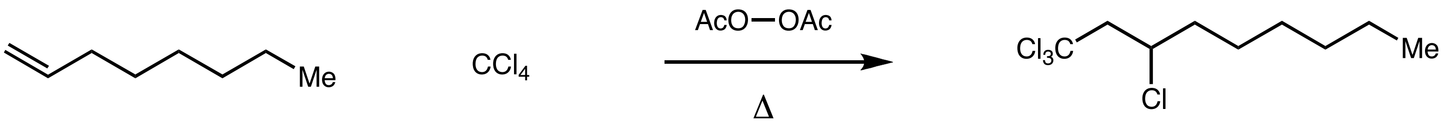
- Kharasch later reported the radical addition of halomethanes to olefins (1945)

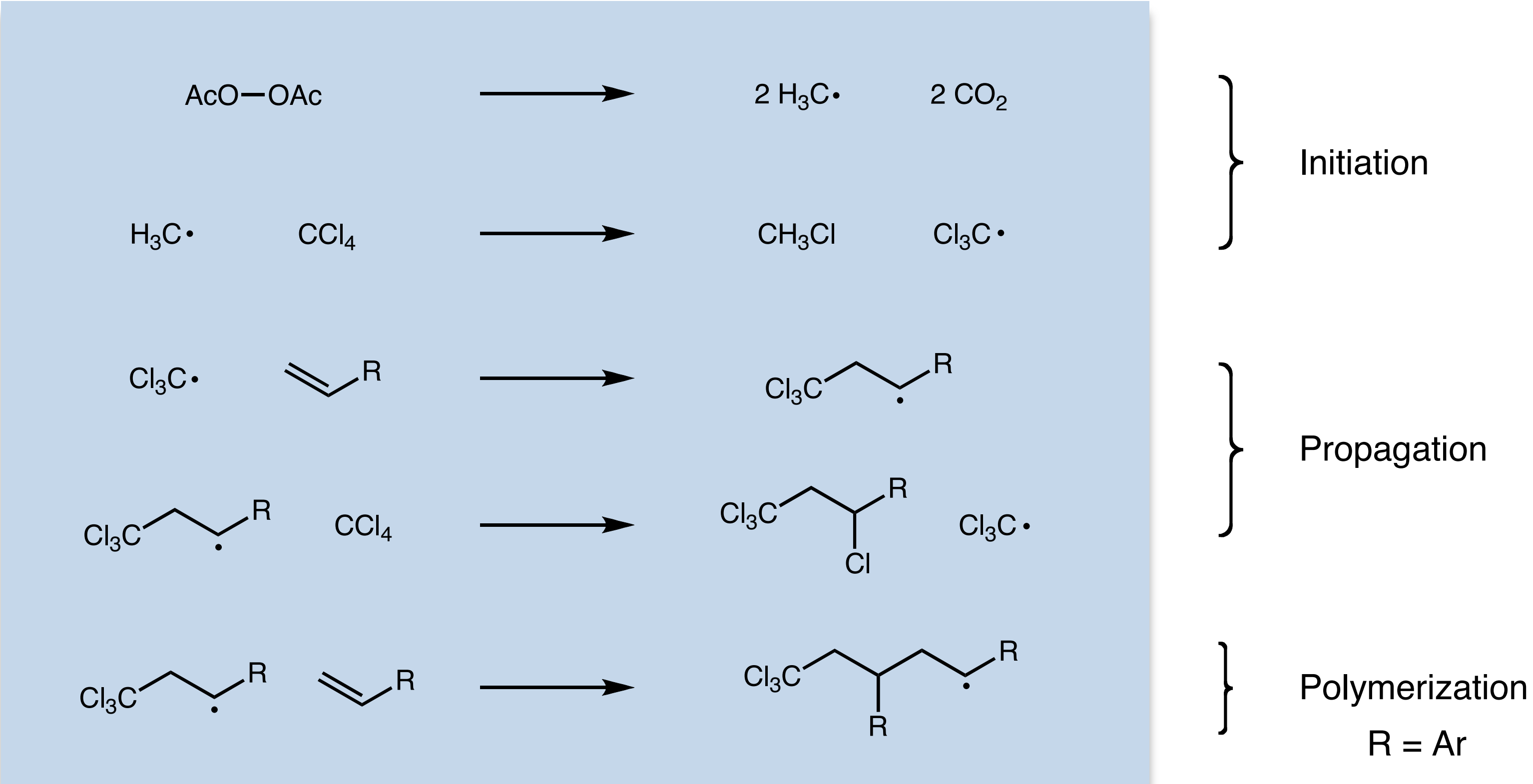


Kharasch, M. S. et al. *Science,* **1945** *122*, 108.

The Kharasch Addition Reaction of Halomethanes to Olefins

- Kharasch reported the radical addition of carbon-based radicals to olefins (1945)

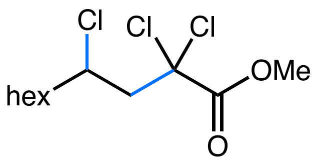




Kharasch, M. S. *Science* **1945**, *122*, 108.

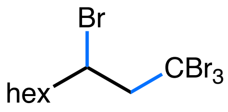
The Kharasch Addition Reaction of Halomethanes to Olefins

- Kharasch reported the use of several radical electrophiles in his new radical reaction



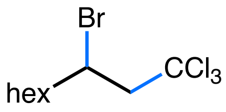
(AcO)$_2$, 40% yield

JACS, **1945**, 1626



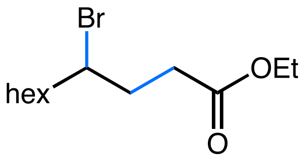
hν, 88% yield

JACS, **1946**, 154



(AcO)$_2$, 78% yield

JACS, **1947**, 1105



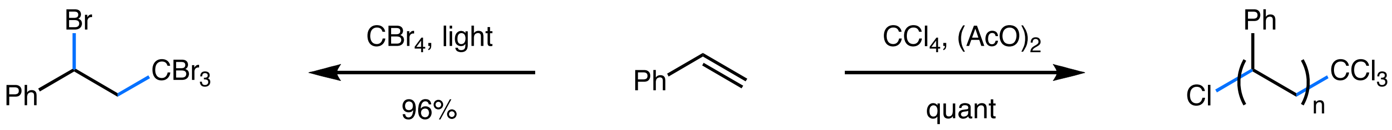
(AcO)$_2$, 54% yield

JACS, **1948**, 1055

Halogen was used in excess (3- or 4-fold) for optimum yields

Higher order products made up mass balances

Highly activated bromomethanes were the best substrates



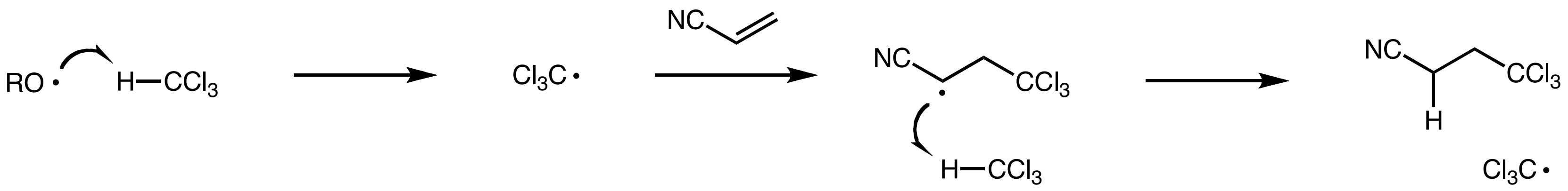
The Failed Polymerizations of Minisci

- Surprisingly, substantial monoadduct formation was observed with carbon tetrachloride

'significant amount'

new regioisomer

- Standard peroxide initiated radical mechanisms occur via hydrogen abstraction

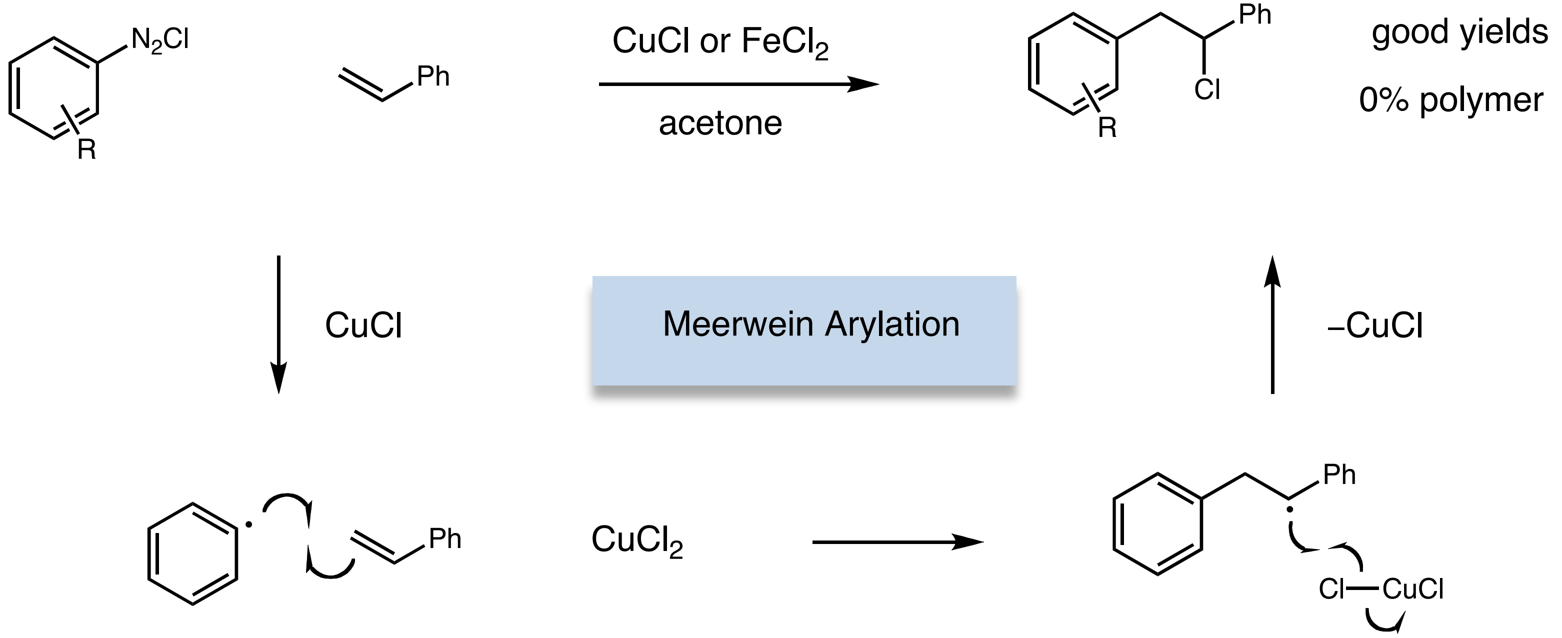


Complete selectivity for opposite regioisomer suggested a new mechanism

Minisci, F. *Chem. Ind. (Milan)*, **1956**, *122*, 371.

Radical Chain Termination by Metal Halide Salts (Jay Kochi)

- Also in 1956, Kochi was studying the oxidation of alkyl radicals by metal salts



1. The rate of benzylic radical oxidation by $CuCl_2$ (or $FeCl_3$) is much faster than styrene addition
2. Oxidation occurs through a 'ligand transfer' mechanism (inner-sphere electron transfer)

⇩

Minisci's reaction could have contained metal halides

Kochi, J. *J. Am. Chem. Soc.* **1956**, *78*, 4815.

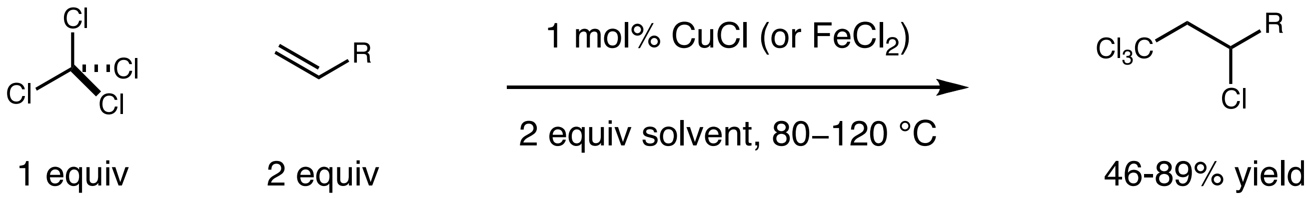
Accidental Discovery of Catalytic Atom Transfer Radical Chemstry

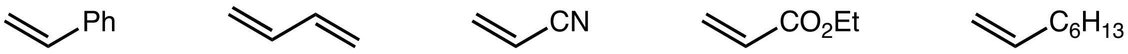
- Minisci's steel autoclave was corroded and had likely leached iron into the reaction and could have been oxidized to $FeCl_3$ by chlorine radicals

$$2\ CCl_4 \qquad Fe\ (s) \longrightarrow 2\ Cl_3C\cdot \qquad FeCl_2$$

$$CCl_4 \qquad FeCl_2 \longrightarrow Cl_3C\cdot \qquad FeCl_3$$

- Minisci's group and Vofsi and Asscher first describe catalytic atom transfer radical addition





Minisci, F. et al. *Gazzeta* **1961**, *91*, 1030.

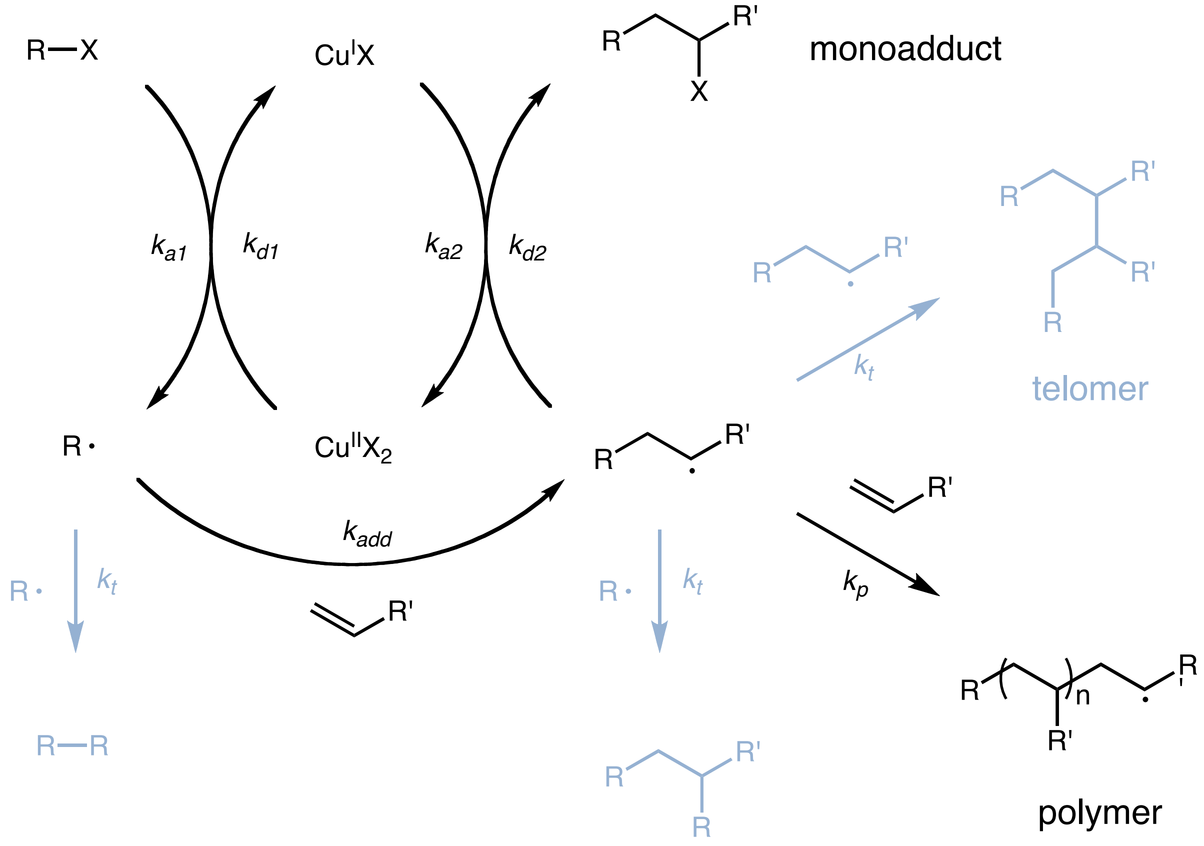
Asscher, M. et al. *J. Chem. Soc.* **1963**, 1887.

