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Review

Tandem catalysis: a taxonomy and illustrative review

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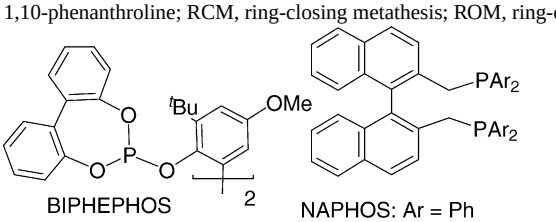
Contents

Abbreviations: ADMET, acyclic diene metathesis; ATRP, atom-transfer radical polymerization; CM, cross-metathesis; COE, cyclooctene; COD, 1,5-cyclooctadiene; dba, dibenzylideneacetone; e.e., enantiomeric excess; en, ethylenediamine; H_2IMes, *N*,*N*′-bis(mesityl)imidazolin-2-ylidenes; IMes, *N*-*N*′-bis(mesityl)imidazol-2-ylidene; MA, methyl acrylate; MMA, methyl methacrylate; NBD, norbornadiene; NHC, *N*-heterocyclic carbene; phen, 1,10-phenanthroline; RCM, ring-closing metathesis; ROM, ring-opening metathesis; ROMP, ring-opening metathesis polymerization; THF, tetrahydrofuran



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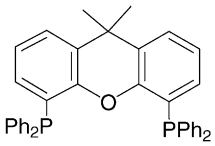
NAPHOS: Ar = Ph
IPHOS: Ar = 3,5-$C_6H_3(CF_3)_2$



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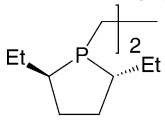

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Abstract

A scheme is advanced for the classification of one-pot, coupled catalytic transformations, which distinguishes between one-pot, domino/cascade, and tandem catalysis. The last of these is divided into three subclasses: orthogonal, auto-tandem, and assisted tandem catalysis. The proposed taxonomy, and the potential of tandem catalysis in organic synthesis, are illustrated with examples drawn from olefin metathesis and hydroformylation chemistry.
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Keywords: Catalysis; Tandem catalysis; Classification; Cascade catalysis; Domino catalysis; Orthogonal catalysis; Olefin metathesis; Hydroformylation

1. Introduction

Devising methodologies for elaboration of simple precursors into complex molecular targets is the underlying theme in much of synthetic organic chemistry. While transition-metal catalyzed processes have enabled transformative developments in organic synthesis, the power and efficiency of such methods are limited by the conventional focus on chemical reactions as discrete events. Much interest has therefore attached to "one-pot" processes involving multiple catalytic transformations followed by a single workup stage. Motivating their development is the continuously-expanding importance in organic chemistry of highly selective transformations mediated by well-defined transition metal catalysts, and the potential process and catalyst efficiencies associated with coupling such transformations [1].The increasing popularity of processes harnessing coupled catalysis is highlighted by the number of recent reviews in this area. Especially well-documented is work on Pd-catalyzed C–C bond formation [2–7]; such processes are well represented in a recent Handbook [8]. Other reviews describe coupled metathesis [9–11] or hydroformylation [12,13] catalysis, enzyme- [14,15] or nickel-catalyzed [16] domino reactions, and multifunctional [17,18] or multicomponent catalysis [17,19]; in some cases, a section on catalysis is included in a broader survey of stoichiometric tandem or cascade reactions [1,20–22]. In surveying the literature, however, it becomes rapidly evident that a general review is hampered by the interchangeable use of near-synonymous terms: among them, tandem, domino, zipper, multifunctional and cascade reaction or catalysis. Moreover, the existing terminology draws no consistent line of demarcation between multiple catalytic, versus stoichiometric, transformations. This blurs mechanistic distinctions, to the detriment of informed exploration or use. With the intention of clarifying the current state of the field, as well as revealing possibilities currently obscured, we propose a brief taxonomy, or classification scheme, with which to codify this increasingly important area.

2. Taxonomy

One-pot procedures involving multiple catalytic events constitute a subset of the broader category of one-pot processes that includes domino, cascade, or tandem *reactions*. All of these terms are commonly used to designate transformation of an organic substrate through two or more individual elaborations with a single workup step [1,5,15,20,23], a sense we shall build on in constructing a parallel terminology for coupled catalyses. For clarity, we begin by defining one-pot catalytic processes that are *not* tandem catalyses.

2.1. Processes that are not tandem catalyses

2.1.1. One-pot reactions involving isolated catalytic events

Modification of an organic moiety via two catalytic elaborations, with addition of the second catalyst only after the first catalytic transformation is complete, is not a tandem catalysis, but a one-pot (bicatalytic) reaction. We define domino and tandem catalyses, in contrast, as having all catalytic species—whether masked or apparent—present from the outset.

2.1.2. Domino reactions involving one catalytic elaboration

A one-pot sequence consisting of a single catalytic transformation and a subsequent stoichiometric modification does not constitute a tandem catalysis, even though the substrate has undergone two distinct transformations. Such a process may be classified as a domino reaction (providing that all reagents are simultaneously present, vide infra), but a mono-catalytic event. The reactions described in the following sections involve sequential elaborations of an organic substrate via *multiple* catalytic transformations. A flowchart is provided in Fig. 1 to aid in classification.

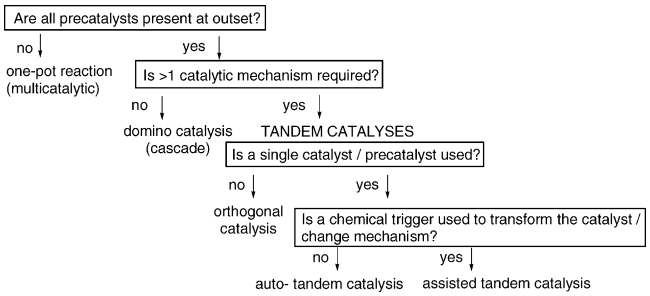


Fig. 1. Flowchart for classification of one-pot processes involving sequential elaboration of an organic substrate via multiple catalytic transformations.

2.1.3. Domino (cascade) catalysis

Tietze defines a domino reaction as involving "two or more bond-forming transformations which take place *under the same reaction conditions, without adding additional reagents and catalysts*, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step" [1] (italics added). Faber adds that the sequential processes are not readily intercepted, i.e. intermediates are not generally isolable [15]. We adopt these proposals for domino catalysis, in which we further stipulate that (in contrast with tandem catalysis, see below), multiple transformations are effected via a *single* catalytic mechanism. Sequential elaborations may be effected in either intermolecular processes (involving release of intermediates from the catalytic cycle) or intramolecular processes; Fig. 2. Cascade catalysis is a virtually synonymous term, reserved for multiple (≥3) domino sequences. Many coupled catalytic processes are of the domino/cascade type, and many beautiful examples (see, for example, Scheme 1 [24]) have been reported.

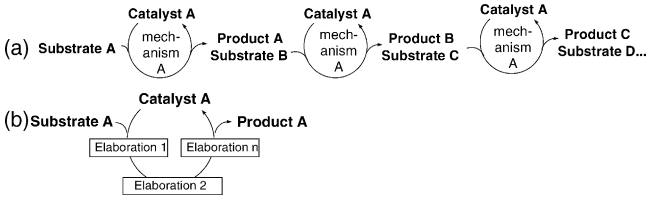


Fig. 2. Schematic illustration of domino catalysis: (a) intermolecular; (b) intramolecular.

2.2. Tandem catalysis

We reserve the term tandem catalysis to describe coupled catalyses in which sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes.

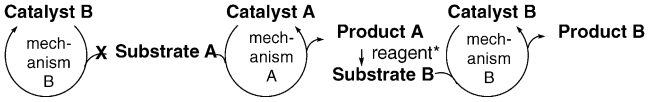
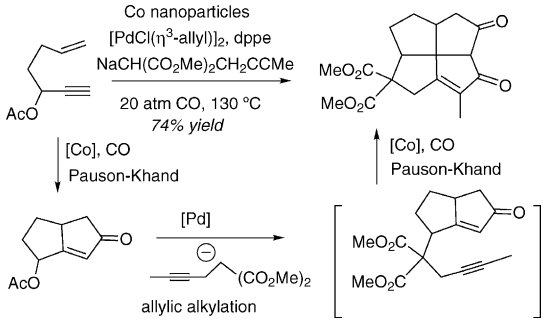


Fig. 3. Schematic illustration of orthogonal catalysis. (*Additional reagent, if required, must be present from the outset of reaction.)



