Concurrent Tandem Catalysis

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1. Introduction

The replacement of multistep, salt-generating chemical synthesis with efficient catalyzed reactions that strive for atom economy[1] is having a significant impact on the manufacture of fine chemicals and pharmaceutical intermediates (Figure 1).[2]

"Tandem" reactions, in which multiple reactions are combined into one synthetic operation, have been reported extensively in the synthetic chemistry literature.[3] More specific terms such as "domino" and "cascade" reactions (which often require a complex substrate with predetermined functionalities) describe closely coupled individual reactions that often yield a product difficult to obtain by a single process.[4] Intermediates need not be stable enough for isolation, because they are quickly transformed by a subsequent reaction into a lower energy species.[5] "Sequential" reactions involve coupling of transformations that may operate independently and often require additional reagents or changes in reaction conditions. In a practical sense, they allow for reactions to be carried out in a single reaction vessel without purification between steps.

The term "tandem catalysis" has been used in the literature to include synthetic strategies that involve the *sequential* use of catalytic reactions with minimum workup, or change in conditions.[6] When considering these sequential tandem reactions, one often needs to consider catalyst compatibility with residual material (solvent, additives and other catalysts) from preceding steps. In this review, we concern ourselves with concurrent tandem catalysis (CTC), which involves the cooperative action of two or more catalytic cycles in a single reactor. In CTC each catalyst must be compatibile with substrates, intermediates and other catalysts and must also exhibit reaction sequence selectivity. While CTC reactions have ample precedent in biological systems, where a number of enzymes operate simultaneously within the same medium to effect multiple transformations,[7] our goal is to review those systems that incorporate at least one synthetic catalytic species that has been designed, synthesized, is somewhat understood mechanistically and can involve either homogeneous or heterogeneous reaction sites.

Scheme 1 shows a simple general example of a CTC cycle, where catalyst **I** transforms substrate **A** to give an intermediate **B**. **B** is subsequently converted to product **P** by catalyst **II**. Other reagents may be required to achieve the desired transformations; however, in CTC these reagents coexist with substrate **A** and both catalysts when the reaction is initiated.

Concurrent tandem catalysis constitutes a significant challenge for synthetic chemists and presents a number of opportunities to improve chemical transformations. Multiple catalysts operating simultaneously could circumvent the time and yield losses associated with the isolation and purification of intermediates in multistep sequences. Generating harmful chemicals *in situ*, followed by incorporation into safer, more stable and larger molecular structures, would eliminate the inherent dangers associated with transportation of chemicals over long distances. Efficient catalysts may allow the coupling of equilibrium-limited reactions with subsequent exothermic ones.

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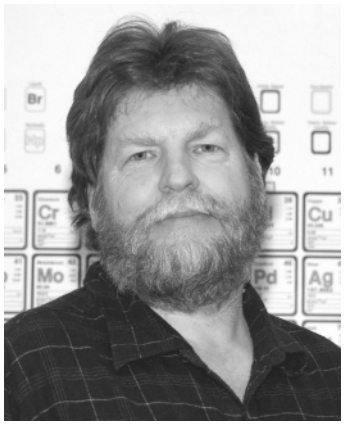
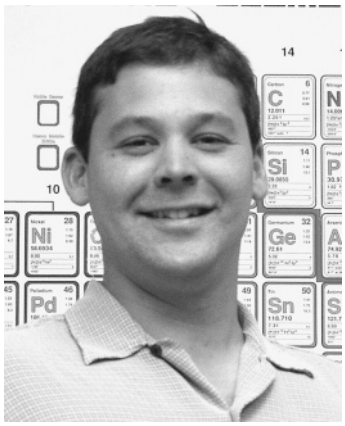
Julia-C. Wasilke was born in Hannover, Germany, in 1978. She received her Diplom in Chemistry from the Westfälische Wilhelms-Universität Münster (WWU), Germany, in 2002. Julia is currently finishing her dissertation under the supervision of Prof. G. Erker at WWU and Prof. G. C. Bazan at the University of California, Santa Barbara (UCSB), in a joint collaboration. Julia's research is concerned with the design and application of novel transition metal catalysts for C–C-bond formation. Outside chemistry, Julia dances Ballet, plays the piano, and enjoys skiing and scuba-diving.



Dr. R. Tom Baker grew up in Tsawwassen, British Columbia, Canada. He received his B.Sc. degree from UBC in 1975 and his Ph.D. from UCLA in 1980 with M. Frederick Hawthorne. After a postdoctoral stint with Philip S. Skell at Penn State, he joined the staff at DuPont Central Research in Wilmington, DE, where he applied inorganic and organometallic chemistry and homogeneous catalysis to the nylon, fluoroproducts, and titanium dioxide businesses. He joined the Chemistry Division at Los Alamos National Laboratory in 1996 and is currently involved in multifunctional catalysis approaches to low-temperature hydrocarbon functionalization, including new applications of alternative reaction media.



Dr. Stephen Obrey was born in Colorado Springs, CO, in 1972. In 1994 he received his B.S. degree in Chemistry from Trinity University, where he was enthusiastically exposed to the field of chemical research, working with Michael P. Doyle on enantioselective metal carbene reactions of diazoacetoacetates. After receiving an M.S. in Organic Chemistry with Simon G. Bott at the University of North Texas, Stephen studied heterogeneous and homogeneous alkylalumoxane catalysts with Andrew R. Barron at Rice University, as a Robert A. Welch Pre-doctoral Fellow, receiving his Ph.D. in Inorganic Chemistry in 2001. He then joined the Chemistry Division at Los Alamos National Laboratory (LANL) as a Postdoctoral Research Associate with R. Thomas Baker and Alfred P. Sattelberger working on bifunctional heterogeneous catalysts and reactivity of dinuclear homoleptic allyls. Stephen is currently a LANL Technical Staff Member in the Advanced Diagnostics and Instrumentation Group.

Guillermo C. Bazan is Professor in the Departments of Materials and Chemistry & Biochemistry and is the Director of the Institute for Polymers and Organic Solids at the University of California, Santa Barbara. He was born in Mendoza, Argentina, in 1963 and was raised in Argentina, Belgium, and Canada. He obtained his B.Sc. in 1986 from the University of Ottawa, where he did undergraduate research with Professors Jean Fréchet and Christian Detellier. His Ph.D. thesis was done with Professor Richard R. Schrock at MIT. After a postdoctoral appointment at Caltech with Professor John Bercaw, he began his independent career in 1992 at the University of Rochester. He moved to UCSB in 1998. His research interests concern the design, synthesis, photophysics, bulk properties, and applications of organic molecules with delocalized electronic structures and the design of homogeneous transition metal catalysts for the controlled polymerization of olefins.

Multienzymatic systems in Nature provide ample evidence of tandem catalysis in an aqueous environment (cf. polyketide biosynthesis).[8] Extending this coordinated catalytic action to artificial processes will allow a wider spectrum of chemical transformations. For example, molecular species that are too thermally unstable for isolation may be transformed into useful products by quickly entering a subsequent catalytic cycle prior to decomposition. To enable this vision, chemists may choose from catalysts available from previous work on molecular, heterogeneous, and biological catalysis.

Although many chemical transformations may be suitable for CTC, the product must retain some functionality, at least prior to the last step. Hydrogenation of a diene to a monoalkene, for example, may be a good initial reaction whereas monoalkene hydrogenation would likely not be, given the current state of alkane functionalization catalysis.[9] In a simple example of concurrent tandem catalysis, whereby a single metal center promotes two different catalytic cycles, alkene hydroformylation can afford alcohols by subsequent hydrogenation of the initial aldehyde product.[10]

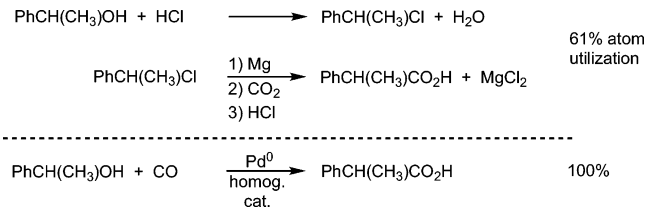
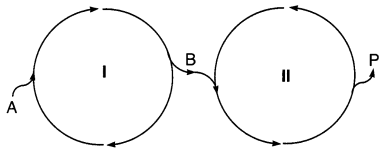


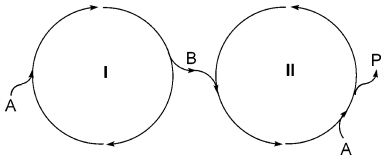
Figure 1. Comparison of stepwise and catalytic C−C bond formation.

Scheme 1



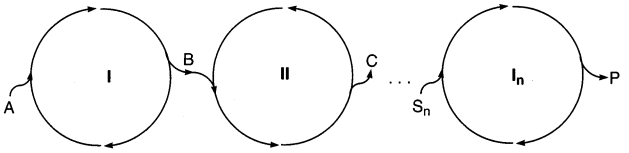
Several factors must be considered for coupling the activity of multiple catalysts in a CTC scheme, the primary and most obvious condition being compatibility. There should be no interference between the catalytic species in an ideal situation. Furthermore, the active site reactivity must be well matched so that the product of one catalyst does not overwhelm the overall CTC sequence. Similarly, if the activity of one catalyst is disproportionately low, then subsequent catalysts may become substrate starved; a condition that can result in decomposition or unwanted side reactions. These considerations are of special concern for systems that are represented by Scheme 2, where two catalysts react with the same substrate.

Scheme 2



More complex combinations may be envisioned (Scheme 3). The underlying concept remains intact, in that the product from the previous cycle is acted upon by another catalyst. Many *possible* catalyst/substrate combinations can be formulated, but it should be apparent that the practical difficulties in devising reaction strategies increase considerably with the number of cycles that need coordination. The metabolic pathways that Nature has been able to organize show that we are at the beginning of artificial concurrent tandem catalysis and provide much inspiration for extending complexity.

Scheme 3



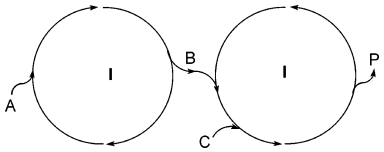
To limit the scope of the review, and re-emphasize the intellectual distinction involved in CTC design, we have arbitrarily not included single-pot tandem catalysis in which additional reagents are added after a given cycle is complete. Reactions in which a single metal species is added, but is capable of two or more distinct chemical transformations involving discrete molecular products, are included.We include biological systems, of which many are available, only where they serve to exemplify a given type of catalytic combination or include an artificial catalytic center. We have excluded reactions employing a cocatalyst that regenerates the active catalyst, such as Wacker-type oxidation[11] where a copper oxidant is used to regenerate the active Pd catalyst, since only one catalyzed reaction involving a substrate takes place. We also exclude domino reactions where multiple transformations of the substrate occur *without discrete metal-free intermediates*.[12] Recently, an overview of cascade catalysis was presented with a perspective to practical applications[13] and Lee et al. reviewed multi-catalyst systems for one-pot organic transformations that included a section on sequential catalytic reactions by compatible catalysts.[14]

In this Review we describe, in general terms, published CTC reaction schemes that have been reported through May 2004. We begin by proposing a simple classification scheme for coupled catalytic cycles. A review of specific examples, grouped by reaction classes, is presented with emphasis placed on methodologies utilized for the development of CTC. We conclude with a future prospects section including developmental approaches related to tandem catalysis. Abbreviations are listed in Section 6.

2. Classification of CTC Cycles

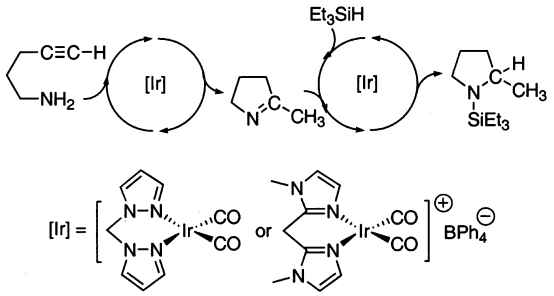
We propose a simple classification of generic CTC cycles based on the number of unique catalytic cycles, the cycles into which the starting materials are incorporated and how the products from each cycle are distributed in subsequent reactions. In the simplest case (Scheme 4), a set of starting materials (**A**) reacts with catalyst **I** to produce a product (**B**). In **A**, we incorporate all of the reagents that are needed for the first cycle. In the second step, the same catalyst, **I**, facilitates the reaction of **B** with **C** to give product, **P**, which will be used to designate the final product after operation of all cycles. As is the case with **A**, **C** corresponds to all of the reagents required for the **B**→**P** transformation. In our system, the cycle below is designated $(A_IB)(BC_IP)$. In each set of parentheses the starting materials are given before the catalyst subscript. The product from each cycle is given after the catalyst.