Proposed Mechanism of Atom Transfer Radical Addition (ATRA)

- Metal catalyst participates in both initiation and termination steps, relative rates dictate selectivity

Catalytic Redox Mechanism:

- Red. halogen abstraction generates radical
- Oxid. halogen abstraction terminates radical



Selective ATRA Requires:

1. Low radical concentration

   k_{d1} and k_{d2} >> k_{a1} and k_{a2}

2. Slow product activation (vs sm)

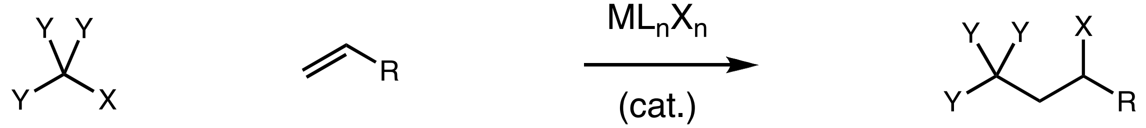
   k_{a1} >> k_{a2}

3. Oxidation must be fast vs prop.

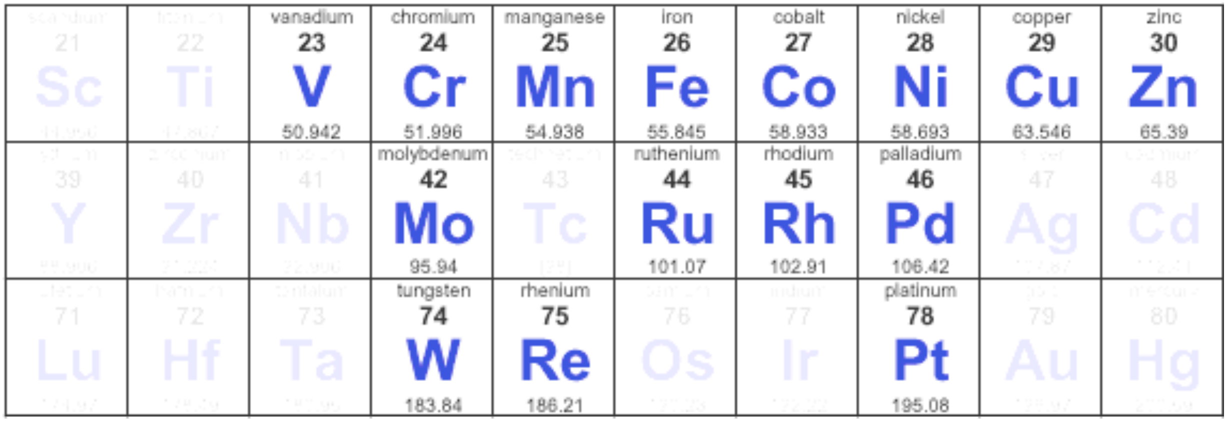
   k_{d2} >> k_p

Figure adapted from: Matyjaszewski, K. et al. *Chem. Soc. Rev.* **2008**, 1087.

So Many Different Catalysts...



- The many metals that catalyze $CHCl_3$, $CHBr_3$, CCl_4, and/or CBr_4 radical addition



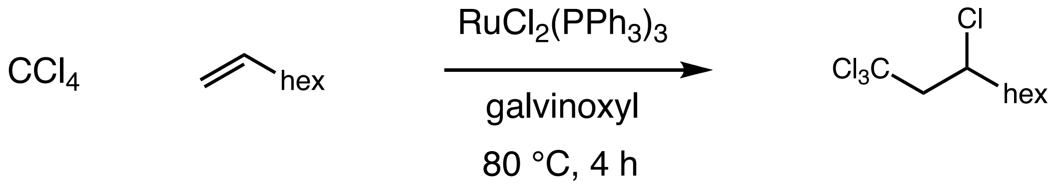
scandium 21 Sc 44.956	titanium 22 Ti 47.867	vanadium 23 V 50.942	chromium 24 Cr 51.996	manganese 25 Mn 54.938	iron 26 Fe 55.845	cobalt 27 Co 58.933	nickel 28 Ni 58.693	copper 29 Cu 63.546	zinc 30 Zn 65.39
yttrium 39 Y 88.906	zirconium 40 Zr 91.224	niobium 41 Nb 92.906	molybdenum 42 Mo 95.94	technetium 43 Tc [98]	ruthenium 44 Ru 101.07	rhodium 45 Rh 102.91	palladium 46 Pd 106.42	silver 47 Ag 107.87	cadmium 48 Cd 112.41
lutetium 71 Lu 174.97	hafnium 72 Hf 178.49	tantalum 73 Ta 180.95	tungsten 74 W 183.84	rhenium 75 Re 186.21	osmium 76 Os 190.23	iridium 77 Ir 192.22	platinum 78 Pt 195.08	gold 79 Au 196.97	mercury 80 Hg 200.59

- The most commonly used catalysts for ATRA reactions are $Cu^{I}X$ and $Ru^{II}X_2$ derivatives

- Exact nature of free radical intermediates is not known

Evaluation of the Proposed Radical Mechanism

- Kharasch systems likely proceed via radical intermediates (Ru, Cu, Fe, Mo, Cr)

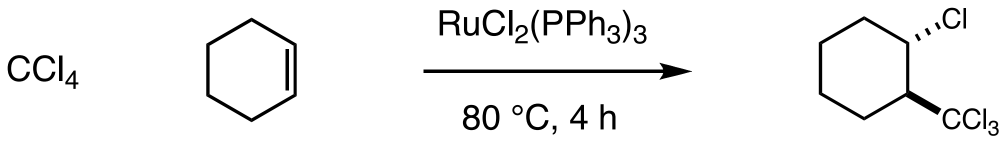


0% yield

(76%, no spintrap)

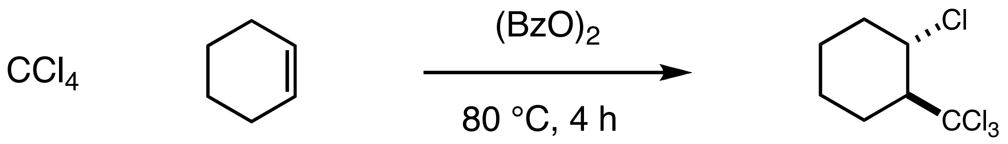
Matsumoto, H. et al. *Tetrahedron Lett.* **1973**, *14*, 5147.

- Metal catalyst impacts diastereoselectivity of CCl_4 addition to cyclohexene



77% yield

96:4 (trans:cis)



low yield

53:47 (trans:cis)

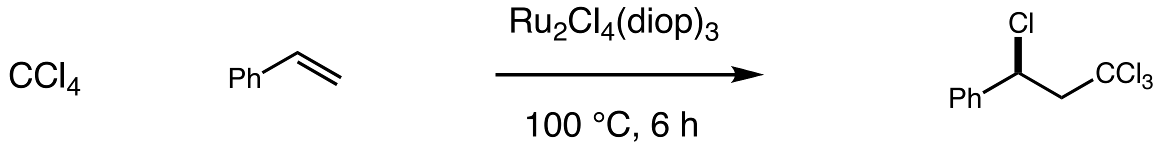
Matsumoto, H. et al. *Tetrahedron Lett.* **1975**, *15*, 899.

Effect not seen with Cu: Asscher, M. et al. *J. Chem. Soc. Perkin Trans. 2* **1973**, 1000.

Intermediate radical species likely exist as coordinated radical pairs (Ru system)

Attempts at Enantioselective Kharasch Addition

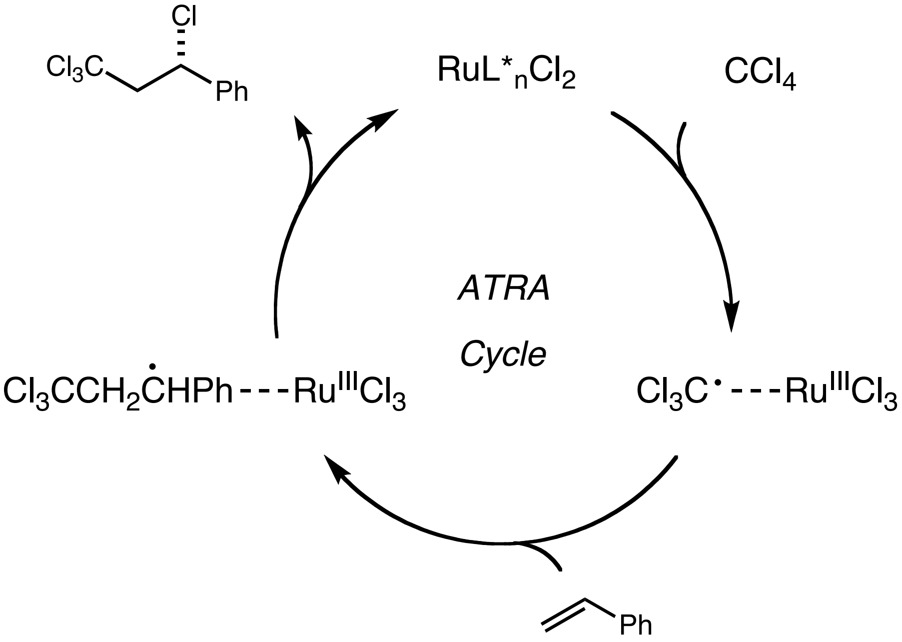
- Chiral ligands could potentially induce enantioselectivity



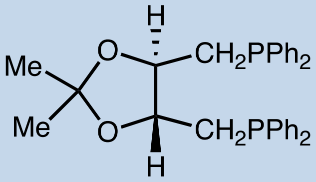
73% yield

13% ee

- Coordinated metal-radical pair should participate in enantiodetermining chlorination



L* = (–)-diop

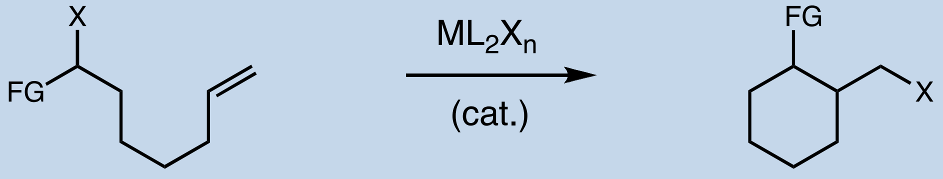


Kamigata, N. et al. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3687.

Similar result with RhCl-diop system: Murai, S. et al. *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 475.

Selected Examples of Atom Transfer Radical Addition Chemistry

■ Area 1. Intramolecular Atom Transfer Reactions (ATRC)

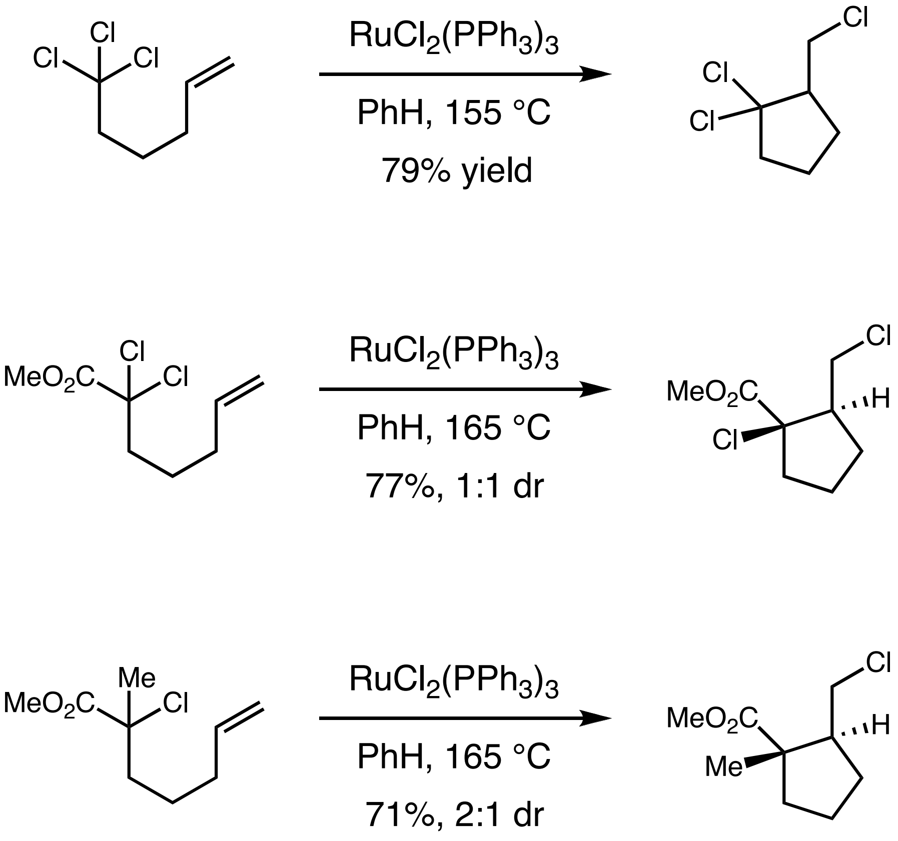


Selected Intramolecular ATRA: 5-Exo Trig Cyclizations

- A variety of cyclization substrates and catalytic systems have been developed over 35+ years

$RuCl_2(PR_3)_3$ catalysts: 1973 (Nagai)

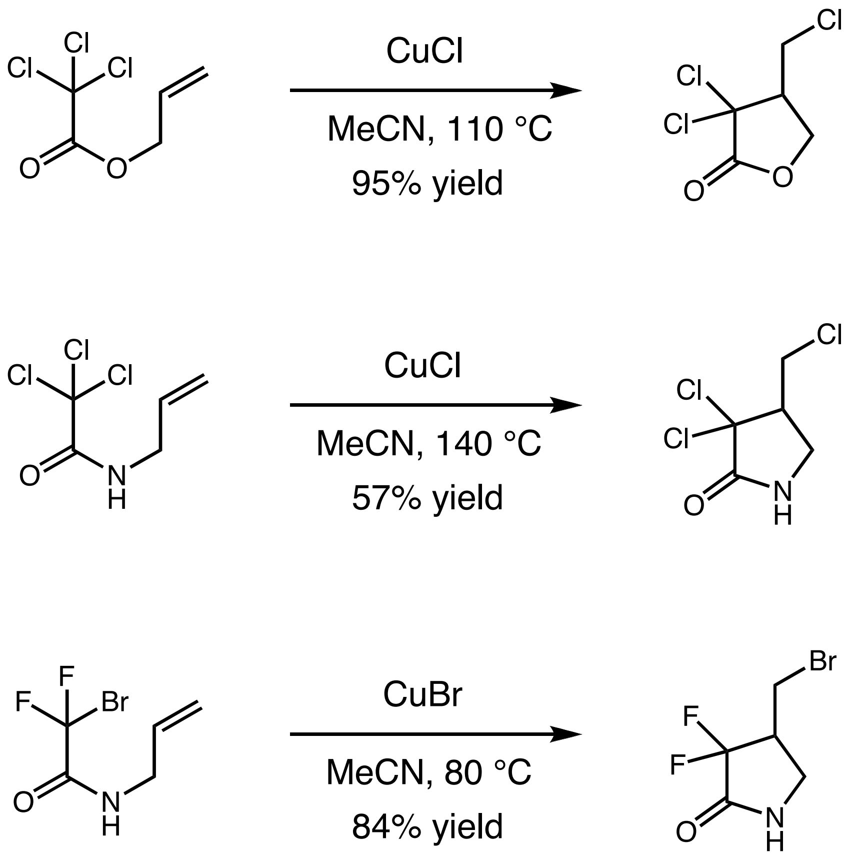
1-10% typical loadings, > 80°C temperatures



Weinreb, S. et al. *J. Org. Chem.* **1990**, *55*, 1281.