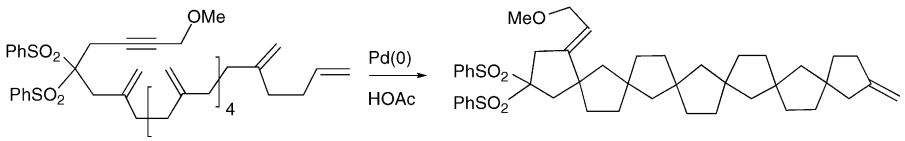
Scheme 2. Example of orthogonal tandem catalysis in the synthesis of fenestranes via tandem allylic alkylation—Pauson–Khand catalysis [27].

We draw on two of the accepted meanings for the word tandem: (a) "an arrangement of two [mechanisms] working in cooperation", and (b) "one after the other" [25]. Three categories may be distinguished: orthogonal, assisted, and auto-tandem catalysis, as indicated in the Flowchart. Advantages and disadvantages of each, noted within the following sections, are summarized in Section 2.2.4.

2.2.1. Orthogonal tandem catalysis

Orthogonal reactions are characterized by their mutual independence. Orthogonal tandem catalysis, by analogy, involves two or more functionally distinct and (in principle) noninterfering catalysts or precatalysts, all of which are present from the outset of reaction. Fig. 3 depicts such a process, in which an organic starting material (Substrate A) undergoes preferential reaction with Catalyst A to generate Product A, which in turn functions as Substrate B (the substrate for Catalyst B). A stoichiometric reagent may also be used to convert Product A into Substrate B. In orthogonal catalysis, the two catalytic cycles operate simultaneously, once Substrate B is generated (though the organic starting material undergoes *sequential* change).

Limitations of such catalytic methodologies [17,26] include inefficient catalyst utilization, compounded by difficulties in recovering individual precious metal components, possible negative interactions between the catalysts used to effect the independent transformations, and the likelihood that one set of reaction conditions is not optimal for both catalytic processes.



Scheme 1. Example of intramolecular domino (cascade) catalysis in the synthesis of a polyspirane via Pd-catalyzed cycloisomerization of a polyenyne [24].

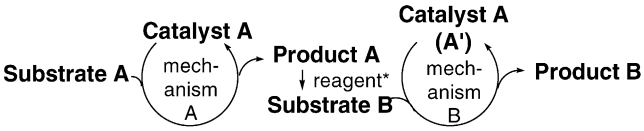


Fig. 4. Schematic illustration of auto-tandem catalysis. (*Additional reagent, if required, must be present from the outset of reaction.)

Scheme 2 shows an example of orthogonal tandem catalysis in ene–yne elaboration to yield fenestranes [27]: the first Pauson–Khand reaction is not part of the tandem catalysis, as the Pd catalyst is added only once this step is complete. Another elegant example of orthogonal catalysis was recently deployed in synthesis of branched polyethylenes [28].

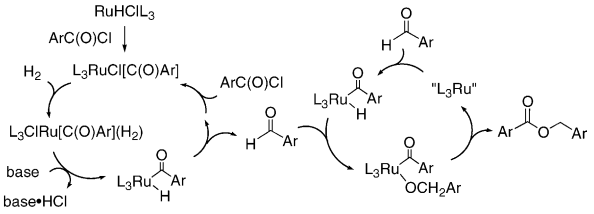
2.2.2. Auto-tandem catalysis

Processes of this type involve two or more mechanistically distinct catalyses promoted by a single catalyst precursor: both cycles occur spontaneously by cooperative interaction of the various species (catalyst, substrate, additional reagents if required) present at the outset of reaction. No reagents beyond those originally present need be added to trigger the change in mechanism. Entry into both cycles is presumed to be mediated by a catalyst species in which the structure is *essentially* conserved, though intermediates will necessarily differ at points in each cycle. In the first mechanism (Fig. 4), Catalyst A acts on Substrate A to convert it to Product A. Product A functions as Substrate B, entering the second type of catalytic transformation mediated by Catalyst A (or A′). As in orthogonal tandem catalysis, auto-tandem processes are (ideally) sequential in terms of transformation of a given molecule of substrate, but they are normally concurrent in a *macroscopic* sense. That is, Cycle B operates simultaneously with Cycle A, once Product A is generated.

Auto-tandem catalysis can be difficult to control, and indeed processes of this type (whether recognized or not) are commonly responsible for side-reactions in catalysis. This is especially true where Substrate A can itself enter into both catalytic cycles (as, for example, in tandem aldol-hydrogenation catalysis of acetone, in which acetone hydrogenation competes with its self-condensation [29]). A more fundamental difficulty, as in orthogonal catalysis, emerges from the likelihood that the conditions for optimal performance differ for the two catalytic processes. Where the appropriate balance can be found, however, auto-tandem catalysis are exceptionally efficient, as evidenced by the success of the Shell Oxo Process, the most important industrial application of this methodology [30] (see Section 3.3). An example of auto-tandem catalysis is given in Scheme 3 [31].

2.2.3. Assisted tandem catalysis

The range, performance, and selectivity of transformations that can be effected by a single catalyst species can be expanded by addition of a further reagent to trigger a change in mechanism, a process we term assisted tandem catalysis. Fig. 5 illustrates the process: Catalyst A is permitted to carry



Scheme 3. Auto-tandem catalysis: synthesis of esters from acid chlorides via sequential (homogeneous) Rosenmund–Tishchenko catalysis (L: PPh_3) [31].

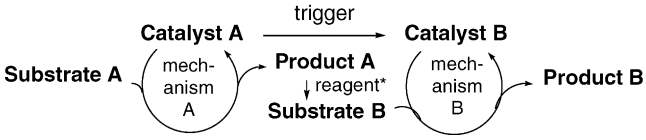


Fig. 5. Schematic illustration of assisted tandem catalysis. (*Additional reagent may or may not be required.)

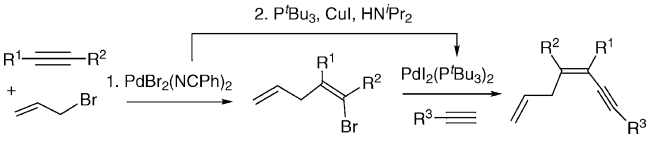
out one function, and is then transformed (often by direct manipulation of the active site) into Catalyst B, which then acts on the product of the original catalytic cycle. In contrast with orthogonal and auto-tandem catalyses, the two catalytic processes cannot occur simultaneously, as the two catalysts do not coexist. An example of assisted tandem catalysis is shown in Scheme 4 [32].

From the perspective of the benchtop chemist, the principal limitation of assisted tandem catalysis is the requirement for intervention. In contrast to orthogonal and auto-tandem catalysis, the coupled transformations do not proceed spontaneously, and the reaction must be monitored in order to determine when the first process is complete, so that the second is not triggered prematurely. Of greater significance in industrial practice may be any increase in time or energy requirements associated with the temporal split in the two processes.

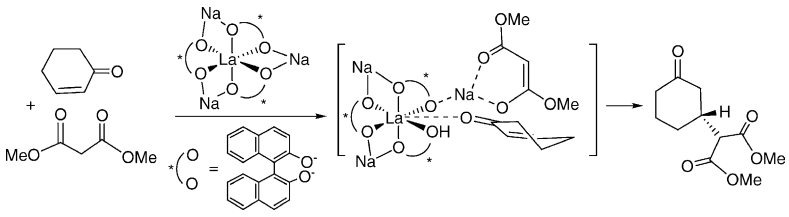
2.2.4. Summary of relative merits

Advantages and disadvantages of the different forms of tandem catalysis are summarized in Table 1. This should be regarded as a general guide, however, as individual exceptions can be envisaged for each parameter considered. The various parameters are clarified with some brief comments below.

An advantage common to all of these processes is the high efficiency associated with elimination of intermediate workup steps. However, auto-tandem and assisted tandem catalyses, which make multiple use of a single (pre)catalyst,



Scheme 4. Example of assisted tandem catalysis: Pd-catalyzed bromoallylation and Sonogashira cross-coupling [32].