Scheme 4



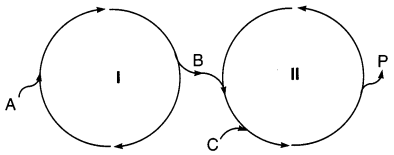
An example for this basic CTC classification utilizes an iridium catalyst for two distinct Ir-catalyzed reactions, namely the hydroamination/hydrosilation of 4-pentyne-1-amine to form the cyclic *N*-silylamine (Scheme 5).[15]

Scheme 5



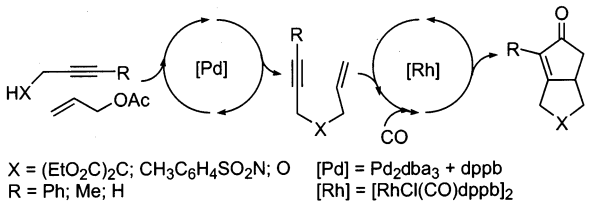
Probably the most common type of reaction reported thus far corresponds to those described by the $(A_IB)(BC_{II}P)$ classification, which utilizes two different catalysts (Scheme 6). Cycle **I** produces **B**, which then is transformed by a second catalyst (**II**) with reagent(s) **C**, to generate **P**.

Scheme 6



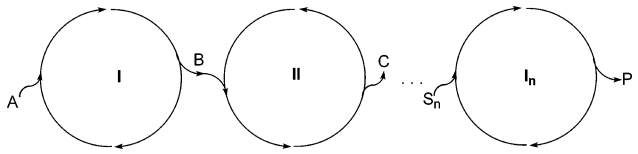
A report by Jeong et al. serves as an example of $(AB_IC)(CD_{II}P)$. Pd-catalyzed allylation generates an enyne intermediate, which then undergoes Rh-catalyzed Pauson-Khand reaction forming the bicyclopentenone product (Scheme 7).[16]

Scheme 7



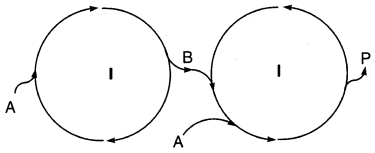
These cycles may be extended as required by the complexity of the specific CTC reaction scheme, creating extended versions, and may be abbreviated by the generic term $(A_IB)(B_{II}C)...(S_{nI_n}P)$, where $\mathbf{S}_n$ is the nth substrate and $\mathbf{I}_n$ is the nth catalyst (Scheme 8).

Scheme 8



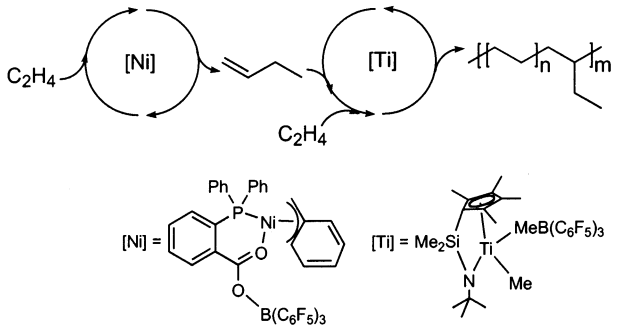
There are circumstances where a single starting material can appear in more than one catalytic cycle. In type $(A_IB)(AB_IP)$ (Scheme 9), **A** provides **B** through the catalytic action of **I**. In a subsequent step, the product **B** in combination with substrate **A** may be catalytically transformed to the desired product. As with other CTC reaction schemes this system may employ one or more catalysts.

Scheme 9



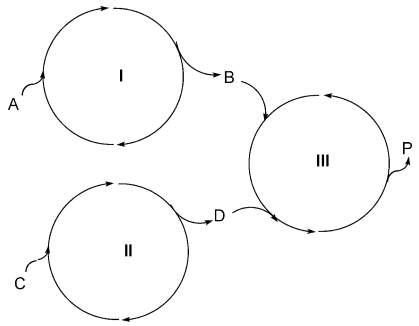
The polymerization of ethylene to branched polyethylene by two different catalysts serves as an example. Catalyst **I** dimerizes ethylene exclusively into 1-butene, whereas catalyst **II** copolymerizes 1-butene and ethylene in a tandem polymerization to high molecular weight poly(ethylene-*co*-butene) materials (Scheme 10).[17]

Scheme 10



In reaction $(A_IB)(C_{II}D)(BD_{III}P)$ the products from two individual cycles are fed into a third independent cycle to yield **P** (Scheme 11).

Scheme 11



We believe that this simple classification may aid in the identification, communication, and understanding of CTC cycles.

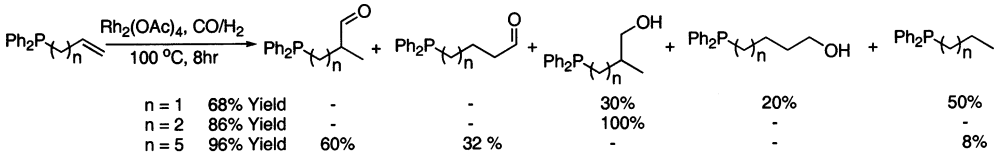
3. Survey of Concurrent Tandem Catalysis

3.1. Carbonylation Reactions

3.1.1. Hydroformylation

Examples of CTC involving an initial hydroformylation step, followed by catalyzed hydrogenation, amidation, or aldol reactions have been recently reported.[18] Many of these schemes involve the same catalyst in the sequential reactions. In neat alkene or solvents such as THF, trialkylphosphine Rh catalysts afford high yields of alcohols by successive alkene hydroformylation and aldehyde hydrogenation.[19] This is an example of the general $(A_IB)(B_IP)$ case. Similar results have been obtained by adding

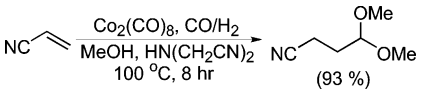
Scheme 12



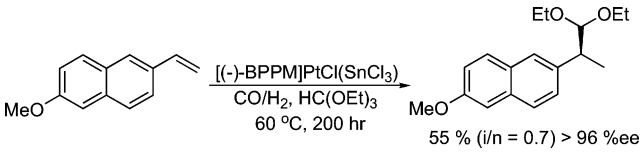
triethylphosphine to zeolite supported Rh catalysts, although yields from unsaturated alcohol substrates suffer from zeolite-promoted aldol chemistry.[10b,c,d] In detailed studies of the regioselective Rh-catalyzed hydroformylation of alkenyl phosphines, Jackson et al. showed that the tandem reaction is favored by intramolecular chelation to the catalyst center (Scheme 12; $n = 1$, 2 gave alcohols; $n = 5$ gave aldehydes).[20]

Alkene hydroformylation in alcohol solvents can give hemiacetals, acetals and enol ethers, some of which can serve as substrates in subsequent reactions. In the presence of an acid cocatalyst, for example, cobalt carbonyl-catalyzed acrylonitrile hydroformylation in methanol affords high yields of the acetal product [$(A_IB)(B_{II}P)$, Scheme 13],[21] and triethylorthoformate can be used to protect Pt-catalyzed asymmetric hydroformylation products from racemization as their acetals (Scheme 14).[22]

Scheme 13

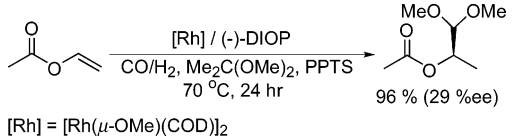


Scheme 14



While addition of acid cocatalyst pyridinium *p*-toluenesulfonate (PPTS) to the Rh(−)-DIOP catalyzed hydroformylation/acetalization of vinyl acetate did not improve the % ee, regioselectivity increased from 20:80 to 4:96 with PPTS (Scheme 15).[23]

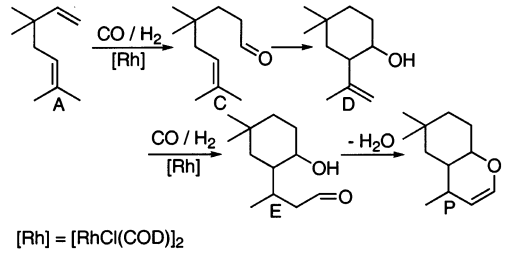
Scheme 15



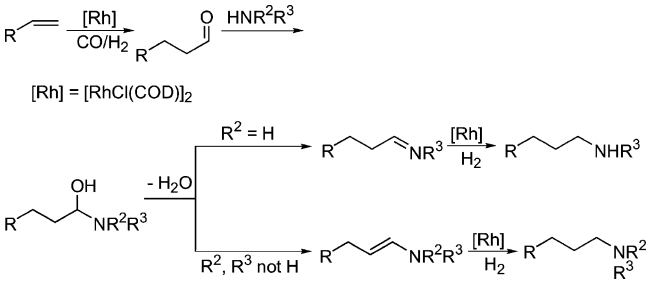
Roggenbuck and Eilbracht combined diene hydroformylation, ene-carbonyl reaction, hydroformylation, and dehydration in a $(AB_IC)(C{\rightarrow}D)(DB_IE)(E{\rightarrow}P)$ scheme (**B** = CO/H_2) using a single catalyst in one pot to yield the enol ether in 40% yield (Scheme 16).[24]

Alkene hydroformylation in the presence of amines gives "hydroaminomethylation" via hydrogenation of intermediate enamines or imines [$(AB_IC)(CD{\rightarrow}E)$-$(E{\rightarrow}F)(FG_IP)$, Scheme 17].[25] The scope of this reaction can be extended to imines and enamines, whereby, in a third catalyzed reaction, hydrogenation to the primary amine can be conducted concurrently.[26] An analogous cycle takes place for the *iso*-compounds.

Scheme 16

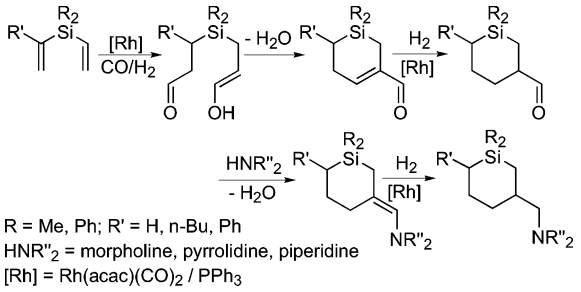


Scheme 17



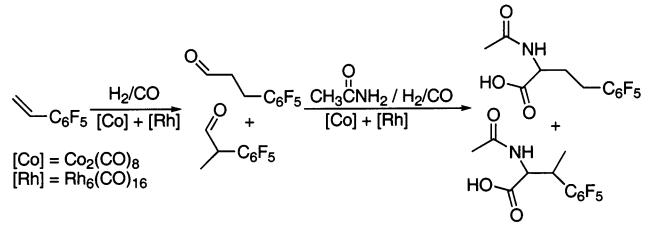
Whereas dienes afford diamines under hydroaminomethylation conditions, divinylsilanes and cyclic amines are converted into aminomethyl-substituted silacyclohexane derivatives in 41−95% yields by a double hydroformylation/aldol/amination/hydrogenation sequence [$(AB_IC)(C{\rightarrow}D)(DE_IF)(FG{\rightarrow}H)(EH_IP)$, Scheme 18].[27]

Scheme 18



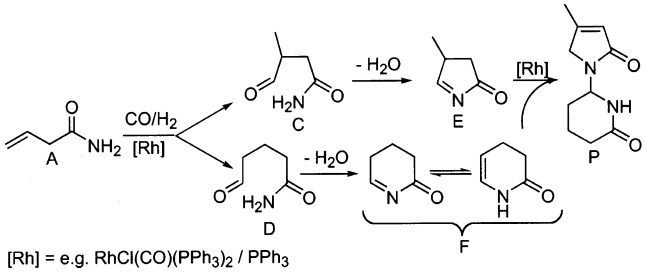
Ojima used a mixture of Co and Rh carbonyls to catalyze the hydroformylation−amidocarbonylation of pentafluorophenyl styrenes to prepare fluoroamino acids [$(AB_{I,II}CD)(CDE_{I,II}P)$, Scheme 19].[28]