CuX catalysts: 1963 (Asscher & Vofsi)

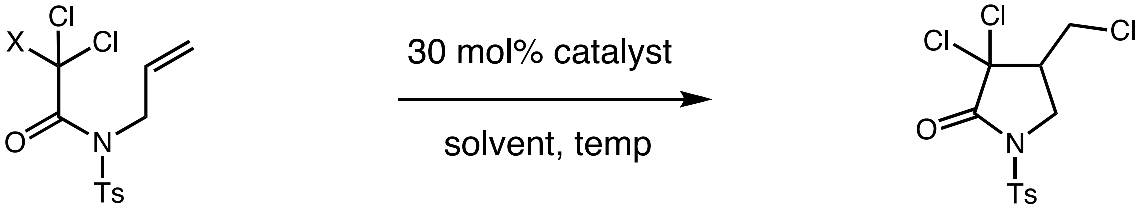
~30% typical loading, > 100°C temperatures



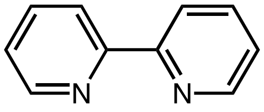
Clark, A. *Chem. Soc. Rev.* **2002**, *31*, 1.

Intramolecular Atom Transfer Radical Cyclization Ligand Effects

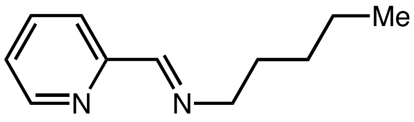
- 5-Exo trig cyclization of unsaturated α-haloamide substrates yields lactam scaffolds



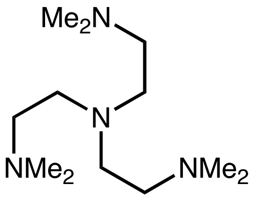
Catalyst	X	Solvent	Temp.	Time	Yield
CuCl	Cl	MeCN	80 °C	24 h	97%
CuCl-bipy (5%)	Cl	CH_2Cl_2	23 °C	0.2 h	91%
CuCl-bipy	H	CH_2Cl_2	23 °C	24 h	0%
CuCl-NPMI	H	CH_2Cl_2	23 °C	72 h	15%
CuCl-tren-Me_6	H	CH_2Cl_2	23 °C	2 h	90%



bipy



NPMI

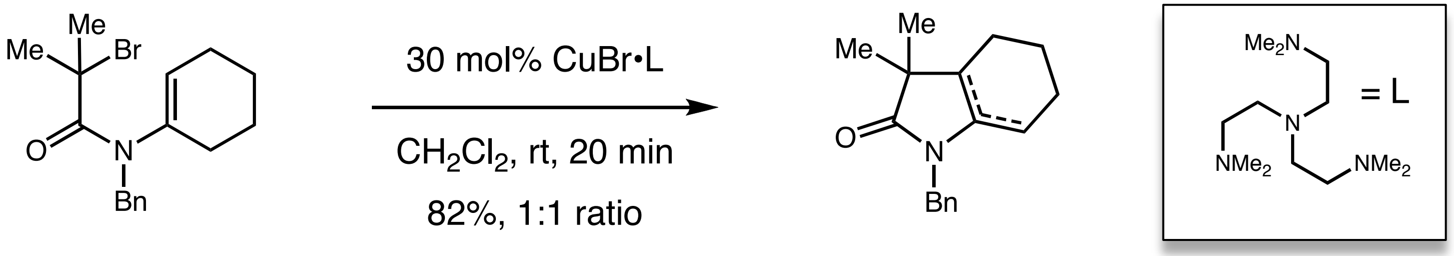


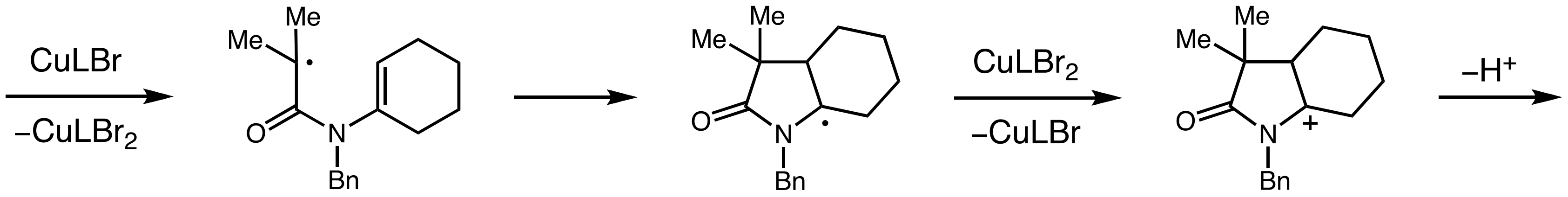
tren-Me_6

Clark, A. *Tetrahdron Lett.* **1999**, *40*, 4885.

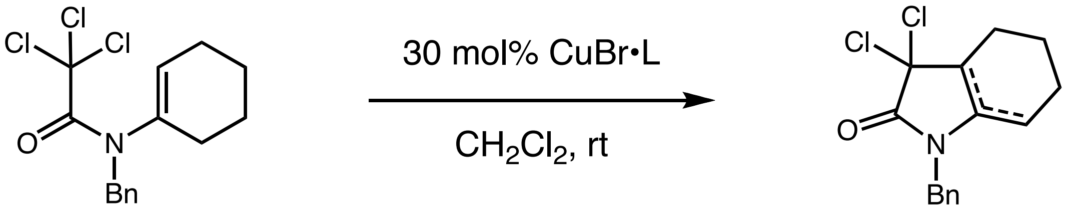
Radical-Polar Crossover Mechanism: Addition to Enamides

- Electrophilic radicals add to acyl enamines, terminate via radical-polar crossover mechanism





- While this triethylenetetramine ligand is highly active, the perfect Cu system remains unknown



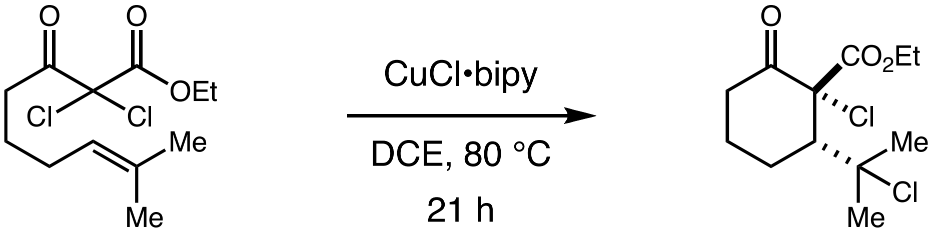
0% yield

complex mixture

Clark, A. *Tetrahdron Lett.* **1999**, *40*, 4885.

Cascade Cyclization Using Copper Redox Catalyst

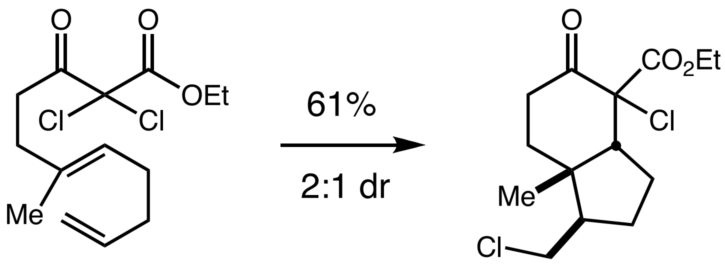
- Radical mono- and bicyclization utilizing copper-bipy as catalyst (Dan Yang)

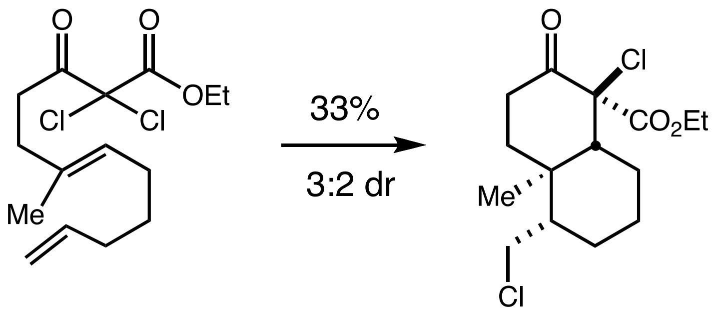


79% yield

3:1 dr

- Bicyclization under the conditions outlined above give modest yields and diastereocontrol

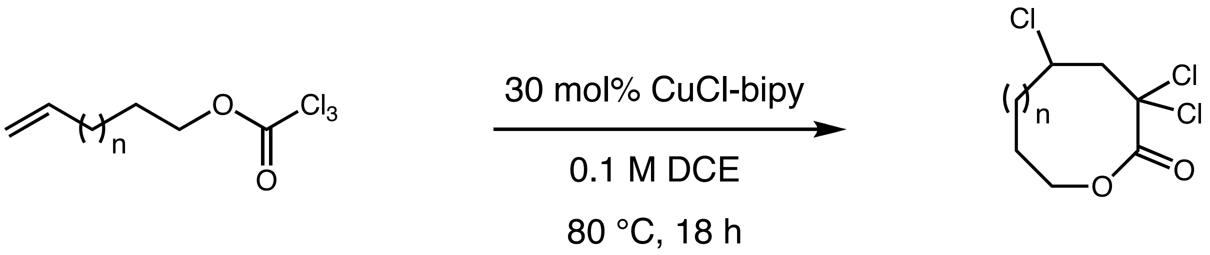




Yang, D. et al. *Org. Lett.* **2006**, *8*, 5757.

Intramolecular Atom Transfer Radical Cyclization

- Medium ring heterocycle formation via redox reaction affords 8 and 9 membered lactones

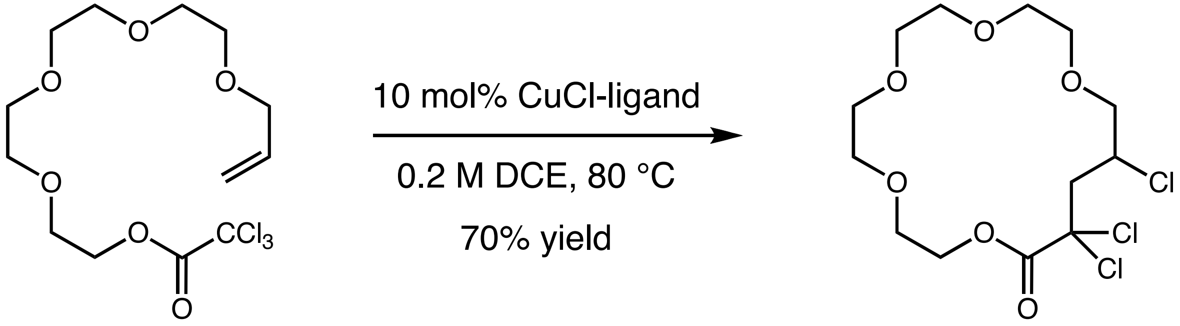


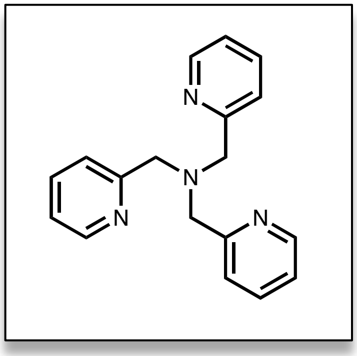
n = 1: 60% yield

n = 2: 59% yield

Pirrung, F. et al. *Synlett.* **1993**, *50*, 739.

- Macrocyclization reactions were also accomplished using a tridentate ligand

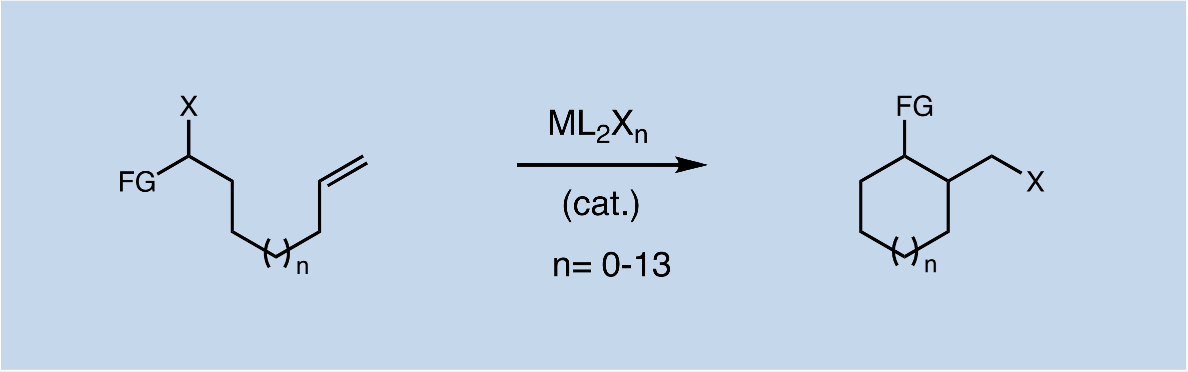




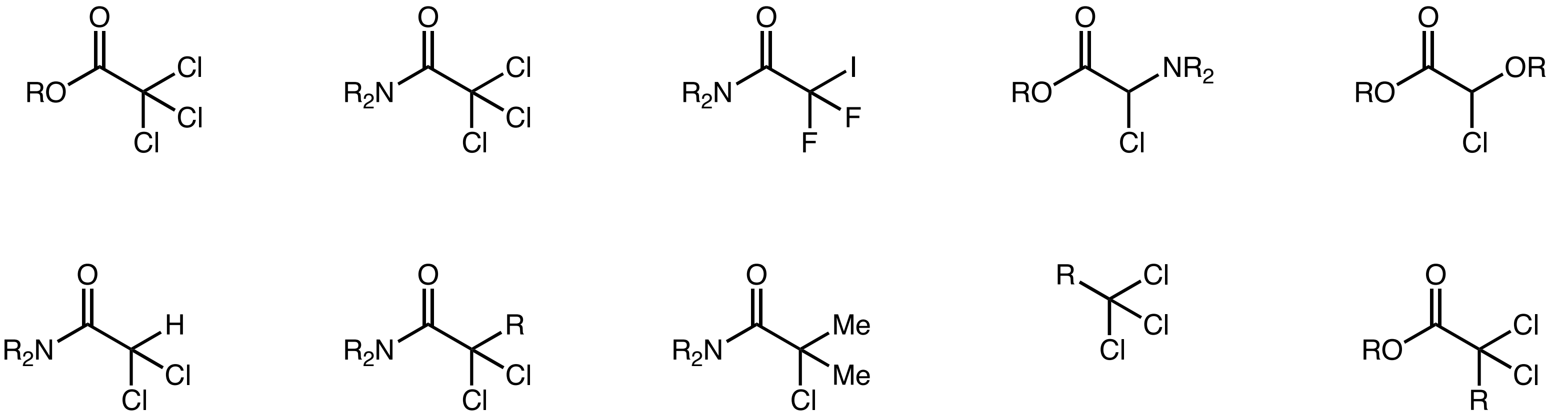
Clark, A. et al. *J. Chem. Soc. Perkin Trans. 1,* **2000**, 671.