Scheme 5. Multifunctional catalysis in the catalytic asymmetric Michael reaction, with structure of proposed intermediate [41].

Table 1
Relative merits of different classes of tandem catalysis

Consideration	Orthogonal	Auto	Assisted
Workup efficiency	High	High	High
Efficiency in catalyst utilization	Poor	High	High
Process efficiency	High	High	Low
Capacity to optimize conditions for both catalyses	Limited	Limited	High
Capacity to control selectivity	Limited	Limited	High
Interaction between catalysts effecting different reactions	Possible	Minimal	None
Ease of catalyst recovery	Poor	Good	Good

are more efficient in catalyst utilization than orthogonal catalysis, which requires a different catalyst for each transformation. Process efficiency, in terms of utilization of time and energy, is higher for orthogonal and auto-tandem catalysis, in which both transformations occur under a single set of reaction conditions, without any need for monitoring or intervention. Against this, however, must be set the inability to optimize reaction conditions for each catalytic process. Assisted tandem catalysis has a lower overall process efficiency, but the fact that reaction conditions can be optimized for each process increases the capacity to optimize selectivity in each transformation.

Interaction between different catalyst species is potentially problematic in orthogonal catalysis, in particular. While ideally the catalyst species do not interfere, in practice interplay between them can be common. This is less of a concern for auto-tandem catalysis, in which the catalyst species are closely related. Because the different catalytic processes occur simultaneously, however, some potential for negative interaction may exist. In assisted tandem catalysis, interaction is precluded because the different catalyst species do not coexist.

Finally, "ease of catalyst recovery" is considered for comparison of *homogeneous* catalyst systems only, and describes the relative difficulty in catalyst recovery, separation, and reuse. In using a mixture of catalysts (as in orthogonal tandem catalysis), recovery is complicated by the need to separate the metal complexes.

2.3. Related processes

For completeness, we include definitions for several related catalytic processes, which are generally, though not invariably, distinct from tandem catalysis.

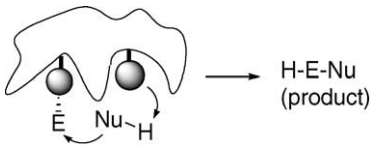


Fig. 6. Schematic illustration of one possible (concerted) mode of operation for a bifunctional catalyst [18].

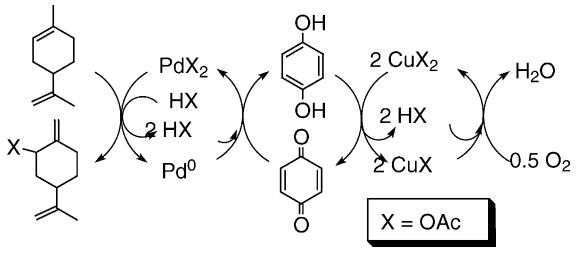
2.3.1. Multifunctional catalysis

In homogeneous, heterogeneous, and enzyme catalysis, multifunctional catalysis is overwhelmingly held to be a process in which two or more active sites, linked together, act *synergically* to effect one or more transformations of a substrate [17,33–36].[2] This sense is highlighted in recent reviews of multifunctional homogeneous catalysis [18,37], one of which [37] undertakes further classification according to type of synergic interaction. Countering this precedent is the emerging use of this term (by one of us [38], among others [39,40]) to describe non-synergic procedures that would preferably be classified as assisted or auto-tandem catalysis, or indeed to describe catalysts that simply have the *potential* to carry out multiple catalytic functions. Finally, we note that the related term "multifunctional initiator", used in polymer chemistry, refers to a species with multiple, usually identical, initiating sites. Schematic and exemplary representations of multifunctional catalysis, in the most broadly accepted sense noted above, are given in Fig. 6 and Scheme 5, respectively.

2.3.2. Multicomponent catalysis

Hesse [17,42] defines a multicomponent catalyst as a mixture of two or more *mono*functional catalysts. (Again, where such a mixture of catalysts effects sequential catalytic transformations of the substrate, the process can be recognized as orthogonal tandem catalysis.) In practice, however, the term "multicomponent" is widely applied to catalyst systems containing, in addition to an active catalyst species, stoichiometric additive(s) that modulate catalytic properties. In other examples (as indeed in the classic Wacker Process for oxidation of ethylene to acetaldehyde [43]), the organic product is generated by cooperative interaction of several (co)catalyst species, but only one of these acts directly on

[2] Where consecutive catalytic transformations of substrate are effected in a synergic fashion (that is, where Weisz's "intimacy criterion" [36] enables rapid diffusion of intermediates between the two sites), multifunctional catalysis can be seen as a subset of auto-tandem catalysis.



Scheme 6. Multicomponent catalysis: allylic oxidation of limonene [44].

the substrate [19]. An example of this is shown in Scheme 6. Such procedures are clearly not coupled catalytic processes of the type discussed in the preceding sections, in which *each catalytic cycle* effects direct modification of the organic substrate.

2.3.3. Combinatorial catalysis

Combinatorial methods in catalysis center around two different strategies: iterative "split-and-pool", versus parallel, catalyst synthesis and screening [45–47].(Reetz notes that the term combinatorial is strictly applicable to split-and-pool methods [48]; although a firm consensus on terminology has not been reached [49,50], the adjective "high-throughput" [47,51,52] is now often appended to parallel screening methods). In neither case are "one-pot" coupled catalytic reactions typically explored at present. However, throughput has been increased in certain cases [53,54] by screening a single catalyst against multiple substrates in one pot (Fig. 7, Scheme 7). Such a process may be termed one-pot parallel catalyst screening.

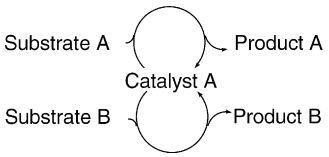
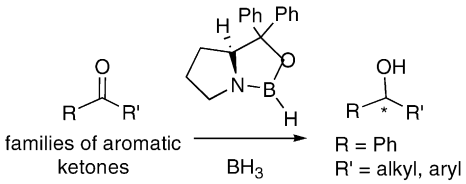


Fig. 7. Schematic illustration of one-pot, parallel catalyst screening.



Scheme 7. One-pot, parallel catalyst screening for activity in ketone reduction [53].

3. Review of tandem catalytic processes involving olefin metathesis or hydroformylation

3.1. Scope of review

In contrast with domino catalysis, the utility of which is now well documented, tandem catalysis is only beginning to be exploited. While the current lack of consensus on terms hampers a comprehensive review, the following review highlights opportunities presented by tandem catalytic methodologies in selected areas. The taxonomic principles proposed above are illustrated with synthetically useful examples drawn from the key areas of olefin metathesis and hydroformylation, each of which has spawned significant advances in tandem catalysis over the past five years. Additional examples may be found in a recent minireview [55].

3.2. Tandem catalyses involving olefin metathesis

While domino processes (including coupled ring-opening and ring-closing metatheses, reactions in which cross-metathesis is used to forestall ROMP, and clever ROM–RCM–CM sequences [9–11,56–58]) dominate coupled metathesis catalyses, this area is also rich in examples of tandem catalysis. Many of these are of the assisted class, though the potential of auto-tandem catalysis is implied by a recent review highlighting the rich *non-metathetical* chemistry of the prototypical ruthenium metathesis catalysts shown in Fig. 8 [56], particularly the Grubbs catalyst **1a** and its *N*-heterocyclic carbene (NHC) derivatives **2**. In the following sections, processes are catalogued on the basis of initial reaction type, and subdivided according to class of tandem catalysis.