Scheme 19



In another CTC sequence, the cobalt carbonyl amidocarbonylation catalyst was mixed with a second catalyst that effected the isomerization of allylic and homoallylic alcohols or oxiranes to the aldehyde intermediate.[29] In a remarkable example of CTC selectivity, intramolecular amidocarbonylation of primary enamides affords a unique heterodimer via Rh-catalyzed cross-coupling of the two amidocarbonylation product regioisomers [$(AB_ICD)(C\rightarrow E)(D\rightarrow F)$-$(EF_IP)$, Scheme 20].[30]

Scheme 20



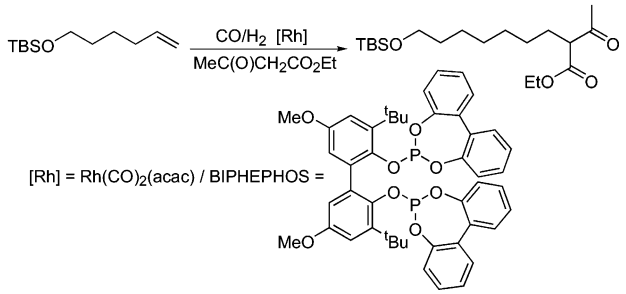
Breit and Zahn combined substrate-directed hydroformylation of methallyl esters with *in situ* Wittig olefination/hydrogenation to obtain saturated products in good yield and diastereoselectivity.[31] A similar one-pot hydroformylation/Knoevenagel/hydrogenation sequence was also effective for homomethallyl *o*-DPPB esters [$(AB_IC)(CD\rightarrow E)(EF_IP)$, Scheme 21].[32]

Regioselective hydroformylation of a monosubstituted alkene using the bulky, chelating bis(phosphite)-ligand BIPHEPHOS was employed in a CTC to prepare linear β-ketoesters in good yield (Scheme 22).[32]

3.1.2. Pauson–Khand Annulation

In an elegant demonstration of CTC, Jeong et al. sought to combine a Pd(dppb)-catalyzed allylation [dppb = 1,4-bis(diphenylphosphino)butane] with a Rh-catalyzed Pauson−Khand-type carbonylation.[16] Initial studies indicated that the allylation reaction to generate the enyne intermediate proceeded smoothly, even in the presence of CO, but the subsequent Rh-catalyzed carbonylative cyclization was problematic and prompted a detailed investigation of Pd and Rh catalyst precursors, supporting ligands, solvent, and accompanying bases. It was discovered that heating a 2-fold excess of the allylation reagent with the propargyl substrate in the presence of 1.2 equiv. of bis(trimethylsilyl)acetamide at 110 °C in toluene with 1.5 mol % $Pd_2(dba)_3$, 3 mol % dppb and 7 mol % $[RhCl(CO)(dppb)]_2$ afforded the enyne, which was

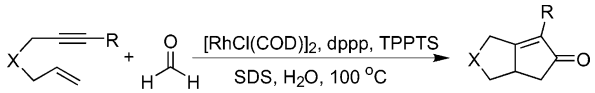
Scheme 22



subsequently transformed to the bicyclopentenone product in excellent yield (73−92% based on propargyl substrate) [$(AB_IC)(CD_{II}P)$, Scheme 7].

Building on their previous work on Rh-catalyzed allylic substitution, Evans et al. developed a single-catalyst ($[RhCl(CO)(dppp)]_2$) allylation/Pauson-Khand tandem scheme that, while requiring different temperatures for the two steps, proceeded with high regio- and diastereoselectivity.[33] A silica-supported Pd−Co (1:20) catalyst was also effective for this tandem reaction at 130 °C and 10 atm CO (88% yield for R = Me, X = $C(CO_2Et)_2$), although Pd-leaching into the solution decreased yields substantially in subsequent runs with recycled catalyst.[34] In a recent extension, Fuji et al. used micelles to effect Rh-catalyzed formaldehyde dehydrogenation in an aqueous phase to generate CO in situ, followed by carbonylation of the organic enyne substrate in the micelle.[35] Extensions of the *in situ* CO generation have been utilized in other reaction schemes.[36] Utilization of both dppp and sulfonated TPPTS ligands is believed to create both hydrophilic and hydrophobic catalysts to function in the appropriate phase. A variety of enynes were rapidly converted to bicyclic cyclopentenones in high yield (mostly 85−95%) without the need for a pressure reactor [$(A_IB)(BC_{II}P)$ where **B** is carbon monoxide, Scheme 23].

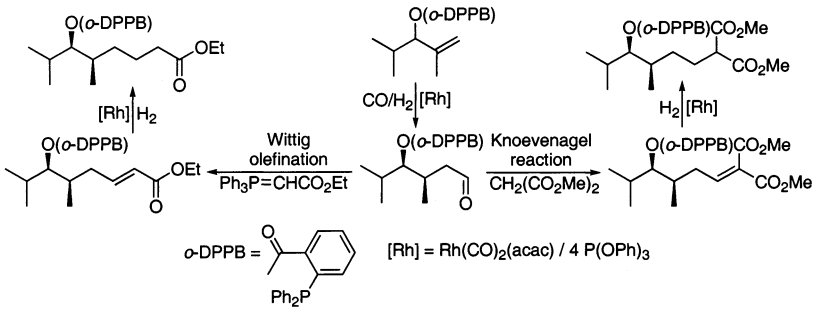
Scheme 23



3.1.3. Alkoxycarbonylation

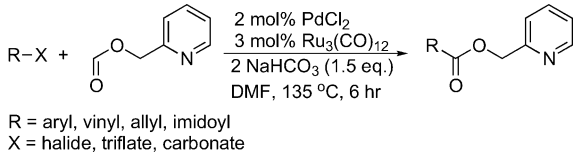
Ko et al. investigated a ruthenium-catalyzed decarbonylation followed by a palladium catalyzed alkoxycarbonylation to couple a chelating formate with aryl

Scheme 21



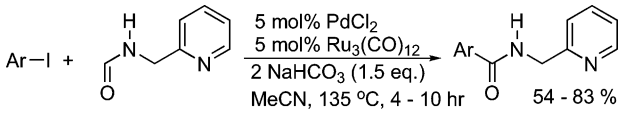
and alkenyl (pseudo)halides. Control studies indicated that chelation plays a key role in the efficiency of both ruthenium-catalyzed decarbonylation and subsequent transfer of the pyridylmethanol fragment from Ru to Pd.[37] Mild hydrolysis of the products affords the carboxylic acid and pyridylmethanol, which could be readily formylated to regenerate the pyridylformate for reuse [$(A_IB)(BC_{II}P)$ Scheme 24].

Scheme 24



This CTC synthetic methodology has been extended to the cooperative aminocarboxylation using pyridylformamide (Scheme 25).[38]

Scheme 25

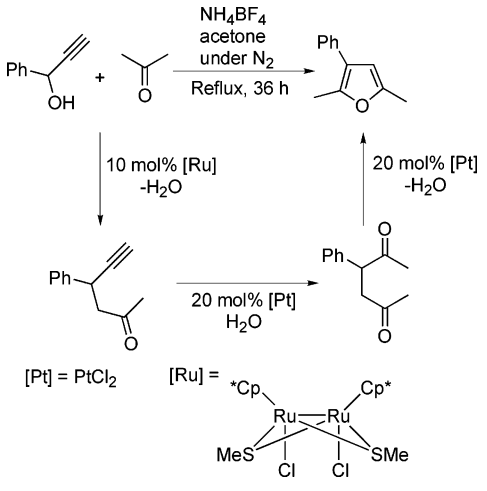


3.2. Addition, Cyclization, and Miscellaneous Reactions

3.2.1. Multiple Catalysts

Nishibayashi et al. investigated the tandem addition/cyclization of propargylic alcohols with various heteroatom- and carbon-centered nucleophiles catalyzed by a combination of $PtCl_2$ and a dinuclear organo-Ru complex (Scheme 26).[39] The resulting

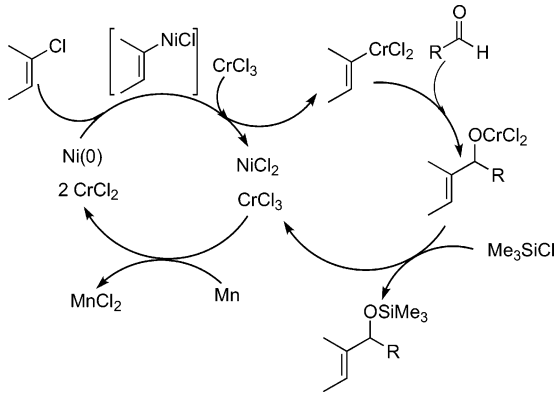
Scheme 26



substituted furans and pyrroles were obtained in moderate to high yields (up to 78%) with complete regioselectivity. For the acetone and 1-phenyl-2-propyn-1-ol, the Ru complex catalyzes the addition reaction, affording the γ-ketoalkyne. $PtCl_2$ catalyzed hydration of the alkyne moiety by the H_2O produced in the first reaction step slowly gives the 1,4-diketone. Intramolecular cyclization of the diketone, also catalyzed by $PtCl_2$, yields the substituted furan. It is noteworthy that the last two reaction steps of this $(AB_IC)(C_{II}D)(D_{II}P)$ scheme proceeded more slowly with $PtCl_2$ as the only catalyst.

Jin et al. and Takai et al.[40] showed that $NiCl_2$ catalyzes the activation of alkenyl halides for subsequent transfer to chromium and an aldehyde addition reaction. Fürstner and Shi developed this into a catalytic reaction by using TMSCl to facilitate alkoxide release from chromium and use of manganese metal to reduce trivalent $CrCl_3$ to the catalytically active $CrCl_2$ (Scheme 27).[41] The product alcohol

Scheme 27



is then obtained after aqueous Bu_4NF workup. Implementation of the use of Mn(0) powder and TMSCl reduced the catalyst loading from 4 mol equivalents of $CrCl_2$ to 7−15 mol % $CrCl_2$ (or $CrCl_3$) with comparable chemo- and diastereoselectivities. In addition, it was found that replacing $CrCl_2$ with as little as 1 mol % chromocene (Cp_2Cr) catalyst was successful with only a slight decrease in diastereoselectivities. Note that this scheme can be classified as $(AI_{II}BC)(BD{\rightarrow}E)(EF{\rightarrow}PC)(CG{\rightarrow}HI)$ in which **I** is CrX_2, **II** is $NiCl_2$, **C** is CrX_3, and **G** is Mn. We recognize that Scheme 27 is a borderline example of CTC, but it was included because it manifests many of the appealing features of transition metal mediated CTC cycles.

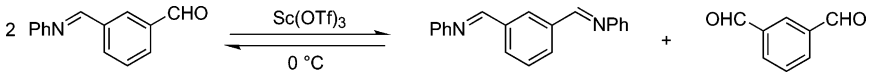
More recent developments have allowed the use of chiral Cr(III)/sulfonamide catalysts for enantioselective conversion of an aldehyde to an allylic alcohol.[42] It was also noted that $CrCl_2$ alone was effective for allyl halides whereas alkenyl- and alkyl halides gave the highest yields with mixed Cr (sulfonamide-based ligand/$Cr(III)Cl_2(THF)$) /Ni ($NiCl_2$ or $Ni(COD)_2$) and Cr/Co (Co-phthalocyanine) catalysts, respectively.

3.2.2. Lewis Acid Catalysis

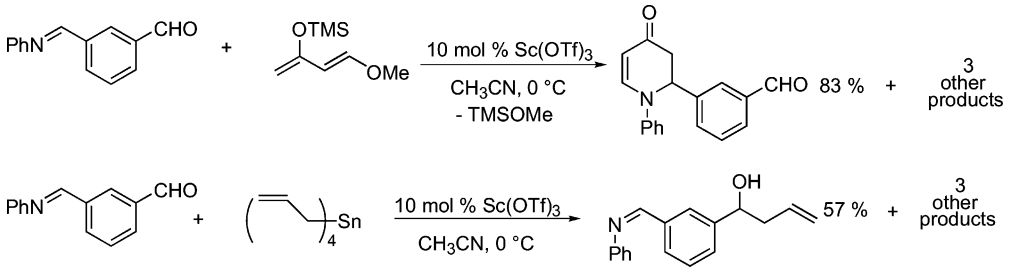
Orita et al.[43] investigated the application of a $Sc(OTf)_3$-catalyzed CTC reaction scheme for the parallel recognition of substrates that are prone to redistribution. In the presence of $Sc(OTf)_3$, 3-formylbenzylidene imines readily redistribute to give the symmetric diimine and dialdehyde (Scheme 28).