Selected Examples of Atom Transfer Radical Addition Chemistry

- Area 1. Intramolecular Atom Transfer Radical Addition Reactions (ATRC)

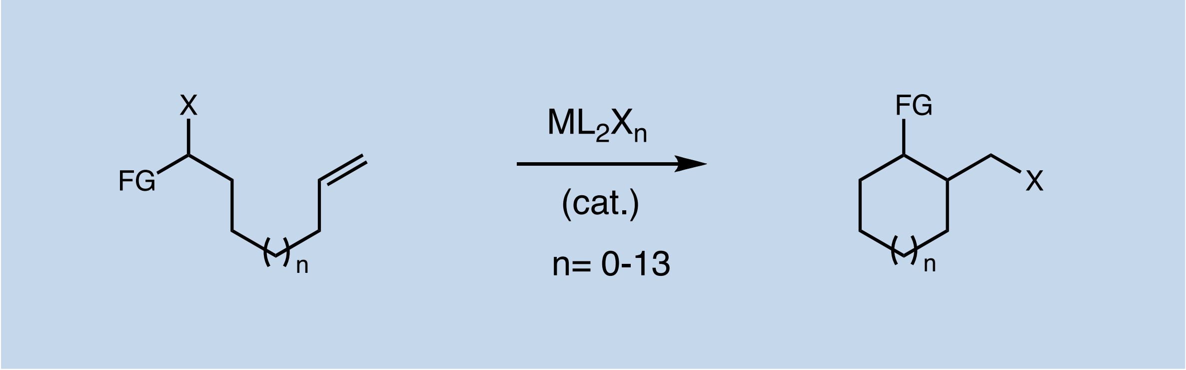


- Successful radical precursors in ATRC reactions so far are highly activated

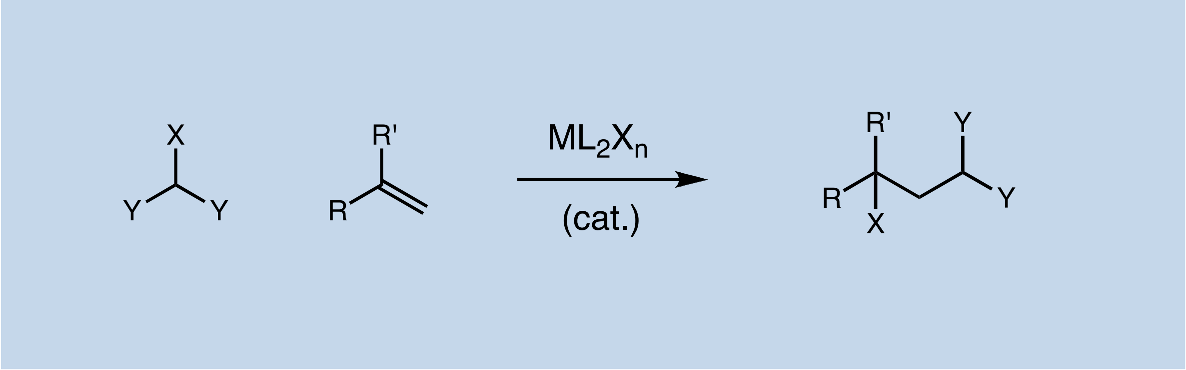


Selected Examples of Atom Transfer Radical Addition Chemistry

■ Area 1. Intramolecular Atom Transfer Radical Addition Reactions (ATRC)

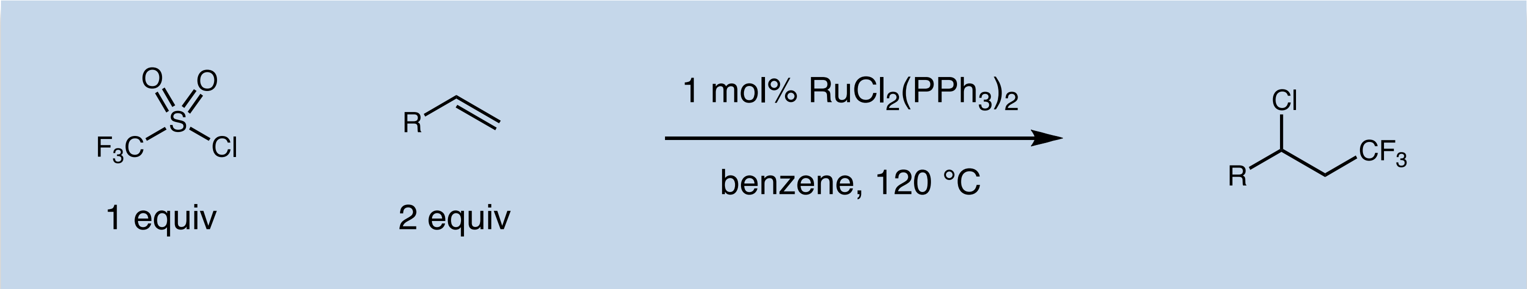


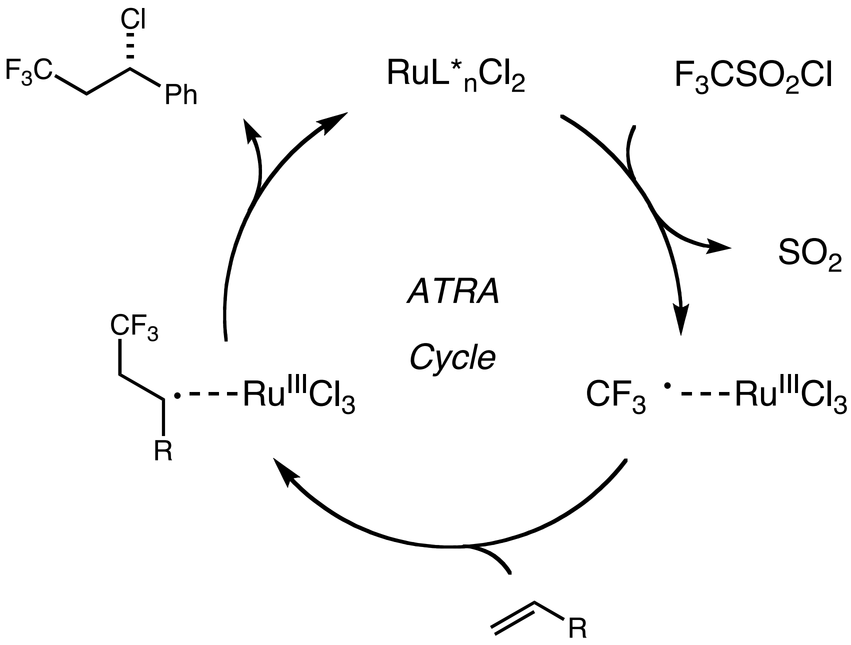
■ Area 2. Intermolecular Kharasch Addition Reactions of Polyhaloalkanes



Perfluoroalkylation of Olefins Using ATRA

- Kamigata's group describe a ruthenium catalyzed radical trifluromethylation protocol

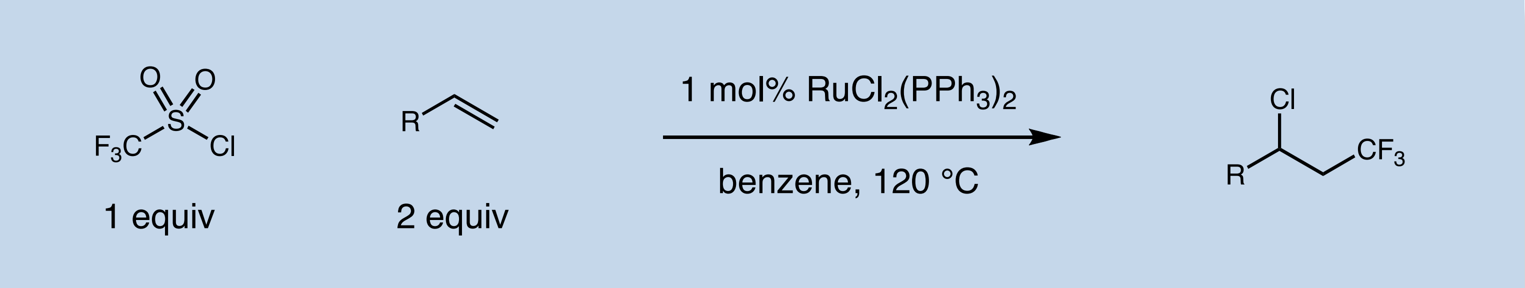




Kamigata. *J. Chem. Soc. Perkin Trans. 1.* **1991**, 627.

Perfluoroalkylation of Olefins Using ATRA

- Kamigata's group describe a ruthenium catalyzed radical trifluromethylation protocol



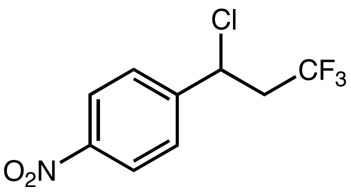
1 equiv

2 equiv

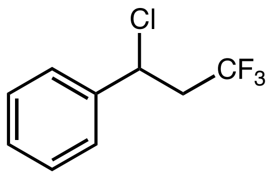
1 mol% $RuCl_2(PPh_3)_2$

benzene, 120 °C

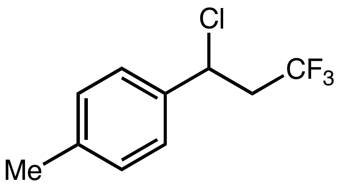
- The reaction works well with highly activated olefins but is sensitive to sterics (1,2-substitution)



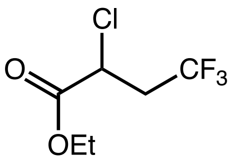
79% yield



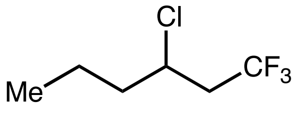
87% yield



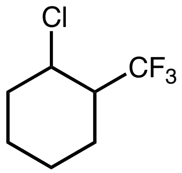
46% yield



41% yield



66% yield

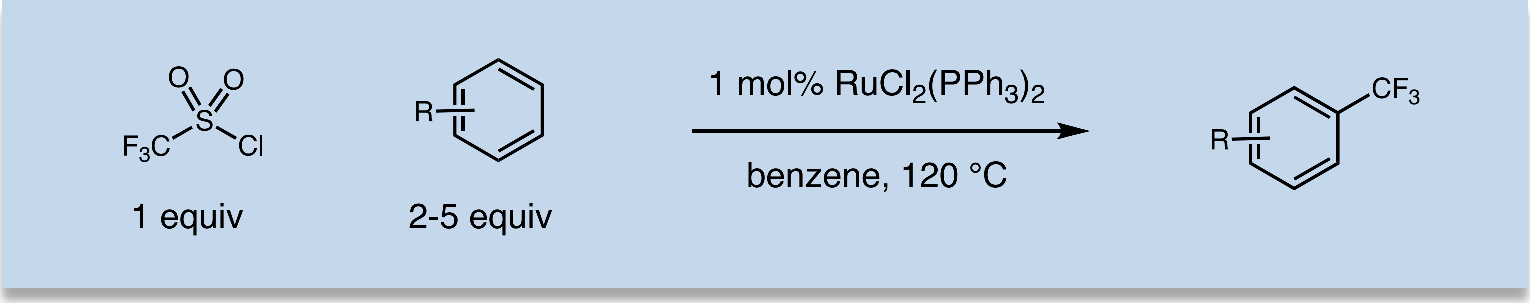


23% yield

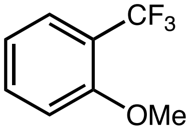
Kamigata. *J. Chem. Soc. Perkin Trans. 1.* **1991**, 627.

Arene Perfluoroalkylation Using Sulfonyl Chloride Reagents

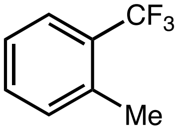
- Kamigata's group describe a ruthenium catalyzed radical trifluromethylation protocol



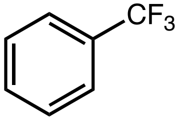
- Benzene substrates react but are completely regio-permiscuous



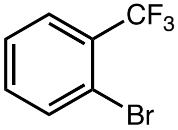
53% yield
2:1:1 (o:m:p)



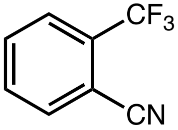
36% yield
1:1:1 (o:m:p)



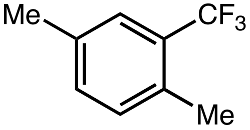
41% yield



39% yield
1:1:1 (o:m:p)



trace

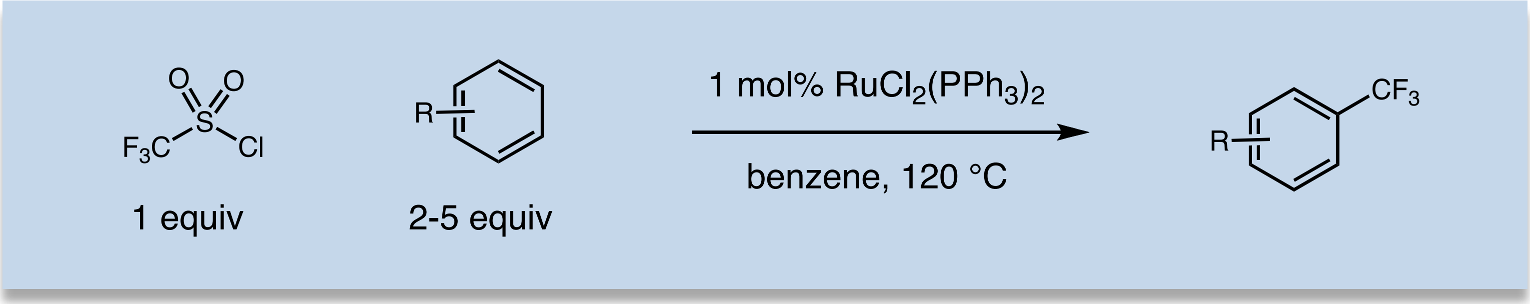


63% yield

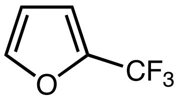
Kamigata. N. *J. Chem. Soc. Perkin Trans. 1.* **1994**, 1339.

Arene Perfluoroalkylation Using Sulfonyl Chloride Reagents

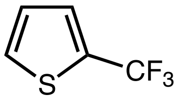
- Kamigata's group describe a ruthenium catalyzed radical triflurometylation protocol



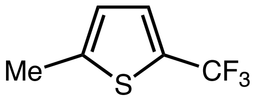
- Five-membered heterocyclic compounds work with increased regiocontrol



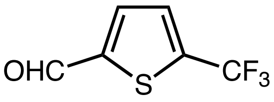
30%



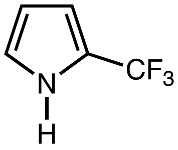
77%



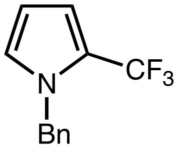
73%



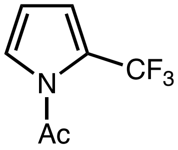
26%



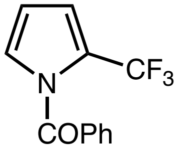
0%



53%



61%

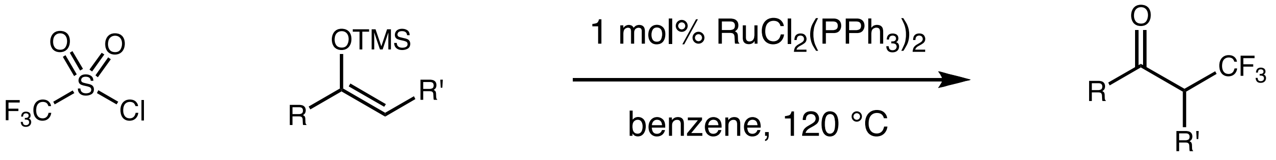


92%

Kamigata. N. *J. Chem. Soc. Perkin Trans. 1.* **1994**, 1339.