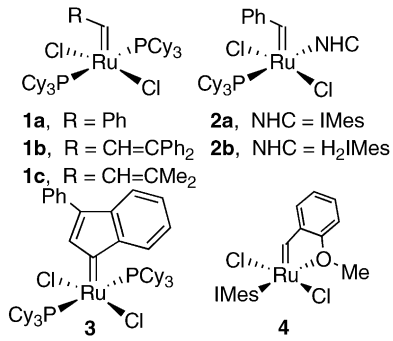
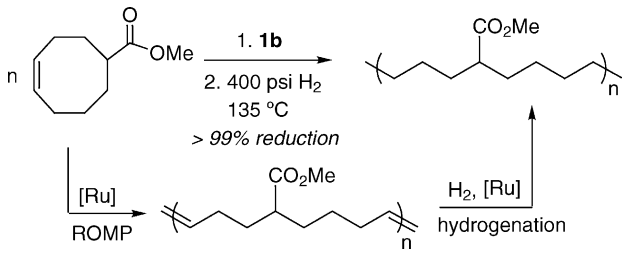


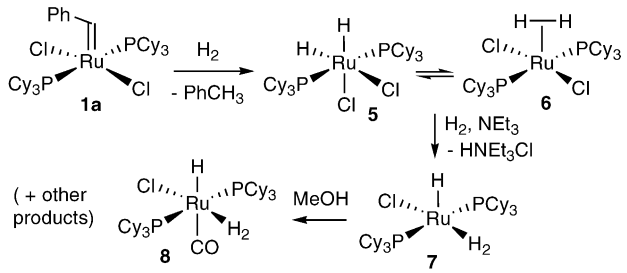
Fig. 8. Selected Ru metathesis catalysts.

3.2.1. Metathesis-hydrogenation

3.2.1.1. ROMP-hydrogenation. Ring-opening metathesis polymerization (ROMP) of cycloolefins, followed by hydrogenation, enables synthesis of high molecular weight, narrow-polydispersity polyolefins [59–61]. The hydrogenation step is critical in order to eliminate the susceptibility to oxidative and thermal degradation, including crosslinking reactions, associated with the olefinic linkages in the polymer backbone. While one-pot reactions in which metathesis is followed by addition of a stoichiometric or catalytic reducing agent remain common, considerable attention has focused on assisted tandem catalysis. In 1997, McLain et al. reported sequential processes of ROMP and hydrogenation of cyclooctene monomers using **1b** as precatalyst



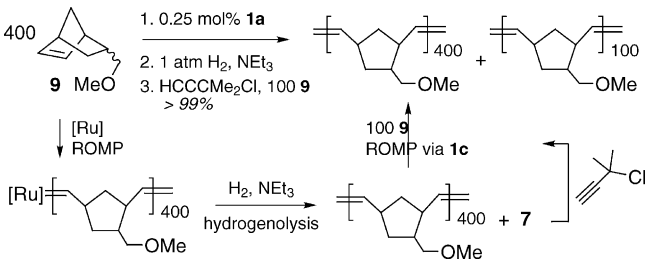
Scheme 8. Synthesis of a functionalized polyethylene by assisted tandem ROMP-hydrogenation of a cyclooctene monomer [59].



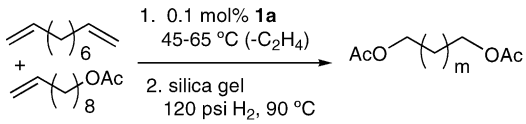
Scheme 9. Ru hydrides formed by hydrogenolysis of Grubbs metathesis catalyst [62].

[59] (Scheme 8). Addition of H_2 after metathesis was complete enabled the switch from metathesis to hydrogenation catalysis, with near-quantitative polymer hydrogenation under forcing conditions (135 °C, 400 psi H_2). Subsequent mechanistic studies on **1a** [62] showed that such species undergo H_2-hydrogenolyis of the Ru-alkylidene functionality to liberate six-coordinate Ru(IV) dihydride **5**, accompanied by its coordinatively unsaturated dihydrogen tautomer **6** (Scheme 9). Treatment with base effects transformation into the more reactive hydridochloro species **7** [62]. Indeed, addition of NEt_3 enables reduction of ROMP polymers at 30–100 psi H_2 for precatalysts of type **1** [60,61], as well as bimetallic Ru–alkylidene species [60]. Further increases in activity were found on carrying out the reduction step with methanol as cosolvent, this treatment generating highly active [63] hydrogenation catalyst $RuHCl(CO)(PCy_3)_2$ **8** via carbonylation of **7**. Thus, reduction of polyoctenes could be accomplished at 1 atm H_2 by adding NEt_3, methanol, and H_2 following ROMP of cyclooctene monomers in CH_2Cl_2 [61]. Recent work indicates that other primary alcohols can convert **1a** into **8** in the absence of added H_2 [64].

Double-tandem cycles of ROMP–hydrogenolysis–ROMP or ROMP–hydrogenation–ROMP can be used to prepare unsaturated or saturated (respectively) polymer blends containing two distinct molecular weight fractions (Scheme 10) [61]. Such tailored blends can overcome processing problems associated with narrow-polydispersity polymers. The procedure requires regeneration of a Ru–alkylidene following hydrogenolysis or hydrogenation of the ROMP polymer in CH_2Cl_2. Addition of propargyl chloride to the reaction solution effects transformation of **7** into alkylidene **1c** [65], which can initiate a second cycle of ROMP to give



Scheme 10. Synthesis of tailored polymer blends via assisted double-tandem ROMP-hydrogenolysis-ROMP [61].

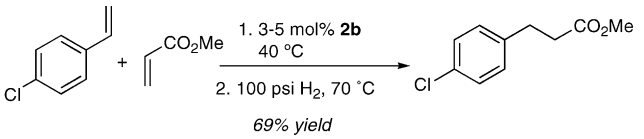


Scheme 11. Assisted tandem ADMET-hydrogenation [66,67].

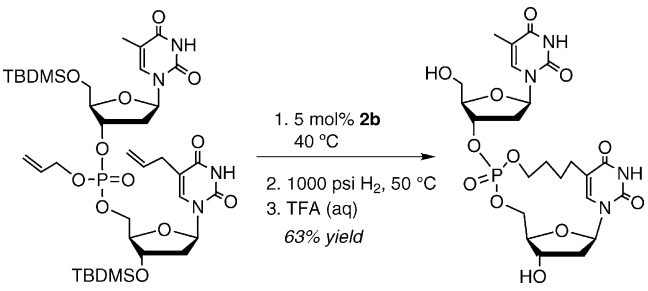
the desired blend of two narrow-polydispersity polymers [61]. Polymer hydrogenation (at 250 psi) was also carried out to obtain the saturated polymers, as above: the higher pressure is necessitated by the steric encumbrance of the polynorbornene substrate, versus polyoctene.

3.2.1.2. ADMET-hydrogenation. Assisted tandem processes involving homogeneously catalyzed ADMET followed by heterogeneously catalyzed hydrogenation have been developed [66,67]. The protocol is extremely straightforward, involving addition of silica and H_2 following metathesis (Scheme 11). The need to separate the reduced polymer from the silica support limits this approach to polymers that remain soluble following reduction. A similar heterogenization procedure might be advantageously applied to (e.g.) RCM-hydrogenation, though no report to this effect has yet appeared.

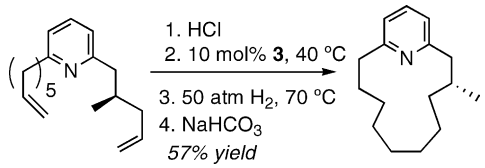
3.2.1.3. CM-hydrogenation, RCM-hydrogenation. Tandem metathesis-hydrogenation techniques have likewise been applied to construction of small molecules (Scheme 12). While RCM (or CM)-hydrogenation chemistry corresponds in many ways to ROMP-hydrogenation, some key differences result from differences in the catalysts typically used. CM and RCM generally require the more reactive Ru-NHC catalysts of type **2**, rather than the bis-PCy_3 complexes **1** typically used for Ru-catalyzed ROMP. However, recent work suggests that the hydrogenation activity follows the opposite trend from metathesis: that is, Ru–NHC complexes are less hydrogenation-active



Scheme 12. Assisted tandem CM-hydrogenation in functionalization of aryl chlorides [69].



Scheme 13. Assisted tandem RCM-hydrogenation in the synthesis of cyclic dinucleotides [70].

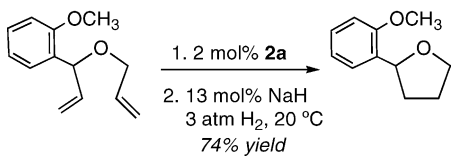


Scheme 14. Assisted tandem RCM-hydrogenation in the synthesis of muscopyridine [71].