Catalyzed reaction of 3-formylbenzylidene imine with Danishefsky's diene afforded the Diels−Alder (DA) adduct in 83% yield, along with three minor products derived from subsequent DA reaction with the aldehyde and initial redistribution products. Alternatively, reaction of 3-formylbenzylidene imine with tetraallyltin gave preferential allylation of the aldehyde (57%), products from the subsequent allyl-

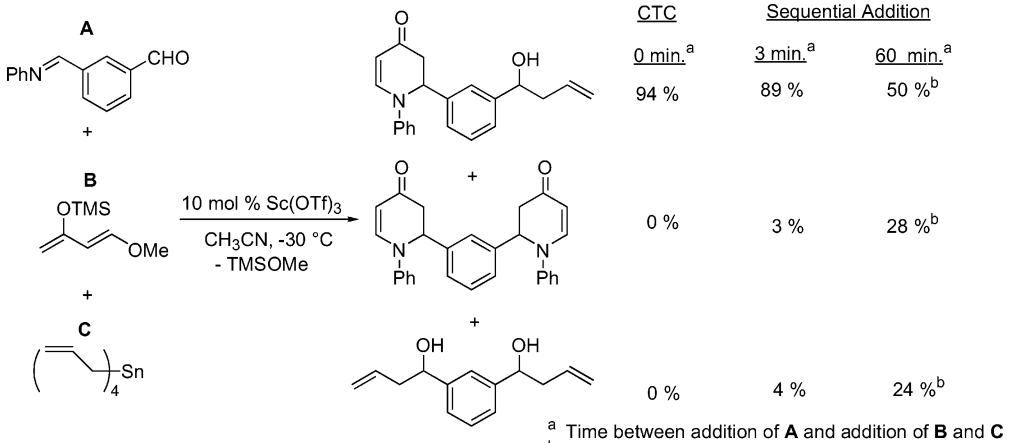
Scheme 28



Scheme 29



Scheme 30



[a] Time between addition of **A** and addition of **B** and **C**
[b] Product distribution as reported

ation of the imine, and products derived from the redistribution reaction (Scheme 29).

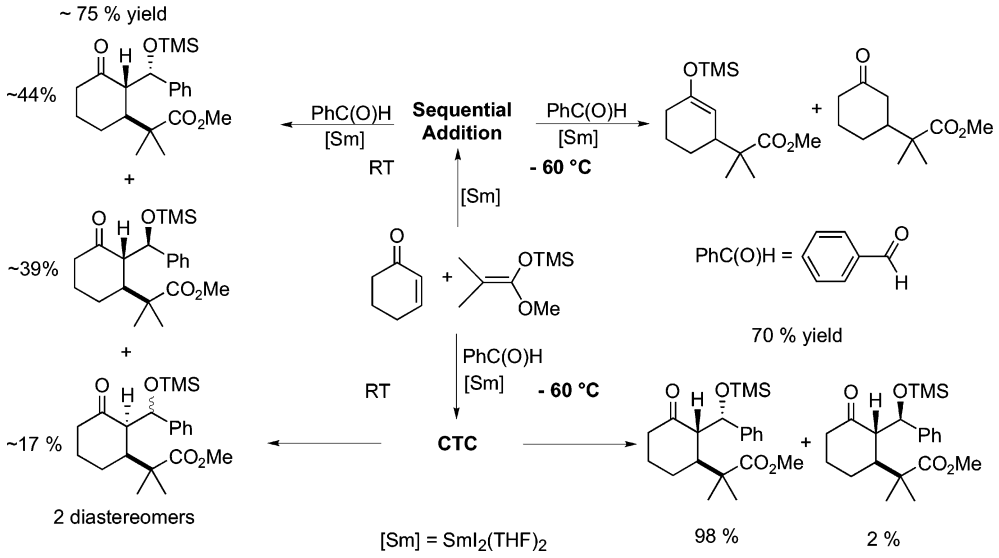
Interestingly, utilization of 3-formylbenzylidene imine, Danishefsky's diene, and tetraallyltin in a CTC reaction scheme not only yielded a single product derived from chemoselective Diels–Alder and allylation of the imine and aldehyde respectively, but also eliminated products derived from Sc-catalyzed redistribution reactions. If addition of diene and tetraallyltin to the reaction mixture is delayed by as little as three minutes the reaction is still chemoselective, but reintroduces the presence of redistribution products [$(AB_IC)(CD_IP)$, Scheme 30].

Giuseppone and Collin employed a samarium diiodide catalyst in a Mukaiyama Michael/aldol tandem catalysis scheme.[44] The first reaction between a silyl ketene acetal and cyclohexene-2-one affords an enoxysilane, which undergoes a subsequent aldol reaction with benzaldehyde. Initially the reaction was optimized in a stepwise fashion and the final products were isolated in 76% yield as a mixture of four diastereoisomers (Scheme 31). Combination of these two reactions in a one-pot tandem reaction with 10 mol % $SmI_2(THF)_2$ yielded the product in similar yield and diastereoselectivity as the stepwise addition product. Based on previous studies, a decrease in reaction temperature afforded better yields for the second aldolization step. Interestingly, application of this methodology to the concurrent tandem catalysis approach gave only two diastereomers (98:2 product ratio) in 70% yield, whereas the analogous stepwise reaction at low temperature (−60 °C) gave only enoxysilane and the corresponding ketone [$(AB_IC)(CD_IP)$, Scheme 31].

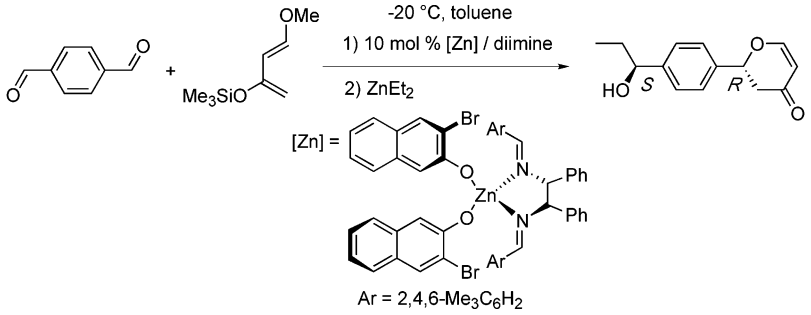
Du and Ding used a high throughput screening method to optimize a single catalyst for subsequent enantioselective hetero-Diels–Alder and diethylzinc addition to terephthaldehyde.[45] This reaction sequence was optimized as two separate reactions using benzaldehyde as a surrogate utilizing two separate catalyst libraries for the Diels–Alder and diethylzinc reactions. Potential candidates were identified and applied to the terephthaldehyde system yielding high % ee and % de (Scheme 32). The obtained enantio- and diastereoselectivity were almost identical to those obtained with the benzaldehyde surrogate indicating minimal "cross-talk" in this CTC reaction scheme. While this example is not strictly CTC, due to intermediate addition of diethylzinc, the future application of high-throughput screening for CTC optimization is certain.

Abbiati et al. have developed a one-pot procedure for the synthesis of pyridine derivatives from commercially available ketones or aldehydes and propargylamine utilizing a sequential regioselective *6-endo-dig* annulation/aromatization reaction sequence.[46] Initially the carbonyl compound undergoes an amine condensation reaction to form an imine, followed by cyclization and aromatization forming the substituted pyridine [$(AB_ICD)(D_IP)$, Scheme 33]. Generally, amination reactions are slow requiring the utilization of high temperatures, long reaction times, acid catalysis or water removal methodologies to drive the reaction to completion. Screening several known late metal

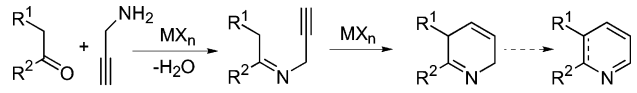
Scheme 31



Scheme 32



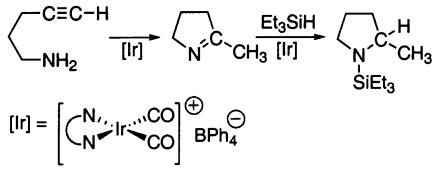
Scheme 33



amination catalysts, the authors found that gold and copper salts best facilitate the CTC sequence.

Field et al. developed a CTC methodology utilizing a cationic iridium complex for sequential hydroamination/hydrosilation of 4-pentyne-1-amine to form a cyclic *N*-silylamine (Scheme 5, Scheme 34).[15] Initially, this reaction was carried out in a one-pot stepwise fashion and was followed by ^{1}H NMR spectroscopy. Monitoring the reaction allows approximation of the reaction kinetics showing that the hydroamination is first order with respect to the aminoalkyne and zero order in the intermediate 2-methyl-1-pyrroline. Due to the complicated nature of these concurrent multistep reactions, understanding reaction rates, thermodynamic equilibrium, and kinetic activation barriers is essential as CTC reaction sequences become more complicated. Transition of this reaction into a one-pot CTC reaction scheme of the type (A_IB)-(BC_IP) yielded the cyclic *N*-silylamine in high yield with minor side-products derived from hydrosilation of the aminoalkyne starting material.

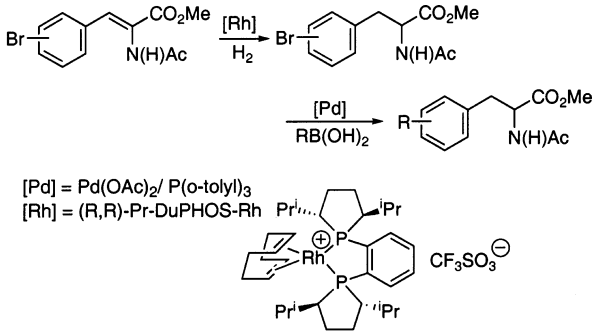
Scheme 34



3.2.3. Hydrogenations

Burk et al. outlined a hydrogenation/Suzuki coupling CTC procedure to effectively synthesize a wide variety of α-amino acid derivatives.[6a] Asymmetric hydrogenation of α-enamides using Rh-DuPhos in the presence of H_2 yields enantiomerically pure α-amino acid derivatives. The resulting α-amino acid undergoes a standard Suzuki boronic acid cross coupling reaction using $Pd(OAc)_2$ in the presence of 2 eq. P(*o*-tolyl)$_3$. Reaction with boronic acid derivatives substituted with heteroatoms and heterocyclic substituents yields a diverse range of α-amino acid derivatives [(AB_IC)($CD_{II}P$), Scheme 35].

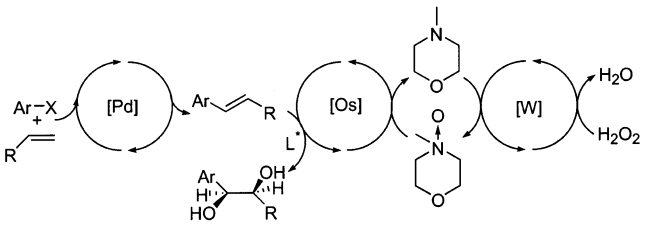
Scheme 35



3.2.4. Miscellaneous Reactions

In another example of multiphasic tandem catalysis Choudary et al. describe the development and application of a trifunctional catalyst embedded in a layered double-hydroxide (LDH) matrix for the enantioselective formation of bis(aryl)diols.[47] The active catalyst was synthesized by the LDH formation under standard conditions in a solution containing Na_2PdCl_4, K_2OsO_4 and Na_2WO_4. A chiral phosphine ligand (L*) is believed to coordinate to the Os-catalyst. The first step of the CTC reaction sequence involves a regioselective Pd-catalyzed Heck reaction to form aryl substituted trans-stilbene. The Na_2WO_4 catalyzes the formation of an oxidant (*N*-methylmorpholine *N*-oxide) that regenerates the oxidant for the oxidation of trans-stilbene to yield the chiral diol in high yield and high % ee [$(AB_IC)(CD_{II}EP)(EF_{III}G)$, Scheme 36].