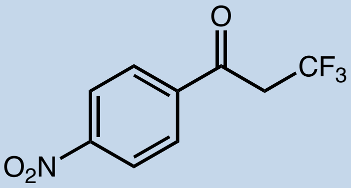
Trifluoromethylation of Electron-Poor Enolsilane Substrates

- Ruthenium catalyzed sulfonyl chloride decomposition also works on silyl enol ethers

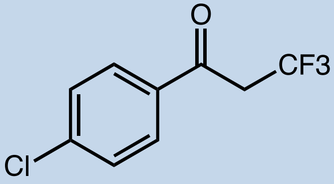


1 equiv

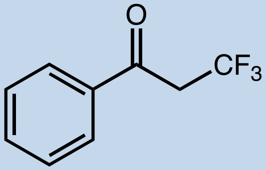
2 equiv



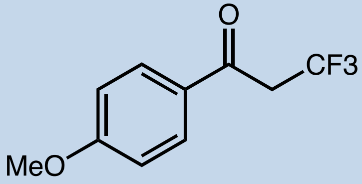
55% yield



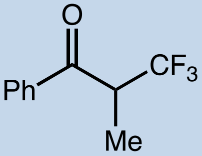
51% yield



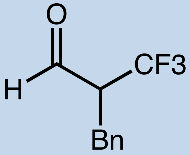
58% yield



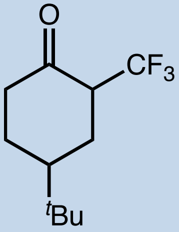
0% yield



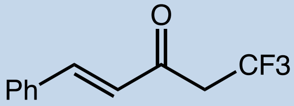
28% yield



35% yield



43% yield

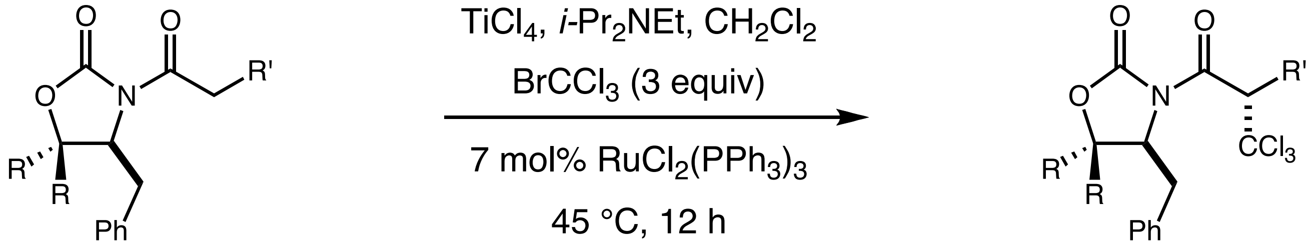


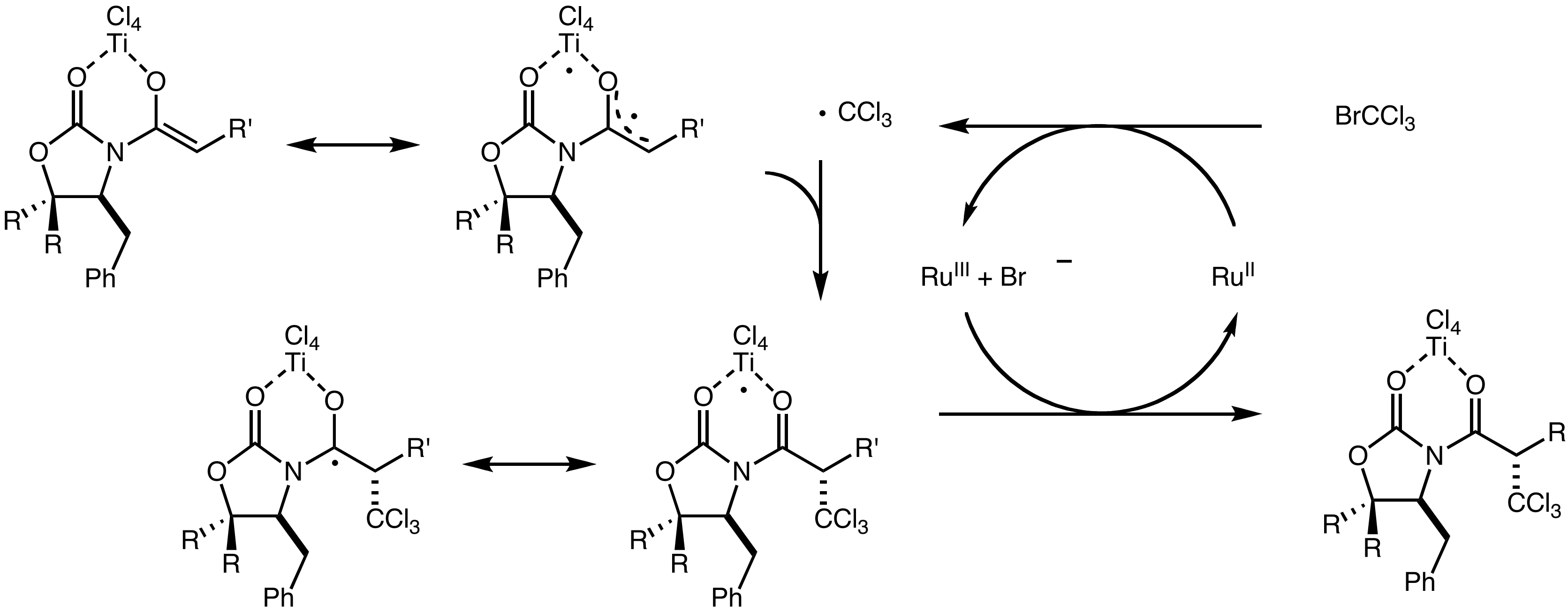
0% yield

Kamigata. N. *Phosporus, Sulphur, and Silicon* **1997**, 155.

Atom Transfer Radical Addition Reactions With Titanium Enolates

- Zakarian group published the first highly diastereoselective intermolecular Kharasch addition

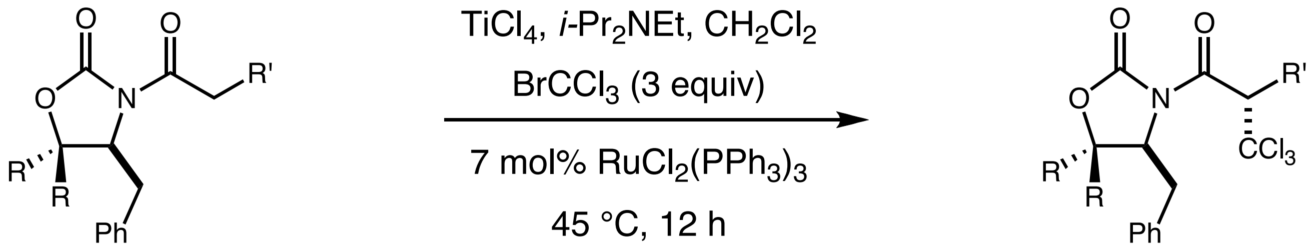




Zakarian, A. et al. *J. Am. Chem. Soc.* **2010**, *ASAP*.

Atom Transfer Radical Addition Reactions With Titanium Enolates

- Zakarian group published the first highly diastereoselective intermolecular Kharasch addition

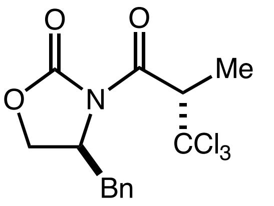


$TiCl_4$, i-Pr_2NEt, CH_2Cl_2

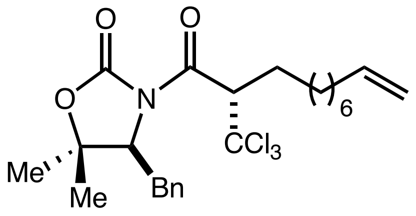
$BrCCl_3$ (3 equiv)

7 mol% $RuCl_2(PPh_3)_3$

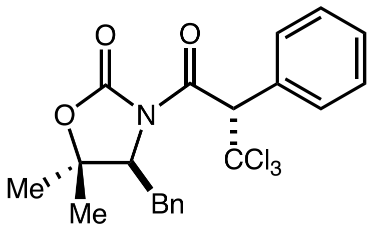
45 °C, 12 h



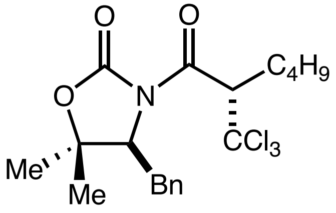
89%, >98:2 dr



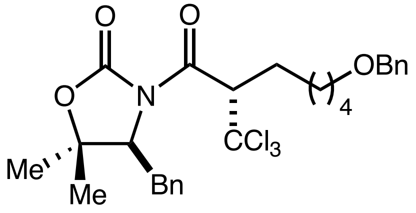
63%, >98:2 dr



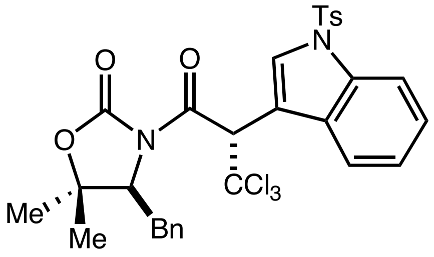
91%, >98:2 dr



99%, >98:2 dr



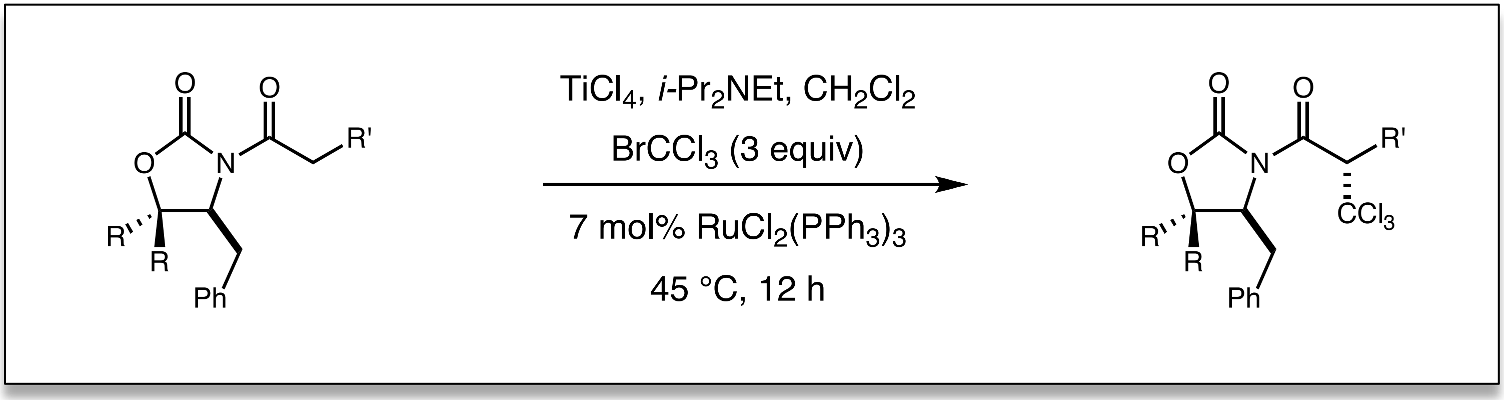
87%, >98:2 dr

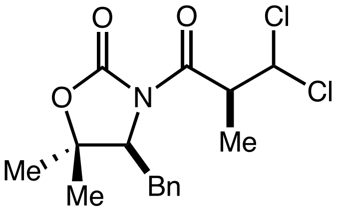


61%, >98:2 dr

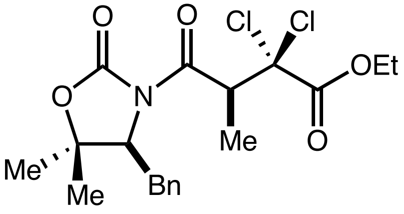
Atom Transfer Radical Addition Reactions With Titanium Enolates

- Zakarian group published the first highly diastereoselective intermolecular Kharasch addition

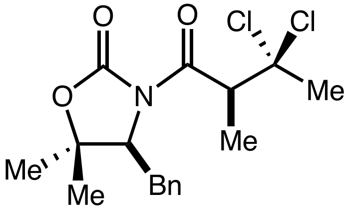




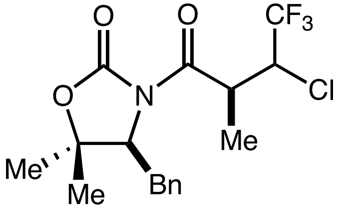
64%, >98:2 dr



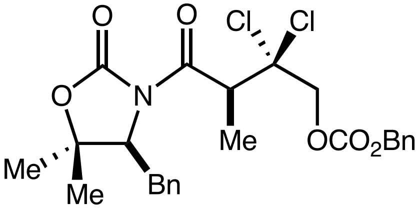
83%, >98:2 dr



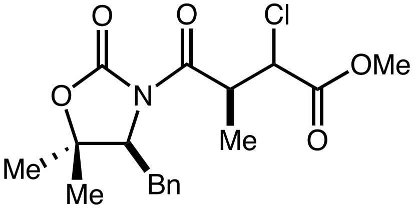
71%, >98:2 dr



71%, 1.6:1 dr



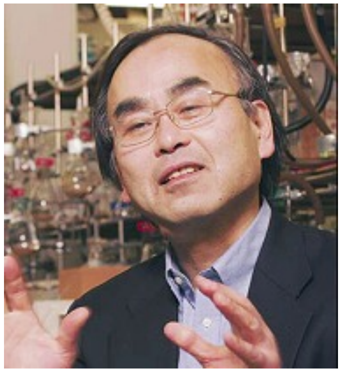
76%, >98:2 dr



75%, 1.3:1 dr

Atom Transfer Radical Polymerization (ATRP)

- In 1995, Krzysztof Matyjaszewski and Mitsuo Sawamoto picked up where Minisci left off (1956)
- They independantly reported a new method (ATRP or living radical polymerization)



Sawamoto

Kyoto University

Matyjaszewski

Carnegie Mellon

'Living Radical Polymerization'

submitted September 6, 1994

Macromolecules, **1995**, *28*, 1721.

cited 1,571 times

'Atom Transfer Radical Polymerization'

submitted February 16, 1995

J. Am. Chem. Soc., **1995**, *117*, 5614.

cited 2,374 times

Atom Transfer Radical Polymerization (ATRP)

- In 1995, Krzysztof Matyjaszewski and Mitsuo Sawamoto picked up where Minisci left off (1956)

Selective ATRA Requires:

1. Low radical concentration

   k_{d1} and k_{d2} >> k_{a1} and k_{a2}

2. Slow product activation (vs sm)

   k_{a1} >> k_{a2}

3. Oxidation must be fast vs prop.

   k_{d2} >> k_p

Polymerization Can Occur If:

1. Above requirements are met
2. Starting Halogen is consumed

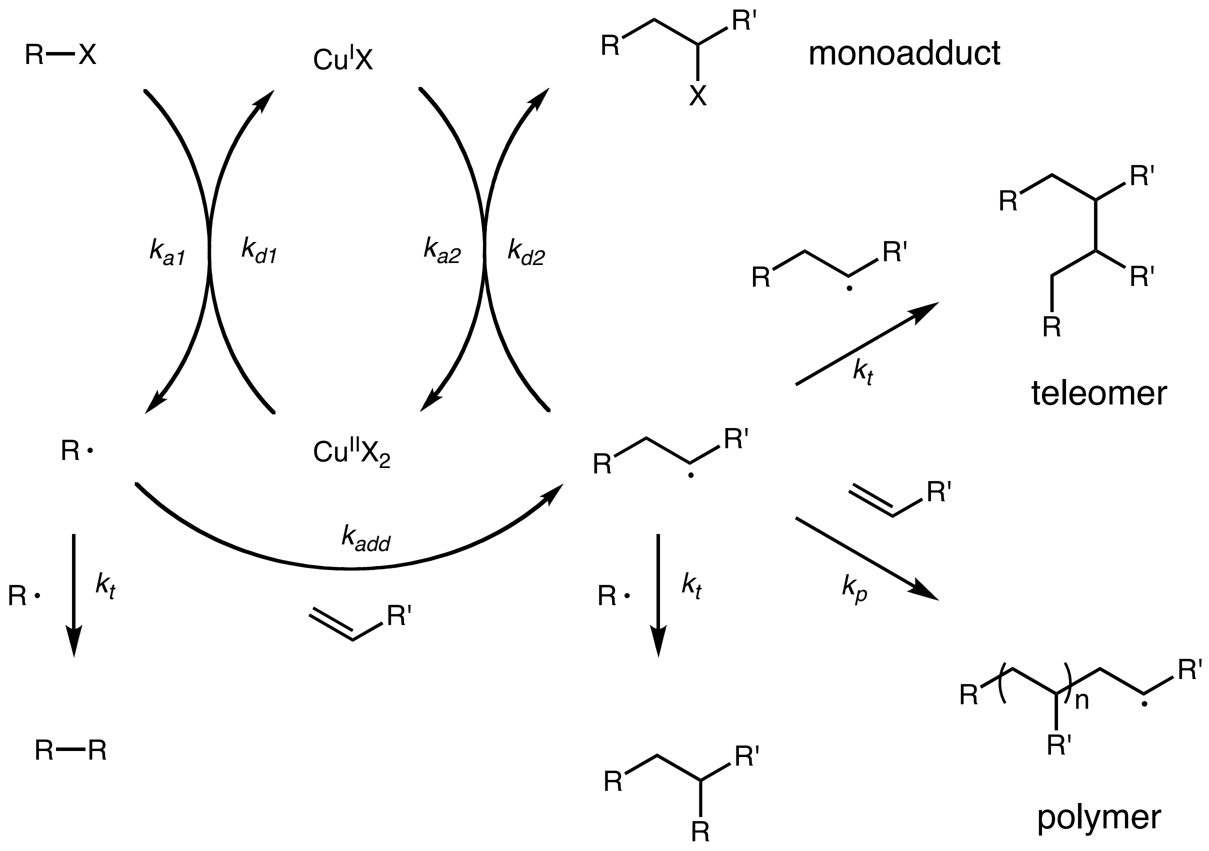


Figure adapted from: Matyjaszewski, K. et al. *Chem. Soc. Rev.* **2008**, 1087.