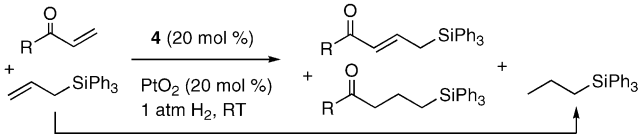
than their PCy_3 analogues [68]. Also contributing to lower activity in the hydrogenation step in tandem RCM (CM)-hydrogenations is the higher dilution required to inhibit competing ADMET, which effectively decreases the concentration of the hydrogenation catalyst. These factors offset the greater reactivity of the olefinic groups in small molecules, versus macromolecular substrates, as well as the higher catalyst loadings typically employed in RCM or CM (1–20 mol.% Ru, versus 0.5 mol.% for much of the ROMP chemistry described above). The hydrogenation step is therefore typically carried out at elevated temperatures and H_2 pressures (50–100 °C; 100–1000 psi H_2; vide infra), although the conditions employed in some cases probably reflect a target-focused procedure, rather than the mildest conditions required. It may be noted that the lower activity of the Ru-NHC catalysts can be advantageous in enhancing selectivity for less substituted C=C bonds [69].

In the first reported synthesis of small molecules via tandem metathesis-hydrogenation (Scheme 12), Grubbs and coworkers applied **1a** and **2b** to CM-hydrogenation of activated and unactivated alkenes, as well as to RCM-reduction of activated dienes containing cis, trans, conjugated, and trisubstituted olefins [69]. Tolerance for amide, ester, aryl chloride, and alcohol functionalities was demonstrated, as well as the usual selectivity for hydrogenation of less substituted olefins. This methodology has since been employed in construction of biologically relevant cyclic dinucleotides (Scheme 13) [70], as well as in a concise recent synthesis of (*R*)-(+)-muscopyridine via indenylidene catalyst **3** [71] (Scheme 14).

Tandem RCM-hydrogenation of diallyl ethers and diallylcarbinols (Scheme 15) has also been carried out at RT using **2a** "activated" for hydrogenation by addition of ca. 15 mol.% NaH [72]. Reduction could be effected at 1–3 atm H_2, or under argon in the presence of excess NaH and water.



Scheme 15. Assisted tandem RCM-hydrogenation in the synthesis of aryltetrahydrofurans [72].

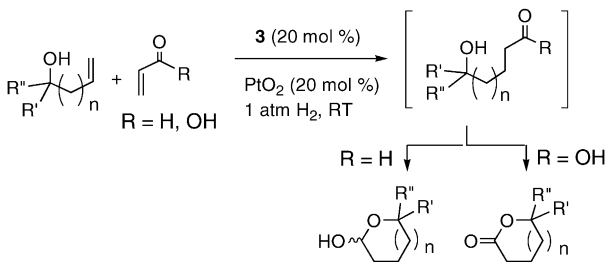


Scheme 16. Orthogonal tandem CM-hydrogenation [73].

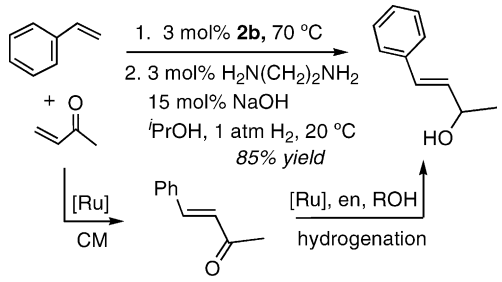
3.2.1.4. Orthogonal CM-hydrogenation. Cossy's group has employed orthogonal catalysis in tandem CM-hydrogenation reactions using the Hoveyda catalyst **4** and PtO_2 (Scheme 16) [73]. For experimental convenience, the entire sequence was performed under hydrogen atmosphere, necessitating use of a metathesis catalyst that resists hydrogenolysis. Under these conditions, **4**-catalyzed CM of allyl-triphenylsilane with α,β-unsaturated carbonyl, carboxylic acid, or ester compounds is followed by PtO_2-catalyzed hydrogenation, affording the saturated carbonyl or carboxylic products in up to 75% yield. Competing reduction of the allylsilane is limited by use of a rather unreactive hydrogenation catalyst: use of Pd/C resulted in preferential reduction of allylsilane.

This methodology enables synthesis of substituted lactones and lactols via **3**-catalyzed CM-hydrogenation of acrylic acid or acrolein with unsaturated alcohols, and spontaneous cyclization of the ω-hydroxy acid or aldehyde products (Scheme 17) [74]. Unsaturated secondary alcohols gave the target lactones or lactols in 45–70% yield. The corresponding unsaturated tertiary alcohols can give good yields (up to 57%) of spirocyclic lactones using homoallylic alcohols: for sterically hindered substrates, however, reduction can dominate over CM.

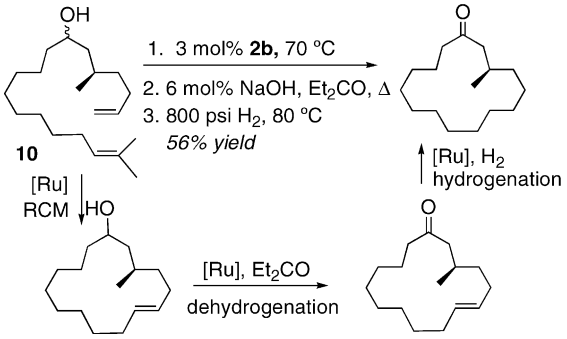
3.2.1.5. CM(RCM)-ketone hydrogenation; CM(RCM)-alcohol oxidation. An elegant strategy reported by the Grubbs group exploits the capacity of RuHCl(en)LL' species



Scheme 17. Synthesis of substituted lactones and lactols via orthogonal tandem CM-hydrogenation [74].



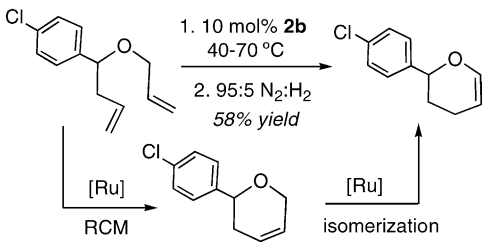
Scheme 18. Assisted tandem CM-transfer hydrogenation [69].



Scheme 19. Synthesis of (−)-muscone by assisted double-tandem RCM-transfer dehydrogenation–H_2–hydrogenation procedure [69].

to promote regioselective transfer hydrogenation of the carbonyl functionality in unsaturated ketones (Scheme 18) [69]. CM or RCM via **1a** or **2b**, followed by addition of ethylenediamine (en) and NaOH, was proposed to effect formation of RuHCl(en)(PCy_3)(L) (L: PCy_3, H_2IMes), a transfer hydrogenation catalyst of the Noyori type. Selective reduction of the ketone functionality was effected at room temperature in isopropanol under an atmosphere of H_2.

Transfer hydrogenation could also be effected without addition of the diamine, though more forcing conditions were then required (80 °C). The reverse reaction, transfer dehydrogenation of alcohols to unsaturated ketones, was also carried out using 3-pentanone as proton acceptor. These methodologies were coupled in a beautiful example of double-tandem catalysis applied to the synthesis of (−)-muscone (Scheme 19) [69]. The product was obtained in 56% yield by RCM of diene **10**, transfer dehydrogenation of the alcohol, and regioselective H_2-hydrogenation of the olefin.



Scheme 21. Synthesis of cyclic enol ethers by assisted tandem RCM-isomerization [80].

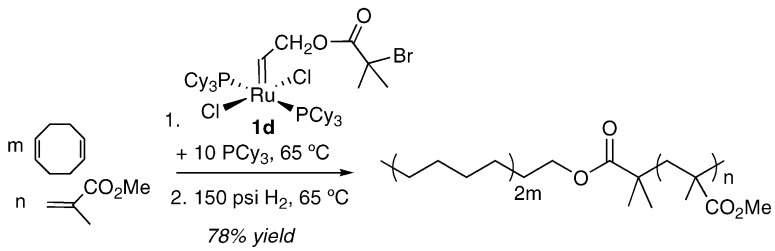
3.2.2. Metathesis-ATRP-hydrogenation

A double-tandem ROMP-ATRP-hydrogenation process was devised using bifunctional catalyst **1d** (Scheme 20) [75]. The [Ru]=CHR site promotes both metathesis and (in conjunction with the 2-bromomethylpropionate initiator that terminates the alkylidene) ATRP. This system was used to effect concurrent ROMP of cyclooctadiene (COD) and ATRP of methyl methacrylate (MMA). The resulting diblock $[COD]_m[MMA]_n$ copolymer was then hydrogenated by exposure to H_2 in toluene–THF. The cumulative process can be classified as an auto-tandem ROMP-ATRP process, accompanied by an assisted tandem ROMP-hydrogenation.