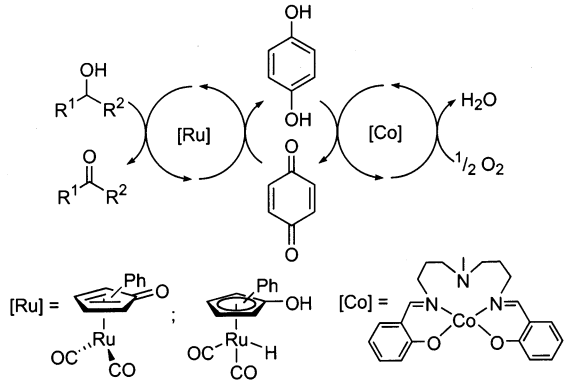
Scheme 36



[Pd] = Na_2PdCl_4/LDH, [Os] = K_2OsO_4/LDH, [W] = Na_2WO_4/LDH

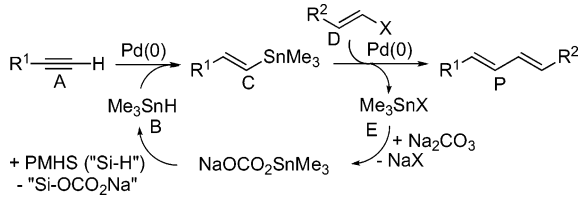
Csjernyik et al. utilized a similar homogeneous methodology for the aerobic oxidation of alcohols to ketones.[48] This two transition metal catalyst system is biomimetic for a three enzyme analogous CTC cycle ($NAD^+/NADH + H^+$, ubiquinone, cytochrome C). The Ru catalyst dehydrogenates the alcohol to form the corresponding ketone. Utilizing the aerobic oxidation of a cobalt catalyst coupled with a quinone/hydroquinone proton shuttle, the Ru catalyst is regenerated [$(AB_ICP)(CD_{II}BE)$ Scheme 37].

Scheme 37



Stille coupling reactions have found extensive use in the synthesis of high-value specialty chemicals but find limited use in other applications due to the high cost, toxicity, and difficulties in purification of organotin reagents.[49] During the course of this reaction R_3SnH is converted to R_3SnX (X = halide), creating a deactivation side reaction in the reaction cycle. In an effort to eliminate this dead end, Gallagher et al.

Scheme 38

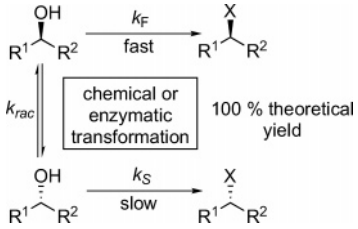


sought to catalytically convert R_3SnX to R_3SnH, thereby regenerating the precursor necessary for Pd-catalyzed coupling reactions.[50] The authors found that addition of R_3SnX, Na_2CO_3 and polymethylhydrosiloxane (PMHS) to the reaction mixture facilitates regeneration of R_3SnH (Scheme 38). Implementation of this catalytic scheme with the Pd-catalyzed Stille coupling creates a tandem catalytic cycle [$(AB_IC)(CD_IEP)(E\rightarrow B)$] that uses 94% less organotin reagent, which is replaced by two more environmentally friendly reagents PMHS and Na_2CO_3.

3.3. Enzyme/Molecular Catalyst Combination: Dynamic Kinetic Resolution

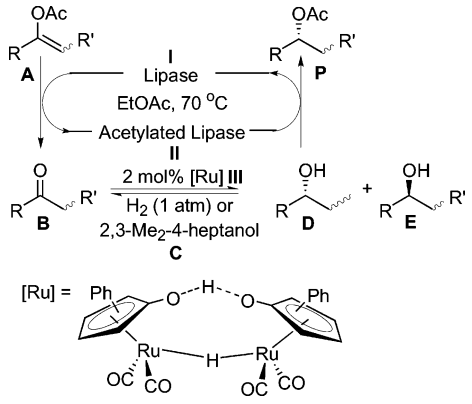
The challenges and potential synthetic utility presented by CTC are exemplified by dynamic kinetic resolution (DKR) and related processes in enzyme and metal catalysis.[51] With continuous equilibration of enantiomers catalyzed by base, enzyme or transition metal complex, DKR should theoretically allow for a quantitative yield of a single enantiomer from a racemic mixture (Scheme 39).

Scheme 39



We focus here on enzyme-catalyzed kinetic resolutions that depend on concurrent metal-catalyzed racemization to achieve high yields of the single enantiomer. Excellent reviews by Bäckvall et al.[52] and Kim et al.[53] summarize recent results for these $(A_IB)(B_IA)(A_{II}P)$ coupled catalytic cycles. Early examples that combined enzymes with homogeneous transition metal complex catalysts in one pot included Pd-catalyzed racemization of allylic acetates (via a Pd π-allyl) in the presence of *Pseudomonas fluorescens* lipase.[54] The substrate scope of these reactions was improved using $Pd(PPh_3)_4$/dppf coupled with lipase-catalyzed transesterification.[55] Under hydrogen transfer catalysis with a Rh complex, the racemization of 1-phenylethanol with basic acetophenone was followed by lipase-catalyzed resolution using vinyl acetate as an acyl donor to afford acetate with 98% ee and 60% conversion.[56] Use of a hydroxy Cp-Ru catalyst (cf. Scheme 40) later obviated the need for added base[57] and further investigations showed that stoichiometric ketone addition was unnecessary as ketones are produced in sufficient amounts by reaction of the catalyst and substrate at the initial

Scheme 40



stage.[58] Use of an analogous aminoCp-Ru [(η^5-C_5Ph_4-NH^iPr)$Ru(CO)_2Cl$] catalyst gives efficient racemization of secondary alcohols at room temperature.[59]

The asymmetric reductive acetylation of ketones by lipase and ruthenium catalysts constitutes a somewhat more complicated (A_IBII)($BC_{III}DE$)(DE_{III}-BC)($D_{II}PI$) combination where **II** is the acetylated lipase (Scheme 40).[60] With enol acetates serving as both acyl donors and ketone precursors, the lipase/Ru catalyst combination in Scheme 40 catalyzes four different reactions: enol acetate deacylation to ketone (lipase), ketone reduction to alcohol (Ru), alcohol racemization (Ru) and enantioselective alcohol acylation (acetylated lipase).

A similar methodology was applied to ketoximes using lipase and heterogeneous Pd/C in the presence of $NEt(i\text{-}Pr)_2$ and ethyl acetate to give acetamides in good yields and high enantioselectivity after 5 days.[61] Using *Candida Antarctica* lipase B and the aforementioned hydroxyCp-Ru catalyst (cf. Scheme 40), DKR of β-hydroxynitriles via transesterification afforded yields up to 85% with up to 99% ee.[62] Acyl donor *p*-chlorophenyl acetate is fully compatible with the Ru catalyst and has been employed with a number of lipases for DKR of halo- and azido alcohols, protected 1,2-diols and hydroxy aldehydes and phosphonates. While enzymatic racemization has attracted attention we are not aware of examples that are coupled with chiral homogeneous catalysts in a CTC process.

Finally, since lipase enzymes used for transesterification all favor the same enantiomer (usually *R*), Kim et al. have developed CTC processes using a protease enzyme (subtilisin) to access the *S* enantiomers.[63]

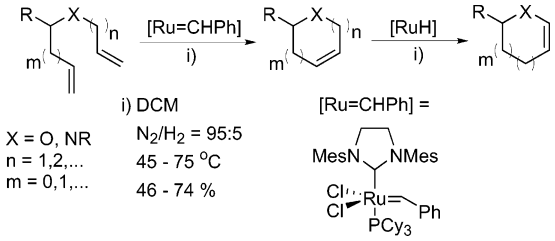
3.4. Alkene Metathesis

The olefin metathesis reaction is an important contribution by well-defined homogeneous catalysts to synthetic organic methodology.[64] The fact that these catalysts have high activity and excellent tolerance for many common functional groups enables their use in the synthesis of cyclic structures containing a wide range of chemical functionality. Due to their use in an increasing number of catalytic reactions, such as alkene isomerization, hydrogenation, and vinylation, Ru-carbene complexes have increased their synthetic applicability beyond traditional application in olefin metathesis.[65] These properties have allowed Grubbs' type catalysts to be widely applied in CTC, coupling traditional ring opening (ROM)/ring closing (RCM) metathesis, cross metathesis (CM), and ring-opening metathesis polymerization (ROMP) with other catalyzed reactions.

An early example of different reactions mediated by the same precursor complex is on the verge of CTC but falls into the category of sequential tandem catalysis.[66] A Ru-benzylidene complex [$Ru(Cl)_2(PCy_3)_2$-(CHPh)] is employed for alkene metathesis and then transformed by hydrogen addition (1 atm H_2 and 60 °C) for subsequent hydrogenation of the alkene product. This methodology was extended to ROMP, followed by hydrogenation of the resulting polymer.

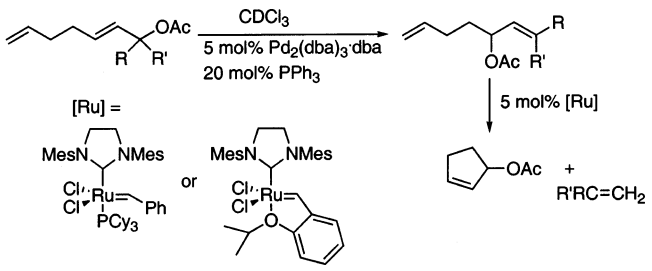
Grubb's ruthenium complexes are known to function as procatalysts for olefin metathesis, atom transfer reactions, and olefin hydrogenations.[67] Sutton et al.[68] sought to determine modifications to the ruthenium-benzylidene complex that facilitate olefin isomerization, relative to other processes. Realizing that in addition to metathesis reactions, these complexes may also be used for the selective isomerization of cyclic olefins, the authors developed a CTC metathesis/isomerization process (A_IB)(I→II)($B_{II}P$). Cyclic enol ethers are generated by ring closing metathesis (RCM) of acyclic dienes, followed by a ruthenium hydride catalyzed olefin isomerization (Scheme 41). The ruthenium alkylidene catalyst was transformed into the hydride species by H_2/N_2 (5:95), introduced directly after slow addition of the substrate. It was shown that it is important to dilute the H_2 with N_2 to avoid undesired hydrogenation of the olefins.

Scheme 41



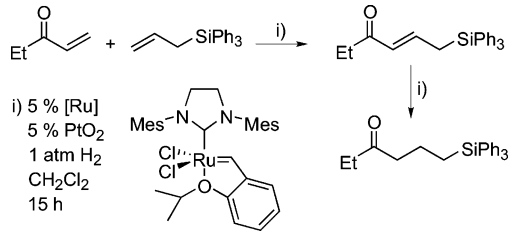
Based on investigations of the CTC compatibility of isomerization and ring closing metathesis, Braddock et al.[69] investigated several Ru and Pd (A_IB)($B_{II}P$) systems to couple allylic acetate isomerization with ring closing metathesis.[70] They found that a mixture of $Pd_2(dba)_3$·dba (5 mol %) and ruthenium catalyst gave the desired cyclic products in 40−57% yield (Scheme 42). Reactions were carried out in $CDCl_3$ and were characterized by ^1H NMR spectroscopy, however the products were not isolated.

Scheme 42



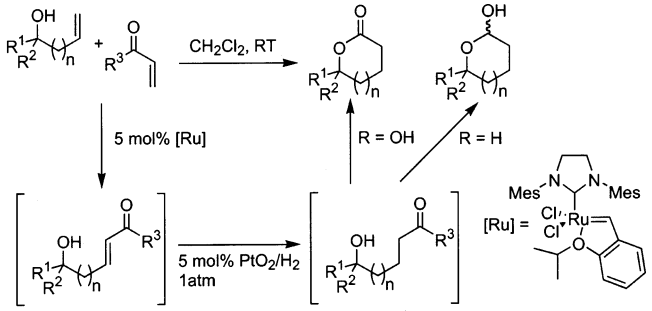
Cossy et al.[71] report on a $(AB_IC)(C_{II}P)$ tandem cross metathesis-hydrogenation reaction between an olefin and α,β-unsaturated ketones, carboxylic acids, and esters. In the presence of the ruthenium catalyst and PtO_2 under 1 atm of H_2 and at room temperature, the desired product was obtained in 80% yield. The unsaturated intermediate underwent complete conversion yielding a series of saturated γ-silyl carbonyl compounds. The amount of hydrogenated starting material generally decreases with less hindered ester groups as well as with the relative activity of the hydrogenation catalyst. For instance, application of Pd/C (5%) significantly increases the amount of hydrogenated triphenylsilylpropene (49%), while PtO_2 showed minimal hydrogenation byproducts (10%) (Scheme 43).