Atom Transfer Radical Polymerization (ATRP)

- In 1995, Krzysztof Matyjaszewski and Mitsuo Sawamoto picked up where Minisci left off (1956)

Selective ATRA Requires:

1. Low radical concentration

   k_{d1} and k_{d2} >> k_{a1} and k_{a2}

2. Slow product activation (vs sm)

   k_{a1} >> k_{a2}

3. Oxidation must be fast vs prop.

   k_{d2} >> k_p

Polymerization Can Occur If:

1. Above requirements are met
2. Starting Halogen is consumed

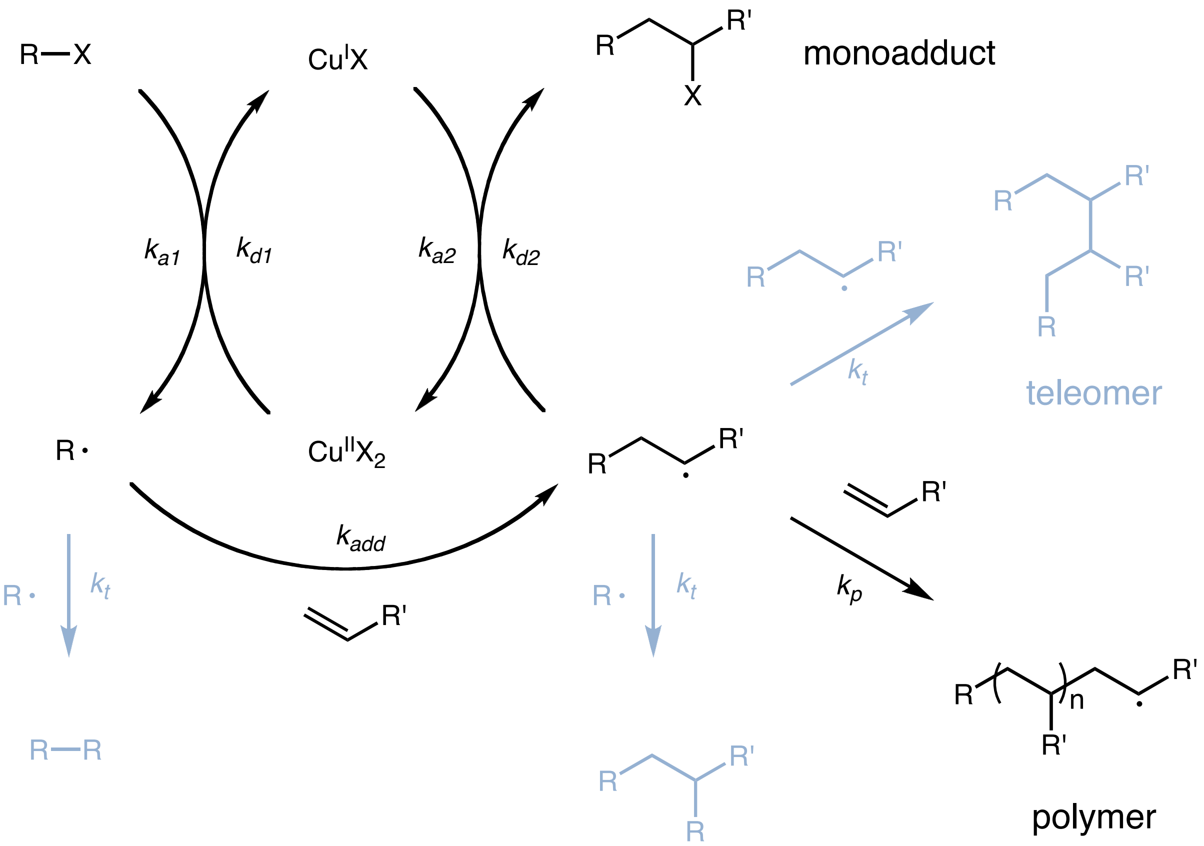


Figure adapted from: Matyjaszewski, K. et al. *Chem. Soc. Rev.* **2008**, 1087.

Atom Transfer Radical Polymerization (ATRP)

- In 1995, Krzysztof Matyjaszewski and Mitsuo Sawamoto picked up where Minisci left off (1956)

Selective ATRA Requires:

1. Low radical concentration

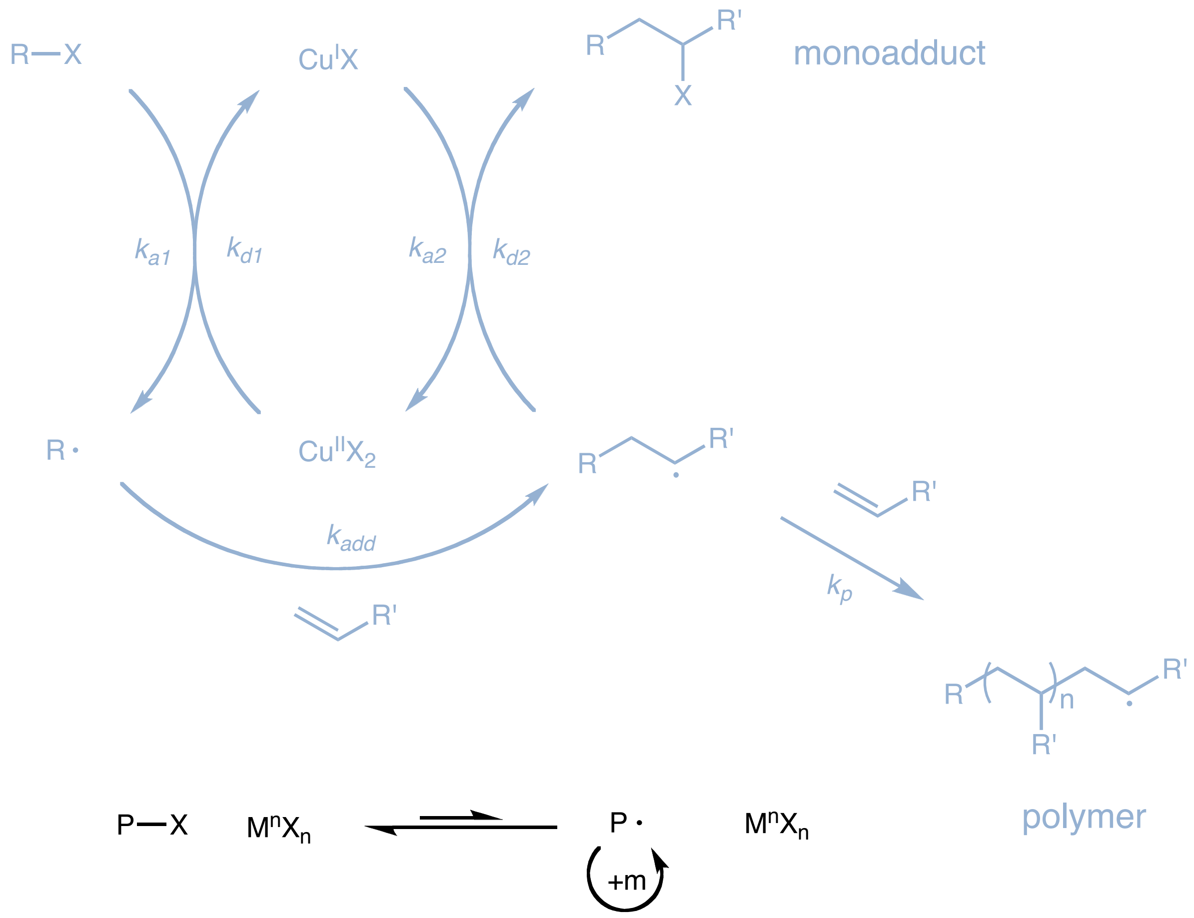
   k_{d1} and k_{d2} >> k_{a1} and k_{a2}

2. Slow product activation (vs sm)

   k_{a1} >> k_{a2}

3. Oxidation must be fast vs prop.

   k_{d2} >> k_p



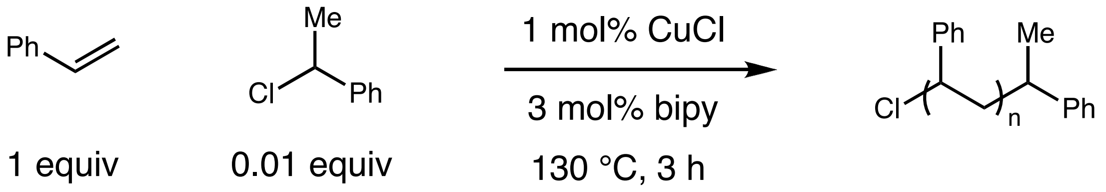
Polymerization Can Occur If:

1. Above requirements are met
2. Starting Halogen is consumed

Figure adapted from: Matyjaszewski, K. et al. *Chem. Soc. Rev.* **2008**, 1087.

Atom Transfer Radical Polymerization (ATRP)

- Matyjaszewski polymerized styrene using a copper chloride bipy system



95% consumption
PDI = 1.3–1.45

- PDI = polydispersity index, a measure of how consistent chain growth is

M_n = number average molecular weight

total weight / number of molecules

PDI = M_n / M_w

M_w = weight average molecular weight

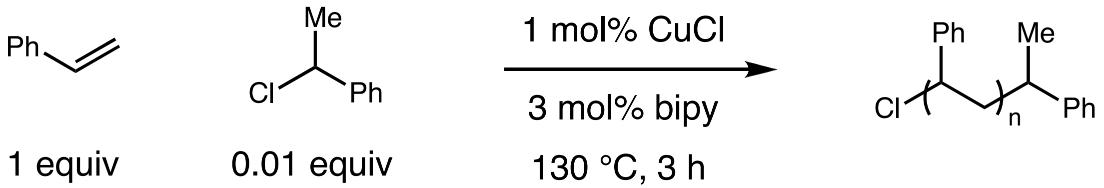
average weight of average molecule

- PDI equal to one: all of the chains in a given sample are of the same length
- Good PDI values are typically > 1.5

Matyjaszewski, K. et al. *J. Am. Chem. Soc.* **1995**, *117*, 5614.

Atom Transfer Radical Polymerization (ATRP)

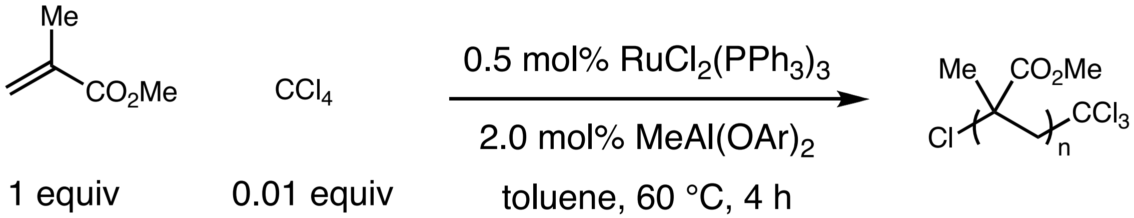
- Matyjaszewski polymerized styrene using a copper chloride bipy system



95% consumption

PDI = 1.3–1.45

- Sawamoto system utilized some well-developed ruthenium phosphine conditions



90% consumption

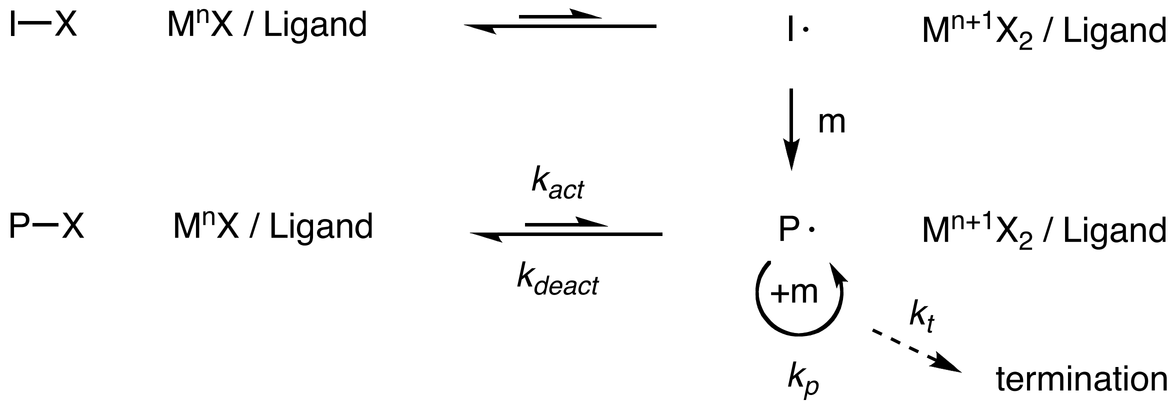
PDI = 1.3–1.4

- Upon complete conversion, more monomer was added and completely incorporated
- Radical scavengers completely inhibited / stopped reactions
- Addition of different monomers allowed for 'Block polymers' (●●●●▲▲▲▲)

Sawamoto, M. et al. *Macromolecules* **1995**, *28*, 1721.

Matyjaszewski, K. et al. *J. Am. Chem. Soc.* **1995**, *117*, 5614.

Atom Transfer Radical Polymerization (ATRP)



I—X M^nX / Ligand $\rightleftharpoons$ I· $M^{n+1}X_2$ / Ligand

m

P—X M^nX / Ligand $\underset{k_{deact}}{\overset{k_{act}}{\rightleftharpoons}}$ P· $M^{n+1}X_2$ / Ligand

+m

k_p

k_t

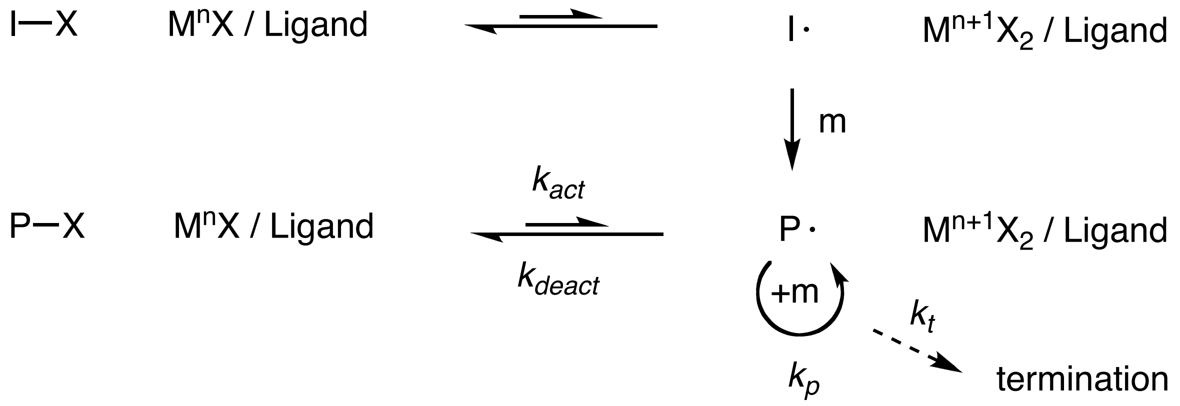
termination

- Different ATRP systems possess discrete rate properties based on the following

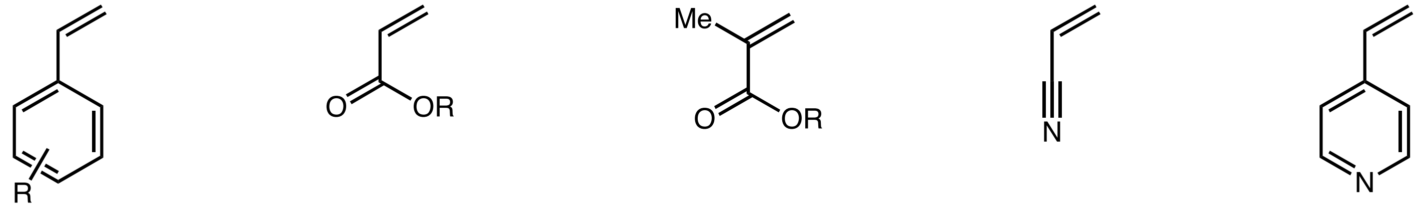
I—X	Initiator (Alkyl Halide)	redox potential
M^nX / Ligand	Catalyst	solubilities, redox potentials
m	monomer	unique ATRP k_{eq}

Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)

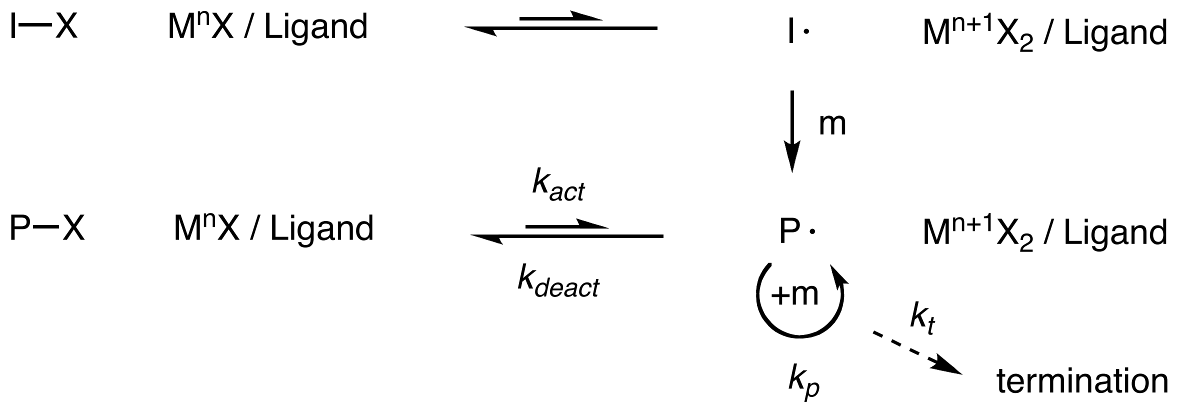


- Different ATRP systems possess discrete rate properties based on the following
- Each monomer has a specific k_{eq} (k_{act}/k_{deact}) and requires specific conditions for ATRP

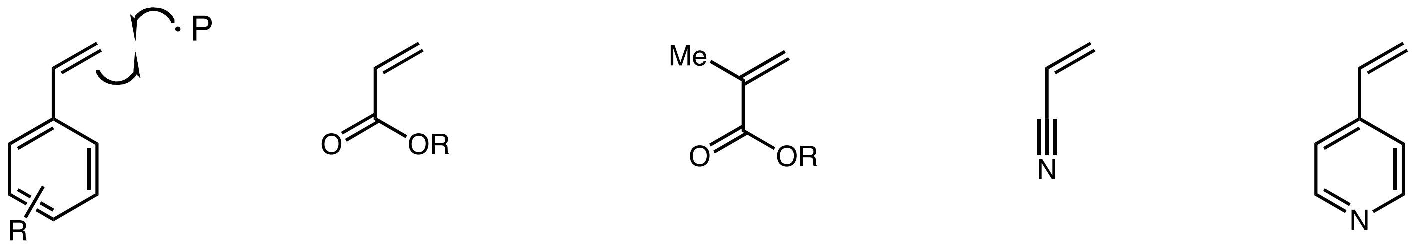


Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)

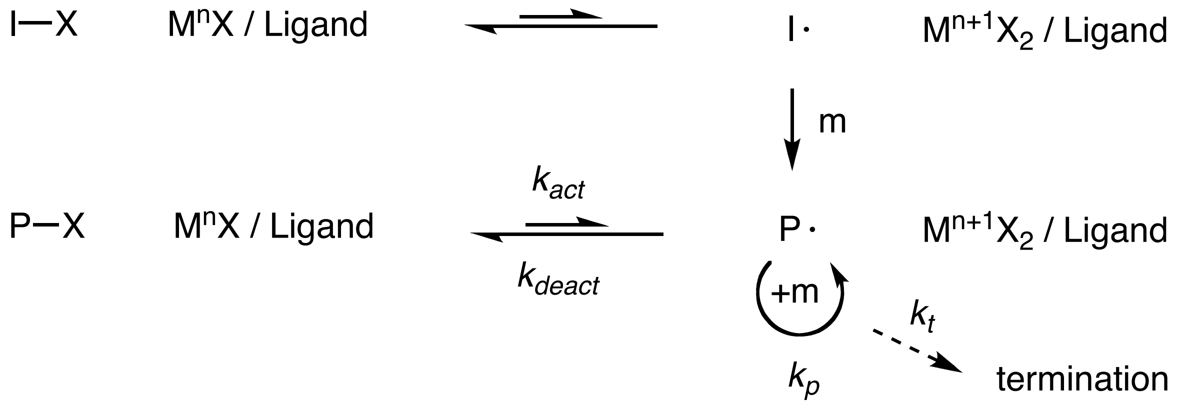


- Different ATRP systems possess discrete rate properties based on the following
- Each monomer has a specific k_{eq} ($k_{\text{act}}/k_{\text{deact}}$) and requires specific conditions for ATRP

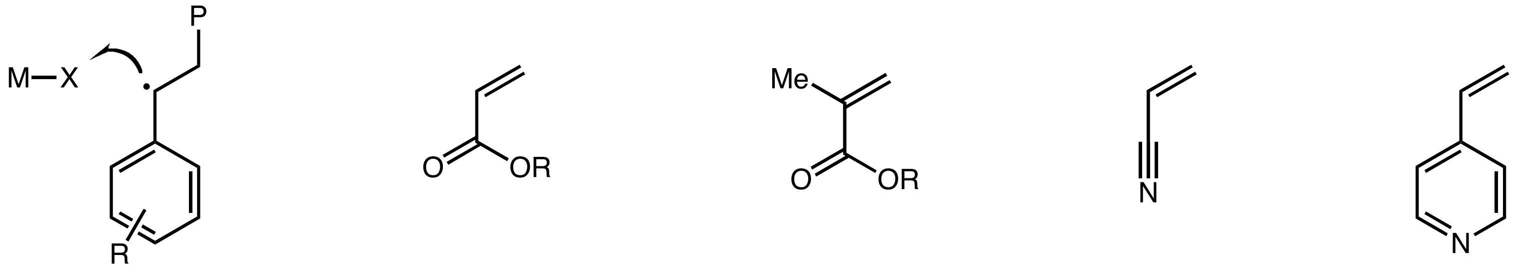


Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)

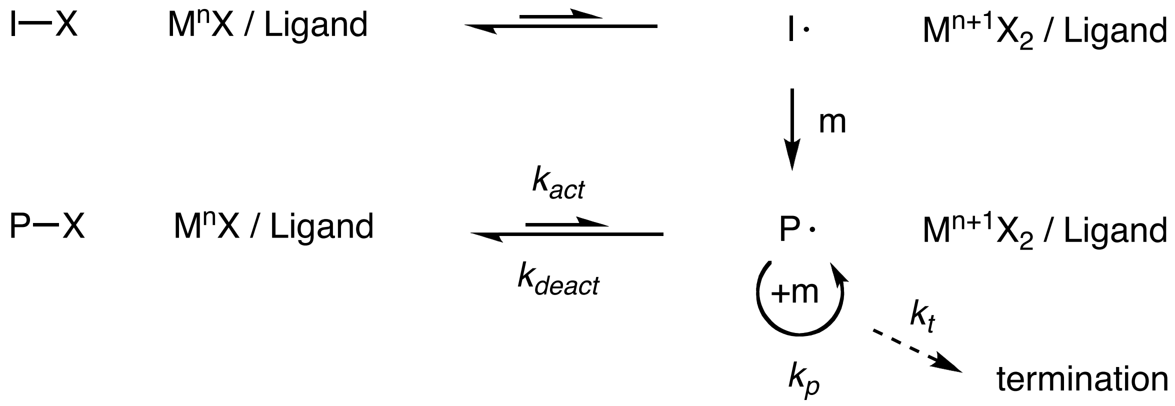


- Different ATRP systems possess discrete rate properties based on the following
- Each monomer has a specific k_{eq} ($k_{\mathrm{act}}/k_{\mathrm{deact}}$) and requires specific conditions for ATRP



Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)



$I{-}X$ M^nX / Ligand $\rightleftharpoons$ $I\cdot$ $M^{n+1}X_2$ / Ligand

m

$P{-}X$ M^nX / Ligand $\underset{k_{deact}}{\overset{k_{act}}{\rightleftharpoons}}$ $P\cdot$ $M^{n+1}X_2$ / Ligand

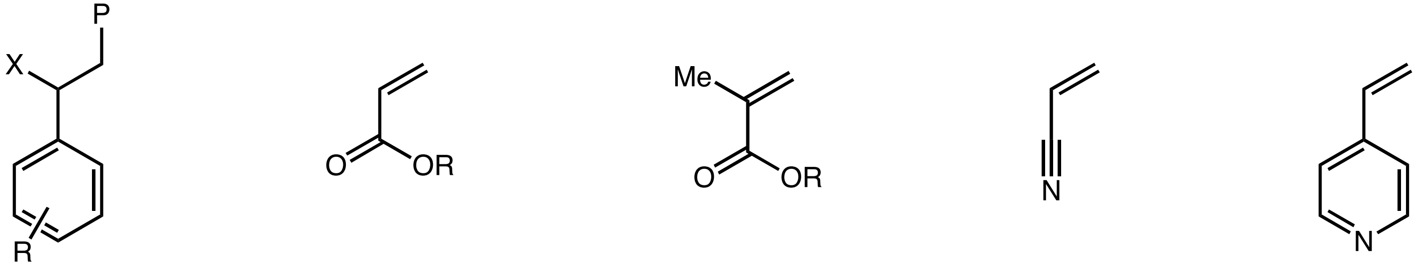
+m

k_p

k_t

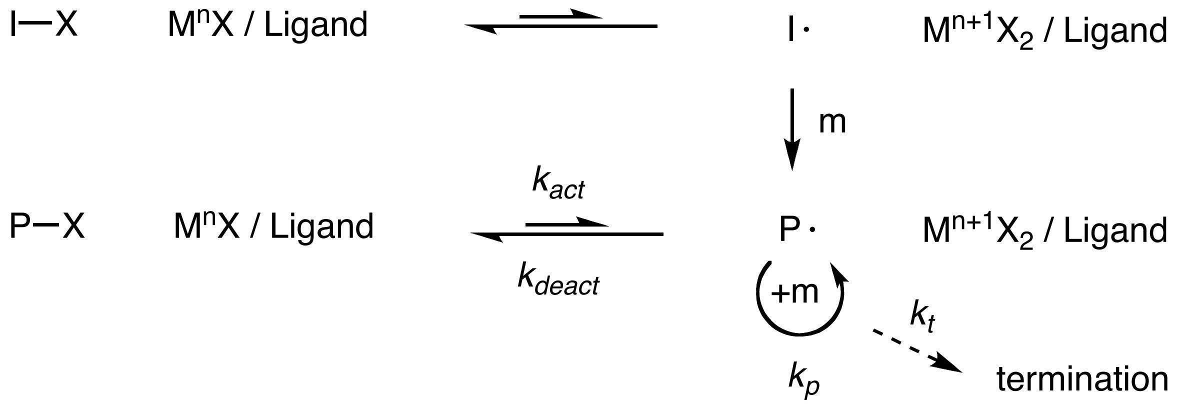
termination

- Different ATRP systems possess discrete rate properties based on the following
- Each monomer has a specific k_{eq} (k_{act}/k_{deact}) and requires specific conditions for ATRP



Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)



$I{-}X \quad M^nX / \text{Ligand} \rightleftharpoons I\cdot \quad M^{n+1}X_2 / \text{Ligand}$

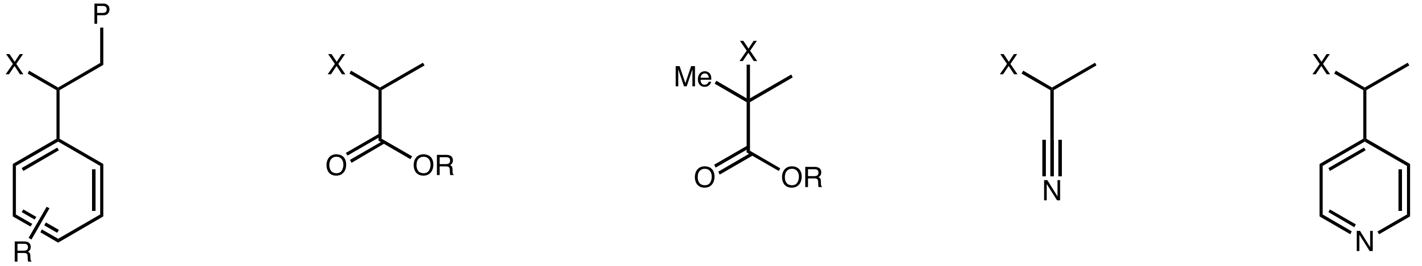
$\downarrow$ m

$P{-}X \quad M^nX / \text{Ligand} \underset{k_{deact}}{\overset{k_{act}}{\rightleftharpoons}} P\cdot \quad M^{n+1}X_2 / \text{Ligand}$

+m k_p

k_t termination

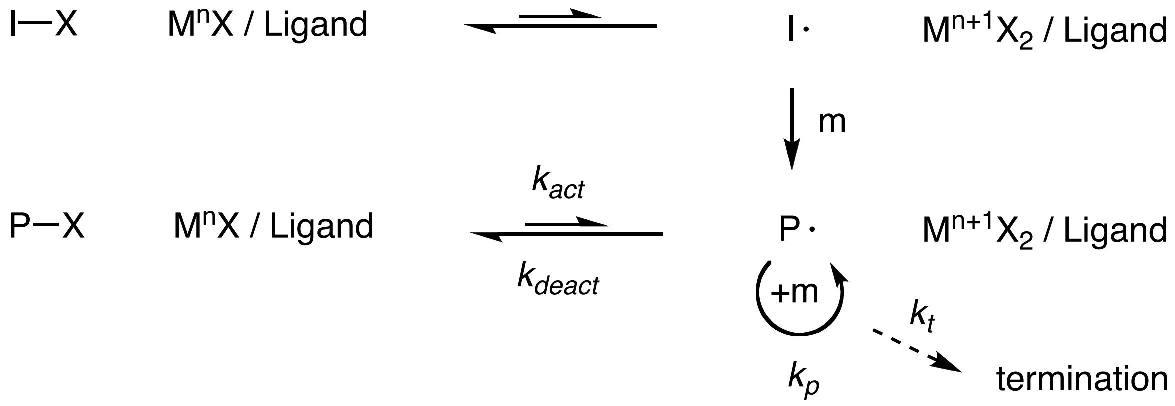
- Different ATRP systems possess discrete rate properties based on the following
- Each monomer has a specific k_{eq} (k_{act}/k_{deact}) and requires specific conditions for ATRP



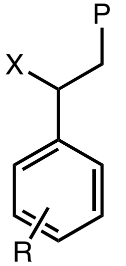
- Initiators tend to look like the desired monomer units (similar redox, kinetic properties)

Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

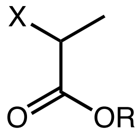
Atom Transfer Radical Polymerization (ATRP)



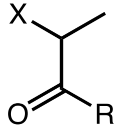
- Different ATRP systems possess discrete rate properties based on the following
- Each monomer has a specific k_{eq} (k_{act}/k_{deact}) and requires specific conditions for ATRP