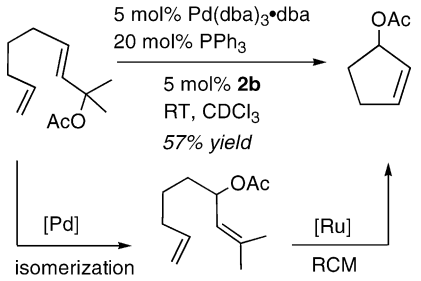
3.2.3. Metathesis-isomerization

Competing olefin isomerization can be problematic for slow Ru-catalyzed RCM or CM reactions, particularly in aromatic solvents [69,76] and for NHC catalysts [76–79]. Although it may be possible that the Ru-alkylidene itself can induce isomerization, a ruthenium hydride contaminant or decomposition product is widely assumed to be the culprit. Snapper's group has achieved controlled tandem RCM-olefin isomerization in five- to seven-membered ring systems by adding a small proportion of H_2 to promote isomerization following RCM of acyclic dienes. Use of 95:5 N_2:H_2 (forming gas) permitted isomerization with <10% hydrogenation. This strategy enabled synthesis of cyclic enol ethers (Scheme 21) [80], with the regiochemistry in all cases favouring the less substituted enol ether. Failure of the isomerization reaction in the absence of H_2 indicates that a Ru-hydride catalyst is almost certainly involved, though attempts at characterization were unsuccessful.

Orthogonal tandem catalysis has been applied to allylic isomerization-RCM, using a Pd–PPh_3 isomerization catalyst in conjunction with **2b** as metathesis catalyst (Scheme 22)



Scheme 20. Synthesis of diblock copolymers of polymethylmethacrylate and ethylene by double-tandem ROMP–ATRP-hydrogenation [75].

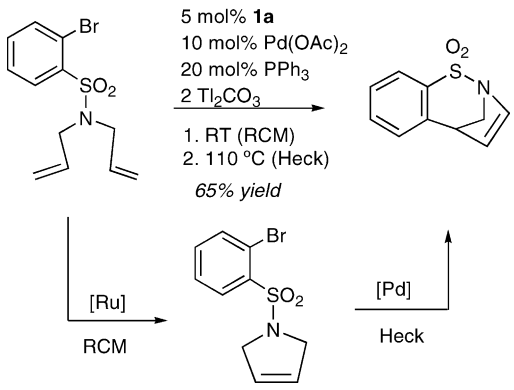


Scheme 22. Orthogonal tandem catalysis in allylic acetate isomerization-RCM; dba: dibenzylideneacetone [81].

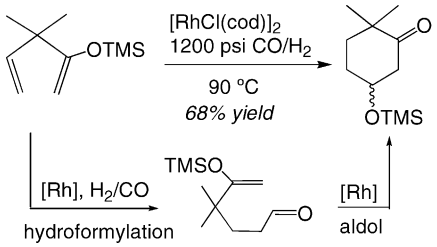
[81]. Competing RCM of the starting allylic acetates is not apparently observed. The failure of the corresponding reaction utilizing **1a** as RCM catalyst [82] exemplifies the difficulty in balancing opposing catalyst requirements in orthogonal catalysis. In this case, either allylic isomerization *or* RCM could be induced, but not both, an observation attributed to deactivation of **1a** by added PPh_3 (required to stabilize the Pd catalyst), or poisoning of the PPh_3-free Pd(0) reagent by the PCy_3 liberated by activation of **1a**.

3.2.4. Metathesis-Heck coupling

Similar difficulties are encountered in attempts to couple Ru-catalyzed RCM and Pd-catalyzed Heck reactions in an orthogonal catalysis approach to construction of bridged rings (Scheme 23) [83,84]. The RCM reaction was carried out at room temperature, following which the mixture was heated to initiate Heck coupling. While satisfactory yields could be obtained where five-membered rings were formed in the RCM step, Heck catalysis predominated for larger ring sizes, presumably due to the slower rate of RCM and competitive poisoning of **1a** by phosphine or Pd. (Notably, poisoning of the RCM reaction was found even in the presence of phosphine-free $Pd(OAc)_2$). Improved results were found on use of a polymer-supported Pd catalyst, in which access to the Pd sites is thought to be promoted only at the higher temperatures used for the Heck chemistry, or on use of a fluorous biphasic solvent system capable of sequestering the Pd precursor [84].



Scheme 23. Construction of bridged rings via orthogonal tandem RCM-Heck catalysis [83,84].



Scheme 24. Skeletal expansion of unsaturated silyl enol ethers via auto-tandem hydroformylation–cyclization [86].

3.3. Tandem catalyses involving hydroformylation

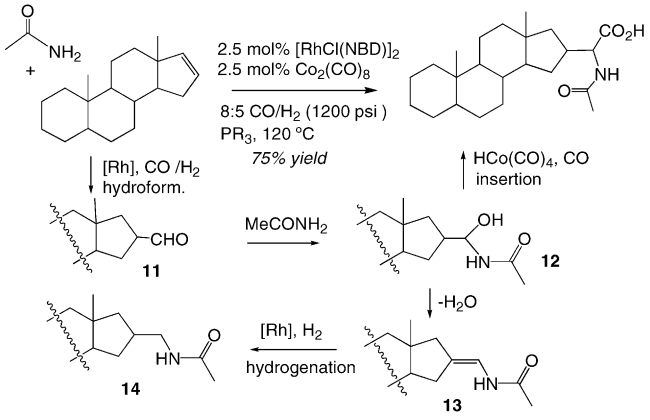
The aldehydes obtained by hydroformylation of α-olefins are commonly transformed into other functionalities: into alcohols via hydrogenation, carboxylic acids via oxidation, amines via hydroamination (aminomethylation), or *N*-acetylated amino acids via amidocarbonylation [85]. Coupled catalytic processes are thus of great interest in this area, which is particularly rich in examples of auto-tandem catalysis. A recent review (highly comprehensive to the end of 1998) described domino or tandem reactions in which all steps are carried out under hydroformylation conditions [13]. Several dozen examples of tandem *catalysis* are included, the majority of which involve acid or base catalysis in the second cycle. Given this coverage, we shall focus on examples emerging since the beginning of 1999. A few of these were noted in a 2003 review of methods for constructing complex organic molecules by reaction sequences that include a hydroformylation step [12].

3.3.1. Hydroformylation-Mukaiyama cyclization

Auto-tandem hydroformylation–cyclization, catalyzed by $[RhCl(cod)]_2$, enables expansion of the organic skeleton of unsaturated silyl enol ethers (Scheme 24) [86]. Linear aldehydes generated in the hydroformylation step undergo a subsequent Rh-catalyzed, intramolecular Mukaiyama aldol addition. Bicyclic ketones are also accessible from cyclic silyl enol ethers.

3.3.2. Hydroformylation–carbonylation (amidocarbonylation)

Derivatives of the steroids androstene and pregnene have been transformed directly into *N*-acyl amino acids by an orthogonal catalysis procedure utilizing $[RhCl(nbd)]_2$ and $Co_2(CO)_8$ (Scheme 25) [87]. The rhodium phosphine catalyst (generated in situ in the presence of syn gas and phosphine) effects hydroformylation of the internal olefin to generate aldehyde **11**. Only in the presence of $Co_2(CO)_8$ are *N*-acyl amino acids obtained as the major products. An unstable amidoalcohol intermediate **12**, formed by reaction of the amide with aldehyde, is proposed to undergo cobalt-catalyzed CO insertion to yield the desired *N*-acyl amino acid. Observation of unsaturated or saturated amidomethylidene products **13** or **14** in the absence

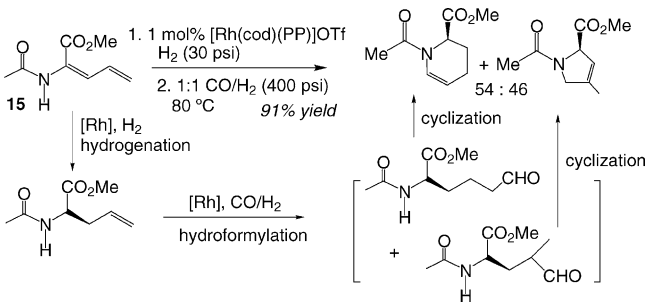


Scheme 25. Orthogonal catalysis in the construction of α-amino acid steroid derivatives [87].