Scheme 43



In another example, a three-step one-pot synthesis of cyclic substituted lactones and lactols was described.[72] Starting from allylic or homoallylic alcohols and acrylic acid or acrolein, the cross metathesis is accomplished by a ruthenium catalyst followed by a PtO_2-catalyzed hydrogenation. Cyclization took place after the formation of the ω-hydroxy acids or ω-hydroxy aldehydes [$(AB_IC)(C_{II}D)(D\rightarrow P)$, Scheme 44].

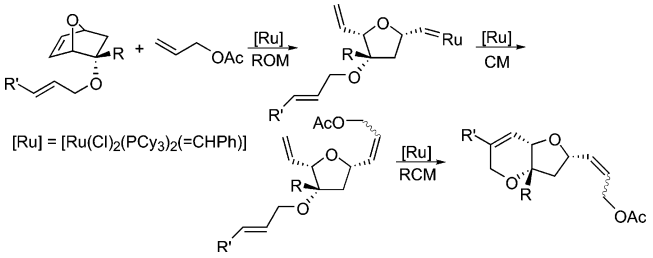
Scheme 44



The ruthenium catalyst proved to be tolerant of all reaction conditions applied. Reaction yields varied between 45 and 70%. An alternative esterification/ring-closing metathesis/hydrogenation sequence could be eliminated, as the combination of the two catalysts does not catalyze the esterification reaction.

Different metathesis reactions can also be combined in a $(AB_IC)(C_ID)(D_IP)$ CTC scheme. Arjona et al. prepared *cis*-fused 2,6-dioxabicyclo[4.3.0]non-8-enes with alkyl chains stereoselectively from 7-oxanorbornene derivatives and allyl or propargyl esters by a ROM/CM/RCM reaction sequence (Scheme 45).[73] The products and their derivatives are ubiquitous in

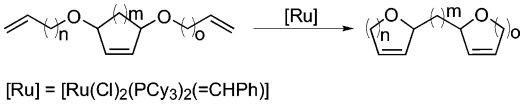
Scheme 45



natural products. Minor amounts of regioisomers were found in some cases. The procedure was found to be suitable for the introduction of a quaternary stereogenic center in the resulting bicycle.

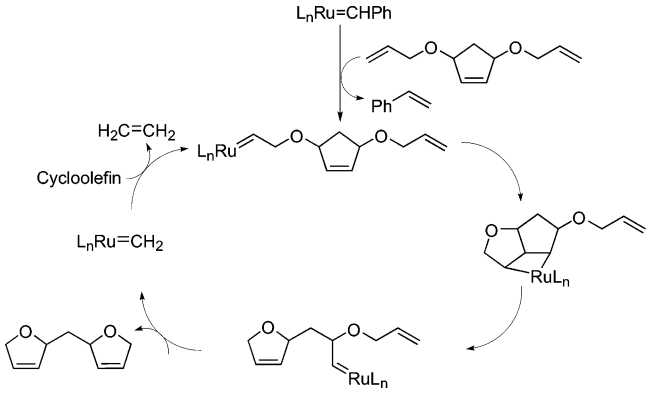
Zuercher et al. combined ROM and RCM of cyclic olefins utilizing ruthenium alkylidenes to form bicyclic molecules.[74] Strained cycloolefins located between olefinic side chains undergo enthalpically driven ROM and entropically driven RCM forming polycyclic ethers (Scheme 46). Two mechanisms are proposed.

Scheme 46

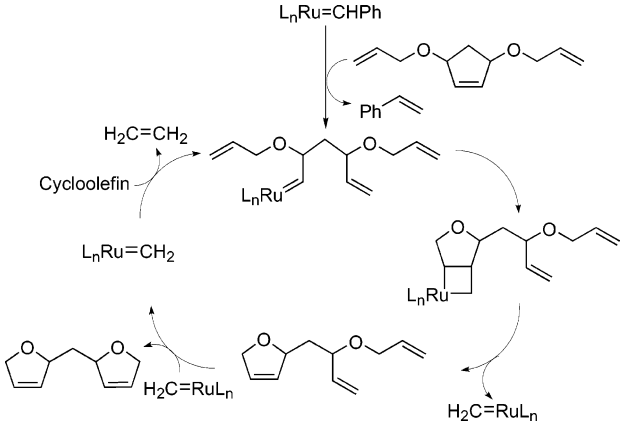


One includes initial metathesis on the olefinic side chain, while the second mechanism is initiated by a ring-opening step. The first mechanism is not strictly CTC, as there is no evidence of formation of a discrete metal-free intermediate (Scheme 47). The second

Scheme 47



Scheme 48

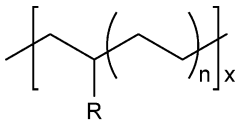


mechanism proposed appears to produce such an intermediate, thus we believe it to be CTC [(A_IBC)-(C_IP), Scheme 48]. Currently, the preferred mechanism is the former but supporting experimental evidence has not been reported to the best of our knowledge.

3.5. Polymerization Reactions

3.5.1. Ethylene Copolymerization[75]

Multiple catalyst combinations to yield polyethylene with branched structures have been examined for some time. Aliphatic groups are introduced along the polymer mainchain, thereby generating linear low-density polyethylene (LLDPE, Figure 2). These pendant groups make the polymer less brittle and more easily processed than nonbranched high-density polyethylene (HPDE).[76,77]

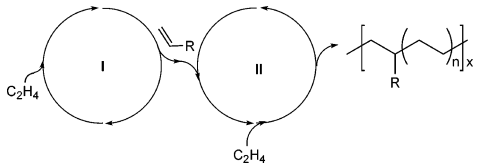


LLDPE

Figure 2.

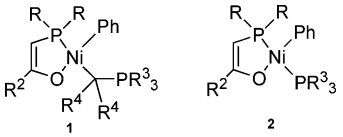
In a CTC preparation of LLDPE, one catalyst oligomerizes ethylene to α-olefins (1-alkenes) (Scheme 49, cycle mediated by **I**). For maximum control of polymer properties, the α-olefins generated would be of a specific chain length (i.e. 1-butene, 1-hexene, 1-octene, etc.), however most oligomerization catalysts do not have such specificity and one typically must deal with a distribution of chain lengths. The second catalyst incorporates the 1-alkenes into a growing polymer chain [$(A_IB)(AB_{II}P)$, Scheme 49, catalyst **II**]. CTC eliminates the need to add comonomer to the ethylene polymerization reactor.

Scheme 49



In one of the earliest reports of tandem preparation of LLDPE, Beach and Kissin reported using nickel and titanium based oligomerization catalysts (Scheme 49, catalyst **I**) with a different titanium polymerization site (Scheme 49, catalyst **II**).[78,79] The catalysts in this combination are not perfectly balanced, and the total consumption of ethylene decreases as the concentration of the oligomerization catalyst increases. The authors attribute this drop in activity to partial poisoning of the polymerization centers and a slower insertion rate for 1-butene. Phillips Petroleum patented a tandem catalyst process based on chromium compounds (such as CrO_3) deposited onto solid supports.[80] The reactivity of *some* of the chromium sites was modified by addition of pyrrole derivatives to generate oligomerization sites. The ethylene oligomers are then copolymerized with ethylene by unmodified chromium sites. In this manner, the branching content of the polymers produced could be adjusted by changing the chromium-to-pyrrole ratio. Using a similar reaction strategy, a chromium(VI) oxide/silica catalyst was partially reduced by $Cr_4(CH_2SiMe_3)_8$ to produce a mixture of supported catalysts.[81] The degree of branching in the polymers and distribution of the branch lengths can be altered by the $Cr_4(CH_2SiMe_3)_8$ loading.

Starzewski at Bayer demonstrated that phosphorus−oxygen chelated nickel ylide complexes of type **1** (Figure 3) oligomerize ethylene to moderately high molecular weight α-olefins. These oligomers are copolymerized with ethylene by using a chromium(II)/silica catalyst.[82] Balancing the ratio of the two catalyst sites is important because at high nickel concentrations only olefins are produced.[82a] When the Cr(II) catalyst is in excess, polyethylene with long chain branches can be obtained. Similar results were obtained by the use of phosphorus−oxygen chelated nickel phosphine complexes of type **2** (Figure 3) as the oligomerization site precursor.[82b,83]



1	2
R = Ph, alkyl	R = Ph, alkyl
R^2 = Ph, alkyl	R^2 = Ph, alkyl
R^3 = Ph, alkyl, alkoxy	R^3 = Ph, alkyl, alkoxy
R^4 = Ph, alkyl, H	

Figure 3.

The advent and diversity of single site ethylene polymerization initiators has opened the opportunity to more rationally control tandem LLDPE production.[84] Work performed at DuPont describes CTC production of LLDPE.[85] Compound **3**,[86] (Figure 4) activated with a modified methylaluminoxane (MMAO), generates ethylene oligomers. Combinations of **3** with *ansa*-zirconocenes produced moderately branched polymers. Catalysts with two fluorenyl ligands produced polymers with as much as 78 methyl groups per 1000 carbons, [Me/1000C], but did not fully incorporate the α-olefins. Similar results were attained with bis(amidinate) zirconium and titanium species. Notably, $([(\eta^5\text{-}C_5Me_4)SiMe_2(\eta^1\text{-}NCMe_3)]ZrCl_2$ gave polymer with 75 Me/1000C with negligible residual α-olefins.[87]

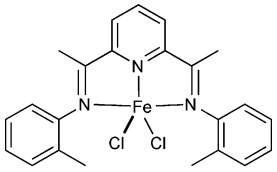


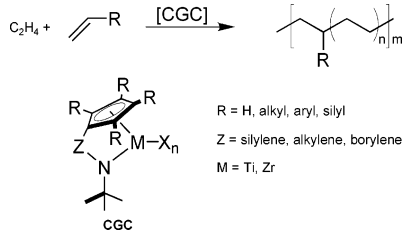
Figure 4.

Fink et al. investigated the use of compounds containing a κ^2-*P,O* nickel complex of type **2** (Figure 3) for ethylene oligomerization and conditions were found that led to the generation of mostly 1-butene and 1-hexene. A variety of zirconocenes, activated with MMAO, and the heterogeneous mixture MgH_2/α-$TiCl_3$/Cp_2TiCl_2 were each used as the polymerization catalyst and examined for copolymerization

aptitude.[88] Other ligand/metal/MMAO combinations have appeared that demonstrate the CTC approach in Scheme 49.[89]

Of particular importance is the demonstration that molecules referred to as "constrained geometry catalysts" (**CGC**) have an excellent aptitude to produce LLDPE by copolymerization of α-olefins and ethylene (Scheme 50).[90,91,92] Insertion into a propagating poly-

Scheme 50



olefin is facilitated by an open ligand framework and reduced electron count at the metal.[90] With the ability of **CGC** catalysts in hand, the challenge becomes the design of compatible oligomerization catalysts with similar activation requirements and ethylene reactivity.