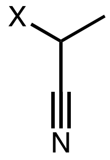
CuX



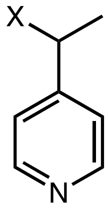
CuX, RuX_2, NiX_2



NiX_2, RuX_2



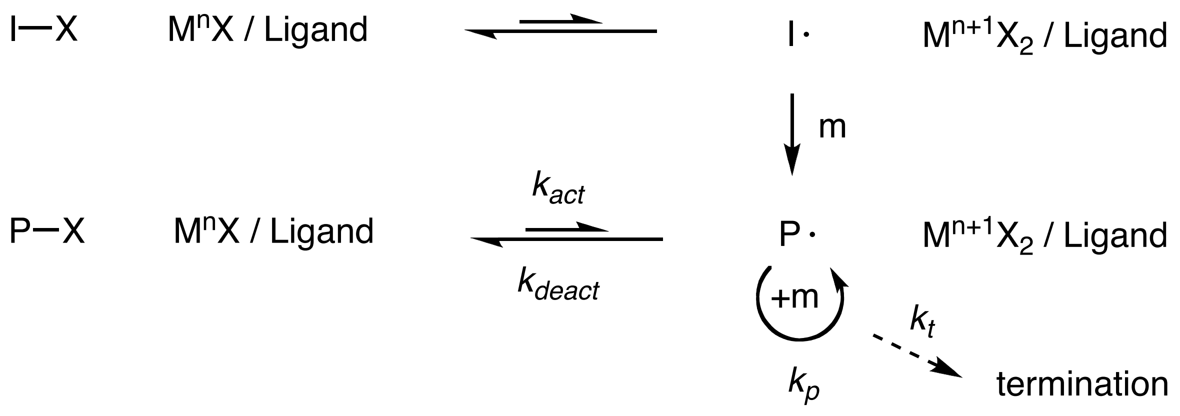
FeX_2, CuX



CuX

- Metals typically used to initiate each indicated monomer class (ligands play huge role)

Atom Transfer Radical Polymerization (ATRP)



$$I{-}X \quad M^nX\ /\ \text{Ligand} \rightleftharpoons I\cdot \quad M^{n+1}X_2\ /\ \text{Ligand}$$

$$\downarrow m$$

$$P{-}X \quad M^nX\ /\ \text{Ligand} \underset{k_{deact}}{\overset{k_{act}}{\rightleftharpoons}} P\cdot \quad M^{n+1}X_2\ /\ \text{Ligand}$$

+m

k_p

k_t

termination

- Different ATRP systems possess discrete rate properties based on the following

more stable cations

faster ATRP catalysts

$Fe^{III}(phen)_3$

+1 V

0.5

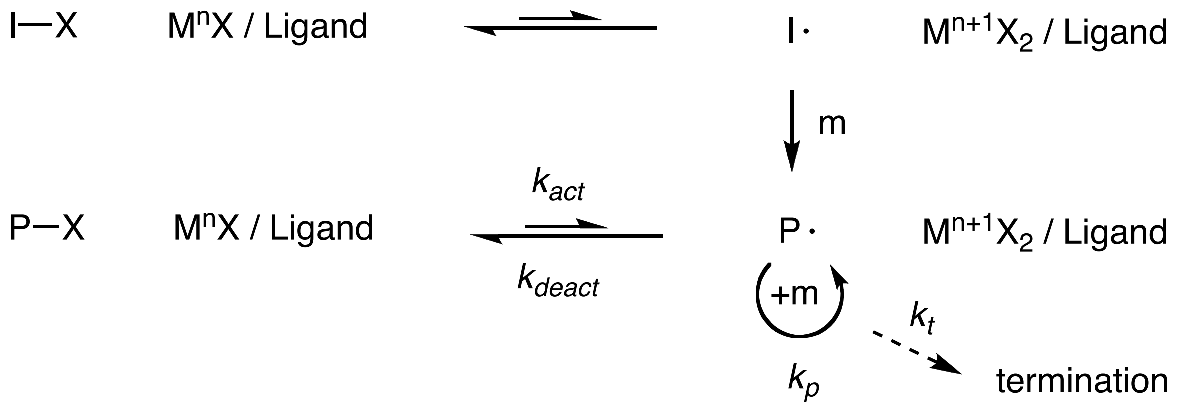
0

-0.5

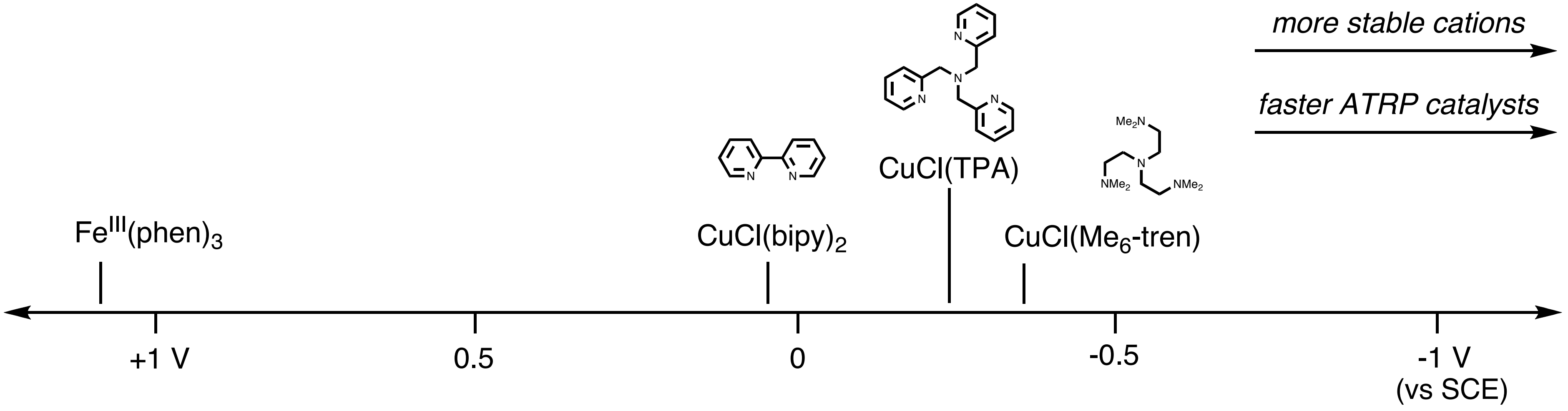
-1 V
(vs SCE)

Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)

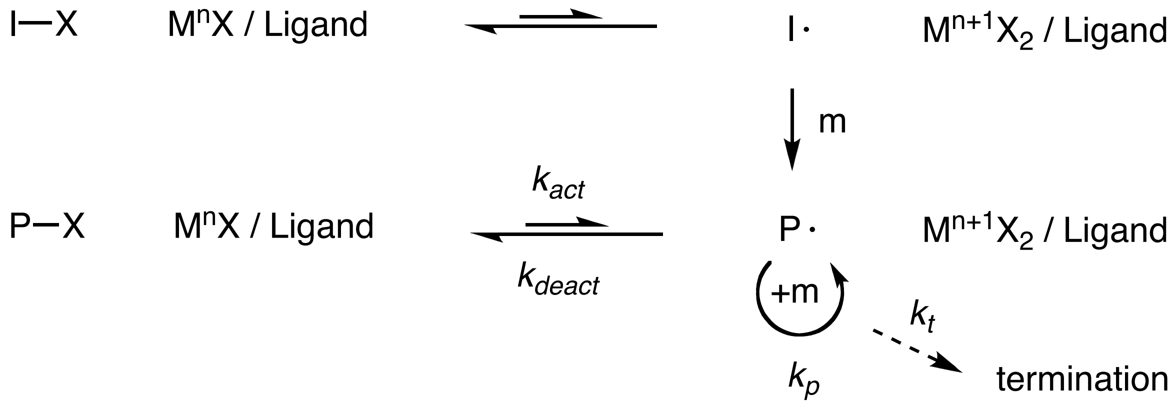


- Different ATRP systems possess discrete rate properties based on the following



Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)



$$\mathrm{I{-}X} \quad \mathrm{M^{n}X\ /\ Ligand} \rightleftharpoons \mathrm{I\cdot} \quad \mathrm{M^{n+1}X_2\ /\ Ligand}$$

$$\mathrm{I\cdot} \xrightarrow{m} \mathrm{P\cdot}$$

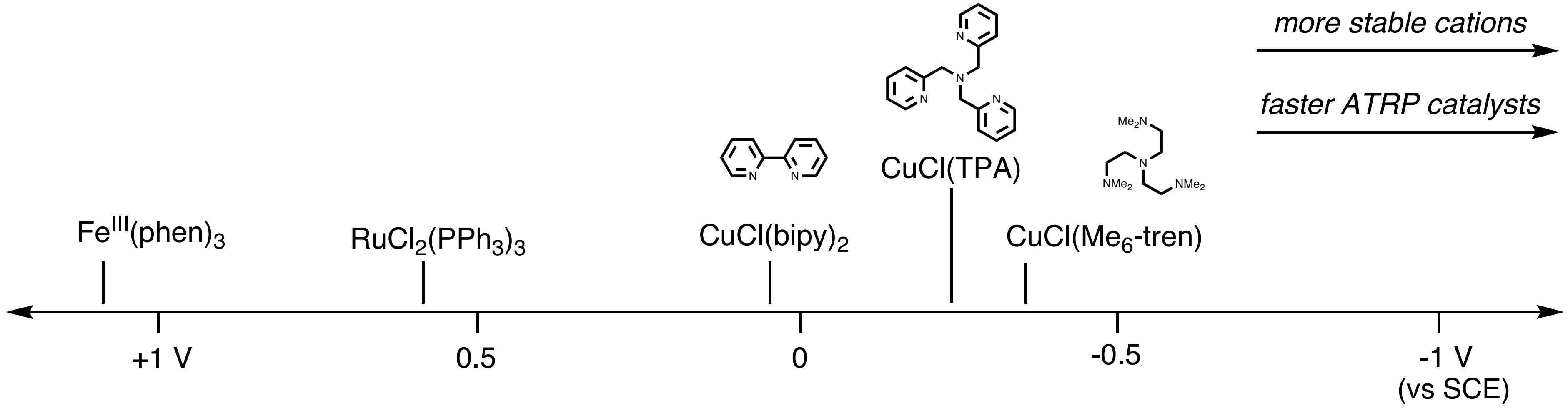
$$\mathrm{P{-}X} \quad \mathrm{M^{n}X\ /\ Ligand} \underset{k_{deact}}{\overset{k_{act}}{\rightleftharpoons}} \mathrm{P\cdot} \quad \mathrm{M^{n+1}X_2\ /\ Ligand}$$

$$\mathrm{P\cdot} \xrightarrow{k_t} \text{termination}$$

+m

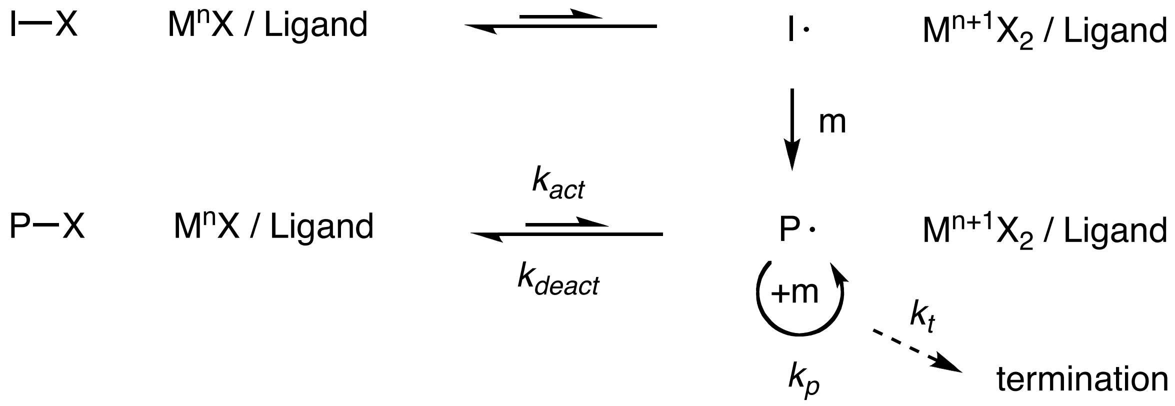
k_p

- Different ATRP systems possess discrete rate properties based on the following

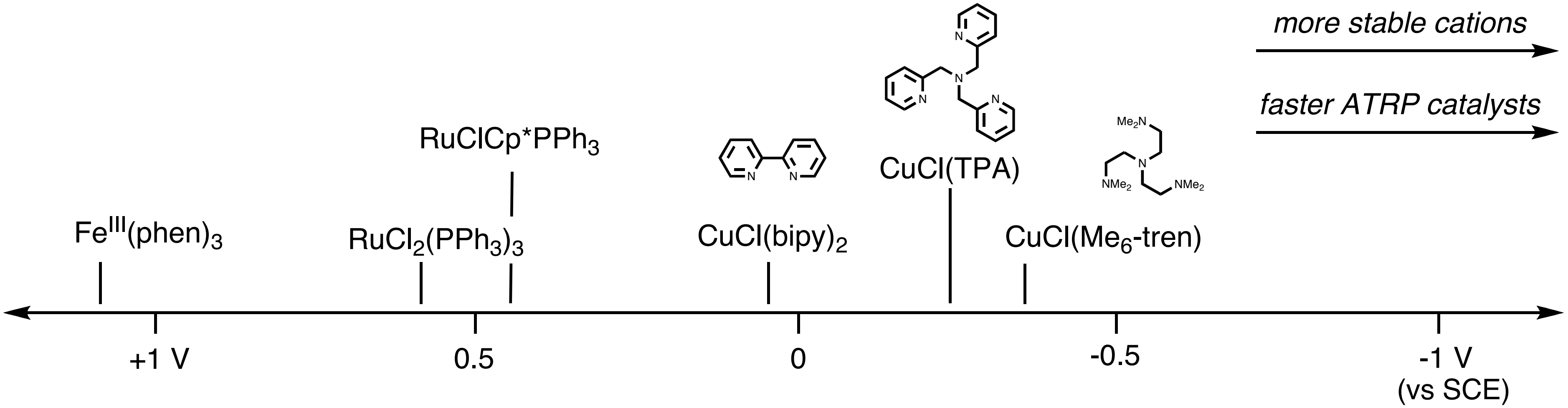


Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

Atom Transfer Radical Polymerization (ATRP)



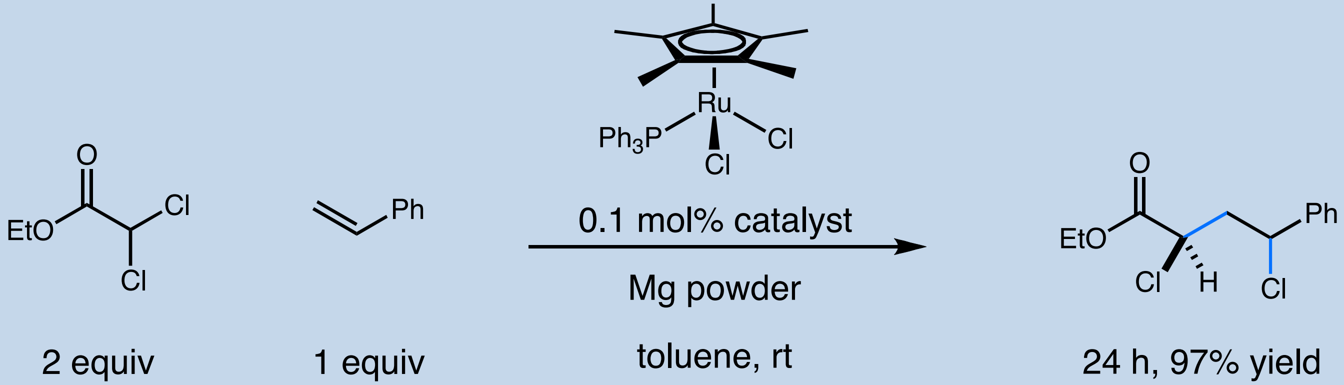
- Different ATRP systems possess discrete rate properties based on the following



Matyjaszewski, K. et al. *Chem. Rev.* **2001**, *101*, 2921.

New Catalyst Systems Allow for ATRA Reactions Under Mild Conditions

- Newer highly active ruthenium catalysts initiate rapidly at room temperature



Severin, K. *Chem. Eur. J.* **2007**, 6899.

Potential Future Atom Transfer Radical Chemistry

- Successful radical precursors in ATRC reactions so far are highly activated