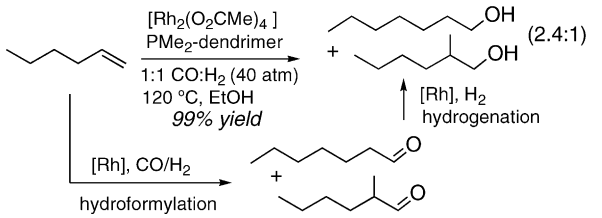
of $Co_2(CO)_8$ was ascribed to (reversible) dehydration, followed by Rh-catalyzed hydrogenation of the double bond where the added phosphine was sufficiently basic. Formation of **14** thus provides an example of undesired auto-tandem catalysis.

3.3.3. Hydrogenation–hydroformylation

Cyclic homochiral precursors of biologically important amino acids have been synthesized using [Rh(cod)(PP)]OTf as catalyst (PP = 2R,5R-Et-DuPHOS), in an elegant example of assisted tandem catalysis (Scheme 26) [88]. Thus, enantioselective (mono)hydrogenation of diene **15** is effected under H_2: introduction of syn gas generates a rhodium carbonyl species, which catalyzes hydroformylation of the remaining double bond. Spontaneous cyclization of the aldehyde product gives a mixture of five- and six-membered cyclic amides in >95% e.e. The sequence was also accomplished (albeit with lower efficiency in Rh utilization) via orthogonal catalysis, using [Rh(cod)(Et-DuPHOS]OTf for the hydrogenation step and $[Rh(OAc)_2]_2/PPh_3$ or $[Rh(OAc)_2]_2$/BIPHEPHOS for hydroformylation. Hydrogenation of the trisubstituted, endocyclic double bond was carried out in a separate procedure requiring use of Pd/C. Subsequent acid hydrolysis yielded the cyclic α-amino acids [88].



Scheme 26. Assisted tandem catalysis in conversion of olefins to amino acid derivatives [88].



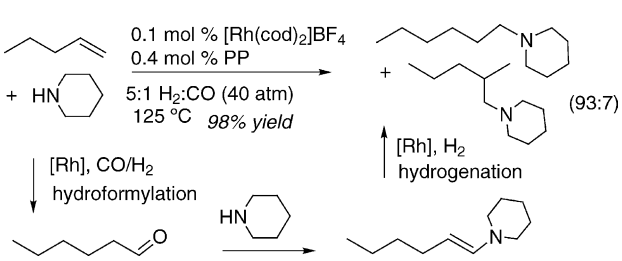
Scheme 27. Auto-tandem catalysis in hydroformylation–hydrogenation of α-olefins to alcohols [89].

3.3.4. Hydroformylation–hydrogenation

Extremely important in hydroformylation chemistry are examples of auto-tandem catalysis in which the aldehydic product of hydroformylation functions directly as a substrate for hydrogenation, yielding alcohol products. The aldehyde can also, however, undergo stoichiometric modification prior to uptake into the hydrogenation cycle, expanding the range of organic products accessible.

3.3.4.1. Alcohol products. A key sequence in the Shell Oxo Process (see Section 3.3.6.1) involves use of a Co-alkylphosphine catalyst to promote both hydroformylation of α-olefins, and the ensuing hydrogenation of the aldehyde products to alcohols [43]. In other applications, tandem hydroformylation–hydrogenation of functionalized alkenes is directed at production of commercially important diols from unsaturated alcohols, alkynes, dienes or esters. Oligosilsesquioxane dendrimers bearing Rh–alkylphosphine groups are effective in the tandem transformation (Scheme 27), but the corresponding arylphosphine derivatives promote only the hydroformylation step [89].

3.3.4.2. Amine products (hydroaminomethylation). Transformation of olefins to homologous amines can be effected by sequential processes of catalytic hydroformylation, stoichiometric trapping with amine or ammonia, and catalytic reduction (Scheme 28). Where the efficiency in metal utilization is high, such auto-tandem catalysis offer an attractive alternative to the classical syntheses of amines via ammonolysis of alcohols, reductive amination of aldehydes, or hydrogenation of nitriles. Complications, however, can emerge from undesired tandem catalytic pathways (isomerization or hydrogenation of the olefin, aldehyde, or



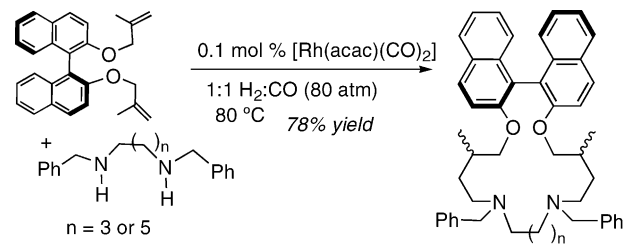
Scheme 28. Auto-tandem catalysis in hydroaminomethylation of olefins. Intermediates shown for linear product only [90].

imine intermediates), as well as from side-reactions, such as amine-catalyzed aldol reactions, or incomplete reduction of intermediate imines and enamines [85]. Regioselectivity during hydroformylation is also critical, as separation of linear and branched products is often problematic. Good to excellent yields of linear amines were obtained in a tandem catalysis protocol applicable to a wide range of olefins and amines, using a Rh-phosphine catalyst generated in situ (Scheme 28) [90]. XANTPHOS afforded regioselectivity in the hydroformylation step superior to that found with other chelating or monodentate phosphines, as well as higher activity in the ensuing enamine hydrogenation.

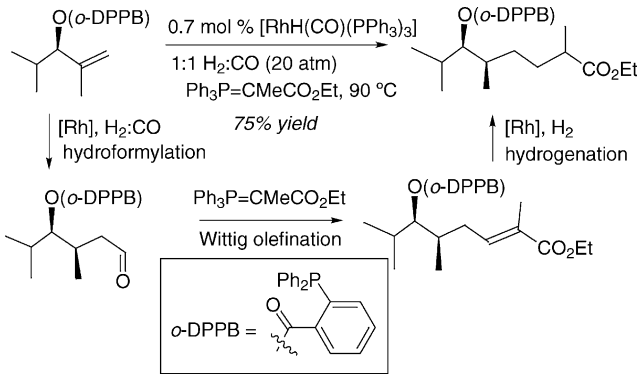
The low hydroaminomethylation activity of Ru catalysts has been attributed to slow rates of hydroformylation [91]. Rhodium catalysis, as indicated above, exhibits higher hydroformylation activity, but this can be offset by low activity in the ensuing C=N hydrogenation (an issue exacerbated by the high cost of Rh). Orthogonal catalysis, involving Rh-catalyzed hydroformylation and Ru-catalyzed C=N hydrogenation, has been used to prepare a series of aliphatic amines by hydroaminomethylation of 1-hexene, 1-octene or 1-dodecene with dimethylamine [85]. Use of $Ru(acac)_3$ in conjunction with $Rh(2\text{-ethylhexanoate})_3$ enables a decrease in rhodium loading from 240 ppm (Rh:olefin) to as low as 3 ppm, with high selectivity for the amine product. Iridium has likewise been used to accelerate the imine hydrogenation step in orthogonal catalysis procedures based on $[RhCl(cod)]_2$ and $[IrCl(cod)]_2$ [92].

Hydroaminomethylation methodologies have been extensively applied to construction of structurally complex organic amines by Eilbracht and co-workers [93–99]. This work has been recently reviewed [13,100]. Substrates with directed reactivity (e.g. 2,2′ or 3,3′-disubstituted olefins, which favour terminal aldehydes) aid in controlling regioselectivity. Macroheterocycles were prepared in moderate to good yields from diolefins and diamines [101,102]. Likewise, 20–28 membered azamacroheterocycles have been obtained in up to 78% yield by tandem Rh-catalyzed hydroformylation of aromatic diallyl ethers of hydroquinone, biphenol and binaphthol, followed by reductive amination of the dialdehydes with α,ω-diamines (Scheme 29) [103].