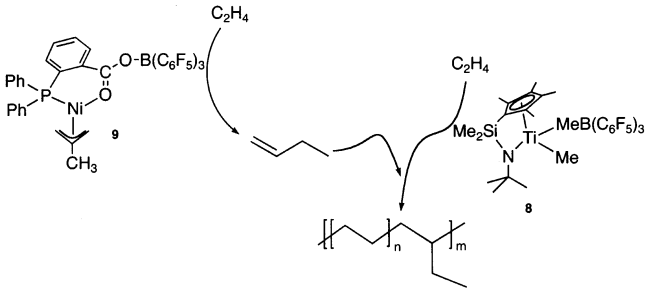
Studies using boron heterocycles as cyclopentadienyl analogues[93] showed that activation of $((\eta^6\text{-}C_5H_5B{-}OEt)_2ZrCl_2$, **4**) with MMAO yields a catalyst that produces a Shultz-Flory distribution of α-olefins.[94] The reactivity of catalysts derived from **4** are therefore complementary to their **CGC** counterparts and, indeed, **4** with $([(\eta^5\text{-}C_5Me_4)SiMe_2(\eta^1\text{-}NCMe_3)]TiCl_2$ (**5**)[95] is a well matched pair for CTC implementation and LLDPE synthesis.[96] Considerable effort was required to optimize polymerization conditions so that the majority of α-olefins is incorporated into the chain and to obtain monomodal molecular weight distributions. Once reaction conditions are optimized, the **4**:**5** ratio controls the melting point (T_m) of the polymer products. Thus, a wide range of polymer structures, with specified properties, can be obtained simply by adjusting the CTC components. Similar results were obtained using the combination $\{Tp^{Ms}\}NiCl$ (Tp^{Ms} = hydridotris(3-mesitylpyrazol-1-yl) and Cp_2ZrCl_2.[89]

A CTC scheme whereby one obtains ethylene-1-hexene copolymers recently appeared.[97] The catalytic system involves $(\eta^5\text{-}C_5H_4CMe_2C_6H_5)TiCl_3$ (**6**)/MMAO and $[(\eta^5\text{-}C_5Me_4)SiMe_2(\eta^1\text{-}N^tBu)]TiCl_2$ (**7**)/MMAO. During the reaction; **6**/MMAO trimerized ethylene to hex-1-ene, while **7**/MMAO copolymerized ethylene with the *in situ* produced 1-hexene to poly(ethylene-*co*-1-hexene). By changing the catalyst ratio and reaction conditions, a series of copolymer grades with different 1-hexene fractions and high purity were effectively produced.

Concurrent action of a heterogeneous ethylene polymerization catalyst and a homogeneous ethylene oligomerization catalyst was also recently reported.[98] Specifically, a MAO-preactivated **CGC** site $[(\eta^5\text{-}C_5Me_4)SiMe_2(\eta^1\text{-}NR)]TiCl_2$ (R = Me or ^{t}Bu) supported on pyridylethylsilane-modified silica and a homogeneous dibromo nickel catalysts having a pyridyl-2,6-diisopropylphenylimine ligand in the presence of MMAO gave polyethylenes with long-chain branches (M_w = 15,000−50,000).

Substantial efforts have been devoted to facilitating CTC LLDPE synthesis that circumvent use of alkylaluminoxane-based co-activators. These studies are motivated by the poorly defined structures of aluminoxanes and by the fact that the ratio of aluminoxanes to transition metal influences the rates of ethylene consumption. Well-defined **CGC** species are available. For example, addition of $B(C_6F_5)_3$ to $[(\eta^5\text{-}C_5Me_4)SiMe_2(\eta^1\text{-}NCMe_3)]TiMe_2$ gives $\{[(\eta^5\text{-}C_5Me_4)SiMe_2(\eta^1\text{-}NCMe_3)]TiMe\}\{MeB(C_6F_5)_3\}$ (**8,** Scheme 51)

Scheme 51



which is well suited for copolymerization of ethylene and α-olefins. A complementary oligomerization component to **8** was discovered when it was observed that the ethylene consumption rate of $[(C_6H_5)_2PC_6H_4C(OB(C_6F_5)_3)O\text{-}\kappa^2P,O]Ni(\eta^3\text{-}CH_2CMeCH_2)$ (**9,** Scheme 51) was within the same order of magnitude as that of **8**.[17] Under specific reaction conditions **9** produces 1-butene exclusively. Furthermore, **8** and **9** do not react with each other.

Scheme 51 $[(A_IB)(AB_{II}P)]$ shows the function of **8**/**9** to produce LLDPE under conditions where **9** produces 1-butene exclusively. With optimized reaction conditions the tandem polymerizations carried out with **8**/**9**/C_2H_4 yield high molecular weight branched polymers, which incorporate the vast majority of the α-olefins produced by **9**. Examination of the polymer structure using ^{13}C NMR spectroscopy showed a linear relationship between the degree of branching in the polymer and the Ti:Zr ratio in the tandem pair.

It is possible to find conditions so that *three* active sites can be coordinated to provide a branched polyethylene structure unattainable by CTC with two active sites.[99] The three catalysts used to demonstrate this concept are **8**, the η^3-benzyl analogue of **9** (**10** in Figure 5) and $\{(H_3C)C[N(C_6H_5)]C[O{-}B(C_6F_5)_3]\text{-}$

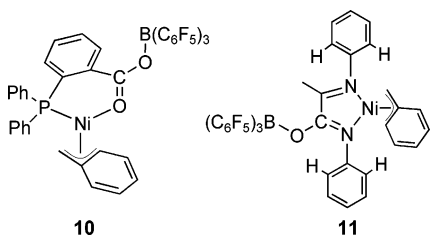
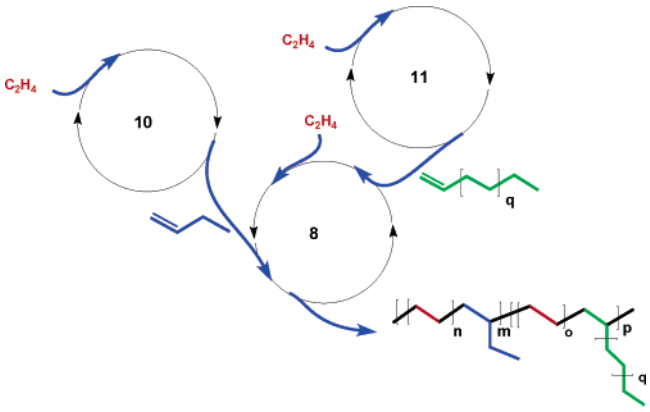


Figure 5.

$[N(C_6H_5)]\text{-}\kappa^2N,N\}Ni(\eta^3\text{-}CH_2C_6H_5)$ (**11** in Figure 5).[100] Scheme 52 shows the overall strategy. Compound **11** generates a Schultz-Flory distribution of 1-alkenes (shown in green) under conditions where **10** generates 1-butene (shown in blue). A coordinated action of **8**, **10** and **11** provides polyethylenes with varying

ratios of ethyl branches and longer branches. Scheme 52 corresponds to a CTC scheme of type $(A_IB)(A_{II}C)$-$(ABC_{III}P)$.

Scheme 52

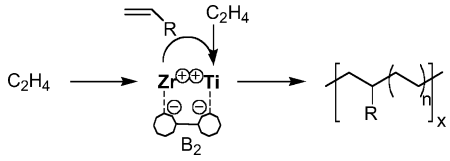


Optimization of the reaction conditions in Scheme 52 to obtain a polymer product with a monomodal molecular weight distribution proved difficult for a variety of reasons. The precatalysts have different initiation rates. The rate of ethylene insertion at the Ti site depends on the substitution of the growing chain in the vicinity of the metal. Different 1-alkenes also display different insertion rates, depending on size. At the moment when ethylene enters the reaction cycle the titanium site produces strictly linear polymer. With increasing reaction time the concentration of 1-alkenes produced by **10**/C_2H_4 and **11**/C_2H_4 increases and 1-alkenes begin to incorporate into the growing polymer chain at Ti, until a steady state is reached. Inefficient mixing (limiting the gas uptake rate) exacerbated by the formation of solid polymer, and the inability to inject the catalyst solutions into a pre-equilibrated system at the desired temperature and pressure, also contribute to nonuniform reaction conditions.

The matrix of variables associated with initiation/propagation and relative insertion rates indicated that a different approach, one which would generate a large number of polymerization experiments in a short time was required to attain optimum conditions. Successful optimization was achieved by using high-throughput parallel reactor technology and computer control of reaction conditions. The resultant polymer materials were examined with high-throughput polymer characterization (GPC and IR spectroscopy) techniques that take advantage of robotic assistance. Structural characterization of the polymers by NMR spectroscopy confirmed a structure that is consistent with that shown in Scheme 52. Perhaps one of the most important lessons obtained from this study is the value of high-throughput techniques in finding the optimum variables for the catalysts to work in a concerted fashion.

A method by which the proximity of the catalytic sites responsible for producing vinyl-terminated low molecular weight polyethylene and enchainment into a longer polymeric structure rests on the use of the binuclear activator ($[Ph_3C]_2[1,4\text{-}\{B(C_6F_5)_3\}_2C_6F_4]$ = **B_2**).[101] The precursor for the oligomerization catalyst was (η^5-3-ethylindenyl)$Me_2Si(\eta^1\text{-}N^tBu)ZrMe_2$ (Zr), while ($\eta^5\text{-}C_5Me_4$)$Me_2Si(\eta^1\text{-}N^tBu)TiMe_2$ (Ti) gave rise to the site responsible for incorporating the oligomers into a growing polyethylene chain (Scheme 53). Under

Scheme 53

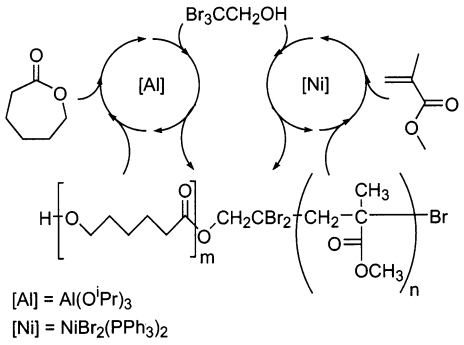


stoichiometrically appropriate ratios of Zr:Ti, use of **B_2** gave rise to polymer products that have narrower molecular weight distributions than those obtained using the monofunctional activator $[Ph_3C][B(C_6F_5)_4]$. Overall, these results highlight the possibilities of enhancing the cooperativity of CTC sites by using electrostatic spatial confinement. In this particular example, the binuclear activator **B_2** increases the efficiency of homogeneous heterobimetallic olefin enchainment processes by generating the α-olefin in close proximity to the Ti site, where incorporation into the larger polymer structure takes place. Their results show that the activator dramatically increases the efficiency of homogeneous heterobimetallic olefin enchainment processes for LLDPE synthesis.

3.5.2. Atom Transfer Radical Polymerization (ATRP)

Traditional formation of block copolymers requires a two-step procedure, either through the coupling of preformed polymers with functional groups at the chain ends or through macromolecular initiators for the polymerization of a second monomer. Mecerreyes et al. investigated a new strategy for a one-step synthesis,[102] using different unsymmetrical difunctional initiators, e.g. Br_3CCH_2OH, which are able to initiate the simultaneous polymerization of two comonomers by different polymerization chemistries. This is an example of a "living" radical polymerization coupled to a ring opening polymerization (ROP) by coordination and insertion mechanisms (Scheme 54). The initiator 2,2,2-tribromoethanol polymerized

Scheme 54

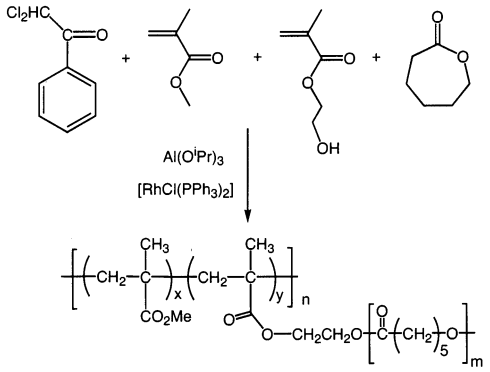


methyl methacrylate (MMA) and ϵ-caprolactone (CL) in the presence of $Al(O^iPr)_3$, as ROP catalyst and $NiBr_2(PPh_3)_2$ as ATRP catalyst. The reaction requires temperatures between 60 and 125 °C and provides 70−90% conversion. ROP seems to be faster than the radical polymerization, reducing the molar

fraction of caprolactone in the product. Transesterification reactions are reduced by addition of pyridine and are confirmed by a narrower molecular weight distribution. One plausible classification of Scheme 54 is $(AP_IP)(BP_{II}P)$, where AP_IP corresponds to the insertion of a monomer into the bifunctional polymer chain. The resulting product is the polymer chain with an additional **A** monomer unit at one of its ends. The other monomer (**B**) can be introduced into the growing chain by the second catalyst (**II**).

The simultaneous dual living polymerization approach is also suitable for the synthesis of graft copolymers (Scheme 55). In this particular case,

Scheme 55



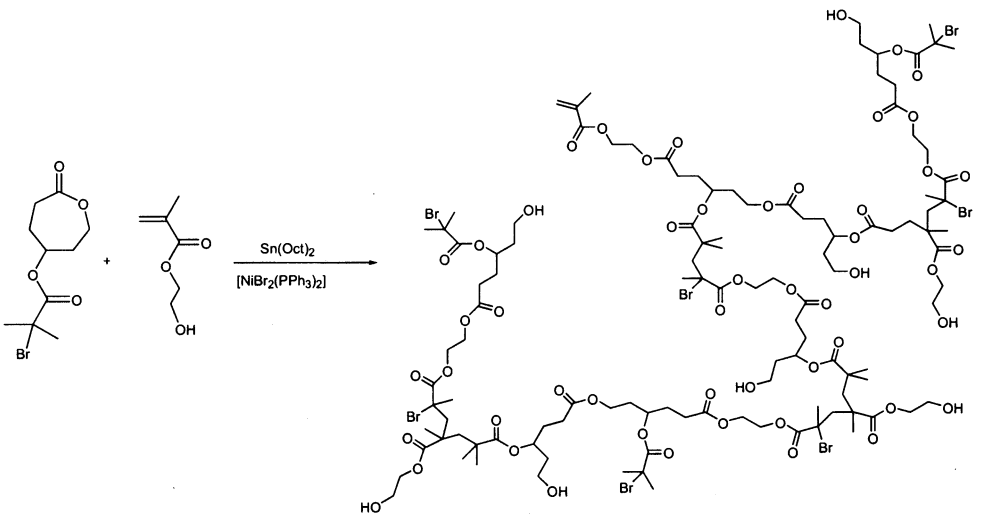
living radical copolymerization of MMA and 2-hydroxyethyl methacrylate (HEMA), initiated by 2,2-dichloroacetophenone and catalyzed by $RhCl(PPh_3)_3$, is simultaneously performed with ROP of ϵ-caprolactone promoted by the hydroxyl groups from the HEMA units and $Al(O^iPr)_3$ as ROP catalyst. As an example, polymerization of a 1:0.1:1 mixture of MMA, HEMA, and ϵ-caprolactone initiated by 2,2-dichloroacetophenone gave the expected poly(MMA-*g*-CL) copolymer after 18 h at 50 °C. The polymer was isolated in 73% yield after purification by precipitation in heptane, and the presence of poly-MMA and poly-CL was confirmed by ^1H NMR spectroscopy. Size-exclusion chromatography of the isolated backbone polymer reveals a molecular weight M_n of 30,000, which is in agreement with that expected from the monomer-to-initiator molar ratio, while the polydispersity was relatively small (M_w/M_n = 1.25).

Branched copolymers from two monomers, polymerized in a one-pot procedure by ring opening polymerization (ROP) and atom transfer radical polymerization (ATRP), have also been reported by Mecerreyes et al.[103] The monomers each bear the initiating center for the chemistry of the other monomer. The first monomer, γ-(ϵ-caprolactone)-2-bromo-2-dimethylpropionate, reacts by ROP with the activated alkyl bromide moiety serving as an initiator for the ATRP of vinyl monomers. The second monomer, 2-hydroxyethyl methacrylate, contains an initiating site for ROP and a vinyl group for ATRP. The catalysts, $NiBr_2(PPh_3)_2$ for the ATRP and $Sn(Oct)_2$ (stannous(II) 2-ethylhexanoate) for the ROP, were employed at temperatures between 80 and 100 °C (Scheme 56).

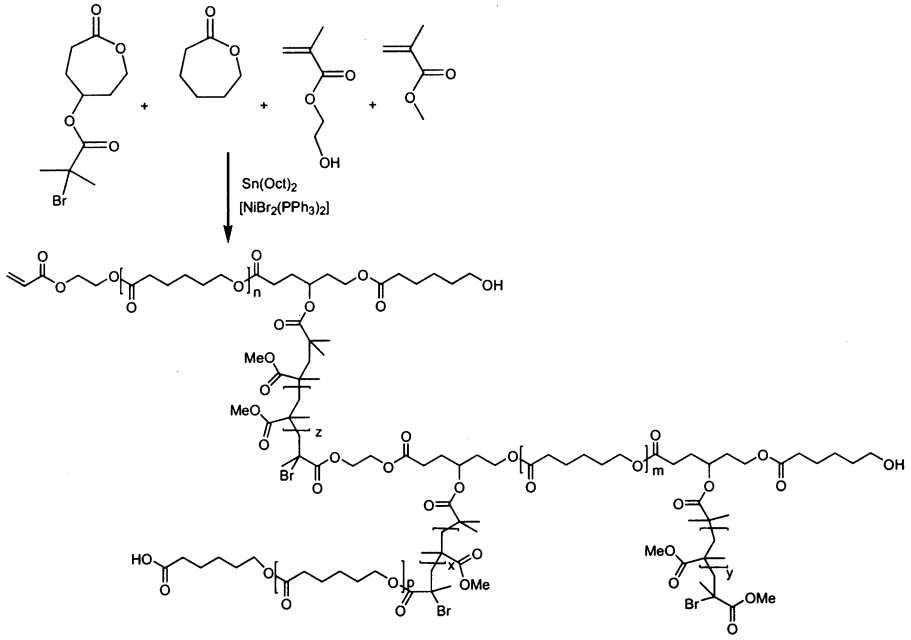
Adding unfunctionalized comonomers, CL and/or MMA, as well as varying the ratio of the monomers alters the molecular architecture as shown in Scheme 57.

Another example is provided by Bielwaski et al.[104] A difunctional catalyst was used, incorporating requirements for ROMP and ATRP, to mediate both polymerizations simultaneously (Scheme 58). After verifying that the initiator mediates the ROMP of COD and the ATRP of MMA individually, the CTC proved successful and after 18−30 h, 58−82% polymer could be obtained. While the two polymerizations differ in their rate (ROMP of COD: $k_{obs} = 3.5 \times 10^{-3}$ s^{-1}; ATRP of MMA: $k_{obs} = 1.2 \times 10^{-5}$ s^{-1}), they are nearly identical when excess PCy_3 (10 equiv) is added (ROMP $k_{obs} = 3.6 \times 10^{-5}$ s^{-1} vs ATRP $k_{obs} = 3.7 \times 10^{-5}$ s^{-1}). Subsequent treatment with H_2 provided the hydrogenated, saturated product in 75% yield. This single multifunctional complex mediates three mechanistically distinct reactions, two of which take place as concurrent tandem catalysis, with the third step employing the same catalyst modified in its structure by hydrogen to provide for a subsequent catalytic hydrogenation.

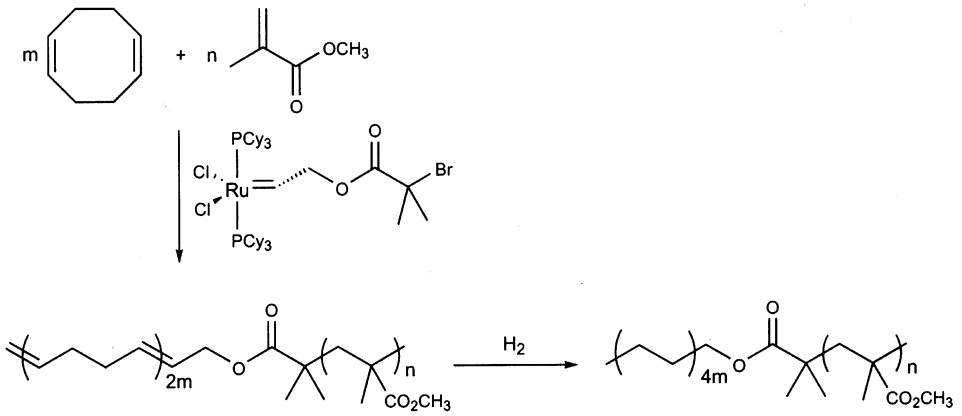
Scheme 56



Scheme 57



Scheme 58



4. Future Prospects

Concurrent tandem catalysis based on artificial systems is in its infancy. As elaborated in the Introduction, several challenges need to be overcome for the successful execution of cooperation between a pair (or more) of catalytic centers. Compatibility of active sites, and the related functional group selectivity, is a challenge where a more precise understanding of structure/reactivity relationships at the molecular level should give better guidelines for choosing catalyst partners. Another dimension of the problem involves matching the rates of the individual catalytic cycles. Insight into the mechanism of individual catalytic cycles, and the resulting ability to control turnover frequencies, together with techniques for transferring cycle products within the same medium need to be further developed in this context. Characterization of active sites in heterogeneous catalysts will provide better defined options to CTC designers. Theory will play an important role in CTC development by delineating several important components of the problem, including reaction energetics, molecular mode of transformations by the catalyst site and overall reaction modeling. Finally, multifunctional catalysts that effect different types of transformations under identical reaction conditions should alleviate compatibility concerns.

While an a priori design should be the goal of CTC research, it is not likely that it can be reached at the present moment, given the present understanding of reaction mechanisms and active site compatibility, especially if one considers including combinations of organic, organometallic, heterogeneous and biological options. High-throughput techniques that allow quick screening of large numbers of possible catalyst combinations with control over the matrix of variables associated with reaction optimization (concentration, pressure, temperature, mass transfer rates, etc.) and accurate identification of products and byproducts are promising tools for overcoming some of the challenges mentioned above.[105] These techniques are likely to be more successful when used in conjunction with mechanistic knowledge and intuition acquired through basic science studies. Other engineering solutions should also be considered, including multiphasic reaction media that keep catalytic centers separated to avoid interference but allow the transfer of products from one site to another.

Concurrent tandem catalysis defines a new frontier in catalysis science with substantial benefits to society. New catalytic schemes that take advantage of unstable intermediates for accessing hitherto inaccessible products are particularly appealing. Circumventing the need to store and transport harmful chemicals by only generating them in situ increases safety and provides for environmental protection. CTC reactions should also yield novel materials for a wide range of applications. One can even envision the emergence of programmable catalytic systems whereby the starting materials are kept constant while the nature of the product is determined and fine-tuned by the composition of the tandem catalyst mixture.

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6. Abbreviations

acac	acetylacetonate
Ar	aryl
ATRP	atom transfer radical polymerization
BIPHEPHOS	2,2′-bis{[(2,2′-bisphenoxy)phosphino]oxy}-3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl
Bn	benzyl
BPPM	1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine
CGC	constrained geometry catalyst
CL	ϵ-caprolactone
CM	cross metathesis
COD	1,5-cyclooctadiene
Cp	cyclopentadienide anion
Cp*	pentamethylcyclopentadienide anion
CTC	concurrent tandem catalysis
Cy	cyclohexyl
DA	Diels−Alder
dba	dibenzylidene acetone
de	diastereomeric excess
DIOP	4,5-bis[(diphenylphosphino)methyl]-2,2′-dimethyl-1,3-dioxalane
DKR	dynamic kinetic resolution
DLH	double layer hydroxide
DMF	*N*,*N*-dimethylformamide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DuPhos	1,2-bis(phospholano)benzene
ee	enantiomeric excess
HEMA	2-hydroxyethyl methacrylate
HDPE	high-density polyethylene
LDPE	low-density polyethylene
LLDPE	linear low-density polyethylene
MAO	methylaluminoxane
MMAO	modified methylaluminoxane
Mes	mesityl (2,4,6-dimethylphenyl)
MMA	methyl methacrylate
NAD^+	nicotinamide adenine dinucleotide, oxidized form
NADH	nicotinamide adenine dinucleotide, reduced form
NMR	nuclear magnetic resonance
OAc	acetate
o-DPPB	*ortho*-diphenylphosphinobenzoyl
o-tolyl	2-Me-C_6H_4
PMHS	polymethylhydrosiloxane
PMP	polymethylpentane
PPTS	pyridinium *p*-toluenesulfonate
RCM	ring-closing metathesis
ROM	ring-opening metathesis
ROP	ring-opening polymerization
RT	room temperature
Sba	*sec*-butylamine
SDS	sodium dodecylsulfonate
TC	tandem catalysis
TBS	*tert*-butyldimethylsilyl
Tf	triflate (trifluoromethylsulfonyl)
THF	tetrahydrofuran
TMS	trimethylsilyl
TPPTS	trisodium triphenylphosphine trisulfonate
Ts	tosyl (*p*-toluenesulfonate)

7. References

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