3.3.4.3. C–C skeleton expansion. Expansion of the C–C skeleton of methallylic alcohol derivatives has been effected by stoichiometric Wittig olefination of the aldehyde obtained by Rh-catalyzed hydroformylation, followed by Rh-catalyzed reduction of the C=C bond in the product (Scheme 30) [104]. The *o*-diphenylphosphinobenzoate directing group used in this reaction promotes *syn* specificity in the hydroformylation step.



Scheme 29. Construction of azamacroheterocycles via auto-tandem catalysis in hydroaminomethylation of olefins [103] (intermediates analogous to those in Scheme 28)

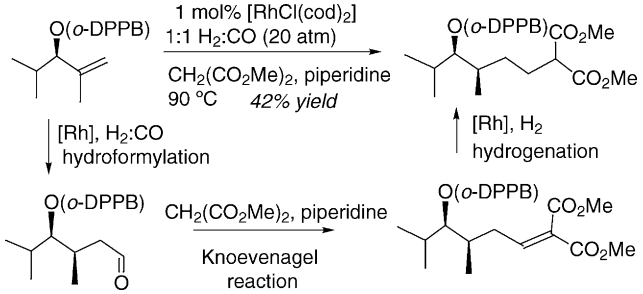


Scheme 30. Auto-tandem catalysis in hydroformylation–Wittig–hydrogenation of methallylic alcohols [104].

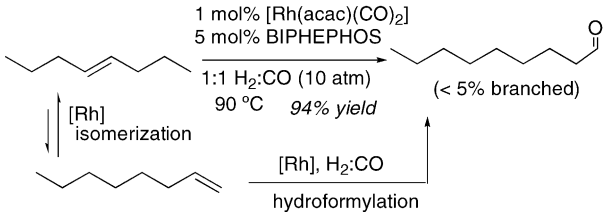
In a closely analogous tandem catalysis sequence, the Wittig olefination step is replaced by a base-catalyzed Knoevenagel condensation with malonates, β-ketoesters and β-diketones (Scheme 31) [105]. This sequence is preferred for its atom economy: in principle, water is the only byproduct, whereas the Wittig route generates stoichiometric quantities of triphenylphosphine oxide.

3.3.5. Isomerization–hydroformylation

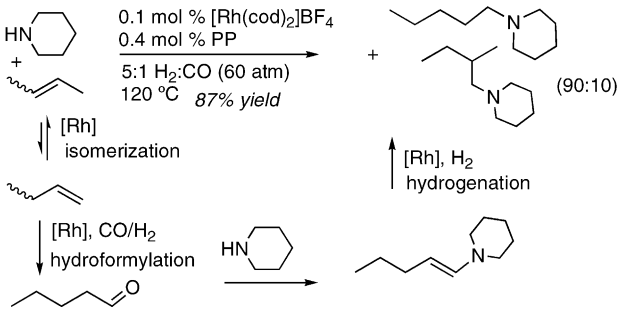
Transformation of internal olefins to linear aldehydes and aldehyde derivatives is attractive both for the low cost of the feedstocks versus α-olefins, and for the value of the linear aldehyde, alcohol, and amine products. Of considerable industrial interest, therefore, are tandem catalytic processes for isomerization of internal to α-olefins, followed by hydroformylation. High rates of isomerization, versus hydroformylation, are desired in order to favour linear product. Owing to the greater thermodynamic stability of the internal olefins, however, α-olefins typically account for <5% of total olefin at equilibrium [106]. High catalyst selectivity is thus required in order to achieve preferential hydroformylation of terminal olefins to linear products. This chemistry of-



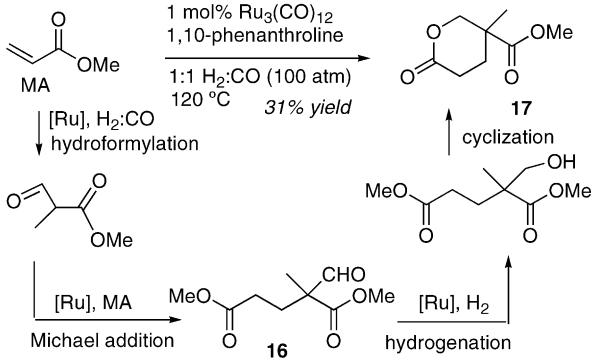
Scheme 31. Auto-tandem catalysis in hydroformylation–Knoevenagel–hydrogenation of methallylic alcohols [105].



Scheme 32. Auto-tandem catalysis in isomerization–hydroformylation of internal olefins to linear products [107].



Scheme 33. (Double) auto-tandem catalysis in isomerization–hydroaminomethylation of internal olefins to linear amines [110]. Intermediates shown for linear product only.



Scheme 34. Auto-tandem catalysis in formation of lactones from acrylates via sequential, Ru-catalyzed hydroformylation, Michael addition, and hydrogenation [111].

fers a challenging opportunity for tandem catalysis, in which catalyst design plays a central role.

Rh complexes of the chelating diphosphite BIPHEPHOS effect efficient tandem isomerization–hydroformylation of internal octenes to the industrially desirable C-9 aldehyde *n*-nonanal (Scheme 32) [107]. Use of propylene carbonate solvent improves selectivity (89–95% yields) as well as the ease of separating products from the catalyst, which remains in the propylene carbonate phase for reuse. A closely related diphosphite containing a 2,2′-dioxydiphenyl fragment affords lower yields (70%) but higher turnover frequencies (4600 h^{-1}, versus 34 h^{-1}) [108]. The low thermal stability of phosphites, however, coupled with their hydrolytic sensitivity, may undermine catalyst integrity in multiple tandem cycles. Chelating diphosphine ligands exhibit greater thermal and chemical stability than phosphites, and their rhodium complexes display high regioselectivity for the linear aldehydes. In comparison to Rh-XANTPHOS complexes [109], improved isomerization activity is found for electron-deficient NAPHOS derivatives (e.g. IPHOS). Turnovers of up to 925 h^{-1} and yields of ca. 70% were obtained in synthesis of linear aldehydes from (e.g.) 2-butene [106].

3.3.6. Double-tandem processes involving hydroformylation

3.3.6.1. Isomerization–hydroformylation–hydrogenation: alcohol products. The Shell Oxo Process, as noted above, is the most important industrial application of tandem catalytic methodology. In a beautiful example of *double* auto-tandem catalysis, a Co-alkylphosphine catalyst effects isomerization of internal olefins in the presence of syn gas, hydroformylation of the α-olefin products, and hydrogenation of the resulting aldehydes to alcohols [43]. High chemoselectivity is critical in this reaction sequence, in order to effect reduction of the aldehyde without significant hydrogenation of the starting olefin.

3.3.6.2. Isomerization–hydroformylation–hydrogenation: amine products. The isomerization–hydroaminomethylation sequence is particularly challenging, even relative to hydroaminomethylation (vide supra), owing to the susceptibility of the isomerization catalysts to poisoning by σ-donor imine and amine products. This transformation has only recently been accomplished in significant yield, the key advance emerging from identification of an optimum phosphine ligand (Scheme 33; PP: IPHOS) [110]. Selectivity in these systems is highly sensitive to small variations in the steric and electronic nature of the phosphine ligands.

3.3.6.3. Hydroformylation–Michael addition–hydrogenation. A serendipitous double auto-tandem catalysis resulted in formation of lactone **17** on attempted hydroformylation of methyl acrylate (MA) using a $Ru_3(CO)_{12}$/1,10-phenanthroline catalyst system (Scheme 34) [111]. Simple hydroformylation products were not observed. Instead, sequential hydroformylation of methyl acrylate, Michael addition of the aldehyde and MA, and hydrogenation of addition product **16** (all three steps being Ru-catalyzed), followed by spontaneous cyclization, yields lactone **17** as the sole carbonylated product. For the corresponding reaction with $Ru_3(CO)_{12}/PPh_3$, the dominant pathway is competing hydrogenation of the acrylate C=C bond, again illustrating the challenges in balancing competing catalytic pathways in auto-tandem catalysis.

4. Conclusions

The past few years have seen an explosion in the development and application of tandem catalysis. Further advances

will be driven by the continuously expanding importance of transition metal catalysis in organic synthesis, and the potential of tandem catalysis to achieve higher molecular complexity while limiting catalyst and process costs. The parallel investment of effort in organic reaction design, and in deconvoluting the inorganic/organometallic chemistry underlying catalyst transformation, will offer key opportunities for the development of sophisticated synthetic strategies incorporating new tandem catalyses.

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